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## COMMUNICATION

Regioselective synthesis of 4-fluoro-1,5-disubstituted-1,2,3-triazoles from synthetic surrogates of  $\alpha$ -fluoroalkynesReceived 00th January 20xx,  
Accepted 00th January 20xxSampad Jana,<sup>\*a</sup> Sweta Adhikari<sup>a</sup> Michael R. Cox,<sup>a</sup> and Sudeshna Roy<sup>\*a</sup>

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$\alpha$ -Fluoroalkynes are elusive molecules due to their instability and inaccessibility. Here, we show that  $\alpha$ -fluoronitroalkenes can serve as synthetic surrogates of  $\alpha$ -fluoroalkynes in [3+2] cycloaddition reactions with organic azides facilitated by a catalytic amount of trifluoroacetic acid (TFA). This work provides the first regioselective method to access 4-fluoro-1,5-disubstituted-1,2,3-triazoles.

The past couple of decades saw a surge of fluorinated heterocycles in pharmaceuticals<sup>1</sup> and agrochemicals,<sup>1, 2</sup> materials,<sup>3</sup> and molecular imaging with positron emission tomography (PET).<sup>4</sup> Yet, despite the recent advances, the preparation of fluorinated heterocycles is still considered challenging due to the lack of practical, general, and regioselective methods.<sup>5</sup> Given the relevance of 1,2,3-triazoles in biomedical research<sup>6</sup> and medicinal chemistry as a prevalent scaffold and an amide bioisostere,<sup>7</sup> surprisingly, only a handful of syntheses of fluorinated triazoles are reported in the literature.<sup>8</sup> Pioneering work by Fokin<sup>9</sup> and Chu<sup>10</sup> has significantly advanced the field, enabling the synthesis of 5-fluoro-1,4-disubstituted-1,2,3-triazoles (Figure 1C). However, the corresponding 1,5-regioisomer is conspicuously absent in the literature. Herein, we address this critical gap in the literature by developing the very first synthesis of 4-fluoro-1,5-disubstituted-1,2,3-triazoles with complete regiocontrol (Figure 1D).

Haloalkynes serve as rich building blocks for numerous chemical transformations, particularly 1,3-dipolar cycloaddition reactions enabling various halogenated heterocyclic systems (Figure 1A).<sup>11–13</sup> While synthesis of iodo-, bromo-, and chloroalkynes have been thoroughly investigated,<sup>11–13</sup> fluoroalkynes remain elusive due to their instability.  $\alpha$ -Fluoroalkynes are notorious for undergoing spontaneous oligomerization under thermal or metal-catalyzed conditions to produce polysubstituted benzene derivatives (Figure 1B)<sup>14, 15</sup> or polymers.<sup>16</sup> Synthetic surrogates of  $\alpha$ -fluoroalkynes would be particularly desirable to assemble fluorinated heterocycles via

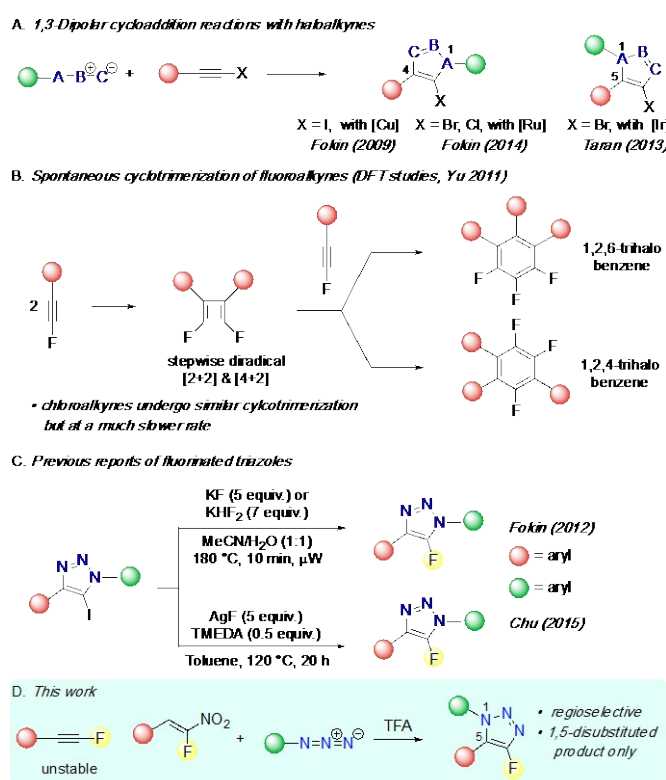


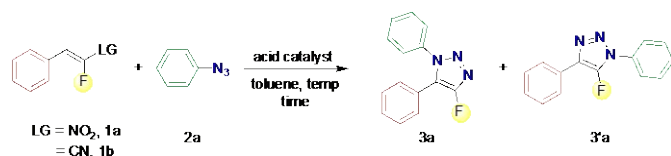
Figure 1. Haloalkynes in 1,3-dipolar cycloaddition reaction.

1,3-dipolar cycloaddition reactions. Herein, we establish that  $\alpha$ -fluoronitroalkenes could be effectively used as surrogates of  $\alpha$ -fluoroalkynes in cycloaddition reactions with organic azides to construct 4-fluoro-1,5-disubstituted-1,2,3-triazoles (Figure 1D). Consequently,  $\alpha$ -fluoronitroalkenes can be regarded as resourceful fluorinated building blocks to synthesize fluorinated molecules that are increasingly growing in all areas of chemistry.<sup>17</sup>

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Both, 1,4- and 1,5-substituted-1,2,3-triazoles, are often used as



**Table 1. Optimization of Reaction Conditions<sup>[a]</sup>**

entry	catalyst	equiv.	LG	temp (°C)	time (h)	yield (%) <sup>[b]</sup>	
						<b>3a</b>	<b>3'a</b>
1	-		NO <sub>2</sub>	100	48	10	3
2	Cu(OTf) <sub>2</sub>	0.2	NO <sub>2</sub>	100	24	19	n.o.
3	Zn(OTf) <sub>2</sub>	0.2	NO <sub>2</sub>	100	24	16	n.o.
4	Sc(OTf) <sub>3</sub>	0.2	NO <sub>2</sub>	100	24	25	n.o.
5	Yb(OTf) <sub>3</sub>	0.2	NO <sub>2</sub>	100	24	11	n.o.
6	Fe(OTf) <sub>3</sub>	0.2	NO <sub>2</sub>	100	24	8	n.o.
7	Ce(OTf) <sub>3</sub>	0.2	NO <sub>2</sub>	100	24	22	n.o.
8	BF <sub>3</sub> •(OEt) <sub>2</sub>	0.3	NO <sub>2</sub>	100	24	28	8
9	AcOH	0.3	NO <sub>2</sub>	100	48	42	10
10	PTSA	0.5	NO <sub>2</sub>	100	48	31	<5
11	10-CSA	0.5	NO <sub>2</sub>	100	48	36	<5
12	TFA	0.3	NO <sub>2</sub>	100	48	60	n.o.
13	TFA	0.5	NO <sub>2</sub>	110	48	74	n.o.
14	TFA	0.8	NO <sub>2</sub>	100	48	69	n.o.
15	H <sub>3</sub> PO <sub>4</sub>	0.5	NO <sub>2</sub>	110	48	45	7
16	MeSO <sub>3</sub> H	0.5	NO <sub>2</sub>	110	48	68	n.o.
17	NH <sub>2</sub> SO <sub>3</sub>	0.5	NO <sub>2</sub>	110	48	20	<5
18	TFA	0.5	CN	110	72	n.o.	n.o.

[a] Standard reaction conditions: 1 equiv. of fluoronitroalkene **1a** (0.15 mmol), 2 equiv. of phenyl azide **2a** (0.30 mmol), and 0.5 equiv. of TFA were mixed in 2M toluene and heated at 110 °C. [b] Isolated yield. PTSA = *p*-toluenesulfonic acid, TFA = trifluoroacetic acid 10-CSA = 10-camphorsulfonic acid.

bioisosteres of *trans*- and *cis*-amides respectively,<sup>7</sup> in addition to their biological and biomedical applications.<sup>18</sup> Hence, regioselective routes to synthesize 1,4- and 1,5-disubstituted-1,2,3-triazoles independently are desirable. This report provides a highly regioselective and versatile method for the preparation of aryl, alkyl, and heteroaromatic containing fluorinated-1,5-disubstituted-1,2,3-triazoles. This method is complementary to the prior methods reported by Fokin and Chu for obtaining 5-fluoro-1,4-disubstituted-1,2,3-triazoles (Figure 1C).<sup>9, 10</sup>

We hypothesized that alkenes with leaving groups such as NO<sub>2</sub> and CN and with a fluorine atom at the 1-position could be used as synthetic equivalents of  $\alpha$ -fluoroalkynes in [3+2] cycloaddition reactions with organic azides.<sup>19</sup> Nitroalkenes, due to their high reactivity, has been widely used in 1,3-dipolar cycloaddition chemistry, especially with sodium azides for the generation of NH-1,2,3-triazoles.<sup>19-24</sup> Although the regioselectivity of the cycloaddition reaction of nitroalkenes with azides is well-known, the incorporation of fluorine can have an influence on chemical reactivity.

Initially, we selected  $\alpha$ -fluoronitroalkenes to investigate the intermolecular [3+2] cycloaddition reaction with organic azides to afford fluoro-1,2,3-triazoles.  $\alpha$ -Fluoronitroalkenes were synthesized in two steps starting from the corresponding aldehydes, tribromofluoromethane, and triphenylphosphine in refluxing THF to afford the  $\alpha$ -fluorobromoalkenes.<sup>25</sup> A

subsequent radical-based nitration-debromination using ferric nitrate nonahydrate gave the  $\alpha$ -fluoronitroalkenes.<sup>26</sup> Alternatively, a one-pot 2-step protocol can be used to synthesize  $\alpha$ -fluoronitroalkenes without having to isolate  $\alpha$ -fluorobromoalkenes, which makes it operationally simple. Unfortunately, the radical-based nitration-debromination step was unreactive towards alkyl  $\alpha$ -fluorobromoalkenes and failed to provide alkyl  $\alpha$ -fluoronitroalkenes.

We observed that 1 equiv. of  $\alpha$ -fluoronitroalkene **1a** and 2 equiv. of phenyl azide **2a** when heated at 100 °C in toluene resulted in the formation of a mixture of regioisomers, 1,5-disubstituted- and 1,4-disubstituted-fluoro-1,2,3-triazoles, in 5:2 (**3a**: **3'a**) ratio along with unreacted starting materials (entry 1, Table 1). The ratio of the regioisomeric products **3a**: **3'a** was determined by <sup>19</sup>F NMR (the <sup>19</sup>F NMR values for **3a** and **3'a** are  $\delta$  -145.1 and -150.4 ppm respectively). We observed that the reaction was extremely sluggish at room temperature. At elevated temperatures (100–110 °C), an excess of phenyl azide (2 equiv.) was required due to the decomposition of organic azides at higher temperatures.

Taking a clue from the previous reports of nitroalkenes in [3+2] cycloaddition reactions, we decided to screen different Lewis acids.<sup>21, 24, 26-28</sup> With Lewis acids Cu(OTf)<sub>2</sub>, Zn(OTf)<sub>2</sub>, Sc(OTf)<sub>3</sub>, Yb(OTf)<sub>3</sub>, Fe(OTf)<sub>3</sub>, Ce(OTf)<sub>3</sub> (entries 2–7), we observed a regioselective formation of the 1,5-product **3a**, however in 8–22% yields. The use of BF<sub>3</sub>•(OEt)<sub>2</sub> led to a slight increase in the yield of **3a** to 28% but also formed **3'a** in 8% yield (entry 8). A decent increase in yield of **3a** up to 42% along with 10% of **3'a** was observed when 30 mol% of AcOH was used as a catalyst. This result led us to screen other Brønsted acids, such as MeSO<sub>3</sub>H, H<sub>3</sub>PO<sub>4</sub>, *p*-TSA•H<sub>2</sub>O, and CF<sub>3</sub>CO<sub>2</sub>H (TFA) (entries 10–17) with our standard substrates. Among the Brønsted acids, TFA gave the best results with the regioselective formation of 1,5-regioisomer **3a** (entries 12–14). A gradual increase in yield was observed when the amount of TFA was increased from 30 mol% to 50 mol%, and the temperature raised from 100 to 110 °C (entry 12 vs. 13). Increasing the amount of TFA to 80% led to a slight decrease in yield (entry 14). However, changing the solvents to DMF, DMSO, DCE, 1,4-dioxane, ACN, and THF resulted in lower yields. Overall, we found **3a** to be either the only product or the predominant regioisomer and **3'a** as the minor regioisomer. A reversed ratio with **3'a** as the predominant regioisomer was never observed (in <sup>19</sup>F NMR).

Our optimized condition resulted in the regioselective formation of 1,5-diaryl-4-fluoro-1,2,3-triazole **3a** in 74% yield. The optimum condition comprised heating 1 equiv. of  $\alpha$ -fluoronitroalkene **1a** (0.15 mmol) and 2 equiv. of phenyl azide **2a** (0.3 mmol with 50 mol% of TFA (0.075 mmol) in 2M toluene at 110 °C for 48 h. Unfortunately, (Z)-2-fluoro-3-phenylacrylonitrile under the same conditions did not lead to any product when treated with organic azides and ensued in the recovery of unreacted starting materials (entry 18). For a complete optimization list with all the conditions that were screened, see supporting information.

With the optimized condition in hand, we first explored the substrate scope around aryl azides (Figure 2). The <sup>19</sup>F NMR chemical shifts of the synthesized 4-fluoro-1,5-disubstituted-

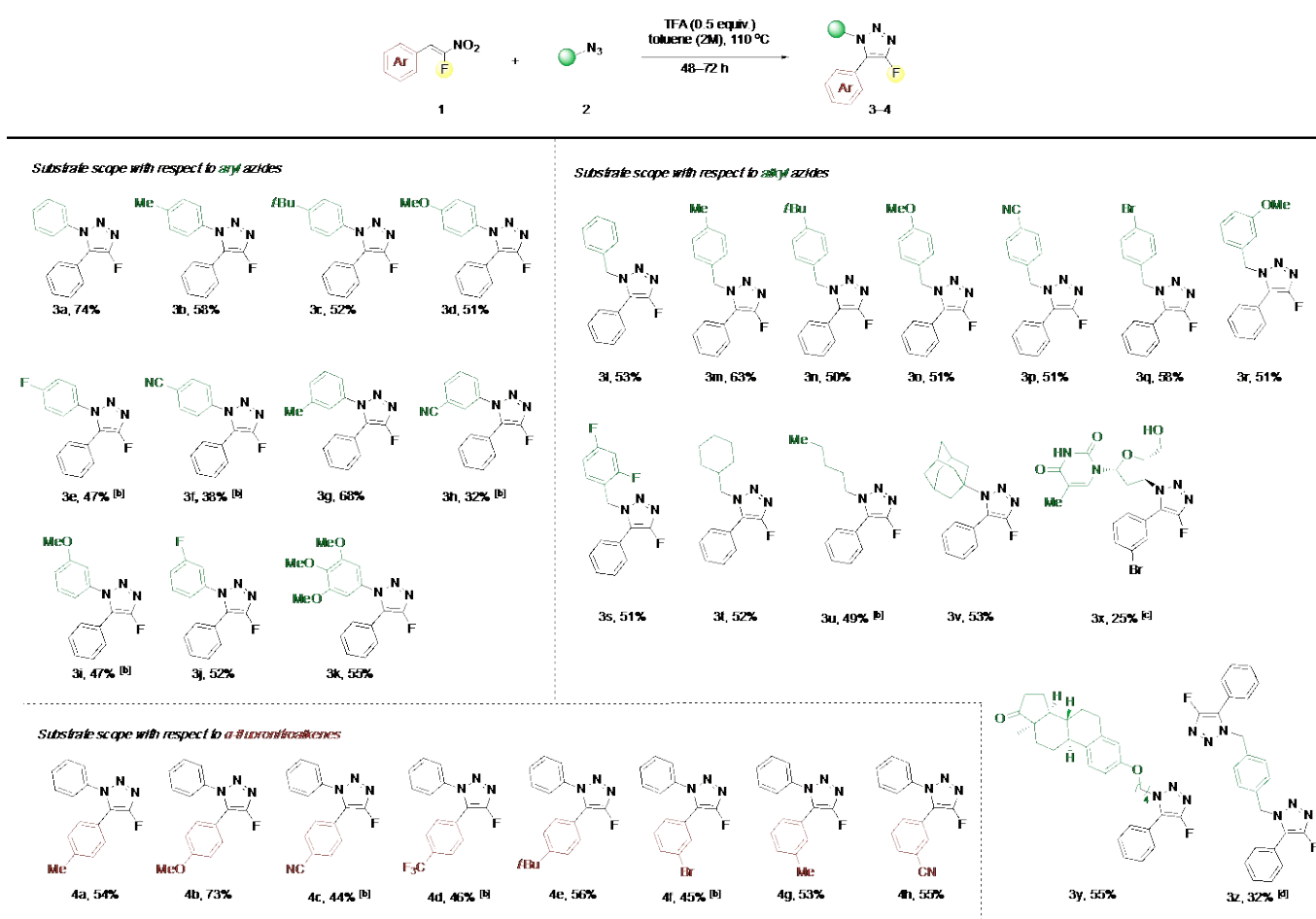
1,2,3-triazoles range from -143.66 to -146.73 ppm. As shown in Figure 2, *para*-substituted phenyl azides with electron-donating groups such as methyl (**3b**), *t*-butyl (**3c**), and methoxy (**3d**) furnished the desired products in 51–58% yields. However, the yields dropped with electron-withdrawing groups such as fluoro (**3e**), and cyano (**3f**) at the *para* position and cyano (**3h**) and methoxy (**3i**) at the *meta* position. In these cases, unreacted starting materials were observed in  $^{19}\text{F}$  NMR spectra and TLCs. A triazole analogue **3k** of the natural product combretastatin A-4 that has anti-cancer properties was prepared in 55% yield using this method. We observed that the  $\alpha$ -fluoronitroalkenes gave poor conversions and lower yields of [3+2] cycloaddition products with organic azides in comparison to the nitroalkenes that could be attributed to attenuated reactivity of the  $\alpha$ -fluoronitroalkenes.

Next, the scope of the reaction for benzyl and alkyl azides were examined (Figure 2). To our delight, an array of *para*- and *meta*-substituted benzyl azides were found to be amenable to the optimized conditions. Both, electron-donating groups such as methyl (**3m**), *t*-butyl (**3n**), methoxy (**3o**) and electron-withdrawing groups such as cyano (**3p**), bromo (**3q**) at the *para*-position of benzyl azides were well tolerated and afforded the corresponding regioselective products in 50–63%. The

extension of this reaction to aliphatic azides (**3t–3y**) resulted in the formation of corresponding 4-fluoro-1,2,3-triazoles in 25–55% yields.

The scope of the reaction was further examined with the substitution patterns on  $\alpha$ -fluoronitrostyrenes (Figure 2). Overall, both electron-donating and -withdrawing groups at the *para*-position in  $\alpha$ -fluoronitrostyrenes exhibited moderate to good reactivity. The substrates with electron-donating groups methyl (**4a**) and methoxy (**4b**) afforded better yields (54–73%) compared to the substrates containing electron-withdrawing groups such as cyano (**4c**) and trifluoromethyl (**4d**) (44–46%). The substituents at the *meta* position afforded low yields (45–56%) irrespective of the electron-donating and withdrawing group (**4e–4h**).

Based on the previous literature reports on cycloaddition of nitroalkenes with 1,3-dipoles,<sup>23, 29</sup> we propose a similar mechanism outlined in Figure 3. Initially, regioselective [3+2] cycloaddition takes place between  $\alpha$ -fluoronitroalkene **1** and organic azide **2** to form a triazoline intermediate **3-int**. For the initial cycloaddition step, both a concerted or a two-step mechanism are possible. Regioselectivity is imparted by the strongly electron-withdrawing nitro group on the dipolarophile **1** that is further activated by TFA, thereby lowering the lowest



[a] Reaction conditions: **1** (1 equiv.), **2** (2 equiv.), toluene (2M), 110 °C, 48–72 h. Isolated yields are reported. [b] 42–65% of unreacted  $\alpha$ -fluoronitroalkenes were observed in  $^{19}\text{F}$  NMR. [c] The starting materials (SM) were fairly unreactive, requiring 120 h of heating at 110 °C. [d] Other side-products were observed. Note: Substrates with lower yields are a result of poor conversion and low reactivity of the  $\alpha$ -fluoronitroalkenes with organic azides.

Figure 2. Substrate Scope.<sup>[a]</sup>



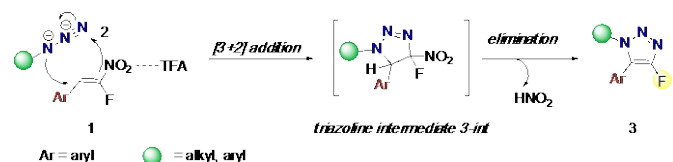


Figure 3. A plausible mechanism.

unoccupied molecular orbital (LUMO) and making the  $\beta$ -carbon most electrophilic.<sup>22, 23</sup> Without TFA, a mixture of 1,5- and 1,4-regioisomers are obtained in a 5:2 ratio, as determined by  $^{19}\text{F}$  NMR. The 1,3-dipolar organic azide attacks the partially positively charged  $\beta$ -carbon of the  $\alpha$ -fluoronitroalkene to form the triazoline intermediate **3-int**—a concomitant elimination of  $\text{HNO}_2$  results in the regioselective formation of the desired 4-fluoro-1,5-disubstituted-1,2,3-triazoles product **3**. An attempt to probe the triazoline intermediate **3-int** via  $^{19}\text{F}$  NMR in deuterated-toluene at 90 °C was unsuccessful—this suggests that the transient intermediate rapidly eliminates  $\text{HNO}_2$  to form the triazole product.

In connection with our ongoing drug discovery efforts, we used principal component analysis to assess the chemical space and physicochemical properties of our fluorotriazole library. These analyses show that the fluorinated triazoles occupy a slight to near-complete overlapping chemical space as the reference set of commercial drugs and pharmaceutical agents and have a distinct set of physicochemical properties. More details are included in the supporting information.

In conclusion, we have shown that the  $\alpha$ -fluoronitroalkenes could be effectively used as synthetic surrogates of  $\alpha$ -fluoroalkynes in a regioselective [3 + 2] cycloaddition chemistry with organic azides. The 1,5-disubstituted-4-fluorotriazoles are conspicuously absent in the literature due to the lack of methods for their preparation. In this report, we describe the very first regioselective method to access 4-fluoro-1,5-disubstituted-1,2,3-triazoles that will be widely applicable in pharmaceutical, biomedical, agrichemical, and materials sciences. A relatively broad-range of 4-fluoro-1,5-disubstituted-1,2,3-triazoles were synthesized in 25–74% yields with high regioselectivity. This work also demonstrates that  $\alpha$ -fluoronitroalkenes can serve as versatile fluorinated building blocks to directly access a slew of fluorinated molecules via various chemical transformations. Further studies to explore the cycloaddition reactions with other dipoles are ongoing in our laboratory. Screening of the fluorinated-triazoles against a variety of targets related to human health and agrisciences is currently being pursued.

## Conflicts of interest

There are no conflicts to declare.

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Table of content entry:

This TFA-catalyzed [3+2] cycloaddition reaction of organic azides with  $\alpha$ -fluoronitroalkenes, used as synthetic surrogates of  $\alpha$ -fluoroalkynes, provides a new route to multi-substituted fluorotriazoles with broader substrate scopes and high regioselectivity.

