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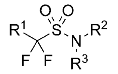
# Difluoro(sulfinato)methylation of N-Sulfinyl Imines Facilitated by 2-Pyridyl Sulfone: Stereoselective Synthesis of Difluorinated β-Amino Sulfonic Acids and Peptidosulfonamides**

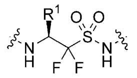
*G. K. Surya Prakash,* Chuanfa Ni, Fang Wang, Zhe Zhang, Ralf Haiges, and George A. Olah*

Fluorine, despite its almost complete absence from biological systems in nature, has become one of the most utilized element for modulating the properties of biologically active molecules and for studying their mechanism of action.[1] The sulfonamide moiety is one of the most important pharmacophores in medicinal chemistry,[2] and α-fluorosulfonamides have been shown to have improved anti-inflammatory activity and enzyme inhibitory potency.[3] It has been rationalized that α-fluorine substitutions of sulfonamides can increase their acidity and lipophilicity,[4] both of which can significantly affect the biological activity of these molecules.[3] However, biological studies on fluorinated sulfonamides have been largely limited to simple α-fluorosulfonamides with the general structure **A**.[3] In contrast, β-sulfonamidopeptides, as structural analogues of peptides with enhanced metabolic stability, have been used to design enzyme inhibitors and haptens in catalytic antibody development.[5] However, to the best of our knowledge, the synthesis of α-fluorinated β-sulfonamidopeptides having a sulfonamide moiety (**B**) has not been reported. Such a challenge is mainly due to the lack of applicable synthetic approaches towards building blocks such as α-difluorinated β-amino sulfonic acids (ASAs).



**A**

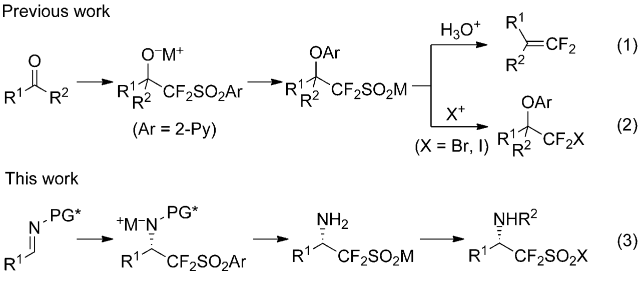
$R^1$ = H, F, alkyl, aryl
$R^2$, $R^3$ = H, alkyl, aryl



**B**

$R^1$ = H, alkyl, aryl

Fluorinated sulfones have recently emerged as versatile nucleophilic fluoroalkylation reagents for the construction of various fluorinated organic compounds.[6] In 2011, we reported an efficient synthesis of difluorinated sulfonates ($RCF_2SO_3^-$) from primary alkyl halides or triflates by using difluoromethyl 2-pyridyl sulfone ($2\text{-}PySO_2CF_2H$) as the masked difluoro(sulfinato)methylating agent.[7] However, in the reaction between carbonyl compounds and 2-$PySO_2CF_2H$, it was shown that the S–O Smiles rearrangement of the alcoholate anions readily took place to give β-(2-pyridyloxy)sulfinates, which could be further transformed into *gem*-difluoroolefins[8a] and halodifluoromethylated compounds[8b] [Scheme 1, Eqs. (1) and (2)]. Although it has been reported that S–N Smiles rearrangenments in the reactions between imines and heteroaryl sulfones could afford N-arylated amines or olefins,[9] we speculated that the unprotected fluorinated β-ASAs could be prepared by choosing proper N-protected imines and proper difluoromethyl sulfones to suppress the undesired rearrangement [Scheme 1, Eq. (3)]. Herein, we report a highly stereoselective nucleophilic difluoro(sulfinato)methylation of *N-tert*-butanesulfinyl imine[10] using 2-$PySO_2CF_2H$ as a masked difluoro(sulfinato)-methylating agent. This protocol allows the efficient synthesis of unknown optically active α,α-difluoro-β-amino sulfinic and sulfonic acids as well as complex fluorinated peptidosulfonamides.



***Scheme 1.*** Nucleophilic addition of the difluorinated sulfone to carbonyls and imines. Py = pyridyl; PG* = chiral protecting group.

To establish the addition reaction conditions, we started our research with the reaction between (*R*)-*N-tert*-butanesulfinyl imine [(*R*)-**1a**] and 2-$PySO_2CF_2H$ (**2a**; Table 1). When the reaction was conducted at −98 °C using (*R*)-**1a**, **2a** (1.0:1.0 molar ratio), and excess lithium hexamethyldisilazide (LiHMDS), **3a** was obtained in a high yield (95%) with a good diastereoselectivity (d.r. = 96:4; entry 2). A comparison of metal cations showed that KHMDS and NaHMDS in THF gave relatively lower yields (entries 3 and 4), and KHMDS in toluene resulted in a dramatic decrease of the diastereoselectivity (entry 6). Gratifyingly, by using LiHMDS as the base, the addition of hexamethylphosphoramide (HMPA) into THF improved the diastereoselectivity (d.r. > 99:1; entry 5). For comparison, reactions with other difluorinated sulfones, **2b** and **2c**, were also tested. Although

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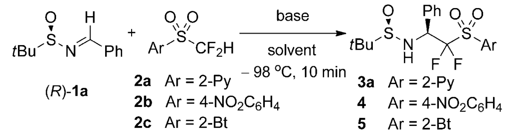
***Table 1:*** Survey of reaction conditions for nucleophilic addition of the sulfones **2** to imine (*R*)-**1a**.



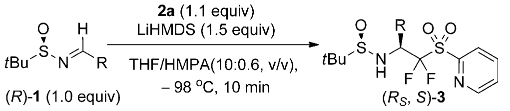
| Entry | 2 | Base | (*R*)-**1a**/**2**/base | Solvent | Yield [%][a] | d.r.[b] |
|---|---|---|---|---|---|---|
| **1**[c] | **2a** | LiHMDS | 1.05:1.0:1.25 | THF | ($R_s$,*S*)-**3a**: 53 | 98:2 |
| **2** | **2a** | LiHMDS | 1.0:1.0:1.5 | THF | ($R_s$,*S*)-**3a**: 95 | 96:4 |
| **3** | **2a** | NaHMDS | 1.0:1.0:1.5 | THF | ($R_s$,*S*)-**3a**: 76 | 99:1 |
| **4** | **2a** | KHMDS | 1.0:1.0:1.5 | THF | ($R_s$,*S*)-**3a**: 87 | 97:3 |
| **5** | **2a** | LiHMDS | 1.0:1.1:1.5 | THF/HMPA[d] | ($R_s$,*S*)-**3a**: 99 | >99:1 |
| **6** | **2a** | KHMDS | 1.0:1.0:1.5 | $PhCH_3$[e] | ($R_s$,*S*)-**3a**: 75 | 75:25 |
| **7** | **2b** | LiHMDS | 1.0:1.0:1.5 | THF | **4**: 84[f] | 97:3 |
| **8** | **2b** | LiHMDS | 1.0:1.1:1.5 | THF/HMPA[d] | **4**: –[g] | n.d. |
| **9** | **2c** | LiHMDS | 1.0:1.1:1.5 | THF/HMPA[d] | **5**: 0 | n.d. |

[a] Yields were determined by $^{19}F$ NMR spectroscopy with $PhCF_3$ as an internal standard. [b] Determined by $^{19}F$ NMR spectroscopy of the crude reaction mixture. [c] Reaction was run at −78 °C. [d] THF/HMPA = 10:0.6 (v/v). [e] The reaction was performed at −94 °C. [f] Yield of isolated product. [g] The yield of (4-nitrophenyl)-amino sulfinate was determined to be 47% by $^{19}F$ NMR spectroscopy with $PhCF_3$ as an internal standard. Bt = 1,3-benzothiazolyl, HMPA = hexamethylphosphoramide, n.d. = not determined, THF = tetrahydrofuran.

the sulfone **2b** reacted with (*R*)-**1a** (entry 7), the alcoholate of **4** readily underwent the S–N Smiles rearrangement in the presence of HMPA to afford the corresponding (4-nitrophenyl)amino sulfinate (entry 8). The sulfone **2c** failed to undergo reaction with (*R*)-**1a** presumably because of the low thermal stability of the corresponding carbanion (entry 9).

By using the optimal reaction conditions (Table 1, entry 5), the substrate scope of (*R*)-*tert*-butanesulfinyl imines was investigated. The results are summarized in Table 2. Both aryl- and alkyl-substituted aldimines (**1**) underwent reaction to give amino sulfones [($R_s$,*S*)-**3**] in good to excellent yields (86–98 %) with high diastereoselectivity (d.r. > 99:1; entries 1–11). Although the benzyl imine **1l** was also obtained with a high diastereoselectivity, the reaction yield was relatively low (51 %), and can be ascribed to the aza-enolization by the deprotonation of acidic α-hydrogen atoms (entry 12). Regarding the styryl imine **1m**, only a moderate yield was obtained under the optimized reaction conditions. This is probably due to the base lability of the produced amino sulfone ($R_s$,*S*)-**3m**. The absolute configuration of the amino sulfone ($R_s$,*S*)-**3f** was determined by single-crystal X-ray analysis (see the Supporting Information),[11] and the configurations of other amino sulfones were assigned by analogy. The stereochemistry is consistent with that observed for the addition of other methyl sulfone anions to N-sulfinyl aldimines, and can be rationalized by an open transition-state model.[12]

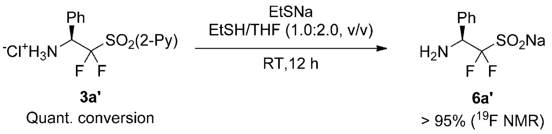
***Table 2:*** Preparation of β-amino sulfones by nucleophilic addition of **2a** to the imines **1**.



| Entry | Imine | Product | Yield [%][a] | d.r.[b] |
|---|---|---|---|---|
| 1 | (*R*)-**1a**: R = $C_6H_5$ | ($R_s$,*S*)-**3a** | 94 | >99:1 |
| 2 | (*R*)-**1b**: R = 4-$MeOC_6H_4$ | ($R_s$,*S*)-**3b** | 98 | >99:1 |
| 3 | (*R*)-**1c**: R = 4-$ClC_6H_4$ | ($R_s$,*S*)-**3c** | 93 | >99:1 |
| 4 | (*R*)-**1d**: R = 2-furyl | ($R_s$,*S*)-**3d** | 89 | >99:1 |
| 5 | (*R*)-**1e**: R = *c*-$C_6H_{11}$ | ($R_s$,*S*)-**3e** | 86 | >99:1 |
| 6 | (*R*)-**1f**: R = $CH_3$ | ($R_s$,*S*)-**3f** | 94 | >99:1 |
| 7 | (*R*)-**1g**: R = $(CH_2)_2CH_3$ | ($R_s$,*S*)-**3g** | 91 | >99:1 |
| 8 | (*R*)-**1h**: R = $(CH_2)_2Ph$ | ($R_s$,*S*)-**3h** | 90 | >99:1 |
| 9 | (*R*)-**1i**: R = $CH_2CH(CH_3)_2$ | ($R_s$,*S*)-**3i** | 95 | >99:1 |
| 10 | (*R*)-**1j**: R = $CH(CH_3)_2$ | ($R_s$,*S*)-**3j** | 91 | >99:1 |
| 11 | (*R*)-**1k**: R = $C(CH_3)_3$ | ($R_s$,*S*)-**3k** | 94 | >99:1 |
| 12 | (*R*)-**1l**: R = $CH_2Ph$ | ($R_s$,*S*)-**3l** | 51 (76)[c] | >99:1 |
| 13 | (*R*)-**1m**: R = (*E*)-PhCH=$CH_2$ | ($R_s$,*S*)-**3m** | 69 | 95:5 |

[a] Yield of the isolated analytically pure product. [b] Diastereomeric ratios were determined by $^{19}F$ NMR spectroscopy of the crude reaction mixture. [c] (*R*)-**1**/**2a**/LiHMDS = 2.0:1.0:2.0.

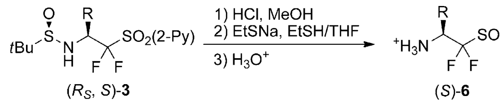
With a series of amino sulfones [($R_s$,*S*)-**3**] in hand, we continued our investigation on the removal of the 2-pyridyl group to prepare difluorinated β-amino sulfinic acids. With ($R_s$,*S*)-**3a** as a model compound, the desired β-amino sulfinate **6a′** was obtained in an excellent yield through the dearylation of **3a′** using a EtSNa/EtSH system (Scheme 2; for details, see SI-2 in the Supporting Information). This transformation was also suitable for the amino sulfones ($R_s$,*S*)-**3b–l** and did not lead to side reactions such as β elimination of 2-pyridylsulfinate and S–N Smiles rearrangement (see Tables 3 and 4). However, the base-labile styryl amino sulfone ($R_s$,*S*)-**3m** failed to be converted into the corresponding amino sulfinate because of a complete decomposition of the amino sulfone **3m′**. The amino sulfinates **6′** could be purified by passing through an acidic cation-exchange resin column with water as the eluent to afford amino sulfinic acids [(*S*)-**6**] in good yields. Some examples of the isolated (*S*)-**6** are shown in Table 3.



***Scheme 2.*** Dearylation of unprotected amino sulfone **3a′**.

We further investigated the oxidation of amino sulfinates to prepare the corresponding amino sulfonates (Table 4). It

***Table 3:*** Preparation of the amino sulfinic acids **6** from amino sulfones ($R_s$,*S*)-**3**.[a]



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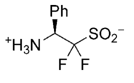
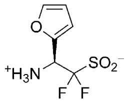
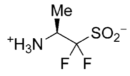
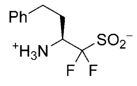
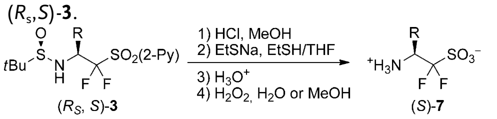
|  |  |  |  |
| (*S*)-**6a**, 80 % | (*S*)-**6d**, 91 % | (*S*)-**6f**, 89 % | (*S*)-**6h**, 70 % |

[a] Yield of isolated **6** based on the amino sulfones ($R_s$,*S*)-**3**.

**Table 4:** Preparation of the amino sulfonic acids (*S*)-**7** from amino sulfones ($R_s$,*S*)-**3**.

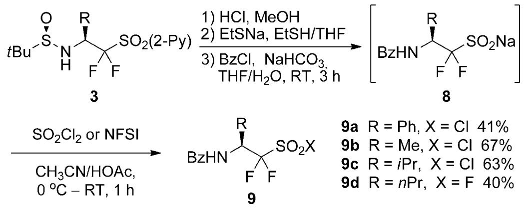


| Entry | Amino sulfone | Amino sulfonic acid | Yield [%][a] |
|---|---|---|---|
| 1 | ($R_s$,*S*)-**3a**: $R=C_6H_5$ | (*S*)-**7a** | 85 |
| 2 | ($R_s$,*S*)-**3b**: $R=4\text{-}MeOC_6H_4$ | (*S*)-**7b** | 82[b] |
| 3 | ($R_s$,*S*)-**3c**: $R=4\text{-}ClC_6H_4$ | (*S*)-**7c** | 81 |
| 4 | ($R_s$,*S*)-**3d**: R = 2-furyl | (*S*)-**7d** | 85[b] |
| 5 | ($R_s$,*S*)-**3e**: $R=c\text{-}C_6H_{11}$ | (*S*)-**7e** | 77 |
| 6 | ($R_s$,*S*)-**3f**: $R=CH_3$ | (*S*)-**7f** | 90 |
| 7 | ($R_s$,*S*)-**3g**: $R=(CH_2)_2CH_3$ | (*S*)-**7g** | 91 |
| 8 | ($R_s$,*S*)-**3h**: $R=(CH_2)_2Ph$ | (*S*)-**7h** | 68[b] |
| 9 | ($R_s$,*S*)-**3i**: $R=CH_2CH(CH_3)_2$ | (*S*)-**7i** | 85 |
| 10 | ($R_s$,*S*)-**3j**: $R=CH(CH_3)_2$ | (*S*)-**7j** | 89 |
| 11 | ($R_s$,*S*)-**3k**: $R=C(CH_3)_3$ | (*S*)-**7k** | 94 |
| 12 | ($R_s$,*S*)-**3l**: $R=CH_2Ph$ | (*S*)-**7l** | 80 |

[a] Yield of isolated (*S*)-**7** starting from the amino sulfones ($R_s$,*S*)-**3**. [b] Prepared by oxidation of the isolated amino sulfinic acids **6**.

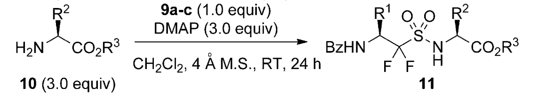
was found that the oxidization of amino sulfinates under neutral conditions afforded amino sulfonates in only moderate yields. Compared with simple fluorinated sulfinates, fluorinated β-amino sulfinates are less stable under oxidative conditions. To our delight, the ASAs (*S*)-**7a–l** were obtained in good to excellent yields with $H_2O_2$ in an aqueous HCl solution at pH 2–3. For most of the substrates under investigation, the transformation from the amino sulfones **3** to ASAs (*S*)-**7** can be performed in one pot without the isolation of amino sulfinic acids, thus considerably simplifying the operation (entries 1, 3, 5–7, and 9–12). In other cases, the ASAs were obtained by oxidizing the isolated amino sulfinic acids in MeOH for various reasons, including the poor aqueous solubility of the amino sulfinic acid (entry 8), the undesired chlorination of the electron-rich aryl substituent in the presence of chloride ion (entry 2), or the oxidative decomposition of 2-furyl substituent in aqueous solution (entry 4). The absolute configuration of **7a** and **7e** was assigned to be *S* by single-crystal X-ray analysis (see the Supporting Information),[11] and the products retained the absolute configuration of amino sulfones ($R_s$,*S*)-**3a** and ($R_s$,*S*)-**3e**, respectively.

To further demonstrate the synthetic utility of this protocol, a series of fluorinated peptidosulfonamides were prepared by the condensation between fluorinated β-amino sulfonyl chlorides and α-amino acid esters (Scheme 3). Starting from amino sulfones [($R_s$,*S*)-**3**], the fluorinated β-amino sulfinate intermediates were protected with the benzoyl group. The protected products **8** were chlorinated with $SO_2Cl_2$ to afford β-amino sulfonyl chlorides (**9a–c**) in one pot in moderate yields (41–67%). The sulfonyl fluoride **9d** could be prepared in a similar manner using *N*-fluorobenzenesulfonimide (NFSI) as the electrophilic fluorination reagent. Note that the well-established protocols for the preparation of sulfonyl halides using β-amino sulfonates were not applicable in the present cases.[13] Using 4-dimethylaminopyridine (DMAP) as the base, the sulfonyl chlorides **9a–c** were smoothly coupled with various α-amino acid esters (**10**) to afford the desired peptidosulfonamides **11** in good yields (60–86%) with high diastereoselectivity (Table 5). Noticeably, the two epimeric peptidosulfonamides **11e** and **11f** were obtained with high d.r. values, which confirmed the high enantiomeric purity of the sulfonyl chloride **9c** and the stereochemical retention of the α-amino carbon atom during the transformations of the amino sulfones **3**.



**Scheme 3.** Preparation of the amino sulfonyl halides **9** from amino sulfones **3**. Bz = benzoyl.

**Table 5:** Preparation of fluorinated peptidosulfonamides **11**.[a]



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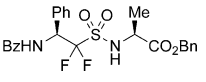
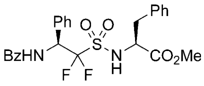
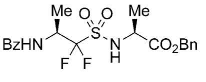
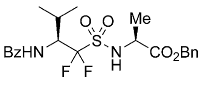
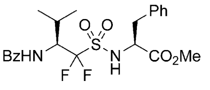
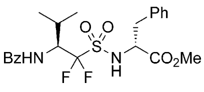
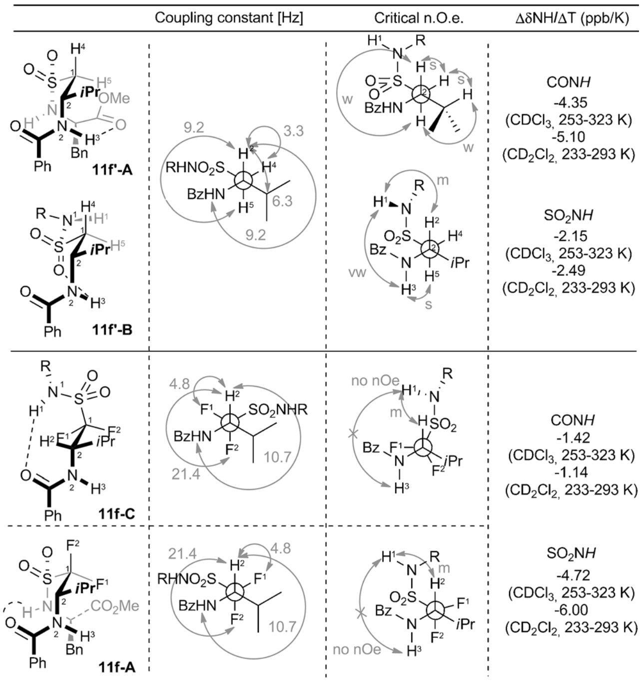
|  **11a**, 85%, >98:2 d.r.[b] |  **11b**, 60%, >99.5:0.5 d.r.[c] |
|  **11c**, 80%, >98:2 d.r.[b] |  **11d**, 86%, >98:2 d.r.[b] |
|  **11e**, 79%, >99.5:0.5 d.r.[c] |  **11f**, 76%, >99.5:0.5 d.r.[d] |

[a] Yield of isolated product. The diastereoselectivity was determined by $^{19}F$ NMR analysis of the crude reaction mixture. [b] L-Alanine benzyl ester (98% *ee*) was used. [c] L-Phenylalanine methyl ester (>99% *ee*) was used. [d] D-Phenylalanine methyl ester (>99% *ee*) was used. M.S. = molecular sieves.

To scrutinize the secondary structural alternation of peptidosulfonamides upon fluorine substitution, we have investigated the conformational behavior of **11f** and its nonfluorinated analogue **11f′** (Scheme 4). Based on the vicinal coupling constants $J_{H2H4}$ and $J_{H2H5}$, the $SO_2NH$ and BzNH groups in **11f′** were inferred to assume gauche conformations (Scheme 4; **11f′-A** and **11f′-B**).[14] The large $^3J_{H3\text{-}N2\text{-}C2\text{-}H2}$ value (9.2 Hz) suggests a *trans* geometry of the $H^2$-$C^2$-$N^2$-$H^3$ backbone,[15] and was further supported by the strong nOe between $H^3$ and $H^5$, and the relatively weak interaction between $H^1$ and $H^3$. As measured by variable-temperature (VT) $^1H$ NMR spectroscopy, the $\Delta\delta_{CONH}/\Delta T$ values of **11f′** were found to be approximately 3–4 times larger than the corresponding $\Delta\delta_{SO2NH}/\Delta T$ values, thereby manifesting the hydrogen-bond donating role of the CON−H bond. Accordingly, two conformations can be deduced,



***Scheme 4.*** Conformational study of **11 f** and **11 f′** using vicinal coupling analysis, NOESY spectroscopy, and VT $^1$H NMR experiments.

namely a nine-membered ring involving CON–H···O=COMe/O(Me)C=O interactions (**11 f′-A**) and a six-membered ring involving CON–H···O=S hydrogen bonding (**11 f′-B**).

In contrast, the large vicinal H-F coupling constant of 21.4 Hz indicated that one of the C–F bonds in **11 f** aligned antiparallel to the C$^2$–N$^2$ bond.[16] In other words, **11 f-C**- and **11 f-A**-like conformations are possible. Such conformations were also suggested by the moderate nOe between the H$^1$ and H$^2$ atoms as well as the absence of H$^1$–H$^3$ through-space interaction. Moreover, $^3J_{\text{H3-N2-C2-H2}}$ was found to be 10.7 Hz, thus indicating the *trans* orientation of the H$^3$–N$^2$ bond to the C$^2$–H$^2$ bond.[15] Further VT $^1$H NMR spectroscopic study in CD$_2$Cl$_2$ and CDCl$_3$ revealed that the $\Delta\delta_{\text{SO2N}H}/\Delta T$ values of **11 f** are approximately three- to fivefold larger than that of **11 f′** within a temperature range from 233 K to 323 K (see the Supporting Information). These observations evidently implied that the SO$_2$NH moiety of **11 f** is likely to operate as a hydrogen-bonding donor, whereas the CON–H bond is not involved in intramolecular interactions.[13a,17,18] In light of our conformational analysis, **11 f** was surmised to adopt eight-membered ring conformations **11 f-A** and/or **11 f-C** involving an intramolecular SO$_2$NH···OCNH hydrogen bonding.

In conclusion, we have reported a highly stereoselective synthesis of chiral optically active α,α-difluoro-β-amino sulfinic and sulfonic acids by fluoroalkylation of chiral imines using 2-PySO$_2$CF$_2$H as a masked difluoro(sulfinato)-methylation reagent. The transformation was found to be fairly feasible and easy-to-handle. The difluorinated β-amino sulfinates are expected to be suitable for constructing difluorinated peptidosulfonamides. The difluorinated β-amino sulfonic acids represent a novel class of functionalized fluoroalkyl sulfonic acids. The preliminary conformational study of **11 f** and its nonfluorinated analogue demonstrated their essentially different behavior, which can be of immense interest in life and materials sciences.

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