Synthetic Methods

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Stereoselective Carbonyl Olefination with Fluorosulfoximines: Facile Access to *Z* or *E* Terminal Monofluoroalkenes

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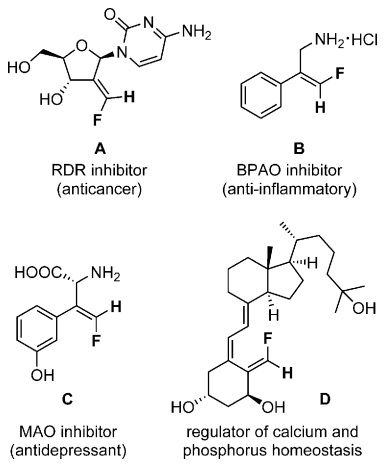
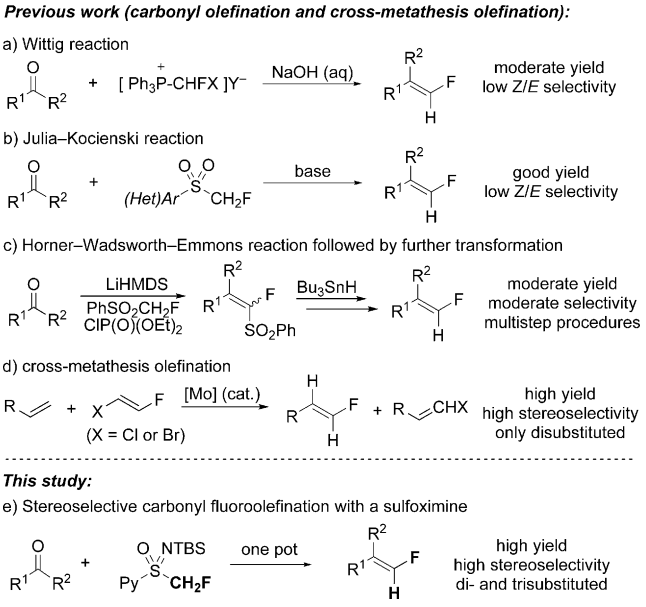
Abstract: *Terminal monofluoroalkenes are important structural motifs in the design of bioactive compounds, such as homeostasis regulators and mechanism-based enzyme inhibitors. However, it is difficult to control the stereoselectivity of known carbonyl olefination reactions, and olefin metathesis is limited to disubstituted terminal monofluoroalkenes. Although sulfoximines have been used extensively in organic synthesis, reports on their use in carbonyl olefination reactions have not appeared to date. Herein, we report highly stereoselective carbonyl monofluoroolefination with a fluorosulfoximine reagent. The potential of this method is demonstrated by the synthesis of MDL 72161 and by the late-stage monofluoromethylenation of complex molecules, such as haloperidol and steroid derivatives.*

Terminal monofluoroalkenes are of vital importance because they are not only widely used in the synthesis of fluorine-containing compounds,[1,2] but also have great relevance to material science[3] as well as the design of mechanism-based enzyme inhibitors (Scheme 1, **A**–**C**)[4] and homeostasis regulators (Scheme 1, **D**)[5] owing to the ability of fluorine to modulate bioactivity.[6] Moreover, the *E* and *Z* stereoisomers of monofluoroalkenes often possess significantly different bioactivities; one notable example is the BPAO inhibitor **B**, which is 10-fold more effective than its *E* isomer on the basis of IC_{50} values.[4d] However, their stereoselective synthesis remains a formidable challenge owing to the minimal energy difference between the two stereoisomeric forms. Therefore, the development of new methods for the facile and stereoselective synthesis of terminal monofluoroalkenes is highly desirable.



Scheme 1. Examples of bioactive terminal monofluoroalkenes. MAO = monoamine oxidase, RDR = ribonucleotide diphosphate reductase.

In the past decades, many methods for preparing terminal monofluoroalkenes have been developed,[7,8] including Wittig reactions (Scheme 2a),[8a–c] Julia–Kocienski reactions (Scheme 2b),[8d,e] a Horner–Wadsworth–Emmons (HWE) reaction followed by further transformation (Scheme 2c),[4c] the selective reduction of difluoroalkenes,[9] the electrophilic monofluorination of alkenes,[10] transition-metal-assisted fluorination,[11] and the alkylation of α-fluorinated sulfur compounds, followed by elimination.[12] Very recently, Hoveyda and coworkers reported olefin metathesis reactions for the highly stereoselective synthesis of terminal monofluoroolefins (Scheme 2d).[13] Among these methods, carbonyl olefination and olefin metathesis are the two most promising processes owing to the ready availability of the substrates as well as the high efficiency of the reactions. However, the stereoselectivity of known carbonyl olefination methods (Wittig, Julia–Kocienski, and HWE reactions), is difficult to control;[14] and olefin



Scheme 2. Synthesis of terminal monofluoroalkenes. HMDS = hexamethyldisilazide, Py = 2-pyridyl, TBS = *tert*-butyldimethylsilyl.

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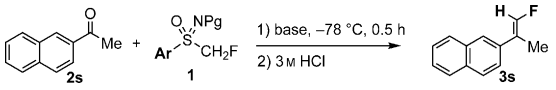
metathesis is limited to the synthesis of disubstituted terminal monofluoroolefins. Therefore, there is still a lack of synthetic methods for the highly stereoselective synthesis of both di- and trisubstituted terminal monofluoroolefins.

Fluorinated sulfoximines[15] have emerged as useful fluoroalkylation reagents for the asymmetric synthesis of organofluorine compounds owing to the ability of the sulfoximidoyl functional group to induce high stereoselectivity. Recently, we reported that an *S*-fluoromethyl-*S*-phenylsulfoximine reacted with carbonyl compounds to yield hydroxy adducts with a fluorinated carbon stereocenter with excellent stereoselectivity; these products could be converted into optically pure monofluoromethyl alcohols.[15e] Inspired by the high steric discrimination of the small H and F atoms in the addition reaction, we envisioned that a stereoselective Julia–Kocienski-type monofluoroolefination might be accessible by the use of an *S*-heteroaryl sulfoximine instead of the *S*-phenylsulfoximine. However, to the best of our knowledge, no stereoselective olefination reaction between a sulfoximine and a carbonyl compound has been reported previously.[8f] Herein, we report a highly efficient, stereoselective, one-pot synthesis of both di- and trisubstituted terminal monofluoroalkenes by an unprecedented Julia–Kocienski-type reaction between an *S*-monofluoromethyl-*S*-(2-pyridyl)sulfoximine and readily available carbonyl compounds. Previously, fluorinated sulfoximine reagents have been used for stereoselective carbonyl fluoroalkylation rather than stereoselective carbonyl fluoroolefination.

We began by investigating the reaction between fluorinated *S*-(2-pyridyl)sulfoximine **1a** bearing an *N*-tosyl substituent and 2-acetonaphthone (**2s**) on the assumption that the electron-withdrawing tosyl group would promote the olefination process (Table 1). We found that the use of KHMDS as a base, as reported for the nucleophilic monofluoromethylation of ketones,[15e] provided the desired olefin **3s** in good yield after an acidic workup, albeit with only moderate *E* selectivity (Table 1, entry 1). To our delight, when **1b** with an electron-donating TBS substituent was used, its reaction with **2s** proceeded smoothly to afford olefin **3s** in moderate yield with high *E* selectivity (entry 2). For comparison, we conducted reactions between **2s** and several other reagents. Reactions with either *N*-tosyl or *N*-TBS-substituted *S*-phenylsulfoximine (substrates **1c** and **1d**) failed to produce the olefination product (Table 1, entries 3 and 4). In the case of **1c**, the formation of the corresponding monofluoroepoxide was detected,[16] whereas in the case of **1d**, the product of addition to the carbonyl group was obtained as reported previously.[15e] When 2-pyridyl sulfone **4** was used, monofluoroolefination took place with nearly 1:1 *E*/*Z* selectivity (entry 5). These results indicate that the 2-pyridyl group plays a key role in promoting the olefination, whereas the sulfoximidoyl group is critical for controlling the stereoselectivity.

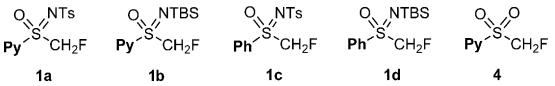
Subsequently, we optimized the conditions for the reaction between **1b** and **2s** by screening several reaction parameters, including different bases, solvents, and molar ratios of reactants (Table 1, entries 6–15). When *n*BuLi or LiHMDS was used as the base, no monofluoroalkene was detected (entries 6 and 7). Interestingly, in the reaction with

Table 1: Survey of reaction conditions.[a]



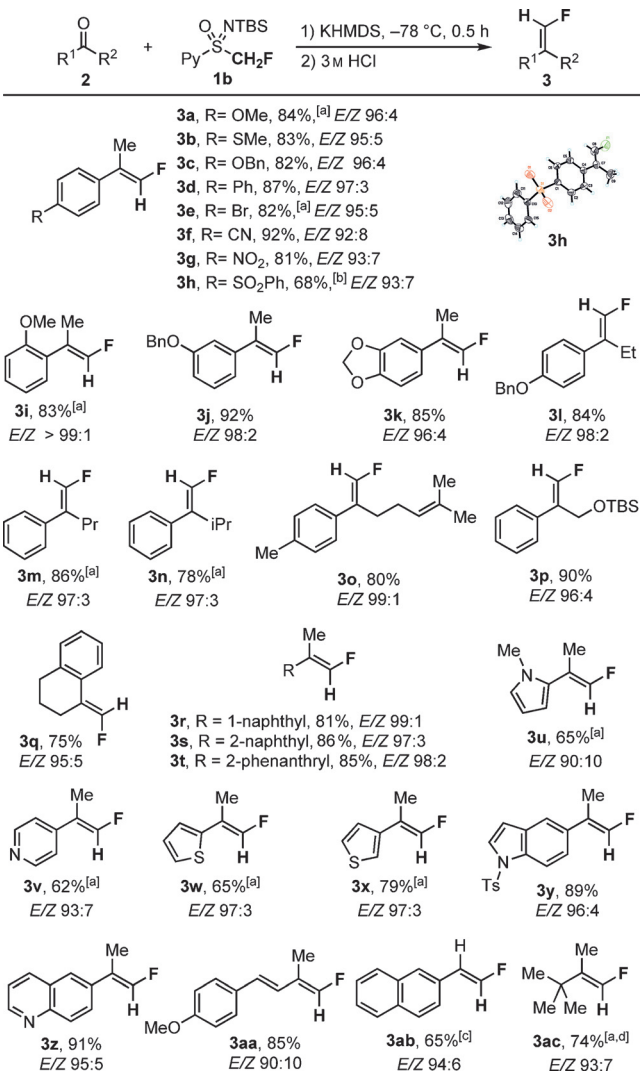
Entry	**2s**/**1**/base	Base	Solvent	Yield [%]	*E*/*Z*[b]
1[c]	1.5/1.0/1.2	KHMDS	THF	84	80:20
2	1.5/1.0/1.2	KHMDS	THF	64	97:3
3[d]	1.5/1.0/1.2	KHMDS	THF	0	–
4[e]	1.5/1.0/1.2	KHMDS	THF	0	–
5[f]	1.5/1.0/1.2	KHMDS	THF	75	52:48
6	1.5/1.0/1.2	*n*BuLi	THF	0	–
7	1.5/1.0/1.2	LiHMDS	THF	0	–
8	1.5/1.0/1.2	NaHMDS	THF	55	91:9
9	1.5/1.0/1.2	KHMDS	DME	6	–
10	1.5/1.0/1.2	KHMDS	Bu_2O	8	–
11	1.5/1.0/1.2	KHMDS	$PhCH_3$	49	73:27
12	1.5/1.0/1.2	KHMDS	CH_2Cl_2	42	71:29
13	1.5/1.0/2.5	KHMDS	THF	75	97:3
14	2.0/1.0/2.5	KHMDS	THF	91	97:3
15	2.0/1.0/2.5	KHMDS	THF/HMPA[g]	60	97:3

[a] Typical procedure: The base was added slowly to a solution of **1** (0.1 mmol) in THF at −78 °C; 0.5 h later, ketone **2s** was added slowly at −78 °C. Unless otherwise noted, **1b** was used. Yields were determined by ^{19}F NMR spectroscopy. [b] The *E*/*Z* ratio was determined by ^{19}F NMR analysis of the crude product. [c] Sulfoximine **1a** was used instead of **1b**. [d] Sulfoximine **1c** was used instead of **1b**. [e] Sulfoximine **1d** was used instead of **1b**. [f] Sulfone **4** was used instead of **1b**. [g] THF/HMPA (10:1, *v*/*v*). DME = 1,2-dimethoxyethane, HMPA = hexamethylphosphoramide, Pg = protecting group, Ts = tosyl.



*n*BuLi, the addition product was observed even after treatment with an acid. Although the use of NaHMDS did afford the monofluoroalkene, the stereoselectivity was significantly lower than with KHMDS (entry 8). With KHMDS as the optimal base, the screening of solvents showed that THF was the best solvent in terms of yield and stereoselectivity (Table 1, entries 9–12). Further optimization of the reaction conditions by changing the ratio of **2s**, **1b**, and KHMDS led to the formation of **3s** in 91 % ^{19}F NMR yield (86 % isolated yield on 0.2 mmol scale, see Scheme 3) with 97:3 *E*/*Z* selectivity (entry 14). Interestingly, the addition of HMPA, a strong coordination solvent, did not affect the *E*/*Z* selectivity, although the yield decreased (entry 15).

Having optimized the reaction conditions, we investigated the scope of the monofluoroolefination of carbonyl compounds with sulfoximine reagent **1b**[17] (Scheme 3). A variety of structurally diverse aromatic ketones were successfully transformed into trisubstituted *E* or *Z* fluoroalkenes in good yield with high stereoselectivity. The reaction tolerated many substituents, such as bromo, methoxy, methylthio, benzoxy, and phenyl sulfonyl groups (products **3a**–**h**). The *E*/*Z* stereoselectivity of the reaction was not sensitive to the electronic nature or position of substituents (products **3a**–**k**). When R^2 was changed to ethyl, propyl, isopropyl, or 2-methylpent-2-enyl, the reaction also gave the desired product **3l** (84 % yield, *E*/*Z* 98:2), **3m** (86 % yield, *E*/*Z* 97:3), **3n** (78 %

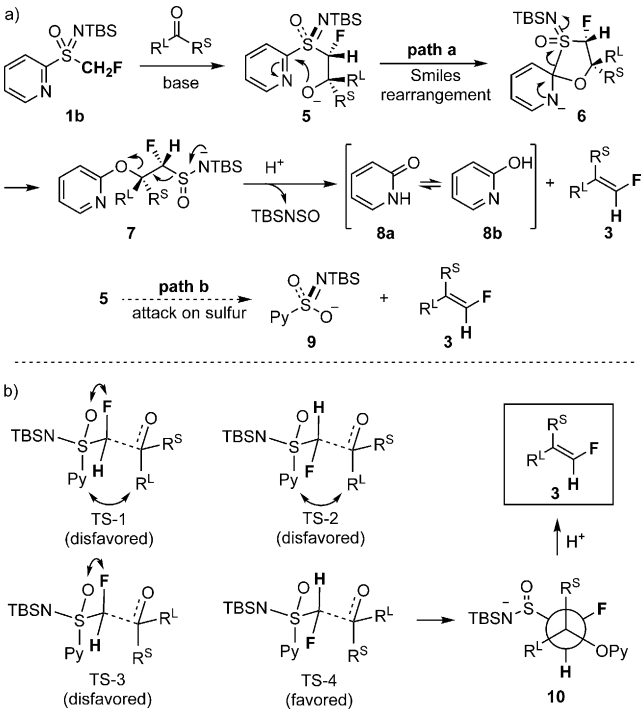


Scheme 3. Stereoselective synthesis of terminal monofluoroalkenes. Typical procedure: The base was added slowly to a solution of **1b** (0.2 mmol) in THF at −78 °C; 0.5 h later, ketone **2** was added slowly. Yields are for the isolated product; *E*/*Z* ratios were determined by ^{19}F NMR analysis of the crude product. [a] The yield and *E*/*Z* ratio were determined by ^{19}F NMR analysis; the product is volatile. [b] Yield of the isolated major isomer. [c] The reaction was quenched at −50 °C. [d] The reaction was carried out at −94 °C. Bn = benzyl.

yield, *E*/*Z* 97:3), or **3o** (80 % yield, *E*/*Z* 99:1), respectively. When TBS-protected α-hydroxyacetophenone was used, **3p**, containing an active site for derivatization, was synthesized in 90 % yield with a 96:4 *Z*/*E* ratio.[18] A cyclic ketone was also a suitable substrate, affording the corresponding product **3q**, an analogue of a fluorosultine precursor for sultine crystallography.[3] Fused aromatic rings, which in some cases can be applied to optoelectronic materials, are also compatible with the current protocol (products **3r**–**t**).[19] Pharmaceutically important heteroaromatic groups, such as pyrryl, pyridyl, thienyl, indolyl, and 6-quinolyl, were well tolerated (products **3u**–**z**).

Besides aromatic ketones, other carbonyl compounds also underwent this transformation. The olefination of benzalacetone proceeded smoothly to provide the conjugated terminal monofluoroalkene **3aa** in 85 % yield with a 90:10 *E*/*Z* ratio (Scheme 3). The dialkyl ketone **2ac** could be transformed into **3ac** in 74 % yield with a 93:7 *E*/*Z* ratio. Notably, the current method can be applied to the synthesis of disubstituted monofluoroalkenes from aldehydes with high *E*/*Z* selectivity (product **3ab**).[20] The absolute configuration of **3h**, **3l**, **3p**, and **3aa** was determined by X-ray crystal-structure analysis[21] or NOESY spectroscopic analysis (see the Supporting Information), and the configuration of all other products was assigned by analogy.

To gain insight into the reaction mechanism, we monitored the progress of the reaction of sulfoximine **1b** and ketone **2s** in THF by variable-temperature ^{19}F NMR spectroscopy. After the addition of **2s** to potassium-metalated **1b** at −78 °C, a new peak was observed at $\delta = -179$ ppm (see the Supporting Information for details). The quenching of this reaction mixture at a low temperature with hydrochloric acid confirmed the formation of intermediate **5** resulting from addition to the carbonyl group with high diastereoselectivity (d.r. > 97:3; see the Supporting Information). In the absence of HCl, intermediate **5** slowly decomposed to **3** when warmed to −18 °C. An increase in the temperature accelerated the formation of **3**. According to the by-products TBSOH (detected by GC–MS) and 2-pyridone (**8a**; detected by NMR spectroscopy) in the final olefination reaction mixture, the formation of the monofluoroalkene is proposed to proceed through Smiles rearrangement of intermediate **5** to a sulfinamidate salt **7**, followed by *anti*-1,2-elimination of thionylimide TBSNSO and 2-pyridone (Scheme 4 a, path a).[22] However, species **9** was not detected, thus indicating that path b involving attack of the oxygen nucleophile in **5** on the S atom to form a four-membered intermediate,

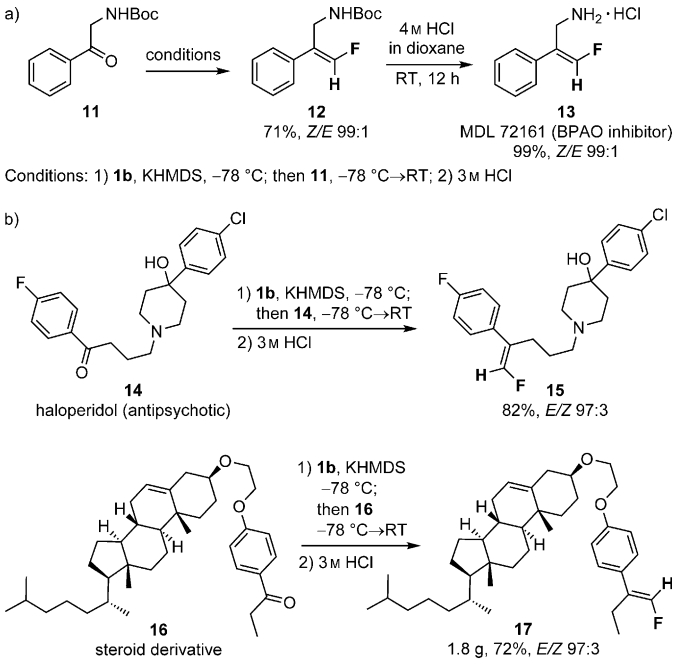


Scheme 4. a) Proposed mechanism of the olefination reaction; b) possible transition states of the diastereoselective carbonyl addition step.

followed by its β-elimination, is less likely (Scheme 4a, path b).

An impressive feature of this reaction is the remarkably high *E*/*Z* selectivity observed in the formation of the terminal monofluoroalkenes. By comparison with the reaction with sulfone **4** (Table 1, entry 5), we suspected that this outcome arose from the excellent 1,2- and 1,3-diastereocontrol of the sulfoximine functionality. Since the addition of HMPA did not influence the *E*/*Z* selectivity (Table 1, entry 15), we envisaged four possible nonchelated transition states in which the bulky group NTBS and the electrophile are in a *trans* relationship due to their strong repulsion (Scheme 4b). Because the steric repulsive interaction between Py and R^L is more significant than that between Py and R^S, TS-1 and TS-2 are less favored. Given that the lone pairs of F and O can result in a strong repulsive interaction, TS-3 is also less favored. Therefore, TS-4 is the most favored transition state, which will lead to the intermediate **10**. A *trans*-1,2-elimination of intermediate **10** will finally afford the major stereoisomer of the monofluoroalkene.

To demonstrate the synthetic utility of the current method in accessing terminal monofluoroalkenes, we applied it to the preparation of MDL 72161, one of the most potent inhibitors of bovine plasma amine oxidase (BPAO; Scheme 5a).[4d,23] Under the standard conditions, the reaction between sulfoximine **1b** and Boc-protected α-aminoacetophenone (**11**) proceeded smoothly to give **12** in 71% yield with 99:1 *Z*/*E* selectivity. Simple deprotection of **12** afforded MDL 72161. The current monofluoroolefination protocol can also be applied to the late-stage modification of complex molecules (Scheme 5b). Haloperidol, an antipsychotic agent, was efficiently converted into the fluorinated analogue **15** in 82% yield with a 97:3 *E*/*Z* value. The presence of a tertiary alcohol functionality did not affect the efficiency and stereoselectivity of the olefination reaction. Moreover, the fluoroolefination reaction can be readily scaled up. For example, a gram-scale reaction of the bioactive steroid derivative **16** with **1b** produced monofluoroalkene **17** in 72% yield with 97:3 *E*/*Z* selectivity.



Scheme 5. Synthetic applications of the current method. Boc = *tert*-butoxycarbonyl.

In conclusion, we have developed an unprecedented stereoselective carbonyl monofluoroolefination with fluorinated sulfoximines through Smiles rearrangement to give a sulfinamidate salt, followed by *anti*-1,2-elimination. In the sulfoximine reagent **1b**, the 2-pyridyl group plays a key role in promoting the olefination, whereas the sulfoximidoyl group is critical for controlling the stereoselectivity. The present method was used to convert a wide range of aldehydes and ketones into di- and trisubstituted terminal monofluoroalkenes. The potential of this method was demonstrated by the synthesis of MDL 72161 and the late-stage modification of complex molecules. Not only does our study provide a valuable tool for synthetic chemists and new insight into the intriguing reactivity of sulfoximines,[15a–c,24] but it should also serve as a basis for the further development of stereoselective carbonyl olefination reactions.

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[17] Reagent **1b** can be readily prepared in multigram quantities (see the Supporting Information for details), whereas BT-, PT-, and TBT-substituted N-TBS sulfoximines are difficult to prepare. BT = 2-benzo[*d*]thiazolyl; PT = 1-phenyl-1*H*-tetrazol-5-yl; TBT = 1-(*tert*-butyl)-1*H*-tetrazol-5-yl.

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