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Organocatalytic synthesis of quaternary stereocenter bearing a fluorine atom: enantioselective conjugate addition of α-fluoro-β-ketoesters to nitroalkenes

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ABSTRACT

The catalytic enantioselective conjugate addition reaction of α-fluoro-β-ketoesters to nitroalkenes promoted by chiral bifunctional organocatalysts is described. The treatment of α-fluoro-β-ketoesters with nitroalkenes under mild reaction conditions afforded the corresponding Michael adducts containing a fluorinated quaternary stereogenic center with excellent enantioselectivity (up to >99% ee).

Fluoroorganic compounds are of importance in organic synthesis because of their use as medicinals and agrochemicals and in fundamental studies of biochemical and metabolic processes.[1] Strategic fluorination is commonly used in medicinal chemistry to improve the metabolic property and bioavailability.[2] Chiral fluoroorganic compounds are interesting and important materials with uses in analytical, biological, and medicinal chemistry and also in the chemistry of polymers and materials.[3] In particular, 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.[4]

The construction of chiral fluorinated quaternary carbon centers is one of the most challenging tasks in organic synthesis, and a number of excellent examples for enantioselective fluorination of tertiary carbon nucleophiles were reported by using chiral transition metal complexes and organocatalysts.[5] The first catalytic enantioselective fluorination was reported by Togni et al. using chiral Ti-complexes.[6] Based on this concept, several groups successfully applied chiral Lewis acids such as BINAP–Pd(II) and transition metal–bis(oxazoline) complexes to the asymmetric fluorination of active methine compounds.[7–9] In 2002, we developed the first organocatalytic fluorination reactions using phase-transfer catalyst as a promoter.[10] Organocatalytic approaches using proline and cinchona alkaloids and their derivatives as catalysts have been shown recently for enantioselective fluorination of carbonyl compounds.[11]

Another approach is asymmetric carbon–carbon bond formation of fluorocarbon nucleophiles to construct chiral fluorine-containing quaternary carbons.[12] Most recently, Lu and Wang independently reported enantioselective Michael reaction of fluorinated methines with nitroalkenes catalyzed by cinchona alkaloid-derived organocatalysts.[13] These reports prompt us to disclose our results with chiral bifunctional organocatalysts for the enantioselective conjugate addition of α-fluoro-β-ketoesters to nitroalkenes.

As part of the research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[14] we recently reported electrophilic amination of α-fluoro-β-ketoesters[15] and asymmetric Michael addition of fluoromalonates to α,β-unsaturated ketones.[12a] Herein, we wish to describe the enantioselective asymmetric conjugate addition of α-fluoro-β-ketoesters to nitroalkenes catalyzed by bifunctional thiourea-type organocatalysts[16] bearing both central and axial chiral elements.

A survey of some reaction parameters was performed, and some representative results are presented in Table 1. Our investigation began with the catalytic enantioselective conjugate addition of methyl 2-fluoro benzoylacetate (**1a**) to β-nitrostyrene (**2a**) in toluene at room temperature in the presence of 10 mol % of catalysts. The nature of the ester group of α-fluoro-β-ketoesters **1** has an impact on the reactivity and selectivity (entries 1–4). When employing *i*-propyl ester of an α-fluoro-β-ketoester **1c**, the

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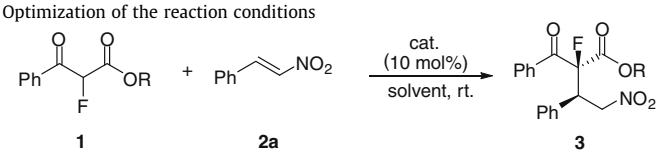
Table 1
Optimization of the reaction conditions



1 2a 3

Entry	1, R	Cat.	Solvent	Time (h)	Yield[a] (%)	dr[b]	ee[c] (%)
1	**1a**, Me	**I**	Toluene	23	**3a**, 95	3:1	88
2	**1b**, Et	**I**	Toluene	20	**3b**, 97	2.9:1	96
3	**1c**, *i*-Pr	**I**	Toluene	40	**3c**, 98	4.3:1	98
4	**1d**, *t*-Bu	**I**	Toluene	57	**3d**, 56	2.3:1	98
5	**1c**, *i*-Pr	**II**	Toluene	24	**3c**, 95	4:1	−90
6	**1c,** *i*-Pr	**III**	Toluene	32	**3c**, 93	3.1:1	97
7	**1c,** *i*-Pr	**IV**	Toluene	80	**3c**, 10	nd[f]	nd[f]
8	**1c,** *i*-Pr	**I**	CH_2Cl_2	32	**3c**, 82	5:1	93
9	**1c,** *i*-Pr	**I**	*m*-Xylene	32	**3c**, 93	2.8:1	97
10	**1c,** *i*-Pr	**I**	THF	41	**3c**, 61	5.4:1	96
11[d]	**1c,** *i*-Pr	**I**	Toluene	48	**3c**, 83	7.9:1	90
12[e]	**1c,** *i*-Pr	**I**	Toluene	60	**3c**, 88	5.4:1	96

[a] Refers to the isolated mixture of diastereomers.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Enantiomeric excess of major diastereomer, determined by chiral HPLC.
[d] The reaction was carried out at −20 °C.
[e] The reaction was carried out at −40 °C.
[f] Not determined.

corresponding adduct **3c** was isolated with an excellent enantioselectivity of 98% ee (entry 3). However, *t*-butyl ester **1d** turned out to be less effective; much longer reaction time was required to achieve a moderate yield (entry 4). We surveyed chiral bifunctional catalysts containing a tertiary amine as catalysts (Fig. 1). High yields with excellent enantioselectivities were observed for structurally variable bifunctional thiourea-type catalysts (entries 3 and 5–7). Under the standard reaction conditions, catalyst **I** exhibited better enantioselectivity (98% ee, entry 3). Compared with catalyst **I**, diastereomeric catalyst **II** gave the desired product **3c** in a slightly lower enantioselectivity with the opposite of the absolute configuration of the major enantiomer (90% ee, entry 5). This suggests that the chirality of (*R*)-binaphthyl moiety and of

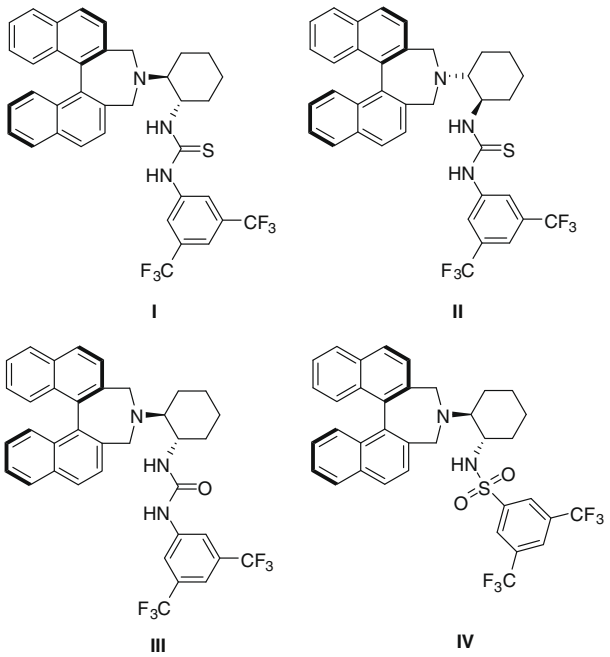
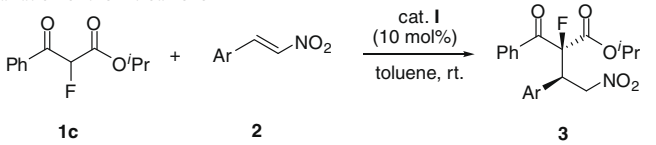


Figure 1. Structure of chiral thiourea-tertiary amine catalysts.

Table 2
Variation of the nitroalkene



1c 2 3

Entry	2, Ar	Time (h)	Yield[a] (%)	dr[b]	ee[c] (%)
1	**2b**, *o*-Cl-Ph	94	**3e**, 93	3:1	>99
2	**2c,** *o*-F-Ph	94	**3f**, 96	4:1	99
3	**2d,** *p*-Me-Ph	115	**3g**, 98	3.6:1	>99
4	**2e,** *p*-OMe-Ph	115	**3h**, 94	3.5:1	98
5	**2f,** 2-Naphthyl	48	**3i**, 84	3.8:1	93
6	**2g,** 2-Furyl	44	**3j**, 84	1.6:1	98
7	**2h,** 2-Thienyl	44	**3k**, 98	2.8:1	88
8	**2i,** Isobutyl	72	**3l**, 91	3.3:1	91

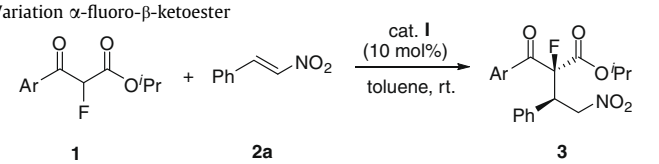
[a] Refers to the isolated mixture of diastereomers.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Enantiomeric excess of major diastereomer, determined by chiral HPLC analysis with chiral columns (Chiralcel OD-H for **3j**, Chiralpak AD-H for **3e–h, 3k–l**, and IC for **3i**).

(1*S*,2*S*)-diaminocyclohexane unit in catalyst **I** are matched in this reaction. Concerning the solvent (entries 3 and 8–10), there is a little influence on the stereochemical outcome of the process. Temperature effect was not significant, with a slightly lower enantioselectivity being given at a lower temperature (entries 11 and 12). The absolute configuration of **3b** was determined to be (2*S*,3*R*) by comparing the chiral HPLC data and specific rotation with those of an authentic sample.[13]

We then carried on with the evaluation of the generality of this protocol under the optimized reaction conditions. The results of a representative selection of aromatic and aliphatic nitroalkenes for the catalytic enantioselective conjugate addition reaction are summarized in Table 2. The corresponding γ-nitro-α-fluorocarbonyl compounds **3e–l** were formed in high yields (84–98%), moderate diastereoselectivities (1.6–4:1), and excellent enantioselectivities (88% to >99%). The effect of the substituents of the aromatic nitroalkenes structures on the reaction efficiency was limited.

To examine the generality of the catalytic enantioselective conjugate addition reaction of α-fluoro-β-ketoesters **1** by using bifunctional organocatalyst **I**, we studied the addition of various α-fluoro-β-ketoesters **1** to β-nitrostyrene **(2a)**.[17] As it can be seen from the results summarized in Table 3, the corresponding products **3m–r** were obtained in high to excellent yields, moderate

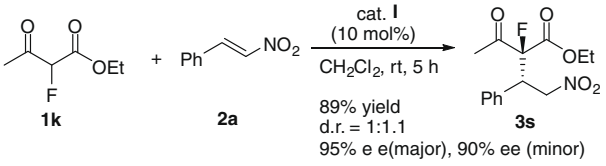
Table 3
Variation α-fluoro-β-ketoester



1 2a 3

Entry	Ar	Time (h)	Yield[a] (%)	dr[b]	ee[c] (%)
1	**1e**, *m*-Cl-Ph	44	**3m**, 96	5:1	91
2	**1f,** *p*-Br-Ph	23	**3n**, 93	3.4:1	94
3	**1g,** *p*-Me-Ph	111	**3o**, 93	3.3:1	83
4	**1h,** *p*-CF_3-Ph	66	**3p**, 93	3.7:1	93
5	**1i,** 2-Naphthyl	38	**3q**, 96	3.4:1	97
6	**1j,** 2-Thienyl	42	**3r**, 95	1.5:1	91

[a] Refers to the isolated mixture of diastereomers.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Enantiomeric excess of major diastereomer, determined by chiral HPLC analysis with chiral columns (Chiralcel OD-H for **3m, 3n**, Chiralpak AD-H for **3p, 3r**, and IC for **3o**, **3q**).



Scheme 1.

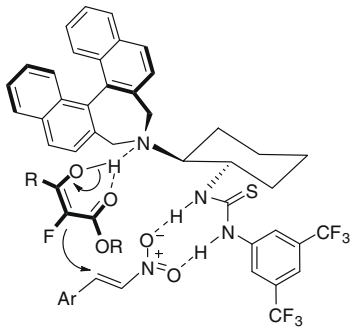


Figure 2. Proposed stereochemical model.

diastereoselectivities, and excellent enantioselectivities (83–97% ee).

We examined the catalytic enantioselective conjugate addition of alkyl α-fluoro-β-ketoesters **1k** with β-nitrostyrene (**2a**) using organocatalyst **I** at room temperature. In the presence of 10 mol % of catalyst **I**, the reaction proceeded to afford the γ-nitro-α-fluorocarbonyl compound **3s** after 5 h in 89% yield, 1.1:1 dr, and 95% ee (Scheme 1). The absolute configuration of compound **3s** was determined by comparing the specific rotation and chiral HPLC data with those of an authentic sample.[13b]

Although the reason for the observed enantioselectivity is still unclear, we believe that a nitro group of the nitroalkene 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 conjugate addition reaction of α-fluoro-β-ketoesters using bifunctional organocatalyst **I**. The desired γ-nitro-α-fluorocarbonyl compounds were obtained in good to high yields, moderate diastereoselectivities, and excellent enantioselectivities (up to >99% ee). A quaternary stereocenter bearing a fluorine atom and an adjacent stereogenic carbon center are created with an excellent level of enantioselectivity and in high yields in the conjugate addition process. Further study on the asymmetric synthesis of fluorine-containing compounds is underway.

References and notes

1. (a) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II*; American Chemical Society: Washington, DC, 1995; (b) Filler, R.; Kobayashi, Y. *Biomedicinal Aspect of Fluorine Chemistry*; Kodansha Ltd, Elsevier Biochemical Press: Tokyo, New York, 1982; (c) Kirk, K. L. J. *J. Fluorine Chem.* **2006**, *127*, 1013; (d) Isanobor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303; (e) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881; (f) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305.
2. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
3. (a) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000; (b)*Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996; p 4.
4. (a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; John Wiley & Sons: Chichester, 1999; (b) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661; (c)*Asymmetric Fluoroorganic Chemistry: Synthesis, Application, and Future Directions*; Ramachandran, P. V., Ed.ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000.
5. 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; (e) Oestreich, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2324; (f) Pihko, P. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 544; (g) Prakash, G. K. S.; Beier, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2172; (h) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065; (i) Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2007**, *128*, 469; (j) Brunet, V. A.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1179; (k) Smits, R.; Cadicamo, C. D.; Burger, K.; Koksch, B. *Chem. Soc. Rev.* **2008**, *37*, 1727.
6. Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359.
7. For β-keto esters (a) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530; (b) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225; (c) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007; (d) Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703; (e) Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4204.
8. For α-cyano acetates: (a) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115; (b) Park, E. J.; Kim, H. R.; Joung, C. W.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2004**, *25*, 1451.
9. For β-keto phosphonates (a) Bernardi, L.; Jørgensen, K. A. *Chem. Commun.* **2005**, 1324; (b) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447; (c) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309; (d) Kim, S. M.; Kang, Y. K.; Lee, K.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 423.
10. Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545.
11. (a) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991; (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703; (c) Steiner, D. D.; Mase, N.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2005**, *44*, 3706; (d) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826; (e) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051; (f) Fukuzumi, T.; Shibata, N.; Sugiura, M.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2006**, *127*, 548; (g) Ishimura, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157.
12. (a) Kim, D. Y.; Kim, S. M.; Koh, K. O.; Mang, J. Y. *Bull. Korean Chem. Soc.* **2003**, *24*, 1425; (b) Mizuta, S.; Shibata, N.; Goto, Y.; Furukawa, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2007**, *129*, 6394; (c) Furukawa, T.; Shibata, N.; Mizuta, S.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8051.
13. (a) Han, X.; Luo, J.; Liu, C.; Lu, Y. *Chem. Commun.* **2009**, 2044; (b) Li, H.; Zhang, S.; Yu, C.; Song, X.; Wang, W. *Chem. Commun.* **2009**, 2136.
14. (a) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299; (b) Kim, D. Y.; Huh, S. C. *Tetrahedron* **2001**, *57*, 8933; (c) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897; (d) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4265; (e) Kang, Y. K.; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135; (f) Cho, M. J.; Kang, Y. K.; Lee, N. R.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2191; (g) Kim, S. M.; Kang, Y. K.; Cho, M. J.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2435; (h) Lee, J. H.; Bang, H. T.; Kim, D. Y. *Synlett* **2008**, 1821; (i) Kim, D. Y. *Bull. Korean Chem. Soc.* **2008**, *29*, 2036; (j) Kang, Y. K.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2008**, *29*, 2093; (k) Mang, J. Y.; Kwon, D. G.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 249; (l) Lee, N. R.; Kim, S. M.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 829.
15. (a) Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2008**, *29*, 2091; (b) Mang, J. Y.; Kwon, D. G.; Kim, D. Y. *J. Fluorine Chem.* **2009**, *130*, 259.
16. (a) Kim, S. M.; Lee, J. H.; Kim, D. Y. *Synlett* **2008**, 2659; (b) Jung, S. H.; Kim, D. Y. *Tetrahedron Lett.* **2008**, *49*, 5527; Recently, Shao et al. reported the asymmetric Michael reaction of 2,4-pentandione promoted by catalyst **I**, see: (c) Peng, G.-Z.; Shao, Z.-H.; Fan, B.-M.; Song, H.; Li, G.-P.; Zhang, H. B. *J. Org. Chem.* **2008**, *73*, 5202.
17. General procedure for the conjugate addition of α-fluoro-β-ketoesters to β-nitrostyrene: To a stirred solution of α-fluoro β-ketoester **1** (0.2 mmol) and catalyst **I** (13.3 mg, 0.02 mmol) in toluene (0.4 mL) was added β-nitrostyrene (**2a**, 29.8 mg, 0.2 mmol) at room temperature. The reaction mixture was stirred for 23–115 h at room temperature. The mixture was diluted with saturated NH_4Cl solution (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography to afford the γ-nitro α-fluoro β-ketoester **3**.