Enantioselective Fluorination of β-Keto Phosphonates and β-Ketoesters Catalyzed by Chiral Palladium Complexes

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The catalytic enantioselective electrophilic fluorinations of active methine compounds promoted chiral palladium complexes have been developed. Treatment of β-keto phosphonates and β-ketoesters with *N*-fluorobenzenesulfonimide as the fluorine source under mild reaction conditions afforded the corresponding 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, β-Keto phosphonates, β-Ketoesters

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] Recently, several groups presented the direct enantioselective electrophilic fluorination of carbonyl compounds in the presence of chiral Lewis acid complexes or chiral organocatalysts.[7-11]

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[12] we report the catalytic enantioselective α-fluorination of active methine compounds with excellent enantioselectivity promoted by chiral palladium complexes.[8,10a] In this paper, we wish to report the catalytic enantioseletive electrophilic α-fluorination of β-keto phosphonates and β-ketoesters using chiral palladium complexes **1** in more details, providing information on its scopes and limitations.[9c]

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).[13]

Enantioselective fluorination of β-keto phosphonates. α-Fluoroalkylphosphonates are better mimics of natural phosphates with matched 2nd p*K*a vaules (~6.5).[14] The enantioselective construction of α-fluoroalkylphosphonates is extremely important because the stereochemistry of α-carbon does affect biological activity.[15]

To determine suitable reaction conditions for the catalytic enantioselcetive fluorination of β-keto phosphonates **4**,[16] we first examined electrophilic fluorination of β-keto phosphonate **4a** with *N*-fluorobenzenesulfonimide (NFSI, **5a**) in the presence of 5 mol% of Pd complex **1g** in acetone at room temperature (Table 1). As can be seen from Table 1, the fluorinated product **6a** was obtained with 86% yield with 89% ee after 13 h (entry 1). Concerning the solvent, the use of

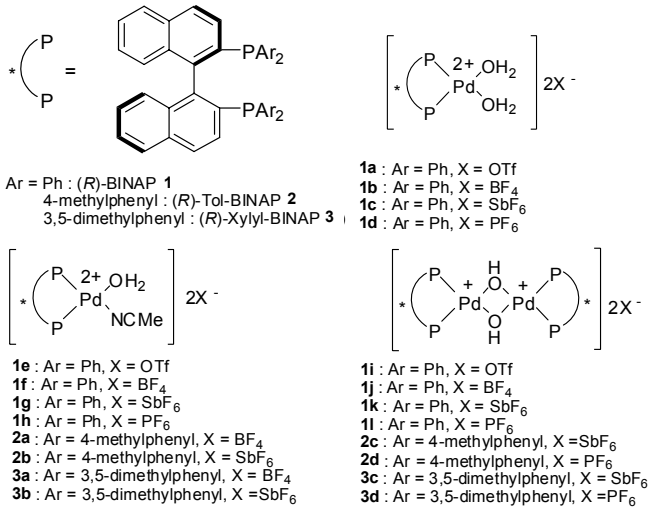
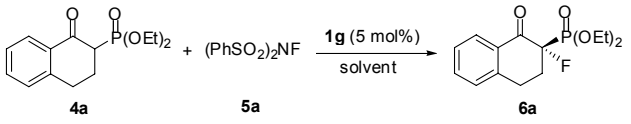


Figure 1. Chiral palladium complexes.

Table 1. Effects of solvents and temperature in the asymmetric fluorination of β-keto phosphonate **4a**

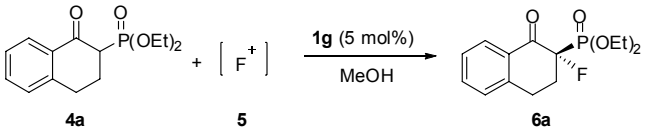


4a **5a** **6a**

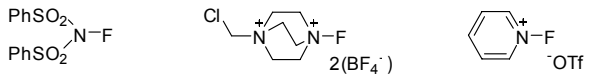
Entry	Solvent	Temp.(°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	acetone	r.t.	13	86	89
2	THF	r.t.	13	92	87
3	DMF	r.t.	13	21	45
4	CH_2Cl_2	r.t.	15	34	75
5	$ClCH_2CH_2Cl$	r.t.	15	54	77
6	$PhCH_3$	r.t.	15	36	81
7	CH_3CN	r.t.	20	29	45
8	EtOH	r.t.	10	87	89
9	^{i}PrOH	r.t.	6	94	87
10	^{t}BuOH	r.t.	6	91	87
11	MeOH	r.t.	6	96	89
12	MeOH	0	6	57	85
13	MeOH	-20	6	37	75
14	MeOH	-40	6	24	63

[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis with a Chiralpak AD column.

Table 2. Effect of fluorinating reagents in the asymmetric fluorination of β-keto phosphonate **4a**



4a **5** **6a**



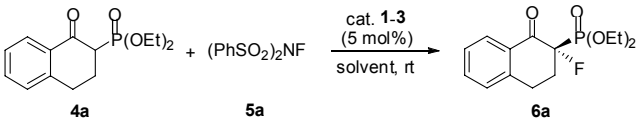
5a **5b** **5c**

Entry	**5**	Time (h)	Yield[a] (%)	eeb (%)
1	**5a**	6	96	89
2	**5b**	22	47	43
3	**5c**	12	0	–

[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis with a Chiralpak AD column.

alcoholic solvents such as EtOH and MeOH gave the best results (entries 8 and 11), whereas the fluorination in acetone, THF, DMF, CH_2Cl_2, PhMe, and CH_3CN led to slightly lower yields and enantioselectivities. Lowering the temperature in MeOH decreased the yields and enantioselectivity (entries 12-14). NFSI (**5a**) was more effective fluorinating agent than Selectfluor (**5b**) in this reaction under the same condition (Table 2). 1-Fluoropyridinium triflate (**5c**) did not give the desired product **6a** in a detectable amount under the same reaction conditions.

Table 3. Effect of Pd-cat. **1-3** in the asymmetric fluorination of β-keto phosphonate **4a**



4a **5a** **6a**

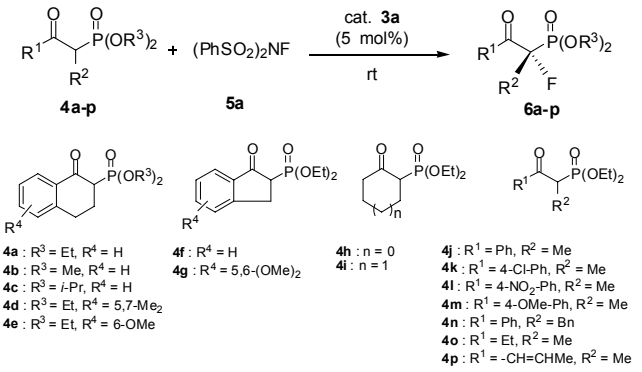
Entry	Cat.	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a**	EtOH	20	43	55
2	**1b**	EtOH	18	79	85
3	**1c**	EtOH	15	38	69
4	**1d**	EtOH	15	83	87
5	**1e**	EtOH	20	46	73
6	**1f**	EtOH	8	77	89
7	**1g**	EtOH	10	87	89
8	**1h**	EtOH	10	24	69
9	**1i**	EtOH	15	55	81
10	**1j**	EtOH	15	82	87
11	**1k**	EtOH	15	67	83
12	**1l**	EtOH	15	85	87
13	**1g**	MeOH	6	96	89
14	**2a**	MeOH	8	96	91
15	**2b**	MeOH	9	96	91
16	**2c**	MeOH	9	21	31
17	**2d**	MeOH	11	64	89
18	**3a**	MeOH	8	93	97
19	**3b**	MeOH	9	95	95
20[c]	**3c**	MeOH	9	94	95
21[c]	**3d**	MeOH	11	59	95
22[c]	**3a**	MeOH	10	71	97
23[d]	**3a**	MeOH	10	64	96
24[e]	**3a**	MeOH	4	94	91
25[f]	**3a**	MeOH	33	53	95
26[g]	**3a**	MeOH	33	36	93

[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis using a Chiralpak AD column. [c]This reaction was carried out using 2.5 mol% of catalyst. [d]This reaction was carried out using 1.0 mol% of catalyst. [e]This reaction was carried out at 70 °C using 0.5 mol% of catalyst. [f]This reaction was carried out using 0.5 mol% of catalyst. [g]This reaction was carried out using 0.1 mol% of catalyst.

We examined a series of chiral diphosphine ligands and anions in catalysts **1-3** (Table 3). The substitution at the meta-positions of the aryl group on phosphine and the anionic counterpart were found to be important. When bulkier ligands such as (*R*)-Xylyl-BINAP palladium complexes **3a-3d** were used in MeOH, the enantioselectivity was improved to 95-97% ee (entries 18-21). Catalyst **3a** was the most effective than other catalysts (entry 18). Decreasing the catalyst loading to 2.5, 1.0, 0.5 and 0.1 mol% showed a significant decrease in yields and slightly decreased the enantioselectivities (entries 18 and 22-26). The absolute configuration of **6a** was determined to be *S* by comparing specific rotation and chiral HPLC data with an authentic sample.[9]

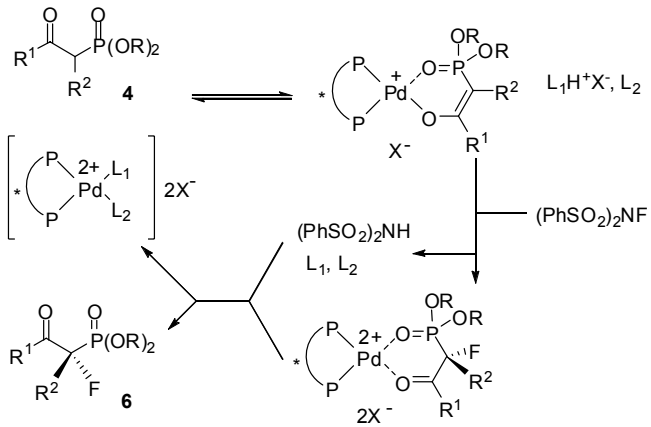
To examine the generality of the catalytic enantioselective fluorination of β-keto phosphonates **4** by using chiral palladium complex **3a**, we studied the fluorination of cyclic and acyclic β-keto phosphonate derivatives **4b-4p**. As it can be seen by the results summarized in Table 4, the corresponding

Table 4. Catalytic enanantioselective fluorination of β-keto phosphonates **4**



Entry	4	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	**4a**	MeOH	8	**6a**, 93	97
2	**4b**	MeOH	6	**6b**, 89	93
3	**4c**	MeOH	23	**6c**, 91	95
4	**4d**	MeOH	12	**6d**, 84	95
5	**4e**	MeOH	10	**6e**, 92	95
6	**4f**	MeOH	3	**6f**, 91	97
7	**4g**	MeOH	11	**6g**, 86	95
8	**4h**	MeOH	45	**6h**, 67	95
9	**4i**	MeOH	86	**6i**, 73	95
10	**4j**	THF	94	**6j**, 62	91
11[c]	**4j**	THF	24	**6j**, 67	90
12	**4k**	THF	94	**6k**, 68	91
13[c]	**4k**	THF	24	**6k**, 65	91
14	**4l**	THF	90	**6l**, 78	87
15[c]	**4l**	THF	24	**6l**, 75	88
16	**4m**	THF	78	**6m**, 61	91
17	**4n**	THF	86	**6n**, 50	91
18	**4o**	THF	90	**6o**, 65	87
19	**4p**	THF	58	**6p**, 79	93

[a]Isolated yield. [b]Enantiopurity of **6** was determined by HPLC analysis with Chiralcel OD-H (for **6i**) and Chiralpak AD columns. [c]Reaction was carried out with 2 equiv of base (2,6-di-*tert*-butyl-4-methylpyridine).

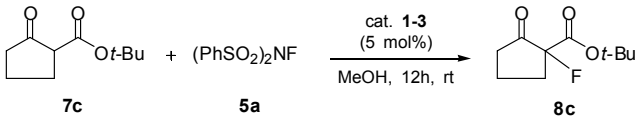


Scheme 1. Assumed catalytic cycle.

α-fluoro β-keto phosphonates **6** were obtained in moderate to excellent yields and excellent enantioselectivities (87-97% ee). The cyclic β-keto phosphonates **4a-4i**, with cyclic aromatic ketones **4a-4g**, and cyclic aliphatic ketones **4h-4i**, reacted with NFSI (**5a**) to give the corresponding α-fluorinated β-keto phosphonates **6a-6i** in 67-93% yields and 93-97% ee in MeOH (Table 4, entries 1-9). Acyclic β-keto phosphonates **4j-4p** were successfully employed, and desired fluorinated products were obtained in moderate to excellent yields (50-79%) and excellent enantioselectivities (87-93% ee) in THF. In the presence of 2,6-di-*t*-butyl-4-methyl pyridine as base, the reaction was proceeded rapidly without significant change of enantioselectivity (entries 10-15) under the same reaction conditions.

On the basis of our results, a plausible mechanism of the catalytic cycle is outlined Scheme 1. The Pd(II) complex activates the substrate through coordination of the keto group, affording the enolate complex. Chiral Pd-coordinated nucleophile reacts with NFSI to produce the fluorinated product **6**.

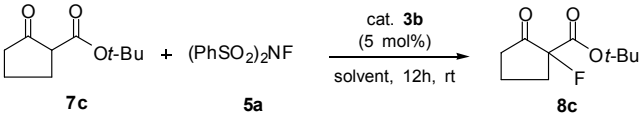
Table 5. Effect of Pd-cat. in the asymmetric fluorination of β-ketoester **7c**



Entry	Cat.	Yield (%)	ee[a] (%)
1	**1e**	80	67
2	**1f**	87	67
3	**1g**	91	69
4	**1h**	85	68
5	**2b**	85	77
6	**3b**	91	91

[a]Enantiopurity was determined by HPLC analysis with a Chiralpak AD-H column.

Table 6. Effect of solvent in the asymmetric fluorination of β-ketoester **7c**



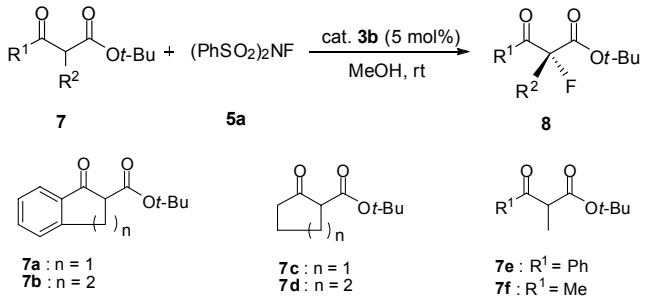
Entry	Solvent	Yield (%)	ee[a] (%)
1	Acetone	69	77
2	THF	71	86
3	MeOH	91	91
4	EtOH	88	91

[a]Enantiopurity was determined by HPLC analysis with a Chiralpak AD-H column.

Enantioselective fluorination of β-ketoesters. Encourged by the success in the catalytic enantioselective fluorination of β-keto phosphonates, we turned our attention to the β-ketoesters which are versatile functional groups for further chemical transformation. The optically active α-fluorinated β-ketoesters would be building blocks in the fields of medicinal chemistry.

To determine optimum reaction conditions for the catalytic enantioselective electrophilic fluorination of β-ketoesters, we initially investigated the reaction of *tert*-butyl 2-oxo-cyclopentanecarboxylate (**7c**) with NFSI (**5a**) as the electrophilic

Table 7. Catalytic asymmetric fluorination of β-ketoesters



Entry	7	Time (h)	Yield[a] (%)	ee[b] (%)
1	**7a**	0.5	**8a**, 90	85 (*R*)
2	**7b**	0.5	**8b**, 92	92
3	**7c**	12	**8c**, 91	91
4	**7d**	0.5	**8d**, 93	99
5	**7e**	24	**8e**, 87	99 (*R*)
6	**7f**	0.5	**8f**, 85	95

[a]Isolated yield. [b]Enantiomeric excess determined by chiral HPLC analysis with Chiralpak AD-H column (for **8a-e**) and chiral GC analysis with Chiraldex column (for **8f**).

fluorinating agent in the presence of 5 mol% of chiral palladium catalysts in MeOH at room temperature (Table 5). When (*R*)-Xylyl-BINAP palladium complexes **3b** was used, the enantioselectivity was improved to 91% ee (entry 6). Concerning the solvent, the use of alcoholic solvents gave the best results, whereas the fluorination in THF and acetone led to slightly lower yields and enantioselectivities (Table 6).

This catalytic system was also applicable to various β-ketoesters **7** to examine the generality of the catalytic enantioselective fluorination (Table 7). All the substrates examined were fluorinated in moderate to excellent yields with high enantioselctivities (85-99% ee) using chiral palladium complex **3b** under optimum reaction conditions. The absolute configuration of **8a** and **8e** was determined to be *R* by comparing specific rotation and chiral HPLC data with an authentic sample.[7]

Conclusion

We have developed the catalytic enantioselective fluorination reactions of β-keto phosphonates **4** and β-ketoesters **7** with excellent enantioselectivity (up to 99% ee). 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 under an atmosphere of air 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 and ^{13}C, spectra were recorded on a Bruker AC 200 (200 MHz for ^{1}H, 50 MHz for ^{13}C) and DPX 300 (300 MHz for ^{1}H). Chemical shift values (δ) are reported in ppm relative to Me_4Si (for ^{1}H). 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. High resolution mass spectra were measured on Jeol HX 110/110A using electrospray ionization techniques. 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, OB-H, and OJ columns.

General procedure for the fluorination of β-keto phosphonates 4. To a stirred solution of β-keto phosphonate **4a** (0.3 mmol) and catalyst **3a** (16.1 mg, 0.015 mmol) in MeOH (3 mL) was added NFSI (**5a**, 141.9 mg, 0.45 mmol) at room temperature. Reaction mixture was stirred for 3-94 h at room temperature. The mixture was diluted with saturated NH_4Cl solution (30 mL) and extracted with ethyl ether (2×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography to afford the α-fluoro β-keto phosphonate **6**.

(*S*)-2-(Diethoxyphosphinyl)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene (6a): $[\alpha]_D^{23}$ +46.64 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (t, *J* = 6.8 Hz, 3H), 1.36 (t, *J* = 6.9 Hz, 3H), 2.31-2.73 (m, 1H), 2.76-2.96 (m, 1H), 3.03-3.18 (m, 1H), 3.40-3.58 (m, 1H), 4.00-4.17 (m, 2H), 4.22-4.37 (m, 2H), 7.24-7.37 (m, 2H), 7.49-7.57 (m, 1H), 8.05 (dd, *J* = 7.8, 1.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0 (d, *J* = 6.2 Hz), 16.4 (d, *J* = 5.7 Hz), 26.0 (d, *J* = 11.0 Hz), 36.7 (d, *J* = 19.8 Hz), 63.9 (d, *J* = 7.2 Hz), 64.6 (dd, *J* = 9.1, 1.7 Hz), 95.6 (dd, *J* = 192.2, 156.5 Hz), 127.0, 128.0, 128.7, 131.5, 134.4, 143.3, 190.7 (dd, *J* = 14.3, 2.7 Hz); HRMS calcd for $C_{14}H_{18}FO_4PNa$ ($[M+Na]^+$) 323.0824, found 323.0816; R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AD column, t_R 6.6 min (major), t_R 8.5 (minor), ee 97%.

2-(Dimethoxyphosphinyl)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene (6b): R_f $[\alpha]_D^{23}$ = +51.36 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.35-2.68 (m, 1H), 2.71-2.95 (m, 1H), 3.03-3.15 (m, 1H), 3.37-3.54 (m, 1H), 3.74 (d, *J* = 10.8 Hz, 3H), 3.93 (d, *J* = 10.7 Hz, 3H), 7.25-7.38 (m, 2H), 7.50-7.58 (m, 1H), 8.07 (dd, *J* = 7.8, 1.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.9 (d, *J* = 11.1 Hz), 31.7 (d, *J* = 20.0 Hz), 54.4 (d, *J* = 7.2 Hz), 55.0 (dd, *J* = 6.8, 2.6 Hz), 95.8 (d, *J* = 192.0, 157.1 Hz), 127.2, 128.3, 128.9, 131.3, 134.6, 143.3, 190.4 (d, *J* = 11.1 Hz); HRMS calcd for $C_{12}H_{14}FO_4PNa$ ($[M+Na]^+$) 295.0511, found 295.0523; R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AD column, t_R 8.6 min (major), t_R 10.2 (minor), ee 93%.

2-(Diisopropoxyphosphinyl)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene (6c): $[\alpha]_D^{23}$ +30.04 (c = 1.0, $CHCl_3$); ^{1}H

NMR (200 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.2 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.35 (s, 3H), 1.38 (s, 3H), 2.31-2.71 (m, 1H), 2.77-2.96 (m, 1H), 3.01-3.12 (m, 1H), 3.40-3.57 (m, 1H), 4.58-4.73 (m, 1H), 4.78-4.94 (m, 1H), 7.22-7.36 (m, 2H), 7.47-7.55 (m, 1H), 8.04 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.4 (d, *J* = 3.5 Hz), 23.5 (d, *J* = 2.8 Hz), 23.7 (d, *J* = 3.6 Hz), 24.2 (d, *J* = 2.9 Hz), 26.1 (d, *J* = 11.3 Hz), 31.6 (d, *J* = 19.9 Hz), 73.0 (d, *J* = 7.7 Hz), 73.6 (d, *J* = 7.4 Hz), 95.4 (dd, *J* = 191.7, 158.8 Hz), 126.8, 127.7, 128.5, 131.8, 134.1, 143.1, 190.7 (dd, *J* = 14.0, 3.0 Hz); HRMS calcd for $C_{16}H_{22}FO_4PNa$ ($[M+Na]^+$) 351.1137, found 351.1145; R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AD column, t_R 5.4 min (major), t_R 7.2 (minor), ee 95%.

2-(Diethoxyphosphinyl)-5,7-dimethyl-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene (6d): $[\alpha]_D^{23}$ +34.08 (c = 1.0, $CHCl_3$, 95% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.0 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 2.27 (s, 3H), 2.33 (s, 3H), 2.38-2.69 (m, 1H), 2.77-3.05 (m, 2H), 3.12-3.29 (m, 1H), 3.95-4.16 (m, 2H), 4.19-4.37 (m, 2H), 7.22 (s, 1H), 7.73 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2 (d, *J* = 5.9 Hz), 16.5 (d, *J* = 5.7 Hz), 19.3, 21.0, 23.6 (d, *J* = 11.1 Hz), 31.2 (d, *J* = 19.5 Hz), 64.0 (d, *J* = 7.1 Hz), 64.7 (d, *J* = 6.9 Hz), 95.6 (dd, *J* = 192.3, 157.0 Hz), 126.1, 131.7, 136.3, 136.5, 137.0, 138.9, 190.7 (dd, *J* = 13.7, 3.7 Hz); R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R 10.4 min (major), t_R 13.6 (minor), ee 95%.

2-(Diethoxyphosphinyl)-6-methoxy-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene (6e): $[\alpha]_D^{23}$ +32.52 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, *J* = 6.9 Hz, 3H), 1.37 (t, *J* = 6.9 Hz, 3H), 2.38-2.70 (m, 1H), 2.73-2.93 (m, 1H), 2.97-3.10 (m, 1H), 3.38-3.55 (m, 1H), 3.86 (s, 3H), 4.00-4.20 (m, 2H), 4.22-4.37 (m, 2H), 6.70 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.8, 2.5 Hz, 1H), 8.02 (d, *J* = 8.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2 (d, *J* = 5.9 Hz), 16.5 (d, *J* = 5.6 Hz), 26.4 (d, *J* = 11.1 Hz), 31.7 (d, *J* = 20.0 Hz), 55.6, 64.1 (d, *J* = 7.1 Hz), 64.6 (dd, *J* = 7.3, 1.6 Hz), 95.3 (dd, *J* = 191.0, 156.3 Hz), 112.4, 114.0, 125.1, 130.6, 145.9, 164.5, 189.1 (dd, *J* = 14.3, 2.7 Hz); R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AD column, t_R 10.1 min (major), t_R 14.1 (minor), ee 95%.

2-(Diethoxyphosphinyl)-2-fluoroindanone (6f): $[\alpha]_D^{23}$ +66.12 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, *J* = 6.9 Hz, 3H), 1.37 (t, *J* = 6.9 Hz, 3H), 3.28-3.62 (m, 1H), 3.87-4.08 (m, 1H), 4.11-4.40 (m, 4H), 7.40-7.49 (m, 2H), 7.63-7.72 (m, 1H), 7.80 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (d, *J* = 5.3 Hz), 16.4 (d, *J* = 5.3 Hz), 36.5 (d, *J* = 21.2 Hz), 64.3, 64.4, 95.9 (dd, *J* = 199.5, 163.8 Hz), 125.1, 126.4, 128.5, 134.1, 136.5, 149.7 (d, *J* = 4.6 Hz), 196.4 (d, *J* = 14.4 Hz); R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R 9.1 min (major), t_R 10.6 (minor), ee 97%.

2-(Diethoxyphosphinyl)-5,6-dimethoxy-2-fluoroindanone (6g): $[\alpha]_D^{23}$ +32.20 (c = 1.0, $CHCl_3$, 95% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, *J* = 6.9 Hz, 3H), 1.39 (t, *J* = 6.9 Hz, 3H), 3.18-3.44 (m, 1H), 3.77-3.89 (m, 1H), 3.91 (s, 3H), 3.99 (s, 1H), 4.14-4.37 (m, 4H), 6.86 (s, 1H), 7.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (d, *J* = 5.3 Hz), 16.4 (d, *J* = 7.6 Hz), 36.2 (d, *J* = 23.5 Hz), 56.3 (dd, *J* = 29.2, 3.8 Hz), 64.4 (dd, *J* = 26.6, 6.9 Hz), 95.9 (dd, *J* = 200.2, 163.1 Hz), 105.1,107.2, 126.8, 126.9, 128.2, 145.7, 150.2, 157.0, 194.6 (d, *J* = 15.2 Hz); R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R 16.4 min (major), t_R 21.2 (minor), ee 95%.

2-(Diethoxyphosphinyl)-2-fluorocyclopentanone (6h): $[\alpha]_D^{23}$ +225.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 2.05-2.59 (m, 5H), 2.68-2.82 (m, 1H), 4.10-4.34 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.4 (dd, *J* = 5.7, 2.9 Hz), 16.9 (dd, *J* = 5.2, 4.1 Hz), 32.1 (dd, *J* = 18.3, 2.7 Hz), 35.4, 35.5, 64.1, 64.3 (d, *J* = 2.1 Hz), 96.3 (dd, *J* = 200.3, 165.8 Hz), 209.0 (d, *J* = 10.2 Hz). For the HPLC analysis, 2,4-dinitrophenylhydrazone derivatives were prepared according to the reported procedure.[18]

2-(Diethoxyphosphinyl)-2-fluoro-1-[(2,4-dinitrophenyl)-hydrazono] cyclopentane: $[\alpha]_D^{23}$ +58.96 (c = 0.5, $CHCl_3$, 95% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37-1.45 (m, 6H), 2.14-2.85 (m, 6H), 4.16-4.40 (m, 4H), 8.05 (d, *J* = 9.3 Hz, 1H), 8.36 (dd, *J* = 9.5, 2.31 Hz, 1H), 9.14 (d, *J* = 2.6 Hz, 1H), 10.93 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.7 (dd, *J* = 5.1, 5.0 Hz), 20.5 (dd, *J* = 7.8, 2.5 Hz), 27.2, 27.3, 35.2 (dd, *J* = 20.1, 3.7 Hz), 63.8 (d, *J* = 7.0 Hz), 64.3 (d, *J* = 6.7 Hz), 97.9 (dd, *J* = 193.4, 178.0 Hz), 117.0, 123.4, 130.3, 139.1, 145.0, 158.5 (d, *J* = 14.6 Hz); R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R 33.8 min (major), t_R 48.3 (minor), ee 95%.

2-(Diethoxyphosphinyl)-2-fluorocyclohexanone (6i): $[\alpha]_D^{23}$ +155.04 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.0 Hz, 3H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.60-2.30 (m, 5H), 2.58-2.73 (m, 2H), 2.83-2.99 (m, 1H), 4.09-4.36 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.4 (dd, *J* = 5.9, 3.6 Hz), 21.4 (dd, *J* = 7.6, 2.8 Hz), 25.1, 26.8, 35.8 (d, *J* = 19.6 Hz), 40.7, 66.2 (d, *J* = 3.0 Hz), 66.3 (d, *J* = 3.5 Hz), 97.6 (dd, *J* = 193.8, 165.0 Hz), 202.5 (dd, *J* = 15.6, 4.3 Hz). For the HPLC analysis, 2,4-dinitrophenylhydrazone derivatives were prepared according to the reported procedure.[18]

2-(Diethoxyphosphinyl)-2-fluoro-1-[(2,4-dinitrophenyl)-hydrazono]cyclohexane: $[\alpha]_D^{23}$ -43.76 (c = 0.5, $CHCl_3$, 95% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32-1.45 (m, 6H), 1.67-2.10 (m, 4H), 2.05-2.83 (m, 4H), 4.16-4.38 (m, 4H), 8.18 (d, *J* = 9.5 Hz, 1H), 8.36 (dd, *J* = 9.5, 2.2 Hz, 1H), 9.13 (d, *J* = 2.4 Hz, 1H), 11.25 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.7 (d, *J* = 5.6 Hz), 20.3 (dd, *J* = 6.9, 5.4 Hz), 24.6, 24.7, 24.9, 34.7 (d, *J* = 14.9 Hz), 63.5 (d, *J* = 7.2 Hz), 64.1 (d, *J* = 6.0 Hz), 95.8 (dd, *J* = 182.9, 173.6 Hz), 117.5, 123.3, 130.4, 138.9, 145.4, 152.7 (d, *J* = 18.5 Hz); R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralcel OD-H column, t_R 20.6 min (major), t_R 25.0 (minor), ee 95%.

Diethyl 1-fluoro-1-methyl-2-oxo-2-phenylethylphosphonate (6j): $[\alpha]_D^{23}$ -15.52 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (t, *J* = 6.7 Hz, 3H), 1.35 (t, *J* = 6.8 Hz, 3H), 1.92 (dd, *J* = 24.0, 15.1 Hz, 3H), 4.16-4.36 (m, 4H), 7.41-7.62 (m, 3H), 8.05-8.11 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.4, 16.6, 21.6 (d, *J* = 21.8 Hz), 64.2 (d, *J* = 1.5 Hz), 64.3 (d, *J* = 2.1 Hz), 100.6 (dd, *J* = 194.3, 160.6 Hz), 128.3, 130.1, 130.6, 133.5, 197.7 (dd, *J* = 23.0, 3.7 Hz); HRMS calcd for $C_{13}H_{18}FO_4PNa$ ($[M+Na]^+$) 311.0824, found 311.0834; R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiral-

pak AD column, t_R 13.4 min (minor), t_R 14.1 (major), ee 91%.

Diethyl 1-fluoro-1-methyl-2-oxo-2-(4-chlorophenyl)ethylphosphonate (6k): $[\alpha]_D^{23}$ -20.12 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.90 (dd, *J* = 24.2, 14.9 Hz, 3H), 4.13-4.36 (m, 4H), 7.43 (d, *J* = 8.7 Hz, 2H), 8.05 (dd, *J* = 8.6, 1.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5 (d, *J* = 1.5 Hz), 16.6 (d, *J* = 1.3 Hz), 21.5 (d, *J* = 21.8 Hz), 64.4, 64.5, 100.7 (dd, *J* = 193.7, 160.0 Hz), 128.7, 131.8, 131.9, 140.2, 196.5 (dd, *J* = 23.1, 3.8 Hz); R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralpak AD column, t_R 12.7 min (minor), t_R 13.6 (major), ee 91%.

Diethyl 1-fluoro-1-methyl-2-oxo-2-(4-nitrophenyl)ethylphosphonate (6l): $[\alpha]_D^{23}$ -34.24 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 3H), 1.39 (t, *J* = 6.9 Hz, 3H), 1.93 (dd, *J* = 24.1, 14.7 Hz, 3H), 4.16-4.39 (m, 4H), 8.21-8.33 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5 (d, *J* = 2.7 Hz), 16.6 (d, *J* = 2.7 Hz), 21.3 (d, *J* = 21.8 Hz), 64.6, 64.7, 100.7 (dd, *J* = 192.4, 159.9 Hz), 123.4, 131.2, 131.3, 150.3, 197.1 (d, *J* = 28.5 Hz); R_t HPLC (95:5, hexane : *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OJ column, t_R 27.0 min (major), t_R 32.2 (minor), ee 87%.

Diethyl 1-fluoro-1-methyl-2-oxo-2-(4-methoxyphenyl)-ethylphosphonate (6m): R_f $[\alpha]_D^{23}$ -6.72 (c = 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (t, *J* = 6.7 Hz, 3H), 1.35 (t, *J* = 6.7 Hz, 3H), 1.91 (dd, *J* = 24.2, 15.1 Hz, 3H), 4.14-4.36 (m, 4H), 6.93 (d, *J* = 9.1 Hz, 2H), 8.14 (dd, *J* = 7.3, 2.1 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5, 16.7, 21.8 (d, *J* = 21.9 Hz), 55.7, 64.2, 64.4, 100.8 (dd, *J* = 194.0, 160.7 Hz), 113.7, 132.9, 133.1, 164.1, 195.5 (d, *J* = 22.1 Hz); R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralpak AD column, t_R 19.2 min (minor), t_R 24.9 (major), ee 91%.

Diethyl 1-benzyl-1-fluoro-2-oxo-2-phenylethylphosphonate (6n): $[\alpha]_D^{23}$ +25.60 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (t, *J* = 6.7 Hz, 3H), 1.36 (t, *J* = 6.7 Hz, 3H), 3.49 (ddd, *J* = 14.2, 13.1, 8.4 Hz, 1H), 3.77 (ddd, *J* = 39.1, 14.4, 5.2 Hz, 1H), 4.17-4.35 (m, 4H), 7.16-7.29 (m, 6H), 7.36-7.46 (m, 2H), 7.52-7.57 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5, 16.6, 40.6 (d, *J* = 19.5 Hz), 64.5 (d, *J* = 6.4 Hz), 64.6 (d, *J* = 6.4 Hz), 102.9 (dd, *J* = 200.7, 157.3 Hz), 127.4, 128.0, 128.5, 129.3, 129.4, 130.9, 132.8, 198.7 (dd, *J* = 24.5, 2.8 Hz); R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralpak AD column, t_R 15.3 min (minor), t_R 17.1 (major), ee 91%.

Diethyl 1-fluoro-1-methyl-2-oxo-butylphosphonate (6o): $[\alpha]_D^{23}$ +147.40 (c = 0.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 6H), 1.71 (dd, *J* = 23.9, 15.6 Hz, 3H), 2.73-2.83 (m, 2H), 4.15-4.29 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 7.0 (d, *J* = 2.7 Hz), 16.5, 16.6, 19.8 (d, *J* = 21.5 Hz), 31.6, 64.1 (d, *J* = 6.7 Hz), 64.3 (d, *J* = 6.8 Hz), 99.4 (dd, *J* = 189.3, 159.0 Hz), 208.1 (dd, *J* = 23.9, 3.6 Hz). For the HPLC analysis, 2,4-dinitrophenylhydrazone derivatives were prepared according to the reported procedure.[18]

Diethyl 1-fluoro-1-methyl-2-[(2,4-dinitrophenyl)hydrazono]-butylphosphonate: $[\alpha]_D^{23}$ -170.24 (c = 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21-1.44 (m, 9H), 1.96 (dd, *J* = 24.9, 9.9 Hz, 3H), 2.57-2.87 (m, 2H), 4.07-4.31 (m, 4H), 7.95 (d, *J* = 9.5 Hz, 1H), 8.35 (dd, *J* = 9.5, 2.5 Hz, 1H), 9.15 (d, *J* = 2.9 Hz, 1H), 11.32 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.7, 16.6, 16.7, 20.2 (d, *J* = 4.4 Hz), 21.5 (d, *J* = 18.8 Hz), 63.9 (d, *J* = 7.5 Hz), 64.1 (d, *J* = 7.7 Hz), 96.9 (dd, *J* = 176.0, 169.1 Hz), 116.8, 123.5, 130.4, 138.9, 145.2, 158.3 (d, *J* = 25.4 Hz); R_t HPLC (9:1, hexane : *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R 12.9 min (major), t_R 17.0 (minor), ee 87%.

Diethyl 1-fluoro-1-methyl-2-oxo-pent-3-enylphosphonate (6p): $[\alpha]_D^{23}$ -81.12 (c = 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31-1.39 (m, 6H), 1.74 (dd, *J* = 24.0, 15.3 Hz, 3H), 1.96 (dd, *J* = 6.9, 1.5 Hz, 3H), 4.09-4.31 (m, 4H), 6.69-6.79 (m, 1H), 7.05-7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.6, 18.9, 19.9 (d, *J* = 21.5 Hz), 64.3, 64.4, 98.8 (dd, *J* = 190.8, 159.2 Hz), 125.0, 146.9, 194.5 (d, *J* = 22.0 Hz); R_t HPLC (99:1, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralpak AD column, t_R 30.7 min (major), t_R 32.2 (minor), ee 93%.

General procedure for the fluorination of β-ketoacetates 7. To a stirred solution of β-ketoacetate (**7**, 0.3 mmol), catalyst **3b** (16.2 mg, 0.015 mmol) in MeOH (3 mL) was added NFSI (**5a**, 94.6 mg, 0.3 mmol) at room temperature. Reaction mixture was stirred for 0.5-24 h at room temperature. The mixture was diluted with saturated NH_4Cl solution (20 mL) and extracted with ethyl ether (2 x 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-fluoro-β-ketoacetate **8**.

(*R*)-*tert*-Butyl 2-fluoro-2-oxoindane-2-carboxylate (8a): $[\alpha]_D^{23}$ +5.4 (c = 0.75, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.43 (s, 9H), 3.40 (dd, *J* = 22 Hz, *J* = 18 Hz, 1H), 3.73 (dd, *J* = 18 Hz, *J* = 12 Hz, 1H), 7.43-7.50 (m, 2H), 7.65-7.73 (m, 1H), 7.83 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.6, 38.2 (d, *J* = 23.8 Hz), 84.2, 95.5 (d, *J* =201 Hz), 125.7, 126.3, 128.8, 133.7, 136.7, 150.8 (d, *J* = 3.6 Hz), 166.2 (d, *J* = 27.0 Hz), 196.8 (d, *J* = 18.0 Hz); R_t HPLC (150:1, hexane : *i*-PrOH, 254 nm, 0.75 mL/min) Chiralpak AD-H column, t_R 13.0 min (minor), t_R 15.1 (major), ee 85%.

***tert*-Butyl 2-fluoro-1,2,3,4-tetrahydro-2-oxonaphtalene-2-carboxylate (8b):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.47-2.81 (m, 2H), 3.17-3.02 (m, 2H), 7.29-7.40 (m, 2H), 7.51-7.59 (m, 1H), 8.06-8.10 (m, 1H); R_t HPLC (95:5, hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD-H column, t_R 5.8 min (major), t_R 6.1 (minor), ee 82%.

***tert*-Butyl 1-fluoro-2-oxocyclopentanecarboxylate (8c):** $[\alpha]_D^{22}$ +69.5 (c = 0.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.07-2.14 (m, 2H), 2.18-2.33 (m, 1H), 2.40-2.59 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.0 (d, *J* = 4.0 Hz), 27.8, 33.6 (d, *J* = 20.5 Hz), 35.7, 84.0, 94.5 (d, *J* = 198.5 Hz), 166.0 (d, *J* = 28.1 Hz), 207.7 (d, *J* = 16.0 Hz), R_t HPLC (99:1, hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H column, t_R 11.9 min (major), t_R 17.9 (minor), ee 91%.

***tert*-Butyl 1-fluoro-2-oxocyclohexanecarboxylate (8d):** $[\alpha]_D^{21}$ -89.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.82-2.12 (m, 5H), 2.40-2.74 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1 (d, *J* = 6.5 Hz), 26.4, 27.7, 36.0 (d, *J* =21.2 Hz), 39.8, 83.8, 96.4 (d, *J* = 194 Hz), 165.7 (d, *J* = 23.7 Hz), 201.5 (d, *J* = 19.0 Hz); R_t HPLC (150:1, hexane : *i*-PrOH, 220 nm, 0.4 mL/min) Chiralpak AD-H column, t_R 21.9 min (major), ee 99%.

(*R*)-*tert*-Butyl 2-fluoro-2-methyl-3-oxo-3-phenylpropionate (8e): $[\alpha]_D^{23}$ +81.4 (c = 0.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.82 (d, *J* = 16 Hz, 3H), 7.43-7.48 (m, 2H), 7.55-7.59 (m, 1H), 8.02-8.06 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5 (d, *J* = 23.7 Hz), 27.5, 84.2, 96.5 (d, *J* = 192 Hz), 128.6, 129.4, 133.8, 167.8 (d, *J* = 25.1 Hz), 191.7 (d, *J* = 25.5 Hz); R_t HPLC (200:1, hexane : *i*-PrOH, 254 nm, 0.4 mL/min) Chiralpak AD-H column, t_R 14.5 min (minor), ee 99%.

***tert*-Butyl 2-fluoro-2-methyl-3-oxobutyrate (8f):** $[\alpha]_D^{22}$ -45.6 (c = 1.0, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.63 (d, *J* = 18 Hz, 3H), 2.30 (d, *J* = 4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7 (d, *J* = 23.0 Hz), 24.8, 27.6, 83.7, 97.6 (d, *J* = 192 Hz), 165.9 (d, *J* = 25.3 Hz), 202.7 (d, *J* = 28.2 Hz); GC (ASTEC CHIRALDEX™ G-TA, 0.25 mm I.D., x 30m, x 0.12μm, Temp. 70 °C Inj. Temp. 300 °C, Det. Temp. 300 °C) t_r 16.9 (major), t_r 20.3 (minor), ee 95%.

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