Lewis Acid-catalyzed Asymmetric Fluorinations of β-Keto Esters: Dramatic Improvement in Enantioselectivity by Changing the Operation Sequence

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Efficient Lewis acid-catalyzed asymmetric fluorination and chlorination of β-keto esters were achieved using hybrid chiral oxazoline ligand **1**. The enantioselectivity of the halogenated products dramatically increased when the reaction procedure was changed.

The enantioselective fluorination of carbonyl compounds is a highly important synthetic strategy because the resulting optically active α-fluorocarbonyl compounds are very attractive intermediates in synthetic organic chemistry as well as in medicinal chemistry. Recently, following Togni's report,[1] several methods for the efficient catalytic asymmetric fluorination of β-keto esters have been proposed.[1–6] We have also reported the Lewis acid-catalyzed asymmetric fluorination of β-keto esters by employing a new chiral N,N,N-tridentate ligand **1** (Figure 1).[6] During the course of our study on the improvement of the asymmetric induction and scope of the substrate in this fluorination, we found that the enantioselectivity of a fluorinated product could be dramatically increased by simply changing the reaction procedure. Herein, we wish to report the Lewis acid-catalyzed highly efficient asymmetric fluorination and chlorination of β-keto esters using **1**.

In our previous study,[6] 2-*tert*-butoxycarbonyl-1-indanone (**2a**) was converted to the corresponding α-fluorinated product **3a** with 94% ee using **1**–$Ni(ClO_4)_2$ catalyst and *N*-fluorobis(benzenesulfonyl)amine (NFSI) as the fluorination reagent (Scheme 1). All the reagents were mixed almost simultaneously in our previous experiment. Surprisingly, the enantioselectivity of **3a** was dramatically increased to 99% ee (Table 1, Entry 2) when a solution of NFSI was slowly added to the mixture of

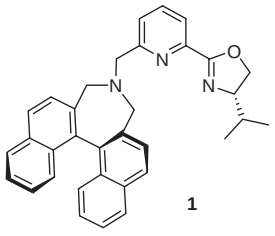
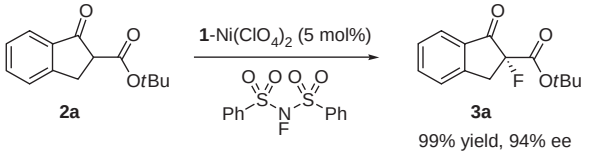


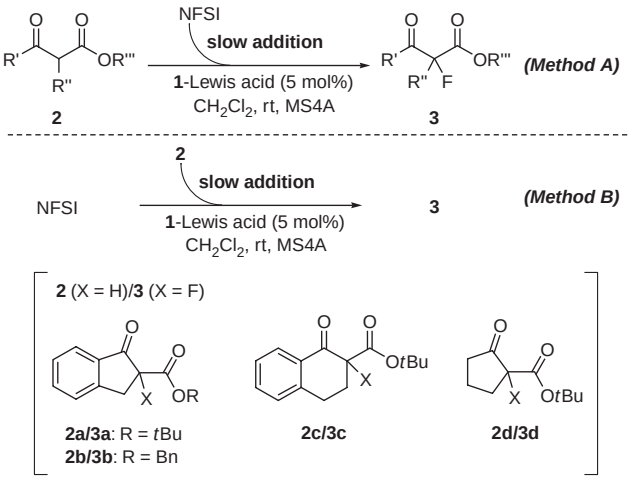
Figure 1. Hybrid chiral N,N,N-tridentate ligand **1**.



Scheme 1. Previously reported asymmetric fluorination of **2a**.

2a and **1**–$Ni(ClO_4)_2$ (Method A).[7] In marked contrast to method A, **3a** was obtained with significantly poor enantioselectivity (44% ee; Entry 3) when a solution of **2a** was slowly added to the mixture of NFSI and **1**–$Ni(ClO_4)_2$ (Method B).[8] The same phenomena were observed when **1**–$Mg(ClO_4)_2$ was used as the Lewis acid catalyst (Entries 4–6). By following method A, we successfully converted several β-keto esters into their corresponding α-fluorinated derivatives with excellent enantioselectivity (Entries 8, 11, and 14), whereas the reactions by method B showed poor enantioselectivity (Entries 9, 12, and 15).

Table 1. Lewis acid catalyzed asymmetric fluorination[a]



Entry	**2**/**3**	Method[b]	Lewis acid	Time /h	Yield /%[c]	%*ee*[d]
1	**2a**/**3a**	C	$Ni(ClO_4)_2$	2	99	94 (R)
2	**2a**/**3a**	A	$Ni(ClO_4)_2$	2	99	99 (R)
3	**2a**/**3a**	B	$Ni(ClO_4)_2$	2	94	44 (R)
4	**2a**/**3a**	C	$Mg(ClO_4)_2$	2	99	91 (R)
5	**2a**/**3a**	A	$Mg(ClO_4)_2$	2	99	99 (R)
6	**2a**/**3a**	B	$Mg(ClO_4)_2$	2	86	27 (R)
7	**2b**/**3b**	C	$Ni(ClO_4)_2$	1	99	83
8	**2b**/**3b**	A	$Ni(ClO_4)_2$	2	99	91
9	**2b**/**3b**	B	$Ni(ClO_4)_2$	2	85	34
10	**2c**/**3c**	C	$Ni(ClO_4)_2$	4	99	34
11	**2c**/**3c**	A	$Ni(ClO_4)_2$	12	99	92
12	**2c**/**3c**	B	$Ni(ClO_4)_2$	12	75	12
13[e]	**2d**/**3d**	C	$Ni(ClO_4)_2$	19	93	64
14[e]	**2d**/**3d**	A	$Ni(ClO_4)_2$	24	90	92
15[e]	**2d**/**3d**	B	$Ni(ClO_4)_2$	24	65	35

[a]All reactions were carried out at room temperature in CH_2Cl_2 with activated MS 4A. **2**/NFSI/catalyst = 1/1.1/0.05. [b]Detailed procedures are described in Refs. 7, 8, and 9. [c]Isolated yields. [d]The ee values were determined by HPLC analysis. [e]10 mol % of catalyst was used.

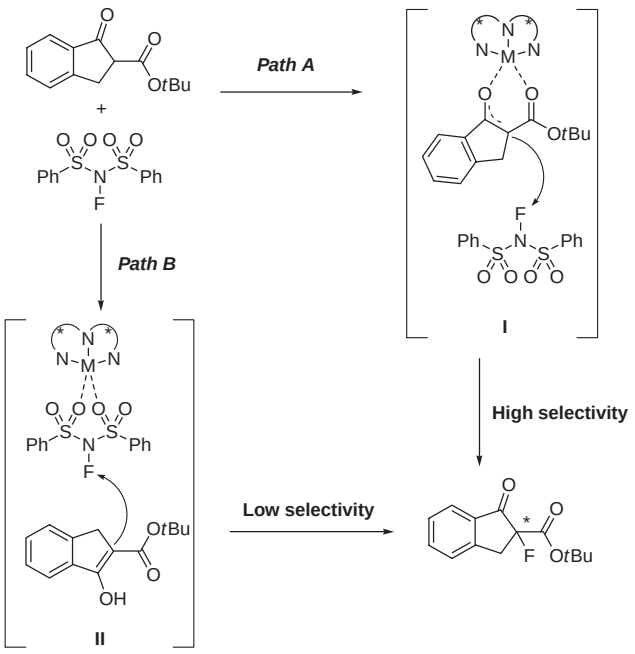
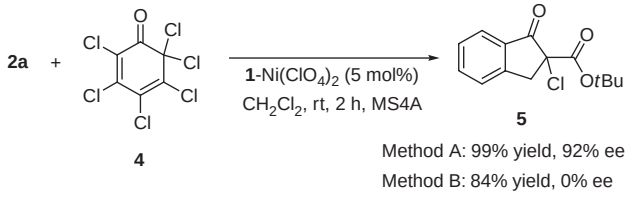


Figure 2. Probable reaction pathways.

These results suggest the existence of two different reaction pathways (Path A and Path B; Figure 2). In the first step in path A, the β-keto ester is activated by coordination of the chiral Lewis acid catalyst with two point binding (intermediate I), following which it reacts with NFSI to afford the fluorinated product. The reaction via path A proceeds with high enantioselectivity because the chiral centers on the catalyst are close to the pre-chiral center on the substrate. Path B proceeds via intermediate II, which is formed by the coordination of the Lewis acid catalyst with the sulfonyl oxygen on NFSI. Then, the activated NFSI reacts with the β-keto ester to afford the fluorinated product.[10] This reaction proceeds with low selectivity because the chiral centers on the catalyst are far from the pre-chiral center on the substrate. Although intermediate I and II are probably in equilibrium with each other, the slow addition of NFSI (Method A) forms intermediate I predominantly and prevents the equilibrium shifting toward intermediate II, while the slow addition of the β-keto ester (Method B) forms intermediate II and prevents the equilibrium shifting toward intermediate I.

Next, our catalyst system was applied to catalytic asymmetric chlorination using 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (**4**). As shown in Scheme 2, the chlorination by method A (slow addition of **4**) afforded the coresponding product **5** in high yield with excellent enantioselectivity,[11] whereas the reaction by method B (slow addition of **2a**) afforded a racemic product. In method B, the nickel catalyst would activate **4** by coordinating with a carbonyl oxygen on **4**.



Scheme 2. Catalytic asymmetric chlorination of **2a**.

In conclusion, efficient Lewis acid-catalyzed asymmetric fluorination and chlorination of β-keto esters were achieved with excellent enantioselectivity by using the hybrid chiral ligand **1**. The existence of two reaction pathways in the present reactions was strongly suggested. These two reaction pathways could be successfully controlled by simply changing the operation sequence.

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This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

References and Notes

1 Recent reviews for asymmetric α-fluorinations: a) V. A. Brunet, D. O'Hagan, *Angew. Chem., Int. Ed.* **2008**, *47*, 1179. b) C. Bobbio, V. Gouverneur, *Org. Biomol. Chem.* **2006**, *4*, 2065. c) P. M. Pihko, *Angew. Chem., Int. Ed.* **2006**, *45*, 544. d) G. K. S. Prakash, P. Beier, *Angew. Chem., Int. Ed.* **2006**, *45*, 2172. e) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119. f) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147.

2 a) L. Hintermann, A. Togni, *Angew. Chem., Int. Ed.* **2000**, *39*, 4359. b) R. Frantz, L. Hintermann, M. Perseghini, D. Broggini, A. Togni, *Org. Lett.* **2003**, *5*, 1709.

3 a) Y. Hamashima, K. Yagi, H. Takano, L. Tamas, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 14530. b) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, Y. Tsuchiya, K.-I. Moriya, T. Goto, M. Sodeoka, *Tetrahedron* **2006**, *62*, 7168.

4 a) N. Shibata, T. Ishimaru, T. Nagai, J. Kohno, T. Toru, *Synlett* **2004**, 1703. b) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem., Int. Ed.* **2005**, *44*, 4204.

5 J.-A. Ma, D. Cahard, *Tetrahedron: Asymmetry* **2004**, *15*, 1007.

6 K. Shibatomi, Y. Tsuzuki, S.-I. Nakata, Y. Sumikawa, S. Iwasa, *Synlett* **2007**, 551.

7 Method A: Lewis acid catalyst was prepared by refluxing a solution of **1** (0.02 mmol) and metal salt (0.1 mmol) in CH_2Cl_2 (2 mL) for 2 h in the presence of activated MS 4A (100 mg). After the complexation, MS 4A and extra metal salt were filtered off. To a mixture of Lewis acid catalyst, **2** (0.4 mmol) and activated MS 4A (100 mg) in CH_2Cl_2, was added dropwise a solution of NFSI (0.44 mmol) in CH_2Cl_2 (1 mL) over 1.5–23 h (1.5 h for **2a** and **2b**; 11 h for **2c**; 23 h for **2d**), and the mixture was stirred for an additional 0.5–1 h (0.5 h for **2a** and **2b**; 1 h for **2c** and **2d**).

8 Method B: Lewis acid catalyst was prepared by the same procedure as method A. To a mixture of Lewis acid catalyst, NFSI (0.44 mmol) and activated MS 4A (100 mg) in CH_2Cl_2, was added dropwise a solution of **2** (0.4 mmol) in CH_2Cl_2 (1 mL) over 2–23 h (2 h for **2a** and **2b**; 11 h for **2c**; 23 h for **2d**), and the mixture was stirred for additional 10 min–1 h (10 min for **2a** and **2b**; 1 h for **2c** and **2d**).

9 Method C: Lewis acid catalyst was prepared by the same procedure as method A. To a mixture of Lewis acid catalyst and activated MS 4A (100 mg) in CH_2Cl_2 (2 mL), **2** (0.4 mmol), and NFSI (0.44 mmol) were added successively. The mixture was stirred for 2–19 h.

10 One of the authors had earlier reported some related halogenation reactions by the Lewis acid activation of certain electrophilic halogenation reagents: a) Y. Zhang, K. Shibatomi, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 15038. b) Y. Zhang, K. Shibatomi, H. Yamamoto, *Synlett* **2005**, 2837. c) K. Shibatomi, H. Yamamoto, *Angew. Chem., Int. Ed.* **2008**, *47*, 5796.

11 The use of *N*-chlorosuccinimide as the chlorination reagent resulted in poor enantioselectivity of **5** (28% ee, 94% yield), even when method A was used.

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