Drug Development

Highly Enantioselective Catalytic Fluorination and Chlorination Reactions of Carbonyl Compounds Capable of Two-Point Binding**

Norio Shibata, Junji Kohno, Kazumi Takai, Takehisa Ishimaru, Shuichi Nakamura, Takeshi Toru,* and Shuji Kanemasa*

The enantioselective electrophilic halogenation of carbonyl compounds represents one of the best established strategies for the construction of chiral C–X bonds in organic chemistry.[1] The resulting chiral halo compounds, especially fluorine-containing chiral organic molecules, are very fascinating in the field of medicinal chemistry.[2] The unique hydrophobic, space-filling, and electronic properties of a fluorine atom can make substrates with C–F bonds useful candidates for drug development. Next to fluorination, enantioselective chlorination is also an important topic with regard to some aspects of pharmaceuticals.[3] Although recent rapid advances in the methodology of enantioselective halogenations have made great contributions in these fields,[4–6] more efficient and more flexible methods are required. In this paper we describe highly enantioselective fluorination and chlorination reactions of carbonyl compounds that are capable of two-point binding. Both of the halogenations are catalyzed by the catalyst dbfox-Ph/Ni^{II} with very high enantioselectivity up to 99% *ee*. Furthermore, we also present the first significant examples of asymmetric amplification in enantioselective halogenations starting with the catalyst at 45% enantiopurity to afford the halogenated compounds with significantly increased *ee* values of $>90\%$.

We initiated the study of asymmetric fluorination reaction of β-keto esters **1a**–**g**, since α-fluorinated β-keto esters such as telithromycin have attractive antibiotic activity.[7] Recently, we found that chiral Cu^{II} and Ni^{II} complexes of phenyl-bis(oxazoline) (box-Ph) effectively catalyze the enantioselec-

[*] Prof. Dr. N. Shibata, Prof. Dr. T. Toru
Department of Applied Chemistry
Graduate School of Engineering, Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555 (Japan)
Fax: (+81) 52-735-5442
E-mail: nozshiba@nitech.ac.jp
toru@nitech.ac.jp

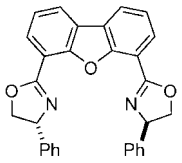
Prof. Dr. S. Kanemasa
Institute for Materials Chemistry and Engineering
Kyushu University
6-1 Kasugakoen, Kasuga 816-8580 (Japan)

J. Kohno, K. Takai, T. Ishimaru, Dr. S. Nakamura
Department of Applied Chemistry
Graduate School of Engineering, Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555 (Japan)

[**] This work was supported in part by the Japan Science & Technology (JST) Agency, Innovation Plaza Tokai. We also thank Dr. Akihiro Ishii of Central Glass Co., Ltd. for a gift of CF_3SO_2Cl.

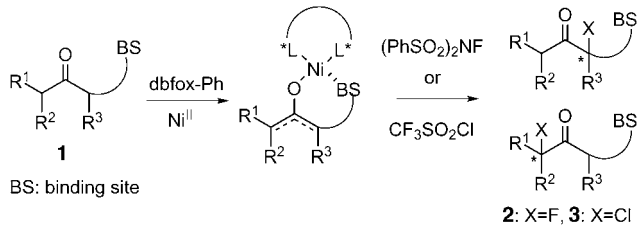
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200501041



dbfox-Ph

tive fluorination of β-keto esters with *N*-fluorobenzenesulfonimide (NFSI); however, the enantioselectivity was not high enough.[6d] In previous works by one of us, the dbfox-Ph ligand was highly effective in asymmetric Diels–Alder and Michael addition reactions.[8] Thus we turned to this ligand to improve the fluorination reaction. A solution of **1a** in CH_2Cl_2 was treated with 1.2 equiv of NFSI in the presence of a catalytic amount of dbfox-Ph/$Ni(ClO_4)_2{\cdot}6H_2O$ at room temperature to afford the α-fluoro compound **2a** in high yield with an extremely high enantioselectivity (Scheme 1; Table 1, entry 1, 99% *ee*). The ester **1a** proved to be the ideal yardstick to measure our results, as it has been studied by many investigators under a variety of conditions for enantioselective fluorinations.[4–6]

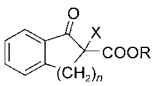
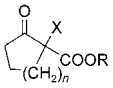
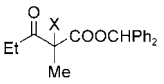
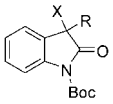
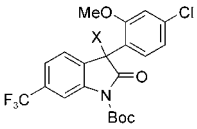
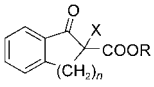


Scheme 1. Enantioselective halogenations of substrates capable of two-point binding using dbfox-Ph/Ni^{II} with NFSI or CF_3SO_2Cl.

The scope of the fluorination of a series of β-keto esters **1b–g** was investigated; we found that the dbfox-Ph/Ni^{II} catalyst exhibits excellent enantioselectivity as well (Table 1, entries 2–7). In most cases, our fluorination was more enantioselective than the reported procedures owing to the remarkable control of the enantioface of enolates by the dbfox-Ph/Ni^{II} complex.[9] It is notable that catalyst loading can be reduced to 2 mol% without loss of enantioselectivity (entries 1 and 11).

To demonstrate the further synthetic utility of this dbfox-Ph/Ni^{II} fluorination system, we tested other substrates capable of two-point binding. Pharmaceutically important fluorooxindoles[10] **2h–j** were selected as target molecules. Although we reported the enantioselective synthesis of fluorooxindoles using a combination of cinchona alkaloids and Selectfluor,[6c] no catalytic enantioselective method has been described. Under similar reaction conditions, a significant degree of enantioselectivity has been obtained irrespective of the substrates used (Table 1, entries 8–10). It is noted that fluorooxindole **2j** was converted into MaxiPost,[6c,10] an effective opener of maxi-K channels, by cleavage of the Boc group. This is the first example of a catalytic enantioselective preparation of MaxiPost.

Table 1: Enantioselective fluorination of **1** (X = H) to give **2** (X = F).[a]

Entry	Substrate **1** (X = H) Product **2** (X = F)		*t* [h]	Yield [%]	*ee* [%]
1		**a**: R = *t*Bu, *n* = 1	3	76	99 (*S*)
2		**b**: R = Ad, *n* = 1	2	71	99
3		**c**: R = L-Men, *n* = 1	2	66	99
4		**d**: Ad, *n* = 2	3	88	95
5		**e**: *t*Bu, *n* = 1	2	84	93
6		**f**: *t*Bu, *n* = 2	2	86	99
7[b]		**g**	18	75	83
8[c,d]		**h**: Me	35	73	93
9[c]		**i**: Ph	5	72	96
10[c]		**j**	14	71	93 (*S*)
11[e]		**a**: R = *t*Bu, *n* = 1	6	93	99 (*S*)

[a] Reaction conditions: A solution of **1** (1.0 equiv), NFSI (1.2 equiv), dbfox-Ph (0.11 equiv), and $Ni(ClO_4)_2{\cdot}6H_2O$ (0.1 equiv) in CH_2Cl_2 was stirred in the presence of 4-Å molecular sieves at room temperature unless otherwise noted. Enantiomeric excess was determined by chiral HPLC analysis. See the Supporting Information for details. Abbreviations: L-Men = L-menthyl, Ad = 1-adamantyl. [b] The reaction was carried out at 0°C. [c] $Ni(OAc)_2{\cdot}4H_2O$ (0.1 equiv) was used instead of $Ni(ClO_4)_2{\cdot}6H_2O$. [d] Enantiomeric excess was determined after cleavage of the Boc group. [e] dbfox-Ph (0.02 equiv) and $Ni(ClO_4)_2{\cdot}6H_2O$ (0.02 equiv) were used.

Highly enantioselective chlorinations of ketones, acid halides, and aldehydes have been reported; however, asymmetric chlorination of β-keto esters has relatively low enantioselectivity.[5] In addition, no enantioselective syntheses of α-chlorooxindoles, which are potentially important in medicinal chemistry, have been reported.[11] We were pleased to find that our dbfox-Ph/Ni^{II} system was also effective for the asymmetric chlorination of a series of substrates including β-keto esters **1a–d** and oxindoles **1i** and **1j** (Table 2). The substrates were chlorinated smoothly with CF_3SO_2Cl under our optimized conditions to produce **3a–d, 3i**, and **3j** with high enantioselectivity. Chlorooxindole **3j** can be converted to BMS225113, a pharmaceutically important chlorooxindole.[11] It is highly noted that CF_3SO_2Cl as a chlorinating agent is essential to achieve high enantioselectivity, since *N*-chlorosuccimide (NCS) under the same conditions provided poorer results (entry 2 vs entry 3).

Table 2: Enantioselective chlorination of **1** (X = H) to give **3** (X = Cl).[a]

Entry	**1**	R	**3**	*t* [h]	Yield [%]	*ee* [%]
1	**1a**	*t*Bu	**3a**	10	72	97
2	**1b**	Ad	**3b**	17	85	97
3[b]	**1b**	Ad	**3b**	3	85	54
4	**1c**	L-Men	**3c**	9	66	94
5	**1d**	Ad	**3d**	45	61 (71)[d]	98
6[c]	**1i**	Ph	**3i**	20	93	61
7[c]	**1j**	–	**3j**	17	93	60

[a] Reaction conditions: **1** (1.0 equiv), CF_3SO_2Cl (1.2 equiv), dbfox-Ph (0.11 equiv), and $Ni(ClO_4)_2 \cdot 6H_2O$ (0.1 equiv) were stirred in CH_2Cl_2 in the presence of 4-Å molecular sieves at room temperature unless otherwise noted. Enantioselectivity was determined by chiral HPLC analysis. See the Supporting Information for details. [b] NCS was used instead of CF_3SO_2Cl. [c] $Ni(OAc)_2 \cdot 4H_2O$ was used instead of $Ni(ClO_4)_2 \cdot 6H_2O$. *t*BuOMe was used as a solvent. [d] Conversion yield.

We finally examined experiments of chiral amplification[12,13] in the halogenations on our systems. Fluorinations of **1a** with NFSI were carried out in the presence of $Ni(ClO_4)_2 \cdot 6H_2O$ and dbfox-Ph, enantiopurities of which were varied from 11% to 60%. Figure 1 shows the relationship

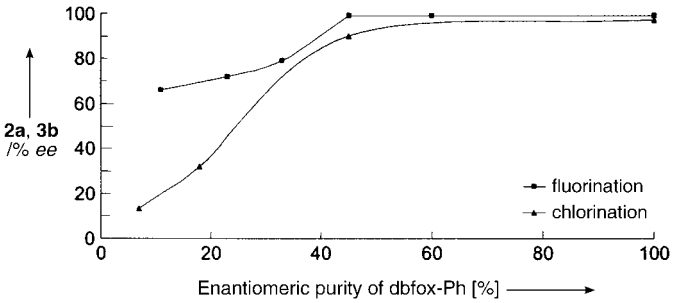


Figure 1. Chiral amplification in the halogenations of **1a**,**b** with NFSI or CF_3SO_2Cl catalyzed by dbfox-Ph/$Ni(ClO_4)_2 \cdot 6H_2O$.

between the enantiomeric purity of the dbfox-Ph ligand used and the enantioselectivity observed for **2a** when the molar ratio of dbfox-Ph to $Ni(ClO_4)_2 \cdot 6H_2O$ was 1.1:1 and the catalyst loading was 10 mol%. When the dbfox-Ph ligand had *ee* values of 45% and 11%, **2a** was obtained with 99% and 66% *ee*, respectively. A similar positive nonlinear effect of chiral amplification was also observed in the chlorination of **1b** with CF_3SO_2Cl under the same conditions, and dbfox-Ph with >45% enantiopurity was required to obtain the enantioenriched products **3b** with >90% *ee*.

In conclusion, the catalytic enantioselective fluorination and chlorination reactions of carbonyl compounds structurally capable of two-point binding were achieved with extremely high enantioselectivity by the use of the dbfox-Ph[14]/Ni^{II} complex. In addition, this system led to not only the first catalytic enantioselective synthesis of MaxiPost and BMS225113, but also the first observation of asymmetric amplification in halogenation reactions of β-keto esters.[13] We assumed octahedral complexes coordinated with a water molecule for **1a**/dbfox-Ph/Ni^{II}, **1j**/ dbfox -Ph/Ni^{II} optimized using MM2 in the light of the X-ray structure of the dbfox-Ph/Ni^{II} complex (Figure 2).[8] In these complexes, one of the faces

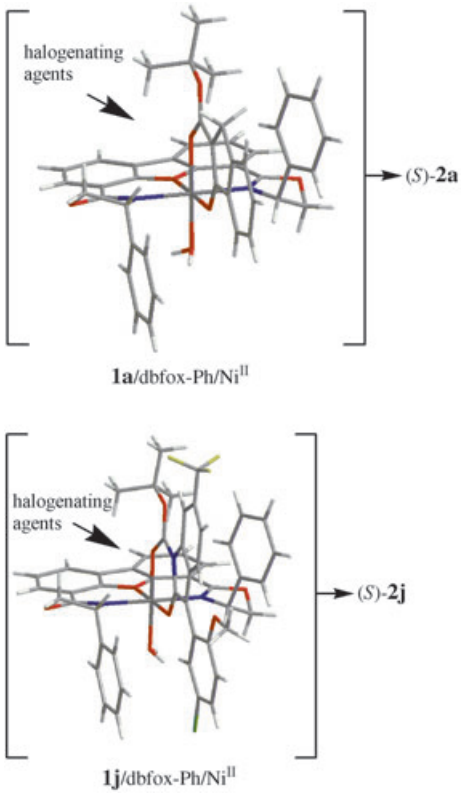


Figure 2. Optimized structures of the complexes of **1a**/dbfox-Ph/Ni^{II} and **1j**/dbfox-Ph/Ni^{II}.

is covered so efficiently that the halogenating agents approach from the *Si* face of the substrates. The details are now under investigation.

Received: March 22, 2005
Published online: June 8, 2005

Keywords: asymmetric amplification · asymmetric synthesis · enantioselectivity · fluorination · halogenation

[1] a) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147; b) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119; c) K. Muñiz, *Angew. Chem.* **2001**, *113*, 1701; *Angew. Chem. Int. Ed.* **2001**, *40*, 1653; d) S. France, A. Weatherwax, T. Lectka, *Eur. J. Org. Chem.* **2005**, *3*, 475.

[2] a) *Biomedical Aspects of Fluorine Chemistry* (Eds.: R. Filler, Y. Kobayashi), Kodansha/Elsevier Biomedical, Tokyo, **1982**; b) "Biomedical Frontiers of Fluorine Chemistry": *ACS Symp. Ser.* **1996**, 639; c) J. T. Welch, *Tetrahedron* **1987**, *43*, 3123.

[3] *The Chemistry of α-Haloketones, α-Haloaldehydes, α-Haloimines* (Eds.: N. D. Kimpe, R. Verhe), Wiley, New York, **1990**.

[4] a) L. Hintermann, A. Togni, *Angew. Chem.* **2000**, *112*, 4530; *Angew. Chem. Int. Ed.* **2000**, *39*, 4359; b) S. Piana, I. Devillers, A. Togni, U. Rothlisberger, *Angew. Chem.* **2002**, *114*, 1021; *Angew. Chem. Int. Ed.* **2002**, *41*, 979; c) D. Cahard, C. Audouard, J.-C. Plaquevent, N. Roques, *Org. Lett.* **2000**, *2*, 3699; d) B. Mohar, J. Baudoux, J.-C. Plaquevent, D. Cahard, *Angew. Chem.* **2001**, *113*, 4339; *Angew. Chem. Int. Ed.* **2001**, *40*, 4214; e) D. Y. Kim, E. J. Park, *Org. Lett.* **2002**, *4*, 545; f) Y. Hamashima, K. Yagi, H. Takano, L. Tamas, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 14530; g) B. Greedy, J. M. Paris, T. Vidal, V. Gouverneur,

Angew. Chem. **2003**, *115*, 3413; *Angew. Chem. Int. Ed.* **2003**, *42*, 3291; h) J.-A. Ma, D. Cahard, *Tetrahedron: Asymmetry* **2004**, *15*, 1007; i) F. A. Davis, P. Zhou, C. K. Murphy, G. Sundarababu, H. Qi, W. Han, R. M. Przeslawski, B.-C. Chen, P. Carroll, *J. Org. Chem.* **1998**, *63*, 2273.

[5] a) L. Hintermann, A. Togni, *Helv. Chim. Acta* **2000**, *83*, 2425; b) H. Wack, A. E. Taggi, A. M. Hafez, W. J. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 1531; c) M. Marigo, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Eur. J.* **2004**, *10*, 2133; d) M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108; e) N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 4790; f) Y. Zhang, K. Shibatomi, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 15038; g) A. M. Hafez, A. E. Taggi, H. Wack, J. Esterbrook, T. Lectka, *Org. Lett.* **2001**, *3*, 2049; h) S. France, H. Wack, A. E. Taggi, A. M. Hafez, T. R. Wagerle, M. H. Shah, C. L. Dusich, T. Lectka, *J. Am. Chem. Soc.* **2004**, *126*, 4245.

[6] a) N. Shibata, E. Suzuki, Y. Takeuchi, *J. Am. Chem. Soc.* **2000**, *122*, 10728; b) N. Shibata, E. Suzuki, T. Asahi, M. Shiro, *J. Am. Chem. Soc.* **2001**, *123*, 7001; c) N. Shibata, T. Ishimaru, E. Suzuki, K. L. Kirk, *J. Org. Chem.* **2003**, *68*, 2494; d) N. Shibata, T. Ishimaru, T. Nagai, J. Kohno, T. Toru, *Synlett* **2004**, 1703; e) N. Shibata, T. Ishimaru, M. Nakamura, T. Toru, *Synlett* **2004**, 2509; f) N. Shibata, T. Tarui, Y. Doi, K. L. Kirk, *Angew. Chem.* **2001**, *113*, 4593; *Angew. Chem. Int. Ed.* **2001**, *40*, 4461.

[7] A. Denis, F. Bretin, C. Fromentin, A. Bonnet, G. Piltan, A. Bonnefoy, C. Agouridas, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2019.

[8] a) S. Kanemasa, Y. Oderaotoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, D. P. Curran, *J. Am. Chem. Soc.* **1998**, *120*, 3074; b) S. Kanemasa, Y. Oderaotoshi, *J. Synth. Org. Chem. Jpn.* **1998**, 368; c) K. Itoh, S. Kanemasa, *J. Am. Chem. Soc.* **2002**, *124*, 13394.

[9] The fluorination reaction occurred with high enantioselectivity for the substrates containing sterically bulky substituents located on the ester side. For the β-keto esters **1** with methyl or cyclohexyl ester groups, slightly lower enantioselectivities were obtained (R = Me, 65% *ee*; R = *c*C_6H_{11}, 91% *ee*).

[10] V. K. Gribkoff, J. E. Starrett, Jr., S. I. Dworetzky, P. Hewawasam, C. G. Boissard, D. A. Cook, S. W. Frantz, K. Heman, J. R. Hibbard, K. Huston, G. Johnson, B. S. Krishnan, G. G. Kinney, L. A. Lombardo, N. A. Meanwell, P. B. Molinoff, R. A. Myers, S. L. Moon, A. Ortiz, L. Pajor, R. L. Pieschl, D. J. Post-Munson, L. J. Signor, N. Srinivas, M. T. Taber, G. Thalody, J. T. Trojnacki, H. Wiener, K. Yeleswaram. S. Yeola, *Nat. Med.* **2001**, *7*, 471.

[11] V. K. Gribkoff, D. J. Post-Munson, S. W. Yeola, C. G. Boissard, P. Hewawasam, WO 2002030868.

[12] *Comprehensive Asymmetric Catalysis* (Eds.: E. R. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[13] For asymmetric amplification of the dbfox-Ph/Ni^{II} catalyst in the Diels–Alder reaction, see ref. [8a].

[14] Just before submission of this manuscript, a report on dbfox/Zn^{II}-catalyzed halogenations appeared. L. Bernardi, K. A. Jørgensen, *Chem. Commun.* **2005**, 1324.

