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Intercepting the Banert cascade with nucleophilic fluorine: direct access to α-fluorinated *NH*-1,2,3-triazoles†

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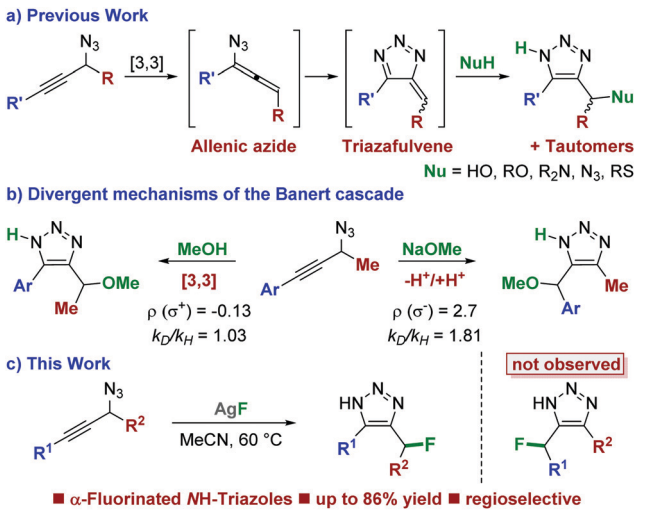
The treatment of propargylic azides with silver(I) fluoride in acetonitrile was found to yield α-fluorinated *NH*-1,2,3-triazoles *via* the Banert cascade. The reaction was regioselective and the products result from an initial [3,3] rearrangement. The reaction is demonstrated on >15 examples with yields ranging from 37% to 86%.

Triazoles are an important class of nitrogen heterocycles that have applications in polymer science,[1–4] medicinal chemistry,[5,6] and drug discovery.[7–9] Triazoles have also gained recognition as pharmacophores, glycoside mimics, and protease-resistant peptidomimetics.[8,10,11] Likewise, the incorporation of fluorine plays a significant role in drug discovery,[12,13] pharmaceutical development,[14,15] and the agrochemical industry.[16,17] In 2019, almost 30% of new FDA approved drugs contained at least one fluorine atom.[18] It is well accepted that the presence of fluorine enhances many pharmacokinetic properties including potency, metabolic stability, and membrane permeability. Therefore, new synthetic methods for incorporating a fluorine atom into heterocycles[19] are highly desirable.[12,20]

Many reactions used to access triazoles rely on azide–alkyne cycloadditions and predominantly form *N*-substituted triazoles.[21–29] While *NH*-triazoles may be desirable,[30–37] the hazards of working with HN_3 or $TMSN_3$ complicates their synthesis.[38] Hydrazoic acid is highly explosive in neat form and it is toxic. Therefore, specialised reactors[39] or designer synthons[40] are often required. TMS-N_3 has shown utility in the synthesis of *NH* triazoles.[38,41,42] However, in the presence of water or acid, HN_3 can be liberated from the reaction.[43]

One exciting reaction of azides[44–48] that directly affords *NH*-triazoles is the Banert cascade of propargylic azides.[49–58] This reaction proceeds *via* a triazafulvene intermediate that can be trapped by various N, O, S, or C centred nucleophiles.[24,56,59] As a complicating feature, the Banert cascade can result in regioisomeric *NH*-1,2,3-triazoles. Recently, the mechanistic divergence of the Banert cascade was investigated (Scheme 1b).[24] To our knowledge, a *NH*-1,2,3-triazole bearing an α-fluorine atom has not yet been reported. We endeavoured to access such molecules utilizing the Banert cascade with a nucleophilic fluoride source that would allow access to this potentially exciting motif (Scheme 1c).

This investigation began by treating propargyl azide **1a** with common nucleophilic fluoride sources in acetonitrile (Table 1, entries 1–9). The modestly elevated temperature was used to promote the sigmatropic rearrangement. Due to the high basicity of fluoride anion in organic media, a competing prototropic pathway was conceivable.[24] Gratifyingly, AgF provided the desired product in excellent yield (Table 1, entry 9). With AgF, the regioisomer originating from the prototropic rearrangement was not observed. This indicates that the silver coordinated fluoride anion was not significantly basic under these conditions. All other fluoride sources examined resulted



Scheme 1 Scope of the Banert cascade.

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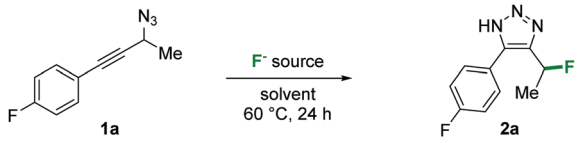
Table 1 Reaction optimisation



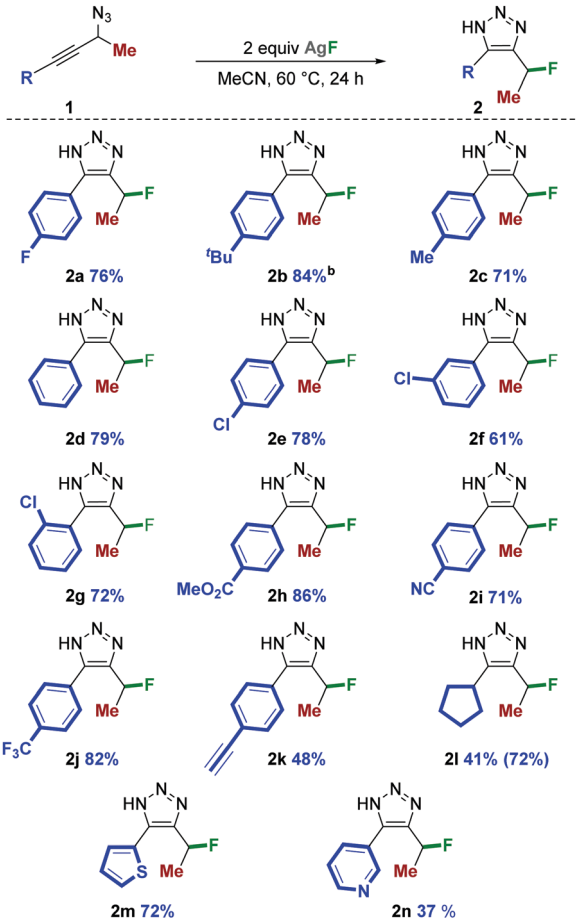
Entry	Fluoride source	Solvent	Yield[a] (%)
1	CsF	MeCN	n.d
2	NH_4F	MeCN	n.d
3	NaF	MeCN	n.d
4	TMAF	MeCN	n.d
5	DMPU-HF	MeCN	n.d
6	HF-Et_3N	MeCN	n.d
7	ZnF_2	MeCN	n.d
8	KF	MeCN	n.d
9	AgF	MeCN	95
10	AgF	DMF	9
11	AgF	CH_2Cl_2	15
12	AgF	PhMe	n.d
13	AgF	Et_2O	n.d
14	AgF	MeOH	n.d
15	AgF	EtCN	83
16	AgF	MeCN/H_2O	45
17	$AgNO_3$ + CsF	MeCN	94
18	$AgNO_3$ + KF	MeCN	51

[a] Reactions conducted with azide **1a** (0.09 mmol) and fluoride source (0.18 mmol) at 0.1 M in varying solvent at 60 °C. Yield determined from the quenched reaction mixture against anisonitrile as an internal standard *via* calibrated HPLC-UV. All yield values reflect the average of duplicate trials. Abbreviation n.d. = not detected (less than 5%).

in partially recovered starting material and/or complex mixtures.

A screen of alternate solvents with AgF did not yield superior results (Table 1, entries 9–15). Presumably, the solubility of AgF is minimal in less coordinating solvents and more nucleophilic solvents may trap the triazafulvene intermediate.[56] In MeOH, the MeOH adduct was exclusively formed (Table 1, entry 14).[24] This may be due to the poor solubility of AgF in MeOH compared to MeCN,[60,61] or due to the weak nucleophilicity of solvated fluoride anion.[62] Furthermore, when azide **1a** was treated with AgF in wet MeCN (10% H_2O), a mixture of adducts were observed (45% fluorinated, Table 1, entry 16). This indicates that while adventitious water may not be problematic, larger quantities are deleterious because water is a competing nucleophile. To probe the importance of silver in the reaction, propargyl azide **1a** was treated with a mixture of $AgNO_3$ and CsF or KF, which lead to the desired fluorinated triazole product (Table 1, entries 17 and 18); whereas, treatment with CsF alone (Table 1, entry 1) yielded unreacted or decomposed azide. Cationic silver is known to activate alkynes[63] and allenes[64,65] to cycloaddition, therefore, it is conceivable that silver activates this system in acetonitrile.[66] The results in entry 9 were taken as optimal.

With optimal conditions in hand, the substrate scope of the reaction was examined (Scheme 2). The model substrate **2a** was isolated in acceptable yield. As anticipated, based on the mechanism of the initial [3,3] rearrangement, the reaction is compatible with electron donating (**2b**-**2c**), neutral (**2d**) and electron withdrawing (**2e**–**2j**) groups on the aromatic ring.



Scheme 2 Substrate scope[a]. [a]Isolated yields are reported. Reactions conducted with azide (0.5 mmol) and AgF (1.0 mmol) in MeCN (0.1 M) at 60 °C. All yield values reflect the average of duplicate trials. [b]Reaction performed on >1 mmol scale.

The reaction forming product **2b** was conducted on a 1 mmol scale, which afforded an identical yield. An *ortho* chlorine was not problematic (**2g**). Several common functional groups were compatible with the conditions including an ester (**2h**), nitrile (**2i**) and alkyne (**2k**) group. The pendent aryl group was not required and could be changed for an alkyl group (**2l**, 72% by NMR analysis, 41% isolated). Lastly both electron rich (**2m**) and poor (**2n**) heterocycles could be incorporated.

Several modifications were tolerated on the azide bearing carbon (Scheme 3). The secondary azide was not required and primary fluorides **2o**–**2q** could be isolated from a primary azide in acceptable yields. Larger groups could also be incorporated into the system (**2r**–**2s**). Lastly, a tertiary fluoride product could be isolated (**2t**).

Other silver salts were examined for reactivity in the presence of propargyl azide **1a** (Scheme 4). The use of AgOAc, cleanly gave acetate **3a** in high yield. Phenyl ether **3b** could be isolated from the use of Ag_2CO_3 in the presence of base. Water can be used as a simple nucleophile (**3c**), and the product resulting from elimination was isolated when using AgTFA (**3d**). Reactions conducted in the absence of silver did not afford comparable yields (see ESI†).

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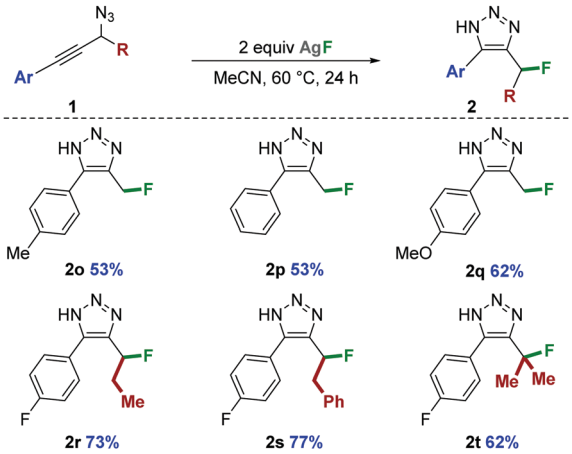
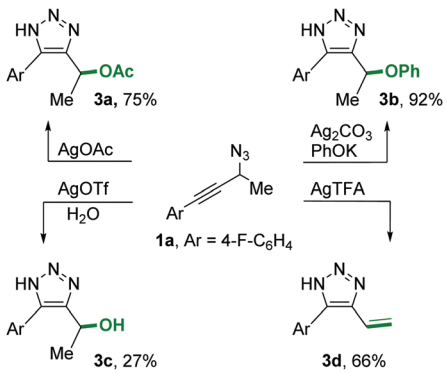
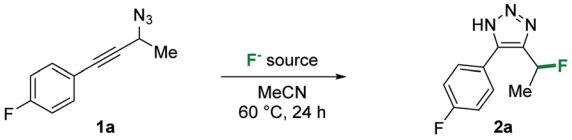


Scheme 3 Modification to Azide[a]. [a]Isolated yields are reported. Reactions conducted with azide (0.5 mmol) and AgF (1.0 mmol) at 0.1 M in MeCN at 60 °C. All yield values reflect the average of duplicate trials.



Scheme 4 Reactivity with Other Silver Salts[a]. [a]Isolated yields are reported. Reactions conducted with azide (<0.5 mmol, 1 equiv.) and at 0.1 M in MeCN at 60 °C. All yield values reflect the average of single trials.

Table 2 Reactions using one gram of compound **1a**



Entry	F^- source	Yield (%)	Mass of **1a** (g)	Mass of **2a** (mg)
1	2 equiv. AgF	74	1.00	817
2	2 equiv. $AgNO_3$ 2 equiv. CsF	57	1.00	634
3	20 mol% $AgNO_3$ 2 equiv. CsF	11	1.00	121

Yield is reported for a single trial. Isolated yield is reported.

This fluorination reaction could be conducted using one gram of azide **1a** (Table 2). At this scale, the reaction afforded a 74% isolated yield of product **2a**, which is comparable to the 76% isolated on a smaller scale. A reaction at the same scale utilizing CsF and $AgNO_3$ afforded a 57% yield (entry 2). Utilizing substoichiometric $AgNO_3$ (20 mol%) was detrimental to the yield (entry 3).

In summary, silver(I) fluoride can intercept the Banert cascade to deliver α-fluorinated *N*H-1,2,3-triazoles. The scope of this process is broad and a range of fluorinated triazoles could be isolated (>15 examples, up to 86% yield). This reaction expands both the scope of the Banert cascade as well as access to *N*H-triazole bioisosteres.

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Conflicts of interest

The authors declare no competing financial interest.

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