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# Stereoselective synthesis of α-difluoromethyl-β-amino alcohols via nucleophilic difluoromethylation with $Me_3SiCF_2SO_2Ph$

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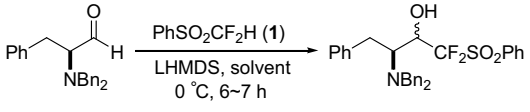
**Abstract**

A facile synthesis of *anti*-α-(difluoromethyl)-β-amino alcohols was accomplished by using a nucleophilic difluoromethylation strategy with $Me_3SiCF_2SO_2Ph$ reagent. Good to excellent chemical yields as well as modest to good diastereoselectivity were achieved in these reactions. We found that the solvent played a crucial role in controlling the diastereoselectivity of the reaction, and an apolar solvent such as toluene helps to improve the diastereoselectivity of the reaction. The *anti*-α-(difluoromethyl)-β-amino alcohol **3a** was demonstrated to be a useful synthetic intermediate to synthesize difluoromethylated oxazolidinone **9**.


*Keywords:* Fluorine; Difluoromethylation; Amino alcohol; Stereoselective

As the incorporation of fluorine atom(s) can often have profound effects on the target molecules, stereoselective introduction of the fluoroalkyl groups into the α-position of β-amino alcohols has attracted much attention.[1] α-Fluoroalkyl-β-amino alcohols have been used as peptidometics and transition state mimics in drug design,[2] as well as chiral auxiliaries or as ligands in asymmetric synthesis.[3] During the past two decades, a number of synthetic methods for the synthesis of α-trifluoromethyl-β-amino alcohols have been reported,[4] including the direct trifluoromethylation of homochiral α-amino aldehydes with Ruppert–Prakash reagent ($Me_3SiCF_3$).[5] On the other hand, the stereoselective synthesis of α-difluoromethyl-β-amino alcohols was less explored, probably due to less availability of difluoromethylated precursors and difluoromethylating reagents.[6] All of the previous reports are based on the synthetic elaboration of difluoromethyl-containing substrates,[7–11] and we are not aware of any report on the stereoselective synthesis of α-difluoromethyl-β-amino alcohols via *nucleophilic difluoromethylation* strategy. In this Letter, we wish to report a stereoselective synthesis of α-difluoromethyl-β-amino alcohols via nucleophilic difluoromethylation of homochiral α-amino aldehydes using $Me_3SiCF_2SO_2Ph$ reagent.

Based on our previous experience in using difluoromethyl phenyl sulfone ($PhSO_2CF_2H$, **1**) as a robust difluoromethylating agent,[12,13] first of all, we tested the nucleophilic (phenylsulfonyl)difluoromethylation reaction between **1** and α-amino aldehyde **2a** (Scheme 1). It turned out that, in the presence of 2 equiv of LHMDS in THF at




**2a** *anti*-**3a** *syn*-**3a**

solvent = THF, yield = 46%, *syn*/*anti* = 33:67
solvent = toluene, yield = 52%, *syn*/*anti* = 33:67

Scheme 1.

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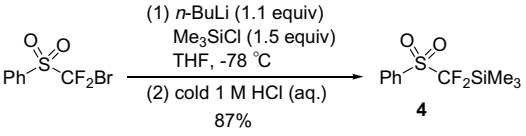
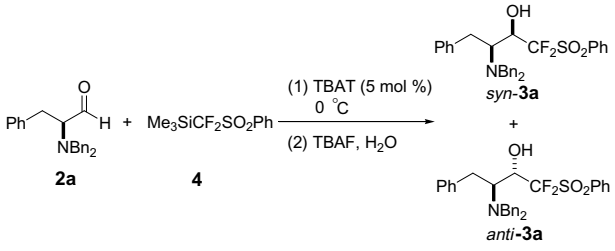
0 °C, the reaction between 1 equiv of **2a** and 1.2 equiv of **1** only gave low yield (46%) of product **3a** with *syn*/*anti* ratio = 33:67. When toluene was used as the solvent, a similar result was obtained (Scheme 1). We envisioned that since LHMDS is a strong base, the low yield of product **3a** was probably caused by the enolization of **2a** and the resulting aldol-type side reactions.[14]

Previously, we had developed [(phenylsulfonyl)difluoromethyl]trimethylsilane ($Me_3SiCF_2SO_2Ph$, **4**) as an alternative nucleophilic (phenylsulfonyl)difluoromethylating agent.[15] Unlike $PhSO_2CF_2H$ (**1**), which usually needs a strong base to generate the $PhSO_2CF_2^-$ intermediate, reagent **4** needs only a catalytic amount of mild Lewis base (such as a fluoride ion) to accomplish the nucleophilic transfer of $PhSO_2CF_2$ group to carbonyl compounds.[15] $Me_3SiCF_2SO_2Ph$ (**4**) was first prepared in 2003 via mCPBA-mediated oxidation of $Me_3SiCF_2SPh$ (**5**) in 51% yield.[16] In 2005, we improved the synthesis of reagent **4** (with 78% isolated yield) by the reaction of $PhSO_2CF_2Br$ (1 equiv), *n*-BuLi (1.8 equiv), and $Me_3SiCl$ (1.5 equiv) in THF at −78 °C.[15] After further optimization of the reaction conditions, we found that when the reactant ratio was changed to $PhSO_2CF_2Br/n\text{-}BuLi/Me_3SiCl = 1.0:1.1:1.5$ and a subsequent acid-quenching procedure was used, an excellent yield of **4** (87–98%) could be obtained (Scheme 2).[17]




Scheme 2.

Table 1
Survey of reaction conditions



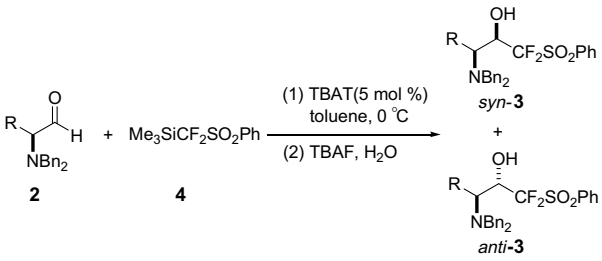

| Entry[a] | Solvent | Time (h) | Yield[b] (%) | dr[c] |
|---|---|---|---|---|
| 1 | THF | 6 | 93 | 17:83 |
| 2 | Toluene | 10 | 92 | 11:89 |
| 3 | DMF | 6 | 94 | 28:72 |
| 4 | *n*-Hexane | 12 | 93 | 16:84 |
| 5 | $CH_3CN$ | 6 | 96 | 25:75 |
| 6 | $CH_2Cl_2$ | 8 | 92 | 20:80 |

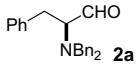
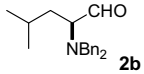
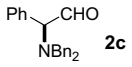
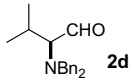
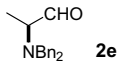
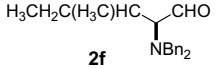
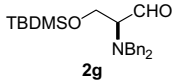
[a] In all cases, reagent **4** (2.0 equiv) was added to a mixture of **2a** (1.0 equiv) and TBAT (0.05 equiv) at 0 °C.
[b] Isolated yield.
[c] Diastereomeric ratios (*syn*/*anti*) were determined by $^{19}F$ NMR spectroscopy on samples from the crude reaction mixture.

With reagent **4** in hand, we chose compound **2a** as a model compound to examine the fluoride-induced (phenylsulfonyl)difluoromethylation, and the results are shown in Table 1. Tetrabutylammonium triphenyldifluorosilicate[18] (TBAT, 5 mol %) was used as a fluoride initiator for the reaction. Different solvents such as THF, toluene, DMF, *n*-hexane, acetonitrile, and dichloromethane were used. In all cases, excellent overall yields (92–96%) of *syn*-**3a** and *anti*-**3a** were obtained, with the *anti*-isomer being the major one. It turned out that better diastereoselectivity could be obtained in apolar solvents (such as toluene and *n*-hexane), and the best diastereomeric ratio was observed in toluene (dr = 11:89, see entry 2). We further tried to lower the reaction temperature to −35 °C, but no improvement of diastereoselectivity was observed. Other fluoride initiators such as tetrabutylammonium fluoride (TBAF) and tetramethylammonium fluoride (TMAF) were also tried (instead of TBAT), but chemical yields decreased.

By using the optimized reaction condition (Table 1, entry 2), we studied the scope of the nucleophilic difluoro-

Table 2
Stereoselective (phenylsulfonyl)difluoromethylation of α-dibenzylamino aldehydes




| Entry | Substrate | Product[a] | Yield[b] (%) | dr[c] |
|---|---|---|---|---|
| 1 |  **2a** | *syn*-**3a** + *anti*-**3a** | 92 | 11:89 |
| 2 |  **2b** | *syn*-**3b** + *anti*-**3b** | 86 | 13:87 |
| 3 |  **2c** | *syn*-**3c** + *anti*-**3c** | 72 | 47:53 |
| 4 |  **2d** | *syn*-**3d** + *anti*-**3d** | 88 | 6:94 |
| 5 |  **2e** | *syn*-**3e** + *anti*-**3e** | 85 | 9:91 |
| 6 |  **2f** | *syn*-**3f** + *anti*-**3f** | 83 | 6:94 |
| 7 |  **2g** | *syn*-**3g** + *anti*-**3g** | 78 | 20:80 |

[a] The absolute configurations of *syn*-**3a** were determined by single-crystal X-ray analysis; the others were assigned by analogy.
[b] Yield of isolated analytically pure material.
[c] Diastereomeric ratios (*syn*/*anti*) were determined by $^{19}F$ NMR spectroscopy on samples from the crude reaction mixture.

methylation between homochiral α-dibenzylamino aldehydes **2** and $Me_3SiCF_2SO_2Ph$ (**4**).[19] The results are summarized in Table 2. In all cases, good to excellent yields (72–93%) of products **3** were obtained. Good diastereoselectivities were generally observed except for the reaction with **2c** (Table 2, entry 3). The absolute configuration of *syn*-**3a** was determined by single-crystal X-ray analysis (Fig. 1), and the other structures were assigned by analogy. It is remarkable that, excellent diastereoselectivities were observed in the cases of **2d** and **2f** (dr = 6:94 and 6:94, respectively; see entries 4 and 6). Compound **5** (the enantiomer of **2a**) was also used to react with reagent **4** under similar reaction conditions (Scheme 3), and similar good result was obtained (93% yield, dr = 11:89).

As shown in Scheme 4, upon reductive desulfonylation by using our previously developed Mg/HOAc/NaOAc system[15] and debenzylation by hydrogenolysis on Pearlman's catalyst,[20] compound *anti*-**3a** was transformed into *anti*-α-(difluoromethyl)-β-amino alcohol **8**. Intermediate **8** was then treated with triphosgene and triethylamine in $CH_2Cl_2$ leading to difluoromethylated oxazolidinone **9**.[21]

In summary, we have demonstrated a facial synthesis of *anti*-α-(difluoromethyl)-β-amino alcohols using a nucleophilic difluoromethylation strategy with $Me_3SiCF_2SO_2Ph$ reagent. Good to excellent chemical yields as well as modest to good diastereoselectivity were achieved in these reactions. We found that the solvent played a crucial role in controlling the diastereoselectivity of the reaction. Apolar solvent such as toluene helps to improve the diastereoselectivity of the reaction. The *anti*-α-(difluoromethyl)-β-amino alcohol **3a** was demonstrated to be a useful synthetic intermediate to synthesize difluoromethylated oxazolidinone **9**.

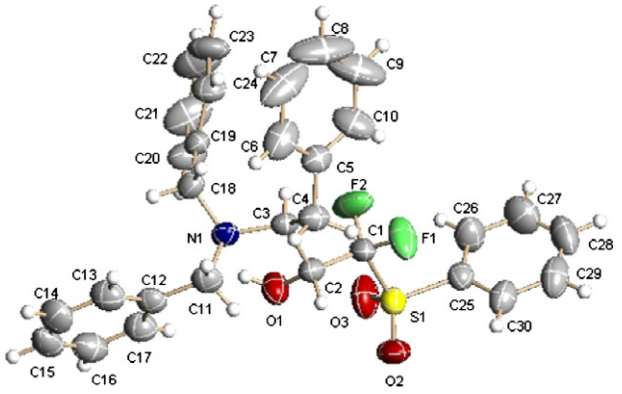
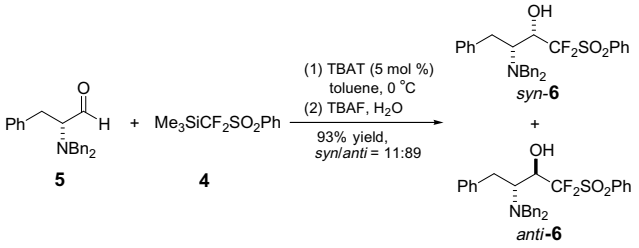
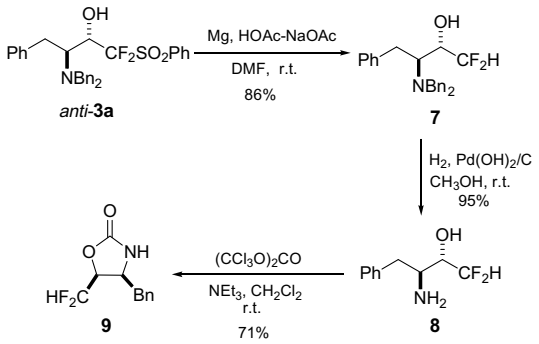



Fig. 1. Single-crystal X-ray structure of *syn*-**3a**.




Scheme 3.




Scheme 4.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.034.

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17. *Improved preparation of $Me_3SiCF_2SO_2Ph$* (**4**): Under $N_2$ atmosphere, *n*-BuLi (hexane solution, 1.6 M, 15.8 mL, 25 mmol) was added to the solution of $PhSO_2CF_2Br$ (6.0 g, 22 mmol) and chlorotrimethylsilane (4.5 mL, 33 mmol) in THF (105 mL) at −78 °C. After the addition of *n*-BuLi (over a period of 1.5 h), the reaction mixture was stirred for additional 2 h at −78 °C. Then the reaction mixture was carefully added into a cold aqueous HCl solution (1 M). The mixture was extracted with $Et_2O$ (70 mL × 3), and the combined organic phase was washed with brine, water, and then dried over $Na_2SO_4$. After the removal of the solvent under vacuum, 5.73 g of crude product was obtained (yield 98.1%). The crude product was further fractionally distilled to afford 5.10 g (yield 87%) of product **4** as a colorless liquid. $^1$H NMR ($CDCl_3$): $\delta$ 0.42 (s, 9H), 7.60 (t, $J = 7.5$ Hz, 2H), 7.73 (t, $J = 7.5$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 2 H). $^{19}$F NMR ($CDCl_3$): $\delta$ −112.9 (s). The data were consistent with the previous report (Ref. 16).
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19. *Typical procedure for the stereoselective nucleophilic (phenylsulfonyl)difluoromethylation of α-amino aldehydes with reagent* **4**: Under $N_2$ atmosphere, a solution of $Me_3SiCF_2SO_2Ph$ (**4**) (265 mg, 1.0 mmol) in 4 mL toluene was added to a solution of amino aldehyde **2a** (0.5 mmol, 165 mg) and TBAT (14 mg, 0.025 mmol) in toluene (6 mL) at 0 °C. The mixture was then stirred at that temperature for about 10 h. Subsequently, TBAF (32 mg, 0.1 mmol) was added, and the reaction mixture was stirred at room temperature for 1 h and then quenched by the addition of saturated NaCl aqueous solution (10 mL). After warming to room temperature, the solution mixture was extracted with diethyl ether (25 mL × 3), and the combined organic phase was washed with brine and dried with anhydrous $MgSO_4$. The solvents were removed under vacuum and the residue was purified by flash chromatography (silica gel; petroleum ether/ethylacetate (12:1)) to give product *syn*-**3a** (27 mg) and *anti*-**3a** (212 mg) as white solid, total yield: 92%. Characterization data for *syn*-**3a**: white solid. Mp 136–138 °C. $[\alpha]_D^{25}$ 25.68 (*c* 1.07, $CHCl_3$). $^1$H NMR: $\delta$ 7.90 (d, $J = 8.1$ Hz, 2H), 7.69 (t, $J = 7.5$ Hz, 1H), 7.54 (t, $J = 7.2$ Hz, 2H), 7.11–7.39 (m, 15H), 5.18 (s, 1H), 4.29 (dd, $J = 19.5$, 7.5 Hz, 1H), 3.84 (d, $J = 13.2$ Hz, 2H), 3.51–3.61 (m, 1H), 3.36 (d, $J = 12.3$ Hz, 2H), 3.12 (dd, $J = 15.0$, 9.3 Hz, 1H), 2.99 (dd, $J = 14.4$, 4.2 Hz, 1H). $^{19}$F NMR: $\delta$ −105.2 (d, $J = 236.1$ Hz, 1F), −116.9 (dd, $J = 235.5$, 19.5 Hz, 1F). $^{13}$C NMR: $\delta$ 139.1, 137.7, 135.2, 133.5, 130.8, 129.4, 129.3, 129.2, 128.8, 128.5, 127.5, 126.9, 122.1 (dd, $J = 298.8$, 289.4 Hz), 68.1 (dd, $J = 24.9$, 21.3 Hz), 57.7, 54.3, 34.7 (d, $J = 3.3$ Hz). IR (KBr): 3301, 1584, 1448, 1347, 1164, 1092, 992, 755, 586 cm$^{-1}$. Elemental Anal. Calcd for $C_{30}H_{29}F_2NO_3S$: C, 69.08; H, 5.60; N, 2.69. Found: C, 68.87; H, 5.58; N, 2.58; MS (ESI, *m*/*z*): 522.2 ($M^+$+1). Characterization data for *anti*-**3a**: white solid. Mp 42–44 °C. $[\alpha]_D^{25}$ 20.50 (*c* 0.93, $CHCl_3$). $^1$H NMR: $\delta$ 8.01 (d, $J = 7.2$ Hz, 2H), 7.74 (t, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 8.1$ Hz, 2H), 6.96–7.26 (m, 15H), 5.03–5.17 (m, 1H), 3.97 (d, $J = 14.1$ Hz, 2H), 3.47 (d, $J = 14.1$ Hz, 2H), 3.39–3.4 (m, 1H), 3.25 (d, $J = 5.4$ Hz, 1H), 3.05–3.17 (m, 1H), 2.82–2.92 (m, 1H). $^{19}$F NMR: $\delta$ −104.7 (d, $J = 234.1$ Hz, 1F), −116.9 (dd, $J = 234.1$, 24.6 Hz, 1F). $^{13}$C NMR: $\delta$ 139.5, 139.1, 135.7, 132.6, 130.8, 129.7, 129.5, 128.7, 128.2, 128.1, 126.9, 126.1, 121.6 (dd, $J = 299.6$, 289.2 Hz), 66.1 (dd, $J = 25.6$, 20.7 Hz), 58.4, 54.1, 32.7. IR (KBr): 3528, 3028, 1496, 1334, 1159, 1097, 743, 698, 587 cm$^{-1}$. Elemental Anal. Calcd for $C_{30}H_{29}F_2NO_3S$: C, 69.08; H, 5.60; N, 2.69. Found C, 69.30; H, 5.46; N, 2.55. MS (ESI, *m*/*z*): 522.2 ($M^+$+1).
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