Supporting Information

An Efficient Enantioselective Fluorination of Various β -Ketoesters Catalyzed by Chiral Palladium Complexes

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General: NMR spectra were recorded on a JEOL JNM-LA400 spectrometer, operating at 400 MHz for ^1H -NMR, 100.4 MHz for ^{13}C -NMR. Chemical shifts were reported downfield from TMS (= 0) for ^1H -NMR. For ^{13}C -NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. ^{19}F -NMR was measured at 400 MHz, and CF_3COOH was used as an external standard. FAB-LRMS was taken on JEOL JMS GCmate II using *m*-nitrobenzyl alcohol (mNBA) as matrix. Optical rotations were measured on a JASCO DIP-370 polarimeter. Column chromatography was performed with silica gel 60 (40-100 μm) purchased from KANTO CHEMICAL Co. The enantiomeric excesses (ee's) were determined by HPLC or GC analysis. HPLC analysis was performed on Shimadzu HPLC systems consisting of the followings: pump, LC-10AD; detector, SPD-10A measured at 254 nm or 280 nm; column, DAICEL CHIRALPAK AS, AD, AD-H or DAICEL CHIRALCEL OJ, OD, OD-H; mobile phase, hexane / 2-propanol (IPA). GC analysis was performed on Shimadzu GC-17A with TOKYO KASEI CHIRALDEX G-TA (0.25 mm I.D., x 30m, x 0.125 μm). In general, reactions were carried out under a nitrogen atmosphere, unless noted otherwise. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. EtOH and *i*-PrOH were distilled from calcium hydride. Other reagents were purified by usual methods.

Preparation of Palladium Complexes 1 and 2

The catalysts including palladium aqua complexes (**1a-1f**) and palladium μ -hydroxo complex (**2b** and **2c**) were synthesized according to the representative procedures ¹ which have been reported from our laboratory.

1. Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450-5458.

Concerning to the structure of the following complexes, we are now trying X-ray analysis. The determination of the exact complex structure will be discussed in a full paper.

1b (X = TfO): $[\text{Pd}\{(R)\text{-dm-binap}\}(\text{H}_2\text{O})_2]^{2+}2\text{TfO}^-$:

^1H -NMR (400 MHz, CDCl_3) δ 1.99 (brs, 12H), 2.40 (s, 12H), 3.73 (brs, >4H, H_2O), 6.53-7.77 (m, 24H);

^{31}P -NMR (202 MHz, CDCl_3) δ 35.9; $[\alpha]_{\text{D}}^{25} +146$ (c = 1.00, CHCl_3).

1c (X = TfO): $[\text{Pd}\{(R)\text{-dtbm-segphos}\}(\text{H}_2\text{O})_2]^{2+}2\text{TfO}^-$:

^1H -NMR (400 MHz, CDCl_3) δ 1.35 (brs, 72H), 3.71 (s, 6H), 3.72 (s, 6H), 5.72 (s, 2H), 5.81 (s, 2H), 6.60-

8.80 (m, 12H); ^{31}P -NMR (202 MHz, CDCl_3) δ 34.5; $[\alpha]_{\text{D}}^{25} +253$ ($c = 1.00$, CHCl_3).

2b (X = TfO): $[\text{Pd}\{(R)\text{-dm-binap}\}](\mu\text{-OH})_2^{2+}2\text{TfO}^-$:

^1H -NMR (400 MHz, CDCl_3) δ -2.31 (s, 2H, $\mu\text{-OH}$), 2.01 (brs, 48H), 6.39 – 7.74 (m, 48H) [Because several peaks were broad in the aromatic range, the sum of distinct peaks was insufficient. But, integration between 6.39 – 7.74 ppm gave 48 H. Distinct peaks in the aromatic range are given as follows; δ 6.41 (d, $J = 8.6$ Hz, 4H), 6.66 (s, 4H), 6.81 (s, 4H), 6.97 (d, $J = 10.7$ Hz, 8H), 7.08-7.13 (m, 9H), 7.73 (t, $J = 7.3$ Hz, 9H)]; $[\alpha]_{\text{D}}^{25} +960$ ($c = 0.19$, CHCl_3).

2c (X = TfO): $[\text{Pd}\{(R)\text{-dtbm-segphos}\}](\mu\text{-OH})_2^{2+}2\text{TfO}^-$:

^1H -NMR (400 MHz, CDCl_3) δ -1.16 (s, 2H, $\mu\text{-OH}$), 1.10 (brs, 72H), 1.57 (s, 36H), 1.59 (s, 36H), 3.57 (s, 12H), 3.79 (s, 12H), 5.39-5.44 (m, 4H), 5.70 (s, 4H), 5.94 (s, 4H), 6.34 (d, $J = 7.8$ Hz, 4H), 6.86-6.92 (m, 4H), 6.92-7.20 (brs, 4H), 7.88-8.04 (brs, 4H), 8.64-8.72 (m, 4H); $[\alpha]_{\text{D}}^{25} +229$ ($c = 0.21$, CHCl_3).

Optimization of the Reaction Conditions Using β -Ketoester **3a**

1) Structure of the ligands: Many catalysts were examined for improving enantioselectivity using **3a** as a model compound. The results are summarized in Table 3.

Table 3. Optimization of the Reaction Conditions Using β -Ketoester **3a**.

3a + NFSI (1.5 eq) $\xrightarrow[\text{solvent, 1 M}]{\text{Pd-cat. 1 or 2 (X = TfO)}}$ **4a**

1a-f

2b,c

entry	catalyst ^a (mol %) ^b	solvent	temp (°C)	time (h)	yield ^c (%)	ee ^d (%)
1	1a (5)	THF	-20	12	72	79
2	1b (5)	THF	-20	39	99	88
3	1c (5)	THF	0	72	89	90
4	1d (5)	THF	-20	7.5	92	80
5	1e (5)	THF	-20	12	87	83
6	1f (5)	THF	-20	39	82	71
7	2c (2.5)	THF	10	48	83	92
8	2c (2.5)	acetone	10	48	93	92
9	2c (2.5)	EtOH	20	18	73	92

1a-f

2b,c

a: Ar = Ph : (*R*)-BINAP
b: Ar = 3,5-dimethylphenyl : (*R*)-DM-BINAP
d: Ar = *p*-MeO-Ph : (*R*)-MeO-BINAP
e: Ar = *p*-Me-Ph : (*R*)-Tol-BINAP

1a-f

2b,c

f: Ar = Ph : (*R*)-SEGPHOS
c: Ar = : (*R*)-DTBM-SEGPHOS

^a **1-2**: Catalyst structure, **a-f**: chiral ligand. ^b Catalyst amount.

^c Isolated yield. ^d Determined by HPLC analysis.

2) Concentration of the reaction: Thick reaction mixture was found to be more beneficial for the rapid conversion. For 1 M **3d**, high chemical yield (92%) was obtained after 40 h. In contrast, the desired product was obtained in insufficient chemical yield (54%, after 40 h) for 0.1 M **3d**. But, the enantioselectivity was not affected by the difference of the reaction concentration (91% ee in both cases).

General Procedure for the Catalytic Enantioselective Fluorination of β -Ketoesters

To a solution of the palladium complex **1** (0.01 mmol) or **2** (0.005 mmol) in EtOH (0.2 mL) was added β -ketoester **3** (0.2 mmol) at room temperature, and the mixture was stirred for 5 min. At the temperature indicated in Table 2, NFSI (95 mg, 0.3 mmol) was added. This suspended reaction mixture was allowed to stir for the time given in Table 2. After the completion of the reaction (TLC, benzene/ether = 5/1), saturated NH₄Cl (3 mL) was added for quenching. The aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with water and brine. After drying with Na₂SO₄, solvent was removed under the reduced pressure. Further purification was performed by flash column chromatography on SiO₂ (hexane : Et₂O = 10 : 1) to give the pure product **4**.

***tert*-Butyl 1-Fluoro-2-oxo-cyclopentanecarboxylate (**4a**):**

¹H-NMR (400 MHz, CDCl₃) δ 1.49 (s, 9H), 2.07-2.15 (m, 2H), 2.21-2.34 (m, 1H), 2.44-2.57 (m, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 18.0 (d, *J* = 4.1 Hz), 27.9, 33.8 (d, *J* = 20.6 Hz), 35.7, 84.0, 94.4 (d, *J* = 199.1 Hz), 166.4 (d, *J* = 27.9 Hz), 208.1 (d, *J* = 16.4 Hz); ¹⁹F-NMR (400 MHz, CDCl₃) δ -163.2; FAB-MS (mNBA) *m/z* 202 (M)⁺, 146 (M-*t*-Bu)⁺; [α]_D³¹ +72.7 (*c* = 1.27, CHCl₃) (92% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 99 / 1, 0.40 mL / min, 280 nm) *t*_r(minor) = 20.3 min, *t*_r(major) = 24.7 min.

***tert*-Butyl 1-Fluoro-2-oxo-cyclohexanecarboxylate (**4b**):**

¹H-NMR (400 MHz, CDCl₃) δ 1.53 (s, 9H), 1.82-2.12 (m, 5H), 2.40-2.74 (m, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 21.2 (d, *J* = 6.6 Hz), 26.5, 27.8, 36.0 (d, *J* = 21.4 Hz), 39.9, 83.8, 96.3 (d, *J* = 195 Hz), 165.7 (d, *J* = 23.9 Hz), 202.2 (d, *J* = 19.0 Hz); ¹⁹F-NMR (400 MHz, CDCl₃) δ -159.6; FAB-MS (mNBA) *m/z* 217 (M+1)⁺, 161 (M+2-*t*-Bu)⁺; [α]_D³³ -88.6 (*c* = 1.39, CHCl₃) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 149 / 1, 0.40 mL / min, 280 nm) *t*_r(minor) = 23.1 min, *t*_r(major) = 28.3 min.

***(R)*-tert-Butyl 2-Fluoro-1-oxo-indan-2-carboxylate (**4c**):**

¹H-NMR (400 MHz, CDCl₃) δ 1.43 (s, 9H), 3.40 (dd, *J* = 17.6, 23.0 Hz, 1H), 3.73 (dd, *J* = 10.7, 17.6 Hz, 1H), 7.43-7.50 (m, 2H), 7.67-7.71 (m, 1H), 7.83 (d, *J* = 7.6 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 27.8, 38.3 (d, *J* = 23.9 Hz), 84.1, 95.4 (d, *J* = 201 Hz), 125.4, 126.4, 128.4, 133.6, 136.4, 150.9 (d, *J* = 3.3 Hz), 166.2 (d, *J* = 27.2 Hz), 195.8 (d, *J* = 18.1 Hz); ¹⁹F-NMR (400 MHz, CDCl₃) δ -164.4; FAB-MS (mNBA) *m/z* 251 (M+1)⁺, 195 (M+2H-*t*-Bu)⁺; [α]_D³⁴ +3.8 (*c* = 0.86, CHCl₃) (83% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 150 / 1, 0.75 mL / min, 254 nm) *t*_r(minor) = 24.1 min, *t*_r(major) = 33.7 min.

The method for the determination of the absolute configuration of **4c** is discussed later.

***(R)*-tert-Butyl 2-Fluoro-2-methyl-3-oxo-3-phenyl-propionate (**4d**):**

¹H-NMR (400 MHz, CDCl₃) δ 1.37 (s, 9H), 1.82 (d, *J* = 22.4 Hz, 3H), 7.43-7.48 (m, 2H), 7.56-7.60 (m, 1H), 8.02-8.06 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ 20.6 (d, *J* = 23.9 Hz), 27.6, 84.0, 96.6 (d, *J* = 193 Hz, 1H), 128.5, 129.5, 133.6, 167.5 (d, *J* = 25.5 Hz), 191.7 (d, *J* = 25.5 Hz); ¹⁹F-NMR (400 MHz, CDCl₃) δ -151.2; FAB-MS (mNBA) *m/z* 253 (M+1)⁺, 197 (M+2H-*t*-Bu)⁺; [α]_D³³ +74.0 (*c* = 1.30, CHCl₃) (91%

ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 200 / 1, 0.40 mL / min, 254 nm) t_r (major) = 17.7 min, t_r (minor) = 19.1 min.

The method for the determination of the absolute configuration of **4d** is discussed later

***tert*-Butyl 2-Fluoro-2-methyl-3-oxo-butyrate (**4e**):**

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.48 (s, 9H), 1.63 (d, $J = 22.2$ Hz, 3H), 2.30 (d, $J = 4.4$ Hz, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 19.5 (d, $J = 23.1$ Hz), 24.9, 27.5, 83.8, 97.7 (d, $J = 192$ Hz), 165.9 (d, $J = 25.5$ Hz), 202.5 (d, $J = 28.8$ Hz); $^{19}\text{F-NMR}$ (400 MHz, CDCl_3) δ -156.6; FAB-MS (mNBA) m/z 191 ($M+1$)⁺; $[\alpha]_D^{34}$ -44.0 ($c = 0.91$, CHCl_3) (89% ee); GC (TOKYO KASEI CHIRALDEX G-TA, 0.25 mm I.D., $\times$ 30m, $\times$ 0.125mm, Temp. 70 °C Inj. Temp. 300 °C, Det. Temp. 250 °C) t_r (minor) = 21.0, t_r (major) = 21.7.

***tert*-Butyl 2-Ethyl-2-fluoro-3-oxo-butyrate (**4f**):**

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 0.95 (t, $J = 7.4$ Hz, 3H), 1.49 (s, 9H), 1.94-2.20 (m, 2H), 2.29 (d, $J = 4.64$, Hz, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 7.00, 25.7, 26.9 (d, $J = 21.4$ Hz), 27.8, 83.8, 100.6 (d, $J = 194$ Hz), 165.3 (d, $J = 26.3$ Hz), 202.4 (d, $J = 32.9$ Hz); FAB-MS (mNBA) m/z 205 ($M+1$)⁺, 147 ($M-t\text{-Bu}$)⁺, 148 ($M+2-t\text{-Bu}$)⁺; $[\alpha]_D^{31}$ -12.6 ($c = 1.45$, CHCl_3) (87% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 150 / 1, 0.40 mL / min, 280 nm) t_r (minor) = 11.6 min, t_r (major) = 12.5 min.

Conversion and Determination of the Absolute Configuration of **4c.**

The absolute configuration of **4c** was determined by comparing the retention times of HPLC analysis after the conversion into **G** as shown below, which has been reported by Takeuchi and Shibata.²

2. Takeuchi, Y.; Suzuki, T.; Sato, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708-5711.

Scheme 2. Conversion and Determination of the Absolute Configuration of **4c**.

***tert*-Butyl 2-Fluoro-1-hydroxy-indan-2-carboxylate (**A**):**

To a solution (MeOH , 1 mL) of **4c** (30 mg, 0.12 mmol) was added NaBH_4 (14 mg) at -78 °C. The reaction mixture was stirred for 1 h. To decompose the excess amount of NaBH_4 , a few drops of acetone were added. After concentrating the reaction mixture to about one third of the original volume, saturated

NH₄Cl (2 mL) was added. The aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. Removal of solvent, followed by flash column chromatography (hexane : ethyl acetate = 8 : 1) afforded the desired product **A** as a colorless oil in 82% (25 mg). The diastereomer ratio was determined to be 2.8 : 1 by ¹H-NMR.

<major>

¹H-NMR (400 MHz, CDCl₃) δ 1.49 (s, 9H), 2.59 (br, 1H), 3.26 (dd, *J* = 17.6, 23.2 Hz, 1H), 3.70 (dd, *J* = 17.6, 19.2 Hz, 1H), 5.34 (d, *J* = 19.0 Hz, 1H) 7.21-7.47 (m, 4H).

<minor>

¹H-NMR (400 MHz, CDCl₃) δ 1.55 (s, 9H), 2.49 (br, 1H), 3.28 (dd, *J* = 17.1, 41.5 Hz, 1H), 3.47 (dd, *J* = 17.1, 33.4 Hz, 1H), 5.48 (d, *J* = 16.4 Hz, 1H) 7.21-7.47 (m, 4H).

tert-Butyl 2-Fluoro-1-methoxymethoxy-indan-2-carboxylate (B):

Fluorohydrin **A** (24 mg, 0.095 mmol) was dissolved in THF (1 mL). NaH (8 mg) was added under ice-bath. After 30 min, MOMCl (40 μL, 0.53 mmol) was added, and the reaction mixture was allowed to stir for 3 h. HCl solution (1 mL, 1 N) was added for quenching. Extraction with ethyl acetate (2 x 10 mL), followed by flash column chromatography (hexane : ethyl acetate = 6 : 1) gave the desired product **B** in 90% yield (28 mg). major : minor = 2.3 : 1

<major>

¹H-NMR (400 MHz, CDCl₃) δ 1.45 (s, 9H), 3.20 (dd, *J* = 17.1, 22.1 Hz, 1H), 3.45 (s, 3H), 3.75 (dd, *J* = 17.1, 19.3 Hz, 1H), 4.88 (d, *J* = 3.1 Hz, 2H), 5.33 (d, *J* = 18.0 Hz, 1H) 7.20-7.41 (m, 4H).

<minor>

¹H-NMR (400 MHz, CDCl₃) δ 1.54 (s, 9H), 3.35 (dd, *J* = 17.1, 28.0 Hz, 1H), 3.41 (dd, *J* = 17.1, 35.6 Hz, 1H), 3.47 (s, 3H), 4.72 (d, *J* = 6.6 Hz, 2H), 5.46 (d, *J* = 15.9 Hz, 1H) 7.20-7.41 (m, 4H).

(2-Fluoro-1-methoxymethoxy-indan-2-yl)-methanol (C):

To a dichloromethane solution (1.0 mL) of **B** (27 mg, 0.091 mmol) was added 2.2 eq. of Dibal-H (20 μL, 1.0 M in hexane) at -78 °C. The reaction mixture was allowed to warm gradually to 0 °C. After 3 h, 1N HCl (2 mL) was added. Separated aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water and brine. Removal of solvent under the reduced pressure, followed by flash column chromatography, afforded the desired product **C** (15 mg, 74%).

major : minor = 2.3 : 1

<major>

¹H-NMR (400 MHz, CDCl₃) δ 1.68 (br, 1H), 2.94-3.10 (m, 2H), 3.39 (s, 3H), 3.86 (dd, *J* = 12.7, 17.9 Hz, 1H), 3.98 (dd, *J* = 12.7, 22.0 Hz, 1H), 4.76 (s, 2H), 5.11 (d, *J* = 16.1 Hz, 1H) 7.10-7.35 (m, 4H).

<minor>

¹H-NMR (400 MHz, CDCl₃) δ 1.68 (br, 1H), 3.20-3.34 (m, 2H), 3.43 (s, 3H), 3.75 (dd, *J* = 12.4, 25.0 Hz, 1H), 3.80 (dd, *J* = 12.4, 24.1 Hz, 1H), 4.83 (dd, *J* = 6.84, 30.5 Hz, 2H), 4.96 (d, *J* = 9.52 Hz, 1H) 7.10-7.35 (m, 4H).

2-Fluoro-2-iodomethyl-1-methoxymethoxy-indan (D):

The alcohol **C** (14 mg, 0.062 mmol) was dissolved in dry benzene (1 mL). Ph_3P (46 mg, 0.176 mmol), I_2 (36 mg, 0.14 mmol) and imidazol (12 mg, 0.176 mmol) were successively added to this solution. The reaction mixture was stirred at 80 °C for 15 min. After cooling to room temperature, saturated NaHCO_3 (1 mL) was added. Separated aqueous layer was extracted with ethyl acetate (2 x 10 mL), and combined organic layers were washed with water and brine. Evaporation of solvent, followed by flash column chromatography (hexane : ethyl acetate = 20 : 1~10 : 1) gave the desired product **D** in 50% (10 mg) yield. The obtained product was found to be single isomer, and the other isomer was not isolated.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 3.21 (dd, $J = 16.8, 19.2$ Hz, 1H), 3.35 (dd, $J = 16.8, 26.2$ Hz, 1H), 3.45 (s, 3H), 3.61 (dd, $J = 11.2, 24.4$ Hz, 1H), 3.75 (dd, $J = 11.2, 19.8$ Hz, 1H), 4.78 (s, 2H), 5.05 (d, $J = 14.1$ Hz, 1H), 7.24-7.42 (m, 4H).

2-Fluoro-1-methoxymethoxy-2-methyl-indan (**E**):

Water was azeotropically removed from **D** by evaporating with toluene. Dried **D** (10 mg, 0.03 mmol) was dissolved in 0.5 mL of toluene. This toluene solution was degassed according to freeze-pump-thaw sequence. Bu_3SnH (22 μL , 0.08 mmol) and AIBN (2 mg, 0.012 mmol) were added, and the reaction mixture was stirred at 100 °C for 15 min. Saturated NH_4Cl was added at room temperature for quenching. Extraction with ether and usual work-up afforded the crude product. Further purification was carried out by flash column chromatography (hexane : ether = 20 : 1) to give the desired product **E** (5.4 mg, 85%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.56 (d, $J = 22.7$ Hz, 3H), 3.13 (dd, $J = 16.4, 30.6$ Hz, 1H), 3.17 (dd, $J = 16.4, 34.8$ Hz, 1H), 3.48 (s, 3H), 4.84 (s, 2H), 5.06 (d, $J = 15.9$ Hz, 1H), 7.20-7.40 (m, 4H).

2-Fluoro-2-methyl-indan-1-ol (**F**):

E (5.4 mg, 0.0257 mmol) was dissolved in MeOH (0.6 mL). A catalytic amount of TsOH (1 mg) and water (1 drop) were added, and the reaction mixture was stirred at 60 °C for 8 h. After the completion of the reaction, ethyl acetate (10 mL) was added for dilution. Organic layer was washed with saturated NaHCO_3 and this aqueous layer was extracted with ethyl acetate (2 x 10 mL). Combined organic layers were washed with brine. Removal of solvent and flash column chromatography afforded the alcohol **F** in 60% yield (2.5 mg, 0.015 mmol).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.56 (d, $J = 22.7$ Hz, 3H), 1.88 (s, 1H), 3.15 (dd, $J = 19.0, 37.2$ Hz, 1H), 3.20 (dd, $J = 20.0, 37.2$ Hz, 1H), 5.06 (d, $J = 16.4$ Hz, 1H), 7.20-7.45 (m, 4H).

2-Fluoro-2-methyl-indan-1-one (**G**):

Alcohol **F** (2.5 mg, 0.015 mmol) was dissolved in CH_2Cl_2 . To this solution was added Dess-Martin periodinane (13 mg, 0.03 mmol) under ice-bath, and the reaction mixture was allowed to stir at room temperature for 12 h. The mixture was passed through celite to remove the white precipitate. After the removal of solvent, purification by flash column chromatography (hexane : ether = 10 : 1) was carried out to give the known compound **G** in 60% yield. This product was found to be identical to the reported compound according to $^1\text{H-NMR}$.²

Correlation between absolute configurations and retention times (HPLC) is as follows. This was

provided by Dr. Shibata at Toyama Medical and Pharmaceutical University.

HPLC condition: DAICEL CHIRALCELL OB, hexane / IPA = 9 / 1, 0.5 mL / min, 254 nm.

t_r (*R*) = 20 min, t_r (*S*) = 55 min.

The observed retention time (major enantiomer) of **G** was 20 min, which was corresponding to *R* enantiomer. Therefore, it was concluded that **2b** bearing (*R*)-DM-BINAP produced **4c** with *R* configuration.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.63 (d, J = 22.7, 3H), 3.30 (dd, J = 11.0, 17.3 Hz, 1H), 3.46 (dd, J = 17.3, 22.3 Hz, 1H), 7.40-7.45 (m, 2H), 7.64-7.69 (m, 1H), 7.82 (d, J = 7.6 Hz 1H).

Conversion and Determination of the Absolute Configuration of **4d**.

The absolute configuration of **4d** was determined to be *R* by comparing the value of optical rotations after the conversion into the reported compound **5**.³

3. Iwaoka, T.; Murohashi, T.; Sato, M.; Kaneko, C. *Tetrahedron Asymmetry* **1992**, 3, 1025-1028.

Scheme 3. Conversion of **4d** into the known compound **H**.

Methyl 2-Fluoro-2-methyl-3-oxo-3-phenyl-propionate (**5**)

In the dried flask was placed **4d** (125 mg, 91% ee), and TFA (0.5 mL) was added. The mixture was allowed to stir room temperature for 2 h. Ether (10 mL) was added for the dilution, and organic layer was washed with water (10 mL) and brine. After drying with Na_2SO_4 , ether was evaporated carefully (< 20 °C). To a stirring solution of the crude product was added CH_2N_2 in ether until the reaction mixture turned yellow. AcOH was added to decompose the excess CH_2N_2 . Usual work-up and purification by preparative TLC (hexane : ethyl acetate = 10 : 1) afforded the desired product **5** in 76% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.88 (d, J = 22.5 Hz, 3H), 3.79 (s, 3H), 7.46 (t, J = 8.0 Hz, 2H), 7.59 (dt, J = 0.7, 7.76 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 21.0 (d, J = 23.8 Hz), 53.2, 97.1 (d, J = 194 Hz), 128.6, 129.6, 129.7, 133.2, 133.2, 133.9, 168.8 (d, J = 25.5 Hz), 191.7 (d, J = 25.5 Hz); $[\alpha]_{\text{D}}^{24}$ -82.9 (c = 1.0, MeOH) {Lit. $[\alpha]_{\text{D}}^{22}$ -85.0 (c = 1.0, MeOH) (98% ee, *R* enantiomer)}

Proposed Transition State

The sense of enantioselection of this fluorination was in accord with the prediction based on the Michael reaction, and well-explained by the proposed transition state model. Figure 1 shows a proposed structure of chiral palladium enolate ((*R*)-dm-binap complex). Since the ester moiety is located at one side of the enolate, avoiding the severe steric interaction with aryl group of phosphine ligand, fluorination occurred from less hindered *re* face more preferably. Due to a small size of fluorine atom and a higher reactivity of NFSI, simple phenyl group on phosphine was not sufficient to shield *si* face of the enolate. Introduction of methyl or *tert*-butyl groups into chiral ligands seems important to effectively prevent the approach of NFSI from the *si* face of the palladium enolate. As a result, NFSI could react from less hindered *re* face of the enolate more preferably to give excellent enantioselectivity.

Figure 1. Proposed Transition State

Mono-fluorination of β -Ketoester **3d'**

Reaction of α -unsubstituted β -ketoester **3d'** was also examined. Mono-fluorinated product (**4d'**) was predominant over difluorinated product (**4d''**). However, the enantioselectivity was not observed. This was probably due to an easily-enolizable nature of mono-fluorinated β -ketoester **4d'**. So far, our catalytic reaction is limited to the formation of the quaternary carbon center. Development of a new method for the synthesis of tertiary fluorides is under investigation.

tert-Butyl 2-fluoro-3-oxo-3-phenyl-propionate (**4d'**):

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.42 (s, 9H), 5.75 (d, $J = 49.2$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.63 (t, $J = 8.7$ Hz, 1H), 8.02 (d, $J = 8.5$ Hz, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 27.7, 84.5, 90.1 (d, $J = 195.8$ Hz), 1287.7, 129.4 (d, $J = 3.3$ Hz), 133.6, 134.2, 163.6, 190.0; HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 200 / 1, 0.40 mL / min, 254 nm) $t_r = 18.9$ min, $t_r = 20.3$ min.

Transformation of **5**: Stereoselective Synthesis of α -Fluoro β -Hydroxy and β -Amino Ester

The stereoselective reductions of keto group were achieved on the basis of Kitazume's report (See ref. 15 in text). The relative configurations of the products were tentatively assigned by the analogy with the stereoselectivity obtained under the reported reaction conditions.

syn-Methyl 2-Fluoro-3-hydroxy-2-methyl-3-phenylpropionate (*syn*-**6**):

To a stirring solution (DMF, 0.2 mL) of **5** (40 mg, 0.19 mmol) were added PhMe_2SiH (120 μL , 0.76 mmol) and TBAF (380 μL , 1M in THF, 0.38 mmol) at 0 $^\circ\text{C}$. Saturated aqueous NH_4Cl (3 mL) was added after 10 min. The aqueous layer was extracted with ether (5 x 10 mL). The organic layer was dried over Na_2SO_4 . Ether was removed under the reduced pressure, and the residue was purified by flash column chromatography (hexane : ethyl acetate = 12 : 1). The desired product (*syn*-**6**) was obtained in 83% as a

colorless oil. The diastereoselectivity of this reaction was found to be more than 95% by $^1\text{H-NMR}$.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.39 (d, $J = 21.7$ Hz, 3H), 3.83 (s, 3H), 4.94 (d, $J = 20.6$ Hz, 1H), 7.32-7.39 (m, 5H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 20.4 (d, $J = 23.0$ Hz), 52.8, 77.4 (d, $J = 19.7$ Hz), 96.6 (d, $J = 192.5$ Hz), 127.8, 127.8, 128.4, 128.7, 137.4, 171.6 (d, $J = 24.7$ Hz): $[\alpha]_{\text{D}}^{30} +22.9$ ($c = 1.45$, CHCl_3)

***anti*-Methyl 2-Fluoro-3-hydroxy-2-methyl-3-phenylpropionate (*anti*-6):**

To a stirring solution (TFA, 0.7 mL) of **5** (37.5 mg, 0.179 mmol) was added Ph_3SiH (140 μL , 0.54 mmol) at 0 $^\circ\text{C}$. The reaction mixture was allowed to stir at room temperature for 2 h. The mixture was diluted with ether (5 mL), and saturated NaHCO_3 was added under ice-bath to neutralize the mixture. Separated aqueous layer was extracted with ether (2 x 10 mL). Combined organic layers were washed with water and brine. Concentration, followed by flash column chromatography (hexane : ethyl acetate = 8 : 1) afforded the desired product (*anti*-**6**) as a colorless oil in 75%. $^1\text{H-NMR}$ showed the high diastereoselectivity (> 95 : 5).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.60 (d, $J = 22.2$ Hz, 3H), 3.70 (s, 3H), 4.98 (d, $J = 15.6$ Hz, 1H), 7.30-7.44 (m, 5H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 19.3 (d, $J = 11.5$ Hz), 52.6, 76.2 (d, $J = 23.0$ Hz), 96.2 (d, $J = 190.1$ Hz), 127.3, 127.4, 128.2, 128.6, 137.5, 171.3 (d, $J = 23.9$ Hz): $[\alpha]_{\text{D}}^{30} +2.68$ ($c = 2.44$, CHCl_3)

***anti*-Methyl 3-*tert*-Butoxycarbonylamino-2-fluoro-2-methyl-3-phenylpropionate (*anti*-7):**

The starting material *syn*-**6** (28 mg, 0.132 mmol) was dissolved in THF (0.3 mL). At room temperature were added Ph_3P (55 mg, 0.21 mmol), DEAD (90 μL , 40% in toluene), and DPPA (37 μL , 0.17 mmol) successively in this order. After stirring for 2 h, saturated aqueous NH_4Cl was added for quenching, and the resulting mixture was stirred for 5 min. Aqueous layer was extracted with ether (3 x 10 mL), and combined organic layers were washed with water and brine. The organic layer was dried over Na_2SO_4 . Further purification was performed by flash column chromatography (hexane : ethyl acetate = 15 : 1) to give the azide in 79% (25 mg).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.76 (d, $J = 21.5$ Hz, 3H), 3.63 (s, 3H), 4.80 (d, $J = 30.0$ Hz, 1H), 7.32-7.43 (m, 5H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 20.7 (d, $J = 23.8$ Hz), 52.6, 68.7 (d, $J = 20.6$ Hz), 95.9 (d, $J = 195.0$ Hz), 128.6, 128.6, 128.6, 129.2, 133.7, 169.9 (d, $J = 23.8$ Hz).

The azide (20 mg, 0.084 mmol) was dissolved in methanol (1 mL). To this solution were added $(\text{Boc})_2\text{O}$ (23 μL , 0.1 mmol) and Pd/C (2 mg). The reaction mixture was stirred under hydrogen atmosphere (balloon) for 1 h at room temperature. The reaction mixture was passed through celite to remove Pd/C , and the residue was washed with CH_2Cl_2 . After the removal of solvent, the residue was

purified by flash column chromatography (hexane : ethyl acetate = 12 :1) to give *N*-protected β -amino ester (*anti*-7) in 80% (20 mg) as a white solid.

^1H -NMR (400 MHz, CDCl_3) δ 1.43 (s, 9H), 1.70 (d, J = 21.7 Hz, 3H), 3.54 (s, 3H), 5.11 (dd, J = 10.0, 27.1 Hz, 1H), 5.31 (d, J = 10.0 Hz, 1H), 7.26-7.39 (m, 5H); ^{13}C -NMR (100 MHz, CDCl_3) δ 21.4 (d, J = 23.9 Hz), 28.3, 52.3, 58.6 (d, J = 17.3 Hz), 80.2, 97.2 (d, J = 192.5 Hz), 127.8, 128.2, 128.5, 137.1, 137.4, 170.3 (d, J = 23.9 Hz): $[\alpha]_{\text{D}}^{29}$ -30.5 (c = 0.51, CHCl_3)

***syn*-Methyl 3-*tert*-Butyloxycarbonylamino-2-fluoro-2-methyl-3-phenylpropionate (*syn*-7):**

According to the same procedure described above, *anti*-7 (29 mg, 0.137 mmol) was converted to the corresponding azide in 73% (23.5 mg).

^1H -NMR (400 MHz, CDCl_3) δ 1.36 (d, J = 21.2 Hz, 3H), 3.88 (s, 3H), 4.85 (d, J = 24.7 Hz, 1H), 7.37-7.48 (m, 5H); ^{13}C -NMR (100 MHz, CDCl_3) δ 20.8 (d, J = 23.0 Hz), 53.0, 69.4 (d, J = 18.9 Hz), 95.7 (d, J = 197.5 Hz), 128.8, 129.1, 129.1, 129.4, 132.9, 170.8 (d, J = 25.5 Hz).

This azide was subjected to the reduction conditions, and the desired *N*-protected β -amino ester (*syn*-7) was obtained in 57% as a white solid.

^1H -NMR (400 MHz, CDCl_3) δ 1.38 (d, J = 21.8 Hz, 3H), 1.39 (s, 9H), 3.80 (s, 3H), 5.07 (dd, J = 9.6, 25.9 Hz, 1H), 5.55 (d, J = 9.6 Hz, 1H), 7.29-7.38 (m, 5H); ^{13}C -NMR (100 MHz, CDCl_3) δ 21.5 (d, J = 23.1 Hz), 28.2, 52.8, 59.3 (d, J = 19.0 Hz), 80.0, 96.5 (d, J = 190.1 Hz), 128.3, 128.3, 128.5, 136.4, 154.6, 171.1 (d, J = 26.3 Hz): $[\alpha]_{\text{D}}^{30}$ $+13.8$ (c = 0.73, CHCl_3).