Fluorinated 1,2,3-Triazoles from α-Fluoronitroalkenes as Surrogates of α-Fluoroalkynes via Regioselective Cycloaddition Reactions with Organic Azides.

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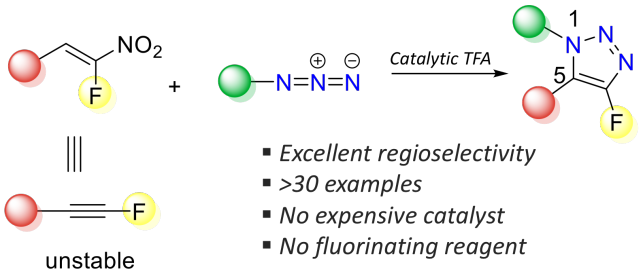
Supporting Information Placeholder



ABSTRACT: Despite the recent advances in the synthesis of fluorinated heterocycles, there are no reports of fluorinated-1,5-disubstituted-1,2,3-triazoles. The precursor for the [3+2] cycloaddition chemistry, in this case, α-fluoroalkynes are elusive molecules due to their instability and inaccessibility. Herein we show that α-fluoronitroalkenes can serve as synthetic surrogates of α-fluoroalkynes in [3+2] cycloaddition reactions with organic azides catalyzed by trifluoroacetic acid (TFA). This method provides a regioselective way to access 4-fluoro-1,5-disubstituted-1,2,3-triazoles that serve as useful building blocks for pharmaceutical, biomedical, agrichemical, and materials applications.

Building blocks containing fluorine are gaining considerable interest with the increasing demands of fluorinated small molecules in all areas of chemistry across academia and industry.[1-2] Heterocyclic motifs with an appended fluorine atom have grown in prevalence in pharmaceuticals[3] and agrochemicals,[3-4] materials,[5] and molecular imaging with positron emission tomography (PET).[6] Yet, despite the recent advances, preparation of fluorinated heterocycles is still considered challenging due to the lack of practical, general, and regioselective methods.[7] Given the relevance of 1,2,3-triazoles in biomedical research[8-9] and medicinal chemistry as an amide bioisostere[10] and a prevalent scaffold,[11]surprisingly only handful syntheses of fluorinated triazoles are reported in the literature. Pioneering work by Fokin[12] and Chu[13] have significantly advanced the field, enabling the synthesis of fluorinated-1,4-disubstituted-1,2,3-triazoles. However, the corresponding 1,5-regioisomer is unreported. Herein we describe the very first synthesis of fluorinated-1,5-disubstituted-1,2,3-triazoles with complete regiocontrol.

Classical and practical syntheses of 1,2,3-triazole involve 1,3-dipolar cycloaddition between alkynes and azides. Alkynes serve as rich building blocks for various chemical transformations, particularly, 1,3-dipolar cycloaddition reactions for the synthesis of a great variety of heterocyclic systems (Figure 1A).[14-15] Synthesis and diversifications of iodo-, bromo-, and chloro-alkynes have been thoroughly investigated.[1614-15, 17] However, fluoro-alkynes remain elusive due to their instability and undergo spontaneous cyclotrimerization under thermal or metal-catalyzed conditions to produce polysubstituted benzene derivatives (Figure 1B).[18-24] Synthetic surrogates of fluoroalkynes would be useful for 1,3-dipolar cycloaddition reactions to assemble fluorinated heterocycles. Fokin and Chu methods enable the synthesis of fluorinated-1,4-disubstituted-1,2,3-triazoles (Figure 1C).[12-13] Herein we establish that α-fluoronitroalkenes could be effectively used as surrogates of α-fluoroalkynes in cycloaddition reactions with organic azides to generate fluorinated-1,5-disubstituted-1,2,3-triazoles with trifluoroacetic acid (TFA) as a catalyst (Figure 1D).

1,4- And 1,5-disubstituted-1,2,3-triazoles, both, possess a wide-ranging biological activity such as antiretroviral, anticancer, antimalarial, antifungal, antitubulin, antibacterial, and antimicrobial properties[25] (some of the representative examples are listed in Figure 2).[10, 26-29] Hence regioselective synthesis of the 1,4- and 1,5-disubstituted-1,2,3-triazoles are always sought out. This report provides a highly regioselective and versatile method encompassing aryl, alkyl, and heteroaromatic containing fluorinated-1,5-disubstituted triazoles. Additionally, we carried out cheminformatics analyses including principle component analysis (PCA) to study the overlap in chemical space with medicinally relevant triazoles and commercially available drugs.

We hypothesized that alkenes with leaving groups such as NO_2 and CN and with a fluorine atom at the 1-position could be used as synthetic equivalents of α-fluoroalkynes in [3+2] cycloaddition reaction with organic azides.[30] Nitroalkenes, due to their high reactivity, have been widely used in 1,3-dipolar cycloaddition chemistry, especially with sodium azides for the generation of NH-1,2,3-triazoles.[30-37] Initially, We selected α-fluoronitroalkenes to investigate the intermolecular [3+2] cycloaddition reaction with azides to afford fluoro-1,2,3-triazoles. α-Fluoronitroalkenes were synthesized in two steps starting from corresponding aldehydes, tribromofluoromethane, and triphenyl phosphine in refluxing THF followed by radical-based nitration-debromination using ferric nitrate nonahydrate following reported procedure (for detail experimental details see the supporting information).[38]

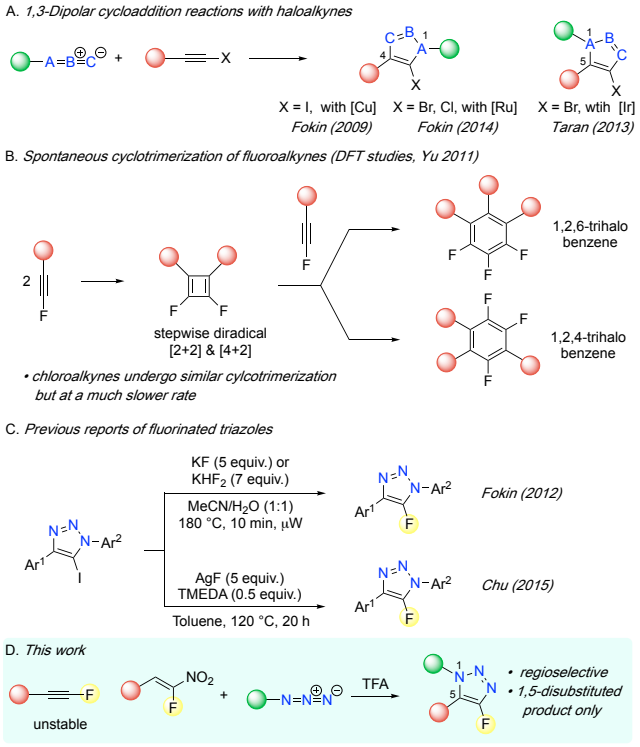


Figure 1. Haloalkynes in 1,3-dipolar cycloaddition reactions.

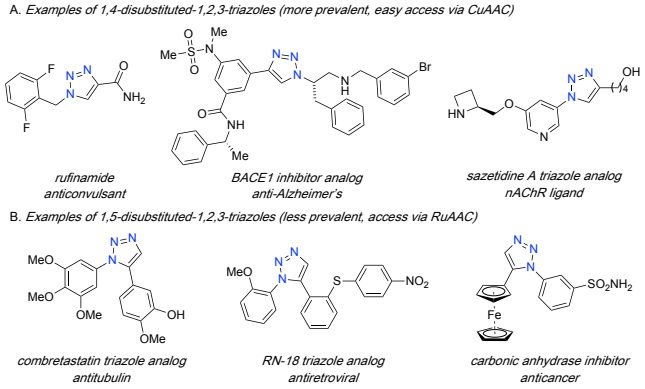


Figure 2. Prevalence of 1,2,3-triazoles in pharmaceuticals.

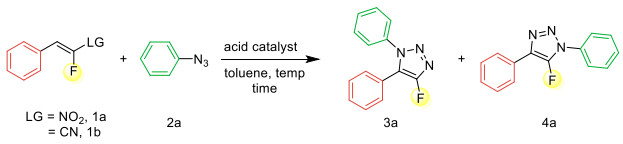


Table 1. Optimization of Reaction Conditions[a]

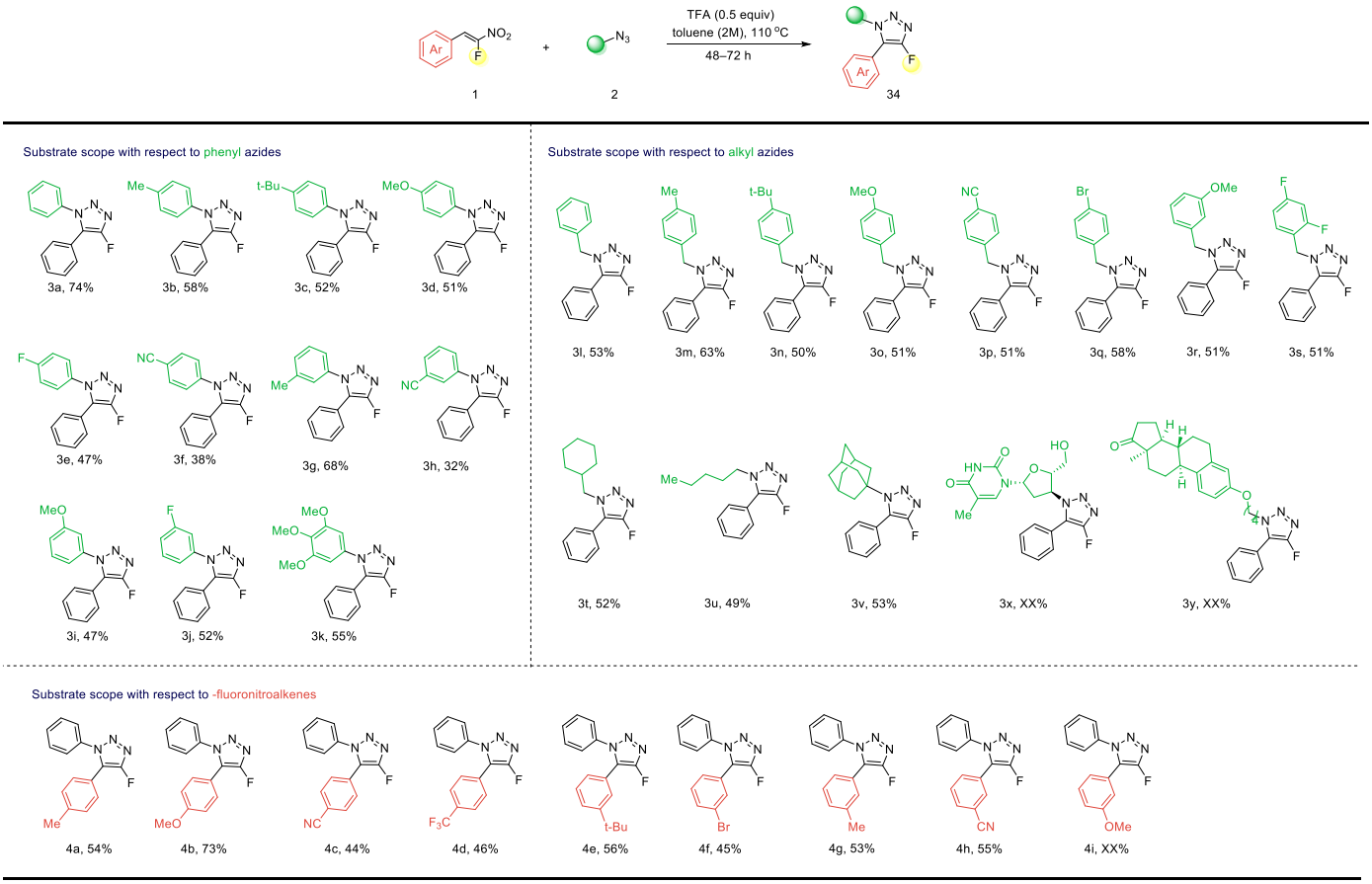
entry	catalyst (equiv.)	LG	temp (°C)	time (h)	yield(%)[b] **3a**	**4a**
1	-	NO_2	100	48	10	3
2	$Cu(OTf)_2$ (0.2)	NO_2	100	24	19	n.o.
3	$Zn(OTf)_2$ (0.2)	NO_2	100	24	16	n.o.
4	$Sc(OTf)_3$ (0.2)	NO_2	100	24	25	n.o.
5	$Yb(OTf)_3$ (0.2)	NO_2	100	24	11	n.o.
6	$Fe(OTf)_3$ (0.2)	NO_2	100	24	8	n.o.
7	$Ce(OTf)_3$ (0.2)	NO_2	100	24	22	n.o.
8	BF_3•$(OEt)_2$ (0.3)	NO_2	100	24	28	8
9	AcOH (0.3)	NO_2	100	48	42	10
10	PTSA (0.5)	NO_2	100	48	31	<5
11	10-CSA (0.5)	NO_2	100	48	36	<5
12	TFA (0.3)	NO_2	100	48	60	n.o.
13	TFA (0.5)	NO_2	110	48	74	n.o.
14	TFA (0.8)	NO_2	100	48	69	n.o.
15	H_3PO_4 (0.5)	NO_2	110	48	45	7
16	$MeSO_3H$ (0.5)	NO_2	110	48	68	n.o.
17	NH_2SO_3 (0.5)	NO_2	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 2 M toluene and heated at 110 °C. [b] Isolated yield. PTSA = *p*-toluenesulfonic acid, TFA = trifluoroacetic acid 10-CSA = 10-camphorsulfonic acid

We found 1 equiv. of α-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**:**4a**) ratio along with unreacted starting materials (entry 1, Table 1). The ratio of the regioisomeric products **3a**:**4a** was determined by ^{19}F NMR (The ^{19}F NMR value for **3a** and **4a** are δ -145.1 and -150.4 ppm respectively). We observed that the reaction was extremely sluggish at room temperature. At elevated temperature (100 °C) an excess of phenyl azide (2 equiv.) was required due to the decomposition of organic azides at higher temperatures.[39] Taking a clue from previous reports of nitroalkenes in [3+2] cycloaddition addition reactions, we decided to screen different Lewis acids.[34, 37, 40-42] With Lewis acids $Cu(OTf)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Fe(OTf)_3$, $Ce(OTf)_3$ (entries 2–7) we observed regioselective formation of the 1,5-product **3a**, however in 19–22% yields. Use of BF_3•$(OEt)_2$ led to a slight increase in the yield of **3a** to 28% but also formed **4a** in 8% (entry 8). A decent increase in yield of **3a** up to 42% along with 10% of **4a** was observed when 30 mol% of AcOH was used as a catalyst. This result led us to screen other Brønsted acids such as $MeSO_3H$, H_3PO_4, *p*-TSA•H_2O, and CF_3CO_2H (TFA) (entries 10–17) with our standard substrates. Among the Brønsted acids, TFA gave the best results with 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% (entry 13). Increasing the amount of TFA to 80% led to a slight decrease in yield (entry 14, see supporting information for more conditions). Further increase in yield was observed by raising temperature from 100 to 110 °C (entry 10). However, changing the solvents to DMF, DMSO, DCE, 1,4-dioxane, ACN, and THF resulted in lower yields (see supporting information). Our optimized condition comprises α-fluoronitroalkene **1a** (0.15 mmol) and phenyl azide **2a** (0.3 mmol) in a respective molar ratio of 1:2 with 50 mol% of TFA (0.075 mmol) in 2M toluene when heated to 110 °C for 48 h regioselctively produced 1,5-diaryl 4-fluoro 1,2,3-triazole **3a** in 74% yield. Unfortunately, treatment of phenyl azide with (*Z*)-2-fluoro-3-phenylacrylonitrile under the same conditions did not result in any product formation and unreacted starting materials were recovered (entry 18). For a complete optimization table 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 3). The ^{19}F NMR chemical shifts of the synthesized 4-fluoro-1,5-disubstituted-1,2,3-triazoles the ranges from -143.66 to -146.73 ppm. As shown in Figure 3, *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}F NMR spectra and TLCs. The combretastatin triazole analogue **3k** was prepared in 55% yield using this method. The lower yields suggest that the α-fluoronitroalkenes are less reactive compared to the corresoding nitroalkenes in [3+2] cycloaddition chemistry with azides.

Next, the scope of the reaction for benzyl and aliphatic azides were examined (Figure 3). To our delight, an array of *para*- and *meta*-substituted benzyl azides were found to be amenable to the optimized reaction conditions. Both, electron-donating group such as methyl (**3m**), *t*-butyl (**3n**), methoxy (**3o**) and electron withdrawing group such as cyano (**3p**), bromo (**3q**) at the *para*-position of benzyl azides were well tolerated and afforded the corresponding regioselective products in 51–63%. The extension of this reaction to aliphatic azides (**3t**–**3y**) resulted in the formation of corresponding 4-fluoro-1,2,3-triazoles in 25–53% yields.



[a] Reaction conditions: 1 (1 equiv.), 2 (2 equiv.), toluene (2M), 110 °C, 48–72 h. Isolated yields are provided.

[b] 42-65% of unreacted α-fluoroalkynes were observed in ^{19}F NMR.

[c] The starting material (SM) was fairly unreactive requiring 120 h of heating at 110 °C. The ratio of the azide 2x and product 3x was found to be 1:1.2 and co-eluted together. Other side-products were observed.

[d] Other side-products were observed.

Figure 3. Substrate Scope.

The scope of the reaction was further examined with the substitution patterns on α-fluoronitrostyrenes (Figure 3). Overall, both electron donating and withdrawing groups at *para*-position in α-fluoronitrostyrenes exhibited good to moderate 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 (45–55%) irrespective of the electron donating and withdrawing group (**4e**–**4h**).

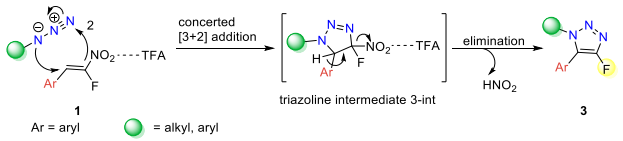


Figure 4. A plausible mechanism.

A plausible mechanism for this reaction is proposed in Figure 4. Initially, regioselective [3+2] cycloaddition takes place between α-fluoronitroalkene **1** and organic azide **2** to form triazoline intermediate **3-int**. Regioselectivity is imparted by the strongly electron-withdrawing nitro group on the dipolarophile **1** that is further activated by TFA; thereby lowering the lowest unoccupied molecular orbital (LUMO) and making the β-carbon most electrophilic.[35-36] Without TFA, a mixture of 1,5- and 1,4-regioisomers are obtained in 5:2 ratio, as determined by ^{19}F NMR. The 1,3-dipolar organic azide attacks the partially positively charged β-carbon of the α-fluoronitroalkene in a concerted manner to form the triazoline intermediate **3-int.** Elimination of HNO_2 results in regioselective formation of the desired 4-fluoro-1,5-disubstituted-1,2,3-triazoles **3**. An attempt to probe the triazoline intermediate **3-int** via ^{19}F NMR in deuterated-TFA at 90 °C was unsuccessful. This suggests that the transient intermediate rapidly eliminates HNO_2 to form the triazole product.

In connection with our ongoing drug discovery efforts, we wanted to assess the chemical space and physicochemical properties of our library of 4-fluoro-1,5-disubstituted-1,2,3-triazoles relative to commercial drugs and triazole-containing pharmaceutical agents. To this end, we performed principal component analysis (PCA) on the library of synthesized triazoles adopting a modified protocol reported by Tan and Aubé.[43-44] The reference set included best-selling drugs, fluoroquinolones, triazole-

containing kinase inhibitors, triazole antifungals, natural product-based drugs, and colchicine triazole derivatives and was chosen based on therapeutic value, similarities in the core triazole nucleus, and overall hybridization of the molecules. We used Swiss ADME[45-46] to calculate the 12 physicochemical properties of the synthesized triazoles and the reference set. The loadings, which are an estimation of the correlation between components and variables, demonstrate the influence of the 12 physicochemical properties and placement of the compounds in the PCA plots.

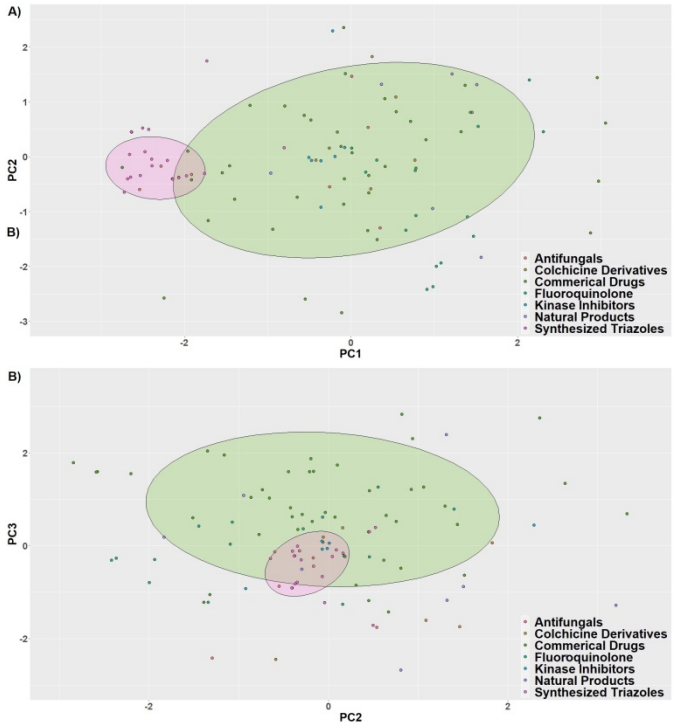


Figure 5. PCA plots of 30 triazole library members, 8 antifungal compounds, 7 triazole kinase inhibitors, 7 triazole colchicine derivatives, 51 best-selling drugs, 12 natural products, and 15 fluoroquinolones. (A) Orthoganal plot of PC1 versus PC2 generated from 12 structural and physicochemical parameters. (B) Orthogonal plot for PC2 vs PC3 generated from 12 structural and physicochemical parameters. Note: the shaded regions in each plot show the t-distribution for commerically avaliable drugs (green) and the triazole synthesized in this work (pink) with a confidence interval of 80%.

Examination of the eigenvector plots (see supporting information) show that topological polar surface area (tPSA), number of oxygen atoms (O), and number of hydrogen bond donor/acceptor (HBD/HBA) have a strong positive impact on the PC1 axes. Whereas, calculated skin permeation rate (LogK) and calculated octanol/water partition coefficient (CLogP) have a strong negative impact on the PC1 axes. For PC2, molecular weight (MW), CLogP, and the number of rotatable bonds (RotB) have the largest impact and shift compounds in the positive direction. However, calculated aqueous solubility (AlogpS) has a significant negative effect on PC2 and shift compounds to the left along the PC2 axes. In PC3, the fraction of sp^3 hybridized carbons (Csp3), RotB, and O have a large positive influence along the PC3 axes, while the number of fluorine atoms (F) and the number of nitrogen atoms (N) have a large negative influence along the PC3 axes.

The orthogonal plots for the first 3 principal components (PC1—3, Figure 5), show a slight overlap between PC1 and PC2 and a near complete overlap between PC2 and PC3. Together, the first 3 principal components account for over 75% of the total variation in the original dataset while the first 5 principal components account for over 90% of the variation. These analyses show, 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. The lower MW for most of the synthesized triazoles (<300) along with the insights gleaned from PCA suggest the potential use of these compounds in fragment-based drug discovery activities.

In conclusion, we have shown that the α-fluoronitroalkenes could be effectively used as synthetic surrogates of α-fluoroalkynes in a regioselective [3 + 2] Huisgen cycloaddition chemistry with organic azides. A relatively broad-range of 4-fluoro-1,5-substituted-1,2,3-triazoles were synthesized in decent yields and high regioselectivity. This work demonstrates that α-fluoronitroalkenes can serve as versatile fluorinated building blocks to directly access a slew of fluorinated molecules via diverse chemical transformations. Further studies to explore the cycloaddition reactions with other diploes is ongoing in our laboratory. Screening of the fluorinated-triazoles against a variety of targets related to human health and agrisciences are currently being pursued.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

SR and SJ conceived the idea. SR wrote the paper. SJ, SA, MRC performed the experiments and the cheminformatic analyses. The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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REFERENCES

1. Liang, T.; Neumann, C. N.; Ritter, T., Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angew. Chem. Int. Ed.* **2013,** *52* (32), 8214-8264.

2. Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A., Zinc-Mediated Formation of Trifluoromethyl Ethers from Alcohols and Hypervalent Iodine Trifluoromethylation Reagents. *Angew. Chem. Int. Ed.* **2009,** *48* (24), 4332-4336.

3. Müller, K.; Faeh, C.; Diederich, F., Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007,** *317* (5846), 1881-1886.

4. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A., Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015,** *58* (21), 8315-8359.
5. Rasmusson, T.; Martyn, L. J. P.; Chen, G.; Lough, A.; Oh, M.; Yudin, A. K., Aromatic Fluorine as a Versatile Control Element for the Construction of Molecules with Helical Chirality. *Angew. Chem. Int. Ed.* **2008,** *47* (37), 7009-7012.
6. Phelps, M. E., Positron emission tomography provides molecular imaging of biological processes. *Proceedings of the National Academy of Sciences* **2000,** *97* (16), 9226-9233.
7. Furuya, T.; Kamlet, A. S.; Ritter, T., Catalysis for fluorination and trifluoromethylation. *Nature* **2011,** *473* (7348), 470-477.
8. Saxon, E.; Bertozzi, C. R., Cell Surface Engineering by a Modified Staudinger Reaction. *Science* **2000,** *287* (5460), 2007.
9. Haugland, M. M.; El-Sagheer, A. H.; Porter, R. J.; Peña, J.; Brown, T.; Anderson, E. A.; Lovett, J. E., 2′-Alkynylnucleotides: A Sequence- and Spin Label-Flexible Strategy for EPR Spectroscopy in DNA. *J. Am. Chem. Soc.* **2016,** *138* (29), 9069-9072.
10. Mohammed, I.; Kummetha, I. R.; Singh, G.; Sharova, N.; Lichinchi, G.; Dang, J.; Stevenson, M.; Rana, T. M., 1,2,3-Triazoles as Amide Bioisosteres: Discovery of a New Class of Potent HIV-1 Vif Antagonists. *J. Med. Chem.* **2016,** *59* (16), 7677-7682.
11. Miyakoshi, H.; Miyahara, S.; Yokogawa, T.; Endoh, K.; Muto, T.; Yano, W.; Wakasa, T.; Ueno, H.; Chong, K. T.; Taguchi, J.; Nomura, M.; Takao, Y.; Fujioka, A.; Hashimoto, A.; Itou, K.; Yamamura, K.; Shuto, S.; Nagasawa, H.; Fukuoka, M., 1,2,3-Triazole-Containing Uracil Derivatives with Excellent Pharmacokinetics as a Novel Class of Potent Human Deoxyuridine Triphosphatase Inhibitors. *J. Med. Chem.* **2012,** *55* (14), 6427-6437.
12. Worrell, B. T.; Hein, J. E.; Fokin, V. V., Halogen Exchange (Halex) Reaction of 5-Iodo-1,2,3-triazoles: Synthesis and Applications of 5-Fluorotriazoles. *Angew. Chem. Int. Ed.* **2012,** *51* (47), 11791-11794.
13. Wang, D.; Sun, W.; Chu, T., Synthesis of 5-Fluorotriazoles by Silver-Mediated Fluorination of 5-Iodotriazoles. *Eur. J. Org. Chem.* **2015,** *2015* (19), 4114-4118.
14. Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V., Copper(I)-Catalyzed Cycloaddition of Organic Azides and 1-Iodoalkynes. *Angew. Chem. Int. Ed.* **2009,** *48* (43), 8018-8021.
15. Oakdale, J. S.; Sit, R. K.; Fokin, V. V., Ruthenium-Catalyzed Cycloadditions of 1-Haloalkynes with Nitrile Oxides and Organic Azides: Synthesis of 4-Haloisoxazoles and 5-Halotriazoles. *Chemistry – A European Journal* **2014,** *20* (35), 11101-11110.
16. For a review on preparation of haloalkynes, see: Zhdankin VV (1995) Alkynyl halides and chalcogenides. In: Katritzky AR, Meth-Cohn O, Rees CW (eds) Comprehensive organic functional group transformations. Pergamon, New York, pp 1011–1038.
17. Rasolofonjatovo, E.; Theeramunkong, S.; Bouriaud, A.; Kolodych, S.; Chaumontet, M.; Taran, F., Iridium-Catalyzed Cycloaddition of Azides and 1-Bromoalkynes at Room Temperature. *Org. Lett.* **2013,** *15* (18), 4698-4701.
18. McAlister, D. R.; Bercaw, J. E.; Bergman, R. G., Parallel reaction pathways in the cobalt-catalyzed cyclotrimerization of acetylenes. *J. Am. Chem. Soc.* **1977,** *99* (5), 1666-1668.
19. Vollhardt, K. P. C., Transition-metal-catalyzed acetylene cyclizations in organic synthesis. *Acc. Chem. Res.* **1977,** *10* (1), 1-8.
20. Alkyne oligomerization. In *The Metal—Carbon Bond (1985).*
21. Skupinska, J., Oligomerization of .alpha.-olefins to higher oligomers. *Chem. Rev.* **1991,** *91* (4), 613-648.
22. Viehe, H. G.; Merényi, R.; Oth, J. F. M.; Valange, P., Formation of 1,2,3-Tri-t-butyltrifluorobenzene by Spontaneous Trimerization of t-Butylfluoroacetylene. *Angewandte Chemie International Edition in English* **1964,** *3* (11), 746-746.
23. Ballester, M.; Castaner, J.; Riera, J.; Tabernero, I., Synthesis and chemical behavior of perchlorophenylacetylene. *The Journal of Organic Chemistry* **1986,** *51* (9), 1413-1419.
24. Yao, Z.-K.; Yu, Z.-X., Mechanisms of the Thermal Cyclotrimerizations of Fluoro- and Chloroacetylenes: Density Functional Theory Investigation and Intermediate Trapping Experiments. *J. Am. Chem. Soc.* **2011,** *133* (28), 10864-10877.
25. Finn, M. G.; Fokin, V. V., Click chemistry: function follows form. *Chem. Soc. Rev.* **2010,** *39* (4), 1231-1232.
26. Monceaux, C. J.; Hirata-Fukae, C.; Lam, P. C. H.; Totrov, M. M.; Matsuoka, Y.; Carlier, P. R., Triazole-linked reduced amide isosteres: An approach for the fragment-based drug discovery of anti-Alzheimer's BACE1 inhibitors. *Bioorg. Med. Chem. Lett.* **2011,** *21* (13), 3992-3996.
27. Liu, Y.; Paige, M.; Olson, T. T.; Al-Muhtasib, N.; Xie, T.; Hou, S.; White, M. P.; Cordova, A.; Guo, J. L.; Kellar, K. J.; Xiao, Y.; Brown, M. L., Synthesis and pharmacological characterization of new neuronal nicotinic acetylcholine receptor ligands derived from Sazetidine-A. *Bioorg. Med. Chem. Lett.* **2014,** *24* (13), 2954-2956.
28. Odlo, K.; Hentzen, J.; dit Chabert, J. F.; Ducki, S.; Gani, O. A. B. S. M.; Sylte, I.; Skrede, M.; Fløtenes, V. A.; Hansen, T. V., 1,5-Disubstituted 1,2,3-triazoles as cis-restricted analogues of combretastatin A-4: Synthesis, molecular modeling and evaluation as cytotoxic agents and inhibitors of tubulin. *Biorg. Med. Chem.* **2008,** *16* (9), 4829-4838.
29. Salmon, A. J.; Williams, M. L.; Wu, Q. K.; Morizzi, J.; Gregg, D.; Charman, S. A.; Vullo, D.; Supuran, C. T.; Poulsen, S.-A., Metallocene-Based Inhibitors of Cancer-Associated Carbonic Anhydrase Enzymes IX and XII. *J. Med. Chem.* **2012,** *55* (11), 5506-5517.
30. Zefirov, N. S.; Chapovskaya, N. K.; Kolesnikov, V. V., Synthesis of 1,2,3-triazoles by reaction of azide ion with αβ-unsaturated nitro-compounds and nitriles. *Journal of the Chemical Society D: Chemical Communications* **1971,** (17), 1001-1002.
31. Payra, S.; Saha, A.; Banerjee, S., On Water Cu@g-C3N4 Catalyzed Synthesis of NH-1,2,3-Triazoles via [2+3] Cycloadditions of Nitroolefins/Alkynes and Sodium Azide. *ChemCatChem* **2018,** *10* (23), 5468-5474.
32. Zheng, L.; Zeng, Z.; Yan, Q.; Jia, F.; Jia, L.; Chen, Y., Copper-Catalyzed Synthesis of 3-NO2 Quinolines from o-Azidobenzaldehyde and Nitro-olefins and its Application in the Concise Synthesis of Quindolines. *Adv. Synth. Catal.* **2018,** *360* (21), 4037-4042.
33. Motornov, V. A.; Tabolin, A. A.; Novikov, R. A.; Nelyubina, Y. V.; Ioffe, S. L.; Smolyar, I. V.; Nenajdenko, V. G., Synthesis and Regioselective N-2 Functionalization of 4-Fluoro-5-aryl-1,2,3-NH-triazoles. *Eur. J. Org. Chem.* **2017,** *2017* (46), 6851-6860.
34. Quan, X.-J.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H., p-Toluenesulfonic Acid Mediated 1,3-Dipolar Cycloaddition of Nitroolefins with NaN3 for Synthesis of 4-Aryl-NH-1,2,3-triazoles. *Org. Lett.* **2014,** *16* (21), 5728-5731.
35. Thomas, J.; John, J.; Parekh, N.; Dehaen, W., A Metal-Free Three-Component Reaction for the Regioselective Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles. *Angew. Chem. Int. Ed.* **2014,** *53* (38), 10155-10159.
36. Wang, Y.-C.; Xie, Y.-Y.; Qu, H.-E.; Wang, H.-S.; Pan, Y.-M.; Huang, F.-P., Ce(OTf)3-Catalyzed [3 + 2] Cycloaddition of Azides with Nitroolefins: Regioselective Synthesis of 1,5-Disubstituted 1,2,3-Triazoles. *The Journal of Organic Chemistry* **2014,** *79* (10), 4463-4469.
37. Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Zunino, E.; Vaccaro, L., Synthesis of 4-Aryl-1H-1,2,3-triazoles through TBAF-Catalyzed [3 + 2] Cycloaddition of 2-Aryl-1-nitroethenes with TMSN3 under Solvent-Free Conditions. *The Journal of Organic Chemistry* **2005,** *70* (16), 6526-6529.
38. Motornov, V. A.; Muzalevskiy, V. M.; Tabolin, A. A.; Novikov, R. A.; Nelyubina, Y. V.; Nenajdenko, V. G.; Ioffe, S. L., Radical Nitration-Debromination of α-Bromo-α-fluoroalkenes as a Stereoselective Route to Aromatic α-Fluoronitroalkenes—Functionalized Fluorinated Building Blocks for Organic Synthesis. *The Journal of Organic Chemistry* **2017,** *82* (10), 5274-5284.
39. L'Abbe, G., Decomposition and addition reactions of organic azides. *Chem. Rev.* **1969,** *69* (3), 345-363.
40. Motornov, V. A.; Tabolin, A. A.; Nelyubina, Y. V.; Nenajdenko, V. G.; Ioffe, S. L., Copper-mediated oxidative [3 + 2]-annulation of nitroalkenes and pyridinium ylides: general access to functionalized indolizines and efficient synthesis of 1-fluoroindolizines. *Organic & Biomolecular Chemistry* **2019,** *17* (6), 1442-1454.
41. Jannapu Reddy, R.; Waheed, M.; Karthik, T.; Shankar, A., An efficient synthesis of 4,5-disubstituted-2H-1,2,3-triazoles from nitroallylic derivatives via a cycloaddition–denitration process. *New J. Chem.* **2018,** *42* (2), 980-987.
42. Arai, T.; Ogawa, H.; Awata, A.; Sato, M.; Watabe, M.; Yamanaka, M., PyBidine–Cu(OTf)2-Catalyzed Asymmetric [3+2] Cycloaddition with Imino Esters: Harmony of Cu–Lewis Acid and Imidazolidine-NH Hydrogen Bonding in Concerto Catalysis. *Angew. Chem. Int. Ed.* **2015,** *54* (5), 1595-1599.
43. Kopp, F.; Stratton, C. F.; Akella, L. B.; Tan, D. S., A diversity-oriented synthesis approach to macrocycles via oxidative ring expansion. *Nature Chemical Biology* **2012,** *8*, 358.
44. McLeod, M. C.; Singh, G.; Plampin Iii, J. N.; Rane, D.; Wang, J. L.; Day, V. W.; Aubé, J., Probing chemical space with alkaloid-inspired libraries. *Nature Chemistry* **2014,** *6*, 133.

45. Daina, A.; Michielin, O.; Zoete, V., SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports* **2017,** *7*, 42717.
46. Daina, A.; Michielin, O.; Zoete, V., iLOGP: A Simple, Robust, and Efficient Description of n-Octanol/Water Partition Coefficient for Drug Design Using the GB/SA Approach. *Journal of Chemical Information and Modeling* **2014,** *54* (12), 3284-3301.