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Toward the Synthesis of Benzothiazolyl Fluoroaminosulfones

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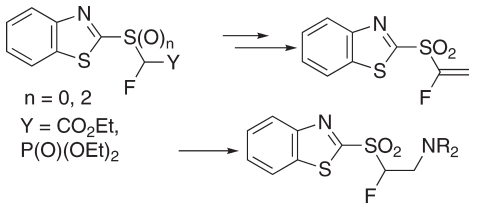
Received July 17, 2009



Due to the importance of allylamines in organic synthesis, the synthesis of reagents as potent precursors of aminofluoroolefins is reported from functionalized benzothiazolylsulfones. The key intermediate, a fluorovinyl sulfone, was prepared and functionalized by addition of aliphatic, aromatic amines and amino acid alkyl esters through an aza-Michael addition reaction.

KEYWORDS:

Introduction

It is known that peptides are not suitable as therapeutic agents due to their in vivo degradation by peptidases. Thus, synthetic peptidomimetics, stable toward enzymatic cleavage, were developed as potential drug substances.[1] Among the large variety of peptidomimetics, it was shown that the replacement of a specific amide bond by a fluorinated carbon−carbon double bond acted as a surrogate of a natural peptide.[2] Recent examples include the preparation of peptide nucleic acid (PNA) analogues and dipeptidyl peptidase IV inhibitors, which exhibit high affinity toward receptors of the original peptides.[3] Most synthetic routes to prepare fluorinated peptidomimetics involved the use of allylamine **III** obtained after further chemical modifications of α-fluoro-α,β-unsaturated esters **I**. In general, this latter was prepared from **II** and carbonyl compounds through Horner−Wadsworth−Emmons, modified Julia, or Peterson reactions (Figure 1).[4]

However, these approaches with **II** were limited by the chemical tolerance of the other functions toward reductive, oxidizing, and cross-coupling reagents. To circumvent these limitations, we decided to prepare functionalized heteroaromatic fluoroalkylsulfones such as **IV** (Y = SO_2Ar) as potential reagents for the synthesis of fluoroallylic amines **III**.

As the HWE reaction cannot be applied to the synthesis of fluoroalkylidene derivatives from fluoroalkylphosphonate such as **IV** (Y = $P(O)(OEt)_2$),[5] we previously developed an alternative one-step synthesis from heteroaromatic fluoroalkylsulfones **1** (Figure 2, R = alkyl) and carbonyl compounds based on the modified Julia reaction.[6] Except for this

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DOI: 10.1021/jo901540c Published on Web 11/18/2009
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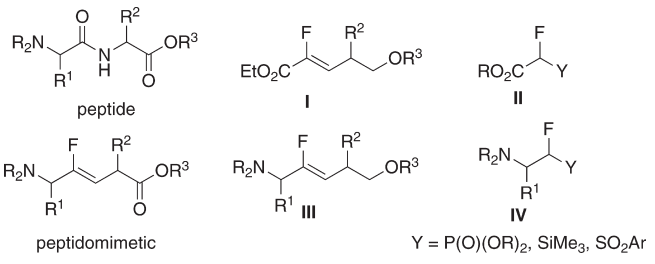

FIGURE 1. Fluoroolefins as peptidomimetics.

example, until now only fluorinated benzothiazolyl, tetrazolyl, and bis-trifluoromethylphenyl sulfones bearing electron-withdrawing or aromatic groups have been known.[7] In continuation of our efforts regarding the synthesis of peptidomimetics, the present work focuses on the synthesis of benzothiazolyl aminosulfones **IV** as potential reagents for the preparation of functionalized fluoroalkylidenes through the modified Julia reaction (Figure 2).

Results and Discussion

Initially, preparation of amine **IV** was attempted from sulfone **2**.[8] The electrophilic fluorination of the carbanion of **2** (NaHMDS) appeared difficult to control. Several attempts realized at −78 °C or from −78 to 0 °C with electrophilic reagents (1.2 equiv of $(PhSO_2)_2NF$ or Selectfluor) were unsuccessful. In most cases, a mixture of mono-, difluorinated products and unidentified byproduct were obtained. Having in hand a straightforward method to prepare fluorinated benzothiazolyl sulfide **3** by alkylation of 2-mercaptobenzothiazole with ethyl bromofluoroacetate,[9] its chemical modification was preferred in order to access to compound **IV**. Sulfide **3** was treated with $NaBH_4$ at 0 °C in EtOH to afford the corresponding alcohol **4** in 75% yield,[10] which after oxidation (*m*-CPBA) led to hydroxysulfone **5** in good yield (Scheme 1). Alcohols **4** and **5** were found to be sensitive, and partial degradation occurred when **4** was submitted to Mitsunobu conditions ($PhCO_2H$, PPh_3, DIAD) or when sulfone **5** was reacted with Ac_2O or MsCl in the presence of amine. In these two cases, the elimination product **8** was mainly formed. In contrast, it was possible to prepare acetate **6** in 81% yield from sulfide **4**. After oxidation (*m*-CPBA) pure sulfone **7** was obtained (Scheme 1). However, compound **7** appeared to be unstable after several days of storage at 20 °C, and traces of elimination product **8** were detected.

As nucleophilic substitution reactions from **4** or **5** were limited, synthesis of aminosulfones **IV** was explored by conjugated addition reactions onto the Michael acceptor **8**. Preparation of vinylsulfone **8** was optimized from sulfone **5**.

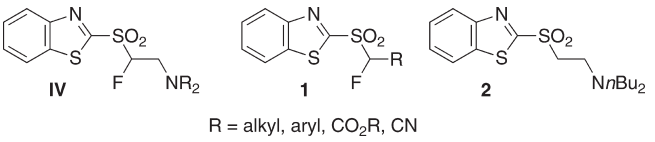

FIGURE 2. Benzothiazolylsulfones as reagents for the modified Julia reaction.

It was converted into its corresponding mesylate and then treated with an excess of triethylamine (2.5 equiv) at 0 °C to afford the expected α-fluorovinylsulfone **8** in 92% yield (Scheme 2).[11] An alternative synthesis, realized from the fluorinated phosphonosulfone **9** and paraformaldehyde through a HWE reaction,[12] proceeded in 77% yield.

To access to a variety of targeted aminosulfones **IV**, the introduction of functional groups onto **8** was studied. Several methods are reported in the literature to introduce a heteroalkyl function or an alkyl group to electron deficient vinylic compounds.[13] The Michael addition constitutes a very useful synthetic method for construction of C−N,[14] C−S,[15] or C−C bonds.[16] To prepare fluoroaminosulfone derivatives **IV**, the aza-Michael addition of aliphatic and aromatic amines onto vinylsulfone **8** was studied first (Scheme 3). Conjugated addition of primary and secondary aliphatic amines (1.3 equiv) onto **8** proceeded smoothly at room temperature (Table 1). The reaction reached completion after 5 min under stirring at 20 °C. Expected aminosulfones **10a**−**g** were isolated in good yield after purification by flash chromatography. The addition reaction worked as well from primary and secondary amines, except from propylamine and allylamine, for which no addition of the amine onto the *ipso* position of the benzothiazolyl ring was observed. In these last two cases, despite a high conversion of **8**, the corresponding aminosulfones **10h**,**i** were not isolated, due to difficulties occurring during their purification by flash chromatography.

However, from aromatic amines, such as aniline, no trace of adduct was observed under these experimental conditions, and an overnight stirring under refluxing CH_2Cl_2 was needed to drive the reaction to completion. Corresponding sulfone **10j** was isolated in quite low yield (29%), probably due to the

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(10) Reduction of the corresponding sulfone with $LiAlH_4$ afforded 2-hydroxybenzothiazole exclusively even when the reaction was conducted at −78 °C.

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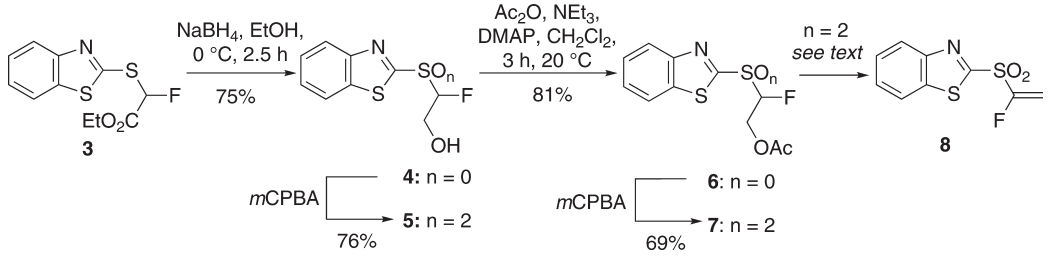
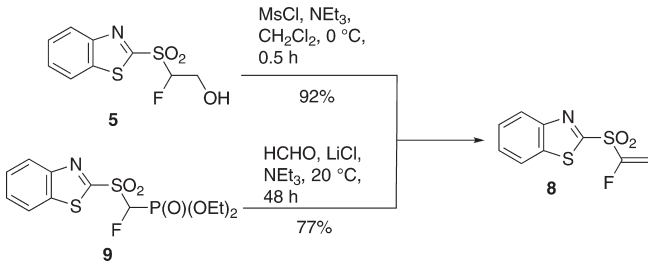
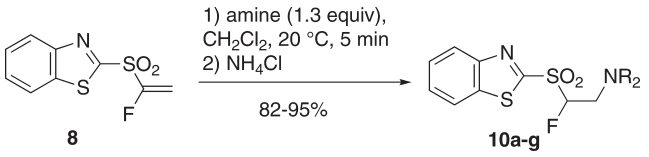
SCHEME 1. Preparation of Fluorohydroxyethyl Sulfone Derivatives



SCHEME 2. Preparation of Fluorovinylsulfone by Elimination or HWE Reactions



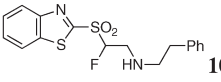
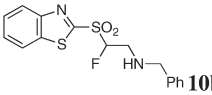
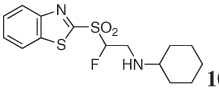
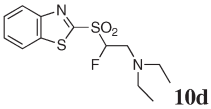
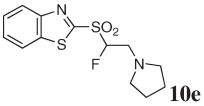
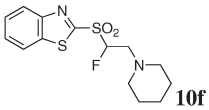
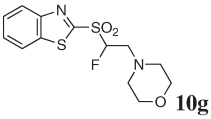
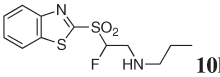
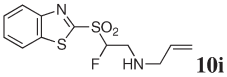
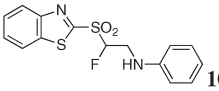
SCHEME 3. Aza-Michael Addition onto Vinylsulfone 8



weak nucleophilic character of the amine. Other reported experimental conditions involving metal catalyst or ionic liquid,[17] $Yt(NO_3)_3 \cdot 6H_2O$,[18] β-cyclodextrin,[19] DBU,[20] silica gel,[21] CAN,[22] or aqueous solvent[23] were tested but unsuccessful. Under these conditions, no addition product was detected, and the starting material was recovered.

To access to the potent precursor of conformationally constrained peptidomimetic and *N*-terminal peptide isosteres, the *N*-alkylation of heterocycles was then tested (Scheme 4). No product was observed at room temperature from pyrrole, pyrazole, and benzimidazole, even in the presence of additives such as silica gel,[21] TBAF,[24] DBU,[20] $TMSCl/PPh_3$,[15a] and CAN.[22] In contrast, alkylation of imidazole proceeded after 16 h under stirring at 20 °C. The addition was slow but realized under milder conditions than those reported from enones as Michael's acceptors.[25] Corresponding imidazolosulfone **11** was isolated in 76% yield. In the presence of TBAF (1 equiv), the reaction reached completion after 1 h at 20 °C, but the isolated yield was much

TABLE 1. Synthesis of Aminosulfones 10a−j

Entry	Products	Yields (%)
1	 **10a**	83[a]
2	 **10b**	87[a]
3	 **10c**	85[a]
4	 **10d**	82[a]
5	 **10e**	95[a]
6	 **10f**	83[a]
7	 **10g**	84[a]
8	 **10h**	(100)[b]
9	 **10i**	(84)[b]
10	 **10j**	29[c]

[a]Isolated yield after 5 min at 20 °C. [b]Conversion of **8** determined by ^{19}F NMR analysis of the crude mixture is shown in parentheses. [c]Isolated yield after 18 h under refluxed solvent.

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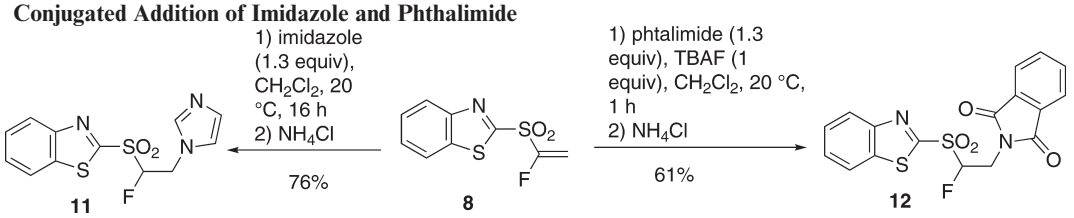
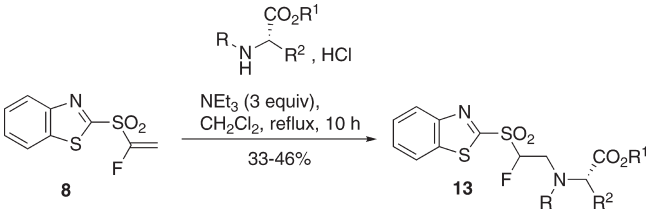
SCHEME 4. Conjugated Addition of Imidazole and Phthalimide



SCHEME 5. Aza-Michael Addition of Amino Acid Alkyl Esters·HCl



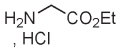
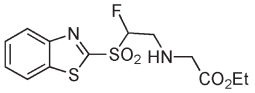
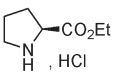
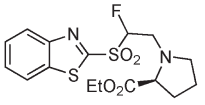
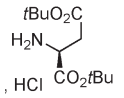
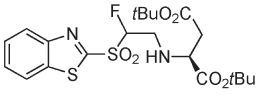
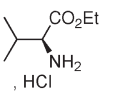
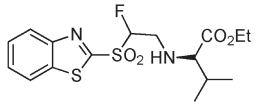
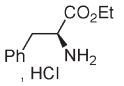
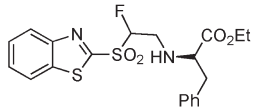
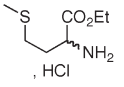
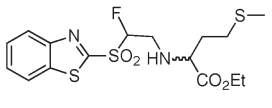
lower (< 55%). However, the conjugated addition of phthalimide was efficient in these conditions, and corresponding phthalimidosulfone **12** was isolated in 61% yield (Scheme 4).

Conjugated addition of amino acid alkyl esters was attempted from vinylsulfone **8**. Three esters of amino acids under their hydrochloride form (glycine, L-proline ethyl esters, and L-aspartate di-*tert*-butyl ester) were tested. The addition reaction performed in the presence of triethylamine (1.5−3 equiv) at room temperature in dichloromethane was slow and did not reach completion after 48 h. In refluxed solvent no trace of starting sulfone **8** was detected after 10 h, and the corresponding fluorinated aminoesters **13** were isolated in modest yields (33−46%) (Scheme 5).

In the presence of silica and an excess of triethylamine (3 equiv) the reaction reached completion after 4−6 h when performed in refluxing acetonitrile.[26] Corresponding sulfone derivatives **13a**−**f** were isolated in 66−90% yields by filtration of the crude product on a short silica pad (Table 2). From L-valine, L-phenylalanine, L-proline, L-aspartine, L,D-methionine, and glycine alkyl esters hydrochloride the products were isolated in good yields. However, from β-amino acid alkyl ester, such as ethyl β-alanine, aminosulfone was obtained in low yield (< 20%) despite a total conversion of **8** (^{19}F NMR).

The last approach investigated to cover the field in the synthesis of functionalized fluorosulfones from **8** was the introduction of an alkyl chain. The most used approaches to functionalized Michael's acceptor are based on the free radical conjugated addition performed from alkyl halides in the presence of indium in protic solvent[27] or complex formed in situ from Zn and CuI.[16] In the first attempts, the free radical addition was explored from alkyl iodide in the presence of free radical initiators ($Na_2S_2O_4$, BEt_3, or lauroyl peroxide). In these cases no addition product was observed and the degradation of the starting sulfone **8** occurred.

TABLE 2. Aza-Michael Reaction with Amino Acid Alkyl Esters·HCl

Amino acid	Product	Yield (%) [a,b]	diast.[c]
	 **13a**	69	/
	 **13b**	71	46:54
	 **13c**	90	47:53
	 **13d**	66	53:47
	 **13e**	75	55:45
	 **13f**	77	54:46

[a]Reagents and conditions: amino acid (1 equiv), silica, NEt_3 (3 equiv), CH_3CN, 4−6 h, 70 °C. [b]Isolated yields. [c]Ratio determined by ^{19}F NMR analysis of the crude product.

Conjugated addition reactions of a carbanion were attempted from organocuprate, -lithium, -magnesium, and -indium.[28] From these anion sources the *ipso* substitution reaction was mainly observed. In contrast, the in situ Zn/CuI

(26) Bigotti, S.; Meille, S. V.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2008**, *129*, 767–774.

(27) (a) Lu, W.; Chan, T. H. *J. Org. Chem.* **2001**, *66*, 3467–3473. (b) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* **2004**, *60*, 4227–4235. (c) Jang, D. O.; Cho, D. H.; Chung, C.-M. *Synlett* **2001**, 1923–1924. (d) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 1523–1525. (e) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131–134. (f) Cho, D. H.; Jang, D. O. *Tetrahedron Lett.* **2005**, *46*, 1799–1802.

(28) (a) Bos, P. H.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2008**, 4219–4222. (b) Desrosiers, J. N.; Bechara, W. S.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2315–2318.

SCHEME 6. Synthesis of Fluoroalkylsulfone

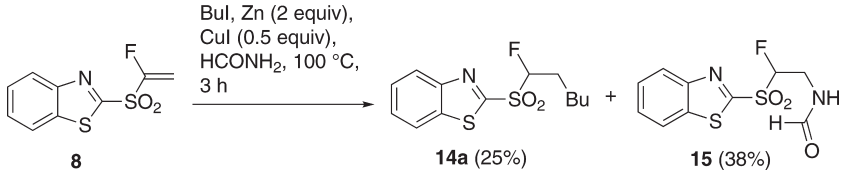
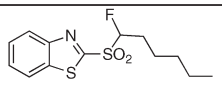
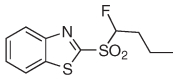
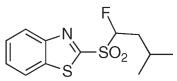
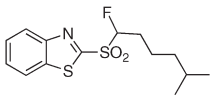


TABLE 3. Preparation of Fluoroalkylsulfones from Alkyl Iodides

Entry	Product	Yield (%)[a,b]
1	 **14a**	55
2	 **14b**	57
3	 **14c**	66
4	 **14d**	53

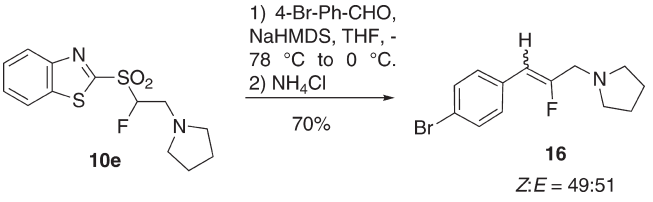
[a]Reagents and conditions: alkyl iodide (1 equiv), Zn (2 equiv), CuI (0.5 equiv), DMSO/formamide (2:1), 100 °C, 3 h. [b]Isolated yield.

complex formation gave us better results and partial conversion of **8** was observed at room temperature,[16a] without formation of *ipso* substitution product. By heating the mixture in formamide at 100 °C over 3 h, the expected product **14a**, and **15** issued from the conjugate addition of the solvent onto the vinylsulfone **8**, were formed (Scheme 6). These were isolated in 25% and 38% yield, respectively.

Other polar solvents were tried such as formic acid, DMSO, and DMF in the same conditions. In these solvents, no total conversion of **8** was observed. Other parameters were changed like the ratio of alkyl iodide, or the ratio between Zn and CuI, and reaction temperature, but these were not successful. The reaction reached completion when performed in the presence of alkyl iodide (1 equiv), Zn (2 equiv), and CuI (0.5 equiv) in anhydrous DMSO/formamide (2:1) at 100 °C over 3 h. From primary alkyl halides, products **14a**−**d** were obtained in 53−66% yields (Table 3).

The synthetic potential of aminosulfones as reagents in the modified Julia reaction was tested by reacting fluorosulfone **10e** with 4-bromobenzaldehyde under Barbier conditions (Scheme 7). The reaction was performed from −78 to 0 °C over 2 h in THF in the presence of NaHMDS (1 M in THF). After workup and flash column chromatography, the expected allylamine **16** was isolated in 70% yield. Although a mixture of *Z* and *E* fluoroolefins was obtained, the isomers were separated on silica gel column chromatography. This

SCHEME 7. Synthesis of a Fluoroallylamine from 10e



preliminary result validates the synthetic potential of functionalized fluorosulfones as fluoroallylamine precursors. Further works are now in progress to cover the limits and the scope of these sulfones in the Julia−Kocienski reaction to open a direct route for the synthesis of functionalized fluoroalkylidene derivatives.

Conclusions

In conclusion, we reported the synthesis of unknown fluorovinylsulfone bearing a benzothiazolyl group prepared by elimination or HWE reactions. This vinylsulfone was involved in aza-Michael reaction allowing the preparation of aminosulfone and amino acid derivatives. The introduction of a heterocycle was realized in good yield, but this addition was limited to imidazole and phthalimide. In addition, alkyl chains were added by using bimetallic complex and alkyl iodides. This large variety of new benzothiazolyl sulfones could open a new route for the preparation of fluoroolefins bearing a functionalized alkyl chain and in particular for the synthesis of allylamines, as exemplified by a preliminary result. Their synthetic potentials as building blocks for the study of the olefination of carbonyl compounds through the Julia−Kocienski reaction are underway, and results will be reported in due course.

Experimental Section

2-Benzothiazolylsulfanyl-2-fluoroethanol (4). To a solution of ethyl 2-benzothiazolylsulfanyl-2-fluoroacetate **3** (7.00 g, 25.79 mmol, 1 equiv) in EtOH (106 mL) cooled to 0 °C was added $NaBH_4$ (1.36 g, 36.12 mmol, 1.4 equiv) in small portions. The mixture was stirred for 2 h and then quenched with a saturated solution of NH_4Cl (30 mL) and brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). Combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, pentane/AcOEt 7:3) to afford **4** (4.47 g, 75%) as a white solid: mp 92−94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.97−4.13 (m, 2H), 6.61 (ddd, $^3J_{HH}$ = 3.9 Hz, $^3J_{HH}$ = 5.0 Hz, $^2J_{HF}$ = 51.5 Hz, 1H), 7.29−7.43 (m, 2H), 7.74−7.76 (m, 1H), 7.90 (d, $^3J_{HH}$ = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 103.4 (d, $^2J_{CF}$ = 8.5 Hz), 121.3, 124.8, 126.9, 127.6, 136.4, 151.7, 155.8, 160.2 (d, $^1J_{CF}$ = 270.6 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −159.5 (ddd, $^2J_{FH}$ = 51.5 Hz, $^3J_{FH}$ = 16.4 Hz, $^3J_{FH}$ = 20.2 Hz); MS (EI) *m*/*z*

230 $[M + H]^+$ (100), 210 (89); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_9H_9FNOS_2$ 230.0110, found 230.0102.

2-Benzothiazolylsulfonyl-2-fluoroethanol (5). To a solution of sulfide **4** (2.00 g, 8.73 mmol, 1 equiv) in CH_2Cl_2 (22 mL) at 0 °C was added dropwise a solution of *m*-CPBA (9.04 g, 52.40 mmol, 6 equiv) in CH_2Cl_2 (18 mL). The mixture was stirred for 48 h at room temperature and washed with a saturated solution of $NaHCO_3$ (2 × 30 mL). Aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, pentane/AcOEt 7:3) to afford **5** (1.60 g, 75%) as a colorless solid: mp 123−125 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.38 (s, 1H), 3.93−4.14 (m, 2H), 6.59 (dt, $^3J_{HH}$ = 4.0 Hz, $^2J_{HF}$ = 46.8 Hz, 1H), 7.18−7.43 (m, 2H), 7.73 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.89 (d, $^3J_{HH}$ = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 59.1 (d, $^2J_{CF}$ = 21.2 Hz), 101.4 (d, $^1J_{CF}$ = 225.4 Hz), 122.4, 125.8, 128.0, 128.7, 137.5, 152.6, 162.3; ^{19}F NMR ($CDCl_3$, 235 MHz) δ −185.4 (dt, $^2J_{FH}$ = 46.8 Hz, $^3J_{FH}$ = 18.8 Hz); MS (EI) m/z 262 $[M + H]^+$ (100), 244 (10), 200 (20), 182 (73); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_9H_9FNO_3S_2$ 262.0008, found 261.9997.

2-[(1-Fluorovinyl)sulfonyl]-1,3-benzothiazole (8). To a solution of 2-benzothiazolylsulfonyl-2-fluoroethanol (**5**) (300 mg, 1.14 mmol, 1 equiv) and MsCl (110 μL, 1.38 mmol, 1.2 equiv) in CH_2Cl_2 (4 mL) cooled to 0 °C was added dropwise NEt_3 (400 μL, 2.85 mmol, 2.5 equiv). The mixture was stirred for 30 min at 0 °C and then quenched with a saturated solution of NH_4Cl (1 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). Combined organic layers were washed with a saturated solution of $NaHCO_3$ (2 × 1 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to furnish pure **8** (259 mg, 92%) as a white solid: mp 141−142 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.65 (dd, $^2J_{HH}$ = 5.0 Hz, $^3J_{HF}$ = 11.7 Hz, 1H), 6.06 (dd, $^2J_{HH}$ = 5.0 Hz, $^3J_{HF}$ = 40.7 Hz, 1H), 7.54−7.64 (m, 2H), 7.96−7.99 (m, 1H), 8.19−8.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 64.1 (d, $^2J_{CF}$ = 25.2 Hz), 99.5 (d, $^1J_{CF}$ = 224.2 Hz), 121.2, 122.4, 125.2, 126.5, 136.0, 152.8, 161.3; ^{19}F NMR ($CDCl_3$, 235 MHz) δ −114.2 (dd, $^2J_{FH}$ = 40.7 Hz, $^3J_{FH}$ = 11.7 Hz); MS (EI) m/z 244 $[M + H]^+$ (100), 214 (8), 158 (13), 141 (7), 99 (4); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_9H_7FNO_2S_2$ 243.9902, found 243.9913.

General Procedure for the Preparation of Aliphatic Fluoroaminosulfones (10a−i). To a solution of 2-[(1-fluorovinylsulfonyl)]-1,3-benzothiazole (**8**) (1 equiv) in CH_2Cl_2 was added aliphatic amine (1.3 to 1.5 equiv). The mixture was stirred for 5 min at room temperature then quenched with a saturated solution of NH_4Cl (3 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give fluoroaminosulfones **10a−i**.

2-[(1-Fluoro-2-pyrrolidin-1-ylethyl)sulfonyl]-1,3-benzothiazole (10e). The general procedure was followed with 2-[(1-fluorovinylsulfonyl)]-1,3-benzothiazole (**8**) (1 g, 4.11 mmol, 1 equiv), pyrrolidine (440 μL, 5.34 mmol, 1.3 equiv), and CH_2Cl_2 (17 mL). The purification by flash column chromatography (silica, pentane/AcOEt 95:5 then 90:10) afforded **10e** (1.23 g, 95%) as a colorless solid: mp 73 −77 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.60−1.70 (m, 4H), 2.60−2.70 (m, 4H), 3.13−3.57 (m, 2H), 5.69−5.93 (m, 1H), 7.61−7.66 (m, 2H), 8.01−8.04 (m, 1H), 8.24−8.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 62 MHz) δ 23.6, 52.5 (d, $^2J_{CF}$ = 19.5 Hz), 54.4, 101.7 (d, $^1J_{CF}$ = 225.2 Hz), 122.3, 125.7, 127.8, 128.3, 137.4, 152.7, 162.6; ^{19}F NMR ($CDCl_3$, 235 MHz) δ −178.5 (ddd, $^2J_{FH}$ = 49.0 Hz, $^3J_{FH}$ = 31.5 Hz, $^3J_{FH}$ = 20.0 Hz); MS (EI) m/z 315 $[M + H]^+$ (87), 244 (100), 180 (5), 116 (88), 84 (22); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{16}FN_2O_2S_2$ 315.0637, found 315.0626.

2-[[1-Fluoro-2-(1*H*-imidazol-1-yl)ethyl]sulfonyl]-1,3-benzothiazole (11). To a solution of 2-[(1-fluorovinylsulfonyl)]-1,3-benzothiazole (**8**) (100 mg, 0.41 mmol, 1 equiv) in CH_2Cl_2 (8 mL) was added imidazole (30 mg, 0.45 mmol, 1.1 equiv). The mixture was stirred for 16 h at room temperature, quenched with a saturated solution of NH_4Cl (3 mL), and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, CH_2Cl_2 then CH_2Cl_2/AcOEt 90:10) to give **11** (100 mg, 76%) as a white solid: mp 129 −132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.59−4.93 (m, 2H), 5.82 (dd, $^2J_{HF}$ = 48.2 Hz, $^3J_{HH}$ = 8.5 Hz, 1H), 6.90 (d, $^3J_{HF}$ = 22.4 Hz, 2H), 7.51−7.77 (m, 3H), 7.96−7.98 (m, 1H), 8.14−8.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.4 (d, $^2J_{CF}$ = 20.5 Hz), 99.7 (d, $^1J_{CF}$ = 227.4 Hz), 119.5, 122.4, 125.8, 128.2, 128.9, 130.5, 137.5, 137.8, 152.7, 161.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −179.0 (ddd, $^2J_{FH}$ = 48.2 Hz, $^3J_{FH}$ = 30.9 Hz, $^3J_{FH}$ = 17.3 Hz); MS (EI) m/z 312 $[M + H]^+$ (100), 244 (85); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{11}FN_3O_2S_2$ 312.0277, found 312.0276.

2-[2-(1,3-Benzothiazol-2-ylsulfonyl)-2-fluoroethyl]phthalimide (12). To a solution of phthalimide (80 mg, 0.53 mmol, 1.3 equiv) in THF (2 mL) were added a 1 M solution of TBAF in THF (410 μL, 0.41 mmol, 1 equiv) and 2-[(1-fluorovinylsulfonyl)]-1,3-benzothiazole (**8**) (100 mg, 0.41 mmol, 1 equiv). The mixture was stirred for 1 h at room temperature, quenched with a saturated solution of NH_4Cl (1 mL), and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, CH_2Cl_2/pentane 80:20) to afford **12** (100 mg, 61%) as a white solid: mp 166−168 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.44−4.53 (m, 2H), 5.99 (ddd, $^2J_{HF}$ = 48.0 Hz, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 4.3 Hz, 1H), 7.48−7.61 (m, 2H), 7.66−7.69 (m, 2H), 7.78−7.82 (m, 2H), 7.93−7.97 (m, 1H), 8.17−8.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.5 (d, $^2J_{CF}$ = 22.1 Hz), 97.5 (d, $^1J_{CF}$ = 226.8 Hz), 122.4, 123.8, 125.9, 128.0, 128.7, 131.6, 134.5, 137.5, 152.8, 161.5, 167.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −182.8 (ddd, $^2J_{FH}$ = 48.0 Hz, $^3J_{FH}$ = 24.2 Hz, $^3J_{FH}$ = 14.3 Hz); MS (EI) m/z 391 $[M + H]^+$ (65), 307 (28), 192 (100), 172 (9); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}FN_2O_4S_2$ 391.0223, found 391.0207.

General Procedure for the Preparation of Fluorinated Sulfonylamino Acid Alkyl Esters (13a−f). To a solution of chlorhydrate amino acid alkyl ester (1 equiv) and NEt_3 (3 equiv) in MeCN were introduced 2-[(1-fluorovinylsulfonyl)]-1,3-benzothiazole (**8**) (1 equiv) and silica (2 equiv w/w). The solution was stirred under reflux for 4−6 h. The reaction mixture was cooled to room temperature, hydrolyzed with a saturated solution of NH_4Cl (1 mL), and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified on a short silica pad to give fluorinated sulfonylamino acid alkyl esters **13a−f**.

***N*-[2-(1,3-Benzothiazol-2-ylsulfonyl)-2-fluoroethyl]glycine Ethyl Ester (13a).** The general procedure was followed with 2-[(1-fluorovinylsulfonyl)]-1,3-benzothiazole (**8**) (100 mg, 0.41 mmol, 1 equiv), chlorhydrate glycine ethyl ester (60 mg, 0.41 mmol, 1 equiv), NEt_3 (170 μL, 1.23 mmol, 3 equiv), and silica (204 mg) for 4 h in refluxing MeCN (2 mL). The purification on a short silica pad (CH_2Cl_2 then CH_2Cl_2/AcOEt 98:2 and CH_2Cl_2/AcOEt 95:5) afforded **13a** (100 mg, 69%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.94−1.95 (m, 1H), 3.37−3.52 (m, 4H), 4.09 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 5.70 (ddd, $^2J_{HF}$ = 48.0 Hz, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 3.4 Hz, 1H), 7.53−7.58 (m, 2H), 7.93−7.95 (m, 1H), 8.15−8.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.1, 49.9 (d, $^2J_{CF}$ = 23.4 Hz), 54.4, 61.4, 102.6 (d, $^1J_{CF}$ = 212.7 Hz), 116.7, 120.4, 123.0, 124.9,

126.6, 144.0, 166.2, 168.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −181.01 (ddd, $^2J_{FH}$ = 48.0 Hz, $^3J_{FH}$ = 28.4 Hz, $^3J_{FH}$ = 19.2 Hz); MS (EI) m/z 347 $[M + H]^+$ (100), 282 (33), 281 (18), 236 (100); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{16}FN_2O_4S_2$ 347.0536, found 347.0541.

General Procedure for the Preparation of Alkylated Fluorosulfones 14a−d. To a suspension of zinc (2 equiv) in dry DMSO were added formamide (few drops) and CuI (0.5 equiv). After 3 min of stirring at room temperature, 2-(1-fluorovinylsulfonyl)-1,3-benzothiazole (**8**) (1.2 equiv) and iodoalkyl (1 equiv) were introduced. The solution was heated to 100 °C for 3 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and hydrolyzed with a 0.6 M aqueous solution of HCl (1 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give alkylated fluorosulfones **14a−d**.

2-[(1-Fluorohexyl)sulfonyl]-1,3-benzothiazole (14a). The general procedure was followed with 2-[(1-fluorovinylsulfonyl)]-1,3-benzothiazole (**8**) (110 mg, 0.45 mmol, 1.2 equiv), iodobutane (40 μL, 0.37 mmol, 1 equiv), Zn (50 mg, 0.75 mmol, 2 equiv), CuI (40 mg, 0.19 mmol, 0.5 equiv), DMSO (340 μL), and formamide (170 μL). The purification by flash column chromatography (silica, CH_2Cl_2/pentane 8:2) afforded **14a** (60 mg, 55%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.25−1.33 (m, 4H), 1.50−1.62 (m, 2H), 2.06−2.25 (m, 2H), 5.58 (ddd, $^2J_{HF}$ = 48.6 Hz, $^3J_{HH}$ = 9.9 Hz, $^3J_{HH}$ = 2.9 Hz, 1H), 7.53−7.60 (m, 2H), 7.96 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 8.20 (d, $^3J_{HH}$ = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 22.2, 24.0 (d, $^3J_{CF}$ = 3.2 Hz), 26.8 (d, $^2J_{CF}$ = 19.2 Hz), 31.0, 102.3 (d, $^1J_{CF}$ = 221.8 Hz), 122.3, 125.8, 127.8, 128.4, 137.4, 152.8, 162.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −177.8 (ddd, $^2J_{FH}$ = 48.6 Hz, $^3J_{FH}$ = 34.5 Hz, $^3J_{FH}$ = 15.9 Hz); MS (EI) m/z 302 $[M + H]^+$ (87), 200 (36), 182 (100); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{17}FNO_2S_2$ 302.0685, found 302.0677.

(*Z*/*E*)-*N*-[3-(4-Bromophenyl)-2-fluoroprop-2-enyl]pyrrolidine (16). To a solution of 2-[(1-fluoro-2-pyrrolidin-1-ylethyl)-sulfonyl]-1,3-benzothiazole (**10e**) (100 mg, 0.32 mmol, 1 equiv) and 4-bromobenzaldehyde (62 mg, 0.33 mmol, 1.05 equiv) in THF (5 mL) cooled to −80 °C was added a 1 M solution of NaHMDS (100 μL, 0.70 mmol, 2.1 equiv) in THF. The reaction mixture was stirred for 5 min at −80 °C and 5 min at room temperature and then quenched with a saturated solution of NH_4Cl (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford a crude mixture of (*E*)- and (*Z*)-alkene **16** in a ratio of 51:49. This crude product was purified by flash column chromatography (silica, pentane/AcOEt gradient from 90:10 to 80:20) to afford successively the (*E*) (32 mg, 35%) and the (*Z*) isomers (30 mg, 33%) as yellow oils. Isomer *E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70−1.74 (m, 4H), 2.48−2.50 (m, 4H), 3.28 (d, $^3J_{HFvic}$ = 22.7 Hz, 2H), 6.19 (d, $^3J_{HFcis}$ = 20.6 Hz, 1H), 7.08 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.37 (d, $^3J_{HH}$ = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5, 51.6 (d, $^2J_{CF}$ = 26.1 Hz), 53.0, 109.1 (d, $^2J_{CF}$ = 28.2 Hz), 119.9, 129.4, 129.5, 129.8, 130.5, 131.6 (d, $^3J_{CF}$ = 13.7 Hz), 158.9 (d, $^1J_{CF}$ = 256.5 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −97.8 (dt, $^3J_{FHcis}$ = 20.6 Hz, $^3J_{FHvic}$ = 22.7 Hz); MS (EI) m/z 284 $[M + H]^+$ (100), 213 (50), 134 (30); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{16}BrFN$ 284.0450, found 284.0444. Isomer *Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75−1.78 (m, 4H), 2.56−2.58 (m, 4H), 3.24 (d, $^3J_{HFvic}$ = 16.9 Hz, 2H), 5.57 (d, $^3J_{HFtrans}$ = 38.2 Hz, 1H), 7.29 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 7.36 (d, $^3J_{HH}$ = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5, 53.0, 56.0 (d, $^2J_{CF}$ = 28.2 Hz), 106.3 (d, $^2J_{CF}$ = 7.0 Hz), 119.8, 119.9, 129.0, 129.1, 130.5, 131.1 (d, $^3J_{CF}$ = 2.0 Hz), 157.3 (d, $^1J_{CF}$ = 269.6 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −103.3 (dt, $^3J_{FHtrans}$ = 38.2 Hz, $^3J_{FHvic}$ = 16.9 Hz); MS (EI) m/z 284 $[M + H]^+$ (70), 213 (100), 134 (33); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{16}BrFN$ 284.0450, found 284.0446.

Acknowledgment. This work was supported by the CNRS and the Crunch (interregional organic chemistry network). The "Région Basse-Normandie" and ERDF (ISCE Chem, INTERREG IVa program) are gratefully thanked for their financial support.

Supporting Information Available: Additional experimental procedures for the preparation of **6**, **7**, **9**, **10a−d**,**f−g**,**j**, **13b−f**, **14b−d** and ^{1}H and ^{13}C NMR spectra of the compounds **4−12**, **10a−g**, **13a−f**, **14a−d**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.