Difluoromethyl 2-Pyridyl Sulfoximine: A Stereoselective Nucleophilic Reagent for Difluoro(aminosulfinyl) methylation and Difluoro (aminosulfonyl)methylation

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1,1-Difluorinated sulfonamides are known to have better anti-inflammatory activity and enzyme inhibitory potency than their nonfluorinated counterparts. Two geminal fluorine atoms cause electronic perturbation of the nearby polar groups enhanced the biological activity of the 1,1-difluorinated sulfonamides. However, because methods for their stereoselective synthesis are scarce, such entities remain entirely unexplored. Here, we outline an efficient method for the stereoselective introduction of the difluoro(aminosulfonyl) methyl group ($CF_2SO_2NH_2$) into carbonyls, imines, and alkyl halides with a new (R)-2-pyridyl difluoromethyl sulfoximine reagent, which provides a unique solution for the synthesis of chiral α,α-difluorinated sulfonamides with a quaternary stereocenter. Its potency is illustrated by the synthesis of fluorinated analogues of bioactive compounds such as 2-OH-SA, an antagonist for the $GABA_B$ receptor in guinea pig ileum, and the late-stage modification of complex molecules such as haloperidol, ebastine, cholesterol, and (+)-δ-tocopherol derivatives. Stereoselective difluoro(aminosulfinyl) methylation to yield chiral sulfinylamides is presented, showcasing other uses of this new reagent.

Easy access to starting materials — Otherwise difficult-to-access products
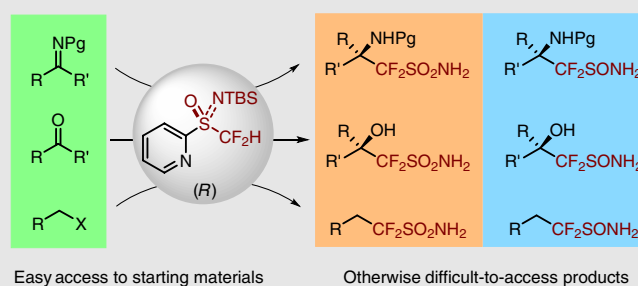
Keywords: difluoro(aminosulfonyl)methylation, difluoro(aminosulfinyl)methylation, stereoselective, nucleophilic, sulfoximine

Introduction

Fluorine, despite its almost complete absence from biological systems in nature, has become one of the most utilized elements for modulating the properties of biologically active molecules.[1,2] The sulfonamide moiety, one of most important pharmacophores, is featured in the structure of more than 150 U.S. FDA-approved drugs and a growing number of experimental drugs, and is known to act on a range of targets, including zinc metalloenzyme carbonic anhydrases, dopamine receptors, ion channels, and solute carriers.[3–8] 1,1-Difluorinated sulfonamides, combining fluorine and sulfonamide moieties, have improved anti-inflammatory activity and enzyme inhibitory

potency and can be used as potent pharmacophores,[9–12] which is rationalized by two facts: (1) the introduction of two fluorine atoms leads to a linear increase of acidity as well as a significant increase of lipophilicity, both of which are beneficial for improving their binding properties[9,10]; and (2) replacement of the bridging oxygen with CF_2 results in an ~18 times increase in inhibition of carbonic anhydrase under different pH conditions[9,11,12]; a demonstration of the beneficial effect of fluorine. Thus 1,1-difluorinated sulfonamides have been used as calcium homeostasis regulators and cryptochrome modulators to treat cryptochrome-dependent diseases (Figure 1a, A–D).[13,14] However, previous synthetic efforts were completely confined to simple sulfonamides with the general structure of $RCF_2SO_2NR'_2$ (R = H, n-alkyl, or aryl), which included stepwise nucleophilic fluorinations, condensations with carboxydifluoromethanesulfonamide,

and so on.[9–12,15,16] The lack of *stereoselective* preparation methods largely limits their applications in the field of biological science and pharmaceutical science.[17–21] Thus, a promising method is highly desired to directly and stereoselectively introduce the difluoro(aminosulfonyl) methyl group ($CF_2SO_2NH_2$) into molecules.[22,23]

Over the past decades, mild and efficient methods for highly stereoselective fluoroalkylations remain a formidable challenge.[24–27] In this context, sulfoximines, because the sulfoximidoyl group has a strong ability to induce stereoselectivity, have attracted much attention in the field of asymmetric synthesis,[28–32] and S-fluoroalkyl-S-aryl sulfoximines have emerged as robust fluoroalkylation reagents.[31] Based on this background, we envisioned the stereoselectively introduction of the difluoro(arylsulfoximidoyl)methyl group into carbonyl compounds or imines (Figure 1b, step a), followed by aromatic C–S bond
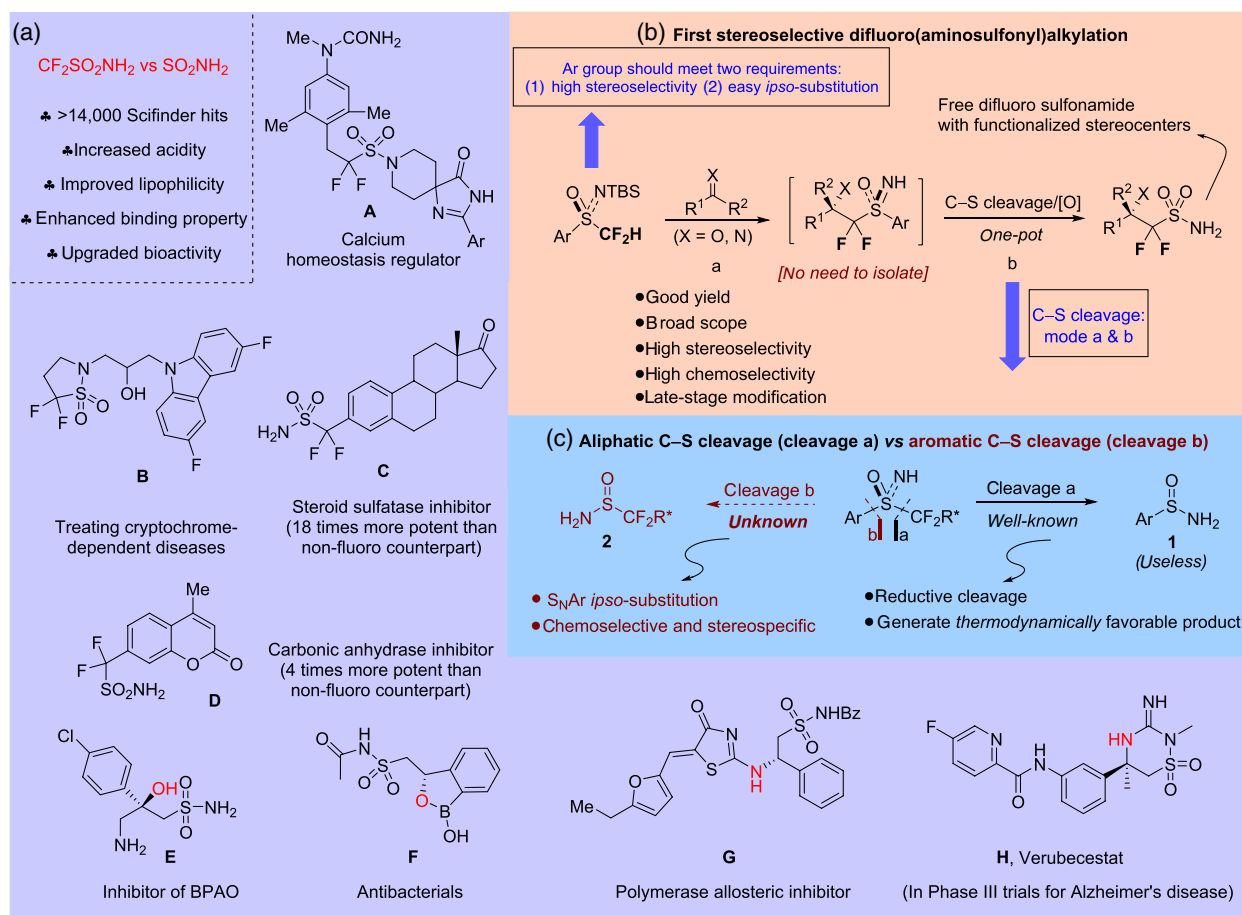
Figure 1 | *Examples of bioactive sulfonamides and difluorinated sulfonamides, and the first stereoselective difluro (aminosulfonyl)methylation with the sulfoximine reagent. (a) Characteristics of difluorinated sulfonamides as compared to non-fluorinated analogues, and examples of bioactive difluorinated and non-fluorinated sulfonamides. (b) First highly stereoselective difluoro(aminosulfonyl)methylation with difluoromethyl sulfoximine reagent, providing a unique solution for the synthesis of chiral 2-hydroxyl- and 2-amino-1,1-difluorinated sulfonamides. (c) Two modes of sulfinamide formation by carbon-sulfur bond cleavages. BPAO, bovine plasma amine oxidase; Bz, benzoyl; TBS, tert-butyldimethylsilyl.*

cleavage and one-pot oxidation (Figure 1b, step b) to generate difluoro(aminosulfonyl)methylated products with high stereoselectivities. However, the previously known C–S bond cleavage reaction typically proceed via reductive cleavage of the *aliphatic* C–S bond of sulfoximines to generate thermodynamically favorable *arene-sulfinamides* **1** (Figure 1c, cleavage a).[28-42] But if we can switch the cleavage mode from the aliphatic C–S bond to the *aromatic* C–S bond (via an S$_N$Ar *ipso*-substitution, Figure 1c, cleavage b), the difluoro sulfinamide motif could be released. To realize our hypothesis, a new reagent, (*R*)-2-pyridyl difluoromethyl sulfoximine, was developed as an equivalent of CF$_2$SO$_2$NH$_2$, which not only can satisfy the requirements of high stereoselectivity but also easy S$_N$Ar *ipso*-substitution (Figure 1b, steps a and b).[a] Based on this reagent, a stereoselective introduction of CF$_2$SO$_2$NH$_2$ into carbonyls, imines, and alkyl halides was realized to construct enantiomerically enriched 2-hydroxyl- or 2-amino-1,1-difluorinated sulfonamides, whose nonfluorinated counterparts have been widely used as enzyme inhibitors, antibiotics, as well as pharmaceutical drugs for Alzheimer's disease (Figure 1a, E–H).[43-47]

Experimental Methods

General procedure for stereoselective difluoroalkylation

Under N$_2$ atmosphere, to a solution of ketone (0.24 mmol, 1.2 equiv) and sulfoximine (*R*)-**3b** (0.2 mmol, 1.0 equiv) in tetrahydrofuran (THF) (4 mL), was added potassium hexamethyldisilazide (KHMDS) (1.0 M in THF, 0.3 mmol, 1.5 equiv) slowly at –94 °C. After 30 min, the reaction was quenched with aqueous saturated ammonium chloride (2 mL), followed by 3M HCl (6 mL). The solution was stirred for 30 min, after which NaOH (20% aq) was added to basify the solution, followed by extraction with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous MgSO$_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography using petroleum ether/ethyl acetate as eluent to give the major diastereoisomer **5**.

General procedure for synthesis of chiral difluorosulfonamide

Under N$_2$ atmosphere, to a schlenk-type reaction vessel containing a magnetic stirrer and NaH (95% wt, 0.38 mmol, 2.0 equiv), was added dry dimethylformamide (DMF) (1 mL). The solution was cooled to 0 °C and EtSH (2 mL) was added dropwise. After the solution was stirred for 5 min, the mixture of **5** (0.19 mmol, 1.0 equiv) in DMF (1 mL) was added dropwise. The mixture was stirred at 0 °C for 6 h, then at room temperature (rt) for

another 6 h. After the solvent was evaporated under vacuum, CH$_3$CN (1 mL), CCl$_4$ (1mL), H$_2$O (2 mL), NaIO$_4$ (0.38 mmol, 2.0 equiv), and ruthenium trichloride hydrate (3 mg) were added to a schlenk-type reaction vessel with the residue. The resulting mixture was stirred at rt overnight. The completion of the reaction was monitored by ^{19}F NMR. After 8 mL of water was added, the resulting black gel was filtered over celite and thoroughly washed with CH$_2$Cl$_2$, followed by extraction with CH$_2$Cl$_2$. The organic phase was washed with brine and then dried over anhydrous MgSO$_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography using petroleum ether/ethyl acetate as eluent to give the desired product. More experimental details are available in the Supporting Information.

Results and Discussion

Investigation of the reaction conditions

To realize this transformation, the reaction between difluoromethyl heteroaryl or electron-deficient aryl sulfoximines and 2-acetonaphthone (**4l**) was examined with extensive screening of the reaction conditions (Table 1). When **3a** was used as the reagent, a moderate yield of difluoromethylation products was observed via ^{19}F NMR spectroscopy with a 91/9 diastereomeric ratio (d.r.) (Table 1, entry 1). However, to our delight, when employing **3b** as the reagent, the yield and the diastereoselectivity increased to 92% and 92/8, respectively (Table 1, entry 2). For comparison, we conducted reactions between **4l** and several other reagents. In the case of **3c**, the diastereoselectivity was 92/8 but the yield was significantly lower than the reaction with **3b** (Table 1, entry 3); whereas in the case of **3d**, the diastereoselectivity was only moderate (Table 1, entry 4). With **3c** and **3d**, decomposition of the difluoromethyl sulfoximine was observed, and the preliminary results showed that these heteroaryl substituents were less effective at stabilizing α,α-difluorinated carbanions compared with the pyridyl group (the 2-pyridyl group is also more beneficial than the phenyl group to the *ipso*-substitution via intermolecular Smiles rearrangement, which will be further discussed in the part of difluoro(aminosulfonyl) methylation).

Regarding the availability, stability, and high stereoselectivity, the explicit combination of ketones and **3b** is advantageous in terms of the general applicability of the protocol. Thus, based on the combination of **3b** and **4l**, we further optimized the conditions by screening several reaction parameters, including different bases, solvents, and molar ratios of reactants (Table 1, entries 5–13). When *n*-butyllithium (*n*-BuLi) or lithium hexamethyldisilazide (LiHMDS) was used as base, both the yield and the diastereoselectivity decreased significantly (entries 5

Table 1 | *Survey of Reaction Conditions*[a,b]

Entry	**4l**/**3**/Base	Base	Solvent	Yield (%)	d.r.
1[c]	1.2/1.0/1.5	KHMDS	THF	57	91/9
2	1.2/1.0/1.5	KHMDS	THF	92	92/8
3[d]	1.2/1.0/1.5	KHMDS	THF	14	92/8
4[e]	1.2/1.0/1.5	KHMDS	THF	34	87/13
5	1.2/1.0/1.5	*n*-BuLi	THF	22	83/17
6	1.2/1.0/1.5	LiHMDS	THF	42	87/13
7	1.2/1.0/1.5	NaHMDS	THF	85	82/18
8[f]	1.2/1.0/1.5	KHMDS	THF/HMPA	52	92/8
9	1.2/1.0/1.5	KHMDS	Et$_2$O	88	90/10
10	1.2/1.0/1.5	KHMDS	PhMe	87	89/11
11	1.2/1.0/1.5	KHMDS	DCM	91	88/12
12[g]	1.2/1.0/1.5	KHMDS	THF	99(91)	94/6(98/2)
13[g]	1.5/1.0/1.5	KHMDS	THF	95	94/6

[a] Typical procedure: The base was added slowly to a solution of **3** and **4l** in THF; 0.5 h later, saturated NH$_4$Cl (aq) was added slowly at −78 °C. Unless otherwise noted, **3b** was used.
[b] Yields and d.r. values were determined by ¹⁹F NMR analysis. The yield in parenthesis is the isolated yield of the major diastereoisomer. The d.r. in parenthesis was determined by ¹⁹F NMR analysis of the isolated major diastereoisomer.
[c] **3a** was used.
[d] **3c** was used.
[e] **3d** was used.
[f] *v/v* = 10/1.
[g] The temperature was −94 °C.

and 6). Although the use of sodium hexamethyldisilazide (NaHMDS) gave a yield of 85%, the stereoselectivity was significantly lower than the reaction with KHMDS (entry 7). Interestingly, the addition of hexamethylphosphoramide (HMPA), a strong coordinating solvent, did not affect the diastereoselectivity, although the yield decreased (entry 8). With KHMDS as the base, solvent screening showed that THF was optimal in terms of yield and stereoselectivity (entries 9–11). When the reaction temperature was lowered, both the yield and diastereoselectivity improved slightly (99% yield, 94/6 d.r.; entry 12). Further optimization of the reaction conditions by changing the ratio of **4l**, **3b**, and KHMDS did not further improve the result (entry 13). Importantly, slow quenching of the reaction at low temperature is essential to prevent the Smiles rearrangement and subsequent elimination that produce 1,1-difluoroalkenes.[48] Notably, this is the first reported synthesis of (*R*)-**3b** (Figure 2), and the optically
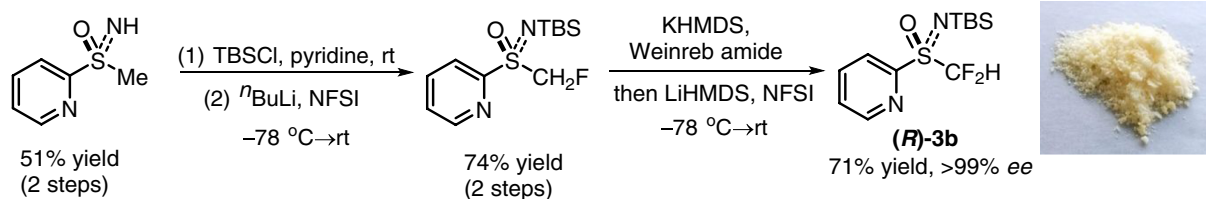
Figure 2 | *Synthesis of* **(R)-3b**. *HMDS, hexamethyldisilazide; TBS, tert-butyldimethylsilyl; NFSI, N-fluorobenzenesulfonimide.*

pure product as a stable solid was obtained on 4.3 g scale (please see the Supporting Information for details).[b]
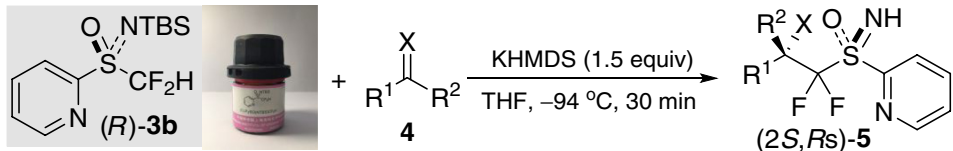
Substrate scope

Having established the reaction conditions, we subsequently examined the substrate scope with (R)-**3b** (Table 2), and the N-desilylated products were obtained, which facilitated subsequent derivations of the products. The reaction could tolerate many functional groups, such as chloro, bromo, iodo, methoxy, methylthio, and ethynyl groups (Table 2, entries 1–7). The facial selectivity was insensitive to both the electronic nature and position of substituents (entries 8 and 9). And fused aromatic rings, such as naphthalene and phenathrene, were also compatible with the current reaction (entries 11–13). In addition, the cyclic aromatic ketone, 3,4-dihydronaphthalen-1(2H)-one, was a suitable substrate to afford the corresponding product **5n** in 88% yield with 95/5 d.r. (entry 14). The reagent also reacted with an aldehyde in excellent diastereo-

selectivity (entry 15). Pharmaceutically important heteroaromatics, such as benzopyridine, pyrrole, and thiophene, furnished the corresponding products in excellent yields with high d.r. values (entries 16–19). Remarkably, when imines were investigated as substrates, products **5t**–**5v** were obtained with high stereoselectivity (entries 20–22). The absolute configuration of **5n** was confirmed by X-ray crystal structure analysis and the newly formed quaternary carbon center was found to be in the S configuration.

Rationalization of diastereoselectivity

Because the addition of HMPA does not influence the diastereoselectivity of the difluoromethylation of **4l** with (R)-**3b** (Table 1, entry 8), we propose that the cation might not participate in the transition state, which is different from the reactions of lithiated sulfoximine and ketone.[49] One can envisage several possible nonchelated transition states, such as TS-1, TS-2, TS-3, and TS-4, as shown in Figure 3. Since the repulsive interactions of

**Table 2** | Investigation of the Substrate Scope[a]

Entry	4	5	Yield (%)	d.r.[b]
1	$C_6H_5COCH_3$ (**4a**)	**5a**	84	99/1(92/8)
2	$4\text{-}ClC_6H_4COCH_3$ (**4b**)	**5b**	86	99/1(92/8)
3	$4\text{-}BrC_6H_4COCH_3$ (**4c**)	**5c**	83	99/1(92/8)
4	$4\text{-}IC_6H_4COCH_3$ (**4d**)	**5d**	78	99/1(93/7)
5	$4\text{-}MeOC_6H_4COCH_3$ (**4e**)	**5e**	82	99/1(96/4)
6	$4\text{-}MeSC_6H_4COCH_3$ (**4f**)	**5f**	90	99/1(94/6)
7	$4\text{-}Ethynyl\text{-}C_6H_4COCH_3$ (**4g**)	**5g**	70	99/1(94/6)
8	$3\text{-}MeOC_6H_4COCH_3$ (**4h**)	**5h**	85	99/1(91/9)
9	$2\text{-}ClC_6H_4COCH_3$ (**4i**)	**5i**	52	99/1(95/5)
10	$C_6H_5COCH_2CH_3$ (**4j**)	**5j**	88	99/1(93/7)
11	1-(Naphthalen-1-yl)ethanone (**4k**)	**5k**	74	99/1(94/6)
12	1-(Naphthalen-2-yl)ethanone (**4l**)	**5l**	91	98/2(94/6)
13	1-(Phenanthren-2-yl)ethanone (**4m**)	**5m**	74	99/1(93/7)
14	3,4-Dihydronaphthalen-1-(2H)-one (**4n**)	**5n**	88	99/1(95/5)
15	$4\text{-}MeOC_6H_4CHO$ (**4o**)	**5o**	91	99/1(95/5)
16	6-Acetylquinoline (**4p**)	**5p**	82	95/5(92/8)
17	2-Acetyl-1-methylpyrrole (**4q**)	**5q**	71	99/1(94/6)
18	1-(Thiophen-2-yl)ethanone (**4r**)	**5r**	92	99/1(94/6)
19	1-(Thiophen-3-yl)ethanone (**4s**)	**5s**	82	99/1(90/10)
20[c]	N-Bus-ketimine (**4t**)	**5t**	85	95/5(90/10)
21[c]	N-Ts-ketimine (**4u**)	**5u**	75	96/4(94/6)
22[c]	N-Bus-aldimine (**4v**)	**5v**	82	95/5(90/10)

[a] Yields indicated are isolated yields of the major diastereoisomer. Diastereomeric ratio (d.r.) values are determined by ^{19}F NMR analysis of the isolated major diastereoisomer. Bus, tert-butylsulfonyl; Ts, toluenesulfonyl.

[b] The d.r. values in parentheses were determined by ^{19}F NMR analysis of the crude products.

[c] Dichloromethane (DCM) was used instead of THF.
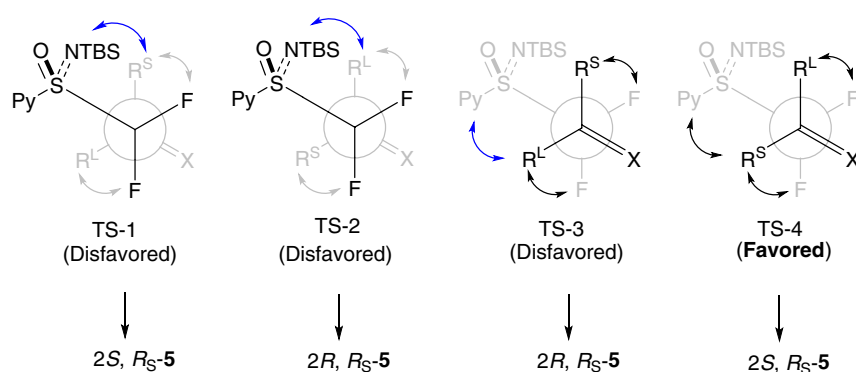
Figure 3 | *Proposed transition states. Repulsive interactions are indicated by curved arrows.*

CH₃···S=NTBS and Ph···S=NTBS are stronger than that of CH₃···S=O in TS-3 and TS-4, TS-1 and TS-2 are disfavored (R^L = Ph; R^s = CH₃). And considering that the steric hindrance of Py···Ph is stronger than that of Py···CH₃, TS-3 is energetically less favorable than TS-4. Thus TS-4 is the most favorable transition state that can give the product of 2S,Rs-**5**.

Difluoro(aminosulfonyl)methylation

With a series of enantiomerically enriched difluorosulfoximines in hand, we continued our investigation on the removal of the pyridyl group to prepare difluorosulfinamides. With the isolated major diastereomer of **5l** as a model compound, the desired (R)-hydroxyl difluorinated sulfinamide was obtained in 85% yield with excellent stereoselectivity when sodium ethanethiolate/ethanethiol was applied in DMF solution (Figure 4a; for details, see Supporting Information Table S1).[50-54] It is worth noting that phenyl sulfoximine **7** failed to undergo Ph–S bond cleavage under the same conditions, indicating the necessity of the 2-pyridyl group in this transformation.

Simple oxidation of unpurified sulfinamides with the neutral aqueous conditions of RuCl₃/NaIO₄ in one pot provided the desired enantiomerically enriched difluorosulfonamides **8–10** in good to excellent yields. The substrate scope was found to be insensitive to the diversity of functional groups and the effects of steric hindrance and electronic induction, and the α-hydroxyl difluorosulfonamides were efficiently generated (**8a–8e**, Figure 4b). Additionally, this method is applicable to other types of substrates, such as imines and alkyl halides, and the β-amino difluorosulfonamides and alkyl difluorosulfonamides were obtained (**9** and **10)**.

To further illustrate the potential value of our present difluoro(aminosulfonyl)methylation reaction in organic synthesis, we applied it to the preparation of a difluorinated analogue of 2-OH-SA, which is one of the antagonism agents for the GABA_B receptor in guinea pig ileum[47] (Figure 4c). The difluoro sulfoximine **12** was

transformed into difluoro sulfonamide **13** in 49% yield with 97/3 enantiomeric ratio (e.r.) without any loss of chirality. Notably, this is the first preparation of enantiomerically enriched fluorinated 2-OH-SA **13** from an easily accessible **11**. And, a one-pot procedure can give **8d** from the starting ketone with high efficiency and stereoselectivity (Figure 4d). In addition, it can also be readily scaled up. For example, a gram-scale reaction with (+)-δ-tocopherol derivative gave **8f** in 74% yield with high stereoselectivity (Figure 4d).
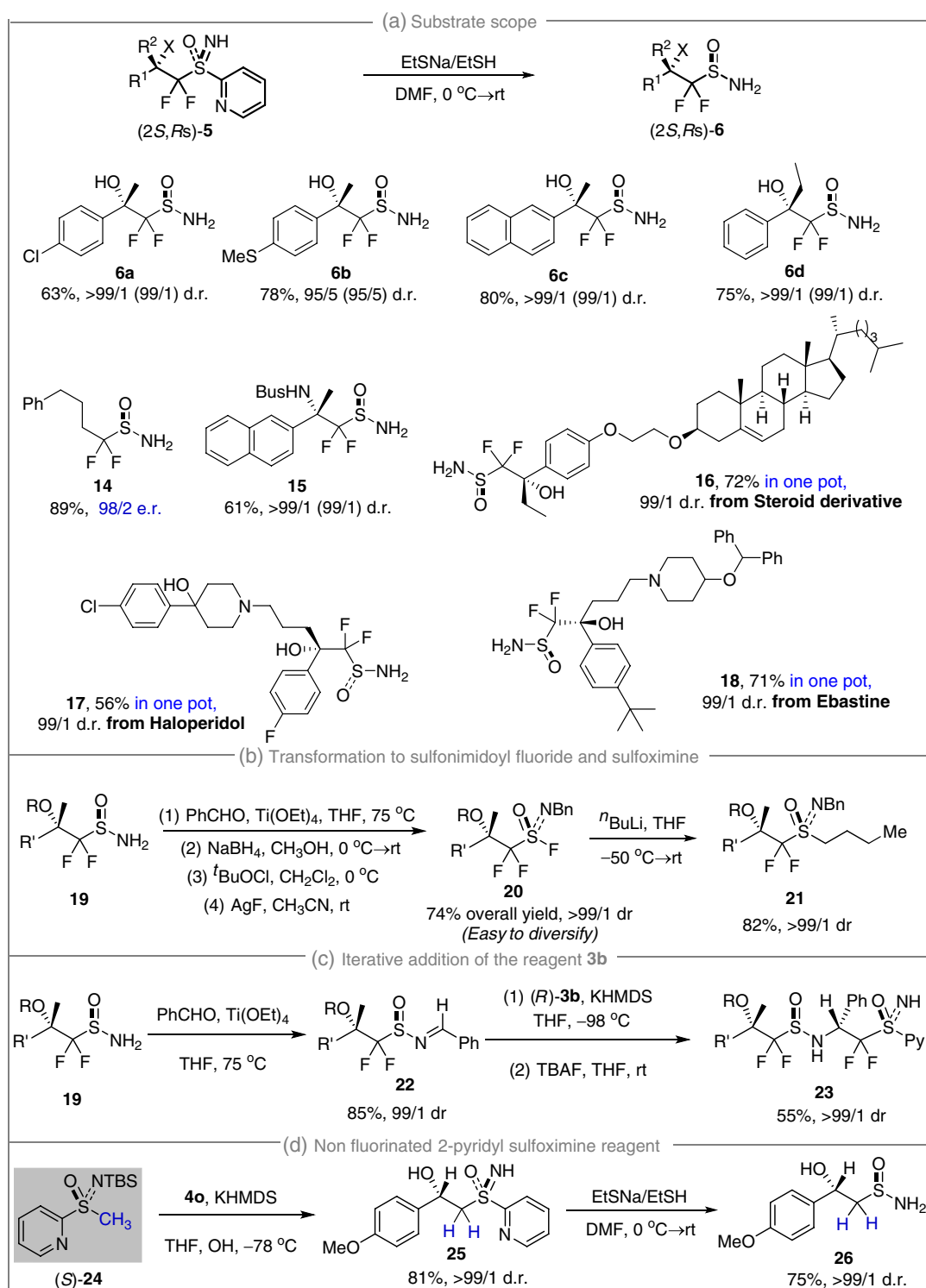
Difluoro(aminosulfinyl)methylation

Considering chiral sulfinamides have been widely used as chiral auxiliaries, as ligands in transition-metal catalysis, and as organocatalysts,[55-58] we were interested in determining whether the corresponding sulfinamide can be obtained. To our delight, with the optimal reaction conditions, various enantiomerically enriched difluorosulfinamides were isolated after S_NAr reaction (Figure 5a). Starting materials bearing electron-rich or -deficient substituents were all able to give **6a** and **6b** in good yields with high d.r. values. When the substituent is an ethyl group, the reaction also proceeded smoothly affording **6d** in 75% yield with 99/1 d.r. The reaction was compatible with imines and alkyl halides such as **14** and **15** without erosion of stereoselectivities.

The method could be utilized in the late-stage modification of complex molecules in a one-pot sequence, directly from carbonyl compounds. For instance, the difluoro(aminosulfinyl)methyl group was introduced into Ebastine (**18**) and cholesterol derivative (**16**) efficiently with high stereoselectivities. Furthermore, the antipsychotic agent Haloperidol, which contains tertiary alcohol and tertiary amine functionalities, was also successfully transformed into an enantiomerically enriched diamine (**17**).

To show the potential application of these sulfinamides, **19** (see Supporting Information, Part 16) was transformed into the chiral sulfonimidoyl fluoride **20** in 74% overall yield with 99/1 d.r. by the sequence of oxidation chlorination and
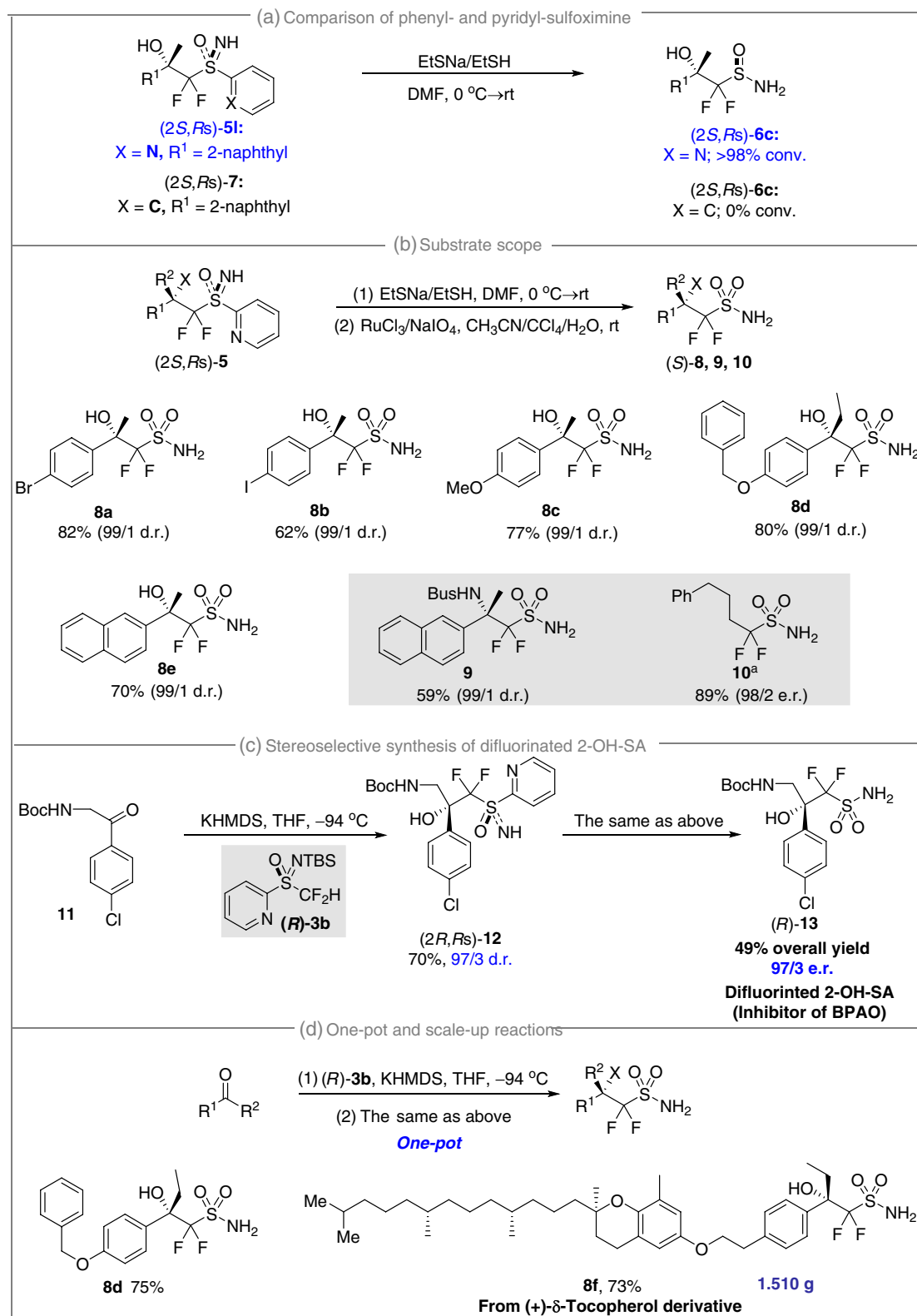
Figure 4 | *(a) Comparison of phenyl sulfoximine and pyridyl sulfoximine. (b) Substrate scope of the stereoselective difluoro(aminosulfonyl)methylation reactions. (c) Highly stereoselective synthesis of difluorinated 2-OH-SA. (d) One-pot and scaled-up reactions. Yields are the isolated yields of the major diastereoisomers. ^{19}F NMR analysis of the isolated product was used to determine d.r. values. The ratios in parentheses were determined by ^{19}F NMR analysis of the crude difluoro sulfinamides. HPLC analysis of the difluoro sulfinamides was used to determine the e.r in parentheses. See the Supporting Information for details. HPLC, high-performance liquid chromatography; Bus, tert-butylsulfonyl; Boc, tert-butoxycarbonyl;. [a]The product was obtained from Ph(CH$_2$)$_3$CF$_2$SO(NH)Py.*

Figure 5 | *(a) Substrate scope of the stereoselective difluoro(aminosulfinyl)methylation reactions. (b) The transformation from aromatic sulfoximine agent to sulfonimidoyl fluoride and alkyl sulfoximine. (c) Iterative procedure with 2-pyridyl difluoromethyl sulfoximine. (d) Extension to the nonfluorinated 2-pyridyl sulfoximine reagent. Yields are the isolated yields of the major diastereoisomers. ^{19}F NMR analysis of the isolated product was used to determine d.r. values. The ratios in parentheses were determined by ^{19}F NMR analysis of the crude product. See the Supporting Information for details. R, 2-pyridyl; R′, 2-naphthyl; Bus, tert-butylsulfonyl; Boc, tert-butoxycarbonyl; Bn, benzyl.*

fluorine-chlorine exchange (Figure 5b; also see Supporting Information, Part 16). Notably, **20** is usually used in the sulfur(VI) fluoride exchange (SuFEx) reaction, in which an S–F moiety easily reacts with C-, N-, and O-nucleophiles to generate sulfoximines, sulfonimidamides, and sulfonimidates.[59,60] As an example, treating **20** with a C-nucleophile constructed the *n*-butyl substituted sulfoximine compound **21** without the erosion of the enantioselectivity (Figure 5b). Sulfoximines are known as a rising star in drug discovery, and this is the first example of conversion of an aryl sulfoximine to alkyl sulfoximine.[61,62] Furthermore, we realized the iterative addition of **3b** to produce a compound **23** with two carbon stereocenters and two sulfur stereocenters (Figure 5c). In addition, when nonfluorinated sulfoximine reagent **24** reacted with carbonyl compound **4o** under the developed reaction conditions, the corresponding product **25** was obtained in good yield with high d.r. (Figure 5d), which not only represents an efficient method for highly stereoselective (aminosulfinyl)methylation but also extends the scope of this methodology.

Conclusion

We have demonstrated a new reagent, (*R*)-difluoromethyl 2-pyridyl sulfoximine, and an unprecedented method for synthesis of chiral β-functionalized α,α-difluorosulfonamides. In contrast to the traditional chiral auxiliary group chemistry, (*R*)-difluoromethyl 2-pyridyl sulfoximine in this method is a bifunctional agent, not only serving as a stereoselective controller but also as an equivalent to chiral sulfinamide, which is conceptually new in sulfoximine chemistry. Practically, it allows accessing and probing the ability of an assortment of new stereochemically defined difluoro sulfonamide analogues as therapeutic agents in biological and pharmaceutical science. The selection of the 2-pyridyl group is crucial for the success of this transformation, which facilitates both the nucleophilic fluoroalkyl addition as well as the subsequent *ipso*-substitution process. This difluoro(aminosulfonyl)methylation was applied to the synthesis of bioactive compounds and the late-stage modification of complex molecules with good tolerance of functional groups. What is more, this reagent allows the synthesis of chiral sulfinylamides and α,α-difluorosulfinylamides. Potential transformations can highlight their applications for the construction of sulfonimidoyl fluorides and multiple stereogenic centers. Not only does our work demonstrate an intriguing new reactivity of sulfoximines, but it also serves as a basis for the further development of stereoselective (aminosulfonyl)methylation or (aminosulfinyl)methylation for many potential applications.[28–32,63–65]

Footnotes

[a] This research not only shows the high stereocontrolling ability of the heteroaryl sulfoximidoyl group, but also uses the difluorosulfoximidoyl group as an equivalent of dilfuorosulfonamide.

[b] CCDC 1444415 (**S1**; see Supporting Information Figure S1 and Tables S2–S8), CCDC 1444416 (**5n**; see Supporting Information Figure S2 and Tables S9–S15), and CCDC 1444417 (**S7**; see Supporting Information Figure S3 and Tables S16–S22) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Supporting Information

Supporting Information is available including experimental details and characterization.

Conflict of Interest

There is no conflict of interest to report.

Acknowledgments

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