Novel Enantioselective Fluorinating Agents, (R)- and (S)-N-Fluoro-3-tert-butyl-7-nitro-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-Dioxides

Norio Shibata, Zhaopeng Liu, and Yoshio Takeuchi*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930–0194, Japan. Received July 3, 2000; accepted August 21, 2000

Enantioselective fluorinating agents, (R)- and (S)-N-fluoro-3-tert-butyl-7-nitro-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxides (BNBT-F, 2) are readily prepared in 3 steps from racemic 3-tert-butyl-7-nitro-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxides (5) via optical resolution and fluorination. These agents make accessible both enantiomers of optically active quaternary α-fluoro carbonyl compounds in modest to high enantioselectivities. X-ray crystallographic analysis of chiral 2 reveals a unique structure wherein the nitrogen atom is highly pyramidalized and fluorine occupies an axial position.

Key words asymmetric fluorination; N-fluorosultam; α-fluoroketone

The extremely high reactivity of electrophilic fluorinating agents such as molecular fluorine, FClO3, and CF3OF made selective fluorination reactions highly problematic. This limitation has been largely overcome by the more recent introduction of easy to handle fluorinating agents, of which N-fluoropyridinium salts, N-fluoroquinuclidinium salts and N-fluorosulfonamides are representative. Among current issues in this field, agent-controlled enantioselective fluorination remains a major challenge. Chiral N-fluorosulfonamide derivatives have been prepared in one approach to solving this problem. For example, we recently reported a novel chiral sultam derivative, N-fluoro-3-cyclohexyl-3-methyl-2,3-dihydro-benzo[1,2-d]isothiazole 1,1-dioxide (CMIT-F, 1), as an enantioselective fluorinating agent. Unfortunately, the results to date with this class of agent have been less than satisfactory with respect to both chemical yield and enantioselectivity. In this paper, we report an additional enantioselective fluorinating agent, N-fluoro-3-tert-butyl-7-nitro-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (BNBT-F, 2) which is effective in the enantioselective fluorination of cyclic ketones.

During our development of CMIT-F (1), we observed that the enantioselectivity of the fluorination reaction was dependent on the difference in steric bulkiness of the two substituents at the chiral center. To take advantage of this, we converted Oppolzer's sultam (3) to the N-fluoro sultam 3, which has both a tert-butyl group and hydrogen at the chiral center. We were disappointed to find that, under the conditions of the reaction with lithium enolates, 3 furnished the corresponding imine 4. The easy loss of HF is clearly associated with the acidity of the proton at the chiral center. With these results in mind, we designed a new N-F type fluorinating agent, BNBT-F (2). The proton at the chiral center in 2 should be significantly less acidic than that in 3, and the differential bulk of two substituents at the chiral center should be efficient enough to induce high enantioselection. Based on a precedent in the literature, the electron withdrawing nitro group was introduced into the aromatic ring to increase the fluorinating ability of the agent.

Preparation of BNBT-F Chiral 2 was easily prepared from racemic 3-tert-butyl-7-nitro-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (5) in 3 steps, including optical resolution. The sultam 5, prepared from 3-tert-butyl-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (5), was derivatized with (+)-10-camphorsulfonyl chloride to furnish the diastereomeric mixture of 6 in moderate yield, accompanied by 45% of unreacted 5. Diastereomer separation of 6 was effected by silica gel chromatography, and eluted with ethyl acetate/hexane to give the less polar isomer, (3R)-6 (21%), and the more polar isomer, (3S)-6 (31%). It is interesting to note that the mother liquid obtained by the recrystallization of recovered 5 (50% hexane in ethyl acetate) gave optical pure (R)-5 in 20% yield. Removal of the chiral auxiliary of (3R)-6 or (3S)-6 was achieved with LiOH in aqueous THF to furnish (R)-5 or (S)-5 in 82% and 87% yield, respectively. Finally, fluorination of (R)-5 with FClO3 in THF gave (R)-2 in 66% yield. In the same way, (S)-2 was obtained in 83% yield (Chart 1). X-ray crystallography was used to unambiguously determine the structure and absolute stereochemistry of (S)-2.

Molecular Structure of (S)-BNBT-F The molecular structure of (S)-BNBT-F (2) is shown in Figs. 2 and 3. The configuration of the nitrogen atom carrying fluorine in 2 is

![Chart 1](image)

Fig. 1

* To whom correspondence should be addressed. e-mail: takeuchi@ms.toyama-mpu.ac.jp © 2000 Pharmaceutical Society of Japan
found to be pyramidal, with the sum of the bond angles around the nitrogen atom equaling 324.6°. The bond lengths of N(1)–S(1) and N(1)–C(1) are 1.685 (2) and 1.490 (3) Å, respectively. The length of the N(1)–F(1) bond is 1.425 (3) Å, slightly longer than that of the N–F bond of typical amines (1.406 (16) Å for F–NR1R2). To our slight surprise, fluorine is antiperiplanar to the hydrogen atom at the chiral center, in contrast to our previous observation. The dihedral angle F(1)-N(1)–C(1)–H(1) is 160.8°. The bulky tert-buty1 moiety occupies the equatorial position, and the small hydrogen atom is axial. Fluorine, rather than the lone pair of nitrogens, takes an axial orientation, probably due to steric interactions with the bulky tert-buty1 moiety.

### Table 1. Enantioselective Fluorination of Ketones 7 with 2

<table>
<thead>
<tr>
<th>Ketone 7</th>
<th>Product 8</th>
<th>ee (%)</th>
<th>Yield (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{7a})</td>
<td>(\text{8a})</td>
<td>62[^a]</td>
<td>79</td>
<td>(R)</td>
</tr>
<tr>
<td>(\text{7b})</td>
<td>(\text{8b})</td>
<td>44[^a]</td>
<td>76</td>
<td>(S)</td>
</tr>
<tr>
<td>(\text{7c})</td>
<td>(\text{8c})</td>
<td>60[^a]</td>
<td>59</td>
<td>(R)</td>
</tr>
<tr>
<td>(\text{7d})</td>
<td>(\text{8d})</td>
<td>49[^b]</td>
<td>55</td>
<td>(R)</td>
</tr>
<tr>
<td>(\text{7e})</td>
<td>(\text{8e})</td>
<td>43[^c]</td>
<td>73</td>
<td>ND[^d]</td>
</tr>
<tr>
<td>(\text{7f})</td>
<td>(\text{8f})</td>
<td>52[^c]</td>
<td>74</td>
<td>(S)</td>
</tr>
<tr>
<td>(\text{7g})</td>
<td>(\text{8g})</td>
<td>57[^c]</td>
<td>40</td>
<td>(R)</td>
</tr>
<tr>
<td>(\text{7h})</td>
<td>(\text{8h})</td>
<td>69[^b]</td>
<td>70</td>
<td>ND[^d]</td>
</tr>
<tr>
<td>(\text{7i})</td>
<td>(\text{8i})</td>
<td>60[^c]</td>
<td>56</td>
<td>ND[^d]</td>
</tr>
</tbody>
</table>

[^a]: Chiralcel OB column (10% iPrOH/hexane).  
[^b]: Chiralcel OJ column (10% iPrOH/hexane).  
[^c]: Chiralcel OJ column (EtOH).  
[^d]: Ref. 7.  
[^e]: ND: not determined.
Enantioselective Fluorination of Prochiral Enolates by BNBT-F

With the target agent BNBT-F (2) in hand, we examined the ability of 2 to effect the enantioselective fluorination of enolates of a series of tetralones and indanones 7. Fluorination of the preformed lithium enolate of 2-methyl-1-tetralone (7a) with (R)-2 in THF at 50 °C furnished (R)-2-fluoro-2-methyl-1-tetralone (8a) in 79% yield with 62% ee. Other results of enantioselective fluorination using both (R)- and (S)-2 are summarized in Table 1. Chiral agents 2 make accessible both enantiomers of optically active quaternary α-fluoro carbonyl compounds in modest to high enantioselectivities. The absolute stereochemistry of 8 was determined by comparison of the specific rotation with that of the authentic samples reported.7)

On the bases of the X-ray crystallographic structure of 2 and the reaction mechanism of the fluorination by CMIT-F (1) reported in a previous paper,7 we propose a working model for the fluorination of 7 with (S)-2. At the asymmetric center of 2, the bulky tert-butyl group occupies a pseudo-equatorial position, whereas the hydrogen atom is in an axial position. The fluorine atom occupies an axial position, and, as a consequence, the N–F bond is almost perpendicular to the benzene ring of 2. The sulfonyle oxygen in the equatorial position can coordinate to the lithium ion of the enolate. 7)

Moreover, a stacking interaction between the benzene rings of 2 and 7 is expected to be energetically favorable. Therefore, 7 is predicted to approach 2 at the less hindered α-face, as shown in Fig. 4. In summary, we have synthesized BNBT-F (2) and have found it to be a new agent for enantioselective fluorination with moderate to high enantioselectivity. X-ray crystallographic analysis of 2 revealed that the N–F bond [1.425(3) Å] is slightly longer than that of Davis's (−) -N-fluoro-2,10-(3,3-dichlorocarbosultam) 1.420(6) Å,8) and slightly shorter than that of CMIT-F [1.435(3) Å].9) A relationship between N–F bond lengths and fluorination efficiency is now under investigation.

Experimental

General Methods

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra (cm⁻¹) were recorded on a Perkin-Elmer 1600 spectrometer. 1H-NMR spectra were measured as solutions in CDCl₃, and chemical shifts are expressed in ppm relative to internal Me₄Si (0.00 ppm) and were recorded on a JEOL GX-270 (270 MHz) or a Varian Gemini 300 (300 MHz) spectrometer. 19F-NMR spectra were measured with CFCI as an internal standard and were taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts are quoted as negative δ values. EI mass spectra were taken with a JEOL JMS-D300 spectrometer. Column chromatography and preparative TLC were performed on BW-Bond Elute silica gel 60 (230–400 mesh).

Fig. 4. Schematic Representation of the Transition State in the Fluorination of Enolates with (S)-2

J = 11.7 Hz, 1H, NH), 7.45 (d, J = 8.5 Hz, 1H, ArH), 8.24 (dd, J = 8.5, 2.4 Hz, 1H, ArH), 8.60 (d, J = 2.4 Hz, 1H, ArH). MS m/z: 284 (M⁺), 269 (M⁺–Me), 227 (M⁺–tert-Bu). HRMS Calcd for C₁₂H₁₀N₂O₄S: 284.0830. Found 284.0838. Anal. Calcd for C₁₂H₁₀N₂O₄S: C, 50.69; H, 5.67; N, 9.85. Found: C, 50.54; H, 5.60; N, 8.99.

N-Camphorsulfonyl-3-tert-butyl-7-nitro-3,4-dihydro-benzol[e][1,2]-thiazine 1,1-Dioxide (6)

A solution of 5 (1.04 g, 3.66 mmol) in THF (50 ml) was treated with NaH (60% oil dispersion, 292 mg, 7.72 mmol) at 0 °C and stirred at room temperature for 1.5 h. (+)-10-камфоро сульфонил хлорид was treated with water, with, and dried (MgSO₄), then concentrated in vacuo. The residue was chromatographed (40% CH₂Cl₂ in hexane) to give the less polar isomer (R)-6 (0.38 g, 21%), the more polar isomer (S)-6 (0.56 g, 31%) and 0.47 g of unreacted 5 as a white powder. The recovered 5 was recrystallized (50% AcOEt in hexane) to give racemic colorless crystals (0.26 g, 25%) and the enantiorp (R)-5 (0.21 g, 20%) from the mother liquid.

(3R)-N-Camphorsulfonyl-3-tert-butyl-7-nitro-3,4-dihydro-benzol[e][1,2]-thiazine 1,1-Dioxide (6a)

A solution of 5 (0.37 g, 1.28 mmol) in THF (50 ml) was treated with 2 M LiOH (7 ml) at room temperature and stirred for 1 h. The reaction mixture was dropped into a solution of 3-tert-butyl-7-nitro-3,4-dihydro-benzol[e][1,2]-thiazine 1,1-Dioxide (6) (0.79 g, 1.58 mmol) in THF (15 ml) at room temperature and stirred for 1 h. The reaction mixture was dropped onto crushed ice and extracted with AcOEt (150 ml × 3). The combined organic layer was washed with water, brine, and dried (MgSO₄), then concentrated in vacuo. The residue was chromatographed (50% CH₂Cl₂ in hexane, then 50% AcOEt in hexane) to give 5 (4.06 g, 68%) as a white powder. mp 194 °C (AcOEt/hexane). IR (KBr) cm⁻¹: 3284, 3019, 2967, 1328, 1215, 758, 669. 1H-NMR (CDCl₃): δ: 1.06 (s, 9H, tert-Bu), 2.96 (dd, J = 17.3, 11.7 Hz, 1H, CH₃H), 3.06 (dd, J = 17.3, 4.1 Hz, 1H, CH₃HAr), 3.61 (dd, J = 12, 11, 4.1 Hz, 1H, NCH<), 4.42 (d, J = 14.9 Hz, 2H, CH₂), 4.56 (d, J = 11.0, 7.36 Hz, 1H, NCH<), 7.58 (d, J = 8.3 Hz, 1H, ArH), 8.40 (d, J = 8.3, 2.4 Hz, 1H, ArH), 8.71 (d, J = 2.4 Hz, 1H, ArH). MS m/z: 499 (M⁺ + 1), 498 (M⁺ – Me), 441 (M⁺–tert-Bu). HRMS Calcd for C₁₂H₁₀N₂O₄S: 498.1495. Found 498.1463. Anal. Calcd for C₁₂H₁₀N₂O₄S: C, 52.99; H, 6.06; N, 5.62. Found: C, 52.76; H, 5.89; N, 5.44.

(3S)-N-Camphorsulfonyl-3-tert-butyl-7-nitro-3,4-dihydro-benzol[e][1,2]-thiazine 1,1-Dioxide (6b)

A solution of 5 (0.35 g, 1.28 mmol) in THF (50 ml) was treated with 2 M LiOH (5 ml) at room temperature and stirred for 1 h. The reaction mixture was dropped onto crushed ice and extracted with AcOEt (50 ml × 3). The combined organic layer was washed with water, brine, and dried (MgSO₄), then concentrated in vacuo. The residue was chromatographed (20% AcOEt in hexane) to give 5 (0.37 g, 82%) as colorless crystals. mp 225 °C (AcOEt/hexane). [α]D²⁰ = +58.6° (c = 0.48, CHCl₃). IR (KBr) cm⁻¹: 3200, 2967, 1745, 1534, 1216, 758, 668. 1H-NMR (CDCl₃): δ: 0.89 (s, 3H, gem Me), 1.10 (s, 3H, gem Me), 1.14 (s, 9H, tert-Bu), 1.40 (m, 1H, 1.64 (m, 1H), 2.05 (m, 3H), 2.36 (2 m, 2H), 2.34 (dd, J = 14.9, 7.3 Hz, 1H, CH₃HAr), 3.35 (dd, J = 14.9, 11.0 Hz, 1H, CH₃HAr), 3.39, 4.38 (ABq, J = 14.9 Hz, 2H, CH₂), 4.56 (d, J = 11.0, 7.6 Hz, 1H, NCH<), 7.58 (d, J = 8.3 Hz, 1H, ArH), 8.40 (d, J = 8.3, 2.4 Hz, 1H, ArH), 8.71 (d, J = 2.4 Hz, 1H, ArH). MS m/z: 499 (M⁺ + 1), 498 (M⁺ – Me), 441 (M⁺–tert-Bu). HRMS Calcd for C₁₂H₁₀N₂O₄S: 498.1495. Found 498.1463. Anal. Calcd for C₁₂H₁₀N₂O₄S: C, 52.99; H, 6.06; N, 5.62. Found: C, 52.98; H, 6.05; N, 5.60.
eral oil, 386 mg, 9.66 mmol) under Ne at 0 °C, and the mixture was stirred at room temperature for 1 h. To this mixture was introduced freshly prepared FClO3 gas generated from KClO4 (4.46 g, 32.2 mmol) and FSO3H (32.2 g, 322 mmol) for 3 h. The reaction was quenched by a saturated aqueous NH4Cl solution and the resulting mixture was extracted with AcOEt (50 mL×3). The combined organic layer was washed with water, dried (Na2SO4), then concentrated in vacuo. The residue was chromatographed on silica gel (30% AcOEt in hexane) to give (R)-BNBTF(2) (1.28 g, 66%) as colorless crystals. mp 143—145 °C (AcOEt/hexane). [α]D 26° (c = 0.61, CHCl3), IR (KBr) cm⁻¹: 3019, 2958, 1534, 1251, 759, 169.19F-NMR (CDCl3, CFCl3) δ : -70.9 (brs, 9F), 1H-NMR (CDCl3) δ : 1.18 (s, 9H, tert-Bu), 3.07 (m, 1H, CH2Ar), 3.37 (m, 1H, CH2Ar), 4.14 (brs, 1H, NCH3), 7.60 (d, J = 8.5 Hz, 3H, ArH), 8.41 (dd, J = 8.5, 2.2 Hz, 1H, ArH), 8.45 (d, J = 2.2 Hz, 1H, ArH). MS m/z: 302 (M⁺) 282 (M⁺ - HF), 264 (M⁺ - 2HF), 246 (M⁺ - 3HF), 127 (89). 

(M)-1-Fluoro-3-tert-butyl-7-nitro-3,4-dihydro-2H-benzo[1,2,3]triazine 1.1-Dioxide (5)-BNBTF(2) In the same way, (S)-0.82 g, 83% was obtained from (S)-8a (0.39 g, 3.26 mmol) as colorless crystals. [α]D 37° (c = 0.69, CHCl3), IR (KBr) cm⁻¹: 1743, 1487, 1473, 1454, 967, 949. 1H-NMR (CDCl3) δ : 7.31 (t, 2H, CH2Ar), 7.25 (d, J = 7.6 Hz, 1H, ArH), 7.35 (t, J = 7.5 Hz, 1H, ArH), 7.52 (td, J = 7.3, 1.5 Hz, 1H, ArH), 8.07 (dd, J = 7.6, 1.5 Hz, 1H, ArH). MS m/z: 178 (M⁺). HRMS Calcd for C10H10O: 178.0794. Found 178.0801. 

General Procedure for Asymmetric Fluorination of Ketones with 1:2-Fluoro-2-methyl-1-tetralone (8a) To a stirred solution of 2-methyl-1-tetralone (16 mg, 0.10 mmol) in THF (1.0 mL) was added a 1.0 mol solution of LHMDS in THF (0.15 ml, 0.15 mmol) under nitrogen at −78 °C. The mixture was stirred for 10 min at −78 °C, warmed to 0 °C, stirred for an additional 1 h, and cooled to −50 °C. A solution of (R)-2 (36 mg, 0.12 mmol) in THF (1 mL) was added to the reaction mixture. After the reaction was complete, as indicated by TLC, the reaction mixture was quenched by the addition of saturated aqueous NH4Cl (1 mL). The aqueous layer was extracted with AcOEt (5 mL×3), the combined organic phase was washed with water (10 mL), brine (10 mL), and dried (MgSO4), then concentrated to give 8a (14.1 mg, 79%, 62% ee) as a light yellow oil after purification by silica gel column chromatography (10% AcOEt in hexane). [α]D 19° (c = 0.60, CHCl3), IR (neat) cm⁻¹: 3023, 1730. 19F-NMR δ : −152.8 (quintet, J = 22.5, 11.0 Hz). [α]D 1734. 19F-NMR (CDCl3, CFCl3) δ : −70.9 (brs, 9F), 1H-NMR (CDCl3) δ : 1.18 (s, 9H, tert-Bu), 3.07 (m, 1H, CH2Ar), 3.37 (m, 1H, CH2Ar), 4.14 (brs, 1H, NCH3), 7.60 (d, J = 8.5 Hz, 3H, ArH), 8.41 (dd, J = 8.5, 2.2 Hz, 1H, ArH), 8.45 (d, J = 2.2 Hz, 1H, ArH). MS m/z: 302 (M⁺) 282 (M⁺ - HF), 264 (M⁺ - 2HF), 246 (M⁺ - 3HF), 127 (89). 

Fluorination of 2-methyl-1-indanone (21 mg, 0.1 mmol) with a 1 M solution of LHMDS (1.5 mL, 1.5 mmol) and (R)-2 (36 mg, 0.12 mmol) gave 8b (9.6 mg, 40%, 57% ee) as a light yellow oil after purification by silica gel column chromatography (benzene): [α]D 32° (c = 0.75, CHCl3). IR (neat) cm⁻¹: 3023, 1726. 19F-NMR δ : −154.72 (m). [α]D 1734. 19F-NMR (CDCl3, CFCl3) δ : −29.2 (dd, J = 29.0, 14.2 Hz, 1H, CH2Ar), 3.15 (dd, J = 29.7, 14.2 Hz, 1H, CH2Ar), 7.25 (d, J = 7.6 Hz, 1H, ArH), 7.35 (t, J = 7.5 Hz, 1H, ArH), 7.52 (td, J = 7.3, 1.5 Hz, 1H, ArH), 8.07 (dd, J = 7.6, 1.5 Hz, 1H, ArH). MS m/z: 240 (M⁺+1). HRMS Calcd for C12H14F5O: 240.0953. Found 240.0958. 

Fluorination of 2-methyl-2-fluoro-1-indanone (8f) Fluorination of 2-methyl-1-indanone (25.2 mg, 0.1 mmol) with a 1 M solution of LHMDS (1.5 mL, 1.5 mmol) and (R)-2 (36 mg, 0.12 mmol) gave 8f (9.6 mg, 40%, 57% ee) as a light yellow oil after purification by silica gel column chromatography (benzene): [α]D 32° (c = 0.75, CHCl3). IR (neat) cm⁻¹: 3023, 1726. 19F-NMR δ : −154.72 (m). [α]D 1734. 19F-NMR (CDCl3, CFCl3) δ : −29.2 (dd, J = 29.0, 14.2 Hz, 1H, CH2Ar), 3.15 (dd, J = 29.7, 14.2 Hz, 1H, CH2Ar), 7.25 (d, J = 7.6 Hz, 1H, ArH), 7.35 (t, J = 7.5 Hz, 1H, CH2Ar), 7.43 (t, J = 7.6 Hz, 2H, ArH), 7.66 (t, J = 7.6 Hz, 1H, ArH), 7.82 (d, J = 7.6 Hz, 1H, ArH). MS m/z: 240 (M⁺+1). HRMS Calcd for C12H14F5O: 240.0953. Found 240.0958. 

Acknowledgement This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan. N. S. wishes to thank the Uehara Memorial Foundation for support. We are also grateful to Dr. Bando Masahiko, Institute of Organic Chemistry, Otsuka Pharmaceutical Company, for his x-ray analysis of the absolute structure of compound (S)-2. We are much indebted to Dr. Kenneth L. Kirk (National Institutes of Health) for his constant advice and Ms. Hiromi Hiroko Kakuda for providing insightful comments on the molecular structure of (S)-2. 

References and Notes
1018 (1986).