J|A|C|S
COMMUNICATIONS

Published on Web 11/14/2002

# An Efficient Enantioselective Fluorination of Various β-Ketoesters Catalyzed by Chiral Palladium Complexes

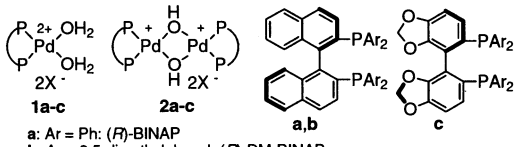
Yoshitaka Hamashima, Kenji Yagi,[1] Hisashi Takano, László Tamás, and Mikiko Sodeoka*

*Institute of Multidisciplinary Research for Advanced Materials, Tohoku University, Katahira, Sendai, Miyagi 980-8577, Japan, and PRESTO, Japan Science and Technology Corporation (JST)*

Received September 9, 2002

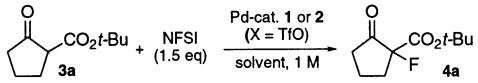
Organic molecules containing fluorine atoms have attracted much attention because they often show different characters from the parent compounds due to the unique properties of the carbon−fluorine bond.[2] Replacement of hydrogen(s) or hydroxyl group(s) in bioactive compounds with fluorine atom(s) is now a common strategy in the field of medicinal chemistry.[2] For this reason, an efficient method for direct enantioselective construction of fluorinated stereogenic carbon centers is extremely important.[3] Most approaches so far have relied on the use of a stoichiometric amount of chiral fluorinating reagents[4] or chiral starting materials.[5] Recently, the first example of a catalytic asymmetric fluorination of β-ketoesters was reported by Togni et al.[6] They examined the reaction of several substrates with a chiral Ti catalyst, and reported an excellent enantioselectivity (90%), but only for one substrate having an unusual ester group. Another example using chinchonine-derived quaternary ammonium salts was reported by Kim and Park,[7] but the best selectivity obtained was 69% ee. Thus, a novel reaction system affording satisfactory selectivity as well as versatility is still required. Herein we wish to report a highly efficient catalytic enantioselective fluorination reaction of various β-ketoesters using chiral palladium complexes.

Optically active α-substituted α-fluorinated β-ketoesters are attractive compounds, because they are regarded as nonenolizable β-ketoesters. In fact, it is known that introduction of a fluorine atom at the α-position of the β-ketoester unit of ketolides such as telithromycin increases their antibiotic activity.[8] In addition, since ketone is easily converted to other functional groups, α-substituted α-fluorinated β-ketoesters would be versatile synthetic precursors of various α-fluorinated carboxylic acid derivatives. Thus, we decided to focus on the enantioselective fluorination of β-ketoesters. Recently we found that a chiral palladium enolate was formed directly from β-ketoesters using palladium complexes **1** or **2**, and reacted with enone to give a highly optically active Michael product.[9]




On the basis of these results, we examined the reaction of *tert*-butyl 2-oxo-cyclopentanecarboxylate **3a** under various conditions, and found that *N*-fluorobenzenesulfonimde (NFSI) was the most effective among the fluorinating reagents tested.[10] The reaction of **3a** with NFSI (1.5 equiv) proceeded smoothly with 5 mol % of **1a** in THF. The desired product was isolated in 72% yield and the ee was determined to be 79% by HPLC (Table 1, entry 1). It should be noted that the palladium complex retained its catalytic activity until the completion of the reaction even though a sulfonimide [$(PhSO_2)_2NH$] with high acidity was increasingly formed during the reaction.

***Table 1.*** Optimization of the Reaction Conditions




| entry | catalyst (mol %)[a] | solvent | temp (°C) | time (h) | yield (%) | ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** (5) | THF | −20 | 12 | 72 | 79 |
| 2 | **1b** (5) | THF | −20 | 39 | 99 | 88 |
| 3 | **1c** (5) | THF | 0 | 72 | 89 | 90 |
| 4 | **2c** (2.5) | THF | 10 | 48 | 83 | 92 |
| 5 | **2c** (2.5) | acetone | 10 | 48 | 93 | 92 |
| 6 | **2c** (2.5) | EtOH | 20 | 18 | 73 | 92 |

[a] Catalyst amount. [b] Determined by HPLC analysis.

To improve the enantioselectivity, we examined a series of chiral phosphine ligands.[11] The substituents at the meta positions of the aryl group on phosphine were found to be important. When (*R*)-DM-BINAP and (*R*)-DTBM-SEGPHOS were used, the ee's were improved to 88 and 90%, respectively (entries 2, 3). In contrast to the Michael reaction,[12] the use of Pd μ-hydroxo complex **2c** (2.5 mol %) also promoted the reaction smoothly and gave the best selectivity (92% ee) (entry 4). This reactivity difference may be attributed to the higher electrophilicity of NFSI than that of enone. Further optimization of the reaction conditions revealed that the reaction proceeded more rapidly in polar solvents (entries 5, 6).

The chemical yield was improved in acetone. Interestingly, EtOH dramatically accelerated the reaction. The reaction was completed within 18 h without any loss of enantioselectivity.

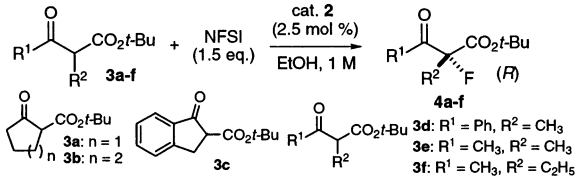
As summarized in Table 2, various substrates were fluorinated smoothly using 2.5 mol % of catalyst.[13] A five-membered ring substrate **3a** reacted similarly in *i*-PrOH and gave a better chemical yield (90%) than that in EtOH (79%). Other cyclic compounds **3b** and **3c** were converted into the desired products in 94 and 83% ee, respectively (entries 2, 3). The reactions of acyclic substrates **3d**, **3e**, and **3f** also afforded fluorinated products with excellent enantioselectivity (91, 91, and 87% ee, respectively) (entries 4−6). In entry 7, the amount of catalyst was reduced to 1 mol %, and comparable results were obtained (82%, 91% ee). In addition, we found that this reaction could be easily scaled up. A representative example is as follows (entry 8). One gram of **3d** (4.3 mmol) was treated with NFSI in EtOH (reagent grade, not distilled) using 5 mol % of **1b** (X = TfO). The desired product **4d** (1.1 g) was obtained without any loss of reaction efficiency (48 h, 96%, 91%

* To whom correspondence should be addressed. E-mail: sodeoka@tagen.tohoku.ac.jp.



10.1021/ja028464f CCC: $22.00 

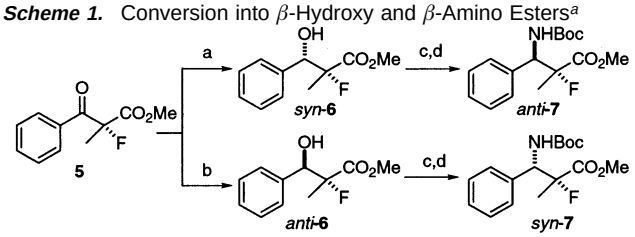
***Table 2.*** Catalytic Enantioselective Fluorination of $\beta$-Ketoesters




| entry | ketoester | catalyst (X) | temp (°C) | time (h) | yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1[a] | **3a** | **2c** (TfO) | 20 | 18 | 90 | 92 |
| 2 | **3b** | **2b** ($BF_4$) | −10 | 20 | 91 | 94 |
| 3 | **3c** | **2b** (TfO) | −20 | 36 | 85 | 83[b] |
| 4 | **3d** | **2b** ($BF_4$) | 20 | 40 | 92 | 91[b] |
| 5 | **3e** | **2c** (TfO) | 20 | 72 | 49[c] | 91 |
| 6 | **3f** | **2b** (TfO) | 20 | 42 | 88 | 87 |
| 7[d] | **3b** | **2b** ($BF_4$) | 0 | 20 | 82 | 91 |
| 8[e] | **3d** | **1b** (TfO) | 20 | 48 | 96 | 91 |

[a] *i*-PrOH was used instead of EtOH. [b] The absolute configuration was determined to be *R* after the conversion. [c] Lower yield due to the volatility of **4e**. [d] **2b** (1 mol %) was used. 2.5 M **3b**. [e] 1-g scale.

***Scheme 1.*** Conversion into $\beta$-Hydroxy and $\beta$-Amino Esters[a]




[a] Conditions: a. $PhMe_2SiH$ (3.0), TBAF (2.0), DMF, 0 °C, 10 min, 83% (dr = >95/5); b. $Ph_3SiH$ (3.0), TFA, rt, 3 h, 75% (dr = >95/5); c. $Ph_3P$ (1.5), DEAD (1.5), DPPA (1.2), THF, rt, 2 h, 79% from *syn*-**6**, 73% from *anti*-**6**; d. Pd/C, $H_2$, $(Boc)_2O$, MeOH, 1 h, 80% for *anti*-**7**, 57% for *syn*-**7**.

ee). In these reactions, we found that **2b** and **2c** were effective catalysts, and various substrates were selectively fluorinated by employing either of these two catalysts according to the nature of the $\beta$-ketoester.

The absolute configurations of the products **4c** and **4d** were determined to be *R* after conversion into a known compound.[11] This selectivity was in accord with the prediction based on the structure of the square-planar chiral Pd enolate.[9,11]

Because $\beta$-hydroxy or $\beta$-amino acids are one of the fundamental units in various natural or unnatural compounds, their α-fluorinated derivatives are of particular interest.[14] Therefore, we next turned our attention to the transformation of the products (Scheme 1). We found that the methyl ester **5**[11] corresponding to **4d** was converted to both diastereomers of the α-fluoro $\beta$-hydroxy ester **6** in a highly diastereoselective manner by simply changing the reducing conditions.[15] These compounds were subjected to azidation with inversion of configuration. Reduction of the azide group, followed by protection of the amino group, afforded the α-fluoro $\beta$-amino ester **7** in good yields.

In conclusion, we have developed a highly efficient catalytic enantioselective fluorination of various $\beta$-keotesters with excellent enantioselectivity (83−94% ee). It is environmentally advantageous that this reaction proceeds well in alcoholic solvents, in particular, EtOH, and is not sensitive to water. In addition, the transformation of the product into both diastereomers of α-fluoro $\beta$-hydroxy- and $\beta$-amino acid derivatives was successfully demonstrated. This report provides a new method for the synthesis of optically active fluorinated compounds, and the availability of α-fluoro $\beta$-hydroxy- or $\beta$-amino acid derivatives for drug design should be valuable in medicinal studies. Further details and an extension of this work will be reported in due course.

**Acknowledgment.** This work was supported in part by The Sumitomo Foundation. We thank Dr. Takao Saito of Takasago International Corporation for providing their chiral phosphine ligands. We also thank Dr. Norio Shibata of Toyama Medical and Pharmaceutical University for providing unpublished analytical data for their fluorinated compound.

**Supporting Information Available:** Experimental details of the determination of the absolute configuration of **4c** and **4d**, and the transformation of **5** into **6** and **7**, as well as spectroscopic characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Visiting Scientist from Takasago International Corporation. Address: 1-4-11 Nishi-Yawata, Hiratsuka, Kanagawa 254-0073, Japan.
(2) (a) Ojima, I.; McCarthy, J. R.; Welch, J. T.; Eds. *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series 639; American Chemical Society: Washington, 1996. (b) Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum: New York, 1994.
(3) (a) Ramachandran, P. V.; Ed. *Asymmetric Fluoroorganic Chemistry*: *Synthesis, Application, and Future Directions*; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000. (b) Soloshonok, V. A., Ed. *Enantiocontrolled Synthesis of Fluoro-Organic Compounds. Stereochemical Challenge and Biomedicinal Targets*; Wiley: New York, 1999.
(4) (a) Differding, E.; Lang, R. E. *Tetrahedron Lett*. **1988**, *29*, 6087−6090. (b) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. *J. Org. Chem.* **1998**, *63*, 2273−2280. (c) Liu, Z.; Shibata, N.; Takeuchi, Y. *J. Org. Chem*. **2000**, *65*, 7583−7587. (d) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc*. **2001**, *123*, 7001−7009. (e) Mohar, B.; Baudoux, J.; Plaquevent, J.-C.; Cahard, D. *Angew. Chem., Int. Ed*. **2001**, *40*, 4214−4216.
(5) (a) Iwaoka, T.; Murohashi, T.; Sato, M.; Kaneko, C. *Tetrahedron Asymmetry* **1992**, *3*, 1025−1028. (b) Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett*. **1998**, *39*, 6135−6138. (c) Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis*, **2001**, *15*, 2307−2319.
(6) (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 4359−4362. (b) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem., Int. Ed*. **2002**, *41*, 979−982.
(7) Kim, D. Y.; Park, E. J. *Org. Lett*. **2002**, *4*, 545−547.
(8) Denis, A.; Bretin, F.; Fromentin, C.; Bonnet, A.; Piltan, G.; Bonnefoy, A.; Agouridas, C. *Bio. Med. Chem. Lett*. **2000**, *10*, 2019−2022.
(9) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc*. **2002**, *124*, 11240−11241.
(10) In contrast, no reaction was observed in THF using salt-type fluorine sources such as Selectfluor and *N*-fluoro-4-methylpyridinium-2-sulfonate.
(11) See Supporting Information.
(12) In the case of the Michael reaction, no reaction occurred with Pd complex **2**. The addition of TfOH, which promoted the reaction as an activator of the enone, was necessary. See ref 9.
(13) **General Procedure**: To a solution of the chiral palladium complex **2** (5 $\mu$mol) in EtOH (0.2 mL) was added $\beta$-ketoester (0.2 mmol) at room temperature. At the temperature indicated in Table 2, NFSI (95 mg, 0.3 mmol) was added, and the resulting suspension was stirred for the time given in Table 2. After the completion of the reaction (TLC), saturated $NH_4Cl$ was added for quenching. Extraction with $Et_2O$, followed by flash column chromatography on $SiO_2$ (hexane/$Et_2O$ = 10/1) gave the pure product.
(14) Recently, the effects of the stereochemistry of the carbon−fluorine bond on the biological activity of HIV protease inhibitor, indinavir, have been described. See: (a) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc*. **2001**, *123*, 7207−7219. In addition, $\beta$-amino acids are reported to show a unique protease-resistant character as components of peptidomimetics. The availability of α-fluorinated derivatives will facilitate studies in this field. See: (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev*. **2001**, *101*, 3219−3232. (c) Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed*. **1999**, *38*, 1223−1226.
(15) The relative configurations of products were tentatively assigned by analogy with the results obtained in the literature. See: Kitazume, T.; Kobayashi, T.; Yamamoto, T.; Yamazaki, T. *J. Org. Chem*. **1987**, *52*, 3218−3223.

JA028464F