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Enantioselective Fluorination of *tert*-Butoxycarbonyl Lactones and Lactams Catalyzed by Chiral Pd(II)-Bisphosphine Complexes

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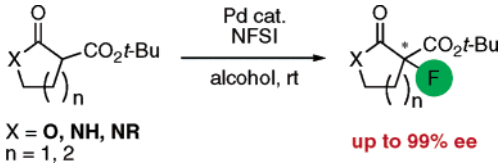
Received October 4, 2006



An efficient catalytic enantioselective fluorination of *tert*-butoxycarbonyl lactones and lactams is reported. Reactions of the lactone substrates proceeded smoothly in an alcoholic solvent with a catalytic amount of chiral Pd(II) complex. In the case of the less acidic lactam substrates, concurrent use of the Pd complex and 2,6-lutidine as a cocatalyst was effective. Under the reaction conditions, the fluorinated lactones and lactams were obtained in good yield with excellent enantioselectivity (94−99% ee).

Introduction

Because replacement of hydrogen atoms or hydroxyl groups in the parent compounds with fluorine atoms sometimes leads to improvement of their biological activity profiles,[1] development of efficient methods for the synthesis of optically active fluorinated compounds is extremely important.[2,3] After pioneering work on enantioselective fluorination using chiral fluorinating reagents, catalytic asymmetric fluorination has witnessed great progress in the past 5 years.[4] Several chiral metal complexes and phase transfer catalysts were developed for the fluorination of active methine compounds.[5−7] In addition, catalytic asymmetric fluorination of aldehydes recently became feasible using chiral secondary amines.[8] Although the scope of the available substrates is rapidly expanding, further study is required to meet the need for various chiral fluorinated compounds.

We previously reported that the chiral palladium bisphosphine complexes **1** and **2** are excellent catalysts for the fluorination of β-ketoesters, β-ketophosphonates, and *N*-Boc-protected oxindoles.[9] These substrates were activated by **1** and **2** to form chiral palladium enolates. On the basis of these results, we next planned to examine the reactions of compounds doubly activated by ester and/or amide groups other than ketone, such as **3** and

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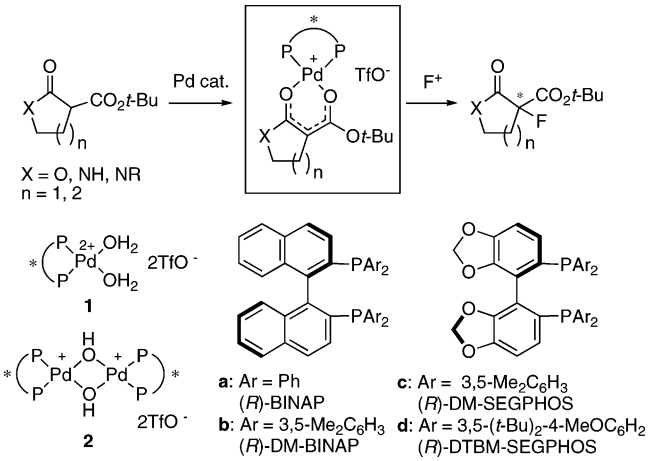
10.1021/jo062048m CCC: $37.00
Published on Web 12/10/2006

SCHEME 1

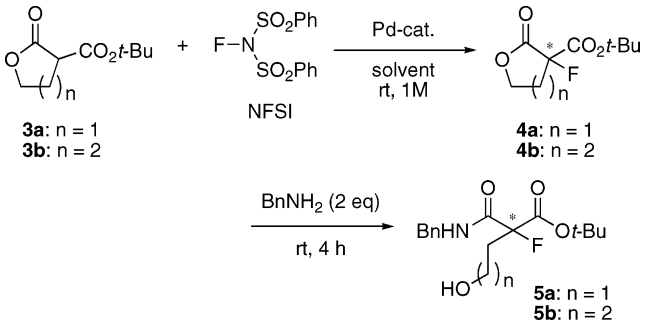


6. Although these compounds are less acidic than β-ketoesters, excellent enantioselectivity is expected assuming the structural motif of the bidentate palladium enolates, if the corresponding enolates can be generated (Scheme 1). As a part of our continuing research project on catalytic enantioselective fluorination, we describe herein a highly enantioselective fluorination of *tert*-butoxycarbonyl lactones and lactams. In this study, we developed a new catalytic system where the chiral Pd(II) complex in combination with 2,6-lutidine as a co-activator allowed the reactions of less acidic lactam substrates. Because lactones and lactams are versatile functional groups for further chemical transformation, the obtained fluorolactones and lactams would be useful in the field of medicinal chemistry.

Results and Discussion

Initially, we examined the reaction of the lactone substrate **3** at room temperature using a catalytic amount of the Pd complex (Table 1). Whereas reactions in usual organic solvents were slow (entries 1−3), those in alcoholic solvents proceeded smoothly, which is in accord with our previous observations. However, the fluorinated lactone was apt to react further with EtOH to give the ring-opened *tert*-butyl ethyl malonate.[10] Careful monitoring of the reaction on TLC revealed that the ring opening started to occur after 6 h. Thus the reaction was stopped after 6 h, and **4a** was isolated in 54% yield with 82% ee (entry 4). Bulkier solvents did not lead to the ring opening (entries 5 and 6), and the reaction in *i*-PrOH afforded **4a** in 96% yield with 79% ee. To improve the enantioselectivity, several chiral bisphosphine ligands were examined (entries 7−10).[11] The ee was improved when **1c** with a smaller bite angle was used (entry 8). Furthermore, the much bulkier ligand (*R*)-DTBM-SEGPHOS was found the most enantioselective, and the reaction using **1d** gave the desired product **4a** with excellent enantioselectivity of 97%, although a longer reaction time was required for satisfactory chemical yield (entry 9). Additionally, the Pd(μ-OH) complex **2d** was also effective, and the comparable results (75%, 98% ee) were obtained (entry 10). Taking advantage of susceptibility of the lactone ring to nucleophilic attack, full characterization was carried out after conversion to amide-ester **5a**. In addition, we examined the reaction of the six-membered substrate **3b** (entry 11). Using *t*-BuOH as a solvent, the fluorination reaction proceeded, and ring opening of the lactone ring was not observed.[12] Because detection of **4b** was difficult on TLC, conversion was necessary for isolation, and the amide-ester **5b** was obtained. Although the isolated yield was only modest, this example indicates that the fluorination reaction of **3b** also proceeded in a highly enantioselective manner (97% ee).

TABLE 1. Catalytic Enantioselective Fluorination of the Lactone Substrates 3



entry	3	solvent	Pd cat. (mol %)	time (h)	yield[a] (%)	ee[b] (%)
1	**3a**	CH_2Cl_2	**1b** (5)	24	trace	
2	**3a**	acetone	**1b** (5)	24	10	51
3	**3a**	THF	**1b** (5)	24	49	75
4	**3a**	EtOH	**1b** (5)	6	54	82
5	**3a**	*i*-PrOH	**1b** (5)	6	96	79
6	**3a**	*t*-BuOH	**1b** (5)	6	89	80
7	**3a**	*i*-PrOH	**1a** (5)	6	79	77
8	**3a**	*i*-PrOH	**1c** (5)	6	78	87
9	**3a**	*i*-PrOH	**1d** (5)	24	74	97
10	**3a**	*i*-PrOH	**2d** (2.5)	24	75	98
11	**3b**	*t*-BuOH	**2d** (2.5)	27	35[c]	97[d]

[a] Isolated yield of **4a** except for entry 11. [b] ee values of **4a** except for entry 11. [c] Isolated yield of **5b**. [d] ee value of **5b**.

Encouraged by this success, we turned our attention to the lactam substrate **6a**. As in the case of **3**, ethanol was superior to other conventional organic solvents (Table 2). The ee of the product was determined after *N*-benzylation. Although high enantioselectivity (~90% ee) was generally observed, the reaction was slow, and chemical yield did not exceed 50% after even 48 h. Neither higher temperature nor longer reaction time improved the chemical yield (entries 5 and 6). Notably, the complex **1d**, which was the most enantioselective in Table 1, was completely inactive for the less acidic lactam substrate (entry 8).

It is likely that lower acidity of the lactam substrate disfavored formation of the nucleophilic palladium enolate, thereby retarding the fluorination reaction. In order to facilitate the formation of the enolate, we next examined the additive effect of organic

(9) β-Ketoesters: (a) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530−14531. (b) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225−3228. (c) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Tsuchiya, Y.; Moriya, K.; Goto, T.; Sodeoka, M. *Tetrahedron* **2006**, *62*, 7168−7179. β-Ketophosphonates: (d) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447−1450. Oxindoles: (e) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164−10165. For a short review: (f) Hamashima, Y.; Sodeoka, M. *Synlett* **2006**, 1467−1478.

(10) We could not determine the ee of the fluorinated *tert*-butyl ethyl malonate, because the enantiomers were inseparable on chiral HPLC.

(11) Kumobayashi, H.; Miura, T.; Sayo, N.; Saito, T.; Zhang, X. *Synlett* **2001**, 1055−1064.

(12) Compound **4b** underwent the ring-opening reaction even in *i*-PrOH, and the corresponding fluorinated diester was obtained in 65% yield. Unfortunately, the enantiomers were inseparable on chiral HPLC.

SCHEME 2. Catalytic Enantioselective Fluorination of the Lactams Substrates 6

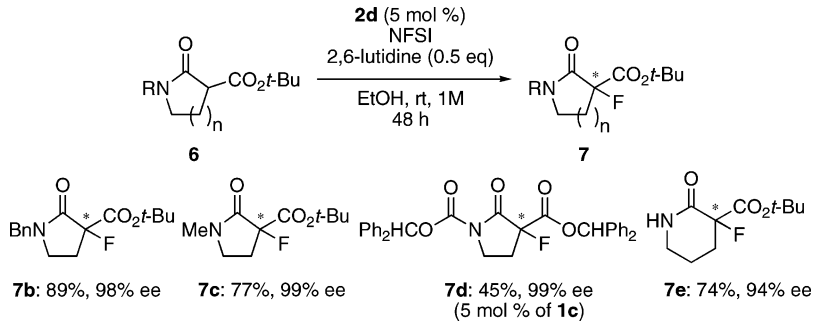
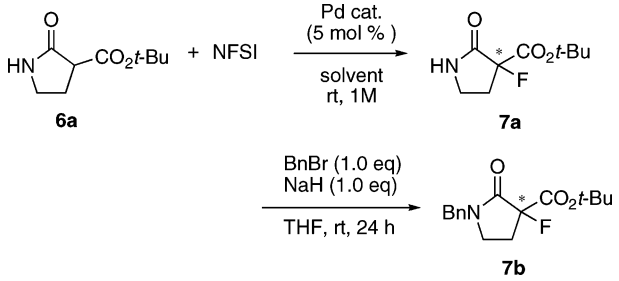


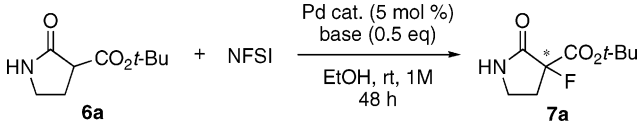
TABLE 2. Fluorination of the Lactam Substrate 6a



entry	solvent	Pd cat.	time (h)	yield (%)	ee[a] (%)
1	CH_2Cl_2	**1b**	48	15	*b*
2	acetone	**1b**	48	32	86
3	THF	**1b**	48	15	*b*
4	EtOH	**1b**	48	43	90
5[c]	EtOH	**1b**	24	36	87
6	EtOH	**1b**	96	52	90
7	EtOH	**1c**	48	49	88
8	EtOH	**1d**	96	trace	*b*

[a] ee values of **7b**. [b] Not determined. [c] 40 °C.

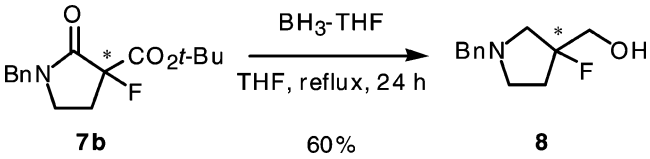
TABLE 3. Effect of Amine Bases



entry	Pd cat.	base	yield (%)	ee[a] (%)
1	**1b**	Et_3N	59	90
2	**1b**	morphorine	49	88
3	**1b**	pyridine	trace	*b*
4	**1b**	quinoline	NR[c]	*b*
5	**1b**	isoquinoline	NR[c]	*b*
6	**1b**	DMAP	trace	*b*
7	**1b**	2,6-lutidine	80	91
8	**1b**	2,6-(*t*-Bu)$_2$-pyridine	65	91
9	**1d**	2,6-lutidine	50	99
10	**2d**	2,6-lutidine	58	>99

[a] ee values of **7b**. The ee was determined after *N*-benzylation. [b] Not determined. [c] No reaction.

SCHEME 3. Conversion of 7b



bases (Table 3).[13] When triethylamine (0.5 equiv) was added, chemical yield was slightly improved (entry 1). Whereas pyridine, quinoline, isoquinoline, and (dimethylamino)pyridine (DMAP) inhibited the reaction, probably as a result of coordination to the catalyst (entries 3−6), 2,6-lutidine improved the chemical yield considerably (80% yield, entry 7). However, the much bulkier 2,6-(*t*-Bu)$_2$-pyridine was found less effective because of the lower basicity (entry 8). It should be noted that even **1d** and **2d**, which were completely inactive in the reactions without base (Table 2), promoted the reactions by the aid of 2,6-lutidine, and the desired product **7a** was obtained in modest yield (58%) but with almost perfect enantioselectivity (99% ee, entry 10).[14]

Interestingly, applying the optimized conditions to the reactions of *N*-protected five-membered lactams improved chemical yield (Scheme 2). Reactions of *N*-benzylated and *N*-methylated lactam substrates **6b** and **6c** proceeded smoothly, and the desired products **7b** and **7c** were obtained in good yield (89% and 77%, respectively) with excellent enantioselectivity (98% and 99% ee, respectively).[15] This improvement in chemical yield might be attributed to suppression of the competitive abstraction of the amide proton, rendering the generation of the desired palladium enolate preferential. In addition to the *N*-alkylated substrates, the acylated substrate **6d** was also fluorinated in a highly enantioselective manner (99% ee) using **1c** as a catalyst, although chemical yield was less satisfactory (45%).[16] In the case of the six-membered substrate **6e**, the reaction proceeded at a synthetically useful level without protection of the amide moiety, and **7e** was obtained in 74% yield with 94% ee. The ee of **7e** was also determined after *N*-benzylation.[17] Further, this fluorination reaction is potentially useful for the preparation of optically active fluorinated cyclic amines. For example, reduction of **7b** by BH_3 in THF afforded the corresponding fluoroamine **8** in 60% yield (Scheme 3).

According to our previous results, the key intermediate in the fluorination reaction would be the chiral palladium enolates of the lactones and lactams. As shown in Table 1, it appears

(13) Effective combination of Lewis acids and trialkylamines were previously reported: (a) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394−13395. (b) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097−13105.

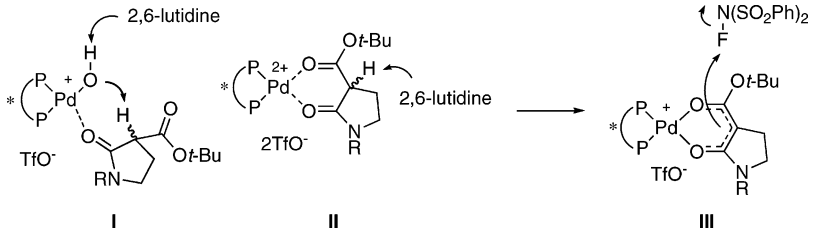
(14) The use of 1 equiv of the base resulted in the slight decrease of enantioselectivity.

(15) In the absence of 2,6-lutidine, the reactions of **6b** in the presence of **1b** afforded the product in 58% yield with 83% ee.

(16) Probably as a result of the severe steric interaction, the use of **2d** resulted in low enantioselection (34% ee).

(17) In contrast to **6b**, the reaction of *N*-benzylated six-membered lactam gave the fluorinated product with lower enantioselectivity (~65% ee), although the reason is not clear at present.

SCHEME 4. Working Hypothesis of the Reaction Mechanism



that the lactone substrates are readily activated. However, the less acidic lactam substrates were reluctant to give the corresponding enolate, and the addition of the 2,6-lutidine was highly effective, especially when **1d** and **2d** were used as a catalyst (Table 3). We speculate that 2,6-lutidine would play an important role in the formation of the enolates (Scheme 4): (**I**) At the beginning of the reaction, the in situ generated PdOH complex derived from **2d** would act as a base to afford the enolate **III**, and 2,6-lutidine might reinforce the basicity of the PdOH complex by abstracting or interacting with a proton to increase a negative charge on the oxygen atom. (**II**) When **1d** was used, the dicationic complex would activate the substrates in a bidentate fashion to enhance the acidity of the α-proton of the lactams, and 2,6-lutidine would abstract the α-proton of the substrates to give the chiral Pd enolates **III**. This may also occur after the second cycle when the Pd complex **2** is used as a catalyst. To suppress the undesired uncatalyzed racemic pathway, the weak basicity of 2,6-lutidine is favorable, and cooperative action of the Pd complex with 2,6-lutidine allowed excellent enantioselectivity of up to 99%.

In conclusion, a highly enantioselecitve fluorination reaction of *tert*-butoxycarbonyl lactones and lactams has been developed. In this paper, we have not only succeeded in expanding the scope of the fluorination catalyzed by the chiral Pd complexes but also developed a new reaction system applicable to less acidic substrates compared with β-ketoesters. In the present work, the combined use of the Pd complex with 2,6-lutidine was revealed to be highly effective for activation of the lactam substrates. Further study to examine the applicability of the reaction conditions is underway in our laboratory.

Experimental Section

General Procedure for Catalytic Enantioselective Fluorination of Lactones 3 and Lactams 6. The fluorination reaction of **6b** is described as a representative example.

The lactam **6b** (55 mg, 0.2 mmol), NFSI (95 mg, 0.3 mmol), and the Pd complex **2d** (29 mg, 0.01 mmol, 5 mol %) were dissolved in EtOH (0.2 mL). To this suspension was added 2,6-lutidine (12 μL, 0.1 mmol), and the reaction mixture was stirred at ambient temperature for 48 h. The reaction was monitored by TLC analysis. Saturated aqueous NH_4Cl was added for quenching, and the water layer was extracted by ethyl acetate (5 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent, followed by flash column chromatography (hexane/ethyl acetate = 3/1), afforded the desired product **7b** as a white solid (52 mg, 89%). The ee was determined by chiral HPLC analysis.

***tert*-Butyl 3-Fluoro-tetrahydro-2-oxofuran-3-carboxylate (4a).** Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 2.59−2.73 (m, 1H), 2.78−2.88 (m, 1H), 4.42−4.48 (m, 1H), 4.53 (td, J = 8.8, 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 33.4 (d, J = 22.2 Hz), 65.5 (d, J = 4.1 Hz), 85.4, 90.5 (d, J = 202.4 Hz), 164.3 (d, J = 27.9 Hz), 168.9 (d, J = 25.5 Hz,); ^{19}F NMR (376 Hz, $CDCl_3$) δ −87.4 (ddd, J = 22.9, 11.3, 2.3 Hz); HPLC (DAICEL CHIRALCEL AS-H, *n*-hexane/IPA = 95/5, 1.0 mL/min, 220 nm) τ_{major} 14.5 min, τ_{minor} 16.3 min; IR (neat) ν 2986, 2938, 2925, 1791, 1759, 1723, 1373, 1282, 1220, 1158, 1126, 1056, 1022 cm^{-1}.

***tert*-Butyl 2-(Benzylcarbamoyl)-2-fluoro-4-hydroxybutanoate (5a).** Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.45 (td, J = 6.1, 2.6 Hz, 1H), 2.51 (q, J = 6.1 Hz, 1H), 3.76−3.87 (m, 2H), 4.41 (dd, J = 14.9, 5.5 Hz, 1H), 4.58 (dd, J = 14.9, 6.1 Hz, 1H), 6.79 (brs, 1H), 7.26−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 36.7 (d, J = 20.6 Hz), 43.4, 57.5 (d, J = 4.9 Hz), 84.2, 95.9 (d, J = 197.4 Hz,), 127.7, 127.7, 128.7, 137.3, 165.5 (d, J = 25.5 Hz), 166.6 (d, J = 21.4 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ −89.1 ∼ −88.9 (m); FAB-LRMS (*m*NBA) *m*/*z* 334 (M + Na)$^+$, 312 (M + 1)$^+$; $[\alpha]^{25}_D$ +29.2 (c = 4.12, $CHCl_3$) (91% ee); HPLC (DAICEL CHIRALCEL OD-H, *n*-hexane/IPA = 98/2, 1.0 mL/min, 220 nm) τ_{major} 50.8 min, τ_{minor} 61.7 min; FAB−HRMS (*m*NBA) calcd for $C_{16}H_{22}FNO_4Na$ (M + Na)$^+$ 334.1431, found 334.1427; IR (neat) ν 3337, 2981, 2936, 1743, 1673, 1532, 1455, 1369,1254, 1155, 1085, 1049 cm^{-1}.

***tert*-Butyl 2-(Benzylcarbamoyl)-2-fluoro-5-hydroxypentanoate (5b).** Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.60−1.73 (m, 2H), 2.22−2.38 (m, 2H), 3.65 (t, J = 6.4 Hz, 2H), 4.41 (dd, J = 14.6, 5.6 Hz, 1H), 4.56 (dd, J = 14.9, 6.4 Hz, 1H), 5.01 (brs, 1H), 6.79 (brs, 1H), 7.26−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0 (d, J = 2.5 Hz), 27.7, 30.2 (d, J = 21.4 Hz), 43.4, 61.9, 84.0, 97.1 (d, J = 197.5 Hz), 127.6, 127.7, 128.7, 137.4, 165.5 (d, J = 24.7 Hz), 166.3 (d, J = 22.2 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ −90.5 ∼ −90.4 (m); FAB-LRMS (*m*NBA) *m*/*z* 348 (M + Na)$^+$, 326 (M + 1)$^+$; $[\alpha]^{24}_D$ +20.9 (c = 1.84, $CHCl_3$) (97% ee); HPLC (DAICEL CHIRALCEL OD-H, *n*-hexane/IPA = 95/5, 1.0 mL/min, 220 nm) τ_{major} 20.2 min, τ_{minor} 22.7 min; FAB−HRMS (*m*NBA) calcd for $C_{17}H_{24}FNO_4Na$ (M + Na)$^+$ 348.1587, found 348.1581; IR (neat) ν 3356, 2981, 2931, 1743, 1674, 1531, 1452, 1370, 1325, 1284, 1255, 1158 cm^{-1}.

***tert*-Butyl 3-Fluoro-2-oxopyrrolidine-3-carboxylate (7a).** White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.33−2.46 (m, 1H), 2.65 (tdd, J = 13.4, 7.1, 4.2 Hz, 1H), 3.38−3.48 (m, 2H), 6.62 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 32.2 (d, J = 22.2 Hz), 38.8 (d, J = 2.5 Hz), 84.1, 92.8 (d, J = 198.3 Hz,), 166.2 (d, J = 28.8 Hz), 170.1 (d, J = 23.0 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ −86.3 (ddd, J = 25.6, 13.4, 4.6 Hz); FAB-LRMS (*m*NBA) *m*/*z* 226 (M + Na)$^+$, 204 (M + 1)$^+$; $[\alpha]^{23}_D$ +16.4 (c = 0.41, acetone) (91% ee); FAB−HRMS (*m*NBA) calcd for $C_9H_{14}FNO_3Na$ (M + Na)$^+$ 226.0855, found 226.0859; IR (neat) ν 3252, 1755, 1719, 1685, 1447, 1371, 1292, 1211, 1169, 1121 cm^{-1}.

***tert*-Butyl 1-Benzyl-3-fluoro-2-oxopyrrolidine-3-carboxylate (7b).** White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.20−2.33 (m, 1H), 2.47−2.56 (m, 1H), 3.21−3.31 (m, 2H), 4.29 (d, J = 14.6 Hz, 1H), 4.64 (d, J = 14.6 Hz, 1H), 7.18−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 30.0 (d, J = 22.3 Hz), 43.1 (d, J = 3.2 Hz), 47.3, 84.0, 93.6 (d, J = 198.3 Hz,), 128.0, 128.2, 128.8, 135.2, 166.2 (d, J = 28.8 Hz), 166.8 (d, J = 23.9 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ −84.0 (dd, J = 25.2, 11.7 Hz); FAB-LRMS (*m*NBA) *m*/*z* 316 (M + Na)$^+$, 294 (M + 1)$^+$; $[\alpha]^{24}_D$ −39.3 (c = 0.67, $CHCl_3$) (91% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 95/5, 1.0 mL/min, 254 nm) τ_{minor} 23.0 min, τ_{major} 27.9 min; IR (neat) ν 2984, 1754, 1697, 1491, 1458, 1364, 1310, 1272, 1141, 1117 cm^{-1}.

***tert*-Butyl 3-Fluoro-1-methyl-2-oxopyrrolidine-3-carboxylate (7c).** White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.26−2.40 (m, 1H), 2.56−2.65 (m, 1H), 2.92 (d, J = 1.0 Hz, 3H), 3.38−3.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 30.0 (d, J = 22.3 Hz), 30.3, 45.7 (d, J = 2.5 Hz), 84.0, 93.5 (d, J = 199.1 Hz,), 166.5 (d, J = 27.9 Hz), 166.8 (d, J = 24.7 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ −83.8 (ddd, J = 25.7, 11.5, 4.6 Hz); FAB-LRMS (*m*NBA) *m*/*z* 240 $(M + Na)^+$, 218 $(M + 1)^+$; $[\alpha]^{24}_D$ +37.6 (c = 0.29, $CHCl_3$) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 95/5, 1.0 mL/min, 254 nm) τ_{minor} 13.2 min, τ_{major} 15.0 min; IR (neat) ν 2978, 2923, 1750, 1705, 1500, 1451, 1406, 1370, 1308, 1261, 1155, 1130, 1110, 1040 cm^{-1}.

Dibenzhydryl 3-Fluoro-2-oxopyrrolidine-1,3-dicarboxylate (7d). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26−2.40 (m, 1H), 2.52−2.61 (m, 1H), 3.71−3.77 (m, 1H), 3.85−3.91 (m, 1H), 6.86 (s, 1H), 6.89 (s, 1H), 7.18−7.29 (m, 16H), 7.39 (t, J = 7.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9 (d, J = 21.4 Hz), 42.4, 79.5, 80.4, 93.7 (d, J = 202.3 Hz), 126.7, 127.0, 127.0, 127.1, 128.2, 128.2, 128.3, 128.5, 128.7, 128.7, 138.5, 138.7, 139.3, 150.4, 164.7 (d, J = 23.8 Hz), 165.1 (d, J = 28.0 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ −85.8 (ddd, J = 22.9, 11.3, 2.3 Hz); FAB-LRMS (*m*NBA) *m*/*z* 546 $(M + Na)^+$, 524 $(M + 1)^+$; $[\alpha]^{24}_D$ +29.2 (c = 2.28, $CHCl_3$) (>99% ee); HPLC (DAICEL CHIRALCEL OD-H, *n*-hexane/IPA = 97/3, 1.0 mL/min, 254 nm) τ_{major} 62.4 min, τ_{minor} 66.2 min; IR (neat) ν 3032, 1764, 1731, 1495, 1453, 1380, 1278, 1185, 1117, 966 cm^{-1}.

***tert*-Butyl 3-Fluoro-2-oxopiperidine-3-carboxylate (7e).** White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 1.92−2.05 (m, 2H), 2.20−2.39 (m, 2H), 3.41−3.45 (m, 2H), 6.17 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3 (d, J = 2.5 Hz), 27.8, 31.1 (d, J = 22.2 Hz), 42.0, 83.7, 90.2 (d, J = 188.4 Hz,), 165.5 (d, J = 23.0 Hz), 167.0 (d, J = 26.3 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ −78.9 (ddd, J = 27.4, 19.4, 2.3 Hz); FAB-LRMS (*m*NBA) *m*/*z* 240 $(M + Na)^+$, 218 $(M + 1)^+$; $[\alpha]^{24}_D$ +26.5 (c = 1.24, $CHCl_3$) (86% ee); FAB−HRMS (*m*NBA) calcd for $C_{10}H_{17}FNO_3$ $(M + 1)^+$ 218.1192, found 218.1198; IR (neat) ν 3306, 2975, 1756, 1687, 1641, 1486, 1458, 1370, 1328, 1292, 1163, 1121, 1073, 1001 cm^{-1}.

***tert*-Butyl 1-Benzyl-3-fluoro-2-oxopiperidine-3-carboxylate (*N*-Benzylated 7e).** White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.77−1.97 (m, 2H), 2.14−2.31 (m, 2H), 3.17−23.29 (m, 2H), 4.38 (d, J = 14.6 Hz, 1H), 4.81 (d, J = 14.6 Hz, 1H), 7.18−7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4 (d, J = 2.5 Hz), 27.9, 31.3 (d, J = 23.0 Hz), 47.1, 50.5, 83.6, 90.5 (d, J = 189.2 Hz), 127.6, 127.9, 128.6, 136.2, 163.4 (d, J = 23.0 Hz), 167.2 (d, J = 25.5 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ −77.2 (ddd, J = 26.3, 19.6, 2.3 Hz); FAB-LRMS (*m*NBA) *m*/*z* 308 $(M + 1)^+$; $[\alpha]^{24}_D$ −16.2 (c = 0.78, $CHCl_3$) (86% ee); HPLC (DAICEL CHIRALCEL OB-H, *n*-hexane/IPA = 9/1, 1.0 mL/min, 220 nm) τ_{major} 18.5 min, τ_{minor} 27.2 min; FAB−HRMS (*m*NBA) calcd for $C_{17}H_{22}FNO_3Na$ $(M + Na)^+$ 330.1481, found 330.1485; IR (neat) ν 2974, 2927, 1758, 1659, 1494, 1453, 1369, 1286, 1206, 1160, 1123, 1106, 1006 cm^{-1}.

Acknowledgment. This research is financially supported by JSPS for Grant-in Aids for Young Scientists (B). We also thank Dr. Takao Saito of Takasago International Corporation for generous support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the products; experimental details for the conversion to **5a** and **8** and *N*-benzylation of **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062048M