Fluorinated Alkenes

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Highly Stereoselective Synthesis of Monofluoroalkenes from α-Fluorosulfoximines and Nitrones**

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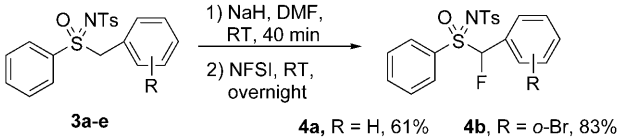
Monofluoroalkenes **1** are widely recognized as nonhydrolyzable mimetics of amides **2** on the basis of the similarity

1 **2**

between the charge distribution of the amide bond and the fluoroalkene moiety, as well as their dipole moments.[1] Therefore, a monofluoroalkene moiety can be used as a peptidomimetic unit in the design of protease inhibitors; this type of rigid isostere of the peptidic bond can facilitate the *cis*/*trans* conformational control of the replaced peptidic fragment.[2] Numerous synthetic endeavors have been undertaken towards the efficient preparation of monofluoroalkenes;[3] among them, many routes focus on the elimination reactions of vicinal halofluorides, fluorohydrins, fluorosulfoxides and fluorocarboxylates, or the addition–elimination processes from *gem*-difluoroalkenes.[4] One-step approaches, such as the Horner–Wadsworth–Emmons reaction,[5] Peterson olefination,[6] and Julia–Kocienski olefination,[7] have also been used to synthesize monofluoroalkenes; however, controlling the *Z*/*E*-stereoselectivity of monofluoroalkene products in these one-step reactions still remains a challenging task.[5–7] Herein, we report a highly efficient stereoselective synthesis of (*Z*)-monofluoroalkenes from an unprecedented reaction between α-fluorosulfoximines and nitrones.

Sulfoximines have been widely used in organic synthesis, but fluorinated sulfoximines still remain a relatively poorly studied class of compounds.[8,9] Previously, Finch and coworkers reported that monofluorinated sulfoximines could react with carbonyl compounds to yield hydroxy adducts, which can be converted into fluoroalkenes (albeit with poor *Z*/*E*-selectivity) by reduction with aluminum amalgam.[9b] Shibata and co-workers reported a trifluoromethylated sulfoximine derivative as an electrophilic trifluoromethylation reagent.[9e] Recently, we reported the use of *N*-tolyl-*S*-difluoromethyl-*S*-phenylsulfoximine as a novel difluoromethylation reagent for transferring the CF_2H group to sulfur, nitrogen, and carbon nucleophiles.[9f] Furthermore, although nitrones have been extensively used in organic synthesis, reports on their use as reaction partners in olefination reactions are rare.[10,11] Indeed, to the best of our knowledge, the olefination reaction between a sulfoximine and a nitrone has not been previously reported.

Our investigation began with the preparation of α-fluoro-*N*-tolyl-*S*-phenylsulfoximines **4a**–**4e** by electrophilic fluorination of non-fluorinated sulfoximines **3a**–**3e** with the *N*-fluorodibenzenesulfonimide (NFSI) reagent (Scheme 1).



3a-e

4a, R = H, 61% **4b**, R = *o*-Br, 83%
4c, R = *p*-Br, 68% **4d**, R = *p*-Me, 71%
4e, R = *p*-F, 69%

Scheme 1. Synthesis of α-monofluorinated sulfoximines **4a**–**4e**. Ts = *p*-toluenesulfonyl. NFSI = *N*-fluorodibenzenesulfonimide.

When compounds **3a**–**3e** were treated with NaH in dry DMF at room temperature and then reacted with NFSI, the α-monofluorinated sulfoximines **4a**–**4e** were obtained in 61–83% yield. With fluorinated sulfoximine **4a** in hand, we were then able to examine its reactivity with *N*-phenyl-*C*-phenylnitrone (**5a**; Table 1). Following initial deprotonation with lithium diisopropylamide (LDA), **4a** reacted with nitrone **5a** to afford the monofluoroalkene (**6a**) with 96:4 *Z*/*E* stereoselectivity (Table 1, entry 1). Inspired by this result, we examined the reaction conditions in more detail. It was found that both NaOH and *t*BuOK were not suitable for this reaction (Table 1, entries 2 and 3). When NaH was used as a base in DMF at −40 °C, product **6a** was obtained in low yield (25%), and the *Z*/*E* ratio decreased to 80:20 (Table 1, entry 4). Using 1.5 equivalents of lithium hexamethyldisilazide (LiHMDS) in THF at −78 °C furnished product **6a** in 75% yield (*Z*/*E* ratio = 96:4; Table 1, entry 5). The optimal conditions were found to be as follows: *n*BuLi (2.0 equiv) was stirred with **4a** for 40 minutes at −78 °C, before the nitrone **5a** was added at the same temperature; the reaction mixture was maintained at −78 °C for 1 h, then warmed to room temperature for 3 h (Table 1, entry 8). The product was formed in 87% yield, and in excellent *Z*/*E* ratio (97:3).

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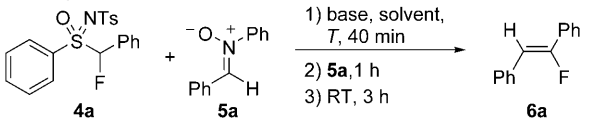
Table 1: Optimization of reaction conditions.



4a **5a** **6a**

Entry	Base	Solvent	Ratio [**4a**:Base:**5a**]	*T* [°C]	Yield [%][a]	*Z*:*E*[b]
1	LDA	THF	1.5:1.5:1.0	−78	60	96:4
2[c]	NaOH	DMF	1.2:1.2:1.0	RT	0	–
3	*t*BuOK	DMF	1.5:1.5:1.0	−40	trace	–
4	NaH	DMF	1.5:1.5:1.0	−40	25	80:20
5	LiHMDS	THF	1.5:1.5:1.0	−78	75	96:4
6	*n*BuLi	THF	1.1:1.1:1.0	−78	48	96:4
7	*n*BuLi	THF	1.5:1.5:1.0	−78	83	97:3
8	*n*BuLi	THF	2.0:2.0:1.0	−78	87	97:3

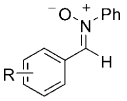
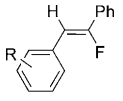
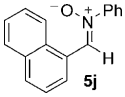
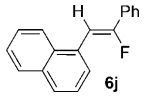
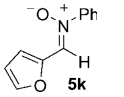
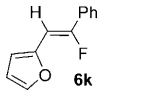
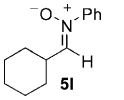
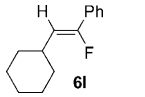
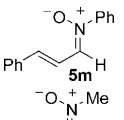
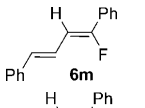
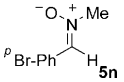
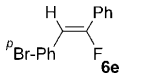
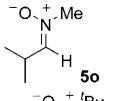
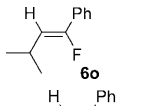
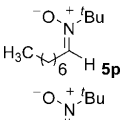
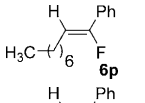
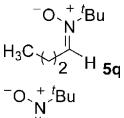
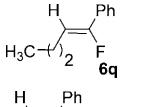
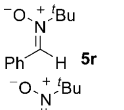
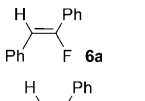
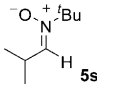
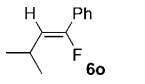
[a] Yield of isolated product. [b] *Z*/*E* ratio was determined by ^{19}F NMR spectroscopy of the crude product. [c] NaOH was added to the mixture of **4a** and **5a**.

With these optimized conditions in hand, we then examined the substrate scope by reacting fluorinated sulfoximine **4a** with different nitrones (Table 2). First, the effect of substitution at the nitrone carbon center on the reaction with *N*-phenyl nitrones was investigated (**5a**–**5m**). It was found that a variety of structurally diverse *C*-aryl substituted nitrones (**5a**–**5i**) showed high reactivities (65–94% yield) with sulfoximine **4a**, affording the products in high *Z*/*E* selectivities (91:9–99:1; Table 2, entries 1–9). Furthermore, recrystallization of **6i** afforded solely the pure *Z*-stereoisomer (*Z*)-**6i** (Table 2, entry 9). When the *C*-naphthyl nitrone **5j** was used, the *Z*/*E* ratio decreased to 74:26 (75% isolated yield; Table 2, entry 10). The reaction was also amenable to *C*-furanyl and cyclohexyl nitrones, affording the corresponding olefins **6k** and **6l** in 87% and 80% yield, respectively, and with high *Z*/*E* ratios (94:6 and 99:1 respectively; Table 2, entries 11 and 12). Furthermore, nitrone **5m** underwent the same transformation to give *Z*-monofluoroalkene **6m**, albeit in a low yield (29%; Table 2, entry 13).

We then examined the reactions of *N*-methyl and *tert*-butyl substituted nitrones (**5n**–**5s**) with sulfoximine **4a** (Table 2, entries 14–19). The reaction of *N*-methyl substituted nitrones **5n** and **5o**, under the same optimal reaction conditions, afforded olefination products **6e** and **6o** with perfect *Z*-stereoselectivity (Table 2, entries 14 and 15). However, in the cases where *N*-*tert*-butyl nitrone was used in conjunction with large *C*-phenyl or *C*-isopropyl groups (**5r** and **5s**), the olefination reaction was unsuccessful (Table 2, entries 18 and 19). When we reacted the less-hindered *C*-substituted nitrones **5p** and **5q** with *N*-*tert*-butyl nitrone, the corresponding monofluoroalkene products **6p** and **6q** were obtained in moderate yields (48% and 30%, respectively; Table 2, entries 16 and 17). Moreover, it is clear from the relative reactivities of **5a** and **5r** (Table 2, entries 1 versus 18) that the sterically bulky *N*-*tert*-butyl group on the nitrone significantly retards fluoroalkene formation.

We extended this fluoroolefination reaction to other α-monofluorinated sulfoximines (**4b**–**4e**; Table 3). By using LiHMDS or *n*BuLi as a base, sulfoximines **4b**–**4e** readily

Table 2: Reaction of fluorinated sulfoximine **4a** with nitrones **5a**–**5s**.

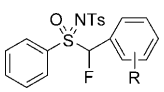
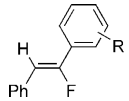
Entry	Nitrone	Product	Yield [%][a]	*Z*:*E*[b]
	 (5a-5i)	 (6a-6i)		
1	**5a** R = H	**6a** R = H	87	97:3
2	**5b** R = *o*-Cl	**6b** R = *o*-Cl	73	99:1
3	**5c** R = *p*-Cl	**6c** R = *p*-Cl	89	93:7
4	**5d** R = *p*-Me	**6d** R = *p*-Me	94	97:3
5	**5e** R = *p*-Br	**6e** R = *p*-Br	89	92:8
6	**5f** R = *p*-MeO	**6f** R = *p*-MeO	86	96:4
7	**5g** R = 2,4-Cl	**6g** R = 2,4-Cl	73	98:2
8	**5h** R = *m*-MeO	**6h** R = *m*-MeO	86	91:9
9	**5i** R = *p*-NO_2	**6i** R = *p*-NO_2	65[c]	92:8 (100:0)[d]
10	 **5j**	 **6j**	75	74:26
11	 **5k**	 **6k**	87	94:6
12	 **5l**	 **6l**	80	99:1
13	 **5m**	 **6m**	29	100:0
14	 **5n**	 **6e**	64	100:0
15	 **5o**	 **6o**	35	100:0
16	 **5p**	 **6p**	48	98:2
17	 **5q**	 **6q**	30	98:2
18	 **5r**	 **6a**	0	–
19	 **5s**	 **6o**	0	–

[a] Yield of isolated product. [b] *Z*/*E* ratio was determined by ^{19}F NMR spectroscopy of the crude product. [c] Recrystallized after flash column chromatography. [d] Recrystallized *Z*/*E* ratio shown in parentheses.

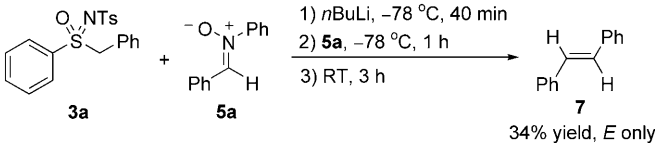
reacted with nitrone **5a** to give the corresponding monofluoroalkenes (**6r**–**6u**) in good yields (73–76%) and with high *Z*/*E* selectivities (90:10–98:2) (Table 3, entries 1–4).

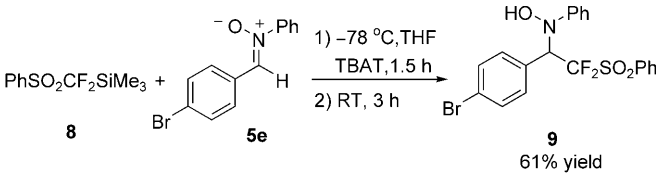
To gain further insight into this fluoroolefination reaction, we attempted other related transformations (Scheme 2). When non-fluorinated sulfoximine **3a** was reacted with nitrone **5a** under similar reaction conditions, (*E*)-stilbene **7** was obtained in low yield (34%), but with complete *E*-stereoselectivity. This result indicates that, compared with their non-fluorinated counterparts, fluorinated sulfoximines, such as **4a**–**4e**, are more reactive towards nitrones **5** for the

Table 3: Reaction of fluorinated sulfoximines **4b–4e** with nitrone **5a**.

Entry	Sulfoximine	Product	Yield [%][a]	*Z*:*E*[b]
				
1[c]	**4b**	**6r** R = *o*-Br	76	98:2
2[c]	**4c**	**6s** R = *p*-Br	73	90:10
3[d]	**4d**	**6t** R = *p*-Me	76	96:4
4[d]	**4e**	**6u** R = *p*-F	73	90:10

[a] Yield of isolated product. [b] *Z*/*E* ratio was determined by ^{19}F NMR spectroscopy of crude product. [c] LiHMDS was used as a base. [d] *n*BuLi was used as a base.

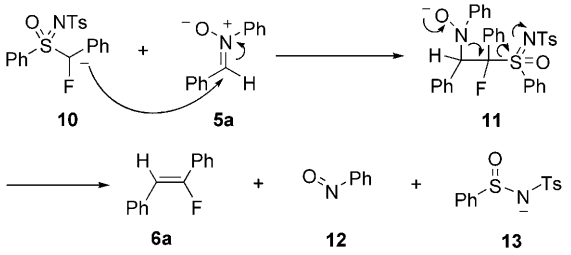




Scheme 2. The reactions between a nitrone (**5a** or **5e**) and non-fluorinated sulfoximine **3a** or fluorinated sulfone **8**.

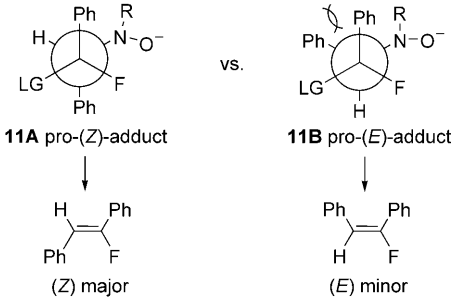
olefination reaction. When fluorinated sulfone **8**[12] (in place of a sulfoximine) was used to react with nitrone **5e**, a fluoroalkylated hydroxylamine product (**9**) was obtained in 61% yield (no alkene product was formed), which demonstrates a remarkable difference in reactivity between the fluorinated sulfoximines and sulfones.

With respect to the reaction mechanism, we proposed that this new type of fluoroolefination reaction proceeds through an addition-elimination pathway (Scheme 3). After an initial



Scheme 3. Proposed reaction mechanism.

addition step, intermediate **11** was formed, which undergoes unusual 1,2-elimination of the nitrosobenzene **12** and *N*-tosyl sulfinamide species **13**. A unique feature of the fluoroolefination reaction is the excellent *Z*/*E* stereocontrol; we suspect that this excellent stereocontrol of the reaction involving sulfoximine anion **10** and nitrone **5a** is because the stereoselective step is the addition of **10** to nitrone **5a**, which occurs in a highly selective manner to produce the less-hindered pro-(*Z*)-adduct **11A**, rather than the more sterically hindered pro-(*E*)-adduct **11B** (Scheme 4). Florio and co-workers have previously reported that the lithiated 2-(chlorormethyl)-4,5-dimethyl-4,5-dihydro-1,3-oxazole could react stereoselectively with nitrones to give *cis*-alkenyloxazolines by the elimination of *t*BuN=O and LiCl.[11]



Scheme 4. Depiction of *Z*/*E* stereocontrol. LG = PhS(O)NTs (**13**).

In conclusion, we report an unusual reaction between α-fluorosulfoximines and nitrones, which turns out to be a novel stereoselective method for the preparation of monofluoroalkenes. The remarkable feature of this fluoroolefination reaction is its practical simplicity and excellent *Z*/*E* stereocontrol of the products, which promises to find many potential applications in life-sciences-related applications. Not only do our results present a new useful synthetic tool for practicing chemists, they also provide important insights into the reactivities of fluorinated sulfoximines[9] (especially when compared with fluorinated sulfones).[13] Further exploration of fluorinated sulfoximine chemistry is currently underway in our laboratory.

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Keywords: alkenes · fluorine · nitrones · stereocontrol · sulfoximines

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