How to cite: *Angew. Chem. Int. Ed.* **2025**, *64*, e202511400
doi.org/10.1002/anie.202511400

Synthetic Methods **Hot Paper**

Stereoselective Nucleophilic Di- and Monofluoro(sulfoximidoyl)Methylation of C=C Bonds: Remote Neighboring Group Participation Enables Facile Access to Chiral γ-Fluorinated Amines

Bo Wang[+], Mengmeng Zheng[+], Xiaomei Chen, Taige Kong, Qian Wang, Xiao-Song Xue, Qinghe Liu,* and Jinbo Hu**

Abstract: There remains an ongoing challenge to develop facile methods for the preparation of chiral γ,γ-difluorinated amines, which are commonly considered a privileged motif in bioactive compounds. In this context, we report a straightforward protocol for the stereoselective nucleophilic difluoro(sulfoximidoyl)methylation of C=C bonds (considered to be more challenging than the reported C=O bonds), which exhibits high stereoselectivity and broad substrate scope. The key features of this chemistry include 1) stereoselective addition of the difluoro(sulfoximidoyl)methyl anion to C=C bonds, although it was considered to be highly unfavorable from the view of hard–soft acid–base (HSAB) theory; 2) intriguing neighboring group participation of the oxygen from the nitro group that was found to play a crucial role in controlling the stereoselectivity and efficiency of the transformation and was supported by mechanistic experiments and DFT calculations. This method has been applied to the late-stage modification of several complex molecules and the preparation of enantioenriched bioactive γ-fluorinated amines, such as a phytopathogenic fungi inhibitor, TRPC6 and CDK11 inhibitors, and even monofluorinated lorcaserin, which further demonstrated the significance and potential of this approach.

Introduction

Selective incorporation of fluorine atoms or fluoroalkyl groups into organic molecules can significantly alter their physical and biological properties due to the unique characteristics of fluorine.[1–5] Among various fluoroalkyl groups, the difluoromethyl (CF_2H) group is of particular interest, as it is isosteric and isopolar with respect to an OH or SH unit and can serve as a lipophilic hydrogen-bond donor.[6–11] In this regard, the incorporation of a difluoromethyl group into small molecules offers advantageous effects, including enhanced bioavailability, improved metabolic stability, and increased lipophilicity, while simultaneously serving as or maintaining a critical recognition motif for biological targets.[6,7] In addition, β-stereogenic amines, such as chiral β-hydroxyl or β-methyl amines, are particularly important compounds that are widely represented in market drugs and bioactive molecules (see Figure 1a).[12,13] Thus, it is extremely attractive to synthesize the corresponding CF_2H analogs of these compounds. On the other hand, when fluorine atoms are introduced into the γ-position of amines, the formed γ-fluoroamines have been recognized as of high value in medicinal chemistry.[14–19] For instance, the γ-fluorinated amines have been identified as the inhibitors of the TRPC6, the CDK11, the phytopathogenic fungi, the cysteine proteinase, etc., which highlight their critical roles in the therapy of various diseases (shown in Figure 1b).[16–18] Therefore, on the basis of the isosteric effect of CF_2H and the direct bioactivities of γ,γ-difluorinated amines, it is of great significance to develop a facile method to prepare the chiral γ,γ-difluorinated amines or the alternative analog of γ-monofluorinated amines. [20–22]

However, the synthetic methods for these compounds are quite limited, and the existing approaches exhibit several deficiencies that require urgent improvements. In 2011, Hunter and co-workers reported the stereoselective formation of fluorohydrins from cinnamyl bromide or hydroxide, followed by difluoromethyl amines, which were obtained after the treatment of DeoxoFluor (see Figure 1c, I).[20] In this case, the preparation of fluorohydrin required 4–6 steps, of which the diastereoselectivity ratio was as low as 3:2 when allylic

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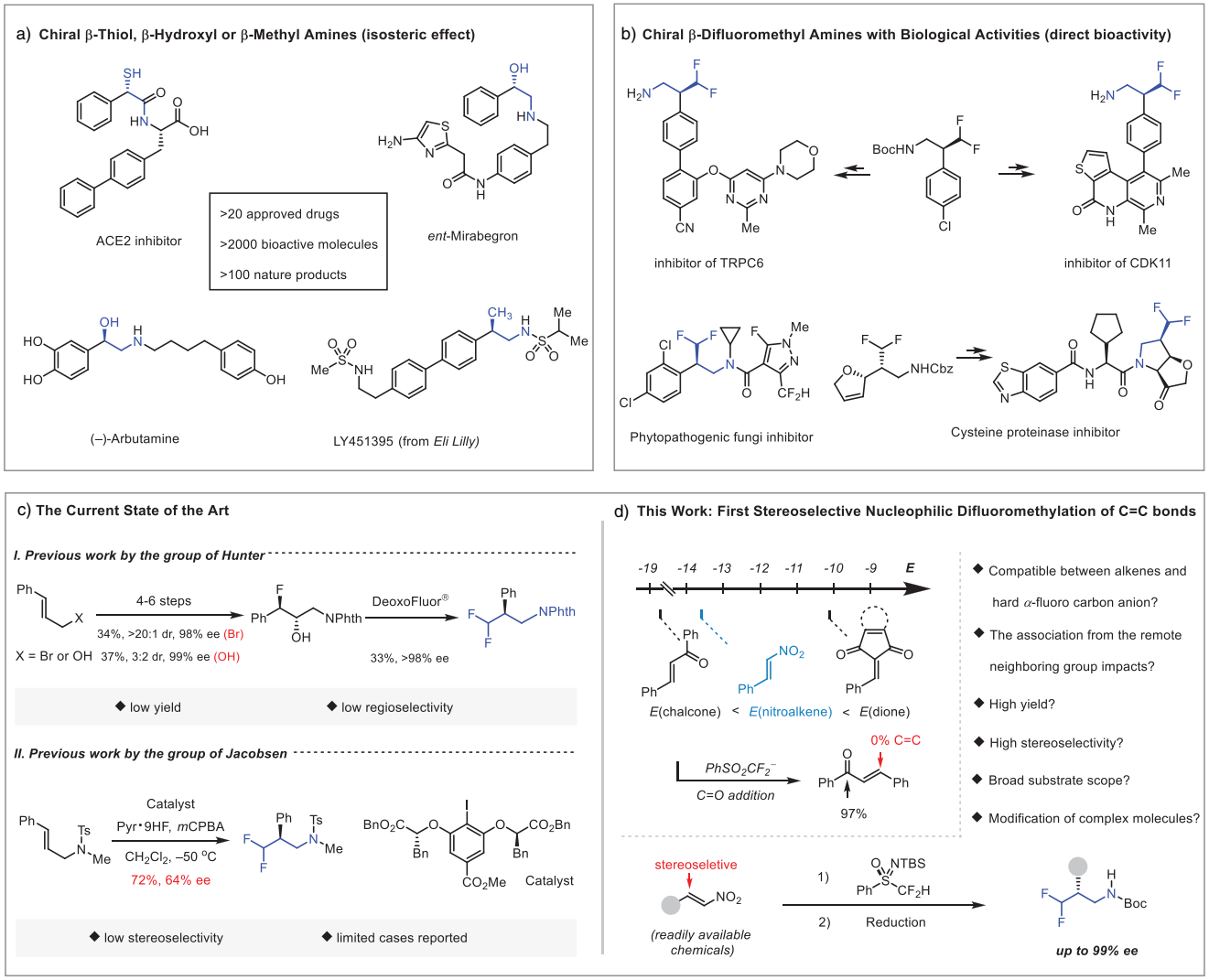


Figure 1. a) Examples of pharmaceutical and bioactive molecules with β-methyl or β-hydroxyl amines. b) Examples of pharmaceutical and bioactive molecules with β-difluoromethyl amines. c) The current state of the art for the synthetic strategies of β-difluoromethyl ethylamine. d) The first stereoselective nucleophilic difluoromethylation of alkenes was proposed. ACE2, angiotensin-converting enzyme 2. E = electrophilicity parameters. Phth = phthalimide.

alcohol was used, and the final step resulted in only 33% yield of β-difluoromethyl amine with 3:2 rr. In 2016, Jacobsen and co-workers reported an elegant method involving phenyl migration to access the chiral building blocks containing β-difluoromethyl amine [21] (see Figure 1c, II). However, moderate enantioselectivity (64% ee) was obtained, and the substrate scope was limited due to the aromatic rings with withdrawing substituents, which were found to be hard to proceed with the aryl migration. [22] In fact, to the best of our knowledge, there is no efficient and stereoselective method for the preparation of such compounds, despite their crucial significance in pharmaceutical and biological sciences. Therefore, the development of a new, efficient, and facile strategy to synthesize optically pure β-difluoromethyl amines is highly desired.

Over the past decades, sulfoximines have been widely used in organic synthesis, but fluorinated sulfoximines still remain relatively poorly studied.[23–29] In our group, we developed several fluorinated sulfoximines to realize fluoroolefinations and fluoroalkylations with C=O bonds.[30–33] However, difluoromethylation of C=C bonds, which can construct C_{sp^3}-CF_2H with a constructed stereogenic center, remains a formidable challenge.[34–40] It could be attributed to the following two reasons: One is the reactivity issue: the C=C *bonds* are less favorable to react with sulfoximidoyl fluorinated carbanion than C=O bonds, due to the incompatibility of the hard/soft nature of the fluorinated sulfoximine anion and the alkenes according to the hard–soft-acid–base theory (HSAB).[37–40] This has been exemplified by the example of (*E*)-chalcone and sulfonyl difluorinated carbanion, in which the only C=O addition products were observed (see Figure 1d, top). The other one is the stereoselectivity issue: the absence of oxygen from C=O bonds, which was thought to precede the coordination by the formation of an oxygen-assisted favorable conformation and to subsequently lower the Gibbs free energy of the reaction intermediate.[41,42] The resulting

six-membered-ring transition state from the metal cation and the carbonyl group has been shown to mainly amplify the stereoselectivity in the carbonyl addition reaction.[43]

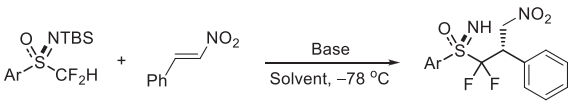
Given the significance and synthetic challenges of chiral γ,γ-difluoroamines, we aimed to develop a highly stereoselective nucleophilic difluoromethylation using sulfoximine reagent **1** and nitroalkenes (see Figure 1d, bottom). The reasons to select nitroalkenes would be as follows: 1) The electrophilicity of nitroalkenes lies between chalcone and benzylidene dione, which indicates that nitroalkenes are moderately electron-deficient; 2) Nitroalkenes are readily available, and the resulting nitroalkanes can be easily converted into amines after a simple reduction. Furthermore, several challenges must be addressed if the reaction proceeds as our proposal: 1) whether the HSAB properties of the α-fluoro carbanion and the nitroalkene are compatible; 2) whether the association effect of the neighboring nitro group and sulfoximidoyl moiety impacts the stereoselectivity and efficiency; and 3) whether the reaction scope can be broadened to complex molecules.

Results and Discussion

Initial Discovery of Stereoselctive Nucleophilic Difluoro(sulfoximidoyl)Methylation of Alkenes

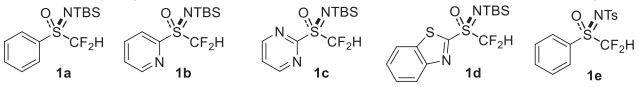
We commenced the study by investigating the diastereoselective reaction between the difluoromethyl phenyl *S*-phenylsulfoximine **1a** and the nitroalkene **2a** by using a chiral carbanion strategy; the results are summarized in Table 1. Typically, a base was added into the mixture of **1a** and **2a**, and the ratio of **1a**, **2a**, and the base was 1.0/1.5/1.2. When lithium hexamethyldisilazide (LiHMDS) was used as the base, a 39% yield of the difluoro(sulfoximidoyl)methylation product was observed by ^{19}F NMR spectroscopy, and the diastereoselectivity was only moderate (88/12 dr; entry 1). However, the yield was slightly decreased (26% yield, 88/12 dr) when NaHMDS was employed as the base (entry 2). Encouragingly, KHMDS was found to be much better for the stereoselective difluoro(sulfoximidoyl)methylation reaction than LiHMDS and NaHMDS (60% yield, 95/5 dr; entry 3). When the base was changed to *n*BuLi, the yield of difluoro(sulfoximidoyl)methylation product was reduced drastically (entry 4). The inefficiency of the reaction was probably attributed to the competing reaction between **2a** and *n*BuLi.[44,45] Surprisingly, when we changed the molar ratios to further optimize the reaction conditions, it was remarkable that the reaction could give a high yield (88%) with 95/5 dr (entry 5). Furthermore, screening of solvents such as toluene, dichloromethane, and ethyl ether showed tetrahydrofuran (THF) to be the optimal solvent (entries 6–8). It was found that hexamethylphosphoramide (HMPA) was fatal to the reaction, because the yield and dr sharply decreased to 26% and 77/23, respectively, when HMPA was used as a cosolvent (entry 9). It indicated that an alkali metal counterion was involved in the transition state of the reaction, probably.[46] This effect also will be discussed in the section of the mechanism study. Additionally, the comparison

Table 1: Optimization of the reaction conditions. [a], [b], [c]



1 2a 3a

Entry	1/2a/Base	Base	Solvent	Yield (%)	dr
1	1.0/1.5/1.2	LiHMDS	THF	39	88/12
2	1.0/1/5/1.2	NaHMDS	THF	26	88/12
3	1.0/1.5/1.2	KHMDS	THF	60	95/5
4	1.0/1.5/1.2	*n*BuLi	THF	5	n.d.
5	1.5/1.0/1.4	KHMDS	THF	88 (88)	95/5
6	1.5/1.0/1.4	KHMDS	$PhCH_3$	70	71/29
7	1.5/1.0/1.4	KHMDS	CH_2Cl_2	44	71/29
8	1.5/1.0/1.4	KHMDS	Et_2O	81	81/19
9	1.5/1.0/1.4	KHMDS	THF/HMPA	26	77/23
10[d]	1.5/1.0/1.4	KHMDS	THF	42	88/12
11[e]	1.5/1.0/1.4	KHMDS	THF	12	90/10
12[f]	1.5/1.0/1.4	KHMDS	THF	6	82/18
13[g]	1.5/1.0/1.4	KHMDS	THF	<2	n.d.
14	1.8/1.0/1.6	KHMDS	THF	80	95/5



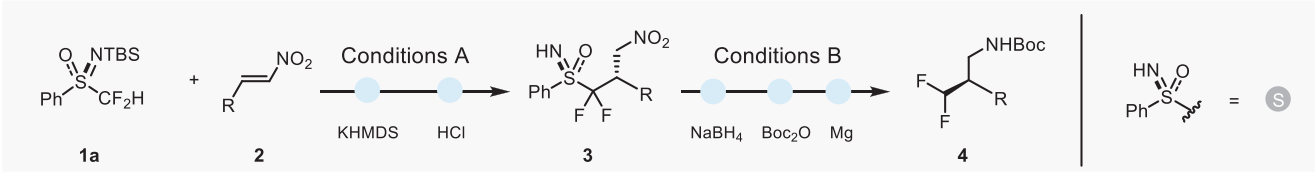
1a 1b 1c 1d 1e

[a] Base was added slowly to the mixture of **1a** and **2a** (0.2 mmol, 1.0 equiv.) in the solvent (4 mL) at −78 °C, which was stirred at −78 °C for 1 h, and worked up; then HCl (4.0 M) in dioxane at rt. [b] Yields refer to the ^{19}F NMR yield of the major diastereoisomer; dr values were determined by ^{19}F NMR; isolated yield was reported in the parenthesis. [c] The sulfoximine reagent used in the reactions was **1a,** unless otherwise specified. [d] Sulfoximine **1b** was used. [e] Sulfoximine **1c** was used. [f] Sulfoximine **1d** was used. [g] Sulfoximine **1e** was used. n.d. = not determined.

of difluoromethyl phenyl sulfoximine with the hetero-aryl sulfoximines was investigated, such as pyridyl (**1b**), pyrimidinyl (**1c**), and phenylthiazolyl (**1d**) groups (entries 10–12). The phenyl sulfoximine represents much greater advantage for both efficiency and stereoselectivity. We speculate that the high reactivity of sulfoximine **1a** may be due to the fact that the $PhSO(NTBS)CF_2^-$ anion possesses the best nucleophilicity toward C=C bonds. When the sulfoximine reagent **1e** was used, the desired product was not observed due to the strong electron-withdrawing effect of the tosyl group on the sulfoximine (entry 13). Finally, when the amounts of phenyl difluoromethyl sulfoximine and KHMDS were increased, the yield and dr could not be further improved (entry 14).

Substrate Scope of Stereoselective Difluoromethylation

Having the optimal reaction conditions in hand, we investigated the scope of the reaction between nitroalkenes **2** and sulfoximine **1a**. The results are summarized in Figure 2. A variety of structurally diverse nitroalkenes were successfully difluoromethylated by **1a**, and the products **3** were obtained in good to excellent yields (55%–94%) with excellent diastereoselectivities (93/7–98/2 dr). The reaction can tolerate many substituents such as fluoro, chloro, methoxy, methyl, isobutyl, and phenyl groups, which provide compounds **3b-3g** in 82%–94% yields with 95/5 to 97/3 dr's. These results



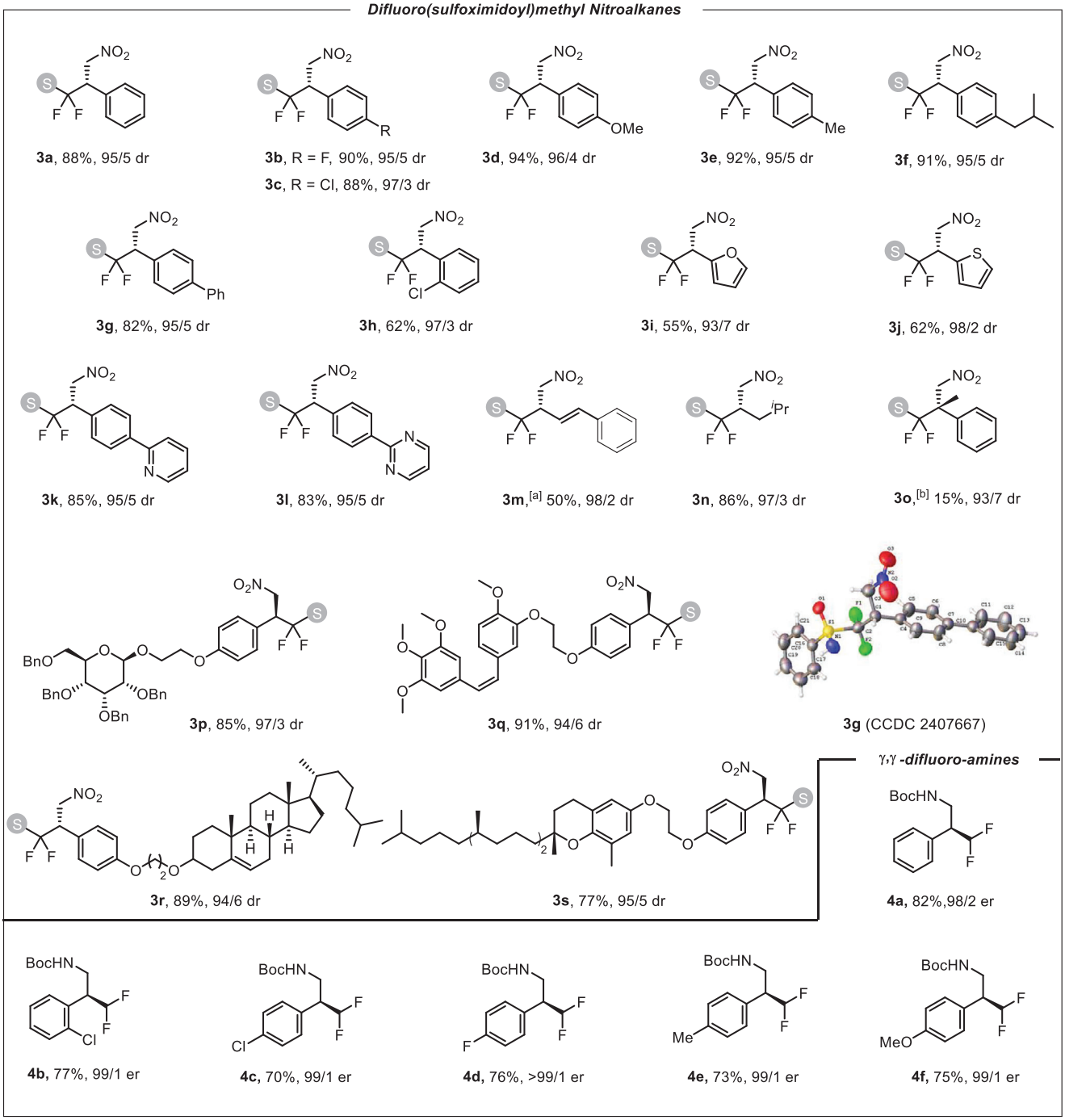


Figure 2. Substrate scope for stereoselective difluoro(sulfoximidoyl)methylation and difluoromethylation with difluoromethyl sulfoximine and nitroalkenes. Conditions A (formation of **3**): KHMDS (1.4 equiv.) was slowly added to the solution of **1a** (1.5 equiv.) and **2** (1.0 equiv.) in THF at −78 °C, and worked up; then HCl (4.0 M) in dioxane at rt. Conditions B (formation of **4**): $NiCl_2{\cdot}6H_2O$ (1.0 equiv.), $NaBH_4$ (6.0 equiv.), in MeOH (0.1 M), and worked up; then $NaHCO_3$ (3.0 equiv.), $(Boc)_2O$ (1.1 equiv.), EtOH (0.05 M) at rt, and workup; Mg (15 equiv.) and $BrCH_2CH_2Br$ (cat.) in MeOH (0.1 M) at rt. The yields refer to the isolated yield of the major diastereoisomers. The dr's were determined by ^{19}F NMR analysis of the crude product unless otherwise specifically noted. The er's were determined by chiral high-performance liquid chromatography. [a] **1a**/**2**/KHMDS = 1.0/1.5/1.4. [b] **1a**/**2**/KHMDS = 2.5/1.0/2.5. Boc = *tert*-butoxylcarbonyl.

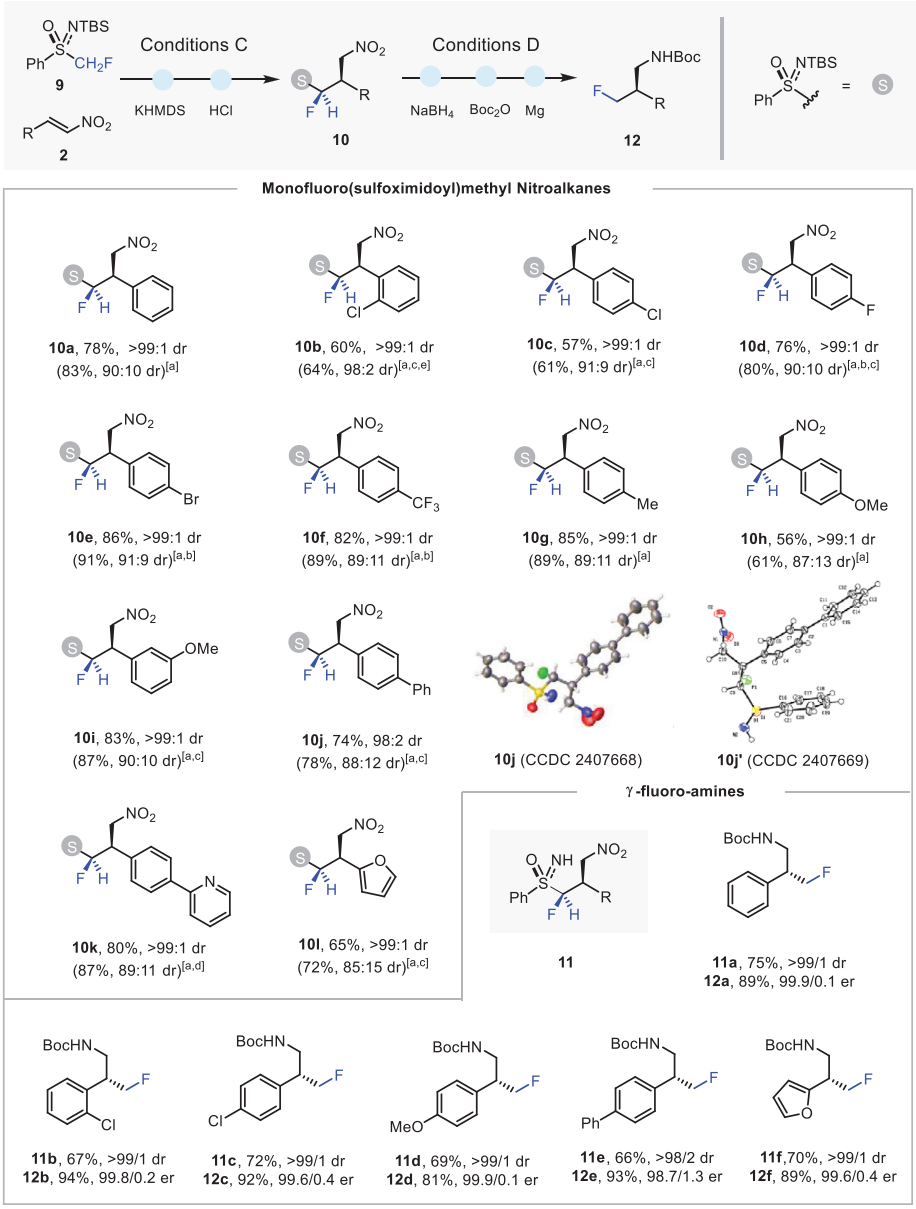
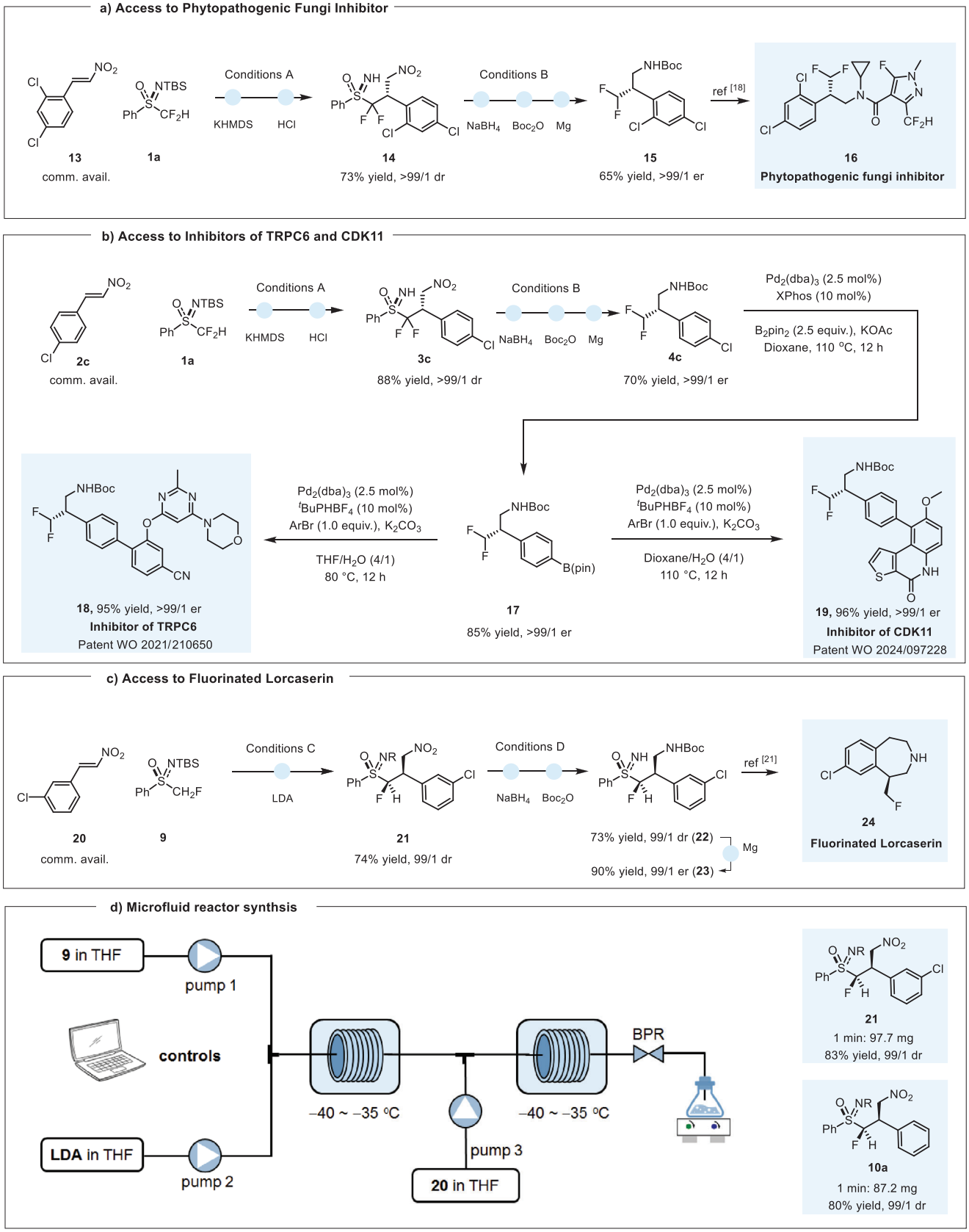


Figure 3. Substrate scope for stereoselective monofluoro(sulfoximidoyl)methylation and monofluoromethylation with monofluoromethyl sulfoximine and nitroalkenes. Conditions C (formation of **10**): PhLi (2.0 equiv.) was slowly added to the solution of **9** (1.0 equiv.) in THF at −78 °C, which was stirred at −78 °C for 10 min; **2** (2.0 equiv.) was added to the solution in one portion and stirred at −78 °C for 10 min. Conditions D: (1) $NiCl_2{\cdot}6H_2O$ (1.0 equiv.), $NaBH_4$ (6.0 equiv.), in MeOH (0.1 M), and worked up; then $NaHCO_3$ (3.0 equiv.), $(Boc)_2O$ (1.1 equiv.), EtOH (0.05 M) at rt (formation of **11**). (2) Mg (15 equiv.) and $BrCH_2CH_2Br$ (cat.) in MeOH (0.1 M) (formation of **12**). [a] The yields in the parentheses were determined by ^{19}F NMR of the crude product with $PhOCF_3$ as an internal standard. The dr's in the parentheses were determined by ^{19}F NMR analysis of the crude product. [b] LDA was used instead of PhLi. [c] The reaction concentration was changed to 0.05 M. [d] The concentration was changed to 0.025 M. [e] The reaction was stirred for 3 hours, which was treated by 4.0 M HCl.

indicate that this reaction can be well compatible with electron-withdrawing and electron-donating substituents with high yields and high diastereoselectivities. An *ortho*-chloro-substituted nitroalkene can react with reagent **1a** smoothly, affording the product **3h** in 62% yield with 97/3 dr, which indicates that the reaction is not sensitive to the steric embracement.

Pharmaceutically important heteroaromatic groups, such as furyl, thienyl, pyridyl, and pyrimidyl, were well tolerated, which furnished products **3i-3l** in 55%–85% yields with 93/7 to 98/2 dr's.[47–49] The alkyl-substituted (*E*)-4-methyl-1-nitropent-1-ene was evaluated, and **3m** could be obtained in 86% yield with 96:4 dr. The conjugated ((1*E*,3*E*)-4-nitrobuta-1,3-dien-1-yl)benzene was evaluated, and **3n** was obtained in 66% yield with 98:2 dr. However, when a trisubstituted nitro alkene of (*E*)-(1-nitroprop-1-en-2-yl)benzene was evaluated, only 15% yield of major isomer **3o** was generated with 93:7 dr. It can be interpreted that the steric hindrance increases significantly due to the introduction of a methyl substituent on the alkene. It was also worthy to note that



this stereoselective reaction could be further utilized in the late-stage modification of complex molecules efficiently.[50,51] For instance, the difluoromethyl group can be efficiently introduced to Ebastine (**3p**), combretastatin (**3q**), cholesterol (**3r**), and (+)-δ-tocopherol derivatives (**3s**) in 77%–91% yields with 94/6 to 97/3 dr's. However, it should be noted that when the chalcone was used as the substrate, we only observed the carbonyl addition product, which indicated that the new reaction system needs to be developed for the conjugated carbonyl compounds. The absolute configurations of **3h** were confirmed by X-ray crystal structure analysis,[52] and the newly formed carbon stereocenter in **3h** was found to be in the *S* configuration. Those of the other products, **3a-g** and **3i-p**, were assigned by analogy.

The products **3** could be readily converted into enantiomerically enriched 2-difluoromethyl amines **4** after simple reduction in one pot. The results are summarized in Figure 2 (bottom). First, the enantiomerically enriched **4a** was achieved in 82% yield with 98/2 er. When the *ortho*-chloride and para-chloride substituents on the aromatic ring were investigated, compounds **4b** and **4c** were furnished in 77% yield with 99/1 er, and 70% yield with 99/1 er, respectively. Then we tried the electron-withdrawing and electron-donating substituents on the aromatic rings, compounds **4d** and **4f** were provided in 76% yield with >99/1 er and 75% yield with 99/1 er. And the para-alkyl substituted substrate can proceed smoothly, generating **4e** in 73% yield with 99/1 er. Thus, based on the abovementioned, this desulfoximination strategy was proved to be efficient to generate desired products, and the high optical purities of **4a-f** (98/2 to >99/1 er as determined by chiral HPLC) indicate that the procedures are reliable for the preparation of enantiomerically enriched γ,γ-difluoro-amines.

Stereoselective Nucleophilic Monofluoromethylation

To further demonstrate the advantages of the methodology between fluorinated sulfoximine reagent and nitroalkenes on the construction of chiral fluorinated propylamine and considering the significance and importance of γ-monofluoroamines in the field of biological and pharmaceutical science,[53,54] we turned to investigate whether it could be expanded to the monofluoromethyl sulfoximine **9**. After careful screening of the reaction conditions (Tables S4–S7), we found that monofluoromethyl sulfoximine **9** could react with nitroalkene **2** under the base of phenyl lithium, which can provide the monofluoromethylation product **10a** in 83% yield with 90/10 dr (determined by the crude NMR). Compared with the difluoromethyl products, there exists one more carbon stereogenic centre which directly connected to fluorine. Thus, we isolated two diastereomers of **10j** and **10j'**, the absolute configurations of which have been confirmed by X-ray single crystal structure analysis.[52] And the formed stereocenters in the structure of the major isomer were found to be in (R_S, *S*, *R*) configurations. In contrast, the stereocenters in the structure of the minor isomer were found to be in (R_S, *S*, *S*) configurations. It indicated that the diastereoselective differentiation could be attributed to the aryl substituted carbon stereocenter.

As follows, we investigated the substrate scope of the reaction between the nitroalkenes and monofluoromethyl sulfoximine. The results are shown in Figure 3. A variety of structurally diverse nitroalkenes were found to be well tolerated, providing the products **10** in 56%–86% isolated yields with 98/2 to > 99/1 dr's. The positions of the substituent on the aromatic rings were investigated. The *ortho*- and para-chloro-substituted substrates could be converted into the monofluoromethyl nitroalkanes **10b** and **10c** in 60% yield with >99/1 dr and 57% yield with >99/1 dr, respectively. When the electron-withdrawing substituents on the nitroalkenes, such as fluoro, bromo, trifluoromethyl, **10d-f** were generated in 76%–86% yields with >99/1 dr's. And the electron-donating substituents on the nitroalkenes were compatible, which furnished products **10g-i** in 56%–85% yields with >99/1 dr's. When the hetero-aromatic rings such as pyridyl and furyl groups were investigated, **10k** and **10l** were furnished in 80% yield with >99/1 dr and 65% yield with >99/1 dr.

The products **10** could be reduced to enantiomerically enriched monofluoromethyl amines **12** via **11** after simple reduction. Phenyl substituted **10a** can be reduced into **11a** in 75% yield with >99/1 dr. The compounds with *ortho*- and para-chloro substituents gave **11b-c** in 67%–75% yields with >99/1 dr's. **11d** with methoxy phenyl group and **11e** with diphenyl group could be generated in 69% yield with >99/1 dr and 66% yield with >98/2 dr, respectively. The corresponding furyl substituted product could be obtained in 70% yield with >99/1 dr. All compounds (**11a-f**) were converted into the desired desulfoximidoyl amines **12** in 81%–94% yields with ≥99/1 er.

Synthetic Applications

We found that the developed methodology could be successfully applied to the synthesis of bioactive molecules. At the beginning, the commercially available 2,4-dichloro-1-(2-nitrovinyl)benzene could react with difluoromethyl

Figure 4. Synthetic applications of γ,γ-difluoroamines and γ-monofluoroamines. a) Synthetic approaches to enantioenriched phytopathogenic fungi inhibitors. b) Synthetic approaches to enantioenriched the inhibitors of TRPC6 and CDK11. c) Synthetic approaches to enantioenriched fluorinated lorcaserin. d) Microfluid reactor synthesis. Conditions A (formation of **3**): KHMDS (1.4 equiv.) was slowly added to the solution of **1a** (1.5 equiv.) and **2** (1.0 equiv.) in THF at −78 °C, and worked up; then HCl (4.0 M) in dioxane at rt. Conditions B (formation of **4**): $NiCl_2{\cdot}6H_2O$ (1.0 equiv.), $NaBH_4$ (6.0 equiv.), in MeOH (0.1 M), and worked up; then $NaHCO_3$ (3.0 equiv.), $(Boc)_2O$ (1.1 equiv.), EtOH (0.05 M) at rt, and worked up; (2) Mg (15 equiv.) and $BrCH_2CH_2Br$ (cat.) in MeOH (0.1 M) at rt. Conditions C (formation of **10**): PhLi (2.0 equiv.) was slowly added to the solution of **9** (1.0 equiv.) in THF at −78 °C, which was stirred at −78 °C for 10 min; **2** (2.0 equiv.) was added to the solution in one portion, and stirred at −78 °C for 10 min. Conditions D: (1) $NiCl_2{\cdot}6H_2O$ (1.0 equiv.), $NaBH_4$ (6.0 equiv.), in MeOH (0.1 M), and workup; then $NaHCO_3$ (3.0 equiv.), $(Boc)_2O$ (1.1 equiv.), EtOH (0.05 M) at rt (formation of **11**). (2) Mg (15 equiv.) and $BrCH_2CH_2Br$ (cat.) in MeOH (0.1 M) (formation of **12**). R = TBS. TBS = *tert*-butyl dimethylsilyl; Boc = *tert*-butoxycarbonyl; B(pin) = boronic pinacol ester.

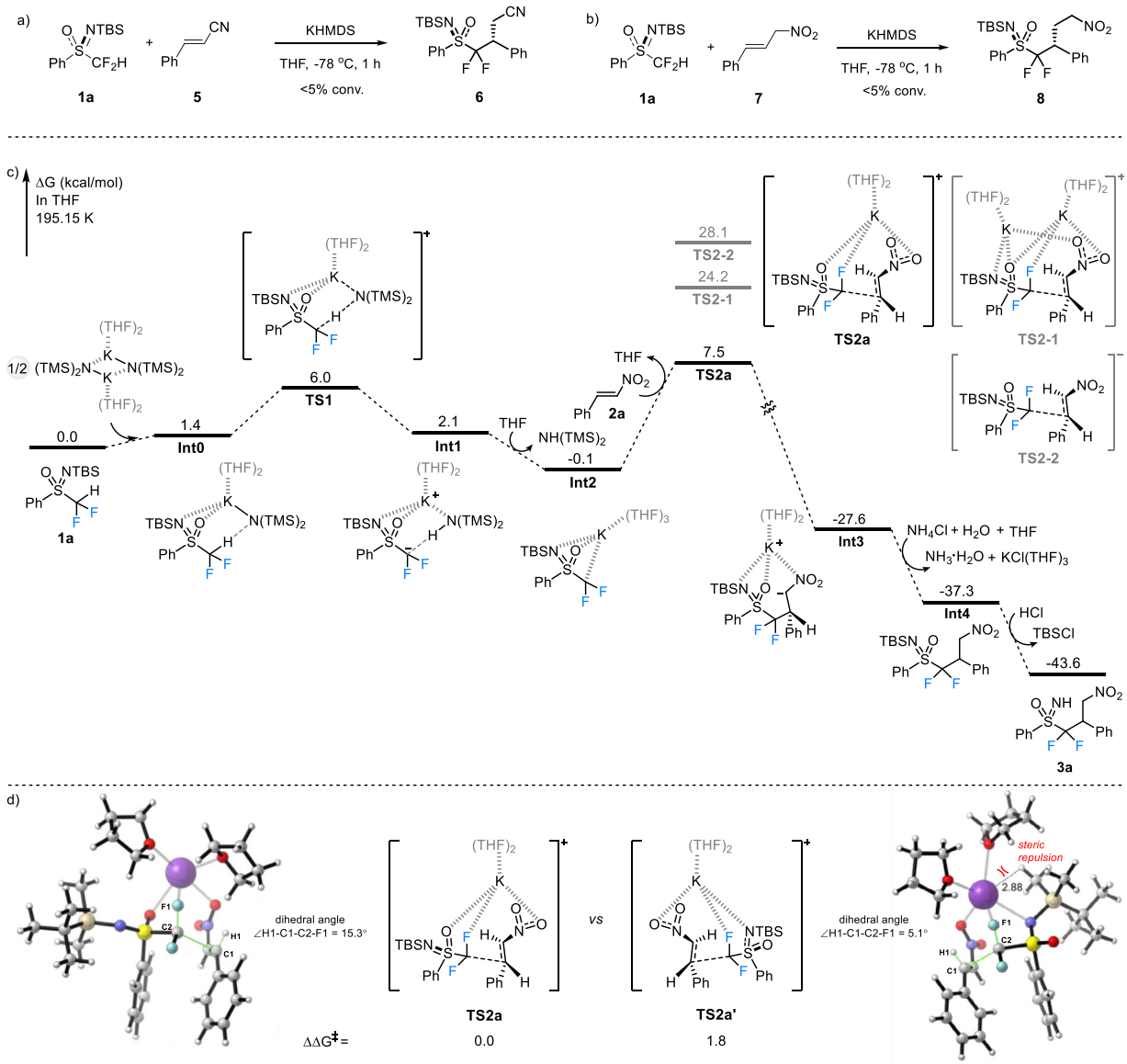


Figure 5. a) The reaction between sulfoximine **1a** and cinnamonitrile. b) The reaction between sulfoximine **1a** and (*E*)-(3-nitroprop-1-en-1-yl)benzene. c) Calculated potential energy profile for the nucleophilic difluoromethylation of difluoromethyl phenyl sulfoximine to alkene at the ωB97X-D/6–311++G(2df,2p)-SMD//ωB97X-D/6–31g(d,p)-SMD level of theory. d) Optimized diastereomeric TS geometries.

sulfoximine to furnish chiral difluoromethyl nitroalkane, which could be transformed to the γ,γ-difluorinated propylamine efficiently by the simple process of the reductions. And the phytopathogenic fungi inhibitor **16** can be achieved in few steps accordingly [53,54] (see Figure 4a). Second, the stereoselective nucleophilic difluoromethylation was performed to provide the product **3c**, which could be transferred into **4c** in 70% yield with >99/1 er. The aryl B(pin) compound **17** was generated in 85% yield with >99/1 er by C─Cl bond boronation, which further reacted with two kinds of aryl bromide to provide the TRPC6 inhibitor [55] **18** and the CDK11 inhibitor [56] **19** in enantiomeric specific behavior, respectively (see Figure 4b). Additionally, when the procedure was applied to 3-chloro-2-nitrovinyl benzene with monofluoromethyl phenyl sulfoximine under the base of phenyl lithium, the addition product was isolated in 74% yield with 99/1 dr. The corresponding γ-fluorinated propylamine was furnished smoothly, which also could be further transformed into the fluorinated lorcaserin **24**, a selective 5-HT_{2C} receptor agonist [57,58] (see Figure 4c). And the stereoselective nucleophilic fluoromethylation reactions were performed in a modular microreaction system, which was recognized as a seamless transition to continuous flow processes for practical-scale production. The products **21** and **10a** could be obtained in 83% yield with 99/1 dr and 80% yield with 99/1 dr (see Figure 4a,d).

Mechanism Experiments and DFT Calculations

In order to illustrate the mechanism of the reaction, we took the reaction between the difluoromethyl sulfoximine

reagent and nitroalkene as the example. First, we conducted the compared experiments between sulfoximine **1a** and the different types of alkenes, consisting of cinnamonitrile **5**, where the nitro group in the substrate was replaced by the cyanide group, and (*E*)-(3-nitroprop-1-en-1-yl)benzene **7**, where the nitro group is located on the allyl position of styrene (see Figure 5a,b). The addition products **6** and **8** could not be detected for both cases, which indicated that both the presence and position of the nitro group played a crucial role in this type of reaction. Subsequently, to shed some light on the mechanism and the stereoselective controlling of the nucleophilic difluoromethylation of alkene, the DFT calculations were performed. Computations of possible KHMDS complexes suggest that the KHMDS-$(THF)_2$ dimer is a stable complex that could work as a base (see Figure S1 for other higher energy KHMDS complexes). As shown in Figure 5c, the dissociation of the KHMDS $(THF)_2$ dimer assisted by **1a** to form **Int0** is endergonic by 1.4 kcal mol^{-1}. The deprotonation of **1a** via **TS1**, generates K coordinated α-fluorocarbanion **Int2** with a barrier of 6.0 kcal mol^{-1}. The following nucleophilic attack of α-fluorocarbanion to C=C double bond of nitroolefin **2a** via **TS2a**, in which a K^+ simultaneously interacts with both difluoromethyl sulfoximine and nitro moieties via the K—O and K—F bonds, leads to **Int3** with a barrier of only 7.5 kcal mol^{-1}. Nevertheless, the presence of additional K^+ (**TS2-1**: 24.2 kcal mol^{-1}) and absence of K^+ (**TS2-2**: 28.1 kcal mol^{-1}) increase the nucleophilic addition barriers. In addition, the calculations indicate that the nucleophilic difluoromethylation of cinnamonitrile **5** (**TS2b**: 13.6 kcal mol^{-1}) and (*E*)-(3-nitroprop-1-en-1-yl)benzene **7** (**TS2c**: 19.1 kcal mol^{-1}) present higher barriers (see Supporting Information for details). Then, the resulting intermediate **Int3** undergoes quenching and deprotection to give product **3a**. The overall process is calculated to be exergonic by 43.6 kcal mol^{-1}, with a very low barrier of 7.6 kcal mol^{-1} (from **Int2** to **TS2a**). Importantly, it is seen that the nucleophilic addition is the stereocontrolling step. The lowest energy TSs leading to the major and minor diastereomers are shown in Figure 5d. The Gibbs free energy of **TS2a** (leading to product *R*-**3a**) is 1.8 kcal mol^{-1} lower than that of **TS2a'** (leading to product *S*-**3a**), which is consistent with the experimental observation. The preferential **TS2a** over **TS2a'** presumably results from steric repulsion between the *t*-butyldimethylsilyl (TBS) group located on the imine of **1** and the K^+ in **TS2a'** due to the coordination of K—N. Such repulsions can be avoided in **TS2a** due to the K—O (from the sulfoximine) coordination. Indeed, the dihedral angle between C1—H1 bond of **2a** and C2—F1 bond of **1a** is 5.1° in **TS2a'** and 15.3° in **TS2a**, which suggests that the repulsions between C1—H1 bond and C2—F1 bond in **TS2a'** are stronger than that in **TS2a**.

Conclusion

In summary, an efficient and easy-to-handle protocol for the highly stereoselective nucleophilic di- and monofluoromethylation of C=C bonds with a broad substrate scope was developed. To the best of our knowledge, it is the first report on the synthesis of optically pure 2-difluoromethyl amines via a direct nucleophilic fluoroalkylation strategy. The late-stage modifications and several synthetic applications of the bioactive complex molecules demonstrated the significance and potential of this approach. The mechanism experiments and DFT calculations suggested the stereoselectivity could be facilitated by the intriguing remote neighboring participations of the nitro group. Not only does our research present a new useful synthetic tool for practicing chemists and medicinal chemists, but it also provides important insights into the reactivities and stereocontrol mode of fluorinated sulfoximine. However, when the chalcone was used as the substrate, only the carbonyl addition products were observed, which indicated that a different reaction system needs to be developed for the conjugated carbonyl compounds in the future. Further exploration on fluorinated sulfoximine chemistry is currently underway in our laboratory.

Acknowledgements

The authors thank Profs. Aijun Lin and Hequan Yao (China Pharmaceutical University) for sharing the basic instruments. They are grateful for the financial support from the National Natural Science Fund for Excellent Young Scholars (Overseas), the Foundation of State Key Laboratory of Natural Medicines (grant no. SKLNMZZ2024JS15), the National Natural Science Foundation of China (Nos. 22122104, 22193012, 21933004, and 22261132514), the CAS Project for Young Scientists in Basic Research (grant no. YSBR-095), and the Strategic Priority Research Program of the Chinese Academy of Sciences (grant no. XDB0590000).

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Diastereoselectivity · Difluoromethylation · Monofluoromethylation · Nucleophilic fluoroalkylation · Sulfoximines

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Manuscript received: May 24, 2025
Revised manuscript received: July 14, 2025
Accepted manuscript online: July 14, 2025
Version of record online: August 17, 2025