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Dynamic Kinetic Resolution-Enabled Highly Stereoselective Nucleophilic Fluoroalkylation to Access Chiral β-Fluoro Amines

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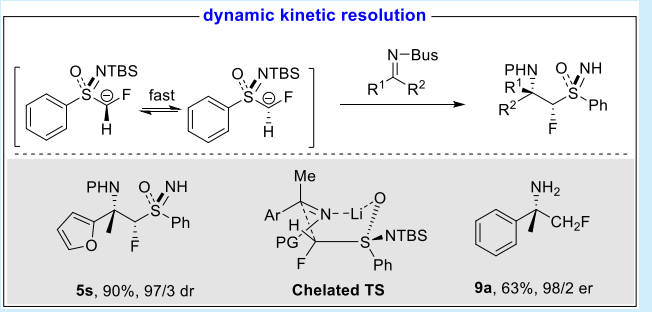
ABSTRACT: β-Fluorinated amine is highly desirable for biological and pharmaceutical science, because replacing a C−H bond with a C−F bond can change the physical and chemical properties of the parent molecule to a large extent but not significantly alter its overall geometry. Herein, the highly stereoselective nucleophilic monofluoromethylation of imines have been developed. It is proposed that the chelated transition state enables the chiral induction by the dynamic kinetic resolution of the chiral α-fluoro carbanions.



Amines are privileged structures present in a myriad of biologically active molecules.[1−4] However, amino groups typically result in a poor ability to penetrate the cell membrane due to their strong basicity, thus leading to an obvious decrease in the biological activity of drug molecules.[5] Due to the peak electronegativity of fluorine atoms, replacing a C−H bond with a C−F bond can strongly affect the basicity of nearby amino groups.[5,6] For example, the pK_a value of the protonated 5-HT_{1D} agonist is 9.7, while that of its β-fluorinated analogue is 8.7 (Figure 1a).[5,6] The change in the pK_a value of the drug molecule has an important impact on the kinetic metabolic properties and the affinity, which improves the cell membrane permeability, thereby improving its biological activity.[7,8] In addition, fluorine has a considerable effect on the electron distribution of the molecule, while not significantly altering or distorting the general geometry of molecules because of the similar size of hydrogen and fluorine.[9] Thus, ready access to β-fluoro amine is highly desirable and significant for the life sciences and pharmaceutical industry.

A number of methods for accessing β-fluoro amines have been developed, including fluoroamination of alkenes,[10−14] nucleophilic fluorination of alcohols,[15,16] and ring opening with metal fluorides.[17−20] However, these methods cannot be applied for chiral β-fluoro amines, given the fact that the potential dangers of racemic drugs have been documented (Figure 1b).[21−28] In 2007, Shibata and Toru developed an elegant catalytic enantioselective fluoromethylation with in situ-generated aldimines and FBSM, to yield chiral β-fluoro amines.[29] However, the reaction time was up to 2 days at −80 °C, and enaminalizable ketimines were not compatible (Figure 1c-i). Hu and co-workers synthesized β-fluoro amines via diastereoselective fluoromethylation of chiral *N*-*tert*-butylsulfinyl ketimines, but with a racemic carbon center at the β-position (due to the difficult differentiation of H/F atoms), and the yield is moderate (Figure 1c-ii).[30,31] In addition, an enzyme-catalyzed kinetic resolution was also reported, but the drawback is the limitation of the 50% maximal yield (Figure 1c-iii).[32,33] Our group was recently devoted to the development of nucleophilic fluoroalkylations by employing sulfoximine as the stereocontrol reagent.[34−38] Herein, a new method for asymmetric synthesis of β-fluoro amines with a sulfoximine reagent is reported (Figure 1c-iv). Our concept relies on the dynamic kinetic resolution of α-fluoro carbanions, which delivers chiral amines with a fluorinated carbon stereogenic center at the β-position. It is worth noting that there has been no report about the reaction of imines with fluorinated sulfoximine. Previously, the reaction of ketones strictly depends on the nonchelated transition state due to the poor chelation ability of oxygen.[36,37] However, is it possible that the strong chelation ability of nitrogen from imines can undermine the dynamic kinetic resolution process? Can we realize the dynamic kinetic resolution in a different mode? Herein, we report the first dynamic kinetic resolution-enabled highly stereoselective fluoroalkylation of imines.

To achieve high stereoselectivity, we first investigated the protecting groups of imines with (*R*)-phenyl monofluoromethyl sulfoximine **1**, considering the relatively easy availability of optically pure phenyl monofluoromethyl sulfoximine (Table S1). When a phenylthio group-protected imine was used, the

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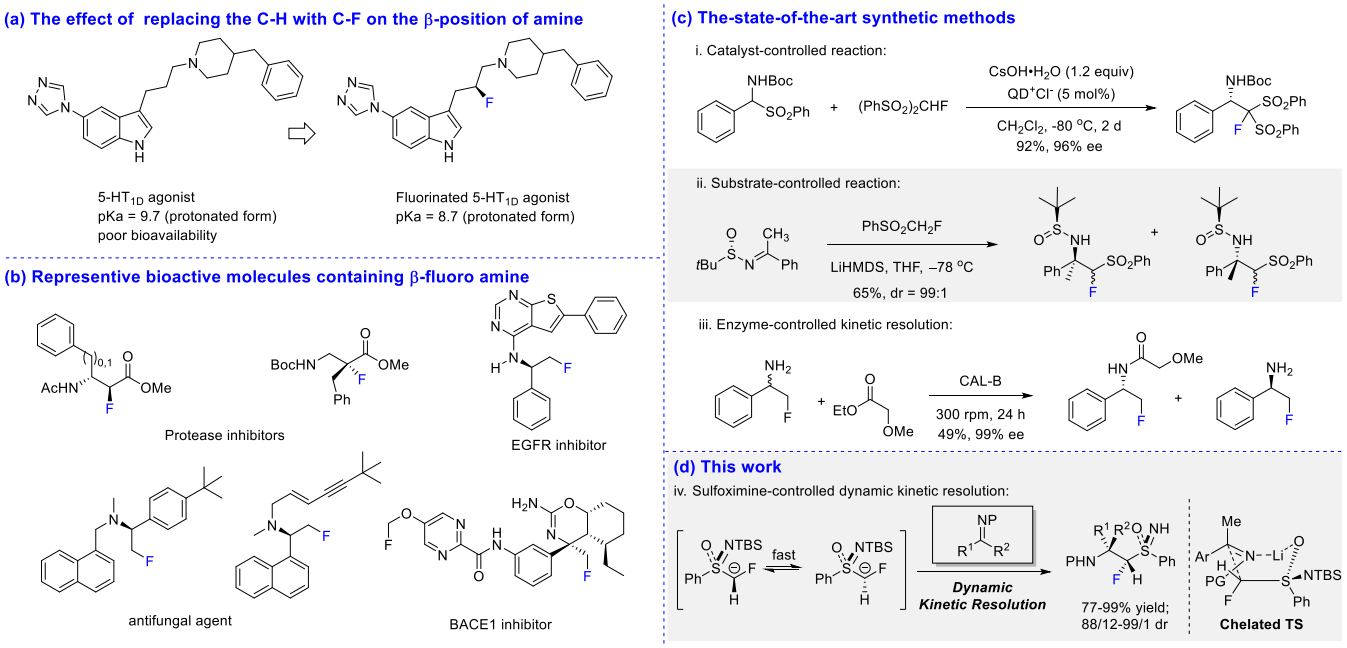


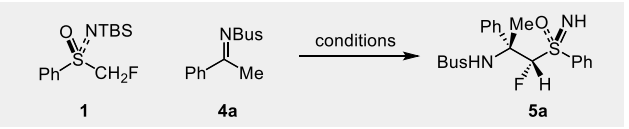
Figure 1. Examples of biologically active β-fluoro amines and state-of-the-art methods for accessing chiral β-fluoro amines. Abbreviations: EGFR, bovine plasma amine oxidase; BACE1, β-site APP-cleaving enzyme 1.

reaction gave 56/44 dr (Table S1, entry 1). When we increased the steric hindrance of the protecting group (using a *tert*-butyloxycarbonyl group), the reaction could give 75/25 dr (Table S1, entry 2). To our delight, using a *tert*-butylsulfonyl group (Bus)-protected imine can give 93/7 dr,[39] but the use of an arylsulfonyl group resulted in a decrease in the dr values (Table S1, entries 3–6).

We subsequently screened a model reaction between Bus-protected enaminalizable ketimine **4a** and sulfoximine reagent **1** for the asymmetric synthesis of β-fluoro tertiary amines (Table 1). It was found that when LiHMDS, NaHMDS, or KHMDS was used as the base, the reaction proceeded with difficulty (Table 1, entries 1–3). When the base was changed to LDA, both the yield and dr increased dramatically [42% yield, dr 98/2 (Table 1, entry 4)].[40] However, when *n*BuLi was used, a yield of 32% was afforded and two diastereoisomers were observed (dr 87/13). After the solvents had been screened, CH_2Cl_2 was found to be the optimal solvent (Table 1, entries 6–9). However, when HMPA was added, the yield and diastereoselectivity were significantly reduced (entry 10). Further optimization showed that when the **1**/**4a**/LDA ratio was changed to 2.5/1/2.5, we can obtain **5a** in 90% yield with 98/2 dr (Table 1, entry 13).

Then we examined the substrate scope of the reaction (Figure 2). Reactions with various aryl methyl ketimines can give **5a–l** in high yields (77–90%) with high diastereoselectivities (dr 95/5–98/2). Many substituents such as fluoro, chloro, bromo, iodo, methyl, isopropyl, and trifluoromethyl groups could be tolerated under the reaction conditions. The reaction was not sensitive to the position of substituents, and **5g–i** can be obtained in high yields with high diastereoselectivities. The reaction with a biphenyl-substituted ketimine can afford product **5m** in 74% yield with 96/4 dr. Disubstituted substrates such as electron-poor **4n** and electron-rich **4o** gave the corresponding products in 70% yield with 96/4 dr and 85% yield with 96/4 dr, respectively. **5p** was afforded in 82% yield with 98/2 dr when a naphthyl-substituted ketimine was used. In addition, the reactions with ketimines **4q** and **4r** afforded the corresponding products **5q** in 87% yield with 95/5 dr and **5r** in 88% yield with 96/4 dr. Moreover, a heteroaryl ketimine could also be applied to the reaction, generating **5s** in 90% yield with 97/3 dr. The reaction with an alkyl-substituted methyl ketimine proceeded smoothly, giving **5t** in 86% yield with 88/12 dr. Secondary amines could be obtained by employing aldimines, such as **5u–w**. The absolute configuration of **5e** was confirmed by X-ray crystal

Table 1. Survey of the Reaction Conditions[a]



entry	**1**/**4a**/base	base	solvent	yield (%)[b]	dr[b]
1	1.0/1.2/1.5	LiHMDS	CH_2Cl_2	NR	ND
2	1.0/1.2/1.5	NaHMDS	CH_2Cl_2	7	ND
3	1.0/1.2/1.5	KHMDS	CH_2Cl_2	<5	ND
4	1.0/1.2/1.5	LDA	CH_2Cl_2	42	98/2
5	1.0/1.2/1.5	*n*BuLi	CH_2Cl_2	32	87/13
6	1.0/1.2/1.5	LDA	Et_2O	41	95/5
7	1.0/1.2/1.5	LDA	THF	35	94/6
8	1.0/1.2/1.5	LDA	DME	<5	ND
9	1.0/1.2/1.5	LDA	toluene	44	96/4
10[c]	1.0/1.2/1.5	LDA	CH_2Cl_2/hmpa	9	50/50
11	1.0/2.0/2.5	LDA	CH_2Cl_2	62	98/2
12	2.0/1.0/2.5	LDA	CH_2Cl_2	90	97/3
13[d]	2.5/1.0/2.5	LDA	CH_2Cl_2	90	98/2

[a]A base was added slowly to the solution of (*R*)-**1** in the solvent at −78 °C; 30 min later, a solution of **4a** in a solvent was added, and the mixture was stirred for an additional 3 h, followed by quenching with a saturated NH_4CI solution. [b]The yield and dr were determined by ^{19}F NMR. NR, no desired reaction; ND, not determined; Bus, *tert*-butanesulfonyl. [c]At 10/1 (v/v). [d]At −94°C.

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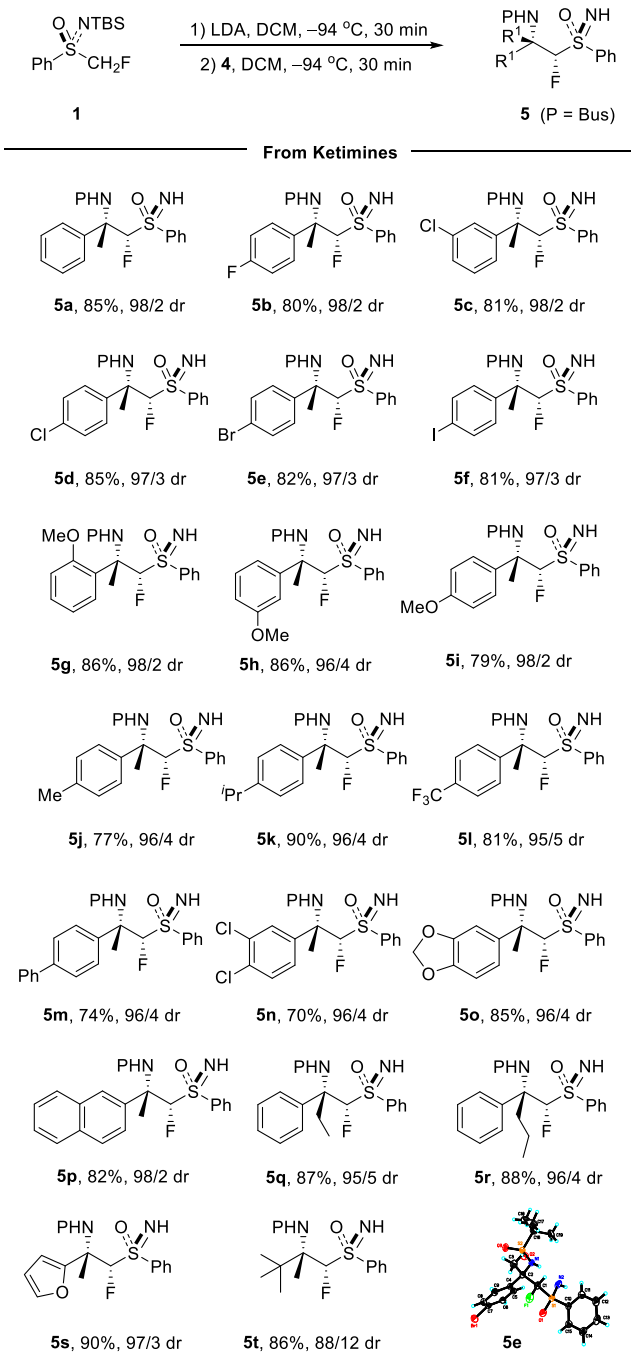

Figure 2. Substrate scope of the highly stereoselective fluoroalkylation reaction. [a]Yields refer to the isolated yield of the major diastereoisomer; dr values were determined by ^{19}F NMR. P = Bus = *tert*-butanesulfonyl. [b]KHMDS and THF were used. The absolute configuration of **5e** was determined by single-crystal X-ray structure analysis, and those of the others were assigned by analogy.

structure analysis, and those of the other products were assigned by analogy.

To gain insights into the reaction mechanism especially in terms of the high stereoselectivity in the generation of the fluorinated carbon stereogenic center, we carried out several mechanistic experiments. First, a reaction of D_2O and the (R_S)-PhSO(NTBS)CHF$^-$ anion was tested (Figure 3a). After

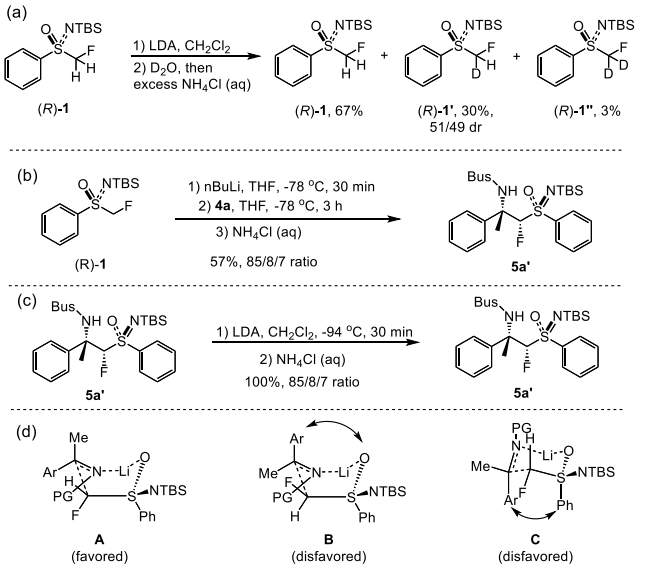

Figure 3. Mechanistic studies and proposed transition states. Bus = *tert*-butylsulfonyl. Repulsive interactions are indicated by a curved arrow.

quenching with excess aqueous ammonium chloride, 30% conversion of (*R*)-**1′** was observed on the basis of ^{19}F NMR. Due to the signal overlap of the diastereomers in ^{19}F spectra, we conducted ^1H NMR analysis and found that the diastereomeric ratio was 51/49, which indicated that carbanioins in both *R* and *S* configurations at the fluorocarbon center were formed without selectivity (part 5 of the Supporting Information). Second, we tried to examine whether the nucleophilic reaction is reversible. Upon treatment of (*R*)-**1** with *n*BuLi and **4a**, compound **5a′** was achieved with three diastereomers (Figure 3b, 85/8/7 dr). Subsequently, compound **5a′** was recovered fully without any changes in dr after being treated with LDA at −94 °C for 0.5 h (Figure 3c), which implied that this reaction was not reversible. We therefore proposed the high stereoselectivity at the fluorinated stereocenter was caused by the dynamic kinetic resolution of the participating carbanions (Figure 1d). It is obvious that the facial selectivity of the addition can be attributed to the chiral induction from the sulfur stereogenic center to the fluorine-bearing carbon stereogenic center.

By comparing different chair- or boat-like chelating transition states **A**−**C**, we rationalized the stereocontrol mode of the reaction (Figure 4d). First, because of the flagpole interaction of oxygen and the Ar group, boat-like transition state **B** is disfavored.[41a] Second, due to the 1,3-diaxial interaction of Ar and the phenyl group, chair-like chelating transition state **C** is energetically unfavorable,[41b] although it leads to the experimentally observed major diastereomer **5a** (Figure 4d, C). Our proposed transition state **A** can be supported by the result that the addition of HMPA, which prevents the chelation of the sulfoximine oxygen atom with the metal (for example, lithium cation), can significantly reduce the yield and diastereoselectivity. It is

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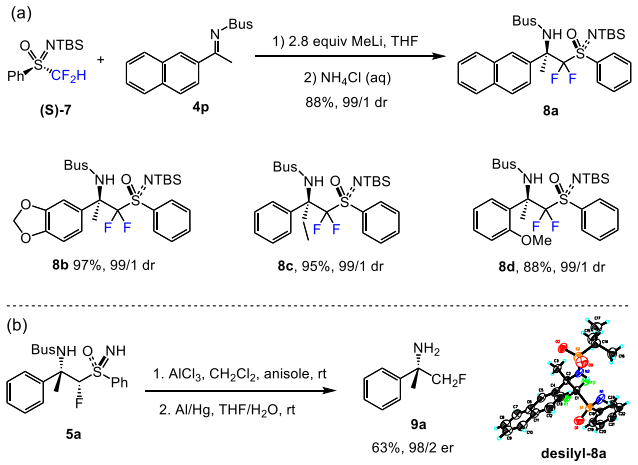

Figure 4. Extension of the reaction and product.

parallel to what is proposed by Pyne regarding the reactions of ketones and sulfoximine[42] (Table 1, entry 10).

On this basis, the highly nucleophilic monofluoroalkylation can also be extended to the difluoroalkylation of imines with high dr. The results are shown in Figure 4a. It was found that 1-(naphthalen-2-yl)ethyl imine **4p** reacted with the (*S*)-phenyl difluoromethyl sulfoximine reagent to afford addition product **8a** in 88% yield with 99/1 dr. The reaction tolerated 1-(benzo[*d*][1,3]dioxol-5-yl)ethyl, 1-phenylpropyl, and 1-(2-methoxyphenyl)ethyl imines, to generate **8b**–**d**, respectively, in high yields and diastereoselectivities, and the configuration of **8a** was confirmed by X-ray crystal analysis. To obtain the monofluoromethylated free amine, **5a** could undergo deprotection of the Bus group with $AlCl_3$ and reductive C–S bond cleavage with aluminum amalgam[43] to yield free amine **9a** in 63% yield and 98/2 er (Figure 4b). Free amines can allow different modifications and provide the possibility of accessing chiral amine derivatives, especially those bioactive molecules.[21−28]

In conclusion, we report the first dynamic kinetic resolution-enabled stereoselective fluoroalkylation of imines with a fluoromethyl sulfoximine reagent **1**. The highly stereoselective nucleophilic fluoroalkylation of imines with a broad substrate scope was developed. Mechanistic studies showed that the chiral induction from the sulfur stereogenic center of the sulfoximine to the fluorine-bearing carbon stereogenic center was enabled by a dynamic kinetic resolution of the α-fluorinated carbanion. The reaction can also be extended to the difluoroalkylation reaction, which further expands the scope of this protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02250.

Detailed experimental procedures and spectra data for all new compounds (PDF)

Accession Codes

CCDC 2166836–2166837 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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