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Short communication

N-Fluoro-(3,5-di-*tert*-butyl-4-methoxy)benzenesulfonimide (NFBSI): A sterically demanding electrophilic fluorinating reagent for enantioselective fluorination

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ABSTRACT

We disclose here a novel electrophilic fluorinating reagent, *N*-fluoro-(3,5-di-*tert*-butyl-4-methoxy)-benzenesulfonimide (NFBSI) as a sterically demanding analogue of popular fluorinating reagent, *N*-fluorobenzenesulfonmide (NFSI). NFBSI improves the enantioselectivity of the products as much as 18% for the cinchona alkaloid-catalyzed enantioselective fluorination of silylenol ether compared to the use of NFSI.

Optically active organic molecules, having a C–F stereogenic center, are important and versatile synthons for a number of medicinally important products [1]. Many papers on the asymmetric syntheses of optically active organo-fluorine compounds have been reported based on a building block approach and a direct method for the construction of the carbon–fluorine bond. Among them, direct enantioselective electrophilic fluorination is going to be quite practical and provides chiral fluoro-organic compounds with a high level of enantioselectivities in the range of 90% ee [2]. In 2000, we reported the enantioselective fluorination of silylenol ethers, β-keto esters and oxindoles using a stoichiometric amount of cinchona alkaloids/Selectfluor® combination [3a–d], and a similar approach was also independently reported by Cahard and co-workers [3e–f]. The catalytic version of this method was not easy but several years later we finally achieved it by using *N*-fluorobenzenesulfonmide (NFSI) and a catalytic amount of cinchona alkaloids in the presence of inorganic salts [4]. Around the same period, metal salt-catalyzed enantioselective fluorination of β-keto esters and related compounds were successively reported by several groups, including ours, since the first report by Togni's group in 2000 [5,6]. Furthermore the enantioselective fluorination of aldehydes catalyzed by proline and its analogues is also a recent topic in this field [7,8]. Research into the development of effective chiral catalysts and ligands for enantioselective fluorination reaction has thus been active. Commercially available fluorinating reagents, Selectfluor® [9] and NFSI [10] are two of the most commonly used reagents for this process, in particular NFSI since it is more effective in many cases. On the other hand, there are few strategies for the development of an enantioselective electrophilic fluorination reaction focusing on fluorinating reagents. We therefore hypothesized that a sterically demanding analogue of NFSI could improve the enantioselectivity of the fluorination products more than with NFSI. In this paper, we report the synthesis of a novel, sterically demanding electrophillic fluorinating reagent, *N*-fluoro-(3,5-di-*tert*-butyl-4-methoxy)benzenesulfonimide (NFBSI) and evaluate its effectiveness as an agent for enantioselective fluorination of silylenol ether in the presence of a catalytic amount of cinchona alkaloids. Our preliminary results demonstrate that NFBSI has an advantage by improving the enantioselectivity of the fluorination process compared to the results obtained by the use of popular NFSI (Fig. 1).

NFBSI (**1**) was readily prepared according to the route outlined in Scheme 1. Namely, sulfonyl chloride **3** [11], which was prepared from 1,3-di-*tert*-butyl-2-methoxybenzene (**2**) with chlorosulfuric acid (2.0 equiv.) in $CHCl_3$ at −10 °C for 10 min [11], was treated with ammonium chloride (3.0 equiv.) and 10 M NaOH at room temperature for 4 h to afford aryl sulfonamide **4**. The treatment of sulfonamide **4** with **3** (3.0 equiv.) in the presence of sodium

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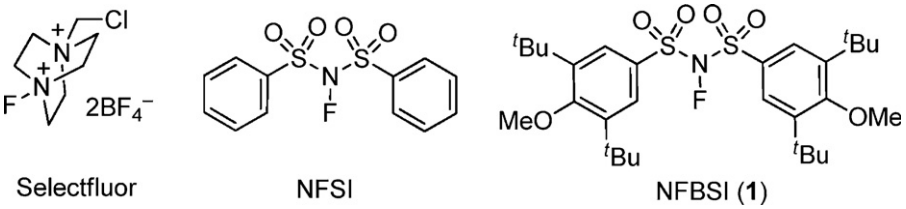


Fig. 1. Structures of electrophilic fluorinating reagents, Selectfluor®, NFSI and NFBSI (**1**).

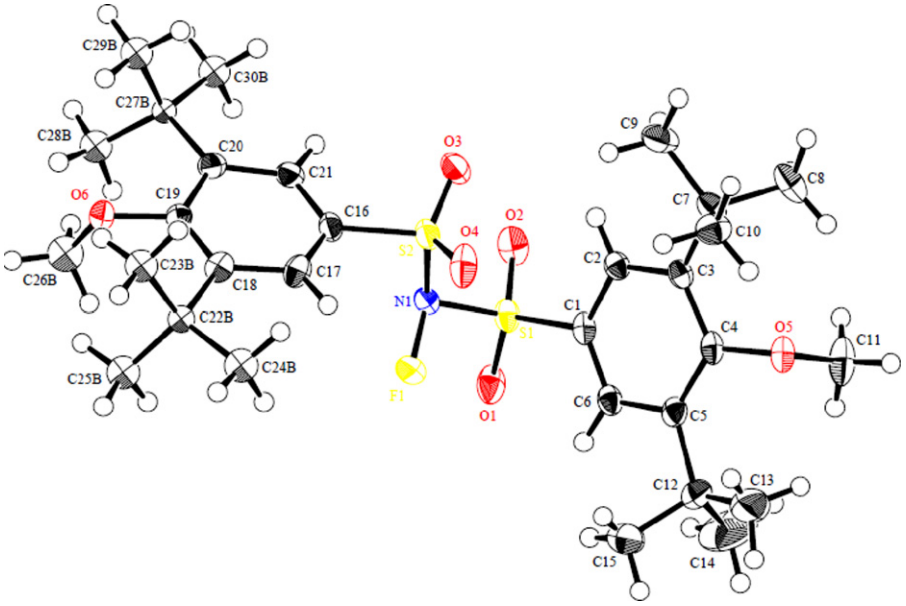
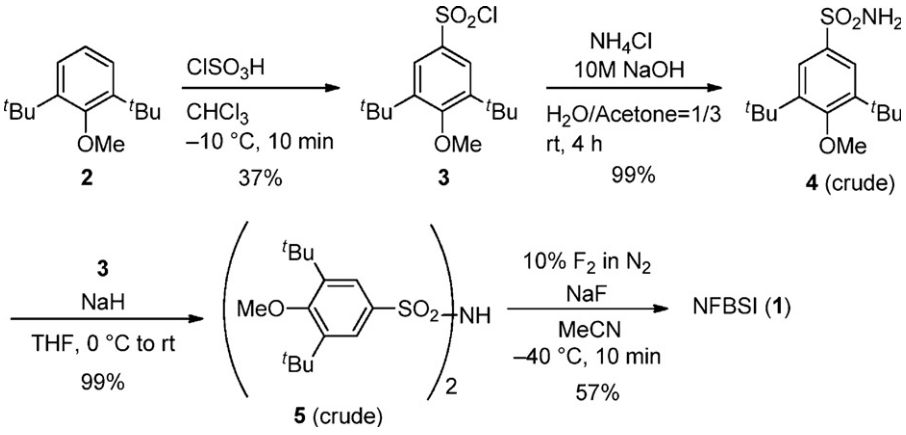


Fig. 2. ORTEP X-ray crystallographic structure of NFBSI (**1**).

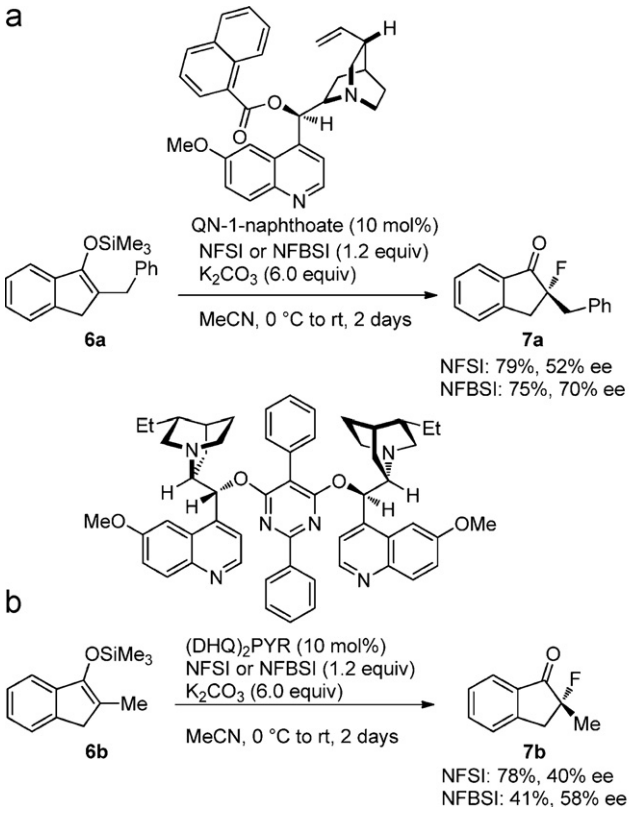
hydride (1.0 equiv.) in THF provided a symmetrical sulfonimide **5**. Finally, target fluorinating reagent, NFBSI (**1**) was obtained in a pure state from **5** in 57% yield by passing 10% molecular fluorine diluted with nitrogen in MeCN in the presence of spray-dried NaF (10 equiv.) at −40 °C for 10 min followed by purification by silica-gel column chromatography (Scheme 1).

NFBSI (**1**) is a colourless crystalline solid, which is stable at room temperature and can be kept in a refrigerator for several months. Single-crystal X-ray crystallographic analysis of NFBSI (**1**) showed that the central fluorine atom of NFBSI is covered by bulky substituents (Fig. 2).

With the target electrophilic fluorinating reagent NFBSI (**1**) in hand, next it was of interest to compare the efficiency and asymmetric induction of NFBSI in the fluorine transfer reaction with the same parameters when the best fluorinating reagent, NFSI, was used. The cinchona alkaloid-catalyzed enantioselective fluorination reaction [4] was selected as a model reaction. The substrates for the reaction were carefully chosen to demonstrate the efficiency of our novel reagent, since enantioselective synthesis of α-fluoroketones still has a challenge [4] different from the case of enantioselective synthesis of α-fluorinated β-keto esters [6]. Selection of cinchona alkaloids for each reaction was based on our previous observations for the same fluorination reaction [4] in which the fluorination products had been isolated via column chromatography on silica-gel and identified by comparison of their MS- and NMR-spectral data as well as HPLC analysis with literature



Scheme 1. Synthesis of fluorinating reagent, NFBSI (**1**).



Scheme 2. Cinchona alkaloid-catalyzed enantioselective fluorination of silylenol ethers **6a**,**b** with NFSI or NFBSI (**1**).

values [4,12]. We first attempted the enantioselective fluorination of silylenol ether of 2-benzyl-1-indanone **6a** in the presence of a catalytic amount of quinine-1-naphtoate with an excess amount of K_2CO_3 with NFBSI or NFSI in MeCN (Scheme 2a). NFBSI provided an improved optical yield of 70% ee for the α-fluorinated indanone **7a**,

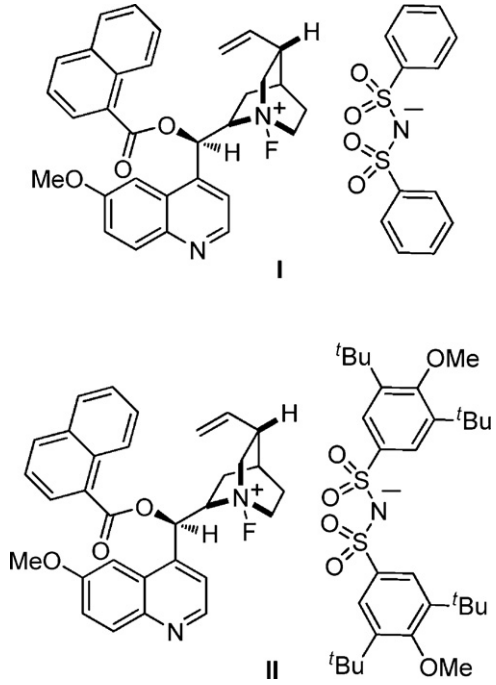


Fig. 3. *N*-fluorinated ammonium salt of cinchona alkaloid **I** and **II** generated *in situ* with NFSI or NFBSI.

while NFSI gave **7a** in 52% ee. The enantioselectivity for the fluorination of less bulky silylenol ether **6b** was also improved from 40% ee to 58% ee by the use of NFBSI instead of NFSI, although the chemical yield decreased (Scheme 2b). The use of NFBSI instead of NFSI thus resulted in as much as an 18% increase in enantioselectivity, but the chemical yield of the fluorinated products was sacrificed. The increase in enantioselectivity and the decrease in chemical yield are surely due to the steric origin of NFBSI. As mentioned in our previous papers and others [3,4], the active fluorinating reagent should be an *in situ* generated common *N*-fluorinated ammonium of cinchona alkaloid **I** and **II** rather than NFSI and NFBSI themselves via transfer-fluorination reaction. However, the anionic parts of **I** and **II** are different. Steric bulk effect originated from an anion of (3,5-di-*tert*-butyl-4-methoxy)benzenesulfonimide in **II** presumably helped to enhance the enantiomeric excess of the products **7**, while the reactivity was sacrificed instead (Fig. 3; Scheme 2).

In conclusion, we have developed a novel electrophilic fluorinating reagent, NFBSI as a sterically demanding analogue of popular fluorinating reagent NFSI, and investigated its utility for cinchona alkaloid-catalyzed enantioselective fluorination of silylenol ethers [13–16]. The enantioselectivities of their fluorinated compounds were improved as much as 18% by using NFBSI (**1**) compared to the use of NFSI; however, the reactivity of the reagent decreased due to steric hindrance. Improvement of enantiomeric excess without any sacrifice in isolated yield of the products controlled by fluorinating reagents is the next challenge. We are now working in this direction.

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[13] Synthesis of **1**: To a stirred solution of **5** (701 mg, 1.21 mmol) in MeCN (25 mL) in the presence of sodium fluoride (508 mg, 12.1 mmol) was introduced 10% F_2 gas in N_2 at −40 °C for 10 min. Insoluble materials were removed by filtration, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (hexane/AcOEt = 98/2) and gave **1** (414 mg, 57%) as a colourless crystalline solid. M.p. = 135–136 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 36H), 3.75 (s, 6H), 7.09 (s, 4H); ^{19}F NMR (188 MHz, $CDCl_3$) δ −38.6 (s); IR (KBr): 2971, 1396, 1182 cm^{-1}; EIMS *m*/*z* (rel intensity): 600 (M^+, 5.0), 582 (14), 283 (28), 91 (47), 57 (100).
[14] General procedure for the catalytic enantioselective fluorination of **6**: Cinchona alkaloid (10 mol%) and **1** (1.2 equiv) in MeCN (1.0 mL) were stirred under nitrogen atmosphere at room temperature for 30 min. The K_2CO_3 (6.0 equiv) was then added to the solution, and the reaction mixture was stirred for 30 min at 0 °C. A solution of **6** in MeCN (0.5 mL) was added to the catalyst solution. The reaction was stirred at the temperature for 2 days with monitoring by TLC. The reaction was then stopped by the addition of 1 N HCl. The reaction mixture was diluted with AcOEt, washed with saturated aqueous sodium bicarbonate solution, brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica-gel eluting with Hexane/AcOEt to give the fluorinated compounds 7. The ees of the products were determined by HPLC analysis on CHIRALCEL OJ-H column.
[15] Synthesis of **7a**: Reaction of **6a** (22.1 mg, 0.075 mmol), **1** (54.0 mg, 0.090 mmol), QN-1-naphthoate (3.6 mg, 0.0075 mmol) and K_2CO_3 (62.2 mg, 0.45 mmol) in MeCN at 0 °C and purification by silica gel column chromatography (hexane/AcOEt = 80/20) gave **7a** (13.5 mg, 75%, 70% ee).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.96 (dd, *J* = 14.3, 30.2 Hz, 1H), 3.15 (dd, *J* = 17.6, 23.1 Hz, 1H), 3.38 (dd, *J* = 13.0, 17.0 Hz, 1H), 3.41 (dd, *J* = 13.9, 14.2 Hz, 1H), 7.24–7.30 (m, 5H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.61 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$) δ −153.3 (dddd, *J* = 13.0, 13.9, 23.1, 30.2 Hz, 1F); ^{13}C NMR (150.9 MHz, $CDCl_3$) (200.8 (d, *J* = 18.2 Hz), 150.4 (d, *J* = 3.9 Hz), 136.2, 134.6 (d, *J* = 4.1 Hz), 133.9, 130.3, 128.4, 128.2, 127.2, 126.6, 125.1, 97.5 (d, *J* = 188.6 Hz), 40.3 (d, *J* = 24.6 Hz), 37.2 (d, *J* = 24.6 Hz); IR (neat): 3066, 3031, 2924, 1726, 1606, 1496, 1468, 1306, 1216, 1092, 1032, 913, 734, 701 cm^{-1}; EI MS: *m*/*z* 240 (M^+); HPLC: (CHIRALCEL OB-H, Hexane/iPrOH = 90/10, 1.0 ml/min, 254 nm) t_R (major-(R)-isomer) = 9.7 min, t_R (minor-(S)-isomer) = 12.6 min (70% ee). The absolute configuration of **7a** has already been determined. See, references [3b,4,12].
[16] Synthesis of **7b**: Reaction of **6b** (21.9 mg, 0.10 mmol), **1** (72.2 mg, 0.120 mmol), $(DHQ)_2PYR$ (8.8 mg, 0.010 mmol) and K_2CO_3 (83.2 mg, 0.600 mmol) in MeCN at 0 °C and purification by silica gel column chromatography (hexane/AcOEt = 90/10) gave **7b** (6.8 mg, 41%, 58% ee).; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.63 (d, *J* = 22.8 Hz, 3H), 3.29 (dd, *J* = 12.2, 17.4 Hz, 1H), 3.41 (dd, *J* = 22.8, 17.4 Hz, 1H), 7.38–7.45 (m, 2H), 7.65 (td, *J* = 7.5, 1.2 Hz, 1H), 7.8 (dd, *J* = 7.9, 0.6 Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$) δ −151.5 (ddq, *J* = 22.8, 12.2, 22.8 Hz, 1F); EIMS: *m*/*z* 164 (M^+); HPLC: (CHIRALCEL OB-H, hexane/iPrOH = 80/20, 1.0 ml/min, 254 nm) t_R (major-(R)-isomer) = 8.5 min, t_R (minor-(S)-isomer) = 27.4 min (58% ee). The absolute configuration of **7b** has already been determined. See, references [3b,4,12].