Asymmetric Electrophilic Fluorination of β-Keto Phosphonates in Ionic Liquid Media Catalyzed by Chiral Palladium Complexes

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The chemistry of bioactive organofluorine compounds is a rapidly developing area of research because of their importance in biochemical and medicinal application.[1] 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.[2] The development of effective methodologies for the preparation of new selectively fluorinated, stereochemically defined compounds is critical to further advances of fluorine chemistry.[3] The catalytic enantioselective construction of fluorinated stereogenic centers is still important challenge in modern organic chemistry.[4]

α-Fluoroalkylphosphonates are better mimics of natural phosphates with matched 2nd p*K*a vaules (~6.5).[5] The enantioselective construction of α-fluoroalkylphosphonates is extremely important because the stereochemistry of α-carbon does affect enzyme binding.[6] Although there have been several reports for the asymmetric synthesis of α-fluoroalkylphosphonates,[7] synthetic methods of chiral α-fluoro β-keto phosphonates are limited.[8]

The employment of ionic liquids as solvents for chemical reactions has been received increased attention because they have essentially no vapor pressure and provide high solubility for a wide range for organic and organometallic compounds.[9] These solvents are reusable, enhance the reactivity of chemical transformations, simplify product isolation and allow for catalysts recycling.[10]

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[4b,11] we report the catalytic enantioselective fluorination of β-keto phosphonate excellent enantioselectivity (87-97% ee) promoted by a chiral palladium complexes.[8a] In this letter, we wish to report the catalytic enantioseletive electrophilic fluorination of β-keto phosphonates using chiral palladium complexes **1** in ionic liquid media.

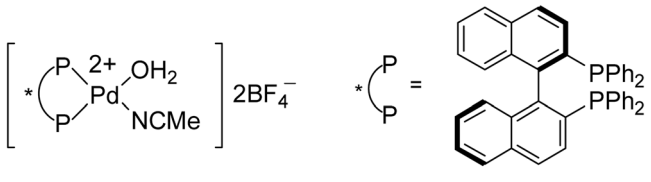

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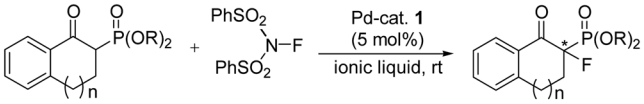
Table 1. Catalytic enantioselective fluorination of β-keto phosphonates in ionic liquid



2a : n = 1, R = Et
2b : n = 1, R = Me
2c : n = 1, R = *i*-Pr
2d : n = 0, R = Et

NFSI

3a-3d

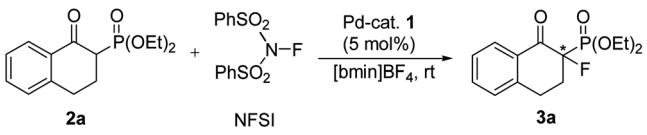
entry	phosphonate	Ionic liquid	time (h)	yield (%)	ee[a] (%)
1	**2a**	[emim]BF_4	13	0	–
2	**2a**	[bmim]BF_4	10	95	93
3	**2a**	[bmim]OTf	13	91	91
4	**2a**	[bmim]SbF_6	13	0	–
5	**2a**	[bmim]PF_6	13	65	83
6	**2b**	[bmim]BF_4	8	88	93
7	**2c**	[bmim]BF_4	20	89	91
8	**2d**	[bmim]BF_4	4	91	90

[a]Enantiomeric excess determined by chiral HPLC using Chiralpak AD column.

We first examined electrophilic fluorination of β-keto phosphonate **2a** with NFSI in the presence of 5 mol% of **1** using [bmim]BF_4 at room temperature (Table 1, entry 2). After stirring for 10 h at room temperature, the reaction was quenched by extraction with ether (5 × 5 mL). The combined organic layers concentrated and the crude product purified by silica-gel chromatography to afford α-fluoro β-keto phosphonate **3a** in 95% yield and 93% ee. Concerning the ionic liquids, the use of [bmim]BF_4 and [bmim]OTf gave the best results, whereas the fluorination in [bmim]PF_6, [bmim]SbF_6 and [emim]BF_4 led to lower yields and enantioselectivities or no reaction. The chemical yield and enantioselectivity were almost similar as those obtained in MeOH (8 h, 93% yield, 97% ee), a longer reaction time was necessary for the completion of the reaction.[8a] The reaction of phosphonates **2b-2d** afforded the corresponding fluorinated phosphonates **3b-3d** in 88-91% yield and 90-93% ee.

We also tested recycling of the catalyst (Table 2). The reaction was performed seven times without affecting the yield and selectivity. The pale pink color [bmim]BF_4 layer and colorless ether layer indicated that chiral palladium catalyst was retained in ionic liquid layer. In the 2nd

Table 2. Catalyst recycling studies



2a NFSI **3a**

cycle	time (h)	yield (%)	ee[a] (%)	cycle	time (h)	yield (%)	ee[a] (%)
1	10	95	93	5	16	91	91
2	10	92	93	6	16	90	91
3	12	93	93	7	16	88	91
4	13	90	93				

[a]Enantiopurity of **3a** was determined by HPLC analysis with Chiralpak AD columns.

recycling experiment, the desired product was obtained 92% yield and 93% ee. Further, the catalyst recycled up to seven times, maintaining the excellent yield and enantioselectivity. The complete reproducibility in this fluorination is a proof for the negligible leaching of the palladium catalyst.

In summary, we have accomplished the highly efficient catalytic enantioselective fluorination of β-keto phosphonates with excellent yield and enantioselectivity in ionic liquid, which simplify product isolation and catalyst recycling.

Experimental Sections

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 precoated 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 NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz for ^{1}H, 50 MHz for ^{13}C). Chemical shift values (δ) are reported in ppm relative to Me_4Si (δ 0.0 ppm). The proton spectra are reported as follows d (multiplicity, coupling constant J, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). 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, and AS columns. The Pd content was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) using Shimadzu ICPS-7500.

General procedure for the fluorination of β-keto phosphonates: To a stirred solution of β-keto phosphonate **2** (0.3 mmol) and catalyst **1** (14.4 mg, 0.015 mmol) in [bmim]BF_4 (0.5 mL) was added NFSI (141.9 mg, 0.45 mmol) at room temperature. Reaction mixture was stirred for 4-20 h at room temperature. Diethyl ether (5 mL × 4) was added for extraction. Ether was decanted with syringe and the combined ether layers were concentrated, and purified by flash chromatography to afford the α-fluoro β-keto phosphonate **3**. The separated [bmim]BF_4 layer containing catalyst **1** was reused in the next cycle.

2-(Diethoxyphosphinyl)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene (3a); R_f 0.47 (EtOAc : CH_2Cl_2 = 1 : 4); $[\alpha]_D^{23}$ = +44.7 (c = 1.0, $CHCl_3$, 93% ee); ^{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); R_t HPLC (9 : 1, *n*-hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AD column, t_R = 6.6 min (major), t_R = 8.5 (minor).

2-(Dimethoxyphosphinyl)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene (3b); R_f 0.51 (EtOAc : CH_2Cl_2 = 1 : 3); $[\alpha]_D^{23}$ = +51.36 (c = 1.0, $CHCl_3$, 93% ee); ^{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); R_t HPLC (9 : 1, *n*-hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AD column, t_R = 8.6 min (major), t_R = 10.2 (minor).

2-(Diisopropoxyphosphinyl)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene (3c); R_f 0.51 (EtOAc : CH_2Cl_2 = 1 : 3); $[\alpha]_D^{23}$ = +29.0 (c = 1.0, $CHCl_3$, 91% ee); ^{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); R_t HPLC (9 : 1, *n*-hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AD column, t_R = 5.4 min (major), t_R = 7.2 (minor).

2-(Diethoxyphosphinyl)-2-fluoroindanone (3d); R_f 0.51 (EtOAc : CH_2Cl_2 = 1 : 3); $[\alpha]_D^{23}$ = +61.3 (c = 1.0, $CHCl_3$, 90% ee); ^{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, *n*-hexane : *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD column, t_R = 9.1 min (major), t_R

= 10.6 (minor).

The analysis of the amount of Pd(II) by ICP-AES. The palladium amount in the ether layers was check by ICP-AES and showed 0.6% leaching from the ionic liquid to the organic layers during 1st run.

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