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# Selectfluor-promoted fluorination of piperidinyl olefins

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ABSTRACT

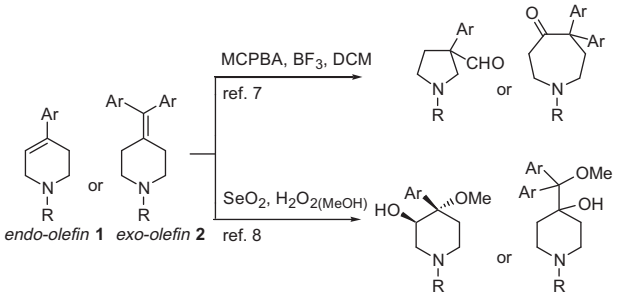
A simple and straightforward synthesis of 1-substituted-4-aryl-5-fluoro-1,2,3,6-tetrahydropyridine (**3**) or 1-substituted 4-diarylmethanoyl-4-fluoropiperidine (**6**) by the treatment of piperidinyl *exo*- or *endo*-olefin with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate (Selectfluor) is reported. Two transformations from *endo*-olefin **1** to allylic fluoride **3** and from *exo*-olefin **2** to fluorohydrin **6** proceed via allylic fluorination and fluorohydroxylation in moderate yields. It presents two novel reactions promoted by Selectfluor and broadens the scope of application.



## 1. Introduction

Notably, Selectfluor™ has been reviewed for reactions involving carbon-fluoride formation.[1] Due to the numerous advantages associated with this mild, stable, and eco-friendly compound, recent investigations have explored its applications as an effective reagent for some interesting reactions. Some representative examples include oxidation,[2] α-fluorination,[3] rearrangement,[4] deprotection[5] etc. Especially, the reaction of olefins with electrophilic fluorinating agents in the presence of nucleophiles was well documented.[6] Recently, we investigated some interesting reactions related to the structures of 4-aryl-1,2,3,6-tetrahydropyridine **1** and 4-diarylmethylenepiperidine **2** by a combination of *m*-chloroperoxybenzoic acid/boron trifluoride etherate-promoted ring-contraction and ring-expansion[7] or selenium dioxide-mediated methoxyhydroxylation[8] (Scheme 1). To explore the synthetic application of two frameworks, a simple strategy for Selectfluor-mediated allylic fluorination of **1** and fluorohydroxylation of **2** was developed.

The unique structural feature of fluoropiperidine prompted many strategies from synthetic chemists.[9] Indeed, the molecular framework of fluoropiperidine has been used as a core template to design unique ligands binding to various molecular targets (Fig. 1).[10] Several research groups have examined the pharmacological activities for these fluorinated piperidines. For instance, 3-arylfluoropiperidne derivatives had been identified the high-throughput assay for important resistance patterns in the Gram-negative pathogens by Thorarensen group.[10g] Stanton et al. had




**Scheme 1.** Reactions of skeletons **1** and **2**.

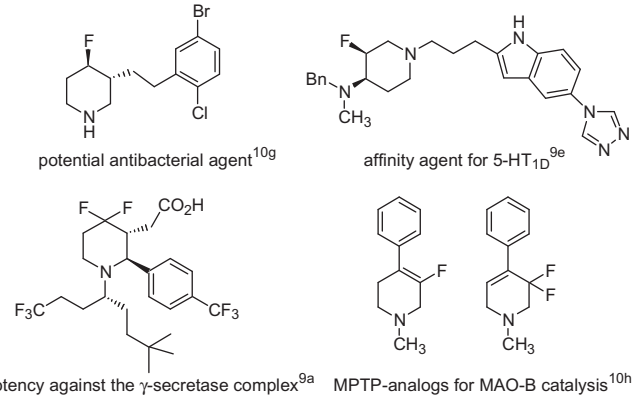



**Figure 1.** Biological active fluoropiperidines.

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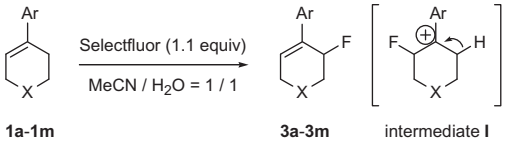
identified that a novel series of fluorinated piperidine acetic acid is the modulator of γ-secretase.[9a] van Niel et al. had found that a novel series of 3-fluoro-4-aminopiperidines have high affinity for 5-$HT_{1D}$.[9e] Rimoldi et al. had reported that β-fluoro-4-phenyl-1,2,3,6-tetrahydropyridine analogs can evaluate the contribution of electronic parameters to monoamine oxidase (MAO-B).[10h]

## 2. Results and discussion

Our initial investigation focused on the reaction of piperidinyl *endo*-olefin **1** or piperidinyl *exo*-olefin **2** with fluorinating reagents, such as Deoxo-Fluor or (diethylamino)sulfur trifluoride (DAST). However, trace amount of the fluoroproduct was isolated and the major starting material **1** or **2** was recovered. When *N*-fluorobenzenesulfonimide (NFSI) or fluoropyridinium salt was chosen as the reagent, complex fluoro-containing product was yielded under a number of reaction conditions. Interestingly, a significant amount of allylic fluorination product or fluorohydroxylation product was observed when Selectfluor was used as a fluorinating reagent under the general condition usually used in this literature. Selectfluor-mediated allylic fluorination of **1** was shown in Table 1. We first applied the condition to a diverse range of *endo*-olefin **1a**. Compared with entries 1–4, the yield of compound **3a** was decreasing under the condition of the prolonged time and elevated temperature. This might be due to the fact that compound **3a** is easily aromatized to the major fluoropyridine product. The optimized reaction system was the reaction of **1** with Selectfluor (1.1 equiv) in the co-solvent of acetonitrile (10 mL) and water (1 mL) at 40–50 °C for 4–5 h.[11]

The resulting products **3** were obtained in 33–65% yields (entries 5–18). The typical experimental procedure offers a general and efficient alternative to the typical allylic monofluorination reaction of **1**. In entry 7, the dr value of (*S*,*S*)-**3d** is determined as the ratio of 94:6 by chiral phase HPLC. But, treatment of **1m**

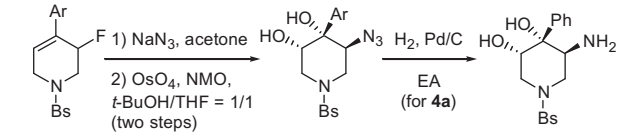
**Table 1**
Allylic monofluorination of *endo*-olefins **1**[a,b]




**1a-1m** **3a-3m** intermediate **I**

| Entry | Ar, X group | Temp/time (h) | Product **3**/yield (%) |
|---|---|---|---|
| 1 | **1a**, Ph, NMs | 40 °C/4 | **3a** (61) |
| 2 | | 40 °C/8 | **3a** (30) |
| 3 | | 40 °C/20 | **3a** (trace) |
| 4 | | Reflux/1 | **3a** (trace) |
| 5 | **1b**, Ph, NBs | 40 °C/4 | **3b** (65) |
| 6 | **1c**, Ph, NTs | 40 °C/4 | **3c** (58) |
| 7 | **1d**, Ph, (1*S*)-$NSO_2$Camphor | 40 °C/4 | **3d** (49) |
| 8 | **1e**, Ph, NBz | 40 °C/4 | **3e** (30) |
| 9 | | 50 °C/5 | **3e** (51) |
| 10 | **1f**, Ph, N-4-FBz | 50 °C/5 | **3f** (43) |
| 11 | **1g**, Ph, N-4-MeOBz | 50 °C/5 | **3g** (48) |
| 12 | **1h**, Ph, N-2-COthiophene | 50 °C/5 | **3h** (45) |
| 13 | **1i**, 2-MeOPh, NBs | 40 °C/4 | **3i** (51) |
| 14 | **1j**, 3-$CF_3$Ph, NBs | 40 °C/4 | **3j** (61) |
| 15 | **1k**, 4-FPh, NBs | 40 °C/4 | **3k** (60) |
| 16 | **1l**, 4-Cl-3-$CF_3$Ph, NBs | 40 °C/4 | **3l** (65) |
| 17 | **1m**, 3-MeOPh, O | 40 °C/4 | **3m** (23) |
| 18 | | 50 °C/5 | **3m** (8) |

[a] Reactions were performed in the co-solvent of MeCN (10 mL) and water (1 mL) using the following mole ratios: **1**/Selectfluor = 1:1.1.
[b] The isolated products are >95% pure as judged by $^1$H NMR analysis.




**3a**, Ar = Ph
**3i**, Ar = 2-MeOPh
**3k**, Ar = 4-FPh
**3l**, Ar = 4-Cl-3-$CF_3$Ph

**4a**, Ar = Ph (62%) **X-Ray**
**4b**, Ar = 2-MeOPh (48%)
**4c**, Ar = 4-FPh (54%)
**4d**, Ar = 4-Cl-3-$CF_3$Ph (42%)

**5** (79%)

**Scheme 2.** Synthesis of 3-azidopiperidin-4,5-diols **4**.

(X = O) with Selectrfluor yielded **3m** in only 8% or 23% yield. The characteristic structural framework of **3b** and **3d** was determined by single-crystal X-ray analysis.[12] The mechanism proposed for the allylic fluorination of **1** by Selectfluor involves the formation of a benzylic carbocation intermediate **I**. Skeleton **3** is afforded from intermediate **I** via hydrogen abstraction.

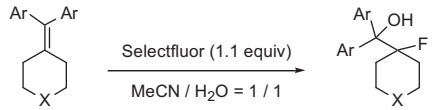
To further explore the application of **3**, synthesis of 3-azidopiperidine-4,5-diol **4** was shown in Scheme 2. Hydroxylated piperidines have demonstrated their utility in the treatment of carbohydrate-mediated diseases.[13,14] Azidodiol **4a** was easily generated by a two-step methodology of nucleophilic substitution of compound **3b** with sodium azide in acetone and subsequently by osmylation of the corresponding allylic azide in 62% yield.[15] The total synthetic procedure could be monitored by TLC until the reaction was complete. Noticeably, allylic azide is unstable. With the results in hand, treatment of compound **3i**, **3k,** or **3l** produced compound **4b**–**d** by the above protocols. Further, hydrogenation was accomplished by treatment of compound **4a** with hydrogen on 10% palladium-activated carbon to yield aminodiol **5**. It presents a new methodology for synthesizing 4-arylazasugar analogs.

Regioselective fluorohydroxylation of piperidinyl *exo*-olefin **2** with Selectfluor was shown in Table 2. The optimized reaction system should be the reaction of *exo*-olefin **2** with Selectfluor (1.1 equiv) in the co-solvent of acetonitrile (10 mL) and water (1 mL) at reflux temperature.[16] During the process, reaction of olefin **2** was only affected by elevated temperature. Under the reflux temperature, reaction of compound **2a** was achieved completely to generate fluorohydrin **6a** without the starting material recovered (entries 1–4). In entries 5–16, the resulting fluorohydrins **6a**–**j** were obtained in 61–93% yields.[11] Further, fluorohydroxylation of compound **2k** with cyclopentane ring or **2l** with acyclic propane unit was transformed to compound **6k** or **6l** and the reaction of compound **2m** with 3-diphenylmethylenyl group was also conducted to the 3-fluoropiperidine skeleton **6m**.

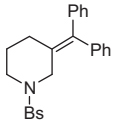
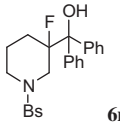
Based on the above results, we examined the fluoroalkoxylation of compound **2b**. Treatment of compound **2b** with several alcohols (e.g., methanol, ethanol, and isopropanol) as the solvent by the similar protocol produced fluoroalkoxides **7a**–**c** in 72–87% yields as shown in Scheme 3. It was also interesting to evaluate the compatibility of fluorinating reagent with nucleophilic reagents. But, no reaction between Selectfluor and TMSCN in dry acetonitrile was noted. In contrast, the combination might cause rapid decomposition of TMSCN to form TMSF.

On the basis of the above-mentioned results, four fluorohydrins **6b**, **6d**, **6e,** and **6g** with piperidinyl and tetrahydropyranyl frameworks were applied to examine the interesting pinacol-type rearrangement as shown in Scheme 4. When compound **6b** was treated with boron trifluoride etherate in dichloromethane, the sole compound **8a** was isolated in 78% yield. The conversion of fluorohydrin **6** to α-aryl arylketone **8** is the type of pinacol to pinacolone rearrangement.[7b] Especially, the aryl group could displace the tertiary fluoride atom during the intramolecular pinacol-type reaction process. Arylketones **8b**–**d** were also prepared in 69–82% yields.

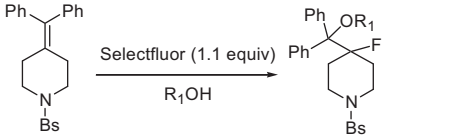
**Table 2**
Fluorohydroxylation of *exo*-olefins **2**[a,b]




**2a-2j** **6a-6j**

| Entry | Ar, X group | Temp/time (h) | Product **6** or **2**/yield (%) |
|---|---|---|---|
| 1 | **2a**, Ph, NMs | 40 °C/20 | **6a** (31) + **2a** (48) |
| 2 | | 40 °C/60 | **6a** (73) + **2a** (11) |
| 3 | | Reflux/1 | **6a** (63) + **2a** (25) |
| 4 | | Reflux/4 | **6a** (93) |
| 5 | **2b**, Ph, NBs | Reflux/4 | **6b** (88) |
| 6 | **2c**, Ph, NTs | Reflux/4 | **6c** (83) |
| 7 | **2d**, 4-MeOPh, NBs | Reflux/4 | **6d** (85) |
| 8 | **2e**, 4-FPh, NBs | Reflux/4 | **6e** (79) |
| 9 | **2f**, Ph, O | Reflux/4 | **6f** (82) |
| 10 | **2g**, 4-MeOPh, O | Reflux/4 | **6g** (88) |
| 11 | **2h**, 4-FPh, O | Reflux/4 | **6h** (85) |
| 12 | **2i**, Ph, $CH_2$ | Reflux/4 | **6i** (70) |
| 13 | **2j**, 4-MeOPh, $CH_2$ | Reflux/4 | **6j** (72) |
| 14 | **2k**,  | Reflux/4 |  **6k** (64) |
| 15 | **2l**,  | Reflux/4 |  **6l** (61) |
| 16 | **2m**,  | Reflux/4 |  **6m** (76) |

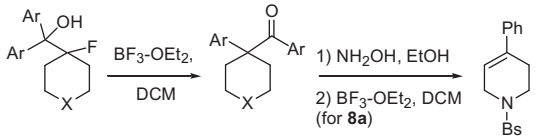
[a] Reactions were performed in the co-solvent of MeCN (10 mL) and water (1 mL) using the following mole ratios: **2**/Selectfluor = 1:1.1.
[b] The isolated products are >95% pure as judged by $^1$H NMR analysis.




**2b**

**7a**, $R_1$ = Me (87%) **X-Ray**
**7b**, $R_1$ = Et (80%)
**7c**, $R_1$ = $CHMe_2$ (72%)

**Scheme 3.** Fluoroalkoxylation of *exo*-olefin **2b**.



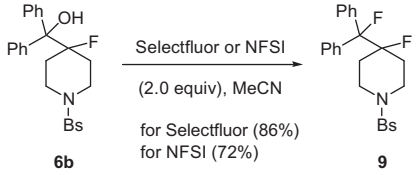

**6b**, Ar = Ph, X = NBs
**6e**, Ar = 4-FPh, X = NBs
**6f**, Ar = Ph, X = O
**6h**, Ar = 4-FPh, X = O

**8a** (78%)
**8b** (82%) **X-Ray**
**8c** (71%)
**8d** (69%)

**1b** (41%)

**Scheme 4.** Degradation of skeletons **2** to **1**.

Next, condensation of compound **8a** with hydroxylamine and subsequently by boron trifluoride etherate-mediated rearrangement of the corresponding oxime yielded phenylnitrile and compound **1b**. The expected Beckmann amide product was not observed during the process. When repeated treatment of compound **6b** with Selectfluor (2.0 equiv) or NFSI (2.0 equiv), difluoropiperidine **9** was provided in 86% or 72% yield, respectively, during the fluorination (Scheme 5). The structural framework of compounds **6a**, **6h**, **7a,** and **8b** was determined by single-crystal X-ray analysis.[17]




**6b** **9**

**Scheme 5.** Fluorination of **6b** with Selectfluor or NFSI.

## 3. Conclusion

In summary, we have successfully presented a synthetic methodology for producing a series of the novel 3- and 4-fluoropiperidine involving Selectfluor-mediated allylic fluorination and fluorohydroxylation. Under the Selectfluor-promoted fluorination system, a wide range of 4-aryl-1,2,3,6-tetrahydropyridines and diarylmethylenyl heterocycles was well studied. Several structures of the target products were nicely confirmed by X-ray crystal analysis. The structure–activity studies of desulfonated compound **3** or **6** in the MAO-B studies will be investigated in following work.

## Acknowledgments

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11. A representative procedure of skeleton **3** or **6** is as follows: A mixture of *endo*-olefin **1** or *exo*-olefin **2** (0.3 mmol) and Selectfluor (0.33 mmol) in the co-solvent of acetonitrile (10 mL) and water (1 mL) was stirred at 40 °C, 50 °C or reflux temperature for 4–5 h. The material was cooled to 25 °C, and after addition of water the mixture was stirred for 5 min. The reaction mixture was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 4:1–2:1) afforded skeleton **3** or **6**. Representative data for **3a**: Mp = 140–141 °C; HRMS (ESI, $M^+$+1) calcd for $C_{12}H_{15}FNO_2S$ 256.0808, found 256.0809; $^1$H NMR (400 MHz): $\delta$ 7.49–7.46 (m, 2H), 7.43–7.32 (m, 3H), 6.40 (dt, $J$ = 2.8, 5.2 Hz, 1H), 5.40 (ddd, $J$ = 2.0, 4.0, 48.0 Hz, 1H), 4.37–4.26 (m, 2H), 3.95 (dd, $J$ = 11.6, 18.0 Hz, 1H), 3.40 (ddd, $J$ = 2.4, 10.4, 34.0 Hz, 1H), 2.96 (s, 3H); $^{13}$C NMR (100 MHz): $\delta$ 137.34, 133.97 (d, $J$ = 15.1 Hz), 128.78 (2×), 128.29, 126.33 (d, $J$ = 7.6 Hz), 125.47 (2×), 83.93 (d, $J$ = 172.1 Hz), 47.48 (d, $J$ = 24.5 Hz), 44.50 (d, $J$ = 3.0 Hz), 38.22 (d, $J$ = 3.8 Hz); Anal. Calcd for $C_{12}H_{14}FNO_2S$: C, 56.45; H, 5.53; N, 5.49. Found: C, 56.67; H, 5.81; N, 5.62. For **6a**: Mp = 173–174 °C; HRMS (ESI, $M^+$+1) calcd for $C_{19}H_{23}FNO_3S$ 364.1383, found 364.1384; $^1$H NMR (400 MHz): $\delta$ 7.58–7.55 (m, 4H), 7.35–7.25 (m, 6H), 3.70–3.66 (m, 2H), 3.00–2.93 (m, 2H), 2.77 (s, 3H), 2.66 (br s, 1H), 2.09–1.93 (m, 4H); $^{13}$C NMR (100 MHz): $\delta$ 142.70 (2×), 128.01 (4×), 127.64 (2×), 127.59 (2×), 127.50 (2×), 97.83 (d, $J$ = 182.7 Hz), 80.15 (d, $J$ = 21.2 Hz), 41.68, 41.66, 34.46, 30.50, 30.30; Anal. Calcd for $C_{19}H_{22}FNO_3S$: C, 62.79; H, 6.10; N, 3.85. Found: C, 63.01; H, 6.39; N, 4.17.
12. CCDC 773596 (**3b**) and 783492 (**3d**) contain the supplementary crystallographic data for this Letter. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
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17. CCDC 776257 (**6a**), 783738 (**6h**), 783739 (**7a**), and 776259 (**8b**) contain the supplementary crystallographic data for this Letter. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).