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Enantioselective fluorination of α-chloro-β-keto phosphonates in the presence of chiral palladium complexes

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ABSTRACT

The catalytic enantioselective electrophilic fluorination of α-chloro-β-keto phosphonates promoted by chiral palladium complexes has been developed, allowing facile synthesis of the corresponding α-chloro-α-fluoro-β-keto phosphonates with excellent enantioselectivity (up to 95% ee).

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Organofluorine compounds are of central importance in the pharmaceutical and agrochemical industries because the replacement of a hydrogen with a fluorine atom in biologically active molecules can be beneficial in terms of physicochemical properties and biological activities.[1] Chiral organofluorine compounds containing a fluorine atom bonded directly to a stereogenic center have been utilized in studies of enzyme mechanisms and as building block for bioactive compounds.[2] The application of chiral organofluorine compounds is restricted by the limited availability of effective synthetic methods for the enantioselective construction of fluorinated quaternary carbon centers. Thus, the development of asymmetric C–F bond formation process has become an important area in organic synthesis.[3] To date, there are a great number of reports on the asymmetric synthesis of organofluorine compounds containing a fluorine atom bonded directly to a stereogenic center.[4] Among the various procedures to produce the enantiopure organofluorine compounds, catalytic enantioseletive fluorinations provide one of the most efficient synthetic methods. Since the first catalytic enantioseletive fluorination reported by Togni and Hintermann in 2000,[5] a number of catalyst systems for the enantioselective electrophilic fluorination of active methane compounds have been reported.[6–9] Recently, several groups have reported catalytic enantioselective fluorination of active methine derivatives using chiral metal complexes such as Binap–Pd(II) and transition metal–bis(oxazoline) complexes and organocatalysts such as cinchonine-derived quaternary ammonium salt, imidazolidinone, and proline derivatives.[6–9]

The chiral *gem*-chlorofluoromethylene group would be synthetic intermediates in asymmetric synthesis for various chiral fluorinated compounds and as a chiral isostere of the difluoromethylene group in biologically active compounds. A few synthetic methods for the preparation of chiral α-chloro-α-fluoro-β-keto esters are reported.[10] Recently, Shibatomi et al. have reported the first catalytic enantioselective synthesis of α-chloro-α-fluoro-β-keto phosphonates using 10 mol % of Cu(II) complex of a chiral spiro oxazoline ligand.[11] There are still some drawbacks to the previously reported procedure, such as the high catalyst loading and anhydrous reaction conditions required for the high enantioselectivity. Accordingly, the development of alternative catalysts for the catalytic enantioselective electrophilic fluorination of α-chloro-β-keto phosphonates is highly desirable.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[12] we recently reported the catalytic enantioselective functionalization of active methines in the presence of chiral palladium(II) complexes.[13] In this Letter, we wish to report the catalytic enantioseletive electrophilic α-fluorination of α-chloro-β-keto phosphonates using air- and moisture-stable chiral palladium complexes **1** (Fig. 1)[14] under practical conditions at low catalyst loadings (as low as 0.5 mol %) with excellent enantiocontrol.

To determine suitable reaction conditions for the catalytic enantioselective fluorination of α-chloro-β-keto phosphonates, we initially investigated the reaction system with α-chloro-β-keto phosphonates **2** and *N*-fluorobenzenesulfonimide (**3**, NFSI) in the presence of 10 mol % of chiral palladium(II) catalyst in methanol at room temperature. We first examined the impact of the chiral diphosphine ligands in catalysts **1** (Table 1, entries 1–8). By screen-

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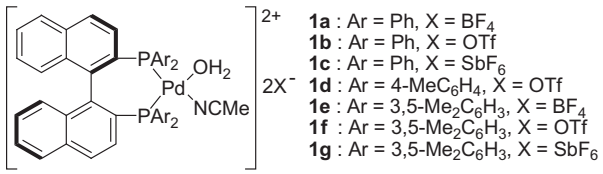
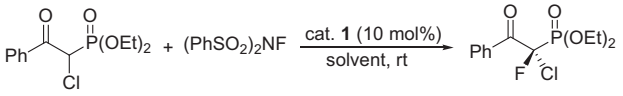


Figure 1. Structures of chiral palladium complexes **1**.

ing chiral palladium(II) complexes **1a–g**, we found that catalyst **1f** was the best catalyst for this enantioselective electrophilic fluorination, affording the corresponding product **4a** with 91% ee at room temperature (Table 1, entry 6). Concerning the solvent, the use of protic polar solvents such as MeOH and EtOH gave the best results (Table 1, entries 6 and 8), whereas the fluorination in *i*-PrOH, CF_3CH_2OH, THF, acetone, dichloromethane, toluene, trifluorotoluene, and hexafluorobenzene led to slightly lower enantioselectivities (entries 9–16). In the presence of 2,6-di-*t*-butyl-4-methyl pyridine as base, the reaction proceeded rapidly without significant change of enantioselectivity (entries 17–21). Bulky organic base such as 2,6-di-*t*-butyl-4-methyl pyridine (DTBMP) is appropriate to accelerate the reaction without coordination to metal complexes. The present catalytic system tolerates catalyst loading down to 5, 1, 0.5, or 0.1 mol % without compromising the enantioselectivity (Table 1, entries 17–20). The absolute configuration of **4** was established by comparison of the optical rotation and chiral HPLC analysis with previously reported values.[11]

Table 1
Optimization of reaction conditions[a]



2a **3** **4a**

Entry	Cat. **1**	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	MeOH	24	50	79
2	**1b**	MeOH	24	52	80
3	**1c**	MeOH	18	52	77
4	**1d**	MeOH	18	48	79
5	**1e**	MeOH	24	55	91
6	**1f**	MeOH	24	56	91
7	**1g**	MeOH	24	52	91
8	**1f**	EtOH	18	51	91
9	**1f**	*i*-PrOH	18	57	83
10	**1f**	CF_3CH_2OH	18	51	71
11	**1f**	THF	18	54	85
12	**1f**	Acetone	18	45	85
13	**1f**	DCM	18	40	75
14	**1f**	PhMe	18	47	81
15	**1f**	$PhCF_3$	18	41	87
16	**1f**	C_6F_6	18	32	79
17[d,e]	**1f**	MeOH	24	90	91
18[d,f]	**1f**	MeOH	24	81	91
19[d,g]	**1f**	MeOH	24	80	91
20[d,h]	**1f**	MeOH	24	62	91
21[d,i]	**1f**	MeOH	24	45	91

[a] Reaction conditions: Diethyl(1-chloro-2-oxo-2-phenylethyl)phosphonate (**2a**, 0.3 mmol), NFSI (**3**, 0.33 mmol), and catalyst **1** at room temperature.
[b] Isolated yield.
[c] Enantiopurity was determined by HPLC analysis using Chiralpak IC column.
[d] 2,6-Di-*tert*-butyl-4-methylpyridine (DTBMP, 2.0 equiv) was added as base.
[e] 5 mol % catalyst loading.
[f] 1 mol % catalyst loading.
[g] 0.5 mol % catalyst loading.
[h] 0.1 mol % catalyst loading.
[i] 0.05 mol % catalyst loading.

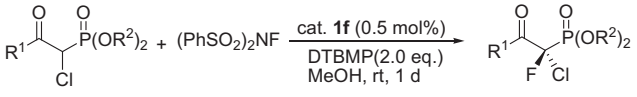
To examine the generality of the catalytic enantioselective fluorination of α-chloro-β-keto phosphonates **2** by using chiral palladium(II) complex **1f**, we studied the fluorination of α-chloro-β-keto phosphonates **2** with *N*-fluorobenzenesulfonimide (**3**, NFSI).[15] As seen from the results summarized in Table 2, the corresponding α-chloro-α-fluoro-β-keto phosphonates **4** were obtained in moderate to high yields with excellent enantioselectivities. The fluorination reaction of dimethyl α-chloro-β-keto phosphonate **2b** proceeded to afford the fluorinated product **4b** with high selectivity under the optimized reaction conditions (89% ee, Table 2, entry 2). A range of electron-donating and electron-withdrawing substitutions on the β-aryl ring of the α-chloro-β-keto phosphonates **2** provided reaction products in high yields and excellent enantioselectivities (83–95% ee, Table 2, entries 3–8). The heteroaryl-, naphthyl-, and alkyl-substituted α-chloro-β-keto phosphonates **2i–2k** provided the products **4i–4k** with high selectivity (85–95% ee, Table 2, entries 9–11).

The present method is operationally simple and efficient and, thus, may be valuable for practical chemical synthesis. As shown in Scheme 1, when α-chloro-β-keto phosphonates **2a** was treated with NFSI under the optimal reaction conditions, the reaction proceeded smoothly to afford the desired α-chloro-α-fluoro-β-keto phosphonates **4a** at the gram scale with 81% yield and 91% ee (Scheme 1).

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 α-chloro-β-keto phosphonates **2**, and DTBMP as Brønsted base abstracts an acidic α-proton of phosphonates, affording the complex **5**. Chiral Pd-coordinated nucleophile **5** reacts with NFSI to produce the fluorinated product **4** (Scheme 2).

In summary, we have accomplished the efficient catalytic enantioselective electrophilic α-fluorination of various α-chloro-β-keto phosphonates **2** with excellent enantioselectivity (up to 95% ee) with palladium complex **1f** as chiral catalyst. It should be noted that this fluorination reaction proceeds well using air- and moisture-stable chiral palladium complexes at low catalyst

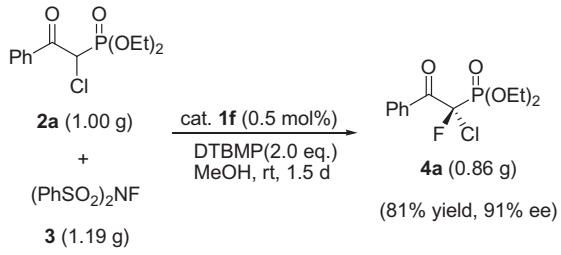
Table 2
Enantioselective fluorination of α-chloro-β-keto phosphonate **2**[a]



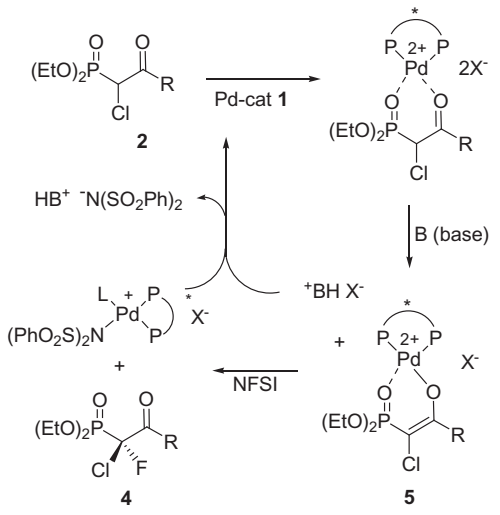
2 **3** **4**

Entry	**2**, R^1, R^2	Yield[b] (%)	ee[c] (%)
1	**2a**, Ph, Et	**4a**, 80	91
2	**2b**, Ph, Me	**4b**, 76	89
3	**2c**, 4-MeC_6H_4, Et	**4c**, 75	95
4	**2d**, 4-$MeOC_6H_4$, Et	**4d**, 79	91
5[d]	**2e**, 4-FC_6H_4, Et	**4e**, 88	93
6	**2f**, 4-ClC_6H_4, Et	**4f**, 64	91
7[e]	**2g**, 4-BrC_6H_4, Et	**4g**, 83	91
8[d]	**2h**, 4-$NO_2C_6H_4$, Et	**4h**, 78	83
9[e]	**2i**, 2-Thienyl, Et	**4i**, 40	85
10	**2j**, 2-Naphthyl, Et	**4j**, 85	95
11[f]	**2k**, *n*-Pentyl, Et	**4k**, 56	93

[a] Reaction conditions: α-Chloro-β-keto phosphonate **2** (0.3 mmol), DTBMP (0.6 mmol), NFSI (**3**, 0.33 mmol), catalyst **1f** (1.5 μmol), and MeOH (1.2 mL) at room temperature.
[b] Isolated yield.
[c] Enantiopurity was determined by HPLC analysis using Chiralpak IC (for **4a–4b**, **4d–4h,** and **4k**) and AD-H (for **4c** and **4i–4j**) columns.
[d] This reaction was conducted using 3 mol % catalyst.
[e] This reaction was conducted using 1 mol % catalyst for 4 d.
[f] This reaction was conducted using 3 mol % catalyst for 3 d.



Scheme 1. Gram scale enantioselective fluorination of diethyl (1-chloro-2-oxo-2-phenylethyl)phosphonate (**2a**) with NFSI (**3**).



Scheme 2. Assumed catalytic cycle.

loadings (as low as 0.5 mol %). Current efforts are toward developing synthetic applications of this α-fluorination reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.054.

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15. *Typical procedure for the fluorination of diethyl(1-chloro-2-oxo-2-phenylethyl)phosphonate (**2a**) with NFSI (**3**)*: To a stirred solution of diethyl(1-chloro-2-oxo-2-phenylethyl)phosphonate (**2a**, 87.2 mg, 0.3 mmol) and catalyst **1f** (1.8 mg, 1.5 μmol) in MeOH (1.2 mL) were added 2,6-di-*tert*-butyl-4-methylpyridine (123.2 mg, 0.6 mmol) and NFSI (**3**, 104.1 mg, 0.33 mmol) at room temperature. The reaction mixture was stirred for 1 day at room temperature. After completion of the reaction, the resulting solution was concentrated in vacuo and the obtained residue was purified by flash column chromatography (EtOAc/hex, 1:3) to afford (*S*)-diethyl(1-chloro-1-fluoro-2-oxo-2-phenylethyl)phosphonate (**4a**, 80% yield, 74.1 mg).

*(S)-Diethyl(1-chloro-1-fluoro-2-oxo-2-phenylethyl)phosphonate (**4a**)*: $[\alpha]_D^{27}$ −5.9 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.16–8.14 (m, 2H), 7.66–7.61 (m, 1H), 7.52–7.48 (m, 2H), 4.48–4.27 (m, 4H), 1.41 (td, *J* = 7.2, 0.8 Hz, 3H), 1.38 (td, *J* = 7.2, 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6 dd, *J* = 25.0, 7.0 Hz), 134.5, 131.8 (dd, *J* = 7.0, 3.0 Hz), 130.5 (d, *J* = 5.0 Hz), 128.6, 103.2 (dd, *J* = 272.0, 185.0 Hz), 65.8 (d, *J* = 6.0 Hz), 65.6 (d, *J* = 6.0 Hz), 16.4 (d, *J* = 6.0 Hz), 16.3 (d, *J* = 5.0 Hz); the enantiomeric ratio was determined by HPLC (*n*-hexane/*i*-PrOH = 83:17, 254 nm, 1.0 mL/min) using a Chiralpak IC column: t_R = 16.2 min (major), t_R = 12.6 min (minor), 91% ee.