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An efficient catalytic enantioselective fluorination of β-ketophosphonates using chiral palladium complexes

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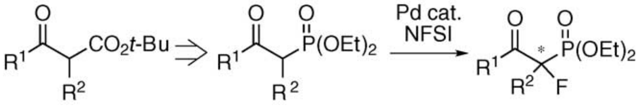
Abstract—On the basis of our Pd enolate chemistry, we have succeeded in developing an efficient catalytic enantioselective fluorination of β-ketophosphonates. In the presence of chiral Pd complexes **1** (1–10 mol %), various substrates including cyclic and acyclic β-ketophosphonates underwent the reaction with *N*-fluorobenzenesulfonimide (NFSI) in EtOH to give the corresponding fluorinated products in a highly enantioselective manner (94–98% ee).

Fluorinated organic molecules play important roles in the field of medicinal chemistry because replacement of hydrogen(s) or hydroxyl group(s) with fluorine atom(s) sometimes improves the biological activity profile of the parent compounds.[1] For this reason, development of efficient methods for the synthesis of chiral fluorinated compounds has received considerable attention.[2] Many excellent procedures have been developed on the basis of well-documented asymmetric reactions such as hydrogenation of olefins, reduction of ketones, aldol reaction, and ene reaction.[3] However, enantioselective construction of fluorinated stereogenic carbon centers via introduction of fluorine atoms is still a formidable challenge in synthetic organic chemistry.[4–6]

Recently we reported a highly efficient catalytic enantioselective fluorination of β-ketoesters (Scheme 1).[7] In the presence of a catalytic amount of chiral Pd complexes **1** and **2**, a variety of β-ketoesters reacted with *N*-fluorobenzenesulfonimide (NFSI) in an alcoholic solvent such as EtOH to afford the corresponding fluorinated products with excellent enantioselectivity (up to 94% ee). In this reaction, formation of configurationally stable chiral palladium enolates (**A**) was the key to success.[8]

We envisaged that other bidentate carbonyl compounds would react with Pd complexes to form a similar chiral palladium enolate. Among several candidates, we focused on β-ketophosphonates, because difluoro- and monofluorophosphonates have been intensively investigated in drug design as mimics of phosphates.[9,10] Compared to nonfluorinated phosphonates and difluorophosphonates, α-monofluorophosphonates are expected to be a better surrogate of phosphates, because they show similar 2nd pK_a values (∼6.5) to those of biological phosphates (∼6.5). Although several non-enantioselective or diastereoselective syntheses of α-monofluorophosphonates have been reported,[10e,11] there has been, to our knowledge, no example of the catalytic enantioselective synthesis of chiral α-fluoro-β-ketophosphonates. As a part of our continuing research project on the direct catalytic enantioselective fluorination of carbonyl compounds, we herein describe a highly enantioselective electrophilic fluorination of various β-ketophosphonates[12] using chiral palladium complexes developed in our laboratory (Eq. 1).



(1)

Keywords: Pd complex; Fluorination; β-Ketophosphonate; Asymmetric catalysis.

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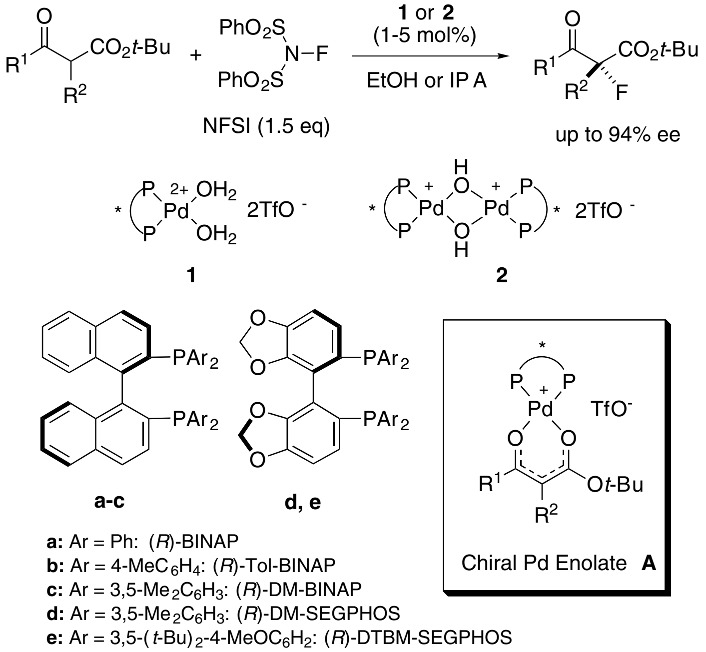
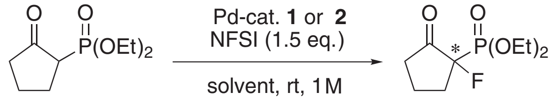


Scheme 1. Catalytic enantioselective electrophilic fluorination developed by our group.

At the outset, we chose the β-ketophosphonate **3a** as a model substrate (Table 1). Because alcoholic solvents were the best in the case of β-ketoesters, the reaction of **3a** with NFSI was first carried out in EtOH using a catalytic amount of the Pd complex **1a** (5 mol %). The reaction was completed after 5 h to give the desired fluorinated product **4a** in 81% isolated yield (entry 1). Encouragingly, the ee of the product was determined to be 75% by chiral HPLC analysis. The catalyst **1b** consisting of (*R*)-Tol-BINAP gave similar results to those obtained with **1a** (82%, 79% ee). As in the case of the reactions of β-ketoesters, the substituents at the meta positions of the aryl groups of BINAP derivatives were found to be important for high asymmetric induction. To our delight, by using the Pd complex **1c** consisting of (*R*)-DM-BINAP, enantioselectivity was greatly improved and the corresponding product was obtained in 91% yield with 95% ee (entry 3). Similar selectivity was also observed when **1d** was used as a catalyst (entry 4). When a bulkier ligand such as DTBM-SEGPHOS was used, a higher enantioselectivity of 98% was achieved (entry 5), but the chemical yield was not satisfactory, probably due to the severe steric repulsion. For comparison, other solvents were examined (entries 6–9). Acetone and THF afforded **4a** with high enantio-selectivities, but the chemical yields were reduced. In DMF and CH_2Cl_2, the reaction was retarded considerably, although high enantioselectivity was still maintained. Because our previous results showed that the selectivity of Pd(μ-OH) complexes **2** sometimes depends on the nature of the substrates, we examined the same reaction using **2c** (entry 10). In this fluorination of β-ketophosphonates, the Pd(μ-OH) complex gave results comparable to those obtained in the case of **1c**. Thus, we decided to choose **1c** as a suitable catalyst and EtOH as a solvent for further experiments.

Table 1. Optimization of the reaction conditions



3a **4a**

Entry	Catalyst (mol %)[a]	Solvent	Time (h)	Yield (%)	Ee[b] (%)
1	**1a** (5)	EtOH	5	81	75
2	**1b** (5)	EtOH	5	82	79
3	**1c** (5)	EtOH	2	91	95
4	**1d** (5)	EtOH	2	87	95
5	**1e** (5)	EtOH	5	46	98
6	**1c** (5)	Acetone	3	70	93
7	**1c** (5)	THF	3	66	92
8	**1c** (5)	DMF	6	20	90
9	**1c** (5)	CH_2Cl_2	6	43	92
10	**2c** (2.5)	EtOH	2	91	95

[a] Catalyst amount.

[b] Determined by HPLC analysis.

A representative experimental procedure is as follows: To a stirred solution of the Pd complex **1c** (11.8 mg, 0.01 mmol) in EtOH (0.2 mL), **3a** (44 mg, 0.2 mmol), and NFSI (94.8 mg, 0.3 mmol) were added successively at ambient temperature. The reaction was monitored by TLC (hexane/ethyl acetate = 1/1). After completion of the reaction, saturated aqueous NH_4Cl was added for quenching. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the obtained crude products were purified by flash column chromatography (hexane/ethyl acetate = 1/1) to afford **4a** as a colorless oil in 91% yield (43.4 mg). The ee of the product was determined to be 95% by chiral HPLC analysis [column: DICEL

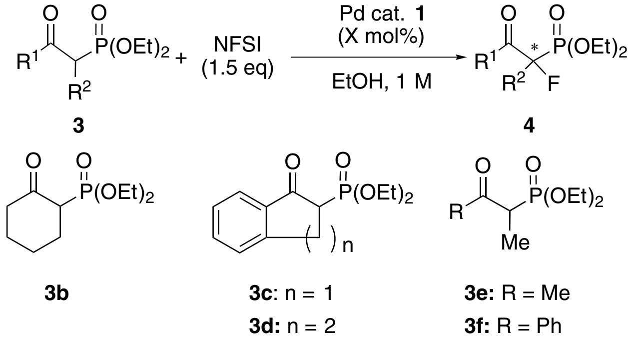
CHIRALPAK AD-H, eluent: hexane/2-propanol = 95/5, wavelength (detector): 280 nm, retention times: t_r = 10.6 min (major), t_r = 11.7 min (minor)].

With these results in hands, we next investigated the substrate scope of this reaction. As summarized in Table 2, the reactions of various β-ketophosphonates proceeded in a highly enantioselective manner.[13] A six-membered substrate **3b** reacted similarly to give **4b** in 93% yield with 96% ee (entry 1). The reactions of other cyclic substrates, an indanone derivative **3c** and a tetralone derivative **3d**, were completed within only 3 h, and excellent enantioselectivities were observed (95% and 94% ee, respectively) (entries 2 and 3). In addition, the amount of the catalyst could be reduced to as little as 1 mol %, and the reaction of **3a** proceeded without any loss of enantioselectivity, although a prolonged reaction time was required for the completion of the reaction (82%, 95% ee after 12 h) (entry 4). In contrast to cyclic β-ketophosphonates, the reaction of acyclic substrates was found to be slow (entries 5 and 6). The starting materials **3e** and **3f** were not consumed at 40 °C even after 48 h. Although the chemical yield was modest to good, the ees of the products **4e** and **4f** were found to be excellent (94% and 95% ee, respectively). For these reactions, **1d** gave a slightly better selectivity than **1c**. Importantly, these reactions were not sensitive to either air or moisture and could be conducted without any particular precautions.

In order to gain insight into the reaction mechanism, preliminary NMR experiments were carried out. Since clean formation of the Pd enolate **A** was observed for the β-ketoesters in the reaction with **2b** in THF-d_8, similar conditions were selected for this purpose. When **3a** was treated with **2b** (0.5 equiv to **3a**) in THF-d_8, the reaction reached equilibrium after 3 h at ambient temperature. In the equilibrium mixture, approximately 50% of the starting material **3a** was consumed. ^{1}H NMR of the newly formed complex showed a similar pattern to that of the Pd enolate of β-ketoesters.[8] Thus, the anisotropic effect of the neighboring tolyl group caused a typical high field shift of the ethyl groups of **3a**, as observed for the *t*-Bu group of the Pd enolate **A**.[14] In addition, the characteristic two singlets of **2b**, which correspond to the methyl groups of the tolyl groups, changed to three peaks, indicating that the newly formed complex was no longer symmetrical.[14] In view of the possible bidentate nature and sufficient acidity of the β-ketophosphonates, it is likely that the Pd enolate was also formed in this reaction. Upon the addition of NFSI (1 equiv to the Pd enolate), rapid formation of **4a** was observed and the ee of the product was found to be 84%. These results strongly indicate that the Pd enolate was an important intermediate in this fluorination reaction. Although further experiments to clarify the reaction mechanism should be carried out, the catalytic cycle shown in Scheme 2 is plausible.

In summary, we have developed a highly efficient catalytic enantioselective fluorination of β-ketophosphonates. Using the chiral Pd complexes, the desired fluorinated products were obtained in good to high yields, and excellent enantioselectivities (up to 98% ee) were observed for all the substrates examined in this report. It should be noted that this reaction proceeds well in environmentally friendly alcoholic solvents such as EtOH. We believe that this report provides a new method for the preparation of chiral α-fluorinated phosphonates, and the availability of these compounds should facilitate medicinal chemical studies in various fields. Further extension of this reaction and mechanistic studies including determination of the absolute configuration of the products are now in progress in our laboratory.

Table 2. Catalytic enantioselective fluorination of β-ketophosphonates

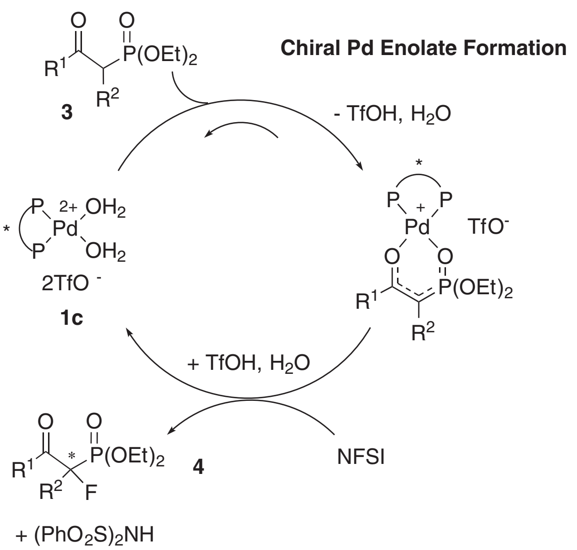


Entry	3	4	1	X	Temp (°C)	Time (h)	Yield (%)[a]	Ee[b] (%)
1	**3b**	**4b**	**1c**	5	rt	8	93	96
2	**3c**	**4c**	**1c**	5	rt	3	84	95
3	**3d**	**4d**	**1c**	5	rt	3	97	94
4	**3a**	**4a**	**1c**	1	rt	12	82	95
5	**3e**	**4e**	**1d**	10	40	48	57	94[c]
6	**3f**	**4f**	**1d**	10	40	48	38	95

[a] Isolated yield.

[b] Determined by HPLC analysis.

[c] The ee was determined after conversion to the corresponding 2,4-dinitrophenylhydrazone.



Scheme 2. Proposed catalytic cycle.

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13. All compounds were characterized by spectroscopic analysis. Spectral data of **4a** are as follows: colorless oil; IR (neat) ν 1756, 1259, 1047, 1022 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.36 (t, $J = 7.1$ Hz, 3H), 1.39 (t, $J = 7.1$ Hz, 3H), 2.03–2.56 (m, 5H), 2.68–2.81 (m, 1H), 4.19–4.30 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 16.2 (d, $J = 5.7$ Hz), 16.3 (d, $J = 5.7$ Hz), 16.8 (dd, $J = 4.2, 5.8$ Hz), 32.0 (dd, $J = 2.5, 18.1$ Hz), 35.4 (d, $J = 2.5$ Hz), 64.0 (d, $J = 6.2$ Hz), 64.1 (d, $J = 6.2$ Hz), 96.2 (dd, $J = 160.0, 200.8$ Hz), 209.0 (dd, $J = 3.3, 13.2$ Hz); ^{19}F NMR (376 MHz, CDCl$_3$, external std.: CF$_3$COOH) δ −98.1 (ddd, $J = 11.7, 25.2, 85.0$ Hz); FAB-LRMS (*m*NBA) *m/z* 239 [M+1]$^+$; $[\alpha]_D^{28}$ +130.2 (*c* 0.75, CHCl$_3$) (95% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 95/5, 1.0 mL/min, 280 nm, $t_{\mathrm{r\,major}}$ 10.6 min, $t_{\mathrm{r\,minor}}$ 11.7 min).
14. Characteristic peaks (ppm) are as follows. For ethyl ester moiety, **3a**: 1.37 (t, $J = 7.0$ Hz, 6H, CH$_3$), 4.11–4.21 (m, 4H, CH$_2$); Pd enolate complex: 1.11 (t, $J = 7.1$ Hz, 3H, CH$_3$), 1.23 (t, $J = 7.1$ Hz, 3H, CH$_3$), 3.38–3.47 (m, 1H, CH$_2$), 3.56–3.64 (m, 1H, CH$_2$), 3.96–4.05 (m, 2H, CH$_2$). For methyl groups of the tolyl group, **2b**: 1.9 (s, 6H), 2.1 (s, 6H); Pd enolate complex: 2.03 (s, 6H), 2.50 (s, 3H), 2.53 (s, 3H). Details of these experiments will be described elsewhere.