COMMUNICATION

Regioselective synthesis of 4-fluoro-1,5-substituted-1,2,3-triazoles from synthetic surrogates of α-fluoroalkynes

Sampad Jana,*[a] Sweta Adhikari[a] Michael R. Cox,[a] and Sudeshna Roy *[a]

α-Fluoroalkynes are elusive molecules due to their instability and inaccessibility. Here, we show that α-fluoronitroalkenes can serve as synthetic surrogates of α-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-substituted-1,2,3-triazoles.

The past couple of decades saw a surge of fluorinated heterocycles in pharmaceuticals[1] and agrochemicals,[1, 2] materials,[3] and molecular imaging with positron emission tomography (PET).[4] Yet, despite the recent advances, preparation of fluorinated heterocycles is still considered challenging due to the lack of practical, general, and regioselective methods.[5] Given the relevance of 1,2,3-triazoles in biomedical research[6, 7] and medicinal chemistry as an amide bioisostere[8] and a prevalent scaffold,[9] surprisingly only handful syntheses of fluorinated triazoles are reported in the literature.[10] Pioneering work by Fokin[11] and Chu[12] have significantly advanced the field, enabling the synthesis of 5-fluoro-1,4-substituted-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 literature by developing the very first synthesis of 4-fluoro-1,5-substituted-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).[13, 14] While synthesis of iodo-, bromo-, and chloro-alkynes have been thoroughly investigated, [13-15] fluoro-alkynes remain elusive due to their instability. α-Fluoroalkynes are notorious for undergoing spontaneous oligomerization under thermal or metal-catalyzed conditions to produce
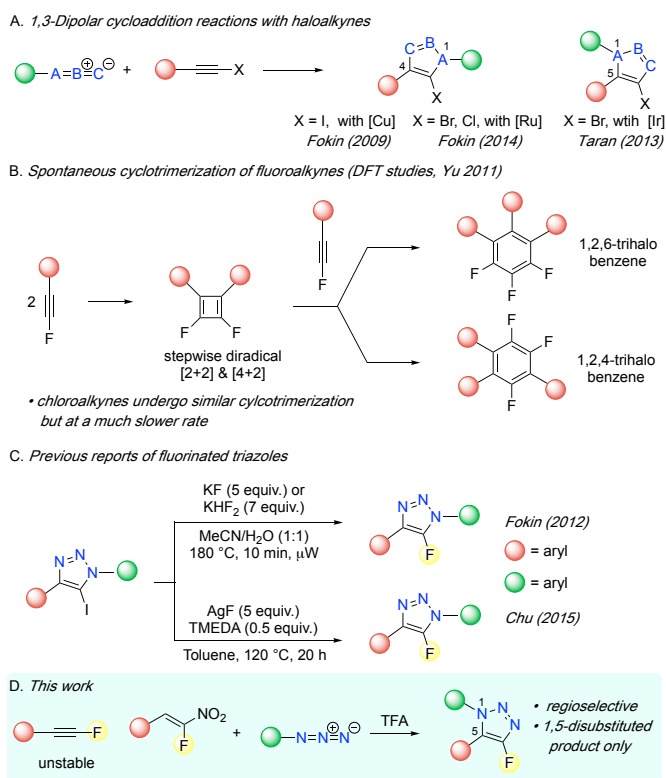

Figure 1. Haloalkynes in 1,3-dipolar cycloaddition reaction.

polysubstituted benzene derivatives (Figure 1B) [16-19] or polymers.[20] Synthetic surrogates of α-fluoroalkynes would be particularly desirable to assemble fluorinated heterocycles via 1,3-dipolar cycloaddition reactions. Herein, we establish that α-fluoronitroalkenes could be effectively used as surrogates of α-fluoroalkynes in cycloaddition reactions with organic azides to construct 4-fluoro-1,5-substituted-1,2,3-triazoles (Figure 1D). Consequently, α-fluoronitroalkenes can be regarded as resourceful fluorinated building blocks to synthesize fluorinated molecules that are increasingly growing in all areas of chemistry.[21]

a. Department of BioMolecular Sciences, School of Pharmacy, University of Mississippi, University, MS 38677.
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x
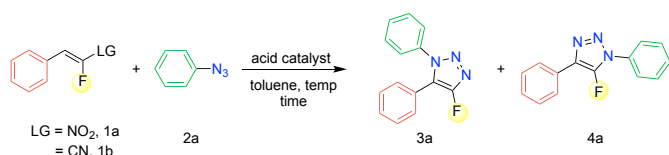
Table 1. Optimization of Reaction Conditions[a]

entry	catalyst	equiv.	LG	temp (°C)	time (h)	yield(%)[b] 3a	yield(%)[b] 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.

Both, 1,4- and 1,5-substituted-1,2,3-triazoles, are often used as bioisosteres of *trans*- and *cis*-amides respectively,[8] in addition to their wide-ranging biological and biomedical applications. [22] Hence, regioselective routes to synthesize 1,4- and 1,5-substituted-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-substituted-1,2,3-triazoles. This method is complementary to the prior methods reported by Fokin and Ch for obtaining 5-fluoro-1,4-substituted-1,2,3-triazoles (Figure 1C).[11, 12] Our cheminformatics analyses of these 5-fluoro-1,4-substituted-1,2,3-triazoles show an overlap of chemical space with medicinally relevant triazoles and commercially available drugs (see supporting information for details).

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 reactions with organic azides.[23] 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.[23-30] 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 α-fluoronitroalkenes to investigate the intermolecular [3+2] cycloaddition reaction with organic azides to afford fluoro-1,2,3-triazoles. α-Fluoronitroalkenes were synthesized in two steps starting from the corresponding aldehydes, tribromofluoromethane, and triphenylphosphine in refluxing THF to afford the α-fluorobromoalkenes.[31] A subsequent radical-based nitration-debromination using ferric nitrate nonahydrate gave the α-fluoronitroalkenes. Alternatively, a one-pot 2-step protocol can be used to synthesize α-fluoronitroalkenes without having to isolate α-fluorobromoalkenes, which makes it operationally simple.

We observed that 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 temperatures (100–110 °C), an excess of phenyl azide (2 equiv.) was required due to the decomposition of organic azides at higher temperatures.[32]

Taking a clue from the previous reports of nitroalkenes in [3+2] cycloaddition reactions, we decided to screen different Lewis acids.[27, 30, 33-35] 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 a regioselective formation of the 1,5-product **3a**, however in 19–22% yields. The use of $BF_3•(OEt)_2$ led to a slight increase in the yield of **3a** to 28% but also formed **4a** in 8% yield (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 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, see supporting information for more conditions). However, changing the solvents to DMF, DMSO, DCE, 1,4-dioxane, ACN, and THF resulted in lower yields (see supporting information).

COMMUNICATION

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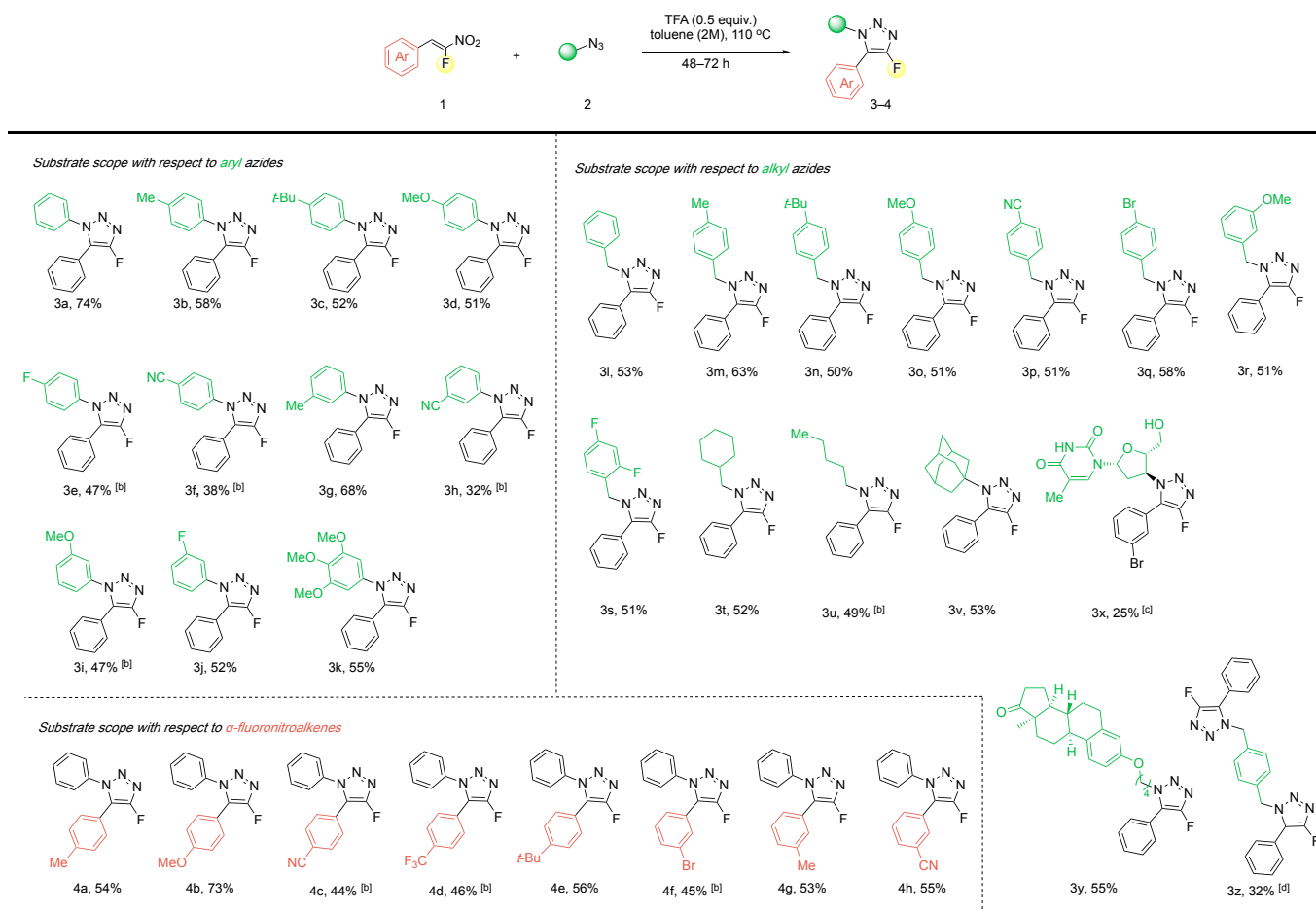
[a] Reaction conditions: **1** (1 equiv.), **2** (2 equiv.), toluene (2M), 110 °C, 48–72 h. Isolated yields are provided. [b] 42–65% of unreacted α-fluoronitroalkenes were observed in ^{19}F NMR. [c] The starting materials (SM) were fairly unreactive, requiring 120 h of heating at 110 °C. [d] Other side-products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

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 α-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 ^{19}F NMR chemical shifts of the synthesized 4-fluoro-1,5-substituted-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}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 α-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 α-fluoronitroalkenes.

Next, the scope of the reaction for benzyl and aliphatic 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 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.

The scope of the reaction was further examined with the substitution patterns on α-fluoronitrostyrenes (Figure 2). Overall, both electron-donating and -withdrawing groups at the *para*-position in α-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 (45–55%) irrespective of the electron donating and withdrawing group (**4e–4h**).

Based on the previous literature reports on cycloaddition of nitroalkenes with 1,3-dipoles,[29, 36] we propose a similar mechanism outlined in Figure 3. Initially, regioselective [3+2] cycloaddition takes place between α-fluoronitroalkene **1** and organic azide **2** to form a triazoline intermediate **3-int**. For the initial cycloaddition step, both a concerted and 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 unoccupied molecular orbital (LUMO) and making the β-carbon most electrophilic.[28, 29] Without TFA, a mixture of 1,5- and 1,4-regioisomers are obtained in a 5:2 ratio, as determined by ^{19}F NMR. The 1,3-dipolar organic azide attacks the partially
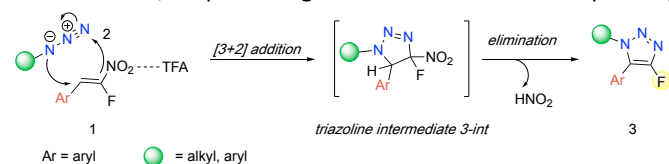
positively charged β-carbon of the α-fluoronitroalkene to form the triazoline intermediate **3-int**—a concomitant elimination of HNO$_2$ results in the regioselective formation of the desired 4-fluoro-1,5-substituted-1,2,3-triazoles product **3**. An attempt to probe the triazoline intermediate **3-int** via ^{19}F NMR in deuterated-toluene 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 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 α-fluoronitroalkenes could be effectively used as synthetic surrogates of α-fluoroalkynes in a regioselective [3 + 2] cycloaddition chemistry with organic azides. The 1,5-substituted-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-substituted-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-substituted-1,2,3-triazoles were synthesized in 25–74% yields with high regioselectivity. This work also demonstrates that α-fluoronitroalkenes can serve as versatile fluorinated building blocks to directly access a slew of fluorinated molecules via various chemical transformations. Further study to explore the cycloaddition reactions with other dipoles is 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.

Notes and references

1. K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881-1886.
2. E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315-8359.
3. T. Rasmusson, L. J. P. Martyn, G. Chen, A. Lough, M. Oh and A. K. Yudin, *Angew. Chem. Int. Ed.*, 2008, **47**, 7009-7012.
4. M. E. Phelps, *Proc. Natl. Acad. Sci. U.S.A.,* 2000, **97**, 9226-9233.
5. T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470-477.
6. E. Saxon and C. R. Bertozzi, *Science*, 2000, **287**, 2007.

Figure 3. A plausible mechanism.

7. M. M. Haugland, A. H. El-Sagheer, R. J. Porter, J. Peña, T. Brown, E. A. Anderson and J. E. Lovett, *J. Am. Chem. Soc.*, 2016, **138**, 9069-9072.

8. I. Mohammed, I. R. Kummetha, G. Singh, N. Sharova, G. Lichinchi, J. Dang, M. Stevenson and T. M. Rana, *J. Med. Chem.*, 2016, **59**, 7677-7682.

9. H. Miyakoshi, S. Miyahara, T. Yokogawa, K. Endoh, T. Muto, W. Yano, T. Wakasa, H. Ueno, K. T. Chong, J. Taguchi, M. Nomura, Y. Takao, A. Fujioka, A. Hashimoto, K. Itou, K. Yamamura, S. Shuto, H. Nagasawa and M. Fukuoka, *J. Med. Chem.*, 2012, **55**, 6427-6437.

10. H.-N. Shin, S. H. Seo, H. Choo, G. Kuem, K. I. Choi and G. Nam, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1193-1196.

11. B. T. Worrell, J. E. Hein and V. V. Fokin, *Angew. Chem. Int. Ed.*, 2012, **51**, 11791-11794.

12. D. Wang, W. Sun and T. Chu, *Eur. J. Org. Chem.*, 2015, **2015**, 4114-4118.

13. J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless and V. V. Fokin, *Angew. Chem. Int. Ed.*, 2009, **48**, 8018-8021.

14. J. S. Oakdale, R. K. Sit and V. V. Fokin, *Eur. J. Chem.*, 2014, **20**, 11101-11110.

15. E. Rasolofonjatovo, S. Theeramunkong, A. Bouriaud, S. Kolodych, M. Chaumontet and F. Taran, *Org. Lett.*, 2013, **15**, 4698-4701.

16. D. R. McAlister, J. E. Bercaw and R. G. Bergman, *J. Am. Chem. Soc.*, 1977, **99**, 1666-1668.

17. H. G. Viehe, R. Merényi, J. F. M. Oth and P. Valange, *Angew. Chem. Int. Ed.*, 1964, **3**, 746-746.

18. M. Ballester, J. Castaner, J. Riera and I. Tabernero, *The Journal of Organic Chemistry*, 1986, **51**, 1413-1419.

19. Z.-K. Yao and Z.-X. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 10864-10877.

20. T. Okano, K. Ito, T. Ueda and H. Muramatsu, *J. Fluorine Chem.*, 1986, **32**, 377-388.

21. T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem. Int. Ed.*, 2013, **52**, 8214-8264.

22. A. J. Salmon, M. L. Williams, Q. K. Wu, J. Morizzi, D. Gregg, S. A. Charman, D. Vullo, C. T. Supuran and S.-A. Poulsen, *J. Med. Chem.*, 2012, **55**, 5506-5517.

23. N. S. Zefirov, N. K. Chapovskaya and V. V. Kolesnikov, *J. Chem. Soc. D*, 1971, DOI: 10.1039/C29710001001, 1001-1002.

24. S. Payra, A. Saha and S. Banerjee, *ChemCatChem*, 2018, **10**, 5468-5474.

25. L. Zheng, Z. Zeng, Q. Yan, F. Jia, L. Jia and Y. Chen, *Adv. Synth. Catal.*, 2018, **360**, 4037-4042.

26. V. A. Motornov, A. A. Tabolin, R. A. Novikov, Y. V. Nelyubina, S. L. Ioffe, I. V. Smolyar and V. G. Nenajdenko, *Eur. J. Org. Chem.*, 2017, **2017**, 6851-6860.

27. X.-J. Quan, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Org. Lett.*, 2014, **16**, 5728-5731.

28. J. Thomas, J. John, N. Parekh and W. Dehaen, *Angew. Chem. Int. Ed.*, 2014, **53**, 10155-10159.

29. Y.-C. Wang, Y.-Y. Xie, H.-E. Qu, H.-S. Wang, Y.-M. Pan and F.-P. Huang, *J. Org. Chem.*, 2014, **79**, 4463-4469.

30. D. Amantini, F. Fringuelli, O. Piermatti, F. Pizzo, E. Zunino and L. Vaccaro, *J. Org. Chem.,* 2005, **70**, 6526-6529.

31. V. A. Motornov, V. M. Muzalevskiy, A. A. Tabolin, R. A. Novikov, Y. V. Nelyubina, V. G. Nenajdenko and S. L. Ioffe, *J. Org. Chem.*, 2017, **82**, 5274-5284.

32. G. L'Abbe, *Chem. Rev.*, 1969, **69**, 345-363.

33. V. A. Motornov, A. A. Tabolin, Y. V. Nelyubina, V. G. Nenajdenko and S. L. Ioffe, *Org. Biomol. Chem.*, 2019, **17**, 1442-1454.

34. R. Jannapu Reddy, M. Waheed, T. Karthik and A. Shankar, *New J. Chem.*, 2018, **42**, 980-987.

35. T. Arai, H. Ogawa, A. Awata, M. Sato, M. Watabe and M. Yamanaka, *Angew. Chem. Int. Ed.*, 2015, **54**, 1595-1599.

36. R. Jasiński, J. Socha and A. Barański, *Chem. Heterocycl. Compd.*, 2013, **49**, 1055-1060.