Journal of Fluorine Chemistry 130 (2009) 1049–1053

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Short communication

Asymmetric synthesis of α-fluoro-α-sulfenyl-β-ketoesters using DBFOX–Ph/Ni(II) complex

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ARTICLE INFO

Article history:
Received 3 August 2009
Received in revised form 19 August 2009
Accepted 20 August 2009
Available online 26 August 2009

Keywords:
Sulfenylation
Fluorination
β-Ketoesters
Chiral catalysis
Enantioselective

ABSTRACT

Enantioselective α-sulfenylation of α-fluoro-β-ketoesters **4** with phenylsulfenyl chloride catalyzed by DBFOX–Ph/Ni(II) complex afforded the corresponding α-fluoro-α-sulfenyl-β-ketoesters **2** in moderate to good yields with excellent enantiomeric excesses up to 93% ee. α-Fluoro-α-sulfenyl-β-ketoesters can be effectively converted to tri-fluorinated α-sulfenylcarboxylates by the use of DAST, which should be useful intermediates for the synthesis of non-racemized fluorinated isosteres of pharmaceutically attractive SM_{32}. The enantioselective α-phenylsulfenylation as well as α-pentafluoro-phenylsulfenylation of non-fluorinated β-ketoesters **5** were also carried out under the same catalyst conditions affording up to 95% ee of the products **6–8**.

1. Introduction

Chiral organosulfur-containing compounds are synthetic targets attracting much recent interest in view of both their ambiguous synthetic utilities as chiral building blocks and chiral ligands, as well as unique biological activities [1]. α-Sulfenylated carbonyl compounds are particularly attractive synthetic intermediates since they have been used for a variety of organic transformations [2]. Among various strategies that have been available for this purpose, enantioselective electrophilic sulfenylation of carbonyl compounds, including aldehydes, ketones, 1,3-dicarbonyl compounds or their equivalents with various electrophilic sulfenylating reagents, which allows the direct conversion of racemic or achiral carbonyl compounds to chiral α-sulfenyl carbonyl compounds in a single operation, is an important process in organic synthesis [3,4]. Despite the undoubted utility of this process, however, there had been relatively few successful reports of catalytic electrophilic enantioselective sulfenylation until recent years [4]. Wang et al. described for the first time the α-sulfenylation of aldehydes and ketones in the presence of chiral pyrrolidine trifluoromethane-sulfonimide [4a]. Subsequently, Jørgensen and coworkers reported an elegant catalytic enantioselective sulfenylation of aldehydes using prolinol organocatalysts in high yields and excellent enantioselectivities [4b–d]. Togni et al. also disclosed the enantioselective α-sulfenylation of β-ketoesters using chiral Ti(TADDOLato) complexes [4e–4g]. Although these methodologies are efficient, clearly more efficient catalysts are required to attain sufficient reactivity, selectivity and versatility. Incidentally, fluorine-containing organic compounds have attracted much attention because of their utility in the field of pharmaceuticals, agrochemicals and material sciences [5]. Chiral organofluorine compounds containing a fluorine atom bonded directly to a stereogenic center have been utilized in the pharmaceutical chemistry and in materials science [6]. As part of our studies on the design and synthesis of biologically active organofluorine compounds [7,8], we required chiral α-fluoro-α-sulphenyl-β-ketoesters **2** as synthetic intermediates for non-racemized fluoro-isosteric analogue of SM_{32} which has potent biological activity (Fig. 1) [9].

A series of α-fluoro-α-sulfenyl-β-ketoesters **2** should also be used as versatile building templates to prepare other pharmaceutically attractive molecules. Two general strategies were devised for this purpose. One of these involves the enantioselective fluorination of α-sulfenyl-β-ketoesters **3** to compounds **2**. The second strategy uses an enantioselective installation of the sulfenyl group to α-fluoro-β-ketoesters **4** (Fig. 1). In this paper, we examined both strategies and found that the enantioselective sulfenylation of α-fluorinated β-ketoesters catalyzed by DBFOX–Ph/Ni(II) catalyst is effective for the synthesis of chiral, non-racemic α-fluoro-α-sulfenyl-β-ketoesters **2** in high enantioselectivities with up to 93% ee. Non-fluorinated β-ketoesters **5** were also nicely sulfenylated under the same catalytic conditions to provide the sulfenylated compounds **6–8** with up to 95% ee.

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doi:10.1016/j.jfluchem.2009.08.004

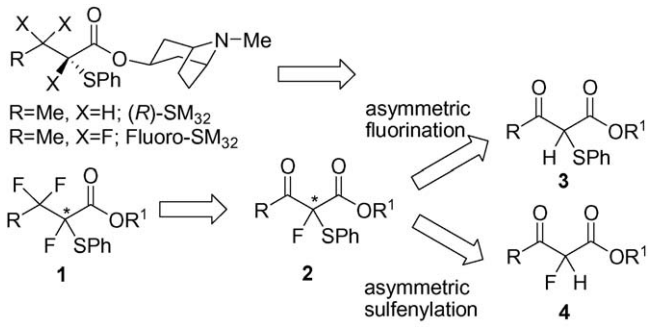
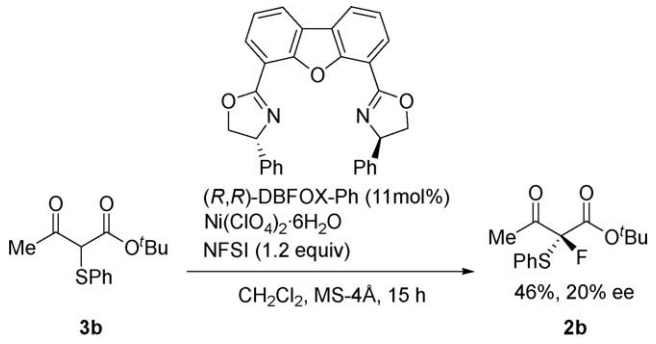
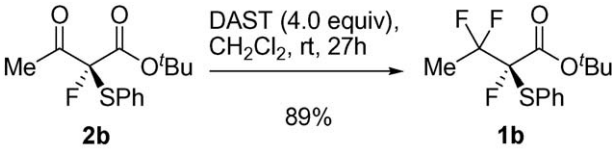


Fig. 1. Two general strategies for the synthesis of fluoro-SM_{32} via chiral, non-racemic α-fluoro-α-sulfenyl-β-ketoesters **2**.



Scheme 1. DBFOX–Ph/Ni(II) catalyzed enantioselective fluorination of α-sulfenyl-β-ketoester **1b**.



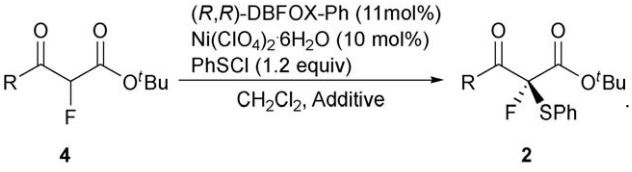
Scheme 2. Synthesis of tri-fluorinated carboxylate **1b** from **2b** by DAST.

2. Results and discussion

Recently, we reported the catalytic enantioselective fluorination of β-ketoesters, oxindoles, malonates and oxa-thiazolidinones by DBFOX–Ph/metal complexes to furnish corresponding fluorinated compounds in high yields with excellent enantioselectivities up to 99% ee [10]. Two-point binding is explained as being indispensable to achieve high enantioselectivity [10–12]. We therefore first attempted the fluorination of α-sulfenylated β-ketoester **3b** with *N*-fluorobenzenesulfonimide (NFSI) under our previously reported conditions; namely, in the presence of $Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol%), DBFOX–Ph (11 mol%) in CH_2Cl_2. However, the level of enantioselectivity in this reaction was disappointingly low even for substrates capable of chelation to the metal center (Scheme 1, 46% yield, 20% ee) [13].

This unsuccessful result prompted us to explore an alternative strategy, i.e., enantioselective α-sulfenylation of α-fluorinated β-ketoesters **4** instead of enantioselective α-fluorination of α-sulfenyl-β-ketoesters. Asymmetric α-functionalization of α-fluorinated carbonyl compounds and their equivalents is an important topic in recent years in the field of organic chemistry [14,15], however, there is only one example available for the asymmetric sulfenylation of α-fluorinated carbonyl compounds [4e]. α-Sulfenylation of α-fluorinated β-ketoester **4a** was examined with phenylsulfenyl chloride (PhSCl) as an electrophilic agent in the presence of a catalytic amount of $Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol%), and DBFOX–Ph (11 mol%) in CH_2Cl_2, at room temperature. Corresponding α-sulfenylated α-fluoro-β-ketoester **2a** was obtained in moderate yield with high enantioselectivity (Table 1, entry 1, 93% ee) [13]. Neither chemical yield nor enantioselectivity was improved in different solvent systems like THF and toluene (runs 2 and 3). It is interesting to note that the addition of a molecular sieve (MS-4 Å) was essential for this reaction (run 4). A stoichiometric amount of organic base such as diisopropylethylamine and proton sponge was not an effective additive in this reaction (runs 5 and 6), but the addition of an inorganic base such as potassium carbonate improved the

Table 1
Enantioselective α-sulfenylation of α-fluorinated-β-ketoesters **4a**–**c** with PhSCl catalyzed by DBFOX–Ph/Ni(II).

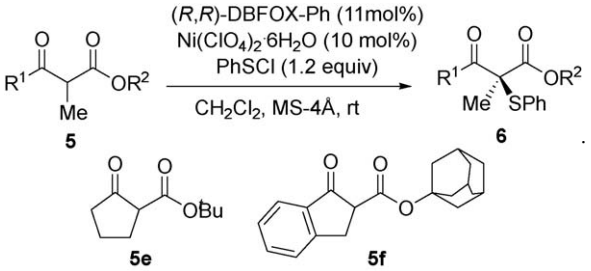


4a: R=Ph, **4b**: R=Me, **4c**: R=Et

Run[a]	4	Additive	Time (h)	2	Yield (%)	ee (%)[b]
1	**4a**	MS-4 Å	17	**2a**	48 (80)[c]	93
2[c]	**4a**	MS-4 Å	84	**2a**	35	82
3[d]	**4a**	MS-4 Å	84	**2a**	7	80
4	**4a**	None	12	**2a**	NR	–
5[e]	**4a**	MS-4 Å + DIEA	24	**2a**	48	17
6[e]	**4a**	MS-4 Å + PS	24	**2a**	8	54
7[e]	**4a**	MS-4 Å + K_2CO_3	27	**2a**	65	87
8[f]	**4a**	MS-4 Å	96	**2a**	Trace	–
9	**4b**	MS-4 Å	18	**2b**	53 (70)[c]	86
10	**4c**	MS-4 Å	17	**2c**	62 (80)[c]	87

[a] The reaction of **4** with PhSCl (1.2 equiv.) was carried out in the presence of $Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol%), (*R*,*R*)-DBFOX–Ph (11 mol%), MS-4 Å in CH_2Cl_2 at room temperature.
[b] ee was determined by HPLC analysis using CHIRALPAK AD-H.
[c] THF was used as solvent.
[d] Toluene was used as solvent.
[e] Diisopropylethylamine (1.0 equiv.), proton sponge (PS) or K_2CO_3 (1.0 equiv.) was added.
[f] $Zn(OAc)_2$ was used instead of $Ni(ClO_4)_2{\cdot}6H_2O$.

Table 2
Scope of the asymmetric α-sulfenylation of non-fluorinated β-ketoesters **5** to **6**.



Entry[a]	5	R^1	R^2	Time (h)	6	Yield (%)	ee (%)[b]
1	**5a**	Me	^{t}Bu	17	**6a**	76 (96)[c]	88
2	**5b**	Me	^{t}Am	18	**6b**	61 (84)[c]	90
3	**5c**	Et	^{t}Bu	17	**6c**	43 (88)[c]	88
4	**5d**	Ph	^{t}Bu	19	**6d**	49 (95)[c]	95
5	**5e**			23	**6e**	78	45
6[d]	**5e**			30	**6e**	61	59
7	**5f**			0.5	**6f**	57	25

[a] The reaction of **5** with PhSCl (1.2 equiv.) was carried out in the presence of $Ni(ClO_4)_2·6H_2O$ (10 mol%), (*R*,*R*)-DBFOX–Ph (11 mol%), MS-4 Å in CH_2Cl_2 at room temperature.
[b] ee was determined by HPLC analysis.
[c] Based upon recovered starting material.
[d] THF was used as solvent.

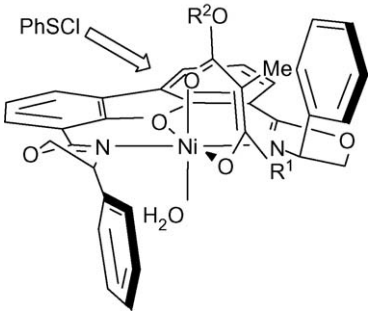
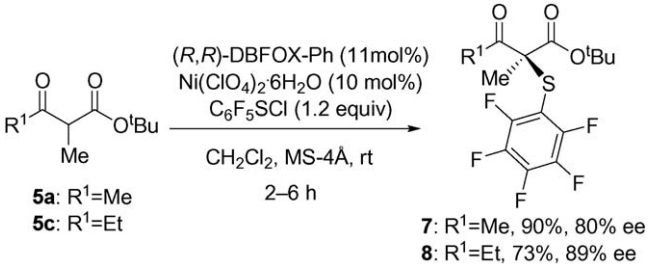


Fig. 2. Proposed transition state structure.



Scheme 3. Pentafluorosulfenylation of **5** by the use of C_6F_5SCl.

conversion of this reaction without a major loss of enantiopurity (run 7). When changing the Lewis acid from $Ni(ClO_4)_2·6H_2O$ to $Zn(OAc)_2$, only a trace amount of the product was obtained even after a longer reaction time (run 8). Therefore, we concluded that the best condition for this reaction was the one mentioned in run 1. Next, to examine the generality of this catalytic enantioselective α-sulfenylation of α-fluoro-β-ketoesters **4** by DBFOX–Ph/Ni(II) complexes, we studied the sulfenylation of other β-ketoesters **4b** and **4c**. As can be seen from the results summarized in Table 1, the corresponding α-fluoro-α-sulfenylated β-ketoesters **2b** and **2c** were obtained in moderate yields with high enantioselectivities (runs 9 and 10) [13]. The molecular sieves play an important role in the reaction (run 4 vs. others), but the exact mechanisms are not clear. It is highly likely that it should activate the $Ni(ClO_4)_2·6H_2O$ by the coordination as one of the ligands.

Resulting α-fluoro-α-sulfenyl-β-ketoester **2b** was nicely transformed to tri-fluorinated α-sulfenyl carboxylate **1b** by DAST in 89%, which should be a useful intermediate for the synthesis of fluoro-SM_{32} (Scheme 2).

To explore the scope of the reaction, non-fluorinated β-ketoesters were next used as substrates for the enantioselective sulfenylation reaction. As expected, the DBFOX–Ph/Ni(II) complex is a general catalyst for the enantioselective sulfenylation of acyclic β-ketoesters to afford corresponding non-fluorinated α-sulfenylated β-ketoesters in good yields with high enantioselectivities up to 95% ee [13]. On the other hand, sulfenylation of cyclic β-ketoesters **5e** and **f** shows a somewhat low enantioselectivity of 59 ee and 25% ee, respectively (entries 5–7), which is a limitation of the present method (Table 2).

On the basis of the reported X-ray structure of the (*R*,*R*)-DBFOX–Ph/Ni(II) complex [10], we assumed octahedral complexes coordinated with a water molecule for DBFOX–Ph/Ni(II)/**5** as shown in Fig. 2. In the complex, the Re face of **5** is shielded by one of the phenyl groups of DBFOX–Ph so that PhSCl approaches from the *Si* face of the substrates (Fig. 2).

Finally, pentafluorosulfenylation of **5a**, **c** was instead examined by the use of C_6F_5SCl as an electrophile. The reaction was completed rapidly and gave both high yields and high enantioselectivities of **7** and **8** (Scheme 3) [13].

3. Conclusion

In conclusion, we have synthesized chiral, non-racemic α-fluoro-α-sulfenyl-β-ketoesters **2** by the enantioselective electrophilic sulfenylation of α-fluoro-β-ketoesters **4** in the presence of a catalytic amount of DBFOX–Ph/Ni(II) complex. The methodology can be applicable for the enantioselective α-phenylsulfenylation as well as α-pentafluoro-phenylsulfenylation of non-fluorinated β-ketoesters **5**. Although DBFOX–Ph–metal(II) complexes have been actively used for asymmetric reactions including halogenation, hydroxylation, Michael addition and Diels–Alder reactions, this sequence serves as the first example of sulfenylation using DBFOX–Ph/metal(II) complex. Total synthesis of the fluoro-SM_{32} is now being developed.

4. Experimental

4.1. General procedure for the enantioselective catalytic sulfenylation reaction

$Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol%) and (*R*,*R*)-DBFOX–Ph (11 mol%) were stirred under vacuum for 2 h at room temperature. Dry dichloromethane (1.0 ml) and MS-4 Å (substrate/MS-4 Å = 1:500 mol/g) were added under nitrogen atmosphere and stirred for 1 h. Then, β-ketoesters **4** or **5** (0.19–0.26 mmol) in CH_2Cl_2 (2.0 ml) was added to the catalyst solution. After stirring for another 30 min at room temperature, PhSCl or C_6F_5SCl (1.2 equiv.) in CH_2Cl_2 (0.8–1.2 ml) were added to the mixture. The reaction was stirred at rt for several hours with monitoring by TLC. The reaction mixture was filtrated and the solvent was evaporated under reduced pressure, and purified by column chromatography on aluminium oxide 90 active basic silica gel eluting with hexane/AcOEt, hexane/CH_2Cl_2 or hexane/Et_2O, hexane/CH_2Cl_2 to give **2** or **6**. The ees of the products were determined by chiral HPLC on a CHIRALPAK AD-H or CHIRALCEL OJ-H column (250 mm × 4.6 mm).

2a: Colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz): 1.40 (*s*, 9H), 2.20 (*d*, *J* = 3.2 Hz, 3H), 7.30–7.40 (*m*, 3H), 7.54–7.58 (*m*, 2H); ^{19}F NMR ($CDCl_3$, 188 MHz): −132.6 (*d*, *J* = 2.6 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 196.1 (*d*, *J* = 28.3 Hz), 161.8 (*d*, *J* = 27.9 Hz), 135.5 (*d*, *J* = 1.6 Hz), 129.7, 128.9, 127.2, 105.0 (*d*, *J* = 242.6 Hz) 85.2, 27.7, 26.1; IR (neat): 3061, 2981, 2929, 1732, 1474, 1441, 1395, 1371, 1279, 1153, 1066, 898, 834, 749, 691 cm^{-1}; MS (EI): *m*/*z* 284 (M^+), 184 (M^++1–COOtBu); HPLC: (CHIRALPAK AD-H, hexane/^{i}PrOH = 99/1, 0.5 ml/min, 211 nm) tR (minor-isomer) = 14.3 min, tR (major-isomer) = 15.7 min (86% ee); α_D^{25} −29.3 (*c* = 0.62, $CHCl_3$ 86% ee).

6a: Pale yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz): 1.45 (*s*, 3H), 1.49 (*s*, 9H), 2.38 (*s*, 3H), 7.29–7.43 (*m*, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 198.8, 168.5, 136.6, 129.5, 129.3, 128.7, 83.5, 66.5, 27.9, 26.1; IR (neat): 3054, 2979, 2934, 1712, 1474, 1440, 1370, 1256, 1162, 1124, 853, 750, 692, 479 cm^{-1}; MS (EI): *m*/*z* 280 (M^+), 180 (M^++1–COOtBu); HPLC: (CHIRALPAK AD-H, hexane/^{i}PrOH = 99/1, 0.8 ml/min, 211 nm) tR (minor-isomer) = 11.9 min, tR (major-isomer) = 13.0 min (88% ee); α_D^{25} −59.9 (*c* = 0.50, $CHCl_3$ 88% ee) ([α]$_D$ −50.8 (*c* = 0.535, CH_2Cl_2 88% ee) [4 g]).

6b: Yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz): 0.90 (*t*, *J* = 7.6 Hz, 3H), 1.45 (*s*, 3H), 1.46 (*s*, 3H), 1.48 (*s*, 3H), 1.72–1.86 (*m*, 2H), 2.39 (*m*, 3H), 7.25–7.42 (*m*, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 198.8, 168.4, 136.6, 129.5, 129.3, 128.7, 86.1, 66.5, 33.8, 26.2, 25.3, 20.9, 8.4; IR (neat): 2977, 2934, 1712, 1370, 1354, 1260, 1156, 1121, 926, 842, 749, 692, 463 cm^{-1}; MS (EI): *m*/*z* 294 (M^+), 194 (M^++1–COO^{t}Bu); HPLC: (CHIRALCEL OJ-H, hexane/^{i}PrOH = 99/1, 0.8 ml/min, 220 nm) tR (minor-isomer) = 17.8 min, tR (major-isomer) = 21.5 min (90% ee); α_D^{25} −55.6 (*c* = 0.67, $CHCl_3$ 90% ee) ([α]$_D$ −49.6 (*c* = 0.48, CH_2Cl_2 86% ee) [4g]).

8: Pale yellow crystal; ^{1}H NMR ($CDCl_3$, 200 MHz): 1.14 (*t*, *J* = 7.2 Hz, 3H), 1.49 (*s*, 3H), 1.51 (*s*, 9H), 2.50 (dq, *J* = 17.9, 7.2 Hz, 1H), 3.08 (dq, *J* = 17.8, 7.2 Hz, 1H); ^{19}F NMR ($CDCl_3$, 188 MHz): −160.1 to −159.8 (*m*, 2F), −148.0 (tt, *J* = 4.0, 20.4 Hz, 1F), −128.2 (ddd, *J* = 4.0, 5.3, 22.4 Hz, 2F); IR (KBr): 2994, 2943, 1710, 1642, 1519, 1489, 1374, 1281, 1163, 1128, 1094, 981, 862, 844, 772, 672, 480, 405 cm^{-1}; MS (EI): *m*/*z* 384 (M^+), 199 (M^+–SC_6F_5); HPLC: (CHIRALPAK AS-H, hexane, 0.2 ml/min, 220 nm) tR (major-isomer) = 26.1 min, tR (minor-isomer) = 33.0 min (89% ee); α_D^{25} −19.1 (*c* = 0.60, $CHCl_3$ 89% ee); mp: 50–51 °C (hexane).

Acknowledgements

This study was financially supported in part by a Joint Project JSPS-CNRS, as well as by Grants-in-Aid for Scientific Research (B) No. 21390030 (JSPS). We thank Kishida Chemical Ltd. for the generous gift of DBFOX–Ph.

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