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Preparation of Fluoroalkenes via the Shapiro Reaction: Direct Access to Fluorinated Peptidomimetics

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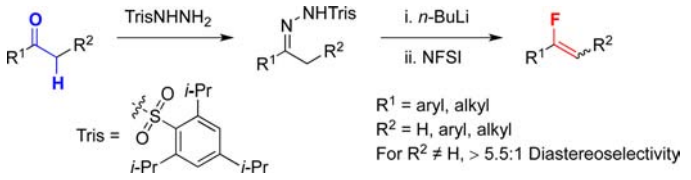
ABSTRACT



Fluoroalkenes represent a useful class of peptidomimetics with distinct biophysical properties. Current preparations of this functional group commonly provide mixtures of *E*- or *Z*-fluoroalkene diastereomers, and/or mixtures of nonfluorinated products. To directly access fluoroalkenes in good stereoselectivity, a Shapiro fluorination reaction was developed. Fluoroalkene products were accessed in one- or two-step sequences from widely available ketones. This strategy should be useful for the preparation of fluorinated analogs of peptide-based therapeutics, many of which would be challenging to prepare by alternate strategies.

Fluoroolefins represent an underappreciated functional group with applications in biological and material chemistry. The fluoroalkene group serves as an isopolar and isosteric mimic of an amide with distinct biophysical properties,[1] including decreased H-bond donating and accepting abilities.[2] Thus, strategic incorporation of a fluoroalkene into a biological probe can increase lipophilicity and membrane permeability of the probe.[3] This peptidomimetic is not subject to hydrolysis by proteases, and incorporation of this group can improve the metabolic stability of a peptide.[3,4] Moreover, fluoroalkenes can serve as probes for conducting conformational analyses of amides by selective preparation of *E*- and *Z*-fluoroalkene isomers.[5] In addition to these biological applications, fluoroalkenes also function as useful intermediates in synthetic sequences. For example, they have been employed as dienophiles in Diels–Alder reactions,[6] converted to cyclopropane derivatives,[7] and polymerized to access materials.[8]

Several methods have been developed for preparing fluoroalkenes, but have traditionally been limited by the formation of complex mixtures of products that are challenging to separate.[9] Strategies including elimination of allyldifluoro compounds,[10] addition–elimination sequences,[11] and Horner–Wadsworth–Emmons,[12] Peterson,[13] and Julia–Kocienski olefination reactions[14] have been used to access fluoroalkene products. Other approaches to generate fluorinated alkenes include fluorination reactions of

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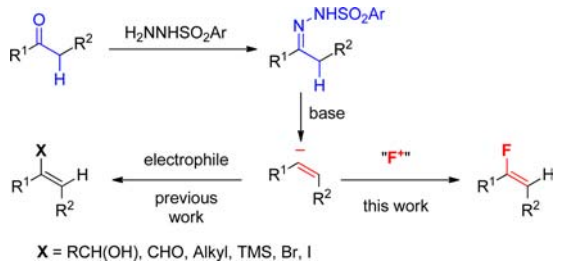
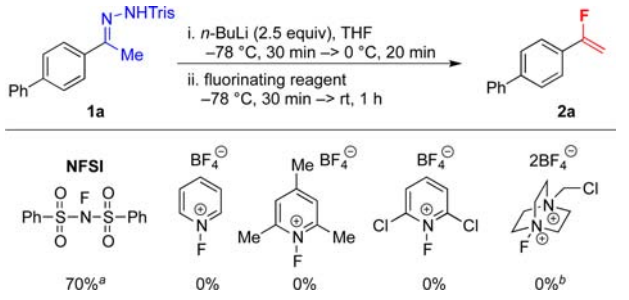
Scheme 1. Shapiro Reactions Have Not Been Employed to Access Fluoroalkenes



Scheme 2. Only NFSI Provided Fluoroalkene Products[a]



[a] Yields were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as an internal standard. [b] The reaction of the phenyl tosylhydrazone substrate was explored.

alkenylstannanes,[15] -silanes,[16] and -boronic acid derivatives[17] and metal-catalyzed coupling reactions.[18] However, these methods typically provide low diastereoselectivities of *E*- and *Z*-isomers (< 1:3 dr).[19] Further, many of these methods are not suitable for introducing the fluoroalkene at a late stage of a synthesis through modification of a compound already in hand. Thus, alternate strategies to access fluoralkenes are desirable.

It was envisaged that fluoroolefins could be accessed through a Shapiro fluorination reaction (Scheme 1).[20] The Shapiro reaction has been widely applied in the synthesis of natural products,[21] and for the preparation of polysubstituted alkenes,[22] many of which are not easily accessed by other means. A prototypical Shapiro reaction involves (1) condensation of an *N*-sulfonyl hydrazide with a ketone to provide a sulfonyl hydrazone; (2) treatment of the sulfonyl hydrazone with a base to provide a vinyllithium intermediate; and (3) trapping of the vinyl anion with H^+ to afford an alkene-based product.[20] Alternatively, the in situ formed alkenyllithium intermediate can also be trapped with a variety of electrophiles to generate allylic alcohols, acrylic acids, acrylic aldehydes, vinylsilanes, and vinyl iodides and bromides.[23] However, the Shapiro reaction has not been employed to access fluoroalkenes. Herein, we describe a Shapiro fluorination reaction to provide fluoroalkenes in high diastereoselectivity (Scheme 1).

The Shapiro fluorination reaction was scouted using a variety of commercially available electrophilic fluorinating reagents[24] and biphenyl 2,4,6-triisopropyl-benzenesulfonyl (Tris) hydrazone (**1a**) as a test substrate (Scheme 2). Tris hydrazones were employed instead of phenylsulfonyl or mesitylsulfonyl moieties because the former group (1) does not undergo ortho-lithiation or α-lithiation, which allows for the reaction to proceed using fewer equivalents of base and electrophilic trapping agent;[25] (2) decomposes more easily than unhindered arylhydrazones, a phenomenon that likely arises from the release of steric compression at the transition state.[26] Decomposition of the Tris hydrazone was accomplished by lithiation with 2.5 equiv of *n*-butyllithium (*n*-BuLi) in THF from −78 to 0 °C, followed by cooling to −78 °C for the addition of the fluorinating reagent. No fluorinated product was observed by ^{19}F NMR when the in situ formed vinyl anion was reacted with *N*-fluoropyridinium salts or Selectfluor. Potentially, the poor reactivity of these reagents arose from the low solubility of the ionic reagents in THF at low temperature. In contrast, employment of

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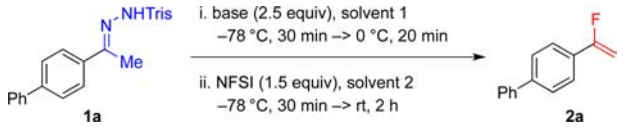
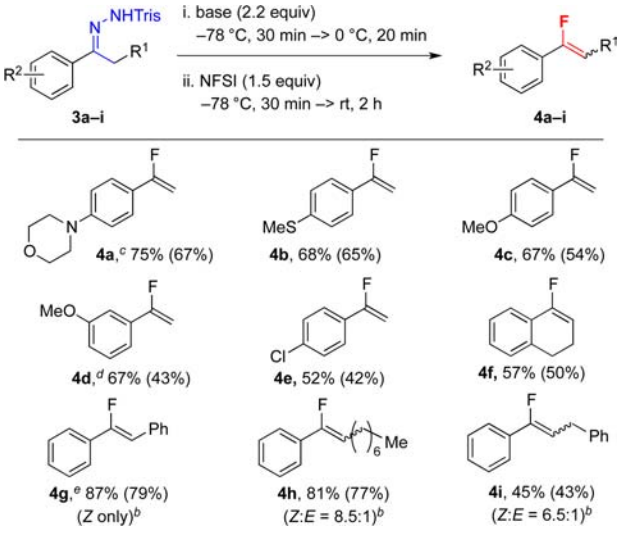
Table 1. Optimization of Shapiro Fluorination Reaction[a]



entry	base	solvent 1	solvent 2	yield[b] (%)
1	*n*-BuLi	THF	THF	70
2	*n*-BuLi	THF	toluene	67
3	*n*-BuLi	THF	solid added	54
4	*n*-BuLi	THF/TMEDA (4:1)	THF	68
5[e]	*n*-BuLi	TMEDA	toluene	48
6	*n*-BuLi	Hexane/TMEDA (9:1)	toluene	53
7[e]	*n*-BuLi	DME	toluene	50
8	*s*-BuLi	THF	THF	68
9	CH3Li	THF	THF	28
10[d]	*n*-BuLi	THF	THF	18
11[e]	*n*-BuLi	THF	THF	68
12[f]	*n*-BuLi	THF	THF	65
13[g]	*n*-BuLi	THF	THF	78 (75)[h]

[a] Standard reaction conditions: **1a** (1.0 equiv, 0.20 M solution), base (2.5 equiv), NFSI (1.5 equiv, 0.50 M THF solution or 0.20 M toluene solution). [b] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [c] Reaction temperatures of −60 °C for 30 min followed by 0 °C for 20 min. [d] HMPA (1.0 equiv) was added during lithiation. [e] NFSI (2.0 equiv). [f] 0.10 M solution was used in step i. [g] *n*-BuLi (2.2 equiv). [h] Isolated yield of material deemed to be >95% pure by ^{1}H NMR.

Scheme 3. Shapiro Fluorination Reaction of Acetophenone-Derived Trishydrazones to Provide Fluorostyrenes[a]



[a] Standard reaction conditions: **3a**–**i** (1.0 equiv, 0.20 M solution in THF), *n*-BuLi (2.2 equiv), NFSI (1.5 equiv, 0.5 M solution in THF). Yields were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as an internal standard (average of two runs) and the figure in the parentheses indicates the isolated yield (average of two runs). [b] The *Z*/*E* ratios were determined by integration of the ^{19}F NMR spectrum of the crude reaction mixture. [c] NFSI (1.1 equiv). [d] *n*-BuLi (2.5 equiv) and NFSI (1.75 equiv). [e] *s*-BuLi (2.2 equiv).

N-fluorobenzenesulfonimide (NFSI), a neutral fluorinating agent that maintains good solubility in ethers and hydrocarbon solvents at lower temperature,[27] provided the desired fluoroalkene product in 70% yield based on ^{19}F NMR.

Optimization of the Shapiro fluorination reaction involved the evaluation of alternate bases, solvents, and additives (Table 1). The use of THF as a solvent (entry 1) proved superior to the use of TMEDA, DME, and hexane/TMEDA (entries 5−7), although the use of a mixture of THF/TMEDA provided a comparable yield (entry 4). The addition of NFSI as a solid provided a lower yield of product (entry 3) than addition of NFSI as a solution in THF (entry 1). The use of *n*-BuLi and *s*-BuLi afforded higher yields than that of MeLi (entries 1, 8, and 9). The use of cation-chelating agents, such as HMPA, did not improve the yield of **2a** (entry 10). Further optimization of the reaction concentration and stoichiometry of base did not improve the yield (entries 11 and 12). Finally, the highest yield was obtained by decreasing the quantity of base employed to 2.2 equiv (entry 13).

Using the optimized reaction sequence, several acetophenone-derived substrates afforded fluoroalkene products (Scheme 3). Electron-rich aryl trisylhydrazones including *p*-morpholine, −SMe, and −OMe were converted to fluoroalkenes **4a**−**d**. The *p*-chloro-subsituted fluorostyrene was provided in 52% yield (**4e**). Reactions of substrates bearing substituents at the β-position provided *Z*-fluoroalkene products in good to excellent diastereoselectivitites (**4g**−**i**). Presumably, the stereochemistry of these reactions was dictated by the unfavorible steric repulsion of the *syn* arrangement of the organic substituents. In contrast, the *E*-fluoroalkene was accessed for a cyclic ketone (**4f**). However, no fluoroalkene products were obtained in reactions of substrates bearing *p*- and *m*-CF_3 and *m*-chloro electron-withdrawing groups. As control experiments, subjection of these three substrates to the Shapiro conditions and quenching of the presumed vinyllithium intermediate with D_2O did not provide the anticipated deuterated or protonated alkenes (GC−MS), indicating that these three substrates were not compatible with the lithiation step.[28]

Aliphatic *N*-trishydrazones also provided the corresponding fluoroalkene analogues (Scheme 4). Using *t*-BuLi, the reaction of 2-phenylcyclohexanone trisylhydrazone provided two regioisomers, **6aA** and **6aB** in a 15:1 ratio (crude reaction mixutre), and 60% of the pure tetrasubstituted fluoroalkene **6aA**, an amide mimic of a δ-lactam. The substrate **5c** afforded *E*-fluoroalkene in 5.7:1 diastereoselectivity. In contrast to the selectivity observed for products **4g**−**i**, the reaction to generate **6c** seems to be controlled by a *syn*-dianion chelation effect, which is frequently observed in Shapiro reactions.[20] Amines protected with benzyl groups were compatible with the reaction conditions and afforded 28−70% yields, depending on the substrates (**6d**−**e**).[29] Pyrrolidine-based derivative **6e** could prove useful

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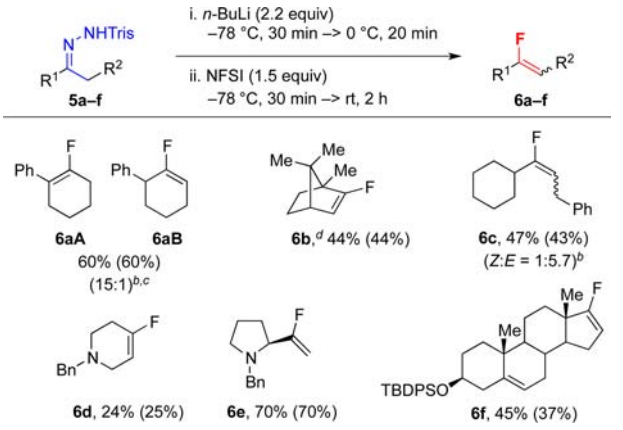
Scheme 4. Shapiro Fluorination Reaction of Aliphatic Trishydrazones to Provide Fluoroalkenes[a]



[a] Standard reaction conditions: **5a**–**f** (1.0 equiv, 0.20 M solution in THF), n-BuLi (2.2 equiv), NFSI (1.5 equiv, 0.50 M solution in THF). Yields were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as an internal standard (average of two runs), and the number in the parentheses represents the isolated yield (average of two runs). [b] The ratios of isomers were determined by integration of the ^{19}F NMR spectrum of the crude reaction mixture. [c] *t*-BuLi (2.2 equiv) afforded improved regioselectivity. [d] *s*-BuLi (2.2 equiv) was used.

for strategic replacement of proline-based residues to form fluorinated peptide-based probes with distinct biophysical properties. Finally, the method was used to rapidly access new fluorinated analogues of natural products, including camphor and a protected steroid (**6b** and **6f**). However, the silyl protecting group was not necessary, and the steroid substrate bearing an unprotected hydroxyl group provided 33% yield by ^{19}F NMR analysis (not shown in Scheme 4, 3.2 equiv *n*-BuLi employed). Thus, the present reaction provides a new entrypoint for the preparation of fluorinated steroids, which are clinically employed for the treatment of vaious disease statess.[30]

In order to accomplish the direct conversion of ketones to fluoroalkenes, a one-pot reaction sequence was developed (Scheme 5). The use of an acid catalyst, in combination with molecular sieves, facilitated the initial condensation reaction and was compatible with the subsequent lithiation and fluorination steps. Using this one-pot procedure, yields of the fluoroalkene products were comparable with those from the isolated hydrazones (**8a** vs **2a**; **8b** vs **4e**; **8c** vs **4c**). This sequence enables easy access to a variety of fluoroalkenes from ketones without purification of intermediates, and it is anticipated that this one-pot procedure could be optimized to access nonstyrenyl fluoroalkenes.

(29) For the 4-piperidone trisylhydrazone, *N*-Bn- and *N*-PMP-protected substrates provided similar yields of fluoroalkene products.

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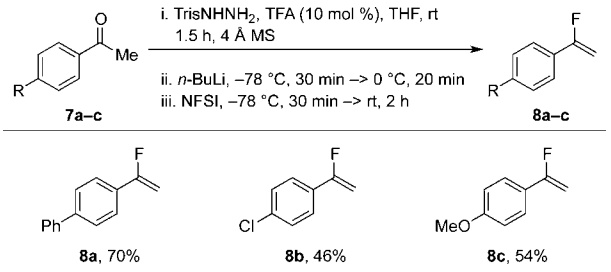
Scheme 5. One-Pot Sequence Converts Ketones to Fluoroalkenes[a]



[a] Standard reaction conditions: (i) **7a**–**c** (1.0 equiv, 0.50 M solution in THF), $TrisNHNH_2$ (1.0 equiv), TFA (0.1 equiv), rt, 1.5 h; (ii) THF (1.5 mL) for dilution, 4 Å molecular sieves (800 mg/mmol), *n*-BuLi (3.0 equiv), −78 °C, 30 min – > 0 °C, 20 min; (iii) NFSI (1.5 equiv, 0.50 M solution in THF), −78 °C, 30 min → rt, 2 h. [b] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

In conclusion, a procedure was developed for converting a ketone into a fluoroalkene analogue through a Shapiro fluorination reaction. The reaction employs inexpensive and readily available reagents, and no expensive transition-metal catalysts/reagents and ligands are required. Compared with many currently available methods, the Shapiro fluorination reaction provides improved diastereoselectivities (dr > 5.5:1) and represents an orthogonal strategy that should be useful for preparing fluoroalkene analogues that might be difficult to access otherwise. Moreover, the extensive number of ketone functional groups that exist in natural products and pharmaceutically important building blocks provides a wide variety of potential substrates for this transformation.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.