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Silver Mediated Banert Cascade with Carbon Nucleophiles

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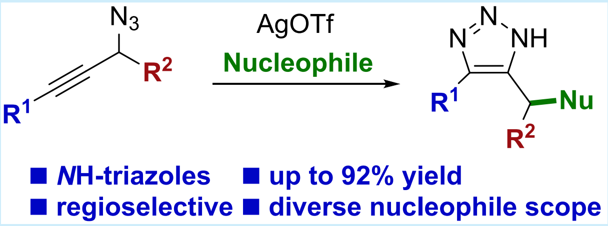
ABSTRACT: The Banert cascade of propargylic azides can be promoted by simple silver salts, and the triazafulvene intermediate can be intercepted by carbon nucleophiles. Various indoles (>25 examples, up to 92% yield) and electron-rich heterocycles were effective. The Mayr nucleophilicity parameter (*N*) was found to correlate to the reaction efficiency, which enabled the formation of $C_{sp^3}-C_{sp^2}$ and $C_{sp^3}-C_{sp^3}$ bonds under otherwise identical conditions from structurally dissimilar nucleophiles.



The triazole heterocycle has been widely adopted as a key molecular building block for a variety of synthetic applications including in drug discovery,[1−4] medicinal chemistry,[5−8] bioconjugation,[9,10] and material science.[11−13] Triazoles are small, polar, and stable *N*-heterocycles that can be used as a peptidomimetic,[2,14,15] amide isostere,[16,17] *N*-acetyl lysine mimic,[7,8] or glycosyl surrogate.[18−20] *NH*-triazoles contain a hydrogen bond donor, more closely resembling sugars and native amides, relative to *N*-substituted triazoles. *NH*-triazoles can adopt three N−H tautomeric structures, providing additional flexibility,[21] and they have demonstrated utility in multiple contexts.[22−26]

Forming *NH*-triazoles by CuAAC or RuAAC has been problematic from the standpoint of reactivity and safety.[27−29] Thus, we focused on the Banert cascade of propargylic azides (Figure 1b).[30−34] This process commences by either a sigmatropic or prototropic rearrangement,[35] resulting in an allenyl azide.[35,36] The allenyl azide undergoes electrocyclization[37] to form a triazafulvene.[38] The triazafulvene will polymerize or can be intercepted by exogenous nucleophiles, including alcohols, water, amines, thiols, or azide anion.[30,32,39,40] We were surprised by a lack of well documented reports utilizing carbon nucleophiles to terminate the Banert cascade.[25,41] Presented herein are silver mediated conditions enabling the construction of carbon−carbon bonds *α* to the newly formed *NH*-triazole (Figure 1c).

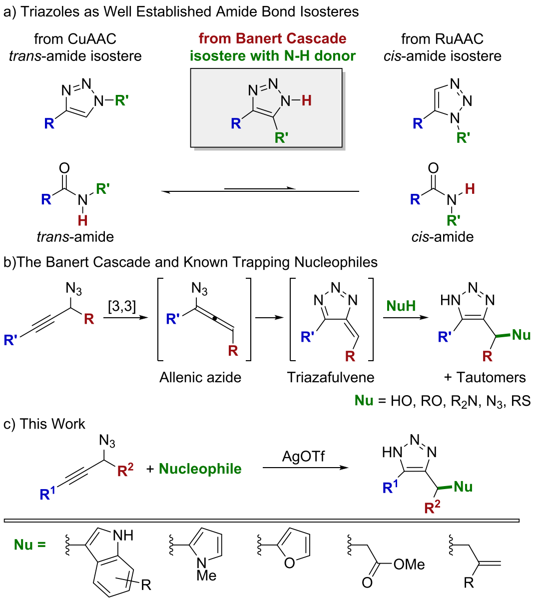


Figure 1. Triazole isosterism and the Banert cascade.

This study began by screening model azide **1a** with 2-methylindole (**2a**), a representative indole of moderate nucleophilicity (*vide infra*). Small quantities of product **3a** were observed upon heating to 60 °C (Table 1, entry 1). Attempts at optimizing this reaction in the absence of a catalyst were not fruitful (not shown). Silver salts are known to activate alkynes[42,43] and allenes[44,45] to cycloaddition reactions. Therefore, it was hypothesized that a silver salt may promote the reaction. The addition of $AgNO_3$ increased the yield of **3a** (entry 2). A silver salt screen (entries 2−5 and Supporting Information) identified AgOTf as an excellent promoter (entry 4). A solvent screen indicated that nitrile solvents were optimal (entries 6−9). Decreasing the loading of AgOTf demonstrated that substoichiometric quantities of silver can catalyze the reaction (entries 10−12 vs entry 1), but did not further increase the yield of compound **3a** relative to entry 4. Increasing the silver loading did not increase the yield (entries 13 and 14). Adding more indole **2a** improved the yield (entries

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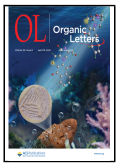

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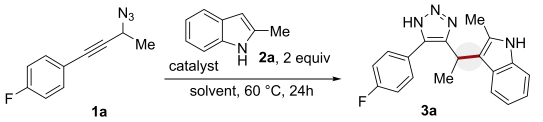
Table 1. Optimization with Indole 2a[a]



entry	AgX	equiv of AgX	equiv 2a	solvent	% yield[b]
1	–	–	1	MeCN	23
2	$AgNO_3$	1	1	MeCN	50
3	$AgBF_4$	1	1	MeCN	55
4	AgOTf	1	1	MeCN	73
5	AgTFA	1	1	MeCN	47
6	AgOTf	1	1	CH_2Cl_2	–
7	AgOTf	1	1	THF	13
8	AgOTf	1	1	DMF	28
9	AgOTf	1	1	CH_3CH_2CN	61
10	AgOTf	0.1	1	MeCN	56
11	AgOTf	0.2	1	MeCN	60
12	AgOTf	0.5	1	MeCN	65
13	AgOTf	1.5	1	MeCN	70
14	AgOTf	2	1	MeCN	70
15	AgOTf	1	1.5	MeCN	81
16	AgOTf	1	2	MeCN	86
17	AgOTf	1	5	MeCN	77

[a] Reactions conducted with azide **1a** (0.1 mmol) and 2-methylindole (**2a**) at 0.1 M in varying solvent at 60 °C. All yield values reflect the average of duplicate trials. [b] Yield determined using calibrated GC-FID with naphthalene as an internal standard.

15–17). The conditions in entry 16 were taken as optimal. Under these conditions, only one triazole regioisomer was observed, originating from a sigmatropic rearrangement. The three N–H tautomers are dynamic on the NMR time scale.

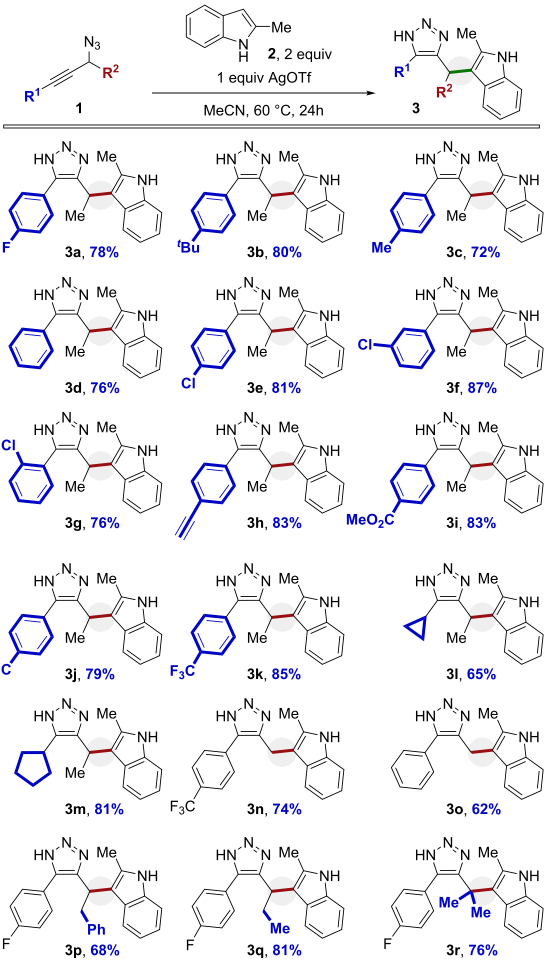
The azide scope was investigated (Scheme 1). The model substrate **3a** was isolated in 78% yield. Other azides containing an aryl group provided similar results (**3b**–**3f**). An *ortho* substituent did not impact the yield (**3g**). Various functional groups were tolerated (**3h**–**3k**). The pendent aryl ring was not required (**3l**–**3m**). The reaction also proceeded with primary (**3n**–**3o**), secondary (**3p**–**3q**), and tertiary (**3r**) azides.

The indole scope was investigated (Scheme 2). Indoles with various substituents worked well (**4a**–**4e**). Even potent withdrawing groups ($-NO_2$) were tolerated (**4f**). A phenyl group at C-2 did not affect the reaction (**4g**). The indole present in cediranib worked (**4h**), and *N*-methylation was tolerated (**4i**).

It seemed prudent to expand the nucleophile scope. Since the product-forming step required nucleophilic attack (Figure 1), the Mayr table of nucleophilicity parameters (*N*) was consulted.[47] The model nucleophile **2a** has an *N* value of 6.91.[48] This is significantly higher than the value for indole ($N = 5.55$, **6a**, Scheme 3).[48] *N*-Methyl pyrrole ($N = 5.85$)[49] led to product **6b**, and imidazole ($N = 11.47$)[50] afforded product **6c**. Furan ($N = 1.33$)[51] did not afford product. However, potassium 2-furanyl-trifluoroborate (*N* value = 5.99)[52] did (**6d**) as did allyl tributylstannane ($N = 5.46$, **6e**),[49] 2-methylallyltributylstannane ($N = 7.48$, **6f**),[49] and silyl-ketene acetal ($N = 10.3$, **6g**).[53] Taken together, these data expand the scope of participating nucleophile well beyond indoles and provide guidance on which untested nucleophiles would be likely to participate ($N > 5.4$).

In conclusion, the Banert cascade can be terminated by a wide array of carbon nucleophiles. The scope of both the azide

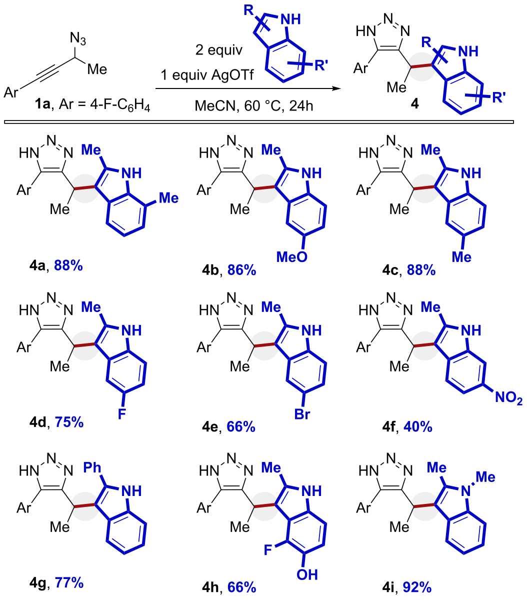
Scheme 1. Substrate Scope with Respect to Azide[a]



3a, 78%
3b, 80%
3c, 72%
3d, 76%
3e, 81%
3f, 87%
3g, 76%
3h, 83%
3i, 83%
3j, 79%
3k, 85%
3l, 65%
3m, 81%
3n, 74%
3o, 62%
3p, 68%
3q, 81%
3r, 76%

[a] Yields are reported for isolated and purified products. Yield values reflect the average of duplicate trials.

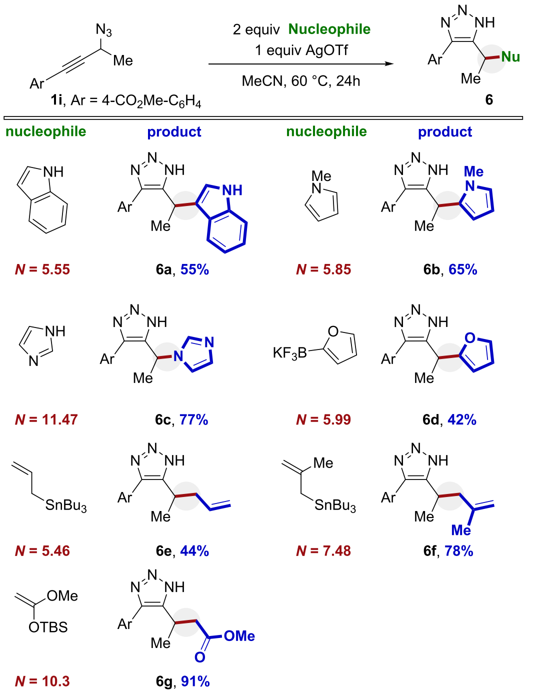
Scheme 2. Substrate Scope for Indole[a]



4a, 88%
4b, 86%
4c, 88%
4d, 75%
4e, 66%
4f, 40%
4g, 77%
4h, 66%
4i, 92%

[a] Yields are reported for isolated and purified products. Yield values reflect the average of duplicate trials.

Scheme 3. Scope of Other Nucleophiles and N Parameter[a]



[a] Yields are reported for isolated and purified products. Yield values reflect the average of duplicate trials.

(1′, 2′, and 3′; α-aryl and α-alkyl) and nucleophile (N values range from 5.46 to 10.3, formation of C_{sp^3}–C_{sp^2} and C_{sp^3}–C_{sp^3} bonds) are quite broad under identical reaction conditions. Due to the well documented utility of 1,2,3-triazoles as amide isosteres, it is noteworthy that these products from this reaction feature side chains mapping onto native amino acids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01032.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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