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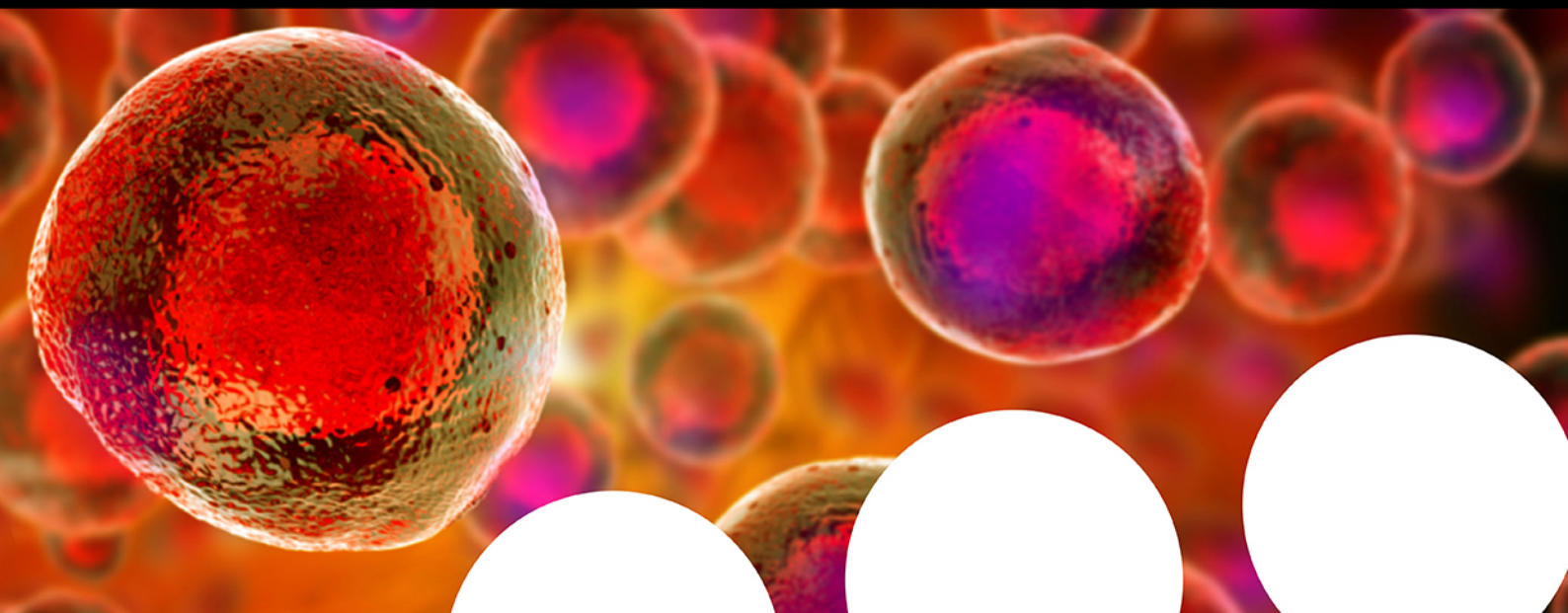
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Radical Amido- and Azido-Fluorination of α -Fluorostyrene Derivatives: An Innovative Approach Towards β -Aryl- β,β -difluoroamino Motifs

Alphonsine Ngo Ndimba,^[a] Émilie Vincent,^[a] and Julien Brioché*^[a]

An innovative one-step synthesis towards β -aryl- β,β -difluorocarbamates and β -aryl- β,β -difluoroazides is presented. The described approach relies on the use of α -fluorostyrene substrates in a radical addition/fluorination reaction with N-centered radicals in the presence of Selectfluor®. The best results were

obtained for the azidofluorination reaction. The resultant β -aryl- β,β -difluoroazides were further transformed into Nitrogen-based heterocycles (e.g. pyrrole, triazole, and tetrazole) and in more elaborated azide derivatives.

Introduction

The *gem*-difluoromethylene ($-\text{CF}_2-$) unit is a versatile fluorine substitution widely employed in medicinal chemistry to modulate the properties of drug candidates (e.g. conformation, lipophilicity, pKa of proximal chemical functions).^[1] Such a fluorinated motif has also been exploited in structure-activity relationship (SAR) studies as a bioisostere of carbonyl or ether groups,^[2] and to improve the metabolic stability when located at a benzylic position.^[3] For instance, the β -aryl- β,β -difluoroamines are useful fluorinated building blocks in order to introduce a β -aryl- β,β -difluoroamino motif into drug candidates. As a result, this motif can be found in several biologically active molecules (Figure 1).^[4]

The synthesis of such a motif remains rather challenging and only few methods have been reported in the literature. For instance, the fluorination of 2*H*-azirines in the presence of Olah's reagent provides a direct access to β -aryl- β,β -difluoroamine albeit a narrow substrate scope (Scheme 1a).^[5] The use of benzene as solvent was found crucial to limit the formation the side-products pyrazine and α -fluoroketone, especially when substituted 2*H*-azirines (R = alkyl) were employed in the transformation. Another straightforward strategy relies on the reduction of either α -aryl- α,α -difluoro-amides or -nitriles into the corresponding amines in the presence of borane (Scheme 1b).^[6] However, the reductive conditions may limit the functional group tolerance of this approach. Recently, tosyl-

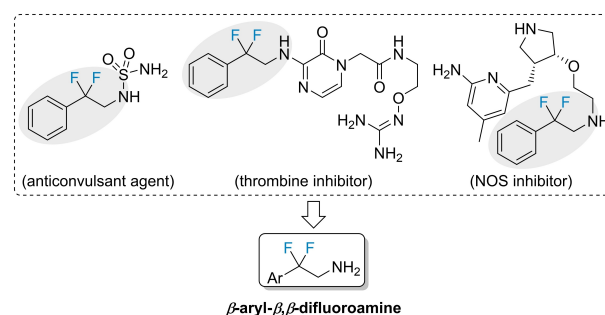
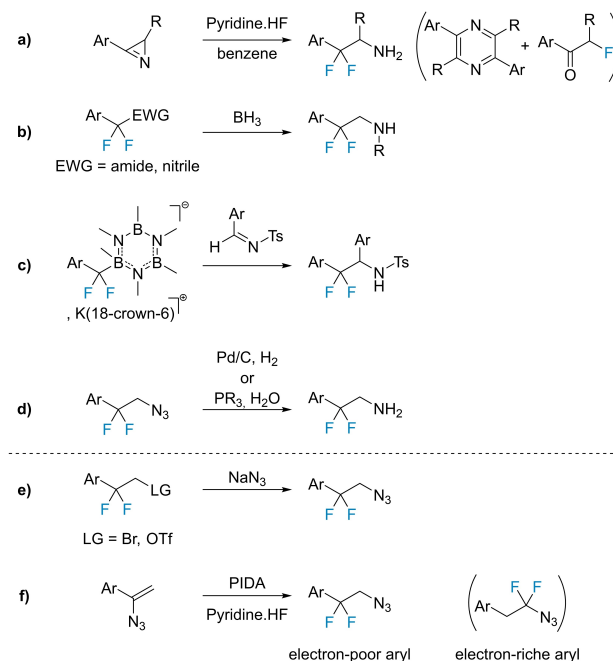


Figure 1. Examples of bioactive molecules featuring β -aryl- β,β -difluoroamino motif, NOS = Nitric Oxide Synthase.



Scheme 1. a-d) Representative synthetic routes towards β -aryl- β,β -difluoroamines; e, f) Representative synthetic routes towards β -aryl- β,β -difluoroazides. PIDA = (Diacetoxyiodo)benzene.

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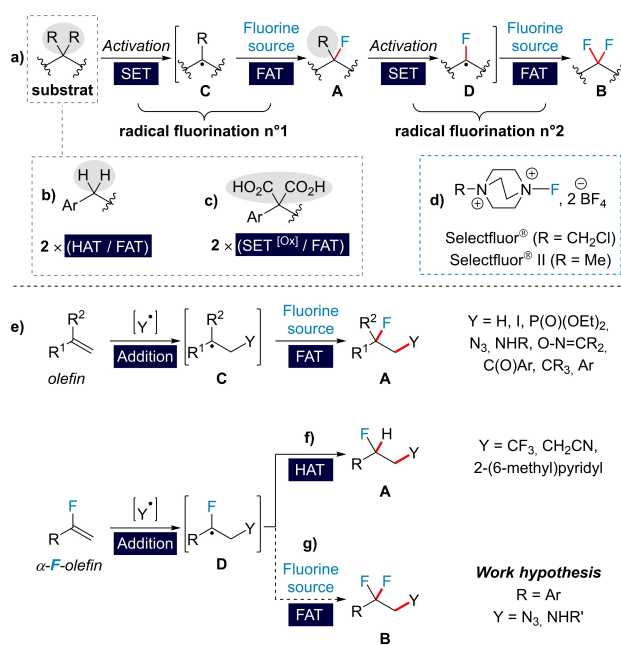
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protected β -aryl- β,β -difluoroamines have been synthesized by the addition of α -aryl- α,α -difluorohexamethylborazine adduct to tosyl-protected aryl imines (Scheme 1c).^[7] Although this method represents a useful route towards substituted β -aryl- β,β -difluoroamines, it requires the prior preparation of the ArCF₂ reagents and final removal of the tosyl group in order to access the free amine. Alternatively, the reduction of β -aryl- β,β -difluoroazides under standard hydrogenolysis or Staudinger conditions represents an attractive strategy towards β -aryl- β,β -difluoroamines (Scheme 1d). Indeed, besides being amine precursors, azides are used in a wide range of transformations towards nitrogen-containing molecules,^[8] in bioorthogonal ligation reactions and are also found in biologically active molecules.^[9,10] Traditionally, the synthesis of β -aryl- β,β -difluoroazides is accomplished by S_N2 type reactions between sodium azide and a difluorinated precursor containing a leaving group (Scheme 1e).^[11] More recently, β -aryl- β,β -difluoroazides have also been prepared from α -azidostyrene derivatives via a 1,2-azide migration/difluorination reaction sequence (Scheme 1f).^[12] The latter is promoted by hypervalent iodine reagents in the presence pyridine.HF complex. Although this method proved to be efficient with electron-poor α -azidostyrenes, the use of electron-rich substrates led predominantly to β -aryl- α,α -difluoroazides via a 1,2-aryl migration/difluorination reaction sequence instead. Given the importance of the β -aryl- β,β -difluoroamino motif in medicinal chemistry, the development of new approaches towards β -aryl- β,β -difluoroamine/azide compounds remains desirable.

Radical fluorination (RF) reactions, which have become over the years a valuable synthetic tool to access mono-fluoro alkyl derivatives **A**,^[13] have also been found, to a lesser extent, suitable for the synthesis of CF₂-containing molecules **B** (Scheme 2a).^[14] In this case, the construction of the CF₂ unit relies on two successive RF reactions; each of them involving the same Single-Electron Transfer (SET)/Fluorine Atom Transfer (FAT) sequence. More specifically, such an approach has been used to access the Ar-CF₂ motif as illustrated by the double RF of benzylic C(sp³)-H (Scheme 2b),^[14a,c,d] and C(sp³)-CO₂H (Scheme 2c) bonds.^[14f] Thus, the initial SET event (respectively, Hydrogen Atom transfer (HAT) and SET^[OX]) of each RF reaction, generates the alkyl radical **C** and the mono-fluoro alkyl radical **D**. In the presence of Selectfluor[®] reagents as a radicophilic fluorine source (Scheme 2d), each of these radicals, respectively participates in a FAT step to form both of the C(sp³)-F bonds. Although these double RF reactions have their own limitations (e.g. selectivity, availability of starting material, efficiency, etc.), overall, they demonstrate that the mono-fluoro alkyl radical **D** is a promising intermediate towards CF₂-containing molecules. In this context, we were wondering: a) Could a new RF transformation towards CF₂-molecules, relying on intermediate **D**, be alternatively developed to the double RF strategy? b) Could such a method be exploited to access β -aryl- β,β -difluoroamines and/or β -aryl- β,β -difluoroazides aforementioned?

Among the RF reactions allowing the synthesis of mono-fluoro alkyl derivatives **A**, the radical addition/fluorination reactions of olefins are of particular interest (Scheme 2e). Indeed, the addition of a radical Y^{*} (e.g. Y = H,^[15] I,^[16] P-,^[17] N-,^[18]

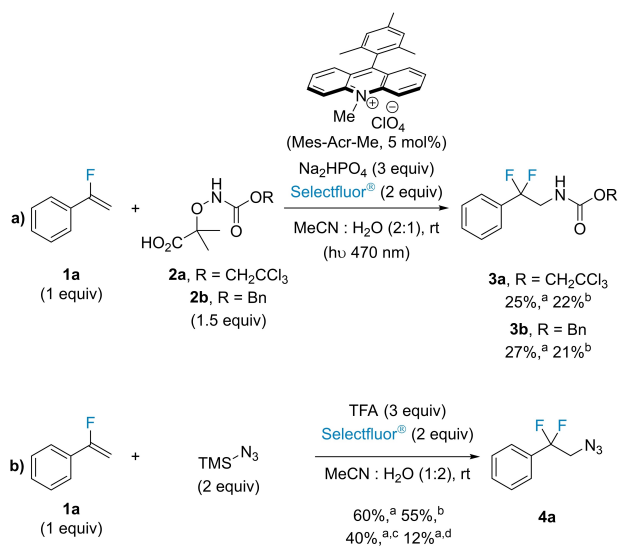


Scheme 2. a) General concept of double RF reactions towards CF₂-containing molecules; b, c) Previous works for the synthesis of the Ar-CF₂ motif based on double RF reactions; d) Examples of radicophilic N-F reagents; e) Radical addition/fluorination reactions towards mono-fluoro alkyl derivatives **A** (previous works); f) Radical hydrofunctionalization reactions of α -fluoroolefins towards mono-fluoro alkyl derivatives **A** (previous works); g) Radical addition/fluorination reactions of α -fluoroolefins towards CF₂-containing molecules **B** and its application towards the β -aryl- β,β -difluoroamino motif (work hypothesis).

O-,^[19] or C-centered radicals)^[20] to an alkene substrate and subsequent FAT between the radical adduct **C** and a fluorine source allows the formation of two bonds in one step, respectively C(sp³)-Y and C(sp³)-F. Alternatively, rare examples of radical hydrofunctionalization reactions of non-activated α -fluoroolefins (R \neq EWG) have also been reported for the synthesis of mono-fluoro alkyl derivatives **A** (Scheme 2f).^[21] In this particular case, the mono-fluoro alkyl radical **D** is generated upon the radical addition of Y^{*}, and a subsequent HAT step gives **A**. By merging the concepts of the aforementioned studies, it occurred to us that the use of α -fluoroolefins^[22] in a radical addition/fluorination transformation could potentially deliver the targeted CF₂-containing molecule **B** (Scheme 2g). More specifically, the development of a radical addition/fluorination of α -fluoroolefins (R = Ar) with N-centered radicals would provide a readily access to the β -aryl- β,β -difluoroamino motif. Herein, we report our finding regarding the proposed work hypothesis.

Results and Discussion

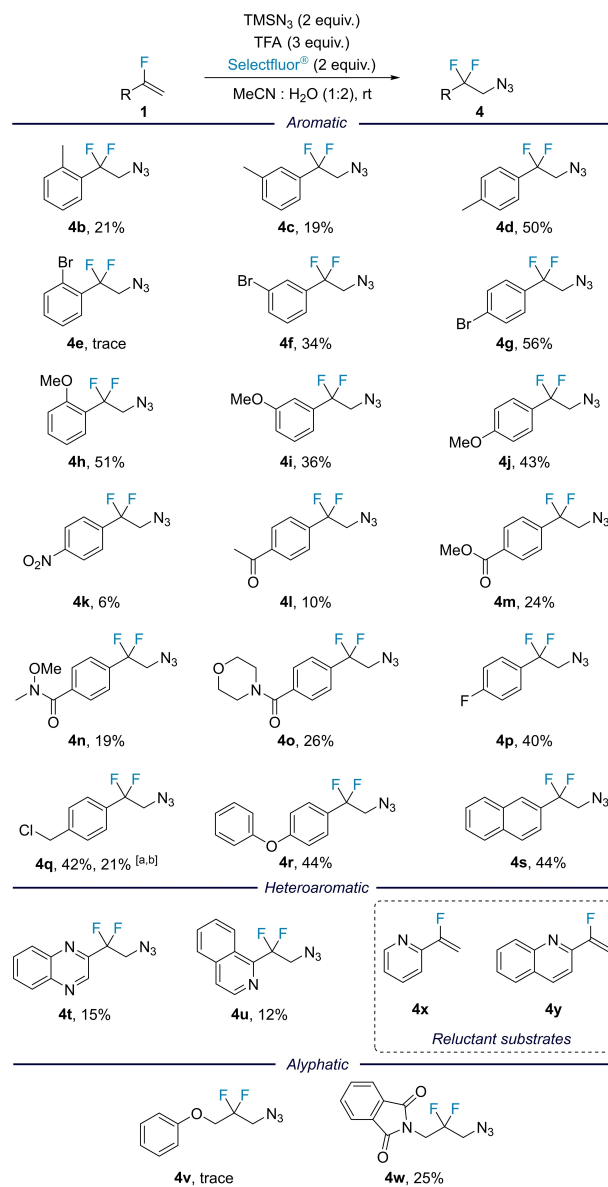
To initiate our study, α -fluorostyrene **1a** was chosen as a model substrate and was first submitted to the conditions of radical amidofluorination of alkenes previously reported by Studer's group (Scheme 3a).^[18d] Both amidyl radical precursors **2a** and **2b** were tested in the presence of the organic photocatalyst



Scheme 3. Proof of concept and preliminary results towards the β -aryl- β,β -difluoroamino/azido motifs. [a] Yield determined by ^{19}F NMR analysis using 3,5-bis(trifluoromethyl)bromobenzene as internal standard. [b] Isolated yield. [c] Reaction run without TFA. [d] Reaction run in acetonitrile only.

Mes-Acr-Me and Selectfluor[®]. In each case, full conversion was reached after 16 h of reaction. ^{19}F NMR analysis of the crude reaction mixtures indicated the formation of the desired products **3a** and **3b** in low yields (25% and 27% NMR yields, respectively) alongside traces of several uncharacterized fluorinated side-products. Although the protected β -aryl- β,β -difluoro-carbamates **3a** and **3b** were respectively isolated only in 22% and 21% yields, these results validated our work hypothesis. Next, we turned our attention to the radical azidofluorination protocol reported by Li's group (Scheme 3b).^[18b] In this case, α -fluorostyrene **1a** was treated with trimethylsilyl azide (TMSN₃) in the presence of trifluoroacetic acid (TFA) and Selectfluor[®]. After 16 h of reaction, ^{19}F NMR analysis of an aliquot indicated full conversion of the substrate. In this case, ^{19}F NMR analysis of the crude reaction mixture was cleaner than those obtained previously from the amidofluorination transformations, and showed the formation of the desired β -aryl- β,β -difluoroazide **4a** in 60% NMR yield. The latter was further isolated in 55% yield. A brief survey of the reaction conditions indicated that both the absence of TFA and water is deleterious to the efficiency of the transformation (**4a**, 40% and 12% NMR yields, respectively).

Without further optimization, we decided to investigate the scope and limitations the radical azidofluorination reaction with various α -fluorostyrene derivatives **1b–y** (Scheme 4). First, the reaction was examined with α -fluorostyrenes **1b–d** possessing a methyl substituent at different positions of the aromatic ring. The efficiency of the reaction dropped significantly with *o*-methyl and *m*-methyl substrates as illustrated by the isolation of difluoroazides **4b** and **4c** in 21% and 19% yields, respectively. However, substitution at the *para* position delivered the difluoroazide **4d** in moderate yield (50%). A similar trend was observed when the aryl group of the α -fluorostyrene was substituted by a bromine atom (**1e–g**). In this case, only



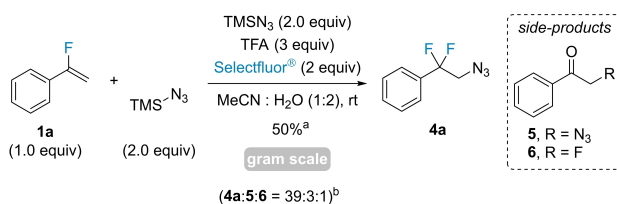
Scheme 4. Scope of the azidofluorination reaction. Isolated Yields. [a] Reaction run in a mixture of AcOH:H₂O (1:2). [b] Yield determined by ^{19}F NMR analysis using 3,5-bis(trifluoromethyl)bromobenzene as an internal standard.

traces of the *o*-bromo-difluoroazide **4e** could be detected by ^{19}F NMR analysis of the crude reaction mixture, while *m*-bromo- and *p*-bromo-difluoroazides **4f** and **4g** were respectively isolated in 34% and 56% yields. The introduction of electron-donating methoxy groups on the aromatic ring of the α -fluorostyrene (**1h–j**) was next investigated. In this case, the difluoroazides **4h–j** were isolated in moderate yields (36–51%). Then, the reaction was applied to a range of *para*-substituted α -fluorostyrenes (**1k–r**). Substrates possessing either a nitro or a methyl ketone group provided the corresponding difluoroazides **4k** and **4l** in low yields (6% and 10%). The presence of an electronic-withdrawing group such as an ester (**1m**) or an amide (**1n**, **1o**) delivered the corresponding difluoroazides **4m–**

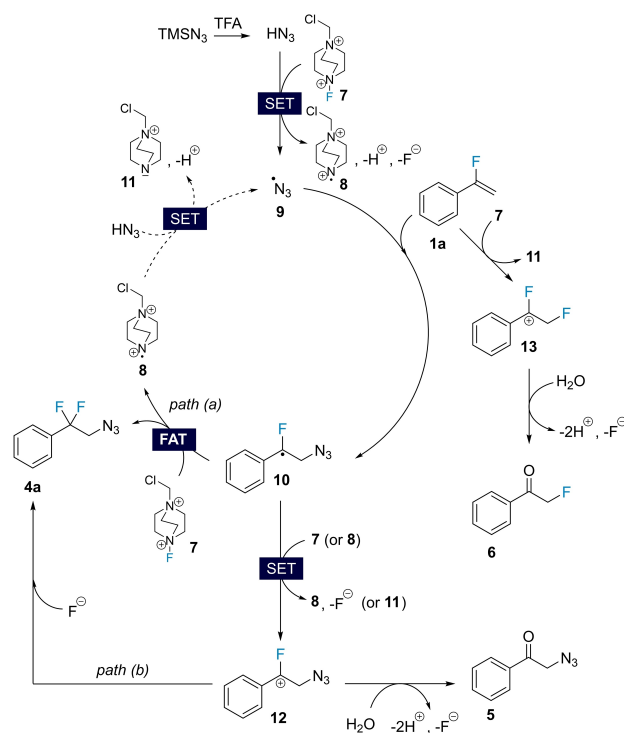
o in low yields (24%, 19% and 26%, respectively). The aryl group of the α -fluorostyrene substrate could also be substituted by a Fluorine atom or a chloromethyl group at the *para* position. In these cases, the anticipated difluoroazides **4p** and **4q** were obtained in moderate yields (40% and 42%, respectively). In the case of **4q**, an attempt was made to perform the reaction in a mixture of AcOH:H₂O (1:2) as solvent but no improvement was observed (21%, ¹⁹F NMR yield). The α -fluorostyrene **1r**, featuring a biarylether motif and the naphthyl derived α -fluorostyrene **1s** were also found suitable for the transformation. In these cases, the corresponding difluoroazides **4r** and **4s** were both obtained in 44% yields. In addition, α -fluoroolefins **1t** and **1u**, respectively derived from isoquinoline and quinoxaline, delivered the expected β -heteroaryl- β,β -difluoroazides **4t** and **4u** albeit in low isolated yields (15% and 12%, respectively). Other α -fluoroolefins, derived from pyridine (**1x**) and quinoline (**1y**), were also tested. In both cases, the corresponding β -heteroaryl- β,β -difluoroazides could not be detected by ¹⁹F NMR analysis of the crude reaction mixtures. Finally, aliphatic α -fluoroolefins **1v** and **1w** were also submitted to the reaction conditions. In both cases, full conversion was observed after a prolonged time of reaction (64 h). Only traces of β -alkyl- β,β -difluoroazide **4v** were observed by ¹⁹F NMR analysis of the crude reaction mixture and β,β -difluoroazide **4w** was isolated in low yield (25%).

Furthermore, the reaction was conducted on gram-scale from **1a** and the expected product **4a** was isolated in 50% yield (Scheme 5). In this case, careful purification allowed us to identify traces of α -azido- and α -fluoro-ketones **5** and **6** as side-products of the reaction (**4a**:**5**:**6** = 39:3:1 ratio, determined by ¹H NMR analysis of the crude reaction mixture).

Based on these observations, additional information can be provided regarding the mechanism previously proposed by Li (Scheme 6).^[18b] Initially, the transformation would start with a SET event (stepwise electron transfer/deprotonation pathway or concerted proton-coupled electron-transfer pathway) between the generated in situ hydrozoic acid (HN₃) and Selectfluor® **7** to generate the N-radical dication **8**, a fluorine anion and the azidyl radical species **9**. Subsequent addition of the latter to the α -fluorostyrene **1a** generates the radical adduct **10**. At this stage, a fluorine atom transfer between **10** and Selectfluor® **7** delivers the desired difluoroazide product **4a** (path a) and **8**. Although the fate of **8** remains unclear, the latter could act as a single electron oxidizing agent and react, like Selectfluor® **7**, with HN₃ to generate **9** and reduced Selectfluor® **11**.



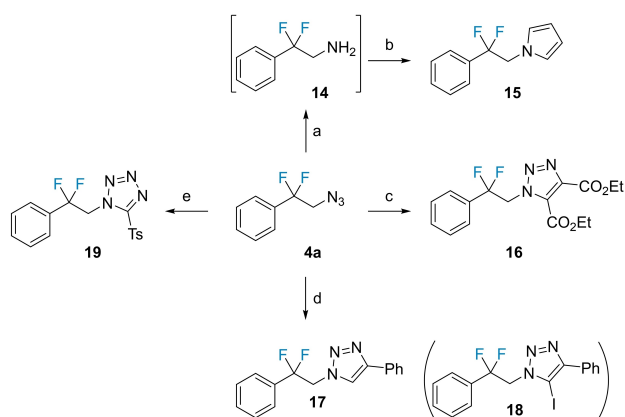
Scheme 5. [a] Isolated yield. [b] Ratio determined by ¹H NMR analysis of the crude reaction mixture.



Scheme 6. Proposed mechanism for the formation of **4a**, **5** and **6**.

Alternatively, the radical adduct **10** could also be oxidized via a SET event by reacting with Selectfluor® **7** (or **8**) to generate **8** and a fluorine anion (or **11**) and the carbocation **12**. The latter could either undergo a nucleophilic addition of a fluorine anion to deliver the difluoroazide product **4a** (path b), or react with water to generate the α -azido-ketone **5** after elimination of protons and a fluorine anion. To probe the radical nature of the proposed mechanism, we carried out an experiment on our model substrate **1a** in the presence of TEMPO (2.0 equiv.) as radical scavenger. In this case, neither the desired product **4a** or the TEMPO adduct derived from **10** could be detected. Instead, the α -azido-ketone **5** was formed as major product of the reaction (see Supporting Information). The presence of TEMPO seems to have no effects on the formation of the radical azide **9** but clearly inhibits the FAT step between Selectfluor® **7** and the radical intermediate **10**. In the same time, the presence of TEMPO appears to promote the oxidation of **10** into **12** resulting in the formation of **5**. Overall, given that fluorine anion is a weak nucleophile in aqueous media due to its large solvation free energy (439 kJ/mol),^[23] we believe that the formation of **4a** occurs predominantly via a radical process (path a). Regarding the formation of the α -fluoro-ketone **6**, the latter can be explained by the electrophilic addition of Selectfluor® **7** to the α -fluorostyrene **1a**. In this case, the resultant carbocation **13** reacts with water and subsequent elimination of protons and a fluorine anion delivers **6**.^[24]

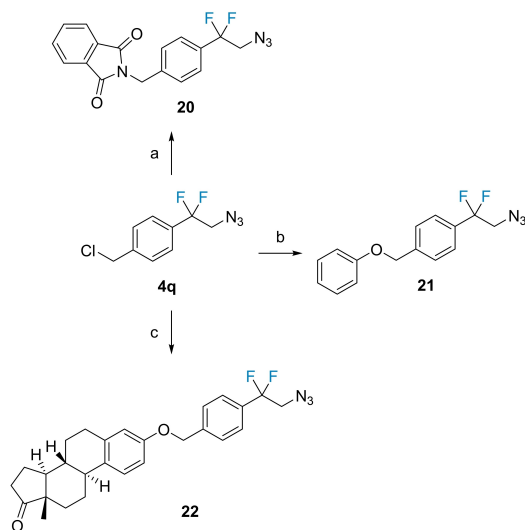
Taking advantage of the azide functional group, we then undertake further synthetic transformations of the latter to access diverse *gem*-difluoro containing heterocycles (Scheme 7). For instance, the reduction of the β -aryl- β,β -difluoroazide **4a**



Scheme 7. Preparation of CF_2 -containing heterocycles from β -aryl- β,β -difluoroazide **4a**. (a) PPh_3 , THF:H₂O (10:1); (b) 2,5-dimethoxy-tetrahydrofuran, NaOAc, AcOH:H₂O:DCE (0.25:1:1), 65% over two steps; (c) diethyl acetylenedicarboxylate, H₂O, 57%; (d) CuI (20 mol%), phenylacetylene, **17** (68%) and **18** (14%); (e) TsCN, neat, 88%. THF = tetrahydrofurane, DCE = dichloroethane.

under Staudinger's conditions furnished the corresponding amine **14** (not further purified), and subsequent treatment with 2,5-dimethoxy-tetrahydrofuran provided the pyrrole **15** in 65% yield over two steps. Furthermore, **4a** was also submitted to various standard 1,3-dipolar cycloaddition protocols. Thus, the treatment of **4a** with diethyl acetylenedicarboxylate delivered the triazol **16** in 57% yield. In the case of Cu-catalyzed azide-alkyne cycloaddition (CuAAC) with phenylacetylene, the expected triazol **17** was isolated in 68% yield, alongside the iodotriazol **18** (14% yield). Finally, the reaction of **4a** with *p*-toluenesulfonyl cyanide gave the tetrazol **19** in 88% yield.

Finally, we briefly examined $\text{S}_{\text{N}}2$ -type reactions of **4q** with various nucleophiles in order to access more elaborated β -aryl- β,β -difluoroazides (Scheme 8). For instance, the reaction of **4q**



Scheme 8. $\text{S}_{\text{N}}2$ -type reactions of β -aryl- β,β -difluoro azide **4q** with various nucleophiles. (a) Potassium phthalimide, DMF, 71%; (b) Phenol, NaH, DMF, 64%; (c) Estrone, NaH, DMF, 93%; DMF = dimethylformamide.

with phthalimide anion provided **20** in 71% yield. Simple phenolate and estrone-derived phenolate were also found to react with **4q** to deliver the anticipated products **21** and **22**, respectively isolated in 64% and 93% yield.

Conclusion

In summary, we have demonstrated that α -fluoroolefins could undergo a radical azidofluorination reaction to deliver the corresponding β -aryl- β,β -difluoroazide derivatives. These compounds could be employed in useful post-functionalization reactions towards heterocycles either by taking advantage of the azide functional group as an amine precursor or as a 1,3-dipole. Overall, these results contribute to expand the repertoire of methods allowing access to the β -aryl- β,β -difluoroamino motif and also highlight the synthetic potential of α -fluoroolefins in radical addition/functionalization reactions towards CF_2 -containing molecules. Further studies to probe this work hypothesis are currently underway and will be reported in due course.

Experimental Section

General procedure for the synthesis of β,β -difluoroazides **4**

To solution of α -fluoroolefin **1** (1.00 equiv.) and Selectfluor® (2.0 equiv.) in MeCN:H₂O (1:2, 0.11 M, previously degassed by sparging with argon for 10 min) were added successively at RT and under Argon atmosphere TFA (3.00 equiv.) and TMSN_3 (2.00 equiv.). The reaction vessel was sealed and stirred at 25 °C for 16 h. After this time, the reaction was diluted with CH_2Cl_2 and H₂O. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 . The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give the corresponding β,β -difluoroazides **4**.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Fluorine · α -Fluoroolefins · Geminal difluoromethylene group · Radical fluorination · Radical reaction

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