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# Enantioselective *gem*-Chlorofluorination of Active Methylene Compounds Using a Chiral Spiro Oxazoline Ligand

**Kazutaka Shibatomi,* Akira Narayama, Yoshinori Soga, Tsubasa Muto, and Seiji Iwasa**

*Department of Environmental and Life Sciences, Toyohashi University of Technology, 1-1 Hibarigaoka, Tempaku-cho, Toyohashi 441-8580, Japan*

*shiba@ens.tut.ac.jp*

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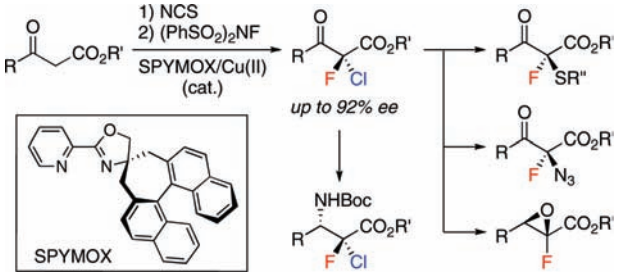


**Highly enantioselective *gem*-chlorofluorination of active methylene compounds was carried out by using a copper(II) complex of a chiral spiro pyridyl monooxazoline ligand. This reaction yielded α-chloro-α-fluoro-β-keto esters and α-chloro-α-fluoro-β-keto phosphonates with up to 92% ee. The resulting dihalo β-keto ester was converted into various α-fluoro-α-heteroatom-substituted carbonyl compounds via nucleophilic substitution without loss of optical purity. A fully protected β-amino acid with a *gem*-chlorofluoromethylene function was also synthesized.**

Optically active organofluorine compounds are becoming increasingly important in pharmaceutical and agricultural chemistry.[1] These compounds, especially those having a fluorinated stereogenic center, are fascinating building blocks for new drug candidates. In the current research, we focus on the stereoselective construction of a *gem*-chlorofluorinated chiral carbon center, which is an attractive functional group because of the following reasons: 1) α-chloro-α-fluoro carbonyl compounds are expected to be useful synthetic intermediates for a variety of chiral fluorinated compounds because the chlorine moiety works as a leaving group; 2) the *gem*-chlorofluoromethylene group would be a chiral isostere of the *gem*-difluoromethylene group in bioactive compounds.[2] Surprisingly, very few researchers have focused on the asymmetric synthesis of *gem*-chlorofluoro compounds.[3,4] One possible reason for this is that it is difficult to discriminate two halogens in the stereochemistry-determining step due to their sterical similarity. Recently, we succeeded in carrying out the asymmetric syntheses of some α-chloro-α-fluoro carbonyl compounds.[3c] We also showed that the nucleophilic substitution of these compounds proceeds with keeping their optical purity. These successful results encouraged us to attempt the development of a method for synthesizing a new class of α-chloro-α-fluoro carbonyl compounds.

Our synthetic strategy is shown in Scheme 1. Electrophilic chlorination of β-keto esters affords α-monochloro-β-keto esters in situ, in the presence of chiral Lewis acid catalyst. Subsequent electrophilic fluorination yields the desired α-chloro-α-fluoro-β-keto esters with asymmetric

(1) (a) *Fluorine in medicinal chemistry and chemical biology*; Ojima, I., Eds.; Wiley & Sons: New York, 2009. (b) Bégué, J.-P.; Bonnet-Delphon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley & Sons: Hoboken, NJ, 2008.

(2) Considerable effort has been made for the synthesis and biological evaluation of $CF_2$-incorporated bioactive compounds. See ref 1

(3) (a) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709. (b) Cho, M. J.; Kang, Y. K.; Lee, N. R.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2191. (c) Shibatomi, K.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5796.

(4) During the preparation of this manuscript, a nice paper appeared describing the highly enantioselective α-fluorination of α-chloro-β-keto esters by using a chiral nickel catalyst (our manuscript was originally submitted on October 14, 2010); see: Kang, S. H.; Kim, D. Y. *Adv. Synth. Catal.* **2010**, *352*, 2783.

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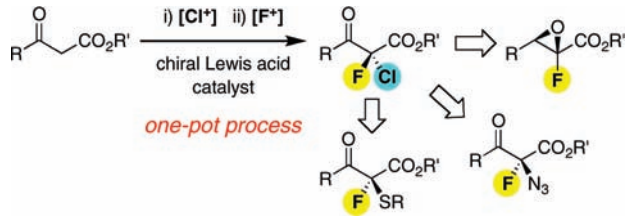
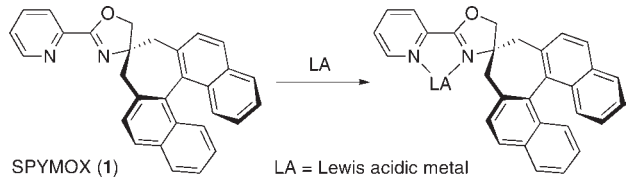
**Scheme 1.** Synthetic Strategy for Chiral Fluorinated Molecules



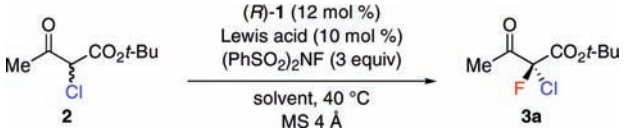

induction. Nucleophilic substitution of the chlorine moiety in the resulting compounds affords a variety of α-fluoro-α-heteroatom-substituted esters. In 2003, Togni and co-workers demonstrated the asymmetric synthesis of α-chloro-α-fluoro-β-keto esters by this sequential double halogenation in one-pot operation in the presence of Ti-TADDOLate catalyst with up to 65% ee.[3a,5] With the aim of achieving high asymmetric induction, we attempted to carry out *gem*-chlorofluorination in the presence of a new chiral Lewis acid catalyst, which we synthesized from a 2-pyridyl monooxazoline ligand (SPYMOX)[6] having a spiro-fused axial chiral binaphthyl backbone (Scheme 2).

**Scheme 2.** Preparation of Chiral Spiro Lewis Acid Catalyst




We started our investigation by screening various Lewis acids for the enantioselective α-fluorination of α-chloro-β-keto ester **2** with *N*-fluorobenzenesulfonimide (NFSI).[7,8] As shown in Table 1, the copper(II) triflate complex of SPYMOX (**1**) was very effective for asymmetric fluorination of **2** in benzene; in this case, the desired α-chloro-α-fluoro-β-keto ester **3a** was obtained in high yield and enantioselectivity (entry 5; 90% ee).

**Table 1.** Asymmetric α-Fluorination of α-Chloro-β-keto Ester[a]




| entry | Lewis acid | solvent | time[b] [h] | yield[c] [%] | ee[d] [%] |
|---|---|---|---|---|---|
| 1 | $Ni(ClO_4)_2 \cdot 6H_2O$ | benzene | 18 | 57 | 0 |
| 2 | $Mg(OTf)_2$ | benzene | 22 | 54 | 6 |
| 3 | $Zn(OTf)_2$ | benzene | 38 | 81 | 80 |
| 4[e] | $Cu(ClO_4)_2 \cdot 6H_2O$ | benzene | 11 | 36 | 76 |
| **5** | **$Cu(OTf)_2$** | **benzene** | **8** | **82** | **90** |
| 6 | $Cu(OTf)_2$ | $CH_2Cl_2$ | 11 | 61 | 52 |
| 7 | $Cu(OTf)_2$ | $Et_2O$ | 13 | 72 | 60 |

[a] All reactions were carried out at 40 °C (bath temperature) with 3 equiv of NFSI in the presence of a chiral catalyst prepared from 12 mol % of **1** and 10 mol % of Lewis acidic metal. [b] All reactions were quenched after the complete consumption of **2** unless otherwise noted. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] About 50% of the starting material remained unreacted.

The high asymmetric induction ability of our new catalyst in the fluorination prompted us to proceed to the next stage, the one-pot asymmetric *gem*-chlorofluorination of β-keto esters. In the first step, β-keto ester **4a** was chlorinated with *N*-chlorosuccinimide (NCS) in the presence of a **1**/$Cu(OTf)_2$ complex. After the complete consumption of **4a** by TLC monitoring, NFSI was added to the reaction mixture. Fluorination was conducted at 40 °C for 8 h to afford the desired product **3a** in 70% yield (over 2 steps) along with the α,α-dichlorinated form in approximately 5% yield (Table 2, entry 1). To our delight, the optical purity of **3a** in this one-pot reaction was sufficiently high (90% ee), and the sense of enantioselection was the same as that in the fluorination of monochloro ester **2** (Table 1, entry 5). This implied that the stereochemical outcome of this double halogenation is determined by the fluorination step. Several β-keto esters were subjected to *gem*-chlorofluorination under similar reaction conditions. As summarized in Table 2, various α-chloro-α-fluoro-β-keto esters, including aliphatic, aromatic, and heterocyclic ketoesters, were successfully synthesized with good to high optical purity (79−92% ee).[9]

Next, we extended the enantioselective *gem*-chlorofluorination to several β-keto phosphonates **5**. As shown in Table 3, the **1**/$Cu(OTf)_2$ complex was very effective for this reaction; thus, the desired α-chloro-α-fluoro-β-keto phosphonates **6a**−**f** were isolated in moderate to good yields with high enantioselectivity (85−92% ee).[9] It is noteworthy

(5) A method for asymmetric chlorination of β-keto esters with a Ti-TADDOLate catalyst: Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425.

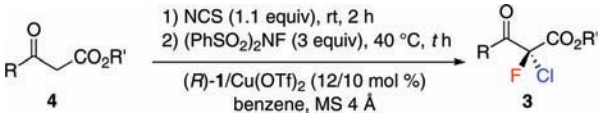
(6) For the synthesis of SPYMOX and its application in palladium-catalyzed asymmetric allylic alkylation, see: Shibatomi, K.; Muto, T.; Sumikawa, Y.; Narayama, A.; Iwasa, S. *Synlett* **2009**, 241.

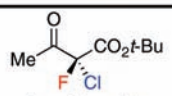
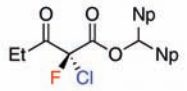
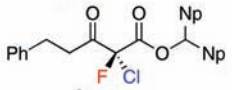
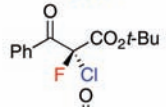
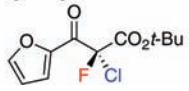
(7) Although the field of asymmetric α-fluorination of active methine compounds is progressing steadily, there are only a few known catalysts that achieve high enantioselectivity (over 90% ee) in the fluorination of acyclic β-keto esters or β-keto phosphonates. For successful examples with acyclic substrates, see: (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359. (b) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530. (c) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447. (d) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309. (e) Reddy, D. S.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 164. (f) Bernardi, L.; Jørgensen, K. A. *Chem. Commun.* **2005**, 1324. (g) See also ref 4.

(8) For a review on the asymmetric functionalization at a halogenated prochiral carbon, see: Shibatomi, K. *Synthesis* **2010**, 2679.

(9) We have confirmed that the optical purity of *gem*-chlorofluoro carbonyl compounds **3a**, **3b**, **3d**, and **6a** does not change even after chromatographic purification using achiral silica gel or solvent evaporation. Therefore, we conclude that the enantiomers do not undergo self-disproportionation during the purification process. For enantiomers self-disproportionation effect of perfluorinated compounds, see:(a) Soloshonok, V. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 766. (b) Soloshonok, V. A.; Ueki, H.; Yasumoto, M.; Mekala, S.; Hirschi, J. S.; Singleton, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 12112. (c) Ueki, H.; Yasumoto, M.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **2010**, *21*, 1396.

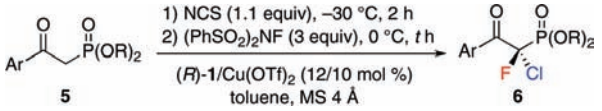
**Table 2.** Asymmetric *gem*-Chlorofluorination of β-Keto Esters[a]

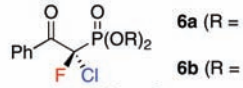
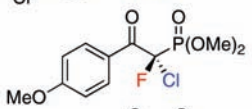
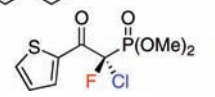



| entry | product | | t [h] | yield [%][b] | ee [%][c] |
|---|---|---|---|---|---|
| 1 |  | **3a** | 8 | 70 | 90 |
| 2[d] |  | **3b** | 17 | 67 | 87 |
| 3[d] |  | **3c** | 19 | 63 | 79 |
| 4[e] |  | **3d** | 4 | 67 | 92 |
| 5[e] |  | **3e** | 6 | 71 | 92 |
| 6[f] |  | **3f** | 24 | 73 | 82 |

[a] See Supporting Information for experimental details. [b] Isolated yield over 2 steps. [c] Determined by chiral HPLC analysis. [d] Np = 1-naphthyl. [e] Fluorination was carried out under reflux conditions. [f] Catalyst was prepared from 30 mol % of $Cu(OTf)_2$ and 36 mol % of **1**.

**Table 3.** Asymmetric *gem*-Chlorofluorination of β-Keto Phosphonates.[a]



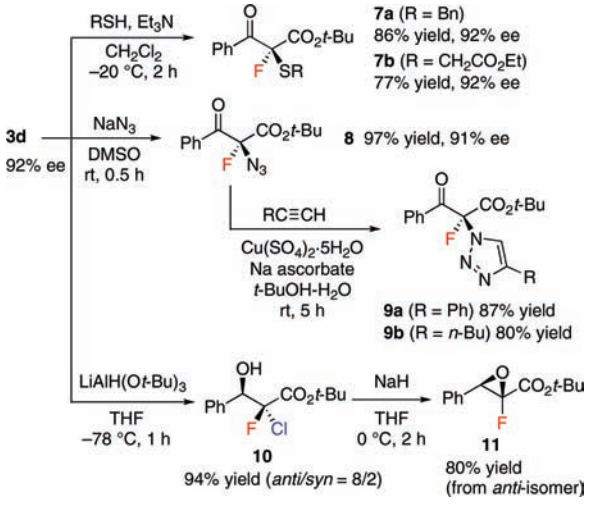

| entry | product | | t [h] | yield [%][b] | ee [%][c] |
|---|---|---|---|---|---|
| 1 |  | **6a** (R = Me) | 24 | 73 | 92 |
| 2 | | **6b** (R = Et) | 24 | 78 | 85 |
| 3 |  | **6c** | 24 | 55 | 90 |
| 4 |  | **6d** | 50 | 52 | 92 |
| 5 |  | **6e** | 65 | 64 | 90 |
| 6[d] |  | **6f** | 70 | 69 | 86 |

[a] See Supporting Information for experimental details. [b] Isolated yield over 2 steps. [c] Determined by chiral HPLC analysis. [d] Catalyst was prepared from 30 mol % of $Cu(OTf)_2$ and 36 mol % of **1**.

that both chlorination and fluorination of β-keto phosphonates proceeded much faster than those of β-keto esters; however, the selectivity toward monochlorination was slightly poor, which resulted in the formation of a considerable amount of α,α-dichloro-β-keto phosphonate (ca. 10−25%) as the byproduct.

After successfully synthesizing optically active *gem*-chlorofluoro carbonyl compounds, we carried out derivatization of these compounds to obtain a variety of chiral fluoro compounds (Scheme 3). Nucleophilic substitution of the optically active **3d** (92% ee) with alkyl thiols proceeded smoothly to yield the corresponding α-fluoro-α-sulfenyl-β-keto esters **7a**,**b**,[10] which are expected to be versatile building templates for biologically active molecules.[10b] It should be noted that the optical purity of products **7** was exactly the same as that of the starting compound **3d**. This result strongly suggested that this nucleophilic substitution proceeded in a rigorous $S_N2$ fashion. Substitution of **3d** with sodium azide also proceeded smoothly to yield the corresponding α-azido-α-fluoro-β-keto ester **8** without loss of optical purity.[11] Azide **8** was further converted into fluorinated 1,2,3-triazoles **9a**,**b** by copper-catalyzed cycloaddition with alkynes. Furthermore, reduction of **3d** with lithium tri(*tert*-butoxy)-aluminum hydride yielded secondary alcohol **10** with good diastereoselectivity (*anti*/*syn* = 8/2). **10** could be successfully converted into fluoro epoxide **11** by alkaline treatment. There are very few reports on the asymmetric

**Scheme 3.** Stereospecific Derivatization of **3d**



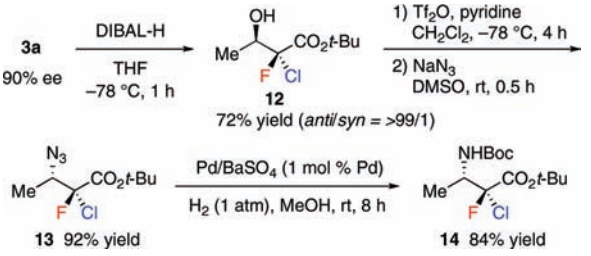

(10) For asymmetric syntheses of α-fluoro-α-sulfenyl-β-dicarbonyl compounds, see: (a) Jereb, M.; Togni, A. *Chem.—Eur. J.* **2007**, *13*, 9384. (b) Ishimaru, T.; Ogawa, S.; Tokunaga, E.; Nakamura, S.; Shibata, N. *J. Fluorine Chem.* **2009**, *130*, 1049. (c) See also ref 7e.

(11) For asymmetric syntheses of α-fluoro-α-nitrogen-substituted-β-dicarbonyl compounds, see: (a) Huber, D. P.; Stanek, K.; Togni, A. *Tetrahedron: Asymmetry* **2006**, *17*, 658. (b) He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 9466. (c) Mang, J. Y.; Kwon, D. G.; Kim, D. Y. *J. Fluorine Chem.* **2009**, *130*, 259. (d) Also see ref 7e.

synthesis of fluoro epoxides, although optically active fluoro epoxides are known to be good synthetic intermediates for various chiral α-substituted ketones.[12]

We next focused on the transformation of α-chloro-α-fluoro-β-keto esters into optically active β-amino acids because fluorinated amino acids have been the subject of intensive research.[1] Reduction of **3a** with diisobutylaluminum hydride (DIBAL-H) afforded *anti*-chlorofluorohydrin **12** with very high diastereoselectivity (Scheme 4).[13] Treatment of **12** with triflic anhydride and subsequent azidation yielded the corresponding azide **13** with inversion of configuration; the obtained azide was converted into a fully protected β-amino acid **14** with a *gem*-chlorofluoromethylene group.

**Scheme 4.** Synthesis of α-Chloro-α-fluoro-β-amino Ester



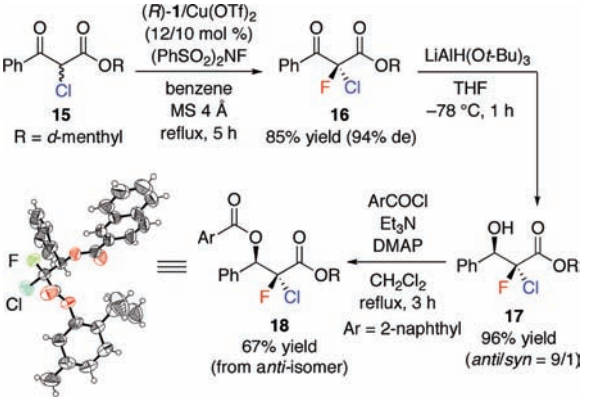

Finally, to establish the absolute stereochemistry of these *gem*-chlorofluoro compounds, we synthesized α-chloro-α-fluoro-β-keto ester **16**, which has a *d*-menthyl group as a chiral auxiliary, by the fluorination of α-chloro-β-keto ester **15** with the (*R*)-**1**/Cu(OTf)$_2$ catalyst (94% de, Scheme 5).[14] Hydride reduction of **16** and subsequent acylation yielded β-acyloxy ester **18**. **18** was recrystallized from Et$_2$O/*n*-hexane to afford single crystals that were suitable for X-ray structural analysis. As shown in Scheme 5, on the basis of the stereochemistry on the *d*-menthyl group, the absolute configuration of the

(12) For asymmetric syntheses of fluorinated epoxides and their transformation, see: (a) Gosmini, C.; Dubuffet, T.; Sauvêtre, R.; Normant, J.-F. *Tetrahedron: Asymmetry* **1991**, *2*, 223. (b) Wong, O. A.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 8377.

(13) The relative configuration of **12** was determined by X-ray crystallographic analysis. See Supporting Information for details.

(14) Fluorination of *ent*-**15**, which has an *l*-menthyl group as a chiral auxiliary, yielded *ent*-**16** as a diastereomixture (dr = 21:79) in the presence of the (*R*)-**1**/Cu(OTf)$_2$ catalyst. The absolute configuration at the chlorofluorinated carbon in the major diastereomer of *ent*-**16** was found to be the same as that in the major diastereomer of **16** obtained in Scheme 5 by comparing their NMR spectra. This clearly indicated that the sense of stereoselection in these fluorination reactions was controlled by the chiral catalyst and not by the chiral auxiliary.

**Scheme 5.** Determination of Stereochemistry




dihalogenated chiral carbon center was determined to be *R*. It was also confirmed that the reduction of **16** and **3d** with lithium tri(*tert*-butoxy)aluminum hydride preferentially affords *anti*-isomers.

In conclusion, we have demonstrated the enantioselective *gem*-chlorofluorination of active methylene compounds in the presence of a new chiral Lewis acid catalyst, the SPYMOX/Cu(II) complex; in this reaction, the corresponding α-chloro-α-fluoro carbonyl compounds were isolated with up to 92% ee. The resulting compounds were successfully converted into various α-fluoro-α-heteroatom-substituted carbonyl compounds via nucleophilic substitution without loss of optical purity. A fully protected β-amino acid with a *gem*-chlorofluoromethylene function was also synthesized.

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**Supporting Information Available.** Experimental procedures, characterization of all new compounds, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.