Catalytic Enantioselective Fluorination Reactions of α-Cyano Acetates and α-Cyanophosphonates Using Chiral Palladium Complexes

Sun Mi Kim, Young Ku Kang, Min Je Cho, Joo Yang Mang, and Dae Young Kim*

*Department of Chemistry, Soonchunhyang University, Asan, Chungnam 336-745, Korea. *E-mail: dyoung@sch.ac.kr*

Received August 25, 2007

The catalytic enantioselective electrophilic fluorinations of active methane compounds promoted chiral palladium complexes have been developed. Treatment of α-cyano acetates and α-cyanoalkylphosphonates with *N*-fluorobenzenesulfonimide as the fluorine source under mild reaction conditions afforded the corresponding α-cyano-α-fluorinated adducts in high yields with excellent enantiomeric excesses (up to 99% ee). These reactions can be conducted in alcoholic solvents without any precaution to exclude water and moisture.

Key Words : Chiral palladium complexes, Electrophilic fluorination, Asymmetric catalysis, α-Cyano acetates, α-Cyanoalkylphosphonates

Introduction

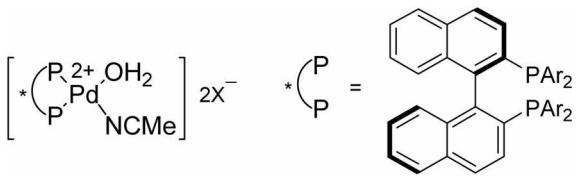
The chemistry of organofluorine compounds is a rapidly developing area of research because of their importance in biochemical and medicinal applications and material science.[1] Introduction of fluorine atom into biologically active compounds often leads to improvement of their biological characteristics due to unique properties of the fluorine atom.[2] Chiral organofluorine compounds containing a fluorine atom bonded directly to a stereogenic center have been utilized in studies of enzyme mechanisms and as intermediates in asymmetric syntheses.[3] However, the use of optically active compounds containing a fluorine atom at a stereogenic carbon center is restricted by the limited availability of effective methods for the enantioselective construction of fluorinated quaternary carbon centers. Thus, the development of effective methodologies for the preparation of chiral organic fluorine compounds through C-F bond formation is still a highly desirable goal in synthetic organic chemistry.[4] Until now, a number of enantioselective fluorinations have been achieved by regent-controlled and catalytic enantioseletive fluorination.[5] Since the first catalytic enantioseletive fluorination by Togni,[6] these reactions have been attracting much attention.[7-11] In 2002, we have developed an efficient method for catalytic enantioselective fluorination of β-ketoesters using chiral ammonium salts with high generality.[7a] Several research groups successfully applied chiral Lewis acids such as Binap-Pd(II) and transition metal-bis(oxazoline) complexes to the enantioselective fluorination of active methine derivatives.[7-10] Recently, several groups have reported the catalytic enantioselective fluorination of aldehydes using imidazolidinone and proline derivatives as organocatalysts.[11]

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[17] we report the catalytic enantioselective α-fluorination of active methine compounds with excellent enantioselectivity promoted by chiral palladium complexes.[9c,9d] In this paper, we wish to report the catalytic enantioseletive electrophilic α-fluorination of α-cyano acetates and α-cyanoalkylphosphonates using chiral palladium complexes **1** in more details, providing information on its scopes and limitations.[8a,10a]

Results and Discussion

The aquapalladium complexes **1** were prepared simply by the reaction of diphosphine ligands with $PdCl_2(NCMe)_2$ and subsequent ligand exchange with silver salts according to the reported procedure (Figure 1).[18]

Enantioselective fluorination of α-cyano acetates. Chiral α-fluoro-α-cyano acetate derivatives can be usefully utilized as chiral synthetic intermediates for organic synthesis[12] and derivatization reagents.[13] Development of fluorination of α-cyano acetates is valuable, because optically active α-substituted α-fluoro-α-cyano acetates are regarded as nonenolizable α-cyano acetates. In addition, since cyano group is easily converted to other functional groups, α-substituted α-fluoro-α-cyano acetates would be versatile synthetic inter-



1a : Ar = Ph : (*R*)-BINAP, X = BF_4
1b : Ar = Ph : (*R*)-BINAP, X = OTf
1c : Ar = Ph : (*R*)-BINAP, X = PF_6
1d : Ar = Ph : (*R*)-BINAP, X = SbF_6
1e : Ar = 4-methylphenyl : (*R*)-Tol-BINAP, X = PF_6
1f : Ar = 3,5-dimethylphenyl : (*R*)-Xylyl-BINAP, X = BF_4
1g : Ar = 3,5-dimethylphenyl : (*R*)-Xylyl-BINAP, X = OTf
1h : Ar = 3,5-dimethylphenyl : (*R*)-Xylyl-BINAP, X = PF_6
1i : Ar = 3,5-dimethylphenyl : (*R*)-Xylyl-BINAP, X = SbF_6

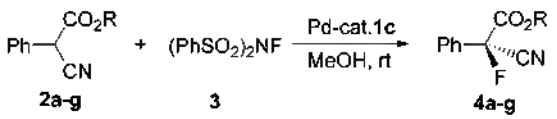
Figure 1. Chiral palladium complexes.

mediates of various α-fluorinated carboxylic acids. However, a few examples have been demonstrated to date for enantioselective fluorination of α-cyano acetates, and only enantioselective fluorination using cinchona alkaloid/Selectfluor combination has proved to be promising as an alternate strategy.[14] The first catalytic enantioselective fluorination of α-cyano acetates was reported by us using chiral phase-transfer catalyst with up to 65% selectivity.[8] A novel reaction system affording satisfactory selectivity as well as versatility is still required. Thus, we planned to examine the asymmetric fluorination reaction of α-cyano acetates using chiral palladium complexes **1**.

To determine suitable reaction conditions for the catalytic enantioselective electrophilic fluorination of α-cyano acetates, we initially investigated the reaction system with α-cyano phenylacetate **2** using *N*-fluorobenzenesulfonimide (NFSI) as the electrophilic fluorinating agent in the presence of 5 mol% of catalyst **1** in MeOH at room temperature (Table 1 and 2). We first examined the effect of ester group on enantioselectivity (Table 1). The best results have been obtained with *t*-butyl ester of substrate **2g**. Using *t*-butyl ester of substrate **2g**, further optimization of the reaction condition including palladium catalysts, temperature, and solvents was carried out (Table 2). Catalyst **1c** was more effective than other catalysts (entries 1-11). Lowering the temperature to 0 and −40 °C with catalyst **1c** dramatically increased enantioselectivities up to 99% ee (entries 4-5). Concerning the solvent, the use of MeOH gave the best results, whereas the fluorination in THF and acetone led to lower yields and enantioselectivities (entries 14-15). NFSI was more effective fluorinating agent than Selectfluor in this reaction under the same condition (entry 12). No reaction was observed in MeOH using *N*-fluoropyridinium triflate as fluorinating source.

This catalytic system was also applicable to various α-cyano acetate derivatives **2** to examine the generality of the catalytic enantioselective fluorination (Table 3). All the substrates examined were fluorinated in excellent enantioselectivite manner (up to 99% ee). This starting material **2l** which have a bulky aromatic group was not consumed at rt

Table 1. Effect of ester group of α-cyano acetate **2**

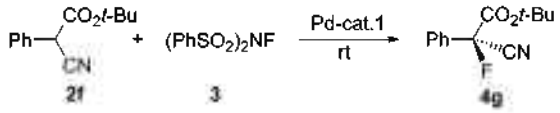


2a-g **3** **4a-g**

entry	R	time (h)	yield (%)	ee[a] (%)
1	**2a**, Me	12.5	**4a**, 56	67
2	**2b**, Et	13.5	**4b**, 79	79
3	**2c**, Bn	12.5	**4c**, 75	81
4	**2d**, *p*-NO_2,Bn	12	**4d**, 75	75
5	**2e**, $CHPh_2$	10	**4e**, 62	83
6	**2f**, Ph	10	**4f**, 74	59
7	**2g**, *t*-Bu	29	**4g**, 72	89

[a]Enantiomeric excess determined by chiral HPLC using Chiralcel OJ (for **4a-4c**) and Chiralpak AD (for **4d-4g**) columns.

Table 2. Further optimization of the reaction conditions

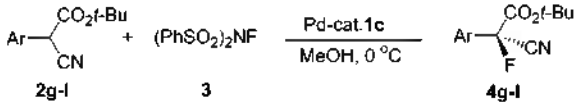


2f **3** **4g**

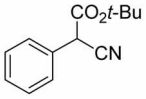
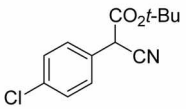
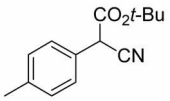
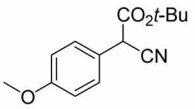
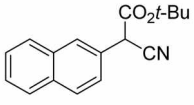
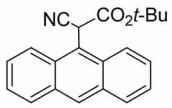
entry	catalyst	solvent	time (h)	yield (%)	ee[a] (%)
1	**1a**	MeOH	48	61	97
2	**1b**	MeOH	48	88	93
3	**1c**	MeOH	29	72	89
4[b]	**1c**	MeOH	60	83	99
5[c]	**1c**	MeOH	60	76	99
6	**1d**	MeOH	48	62	93
7	**1e**	MeOH	24	80	89
8	**1f**	MeOH	24	74	83
9	**1g**	MeOH	24	67	75
10	**1h**	MeOH	29	71	79
11	**1i**	MeOH	24	60	85
12[d]	**1c**	MeOH	48	81	59
13	**1c**	EtOH	19	82	81
14	**1c**	THF	25	74	87
15	**1c**	acetone	50	10	60

[a]Enantiomeric excess determined by chiral HPLC using Chiralpak AD column. [b]Reaction carried out at 0 °C. [c]Reaction carried out at −40 °C. [d]Reaction carried out using Selectfluor™ as fluorinating reagent.

Table 3. Catalytic enantioselective fluorination of α-cyano acetates **2**

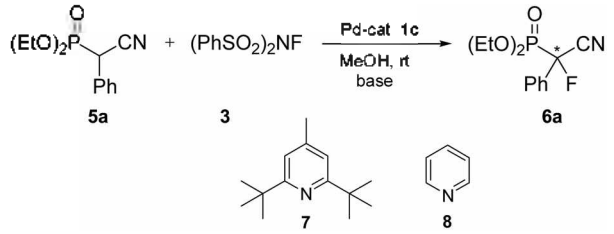


2g-l **3** **4g-l**

α-cyano acetate	time (h)	yield (%)	ee[a] (%)
	60	**4g**, 83	99 [*R*][c]
	17	**4h**, 94[b]	85
	60	**4i**, 85	93 [*R*][c]
	72	**4j**, 85[d]	99
	60	**4k**, 88	93
	72	**4l**, 62[b,e]	93

[a]Enantiopurity of **4** was determined by HPLC analysis with Chiralpak AD (for **4g-4i** and **4k**), Chiralcel OJ (for **4j**) and OD-H (for **4l**) columns. [b]Reaction carried out at room temperature. [c]Absolute configuration was determined by comparison of the optical rotation of the corresponding acid with literature value.[3,6b] [d]Reaction carried out using catalyst **1a**. [e]Reaction carried out using THF:MeOH (1:1).

Table 4. Effect of base in the asymmetric fluorination of phosphonate **5a**



entry	base (mol%)	time (h)	yield (%)	ee[a] (%)
1	–	96	52	71
2	**7** (5)	72	48	71
3	**7** (100)	71	70	73
4	**7** (200)	12	94	71
5	**8** (200)	25	45	39

[a]Enantiomeric excess determined by chiral HPLC analysis with Chiralcel OJ.

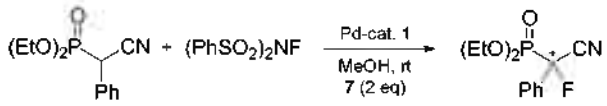
even after 72 h. Although the chemical yield was moderate, enantioselectivity of product **4l** was to be excellent (93% ee). Unfortunately, the fluorination of α-alkyl substituted α-cyano acetates was not proceeds in this reaction conditions.

Enantioselective fluorination of α-cyanoalkylphosphonates. α-Fluoroalkylphosphonates are better mimics of natural phosphates with matched 2nd p*K*a vaules (~6.5).[15] The enantioselective construction of α-fluoroalkylphosphonates is extremely important because the stereochemistry of α-carbon does affect biological activity.[16] Although there have been reports for the catalytic enantioselective fluorination of β-keto phosphonates,[9] no analogous protocol for the fluorination of α-cyanoalkylphosphonates has been established so far.

To determine suitable reaction conditions for the catalytic enantioselcetive fluorination of α-cyanoalkylphosphonate **5**,[19] we first examined electrophilic fluorination of 1-phenyl-1-cyanomethylphosphonate **5a** with NFSI in the presence of 5 mol% of **1c** in MeOH at room temperature (Table 4). As can be seen from Table 4, the fluorinated product was obtained with 52% yield with 71% ee after 96 h (entry 1). In the presence of 2,6-di-*t*-butyl-4-methyl pyridine as base, the reaction was proceed rapidly without significant change of enantioselectivity (entries 1-4). Using 2 equiv. of pyridine as a base under the same conditions, enantioselectivity was decreased to 39% (entry 5). Bulky organic base such as 2,6-di-*t*-butyl-4-methyl pyridine is appropriate to accelerate the reaction without coordination to metal complexes. To improve the enantioselectivity, we examined a series of chiral diphosphine ligands and anions in catalysts **1** (Table 5). The substitution at the meta-positions of the aryl group on phosphine and the anionic counterpart were found to be important. When a bulkier ligand such as (*R*)-Xylyl-BINAP palladium complex **1g** (X = OTf) was used in MeOH, the enantioselectivity was improved to 81% ee (entry 7).

Concerning the solvent, the use of alcoholic solvents such as MeOH and EtOH gave the best results, whereas the fluorination in acetone, THF, CH_2Cl_2, and PhMe led to lower

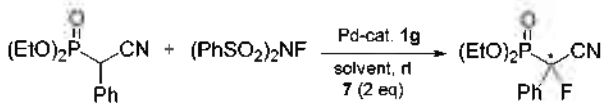
Table 5. Effect of Pd-cat. **1** in the asymmetric fluorination of phosphonate **5a**



entry	catalyst	time (h)	yield (%)	ee[a] (%)
1	**1a**	12	94	75
2	**1b**	12	95	73
3	**1c**	12	94	71
4	**1d**	12	93	71
5	**1e**	12	95	57
6	**1f**	12	95	77
7	**1g**	12	94	81
8	**1h**	12	95	80
9	**1i**	12	96	79

[a]Enantiomeric excess determined by chiral HPLC analysis with Chiralcel OJ.

Table 6. Effect of solvent in the asymmetric fluorination of phosphonate **5a**



entry	solvent	time (h)	yield (%)	ee[a] (%)
1	MeOH	12	94	81
2	EtOH	12	90	85
3	*i*-PrOH	24	63	63
4	*t*-BuOH	24	72	79
5	Acetone	24	70	66
6	CH_2Cl_2	24	90	67
7	THF	24	80	59
8	Toluene	24	87	73
9[b]	MeOH	24	82	33

[a]Enantiomeric excess determined by chiral HPLC analysis with Chiralcel OJ. [b]Reaction carried out using Selectfluor™ as fluorinating reagent.

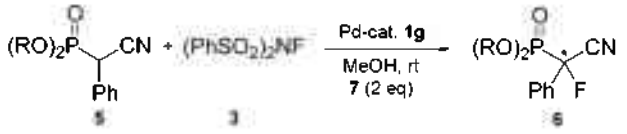
yields and enantioselectivities (Table 6). NFSI was more effective fluorinating agent than Selectfluor in this reaction under the same condition (entry 9). Using 1-fluoropyridinium triflate as fluorination reagent under similar conditions, the reaction was not proceeded.

Effect of ester group of phosphonates **5** was studied by use of Pd-cat **1** in MeOH and the results are shown in Table 7. Ethyl 1-phenyl-1-cyanomethylphosphonate **5a** exhibited the best enantioselectivity (entry 1).

With the optimized reaction conditions in hand, we next examined the generality of our catalytic enantioselective electrophilic fluorination of α-cyanoalkylphosphonate **5**. As can be seen in Table 8, the corresponding 1-fluoro-1-cyanomethylphosphonates **6** were obtained in moderate to excellent yields with excellent enantioselctivities (80-91% ee).

On the basis of our results, a plausible mechanism of the catalytic cycle is outlined Scheme 1. The Pd(II) complex

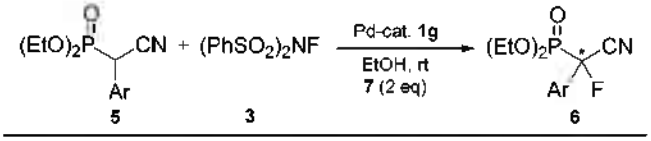
Table 7. Effect of ester group of phosphonates **5**



entry	5, R	time (h)	yield (%)	ee[a] (%)
1	Et	12	**6a**, 94	81
2	*i*-Pr	18	**6b**, 94	77
3[b]	*n*-Bu	18	**6c**, 93	72
4	Ph	18	**6d**, 95	75

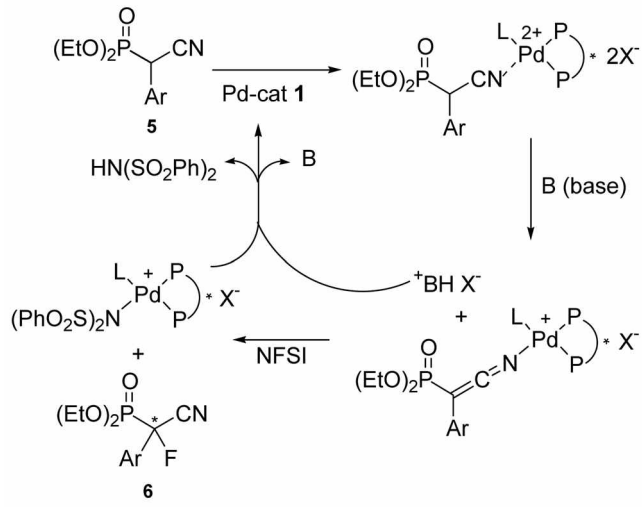
[a]Enantiomeric excess determined by chiral HPLC analysis with Chiralcel OJ (for **6a**, **6c**, and **6d**) and Chiralpak AD (for **6b**). [b]Reaction carried out using catalyst **1c**.

Table 8. Catalytic enantioselective fluorination of α-cyanoalkylphosphonates **5**



entry	5, Ar	time (h)	yield (%)	ee[a] (%)
1	Ph	12	**6a**, 90	85
2	*p*-OMe, Ph	12	**6e**, 98	85
3[b]	*p*-Me, Ph	12	**6f**, 96	80
4	*p*-Cl, Ph	12	**6g**, 98	91
5	*p*-F, Ph	15	**6h**, 95	87
6	1-Naphthyl	120	**6i**, 73	83
7	2-Thienyl	18	**6j**, 94	81

[a]Enantiomeric excess determined by chiral HPLC analysis with Chiralcel OJ (for **6a** and **6j**) and Chiralpak AD (for **6e-6i**). [b]Reaction carried out using catalyst **1i** in MeOH.



Scheme 1. Assumed catalytic cycle.

activates the substrate through coordination of the cyano group, and 2,6-di-*t*-butyl-4-methyl pyridine as base abstracts an acidic α-proton of phosphonates, affording the complex **8**. Chiral Pd-coordinated nucleophile **8** reacts with NFSI to produce the fluorinated product **6**.

Conclusion

We have developed the catalytic enantioselective fluorination reactions of α-cyano acetates **2** and α-cyanoalkylphosphonates **5** with excellent enantioselectivity (up to 99% ee). In the enantioselective fluorination of α-cyanoalkylphosphonates **5**, the use of the bulky organic base gave an advantage to shorten the reaction time without loss of selectivity. This reaction system will be applicable to other Pd(II) catalyzed reaction of less acidic substrate. It should be noted that these fluorination reactions are operationally convenient using air- and moisture-stable chiral palladium catalysts. These catalytic enantioselective fluorination reactions in alcoholic solvents have been shown to be practical from environmental and economical points of view.

Experimental Section

General. All reactions were carried out in oven-dried glassware under an atmosphere of dry nitrogen unless otherwise noted. All reaction were magnetically stirred and monitored by analytical thin layer chromatography using Merck pre-coated silica gel plates with F_{254} indicator. Flash column chromatography was performed according to the method of still using silicagel 60 (mesh 230-400) supplied by E. Merck. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AC 200 (200 MHz for ^{1}H, 50 MHz for ^{13}C) and DPX 300 (282 MHz for ^{19}F). Chemical shift values (d) are reported in ppm relative to Me_4Si (for ^{1}H) and $CFCl_3$ (for ^{19}F). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Mass spectra were recorded on a Finnigan TSQ or a Shimadzu QP5050A instrument using electron spray ionization or electron impact ionization, respectively. Optical rotations were measured with a JASCO-DIP-1000 digital polarimeter. High-performance liquid chromatography (HPLC) was performed on a Younglin M930 Series equipped with variable wavelength detector using chiral stationary column (250 mm, 4.6 mm) such as Chiralpak AD, Chiralcel OD-H and OJ columns.

General procedure for the fluorination of α-cyano acetates 2: To a stirred solution of α-cyano acetate (**2**, 0.3 mmol), catalyst **1c** (16.2 mg, 0.015 mmol) in MeOH (3 mL) was added *N*-fluorobenzenesulfonimide (**3**, 94.6 mg, 0.3 mmol) at room temperature. Reaction mixture was stirred for 10-72 h at room temperature. The mixture was diluted with saturated NH_4Cl solution (20 mL) and extracted with ethyl ether (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (silica gel, ethyl acetate:hexane) to afford the α-cyano α-fluoro acetate **4**.

***tert*-Butyl 2-cyano-2-fluoro-2-phenyl acetate 4g.** $[\alpha]_D^{26}$ = +20.38 (c = 0.42, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 7.47-7.54 (m, 3H), 7.60-7.64 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.7, 87.3 (d, J = 195.8 Hz), 86.9, 114.6 (d, J = 33.1 Hz), 125.5, 125.6, 129.3, 131.1, 131.2,

161.8 (d, J = 29.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −146.7; MS (ESI, m/z) 236.2 ($M+H^+$, 100), 219.2 (45), 163.1 (92), 106.9 (75); R_t HPLC (95:5, *n*-hexane: *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R = 4.5 min (major), t_R = 5.0 (minor).

***tert*-Butyl 2-cyano-2-fluoro-2-(4-chlorophenyl) acetate 4h.** $[\alpha]_D^{26}$ = +11.76 (c = 0.415, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9H), 7.46 (d, J = 8.7 Hz , 2H), 7.58 (d, J = 9.0 Hz , 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.7, 87.7 (d, J = 196.7 Hz), 87.2, 114.8 (d, J = 33.1 Hz), 127.0, 127.1, 129.6, 161.3 (d, J = 29.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −147.2; MS (ESI, m/z) 270.0 ($M+H^+$, 100), 205.9 (36); R_t HPLC (95:5, *n*-hexane: *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R = 4.0 min (major), t_R = 4.5 (minor).

***tert*-Butyl 2-cyano-2-fluoro-2-(4-methylphenyl) acetate 4i.** $[\alpha]_D^{26}$ = −26.49 (c = 0.305, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5 (s, 9H), 2.4 (s, 3H), 7.3 (d, J = 8.1 Hz , 2H), 7.5 (d, J = 8.2 Hz , 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 27.6, 87.3 (d, J = 194.8 Hz), 86.7, 114.6 (d, J = 27.6 Hz), 125.6, 125.7, 130.0, 161.9 (d, J = 29.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −146.5; MS (ESI, m/z) 250.1 ($M+H^+$, 100), 218.3 (38); R_t HPLC (95:5, *n*-hexane: *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R = 5.2 min (major), t_R = 6.3 (minor).

***tert*-Butyl 2-cyano-2-fluoro-2-(4-methoxyphenyl) acetate 4j.** $[\alpha]_D^{26}$ = +22.06 (c = 0.7, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9H), 3.8 (s, 3H), 7.0 (d, J = 8.8 Hz , 2H), 7.6 (d, J = 8.8 Hz , 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.8, 55.65, 87.1 (d, J = 194.8 Hz), 86.7, 124.1 (d, J = 23.9 Hz), 114.7, 127.5, 127.6, 162.1 (d, J = 29.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −146.1; MS (ESI, m/z) 265.9 ($M+H^+$, 100), 210.1 (72), 180.6 (72); R_t HPLC (95:5, *n*-hexane: *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R = 6.2 min (major), t_R = 9.0 (minor).

***tert*-Butyl 2-cyano-2-fluoro-2-(2-naphthyl) acetate 4k.** $[\alpha]_D^{26}$ = +31.4 (c = 0.58, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 7.5-7.7 (m, 3H), 7.9-8.0 (m, 3H), 8.2 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.8, 87.5 (d, J = 195.7 Hz), 87.0, 114.6 (d, J = 32.4 Hz), 121.7, 121.8, 126.1, 126.2, 127.0, 127.5, 128.0, 128.2, 129.0, 129.6, 161.8 (d, J = 29.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −146.3; MS (ESI, m/z) 286.2 ($M+H^+$, 100), 266.4 (45); R_t HPLC (95:5, *n*-hexane: *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OJ column, t_R = 6.7 min (major), t_R = 6.4 (minor).

***tert*-Butyl 2-cyano-2-fluoro-2-(9-anthracenyl) acetate 4l.** $[\alpha]_D^{25}$ = +23.23 (c = 0.105, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9H), 7.5-7.6 (m, 4H), 8.0-8.1 (m, 2H), 8.56 (s, 1H), 8.65 (d, J = 2.2 Hz , 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.8, 89.5 (d, J = 204.8 Hz), 87.7, 115.6 (d, J = 33.1 Hz), 124.6, 124.7, 125.4, 127.4, 129.6, 131.6, 132.5, 134.3, 162.3 (d, J = 26.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −146.3; MS (ESI, m/z) 336.1 ($M+H^+$, 100), 303.9 (65), 286.4 (15); R_t HPLC (95:5, *n*-hexane: *iso*-PrOH, 254 nm, 1.0 mL/min) Chiracel OD-H column, t_R = 6.8 min (major), t_R = 11.3 (minor).

General procedure for the fluorination of 1-aryl-1-cyanomethylphosphonates 5: To a stirred solution of 1-aryl-1-cyanomethylphosphonate (**5**, 0.05 mmol) and palladium catalyst **1g** (3.0 mg, 0.0025 mmol) and 2,6-di-*t*-butyl-4-methyl pyridine (20.5 mg, 0.1 mmol) in EtOH (0.5 mL) was added NFSI (**3**, 18.9 mg, 0.06 mmol) at room temperature. Reaction mixture was stirred for 12 h at room temperature. The mixture was diluted with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography to afford 1-fluoro-1-aryl-1-cyanomethylphosphonate **6**.

Diethyl 1-fluoro-1-phenyl-1-cyanomethylphosphonate 6a. $[\alpha]_D^{17}$ = −27.7 (c 0.6, $CHCl_3$, 85% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26-1.38 (m, 6H), 4.03-4.32 (m, 4H), 7.42-7.50 (m, 3H), 7.55-7.67 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1, 65.7 (d, J = 7 Hz), 65.8 (d, J = 7 Hz), 87.6 (dd, J = 170, 195 Hz), 114.3 (d, J = 27 Hz), 125.8, 125.9, 128.7, 131.4; MS (EI, m/z) 271 (M^+, 5), 134 (61), 109 (100), 91 (72); R_t HPLC (9:1, hexane: *i*-PrOH, 220 nm, 1.0 mL/min) Chiralcel OJ column, t_R = 11.1 min (minor), t_R = 14.8 (major).

Diethyl 1-fluoro-1-(4-methoxyphenyl)-1-cyanomethylphosphonate 6e. $[\alpha]_D^{16.5}$ = −282.18 (c = 0.08, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 3.84 (s, 3H), 3.95-4.34 (m, 4H), 6.98 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.5, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2 (d, J = 6 Hz), 16.3 (d, J = 5 Hz), 55.4, 65.63 (d, J = 7 Hz), 65.8 (d, J = 7 Hz), 87.5 (dd, J = 193, 175 Hz), 114.1, 114.4 (d, J = 30 Hz), 121.6 (dd, J = 11, 3 Hz), 127.9 (dd, J = 4, 4 Hz), 161.3 (dd, J = 2, 2 Hz); MS (EI, m/z) 301 (M^+, 6), 164 (43), 139 (100); R_t HPLC (9:1, hexane: *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R = 11.1 min (major), t_R = 13.5 (minor).

Diethyl 1-fluoro-1-(4-methylphenyl)-1-cyanomethylphosphonate 6f. $[\alpha]_D^{21.3}$ = +58 (c = 0.79, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26-1.40 (m, 6H), 2.40 (s, 3H), 3.98-4.37 (m, 4H), 7.29 (d, J = 6.1 Hz, 2H), 7.55 (d, J = 7.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1 (d, J = 5 Hz), 16.2 (d, J = 5 Hz), 21.1, 65.6 (d, 7 Hz), 65.8 (d, 7 Hz), 87.6 (dd, J = 193, 172 Hz), 114.4 (d, J = 28 Hz), 125.9 (dd, J = 5, 4 Hz), 126.9 (dd, J = 22, 2 Hz), 129.3 (d, J = 2 Hz), 140.8 (d, J = 3 Hz); MS (EI, m/z) 285 (M^+, 5), 148 (100); R_t HPLC (9:1, hexane: *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD column, t_R = 9.5 min (major), t_R = 10.5 (minor).

Diethyl 1-fluoro-1-(4-chlorophenyl)-1-cyanomethylphosphonate 6g. $[\alpha]_D^{18.2}$ = +172.67 (c = 0.04, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26-1.40 (m, 6H), 4.03-4.35 (m, 4H), 7.47 (d, J = 8.6, 2H), 7.60 (d, J = 7.4, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) d 16.2 (d, J = 4 Hz), 16.3 (d, J = 5 Hz), 65.9 (d, J = 7 Hz), 66.1 (d, J = 7 Hz), 87.1 (dd, J = 195, 172 Hz), 114.0 (d, J = 28 Hz), 127.5 (dd, J = 5, 5 Hz), 128.7 (dd, J = 22.1, 2.7 Hz), 129.0 (d, J = 2 Hz), 136.9 (dd, J = 2, 2 Hz); MS (EI, m/z) 305 (M^+, 6), 307 (M^++2, 6), 168 (48), 170 (16), 143 (100), 145(33); R_t HPLC (9:1, hexane: *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R = 11.1 min (major), t_R = 13.5 (minor).

Diethyl 1-fluoro-1-(4-fluorophenyl)-1-cyanomethyl-

phosphonate 6h. $[\alpha]_D^{21.3} = -74.8$ (c = 0.66, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.27-1.43 (m, 6H), 4.02-4.35 (m, 4H), 7.18 (t, J = 8.6 Hz, 2H), 7.64-7.70 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1 (d, J = 5Hz), 16.2 (d, J = 5 Hz), 65.8 (d, J = 7 Hz), 66.0 (d, J = 7 Hz), 87.1 (dd, J = 194, 172 Hz), 114.2 (d, J = 27 Hz), 116.0 (d, J = 21 Hz), 126.0 (dd, J = 22, 3 Hz), 128.3 (m), 163.9 (dd, J = 250, 2, 2 Hz); MS (EI, m/z) 289 (M^+, 7), 152 (53) 127 (100), 109 (43); R_t HPLC (95:5, hexane: *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD column, t_R = 10.2 min (major), t_R = 10.9 (minor).

Diethyl 1-fluoro-1-(1-naphthyl)-1-cyanomethylphosphonate 6i. $[\alpha]_D^{16.5} = 324$ (c = 0.02, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1, 6H), 4.00-4.33 (m, 4H), 7.48-7.65 (m, 3H), 7.87-7.98 (m, 3H), 8.50 (d, J = 8.1, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2 (d, J = 5 Hz), 65.8 (d, J = 7 Hz), 65.9 (d, J = 6 Hz), 89.3 (dd, J = 192, 171 Hz), 114.8 (d, J = 29 Hz), 124.4 (d, J = 2 Hz), 125.5 (d, J = 6 Hz), 126.0 (d, J = 5 Hz), 126.3 (d, J = 5 Hz), 126.5, 126.8, 128.8, 129.4 (d, J = 3 Hz), 131.9, 134.1; MS (EI, m/z) 321 (M^+, 15), 184 (51), 158 (100); R_t HPLC (9:1, hexane: *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R = 9.5 min (major), t_R = 11.2 (minor).

Diethyl 1-fluoro-1-(2-thienyl)-1-cyanomethylphosphonate 6j. $[\alpha]_D^{16.5} = -77.4$ (c = 0.67, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J = 6.9 Hz, 3H), 1.43 (t, J = 7.3 Hz, 3H), 4.13-4.45 (m, 4H), 7.12 (t, J = 4.4 Hz, 1H), 7.57-7.62 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1 (d, J = 5 Hz), 16.3 (d, J = 6 Hz), 66.0 (d, J = 7 Hz), 66.2 (d, J = 7 Hz), 84.0 (dd, J = 192, 178 Hz), 113.8 (d, J = 29 Hz), 127.2, 130.8, 130.9, 131.0; MS (EI, m/z) 283 (M^+, 2), 156 (71), 129 (100); R_t HPLC (9:1, hexane: *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OJ column, t_R = 10.2 min (major), t_R = 10.9 (minor).

Acknowledgement. This research was financially supported by the Ministry of Commerce, Industry and Energy (MOCIE) and Korea Industrial Technology Foundation (KOTEF) through the Human Resource Training Project for Regional Innovation.

References

1. (a) Chambers, R. D. *Fluorine in Organic Chemistry*: Blackwell: Oxford, 2004. (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (c) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds: Chemistry and Applications*; Springer-Verlag: Berlin, 2000. (d) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. For reviews: (e) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013-1029. (f) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303-319.
2. (a) Bohm, H.-J.; Banmer, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637-643. (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3-11. (c) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27-33.
3. (a) *Asymmetric Fluoroorganic Chemistry: Synthesis, Application, and Future Directions*; Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000. (b) *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Ed.; John Wiley & Sons: Chichester, 1999. For review: (c) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661-692.
4. For reviews: (a) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737-1755. (b) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431-12477.
5. For reviews: (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1-16. (b) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147-1155. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119-6149. (d) France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475-479. (e) Prakash, G. K. S.; Bier, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2172-2174.
6. (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359-4362.
7. For β-ketoesters: (a) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545-547. (b) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530-14531. (c) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225-3228. (d) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007-1011. (e) Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703-1706. (f) Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4204-4207. (g) Cho, M. J.; Kang, Y. K.; Lee, N. R.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2191.
8. For α-cyano acetates: (a) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115-3117. (b) Park, E. J.; Kim, H. R.; Joung, C. W.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2004**, *25*, 1451-1452.
9. For β-keto phosphonates: (a) Bernardi, L.; Jørgensen, K. A. *Chem. Commun.* **2005**, 1324-1326. (b) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447-1450. (c) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309-2311. (d) Kim, S. M.; Kang, Y. K.; Lee, K.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 423-425.
10. For α-cyanophosphonates: (a) Kang, Y. K.; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135-1138. (b) Moriyama, K.; Hamashima, Y.; Sodeoka, M. *Synlett* **2007**, 1139-1142.
11. (a) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991-993. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703-3706. (c) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706-3710. (d) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826-8828. (e) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051-15053.
12. (a) *Asymmetric Fluoroorganic Chemistry: Synthesis, Application, and Future Directions*; Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000. (b) *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Ed.; John Wiley & Sons: Chichester, 1999.
13. (a) Takeuchi, Y.; Konishi, M.; Hori, H.; Takehashi, T.; Kometani, T.; Kirk, K. L. *Chem. Commun.* **1998**, 365-366. (b) Takeuchi, Y.; Konishi, M.; Hori, H.; Takehashi, T.; Kometani, T.; Kirk, K. L. *Enantiomer* **1999**, *4*, 339. (c) Takeuchi, Y.; Fukushima, A.; Tanaka, Y.; Takeuchi, Y.; Kabuto, K.; Kabuto, C. *Chem. Commun.* **2000**, 787-788. (d) Fugiwara, T.; Sasaki, M.; Omata, K.; Kabuto, C.; Kabuto, K.; Takeuchi, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 555-563.
14. (a) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728-10729. (b) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001-7009.
15. Berkowitz, D. B.; Bose, M. *J. Fluorine Chem.* **2001**, *112*, 13.
16. (a) Blackburn, G. M. *Chem. Ind. (London)* **1981**, 134. (b) McKenna, C. E.; Shen, P. *J. Org. Chem.* **1981**, *46*, 4573. (c) Nieschalk, J.; O'Hagan, D. *Chem. Commun.* **1995**, 719. (d) Nieschalk, J.; O'Hagan, D. *Chem. Commun.* **1995**, 719. (e) Jakeman, D. L.; Ivory, A. J.; Willamson, M. P.; Blackburn, G. M. *J. Med. Chem.* **1998**, *41*,

4493. (f) Jakeman, D. L.; Ivory, A. J.; Williamson, M. P.; Blackburn, G. M. *J. Med. Chem.* **1998**, *41*, 4493. (g) Berkowitz, D. B.; Bose, M.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498.

17. (a) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4265-4568. (b) Cho, M. J.; Cho, M. G.; Huh, S. C.; Kim, S. M.; Lee, K.; Koh, K. O.; Mang, J. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 857-861. (c) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897-6899. (d) Kim, D. Y.; Huh, S. C. *Bull. Korean Chem. Soc.* **2004**, *25*, 347-348. (e) Kim, D. Y.; Kim, S. M.; Koh, K. O.; Mang, J. Y. *Bull. Korean Chem. Soc.* **2003**, *24*, 1425-1426. (f) Kim, D. Y.; Choi, Y. J.; Park, H. Y.; Joung, C. U.; Koh, K. O.; Mang, J. Y.; Jung, K.-Y. *Synth. Commun.* **2003**, *33*, 435-443. (g) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299-6301. (h) Kim, D. Y.; Huh, S. C. *Tetrahedron* **2001**, *57*, 8933-8938.
18. (a) Li, K.; Hii, K. K. *Chem. Commun.* **2003**, 1132-1133. (b) Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Organometallic Chem.* **2003**, *665*, 250-257. For Pd(II) chemistry, see (c) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for 21st Century*; John Willey & Son: Chichester, 2004. For a aquapalladium complex, see (d) Shimada, T.; Bajracharya, G. B.; Yamamoto, Y. *Eur. J. Org. Chem.* **2005**, 59-62, and references cited therein.
19. For the preparation of α-cyanoalkylphosphonates: (a) Kim, D. Y.; Oh, D. Y. *Synth. Commun.* **1987**, *17*, 953-957. (b) Kim, D. Y.; Oh, D. Y. *Bull. Korean Chem. Soc.* **1997**, *18*, 994-998.