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

Sung Min Kim, Hye Ran Kim, and Dae Young Kim*

Department of Chemistry, Division of Applied Science, Soonchunhyang University, 644 Eupnae-ri, Shinchang, Asan, Chungnam 336-745, Korea

dyoung@sch.ac.kr

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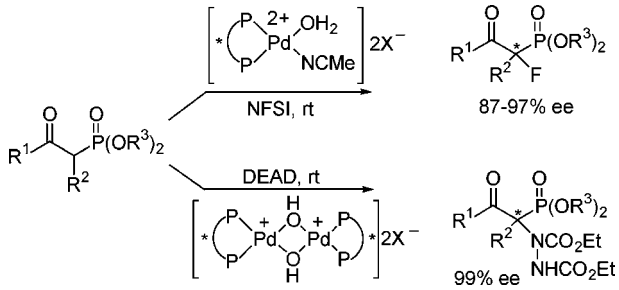
ABSTRACT



The catalytic enantioselective fluorination and amination of β-keto phosphonates catalyzed by chiral palladium complexes is described. Treatment of β-keto phosphonates with *N*-fluorobenzenesulfonimide (NFSI) as electrophilic fluorinating reagent and diethyl azodicarboxylate (DEAD) as electrophilic amination reagent under mild reaction conditions afforded the corresponding α-substituted β-keto phosphonates in moderate to excellent yields with excellent enantiomeric excesses.

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.[1] The development of effective methodologies for the preparation of new selectively fluorinated, stereochemically defined compounds is critical to further advances of fluorine chemistry.[2] Until now, a number of enantioselective fluorination of β-keto esters have been achieved by reagent-controlled and catalytic enantioselective fluorination.[2e] Recently, the efficient example of a catalytic enantioselective fluorination of β-keto esters was reported by Sodeoka et al.[3a] They examined the reaction of several substrates with a chiral palladium complex and reported excellent enantioselection (83−94% ee). Although there have been several reports for the asymmetric synthesis of α-fluoro β-keto esters,[2e] synthetic methods toward chiral α-fluoroalkylphosphonates are limited.[4] α-Fluoroalkylphosphonates are better mimics of natural phosphates[5] with matched second

(1) (a) Ramachandran, P. V., Ed. *Asymmetric Fluoroorganic Chemistry: Synthesis, Application, and Future Directions*; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000. (b) *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1999.

(2) For reviews, see: (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. (c) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1−16. (d) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147−1155. (e) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119−6149. (f) France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475−479. The first catalytic enantioselective fluorination of β-keto esters was reported by Togni; see: (g) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359−4362.

(3) (a) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530−14531. (b) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, *6*, 1861−1864. (c) Fujii, A,; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450−5458.

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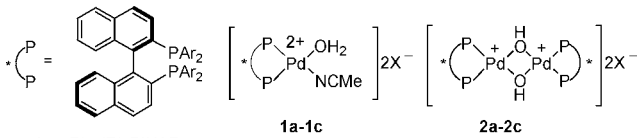
pK_a values.[6] Recently, reported enzyme kinetic data on the α-fluoroalkylphosphonates suggest that the stereochemistry of the α-carbon does affect enzyme binding.[7]

α-Amino phosphonic acids and their derivatives are important compounds as surrogates and analogues of α-amino acids.[8] Thus, the enantioselective synthesis of α-amino phosphonates has received considerable attention, and numerous methods using stoichiometric amounts of chiral auxiliaries were reported.[9] However, there are few catalytic enantioselective methods available to access this class of compounds.[10] As part of a research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[11] we have recently reported the catalytic enantioselective fluorination of α-cyano acetates promoted by chiral palladium complexes.[11a] In this paper, we wish to report the catalytic enantioselective electrophilic fluorination and amination of β-keto phosphonates using palladium complexes **1**[12] and **2**.[3]



1a-1c 2a-2c

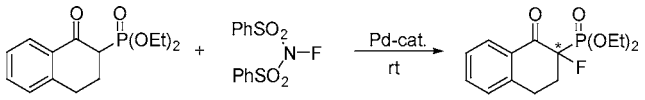
a: Ar = Ph: (R)-BINAP
b: A = 4-methylphenyl: (R)-Tol-BINAP
c: Ar = 3,5-dimethylphenyl: (R)-Xylyl-BINAP

To determine suitable reaction conditions for the catalytic enantioselective fluorination of β-keto phosphonates, we first examined electrophilic fluorination of β-keto phosphonate **3a** with *N*-fluorobenzenesulfonimide (NFSI) in the presence of 5 mol % of **1a** in EtOH at room temperature (Table 1).[13] Catalyst **1a** (X = BF_4, SbF_6) was more effective than the other catalyst **1a** (X = OTf, PF_6) (entries 1−4). Concerning the solvent, the use of alcoholic solvents, acetone, and THF gave the best results, whereas the fluorination in DMF, CH_2Cl_2, PhMe, and CH_3CN led to lower yields and enantioselectivities (entries 3 and 5−11).

Lowering the temperature to −20 °C with catalyst **1a** (X = SbF_6) decreased the yields and enantioselectivities (entry 12). NFSI was a more effective fluorinating agent than Selectfluor in this reaction under the same conditions (entries 5 and 13). To improve the enantioselectivity, we examined a series of chiral diphosphine ligands. The substitutions at the meta positions of the aryl group on phosphine were found to be important. When (*R*)-Xylyl-BINAP (**1c**, X = BF_4) was used, the enantioselectivity was improved to 97% ee (entry 16). Decreasing the catalyst loading to 1.0 and 0.1 mol % showed a significant decrease in yields and slightly decreased the enantioselectivities (entries 16, 20, and 21).

To examine the generality of the catalytic enantioselective fluorination of β-keto phosphonates **3** by using chiral palladium complex **1c** (X = BF_4), we studied the fluorination of cyclic and acyclic β-keto phosphonate derivatives **3b**−**p**.

Table 1. Optimization of the Reaction Conditions



3a NFSI **4a**

entry	catalyst (X)	solvent	time (h)	yield (%)	ee[a] (%)
1	**1a** (OTf)	EtOH	20	46	73
2	**1a** (BF_4)	EtOH	8	77	89
3	**1a** (SbF_6)	EtOH	10	87	89
4	**1a** (PF_6)	EtOH	10	24	69
5	**1a** (SbF_6)	MeOH	6	96	89
6	**1a** (SbF_6)	acetone	13	86	89
7	**1a** (SbF_6)	THF	13	92	87
8	**1a** (SbF_6)	DMF	13	21	45
9	**1a** (SbF_6)	CH_2Cl_2	15	34	75
10	**1a** (SbF_6)	PhMe	15	36	81
11	**1a** (SbF_6)	MeCN	20	29	45
12[b]	**1a** (SbF_6)	MeOH	6	37	75
13[c]	**1a** (SbF_6)	MeOH	22	47	43
14	**1b** (BF_4)	MeOH	8	96	91
15	**1b** (SbF_6)	MeOH	9	96	91
16	**1c** (BF_4)	MeOH	8	93	97
17	**1c** (SbF_6)	MeOH	9	95	95
18[d]	**2b** (PF_6)	MeOH	11	64	89
19[d]	**2c** (PF_6)	MeOH	11	59	95
20[e]	**1c** (BF_4)	MeOH	10	64	96
21[f]	**1c** (BF_4)	MeOH	33	36	93

[a] Enantiomeric excess determined by chiral HPLC using a Chiralpak AD column. [b] Reaction carried out at −20 °C. [c] Reaction carried out using Selectfluor as fluorinating reagent. [d] Reaction carried out using 2.5 mol % of catalyst. [e] Reaction carried out using 1.0 mol % of catalyst. [f] 0.1 mol % of catalyst.

(4) (a) Glover, N. R.; Tracey, A. S.; *Biochemistry* **1999**, *38*, 5256−5271. (b) Yokomatsu, T.; Yamagishi, T.; Matsumoto, K.; Shibuya, S. *Tetrahedron* **1996**, *52*, 11725−11738. For a synthesis of achiral α-fluoro β-keto phosphonates, see: Kim, D. Y.; Choi, Y. J. *Synth. Commun.* **1998**, *28*, 1491−1498.

(5) (a) Blackburn, G. M. *Chem. Ind. (London)* **1981**, 134−138. (b) McKenna, C. E.; Shen, P. *J. Org. Chem.* **1981**, *46*, 4573−4576.

(6) (a) Nieschalk, J.; O'Hagan, D. *Chem. Commun.* **1995**, 719−720. (b) Jakeman, D. L.; Ivory, A. J.; Willamson, M. P.; Blackburn, G. M. *J. Med. Chem.* **1998**, *41*, 4439−4452.

(7) (a) Berkowitz, D. B.; Bose, M. *J. Fluorine Chem.* **2001**, *112*, 13−33. (b) Berkowitz, D. B.; Bose, M.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498−4508.

(8) (a) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Silicon* **1991**, *63*, 193-215. (b) Seto, H.; Kuzuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589−596. (c) Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids—Chemistry and Biological Activity*; John Wiley and Sons: Chichester, 2000.

(9) For reviews, see: (a) Dhawan, B.; Redmore, D. *Phosphorous Sulfur* **1987**, *32*, 119−144. (b) Kukhar, V. P.; Soloshonok, V. A.; Solodenko, V. A. *Phosphorous Sulfur Silicon* **1994**, *92*, 239−264. (c) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279−1332.

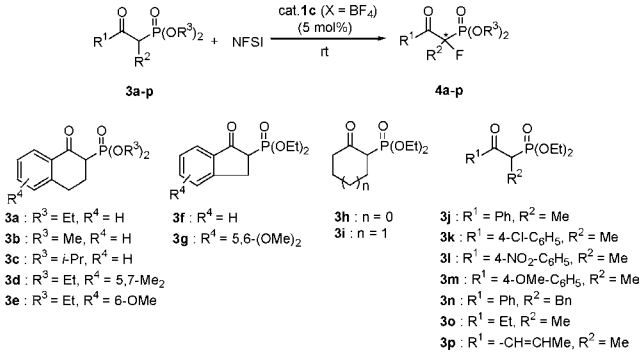
(10) (a) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102−4103. (b) Kobayashi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. *J. Am. Chem. Soc.* **2004**, *126*, 6558−6559. (c) For a review, see: Gröger. H.; Hammer. B. *Chem. Eur. J.* **2000**, *6*, 943−948.

(11) (a) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115−3117. (b) Kim, D. Y.; Park E. J. *Org. Lett.* **2002**, *4*, 545−547. (c) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897−6899.

(12) (a) Li, K.; Hii, K. K. *Chem. Commun.* **2003**, 1132−1133. (b) Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Organomet. Chem.* **2003**, *665*, 250−257. For an aquapalladium complex, see: (c) Shimada, T.; Bajracharya, G. B. Yamamoto, Y. *Eur. J. Org. Chem.* **2005**, 59−62 and references therein.

(13) Prior to submission of this manuscript, chiral Pd complex and Zn(II)-bis(oxazoline) catalyzed fluorinations were reported: (a) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447−1450. (b) Bernardi, L.; Jorgensen, K. A. *Chem. Commun.* **2005**, 1324−1325.

Table 2. Catalytic Enantioselective Fluorination of β-Keto Phosphonates



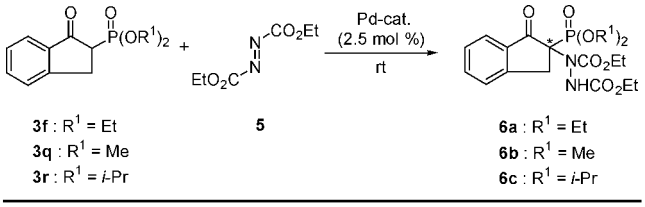
entry	β-keto phosphonate	solvent	time (h)	yield (%)	ee[a] (%)
1	**3a**	MeOH	8	93	97
2	**3b**	MeOH	6	89	93
3	**3c**	MeOH	23	91	95
4	**3d**	MeOH	12	84	95
5	**3e**	MeOH	10	92	95
6	**3f**	MeOH	3	91	97
7	**3g**	MeOH	11	86	95
8	**3h**	MeOH	45	67	95
9	**3i**	MeOH	86	73	95
10	**3j**	THF	94	62	91
11	**3k**	THF	94	68	91
12	**3l**	THF	90	78	87
13	**3m**	THF	78	61	91
14	**3n**	THF	86	50	91
15	**3o**	THF	90	65	87
16	**3p**	THF	58	79	93

[a] Enantiopurity of **4** was determined by HPLC analysis with Chiralcel OD-H (for **4i**), OJ (for **4m**), and Chiralpak AD columns.

As can be seen by the results summarized in Table 2, the corresponding α-fluoro β-keto phosphonates **4** were obtained in moderate to excellent yields and excellent enantioselectivities (87−97% ee). Acyclic β-keto phosphonates **3j**−**p** were successfully employed, and the desired fluorinated products were obtained in moderate to excellent yields and excellent enantioselectivities in THF.

We examined the catalytic enantioselective electrophilic amination[14] of β-keto phosphonate **3f** with diethyl azodicarboxylate (**5**) using palladium complexes **1** and **2** at room temperature (Table 3).[15] In the presence of 5 mol % of catalyst **1a** (X = BF_4), the reaction proceeded to afford the α-aminated product **6a** after 18 h with 91% ee (Table 3, entry 1). In the case of 2.5 mol % of catalyst **2c** (X = BF_4), the enantioselectivity was improved up to 99% ee in acetone (entries 3 and 4).

Table 3. Catalytic Enantioselective Amination of β-Keto Phosphonates



entry	β-keto phosphonate	cat.[a]	solvent	time (h)	yield (%)	ee[b] (%)
1	**3f**	**1a**[c]	THF	18	**6a**, 62	91
2	**3f**	**2c**	THF	17	**6a**, 94	98
3	**3f**	**2c**	MeOH	20	**6a**, 51	99
4	**3f**	**2c**	acetone	20	**6a**, 92	99
5	**3q**	**2c**	acetone	35	**6b**, 81	99
6	**3r**	**2c**	acetone	60	**6c**, 68	99

[a] X = BF_4. [b] Enantiomeric excess determined by chiral HPLC using Chiralhyun-Leu-1 (for **6a**) and Chiralpak AD (for **6b** and **6c**) columns.[c] 5 mol % of catalyst.

In summary, we have accomplished the efficient catalytic enantioselective electrophilic α-fluorination of various β-keto phosphonates with excellent enantioselectivity (87−97% ee) with catalyst **1c** (X = BF_4) and highly enantioselective electrophilic α-amination of β-keto phosphonates with catalyst **2c** (X = BF_4) up to 99% ee. Studies into substrate variation allowing access to libraries of α-amino phosphonates, and the mechanistic elucidation and scope of these enantioselective α-fluorinations and α-aminations are in progress, and results will be reported in due course.

Acknowledgment. This research was supported by a Korea Research Foundation Grant (KRF-2003-015-C00359).

Supporting Information Available: Typical experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For catalytic enantioselective amination of β-keto esters, see: Marigo, M.; Juhl, K.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367−1369. (b) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, *12*, 2115−2118. (c) Saaby, S.; Bella, M.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120−8121. (d) Ma, S.; Jioa, N.; Zheng, Z.; Ma. Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193-2196.

(15) After the submission of this paper, Zn(II)-bis(oxazoline)-catalyzed amination of β-keto phosphonates has been reported; see: Bernardi, L.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5772−5773.