

Enantioselective α -Hydrazination of α -Fluoro- β -Ketoesters Catalyzed by Bifunctional Organocatalysts

Joo Yang Mang and Dae Young Kim*

Department of Chemistry, Soonchunhyang University, Asan, Chungnam 336-745, Korea. *E-mail: dyoung@sch.ac.kr
Received September 2, 2008

Key Words : Bifunctional organocatalyst, Hydrazination, Asymmetric reactions, α -Fluoro- β -ketoesters

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 Fluorinated amino acids are becoming increasingly important in pharmaceuticals and other biological applications³ such as the development of anticancer drugs for the control of tumor growth, drugs for control of blood pressure and allergies,⁴ enzyme inhibitors.⁵ One of the important approaches toward the asymmetric synthesis of α -amino acids is enantioselective electrophilic amination of carbonyl compounds.⁶⁻⁸ Recently, Togni reported hydrazination of α -fluoro- β -ketoesters using chiral Cu-bisoxazoline complexes afforded α -fluoro- α -hydrazino- β -ketoesters.⁹

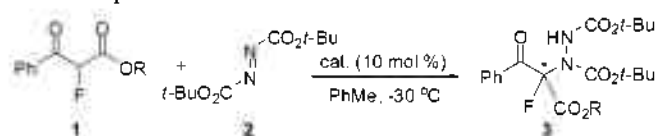
Bifunctional organocatalysts possessing a combination of thiourea and amine groups have been developed for activation of both electrophilic and nucleophilic components. They have emerged as powerful tools for the enantioselective formation of carbon-carbon bond and carbon-heteroatom bonds.¹⁰ Nonetheless, substrate dependence still remains an important issue in asymmetric reactions using bifunctional organocatalysts. Therefore, the development of highly efficient chiral amine-thiourea catalysts, which show high enantioselectivity for a broad scope of substrate, is still in great demand. Recently, we reported a new class of bifunctional organocatalyst **I** which is assembly of a structurally well-defined chiral 1,2-diamine and binaphthyl scaffold with thiourea motif.¹¹

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,¹² we report the catalytic enantio-

selective amination of ester derivatives promoted by organocatalyst¹¹ or chiral palladium complexes.^{7a} In this communications, we wish to report the direct α -hydrazination of α -fluoro- β -ketoesters **1** catalyzed by bifunctional organocatalysts with azodicarboxylates **2** as the electrophilic nitrogen source.

To determine suitable reaction conditions for the catalytic enantioselective electrophilic amination of α -fluoro- β -ketoesters, we initially investigated the reaction system with α -fluoro benzoylacetate **1** using *t*-butyl azodicarboxylates (**2**) as the electrophilic aminating agent in the presence of 10 mol% of catalyst in toluene for 36 h at -30 °C. We first examined the nature of ester group of β -ketoesters on enantioselectivity (Table 1, 73-93% ee, entries 1-5). When employing synthetically attractive, but sterically encumbered, *t*-butyl ester of α -fluoro benzoylacetate **1e**, the corresponding aminated adduct **3e** was isolated with high enantioselectivity of 93% ee (entry 5). We examined the impact of the structure of catalysts on enantioselectivity (Table 1, entries 5 and 6). The high selectivity was obtained with catalysts **I**, which is prepared from 1,2-diaminocyclohexane as a new organocatalyst. Lower selectivity was observed in the presence of 9-*epi*-aminoquinine thiourea catalyst (**II**).¹³ At room temperature, enantioselectivity goes down into 30% ee (entry 7). Varying the structure of the azodicarboxylates had an impact on asymmetric induction (entries 5 and 8). The best results have been obtained with *t*-

Table 1. Optimization of the reaction conditions



entry	1 , R	cat.	yield ^a (%)	ee ^b (%)
1	1a , Me	I	85	73
2	1b , Et	I	84	81
3	1c , <i>i</i> -Pr	I	92	77
4	1d , Bn	I	86	77
5	1e , <i>t</i> -Bu	I	95	93
6	1e , <i>t</i> -Bu	II	84	75
7 ^c	1e , <i>t</i> -Bu	I	96	30
8 ^d	1e , <i>t</i> -Bu	I	90	10

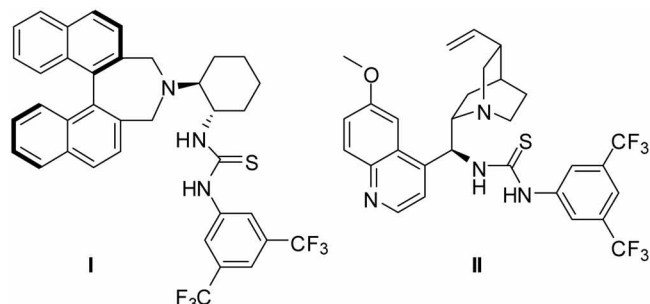
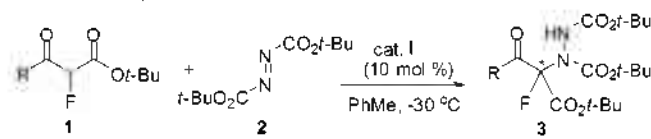


Figure 1. Structures of bifunctional organocatalysts.

^aYield of isolated product. ^bEnantiopurity of **3** was determined by HPLC analysis with Chiralpak AD-H column. ^cReaction carried out at 21 °C. ^dReaction carried out using DEAD as nitrogen source.

Table 2. Catalytic enantioselective amination of α -fluoro- β -ketoesters


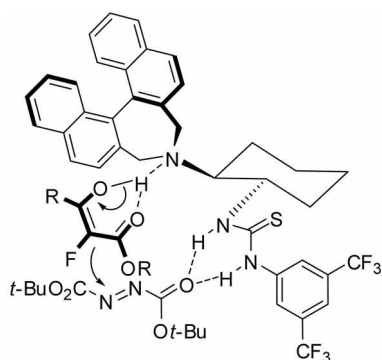
entry	1	time (h)	yield ^a (%)	ee ^b (%)
1	1e , Ph	36	3e , 95	93
2	1f , 4-Cl-Ph	12	3f , 92	91
3	1g , 3-Br-Ph	20	3g , 93	80
4	1h , 4-NO ₂ -Ph	24	3h , 90	81
5	1i , 2-thienyl	12	3i , 89	95
6	1j , Me	20	3j , 90	70

^aYield of isolated product. ^bEnantiopurity of **3** was determined by HPLC analysis with Chiralpak AD-H column.

butyl ester of azodicarboxylates.

To examine the generality of the catalytic enantioselective amination of α -fluoro- β -ketoesters **1** by using new bifunctional organocatalyst **I**, we studied the amination of various α -fluoro- β -ketoesters **1e-j**.¹⁴ As it can be seen by the results summarized in Table 2, the corresponding α -aminated β -ketoesters **3e-j** were obtained in high to excellent yields and enantioselectivities. The α -fluoro benzoylacetates **1e-i**, and α -fluoro acetoacetate **1j** reacted with *t*-butyl azodicarboxylates (**2**) to give the corresponding α -aminated α -fluoro- β -ketoesters **3e-j** in 89–95% yields and 70–95% ee. Although the reason for the observed enantioselectivity is still unclear, we believe that a carbonyl group of the azodicarboxylate is activated by a thiourea moiety through hydrogen bonding, and α -fluoro- β -ketoester is activated by the basic nitrogen atom in tertiary amine (Fig. 2). These interactions control the stereochemical outcome of the reaction and accelerate the reaction rate.

In conclusion, we have developed a highly efficient catalytic enantioselective α -amination of α -fluoro- β -ketoesters using new bifunctional organocatalyst **I**. The desired α -aminated products were obtained in good to high yields, and excellent enantioselectivities (up to 93% ee) were observed. We believe that this method provides a practical entry for the preparation of chiral α -fluoro- α -amino acid derivatives, and the availability of these compounds should facilitate medicinal chemical studies in various fields. Further details and application of this amination will be presented in due course.

**Figure 2.** Proposed stereochemical model.

References and Notes

- Ramachandran, P. V.; Ed. *Asymmetric Fluoroorganic Chemistry: Synthesis, Application, and Future Directions*, ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000.
- For reviews, see: (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1. (b) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (d) France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475.
- (a) Qiu, X.-L.; Meng, W.-D.; Quing, F.-L. *Tetrahedron* **2004**, *60*, 6711. (b) Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621. (c) Kelly, N. M.; Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **1997**, *14*, 205. (d) Dev, R.; Badet, B.; Meffre, P. *Amino Acids* **2003**, *24*, 245. (e) Kukhar, V. P.; Soloshonok, V. A. *Fluorine-Containing Amino Acids: Synthesis and Properties*; Wiley: New York, 1995.
- Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1993.
- (a) Relimpio, A.; Slebe, J. C.; Martínez-Carrion, M. *Biochem. Biophys. Res. Commun.* **1975**, *63*, 625. (b) Bai, P.; Luo, L.; Peng, Z. *Biochemistry* **2000**, *39*, 372.
- Reviews on synthesis of α -amino acids, see: (a) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342. (b) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.
- (a) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4565. (b) Comelles, J.; Pericas, A.; Moreno-Manas, M.; Vallribera, A.; Drudis-Sole, G.; Lledos, A.; Parella, T.; Roglans, A.; Garcia-Grands, S.; Rocas-Fernandez, L. *J. Org. Chem.* **2007**, *72*, 2077. (c) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kunagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342. (d) Hasegawa, Y.; Watanabe, M.; Gridnev, I. D.; Ikariya, T. *J. Am. Chem. Soc.* **2008**, *130*, 2158.
- (a) Piikko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115. (b) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137. (c) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044.
- Huber, D. P.; Stanek, K.; Togni, A. *Tetrahedron: Asymmetry* **2006**, *17*, 658.
- For selected recent reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (b) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (c) Tylor, M. S.; Jacobson, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520. (d) Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3909. (e) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (f) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (g) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516.
- Jung, S. H.; Kim, D. Y. *Tetrahedron Lett.* **2008**, *49*, 5527.
- (a) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545. (b) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897. (c) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309. (d) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115. (e) Kim, S. M.; Kang, Y. K.; Lee, K.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 423. (f) Kang, Y. K.; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135. (g) Cho, M. J.; Kang, Y. K.; Lee, N. R.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2191. (h) Kim, S. M.; Kang, Y. K.; Cho, M. J.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2435. (i) Lee, J. H.; Bang, H. T.; Kim, D. Y. *Synlett* **2008**, 1821.
- Review on asymmetric catalysis with cinchona based thiourea catalysts, see: Connon, S. J. *Chem. Commun.* **2008**, 2499.
- General procedure for the α -hydrazination of α -fluoro- β -ketoesters 1:** A mixture of α -fluoro- β -ketoester **1** (0.2 mmol) and catalyst **I** (13.24 mg, 0.02 mmol) in toluene (0.12 mL) was stirred for 10 min and then was cooled to -30 °C. A solution of *t*-butyl azodicarboxylate (**2**, 46.05 mg, 0.4 mmol) in toluene (0.2 mL) was added dropwise over a period of 5 min. The reaction mixture was stirred for 12–36 h at -30 °C. After completion of the reaction, the resulting solution was allowed to warm to room temperature, concentrated and purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the α -aminated α -fluoro- β -ketoester **3**.