Sequential One-Pot Ruthenium-Catalyzed Azide-Alkyne Cycloaddition from Primary Alkyl Halides and Sodium Azide

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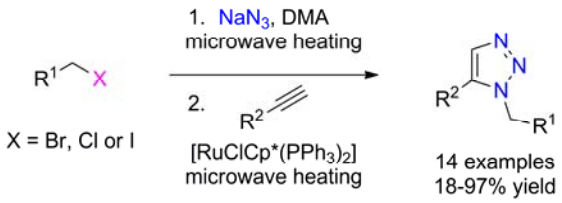


ABSTRACT An experimentally simple sequential one-pot RuAAC reaction, affording 1,5-disubstituted 1*H*-1,2,3-triazoles in good to excellent yields starting from an alkyl halide, sodium azide and an alkyne, is reported. The organic azide is formed *in situ* by treating the primary alkyl halide with sodium azide in DMA under microwave heating. Subsequent addition of [RuClCp*(PPh$_3$)$_2$] and the alkyne yielded the desired cycloaddition product after further microwave irradiation.

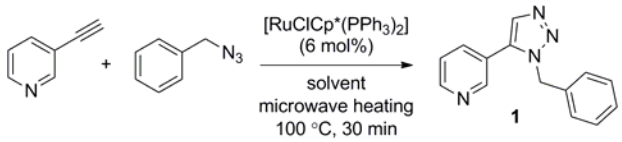
MANUSCRIPT TEXT One of the most well known click reactions, the copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) to form 1,4-disubstitued triazoles,[1] has found numerous applications, not only within the organic chemistry community but also in other areas such as bioconjugation and materials science.[2] More recently, Fokin and Jia have reported a versatile ruthenium-catalyzed azide-alkyne cycloaddition reaction (RuAAC) that gives access to the isomeric 1,5-substituted triazoles, using a [RuClCp*] catalyst with different ligands either under conventional heating[3] or microwave conditions.[4] However, applications of the RuAAC reaction are as yet less prevalent in comparison to the CuAAC reaction.[5] Recently a mild and efficient base-catalyzed metal-free reaction, giving access to 1,5-diaryl-substituted triazoles has also been disclosed. Despite the many advantages in terms of mild reaction conditions, facile isolation and purification as well as environmental benefits, this reaction is limited to aryl alkynes and aryl azides as substrates.[6]

One restriction of organic reactions involving azides is that the selection of commercially available aryl and alkyl azides is limited, and also the fact that low-molecular weight organic azides, especially those with a low carbon-to-nitrogen ratio, are considered to be highly energetic and potentially explosive.[7] For the CuAAC reaction, this problem has been addressed by developing one-pot procedures where the organic azide is generated *in situ*.[8] However, for the RuAAC reaction affording 1,5-disubstitued triazoles, no such convenient method has been reported. We here report a simple sequential one-pot procedure, starting from primary alkyl halides and sodium azide, that avoids handling of the neat hazardous alkyl azide.

Initially, as a test reaction, the RuAAC reaction between benzyl azide and 3-ethynylpyridine was studied in different solvents under microwave heating using [$RuClCp^*(PPh_3)_2$] as the catalyst, and the results are summarized in Table 1. Ethers like dioxane, THF and 2-MeTHF gave full conversion of the alkyne. In polar solvents such as DMSO, acetonitrile and water or mixtures of water with an organic solvent, low or only trace amounts of product were obtained. However, the use of DMA as solvent afforded complete consumption of the alkyne but with competing formation of dimerization by-

products[9] to a larger extent than when THF was used. However, by using two equivalents of the azide, this side reaction could be suppressed. Since the formation of alkyl azides from alkyl halides and sodium azide is normally performed in polar solvents such as DMSO, DMF or water, DMA was thus the obvious choice for a one-pot procedure. Fokin and Jia have reported the isolation of [RuClCp*] tetraazadiene complexes when an excess of the azide was used or when the azide was added to the catalyst before the alkyne, and found such species to be catalytically inactive.[3b] This was not the case for the substrates used in our study, however.

Table 1. RuAAC reaction to form triazole **1** with an alkyne/azide ratio of 1:1 in different solvents.

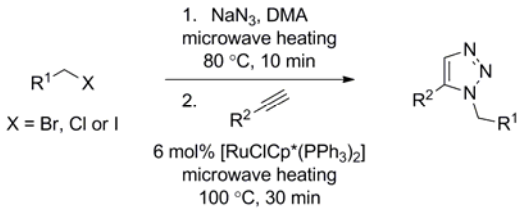


Solvent	Conv.	Solvent	Conv.	Solvent	Conv.
Dioxane	~95%	DMA	~95%	H_2O	~5%
THF	100%	DMSO	<5%	THF/H_2O 3:1	~10%
2-MeTHF	100%	CH_3CN	~5%	CH_3CN/H_2O 3:1	~5%

We then explored the possibility of developing a one-pot procedure for the RuAAC starting directly from an alkyl halide. When benzyl bromide (2 equiv.), sodium azide (2 equiv.), 3-ethynylpyridine (1 equiv.) and 6 mol% [RuClCp*(PPh_3)$_2$] were mixed in DMA and heated to 100 °C for 30 min in a microwave reactor in a one-pot procedure, only traces of product were obtained and most of the alkyne remained unreacted. This can be due to a side-reaction of the ruthenium catalyst with sodium azide.[10] However this problem can easily be overcome by simply running the reaction as a *sequential* one-pot procedure instead. When the alkyne and catalyst were added after the generation of the alkyl azide, full conversion of the alkyne to 1,5-disubstituted 1,2,3-triazole was obtained. The 1,5-substitution pattern was confirmed by 2D NOESY experiments. The use of [RuClCp*COD] as the catalyst was also investigated at several different temperatures ranging from ambient temperature to 100 °C, however the conversion was much lower under these conditions.

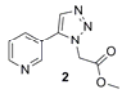
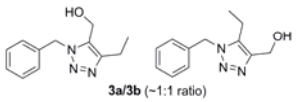
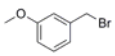
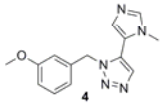
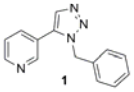
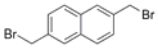
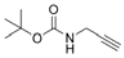
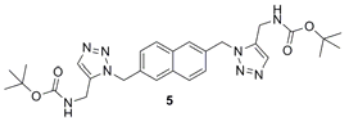
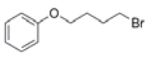
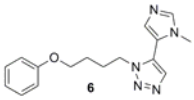
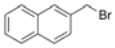
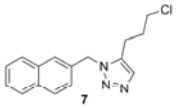
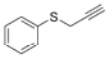
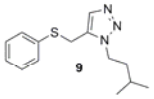
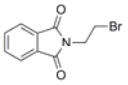
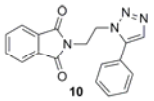
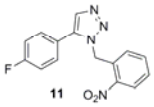
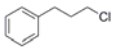
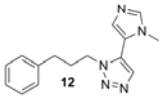
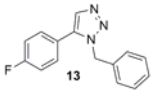
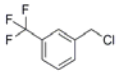
With this novel sequential one-pot procedure in hand (Scheme 1), the scope of the method was investigated with a range of different alkyl halides and alkynes. The results are summarized in Table 2.

Scheme 1. Sequential one-pot RuAAC reaction.[a]



[a] 2.0 equiv of alkyl halide, 2.0 equiv of sodium azide and 1.0 equiv of alkyne was used.

Table 2. Scope of the sequential one-pot RuAAC reaction to form 1,5-disubstituted 1,2,3-triazoles[a]

Entry	Halide	Alkyne	Conditions[b]	Product	Isolated Yield
1			A	 **2**	88%
2			A	 **3a/3b** (~1:1 ratio)	85%
3			A	 **4**	93%
4			A	 **1**	82%
5			A	 **5**	52%
6			B	 **6**	70%
7			A	 **7**	58%
8			A	 **8**	18%
9			B	 **9**	73%
10			B	 **10**	92%
11			A	 **11**	92%
12			B	 **12**	47%
13			B	 **13**	97%
14			B	**14**	61%

[a] 2.0 equiv of alkyl halide, 2.0 equiv of sodium azide, 1.0 equiv of alkyne and 6 mol% [$RuClCp^*(PPh_3)_2$] in DMA was used. [b] Conditions A: heated to 80 °C for 10 min to generate the alkyl azide and 100 °C for 30 min for the cycloaddition step. Conditions B: heated to 100 °C and 120 °C respectively.

Benzylic bromides (entries 2-5, 7 and 11) as well as other activated halides such as methyl 2-bromoacetate (entry 1), afforded 1,5-disubstituted 1,2,3-triazoles in good to excellent yields. Aliphatic bromides gave slower reactions but otherwise performed well and the desired cycloaddition products were obtained in good yields when the temperature was increased from 80 °C to 100 °C for the first step and from 100 °C to 120 °C for the subsequent cyclization reaction. When the internal alkyne pent-2-yn-1-ol was used (entry 2) a ~1:1 mixture of the two isomers was formed. This is in contrast with results reported by Weinreb for similar propargylic alcohols,[3c] where only one isomer is obtained. To understand if the reaction conditions used in our method gave rise to this regionselectivity, the RuAAC reaction between benzyl azide and pent-2-yn-1-ol catalyzed by [RuClCp*(PPh_3)$_2$] was performed in benzene at 100 °C for 20 min in a microwave reactor. However, the same regioisomeric ratio as previously was obtained, and we thus conclude that the regioselectivity is substrate dependant in this particular case. Small halides of low molecular weight were problematic, probably due to the instability and potential decomposition of the corresponding azide at the reaction temperature. However, despite the low boiling point of methyl azide (21 °C),[11] the triazole was obtained in 18% yield when methyl iodide (entry 8) was used in a sealed microwave vial at 80 °C in a microwave reactor. (CAUTION! The reaction generating methyl azide and other small alkyl azides is potentially explosive and can be dangerous to scale up. The reaction should only be carried out in a microwave reactor which can withstand an explosion of the reaction vial.) Primary alkyl chlorides (entries 12-14), reacted more slowly compared to the alkyl bromides and needed higher reaction temperatures to obtain moderate to excellent yields of the corresponding products.

Secondary alkyl halides such as cyclohexyl bromide did not afford any product in our case even at higher temperatures, although previous reports show that secondary azides can participate in the cycloaddition reaction but react more slowly compared to primary azides.[3b,c] Another limitation is that the presence of acidic groups (carboxylic acid or boronic acid) in the alkyl halide or alkyne substrate, inhibited the reaction and no triazole product was formed in these reactions. Likewise, pyridine or amine functionalities in the form of the HCl- or HBr- salt present in the substrates were not tolerated.

Further work is in progress to investigate if the scope of the sequential one-pot reaction can be expanded to include also these classes of substrates.

In summary, a simple and practical sequential one-pot method for the generation of 1,5-disubstituted 1,2,3-triazoles has been developed. We hope this method will increase the use of the RuAAC reaction by enabling direct use of the more easily accessible primary halides, thus avoiding the hazardous handling of alkyl azides. We envision that this procedure can find many applications in the pharmaceutical industry for making small focused libraries of the 1,5-regioisomer, difficult to access by other means.

Experimental Section

General information: Chemicals were obtained from commercial suppliers and used without purification unless otherwise noted. [RuClCp*(PPh_3)$_2$] (orange solid) was purchased from Strem Chemicals Inc and used as such. All microwave reactions were carried out in a Biotage Series 60 Initiator (actual vial temperature was monitored using an IR sensor), using fixed hold time. Abbreviations for NMR are: s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet; app, apparent. Chemical shifts (δ) are given in ppm relative to the solvent residual peak (CHCl3: 7.26 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C NMR and DMSO: 2.50 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR) or an internal standard (TMS: 0.00 ppm for ^{1}H NMR). The 1,5-substitution pattern was confirmed for triazoles **5** and **9** by 2D NOESY experiments.

General procedure for solvent investigation

In a microwave vial were placed 3-ethynylpyridine (20.6 mg, 0.20 mmol), 6 mol% [RuClCp*(PPh_3)$_2$] (9.6 mg, 0.012 mmol) and solvent (3 mL). Benzyl azide (53.2 μL, 0.4 mmol) was added and the vial was sealed and flushed with N_2 for 1-2 min. The reaction mixture was heated to 100 °C for 30 min in a microwave reactor. The reaction was analyzed with LCMS and TLC.

General procedure A and B

In a microwave vial were placed sodium azide (13.0 mg, 0.20 mmol or 26.0 mg, 0.40 mmol), alkyl halide (see Table 2) (0.20 mmol or 0.40 mmol) and DMA (3 mL). The reaction mixture was heated to 80 °C (**A**) or 100 °C (**B**) for 10 min in a microwave reactor. CAUTION! The reaction generating small alkyl azides is potentially explosive and can be dangerous to scale up. The reaction should only be carried out in a microwave reactor which can withstand an explosion of the reaction vial. The vial was uncapped and the alkyne (0.10 mmol or 0.20 mmol) was added followed by addition of 6 mol% [RuClCp*(PPh_3)$_2$]. The vial was sealed and flushed with nitrogen for 1-2 min without stirring. The reaction mixture was heated to 100 °C (**A**) or 120 °C (**B**) for 30 min in a microwave reactor. The resulting product mixture was purified by flash chromatography on silica using a gradient system of 0-30% ethyl acetate in heptane followed by 0-30% methanol in CH_2Cl_2. Fractions were collected using UV-detection at 254 and/or 280 nm to obtain the entitled product.

3-(1-Benzyl-1*H*-1,2,3-triazol-5-yl)pyridine (1): Following the general procedure **A** using benzyl bromide (23.9 µL, 0.20 mmol), sodium azide (13.0 mg, 0.20 mmol) and 3-ethynylpyridine (10.3 mg, 0.10 mmol) to obtain 3-(1-benzyl-1*H*-1,2,3-triazol-5-yl)pyridine (**1**) as a yellowish oil. Yield: 19.4 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (br d, *J* = 3.8 Hz, 1H), 8.53 (br s, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.52 (dt, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.32 – 7.26 (m, 3H), 7.08 – 7.03 (m, 2H), 5.57 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 149.4, 136.3, 135.1, 135.0, 134.2, 129.2, 128.6, 127.2, 123.7, 52.3 (two aromatic signals overlap). HRMS (ESI-TOF) calculated for $C_{14}H_{13}N_4^+$ (M + H) 237.1140, found 227.1148.

Methyl 2-(5-(pyridin-3-yl)-1*H*-1,2,3-triazol-1-yl)acetate (2): Following the general procedure **A** using methyl 2-bromoacetate (18.9 µL, 0.20 mmol), sodium azide (13.0 mg, 0.20 mmol) and 3-ethynylpyridine (10.3 mg, 0.10 mmol) to obtain methyl 2-(5-(pyridin-3-yl)-1*H*-1,2,3-triazol-1-yl)acetate as a brownish oil. Yield: 19.1 mg (88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 – 8.59 (m, 2H), 7.82 (s, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.51 – 7.41 (m, 1H), 5.15 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.9, 151.1, 149.3, 136.4, 135.9, 133.9, 124.0, 123.2, 53.3, 49.3. HRMS (ESI-TOF) calculated for $C_{10}H_{11}N_4O_2^+$ (M + H) 219.0882, found 219.0883.

(1-Benzyl-4-ethyl-1*H*-1,2,3-triazol-5-yl)methanol/(1-benzyl-5-ethyl-1*H*-1,2,3-triazol-4-yl)methanol (3a/3b): Following the general procedure **A** using benzyl bromide (23.9 μL, 0.20 mmol), sodium azide (13.0 mg, 0.20 mmol) and pent-2-yn-1-ol (8.4 mg, 0.10 mmol) to obtain a ~1:1 mixture of the regioisomers of **3** as a yellowish-brown oil. Yield: 18.4 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.12 (m, 5H), 5.58 (s, minor isomer) and 5.48 (s, major isomer, 2H), 4.70 (s, major isomer) and 4.55 (s, minor isomer, 2H), 3.52 (br s, minor isomer) and 3.08 (br s, major isomer, 1H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, minor isomer) and 1.03 (t, *J* = 7.6 Hz, major isomer, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.9, 144.6, 136.5, 135.4, 135.2, 131.6, 129.2, 129.1, 128.6, 128.5, 127.7, 127.3, 56.1, 52.5, 52.3, 52.1, 18.5, 16.3, 14.5, 13.5. HRMS (ESI-TOF) calculated for $C_{12}H_{16}N_3O^+$ (M + H) 218.1293, found 218.1297.

1-(3-Methoxybenzyl)-5-(1-methyl-1*H*-imidazol-5-yl)-1*H*-1,2,3-triazole (4): Following the general procedure **A** using 1-(bromomethyl)-3-methoxybenzene (28.0 μL, 0.20 mmol), sodium azide (13.0 mg, 0.20 mmol) and 5-ethynyl-1-methyl-1*H*-imidazole (10.2 μL, 0.10 mmol) to obtain 1-(3-methoxybenzyl)-5-(1-methyl-1*H*-imidazol-5-yl)-1*H*-1,2,3-triazole (**4**) as a yellowish oil. Yield: 25.0 mg (93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.55 (br s, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.11 (br s, 1H), 6.82 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.61 – 6.53 (m, 2H), 5.46 (s, 2H), 3.71 (s, 3H), 3.16 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.1, 140.4, 136.4, 135.2, 131.8, 130.1, 126.6, 119.8, 118.4, 114.4, 112.9, 55.4, 52.4, 31.9. HRMS (ESI-TOF) calculated for $C_{14}H_{16}N_5O^+$ (M + H) 270.1355, found 270.1357.

Di-*tert*-butyl ((1,1'-(naphthalene-2,6-diylbis(methylene))bis(1*H*-1,2,3-triazole-5,1-diyl))bis-(methylene))dicarbamate (5): Following the general procedure **A** using 2,6-bis(bromomethyl)-naphthalene (62.8 mg, 0.20 mmol) and *tert*-butyl prop-2-yn-1-ylcarbamate (31.0 mg, 0.20 mmol) to obtain di-*tert*-butyl ((1,1'-(naphthalene-2,6-diylbis(methylene))bis(1*H*-1,2,3-triazole-5,1-diyl))bis-(methylene)) dicarbamate (**5**) as an off-white solid. Yield: 57.0 mg (52%, purity 96%). ^{1}H NMR (800 MHz, DMSO-d_6) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.68 (s, 2H), 7.55 (s, 2H), 7.48 – 7.44 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.75 (s, 4H), 4.18 (d, *J* = 5.2 Hz, 4H), 1.29 (s, 18H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.5, 136.0, 133.7, 132.8, 132.2, 128.5, 125.9, 125.8, 78.4, 50.6, 32.9, 28.0. HRMS (ESI-TOF)

calculated for $C_{28}H_{37}N_8O_4^+$ (M + H) 549.2938, found 549.2943. The 1,5-substitution pattern was confirmed by a 2D NOESY experiment**.**

5-(1-Methyl-1*H*-imidazol-5-yl)-1-(4-phenoxybutyl)-1*H*-1,2,3-triazole (6): Following the general procedure **B** using (4-bromobutoxy)benzene (106.0 mg, 0.46 mmol), sodium azide (13.0 mg, 0.20 mmol) and 5-ethynyl-1-methyl-1*H*-imidazole (20.4 µL, 0.2 mmol) to obtain 5-(1-methyl-1*H*-imidazol-5-yl)-1-(4-phenoxybutyl)-1*H*-1,2,3-triazole (**6**) as a brownish oil. Yield: 41.7 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.64 (s, 1H), 7.31 – 7.19 (m, 3H), 6.95 – 6.91 (m, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 4.39 (t, *J* = 7.1 Hz, 2H), 3.93 (t, *J* = 5.9 Hz, 2H), 3.55 (s, 3H), 2.10 – 2.01 (m, 2H), 1.82 – 1.72 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.8, 140.6, 134.4, 131.6, 129.6, 126.5, 121.0, 118.7, 114.5, 66.8, 48.3, 32.4, 27.2, 26.4. HRMS (ESI-TOF) calculated for $C_{16}H_{20}N_5O^+$ (M + H) 298.1668, found 298.1673.

5-(3-Chloropropyl)-1-(naphthalen-2-ylmethyl)-1*H*-1,2,3-triazole (7): Following the general procedure **A** using 2-(bromomethyl)naphthalene (45.1 mg, 0.20 mmol, purified by flash chromatography), sodium azide (13.0 mg, 0.20 mmol) and 5-chloropent-1-yne (10.7 µL, 0.1 mmol) to obtain 5-(3-chloropropyl)-1-(naphthalen-2-ylmethyl)-1*H*-1,2,3-triazole (**7**) as a brownish oil. Yield: 16.7 mg (58%, purity 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 3H), 7.60 (s, 1H), 7.54 (s, 1H), 7.52 – 7.47 (m, 2H), 7.32 – 7.25 (m, 1H), 5.70 (s, 1H), 3.46 (t, *J* = 6.0 Hz, 1H), 2.74 (t, *J* = 7.6 Hz, 2H), 1.98 – 1.90 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 133.4, 133.2, 133.1, 132.4, 129.3, 128.1, 128.0, 126.9, 126.8, 126.4, 124.8, 52.2, 43.7, 30.7, 20.5. HRMS (ESI-TOF) calculated for $C_{16}H_{17}ClN_3^+$ (M + H) 286.1111, found 286.1114.

3-(1-Methyl-1*H*-1,2,3-triazol-5-yl)pyridine (8): Following the general procedure **A**, but was not flushed with nitrogen after catalyst addition, using iodomethane (12.5 µL, 0.20 mmol), sodium azide (13.0 mg, 0.20 mmol) and 3-ethynylpyridine (10.3 mg, 0.10 mmol) to obtain 3-(1-benzyl-1*H*-1,2,3-triazol-5-yl)pyridine (**8**) as a brownish oil. Yield: 2.9 mg (18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (br s, 1H), 8.65 (br s, 1H), 8.22 (d, *J* = 7.5 Hz, 1H), 7.84 (s, 1H), 7.41 (br s, 1H), 4.19 (s, 3H). ^{13}C NMR

(151 MHz, $CDCl_3$) δ 149.5, 147.3, 133.2, 132.3, 124.0, 121.1, 37.1 (two aromatic signals overlap). HRMS (ESI-TOF) calculated for $C_8H_9N_4^+$ (M + H) 161.0827, found 161.0835.

1-Isopentyl-5-((phenylthio)methyl)-1*H*-1,2,3-triazole (9): Following the general procedure **B** using 1-bromo-3-methylbutane (49.9 μL, 0.40 mmol), sodium azide (26.0 mg, 0.40 mmol) and phenyl(prop-2-yn-1-yl)sulfane (28.4 μL, 0.20 mmol) to obtain 1-isopentyl-5-((phenylthio)methyl)-1*H*-1,2,3-triazole (**9**) as a yellowish-brown oil. Yield: 38.1 mg (73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.32 – 7.27 (m, 5H), 4.32 – 4.24 (m, 2H), 4.06 (s, 2H), 1.83 – 1.75 (m, 2H), 1.68 – 1.59 (m, 1H), 0.97 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.9, 133.5, 132.7, 132.2, 129.4, 128.2, 46.6, 38.8, 27.5, 25.9, 22.4. HRMS (ESI-TOF) calculated for $C_{14}H_{20}N_3S^+$ (M + H) 262.1378, found 262.1384. The 1,5-substitution pattern was confirmed by a 2D NOESY experiment**.**

2-(2-(5-Phenyl-1*H*-1,2,3-triazol-1-yl)ethyl)isoindoline-1,3-dione (10): Following the general procedure **B** using 2-(2-bromoethyl)isoindoline-1,3-dione (112.9 mg, 0.40 mmol), sodium azide (26.0 mg, 0.40 mmol) and ethynylbenzene (22.4 μL, 0.20 mmol) to obtain 2-(2-(5-phenyl-1*H*-1,2,3-triazol-1-yl)ethyl)isoindoline-1,3-dione (**10**) as a yellow oil. Yield: 58.5 mg (92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 4H), 7.65 (s, 1H), 7.36 (s, 5H), 4.76 – 4.72 (m, 2H), 4.01 – 3.96 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 138.2, 134.2, 133.5, 131.8, 129.6, 129.2, 128.8, 126.7, 123.5, 46.2, 37.8. HRMS (ESI-TOF) calculated for $C_{18}H_{15}N_4O_2^+$ (M + H) 319.1195, found 319.1209.

5-(4-Fluorophenyl)-1-(2-nitrobenzyl)-1*H*-1,2,3-triazole (11): Following the general procedure **A** using 1-(bromomethyl)-2-nitrobenzene (86.4 mg, 0.40 mmol, purified by flash chromatography), sodium azide (26.0 mg, 0.40 mmol) and 1-ethynyl-4-fluorobenzene (23.2 μL, 0.20 mmol) to obtain 5-(4-fluorophenyl)-1-(2-nitrobenzyl)-1*H*-1,2,3-triazole (**11**) as an off-white solid. Yield: 54.6 mg (92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 8.1, 1.4 Hz, 1H), 7.82 (s, 1H), 7.60 (td, J = 4.6, 2.3 Hz, 1H), 7.52 (td, J = 8.1, 1.4 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.14 – 7.08 (m, 2H), 6.80 (dd, J = 7.7, 0.9 Hz, 1H), 5.97 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 (d, $^1J_{CF}$ = 251.2 Hz), 147.0, 138.1, 134.6, 133.6, 131.8, 130.6 (d, $^3J_{CF}$ = 8.5 Hz), 129.4, 128.8, 125.6, 122.5 (d, $^4J_{CF}$ = 3.5 Hz), 116.7 (d, $^2J_{CF}$ = 22.0 Hz), 49.2. HRMS (ESI-TOF) calculated for $C_{15}H_{12}FN_4O_2^+$ (M + H) 299.0944, found 299.0943.

5-(1-Methyl-1*H*-imidazol-5-yl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (12): Following the general procedure **B** using (3-chloropropyl)benzene (57.9 µL, 0.40 mmol), sodium azide (26.0 mg, 0.40 mmol) and 5-ethynyl-1-methyl-1*H*-imidazole (20.4 µL, 0.2 mmol) to obtain 5-(1-methyl-1*H*-imidazol-5-yl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (**12**) as a brownish oil. Yield: 25.2 mg (47 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.64 (s, 1H), 7.31 – 7.25 (m, 2H), 7.23 – 7.18 (m, 1H), 7.16 – 7.11 (m, 3H), 4.31 (t, *J* = 7.3 Hz, 2H), 3.54 (s, 3H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.23 – 2.14 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 140.1, 134.2, 131.4, 128.7, 128.4, 126.5, 126.4, 118.5, 47.8, 32.6, 32.3, 31.6. HRMS (ESI-TOF) calculated for $C_{15}H_{18}N_5^+$ (M + H) 268.1562, found 268.1562.

1-Benzyl-5-(4-fluorophenyl)-1*H*-1,2,3-triazole (13): Following the general procedure **B** using benzyl chloride (46.5 µL, 0.40 mmol), sodium azide (26.0 mg, 0.40 mmol) and 1-ethynyl-4-fluorobenzene (23.2 µL, 0.20 mmol) to obtain 1-benzyl-5-(4-fluorophenyl)-1*H*-1,2,3-triazole (**13**) as a yellowish oil. Yield: 49.1 mg (97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.31 – 7.26 (m, 3H), 7.24 – 7.18 (m, 2H), 7.13 – 7.08 (m, 2H), 7.08 – 7.04 (m, 2H), 5.52 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5 (d, $^{1}J_{CF}$ = 250.4 Hz), 137.3, 135.5, 133.6, 131.1 (d, $^{3}J_{CF}$ = 8.5 Hz), 129.0, 128.4, 127.2, 123.1 (d, $^{4}J_{CF}$ = 3.5 Hz), 116.3 (d, $^{2}J_{CF}$ = 21.9 Hz), 52.0. HRMS (ESI-TOF) calculated for $C_{15}H_{13}FN_3^+$ (M + H) 254.1093, found 254.1083.

2-(1-(3-(Trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-5-yl)pyridine (14): Following the general procedure **B** using 1-(chloromethyl)-3-(trifluoromethyl)benzene (60.8 µL, 0.40 mmol), sodium azide (26.0 mg, 0.40 mmol) and 2-ethynylpyridine (20.6 µL, 0.20 mmol) to obtain 2-(1-(3-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-5-yl)pyridine (**14**) as a yellowish oil. Yield: 37.4 mg (61%, purity 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 – 8.66 (m, 1H), 8.04 (s, 1H), 7.78 – 7.72 (m, 1H), 7.60 – 7.56 (m, 2H), 7.50 – 7.43 (m, 2H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.31 – 7.27 (m, 1H), 6.21 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 146.8, 137.4, 137.2, 135.7, 133.8, 131.5 (q, $^{4}J_{CF}$ = 1.3 Hz), 130.9 (app d, $^{2}J_{CF}$ = 32.4 Hz), 129.2, 125.2 (q, $^{3}J_{CF}$ = 3.9 Hz), 124.9 (q, $^{3}J_{CF}$ = 3.8 Hz), 124.0 (app d, $^{1}J_{CF}$ = 272.3 Hz), 123.7, 122.9, 52.9. HRMS (ESI-TOF) calculated for $C_{15}H_{12}F_3N_4^+$ (M + H) 305.1014, found 305.1009.

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Supporting Information Available. Copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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