JOC The Journal of Organic Chemistry

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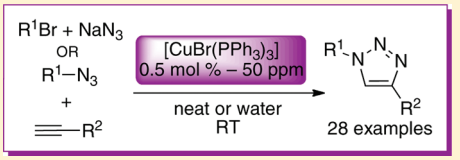
[CuBr(PPh$_3$)$_3$] for Azide−Alkyne Cycloaddition Reactions under Strict Click Conditions

Steven Lal and Silvia Díez-González*

Department of Chemistry, Imperial College London, Exhibition Road, South Kensington, London SW7 2AZ, U.K.

Supporting Information

ABSTRACT: A careful methodological study revealed a true Click catalytic system based on commercially available [CuBr(PPh$_3$)$_3$]. This system is active at room temperature, with 0.5 mol % [Cu] (or less), in the absence of any additive, and it does not require any purification step to isolate pure triazoles.



Click chemistry is a philosophy focused on efficiently creating molecular diversity from readily available starting materials under simple reaction conditions.[1] For a transformation to belong to Click chemistry, it has to fulfill its strigent criteria. In particular, the process should be insensitive to oxygen and water and proceed under mild conditions neat or in benign solvents, and no chromatographic purification techniques should be employed.

1,3-Dipolar cycloadditions, also known as Huisgen cycloadditions,[2,3] are a convenient and straightforward approach for the preparation of a wide range of five-membered ring heterocycles. Among these reactions, the copper(I)-catalyzed [3 + 2] cycloaddition of organic azides and alkynes has attracted enormous interest because of its status as the best Click reaction to date. This transformation leads to the extremely efficient formation of the corresponding 1,4-disubstituted [1,2,3]-triazoles as a sole regioisomer.[4−6] Because of the instability of simple copper(I) salts, the active species are often generated *in situ* from a copper(II) salt and a reducing agent (most often sodium ascorbate). These systems can be extremely efficient, but they are intrinsically limited to water-tolerant substrates, and only marginal leeway is left for unsuccessful reactions. Alternatively, the addition of ligands has been shown not only to protect Cu^I centers from oxidation but also to greatly improve their activity, allowing for milder reaction conditions or broader applicability.[7−12]

Ubiquitous in organometallic catalysis, it is not surprising that phosphorus-containing ligands were among the first ligands applied to the cycloaddition of azides and alkynes. In 2003, only one year after the discovery of copper(I) species as catalysts for azide−alkyne cycloadditions, the previously reported [CuBr(PPh$_3$)$_3$] **1** and {CuI[P(OEt)]} **2** complexes were applied to the preparation of various glyco-derived triazoles in good yields.[13,14] Reactions were typically run using 10−20 mol % of copper catalyst under microwave irradiation in the presence of an organic base (DIPEA or DBU for the most difficult substrates), which can also be considered as competitive ligands for the copper center. Moreover, the obtained triazoles had to be purified on silica gel. These conditions have been widely applied, particularly for the preparation of glycopolymers[15,16] and oligomers[17] or biologically active molecules.[18]

Despite the numerous applications reported to date, no true Click system has been reported so far for these complexes, which prompted us to explore the potential and limitations of [CuBr(PPh$_3$)$_3$] **1** (which is more stable than **2**) in this reaction.

We started our studies with the cycloaddition of benzyl azide with phenylacetylene as model reaction under standard cycloaddition conditions (Table 1, entry 1). All organic solvents tested led to slower reactions than the original water/*t*-BuOH mixture. Interestingly, more polar solvents systematically led to shorter reaction times (with the notable exception of alcoholic solvents which after 8 h afforded only incomplete conversions), and therefore, it was not surprising that the reaction proceeded in only 2 h when using water as reaction media. Noteworthy, **1** was first used for this cycloaddition reaction for being soluble in organic solvents, therefore allowing for homogeneous reaction mixtures. However, it is apparent that this catalyst can display high catalytic activities in diverse reaction media. Even shorter reaction times were required when the reaction was carried out in the absence of solvent (Table 1, entry 8).[19] No undesirable byproduct could be detected under neat conditions, and gratifyingly, the catalyst loading could be lowered to 0.5 mol % [Cu] while keeping short reaction times (Table 1, entry 9). Significantly, under these optimized conditions, no triazole formation was observed when CuBr was used as catalyst, highlighting the key role of the phosphine ligands.

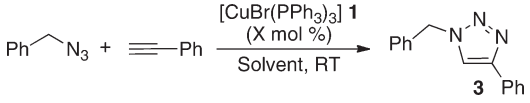
With an optimized catalytic system in hand, we next investigated the scope of the reaction. Results are presented in Scheme 1. A variety of triazoles could be isolated in excellent yields and high purity after a simple extraction or filtration. Aryl, benzyl, and alkyl azides were employed as well as alkynes with various electronic and steric properties. Pleasantly, a variety of reactive functional groups were tolerated, such as alcohol, ester,

Received: January 24, 2011
Published: March 08, 2011

amine, pyridine, nitrile, and halogen atoms. However, highly encumbered adamantyl azide only led to incomplete conversions, even at higher catalyst loadings (2 mol %, **3n** in Scheme 1). Moreover, when the same starting materials were heated at 40 °C, formation of around 10% of the corresponding 1,5-disubstituted triazole was also evidenced by ^{1}H NMR analysis of the reaction crude.

The developed reaction conditions constitute a clear improvement when compared to the original report, particularly the absence of addives and the very low copper loadings. Nevertheless, the substrates reported by Santoyo-González and co-workers were challenging glycosides. Hence, we decided to apply our reaction conditions to sugar derivatives, as shown in Figure 1. We prepared three triazoles differently substituted in very high yields at room temperature with only 0.5 mol % **1**, except in the case of **3s**, where 2 mol % **1** was required to ensure good conversions. Compounds **3t** and **3u** were prepared in solution to facilitate the interaction between the starting materials (solids) and the catalyst. A quick solvent screening for these substrates showed that toluene was a better solvent than water or DMSO, for instance. Of note, practically identical conversions were obtained for **3t** in toluene and in the absence of solvent, although the resulting product was somewhat less clean in the latter case. Remarkably, the use of a base/additive or heating was not necessary to ensure excellent yields.

Table 1. Optimization Studies



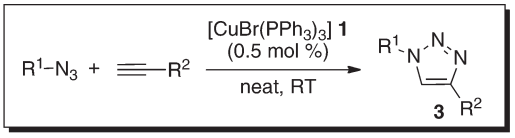
entry	solvent	[Cu] (mol %)	time (h)	conv[a] (%)
1	water/*t*-BuOH	5	2	>95
2	acetone	5	6	>95
3	ethanol	5	8	70
4	*i*-PrOH	5	8	69
5	MeCN	5	6	>95
6	DMSO	5	3	>95
7	water	5	2	>95
8	neat	5	1	>95
9	neat	0.5	3	>95
10	neat	0.1	9	>95

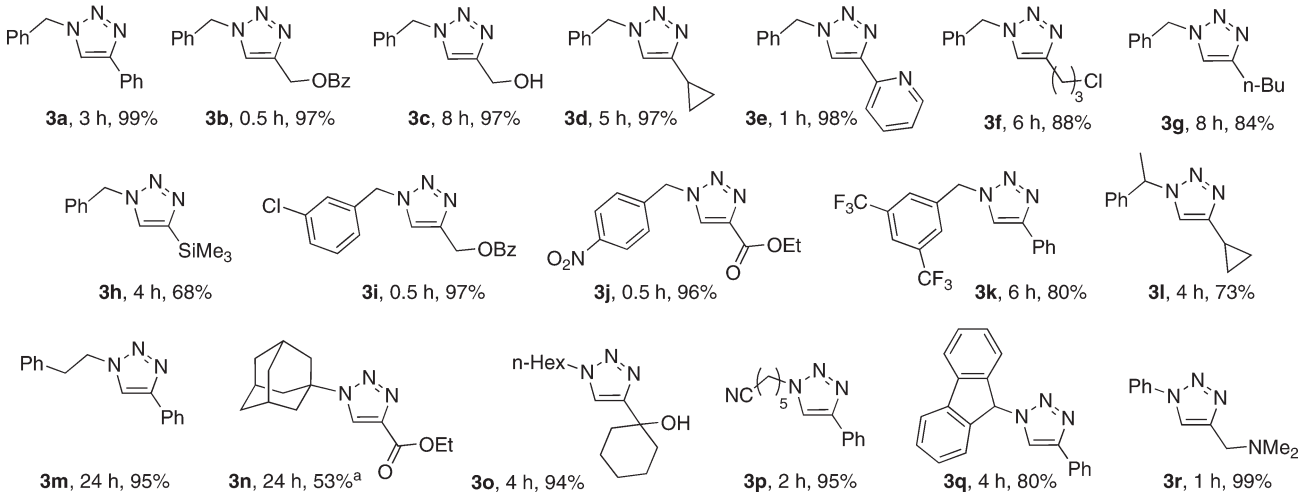
[a] ^{1}H NMR conversions are the average of two or more independent runs.

The remarkable activity of our catalytic system led us to closely examine the possibility of further decreasing the amount of copper used in this transformation. We tested different catalyst loadings at room temperature under neat conditions (Table 2). In all cases the copper loading could be lowered at least to 100 ppm while reaching high conversions after reasonable reaction times. Surprisingly, the best results were not obtained for triazole **3a**, the most often prepared one at low copper loading but for **3r**. In this case, a copper loading as low as 50 ppm led to remarkable turnover numbers (TONs) near 20000. Noteworthy, raising the reaction temperature to 40 °C did not lead to any improvement in catalytic activity. This observation is rather surprising since no evident decomposition of the catalyst took place upon heating.

It is important to note that while carrying out these studies, the preparation of triazole **3j** could be performed with only 10 ppm of copper catalyst. However, under such conditions the formation of two regioisomeric products was observed. Control experiments showed that identical results were obtained in the absence of copper, with around 80% of the starting materials converted into a 85:15 mixture of regioisomeric triazoles after 24 h of stirring at room temperature. Gratifyingly, just 0.5 mol % **1** ensured the reaction to proceed via a copper-catalyzed process, suppressing the formation of the undesired 1,5-disubstituted triazole.

Scheme 1. [CuBr(PPh$_3$)$_3$]-Catalyzed Cycloaddition Reactions





[a] ^{1}H NMR conversion.

dx.doi.org/10.1021/jo200085j |*J. Org. Chem.* 2011, 76, 2367–2373

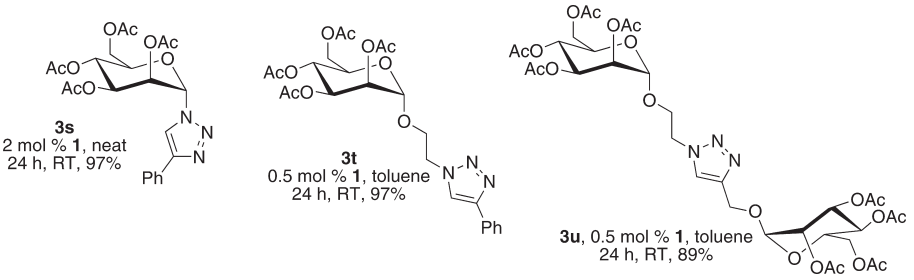
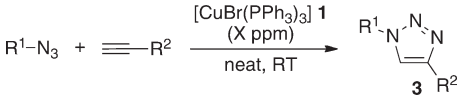


Figure 1. $[CuBr(PPh_3)_3]$-mediated preparation of glyco derivatives.

Table 2. $[CuBr(PPh_3)_3]$-Catalyzed Formation of Triazoles at Low Catalyst Loadings[a]



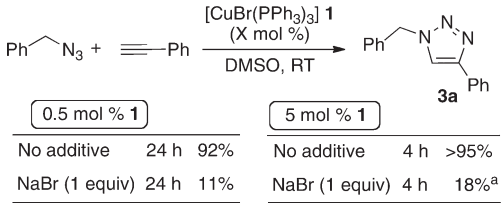
Triazole	[Cu] (ppm)	Time (h)	Conv. (%)	TON
3a	500	24	100	2000
	100	24	75	7500
3p	100	48	84	8400
3r	100	8	100	10000
	50	24	91	18200

[a] ^{1}H NMR conversions are average of two or more independent experiments.

Although organic azides are generally safe and stable toward water and oxygen,[20] those of low molecular weight can be particularly dangerous and difficult to handle.[21,22] In consequence, a number of methodologies can be found in the literature in order to avoid the handling and isolation of organic azides for [3 + 2] cycloadditions. Hence, azides can be generated in situ for the one-pot triazole preparation from *N*-sulfonylaziridines,[23] aromatic halides,[24,25] amines,[26,27] boronic acids,[28] or diaryliodonium salts.[29] The use of alkyl halides as precursors has also been studied,[30] and we decided to test our catalytic system in this transformation since the azides used in this study were all prepared from their corresponding halo-derivatives. When carrying out the multicomponent model reaction of benzyl bromide, NaN_3, and phenylacetylene, we were surprised to notice that in the presence of 0.5 mol % of **1** no triazole formation was observed in acetone or DMSO. It is important to note that these two organic solvents are often used for the preparation of azides from organic halides, and we also found them competent solvents for the cycloaddition reactions with **1** (see Table 1). Only the formation of the organic azide was observed in these reactions, with no traces of the expected cycloadduct. These surprising results led us to uncover the critical effect of salts in these cycloaddition reactions. We hypothesized that the NaBr formed from the starting halide and NaN_3 might inhibit the cycloaddition reaction.

Hence, while the reaction of benzyl azide and phenylacetylene with **1** proceeded smoothly in DMSO at room temperature, in the presence of 1 equiv of NaBr (saturated solution) only sluggish reactions were observed (Scheme 2). For this particular reaction, a considerably higher copper loading of 5 mol % was required for achieving a total conversion after 24 h, highlighting the inhibitory effect of the salt in the reaction mixture. Similar results were obtained using acetone as reaction solvent.

Scheme 2. Salt Effect in the Formation of Triazoles



[a] Reaction completed after 24 h of stirring.

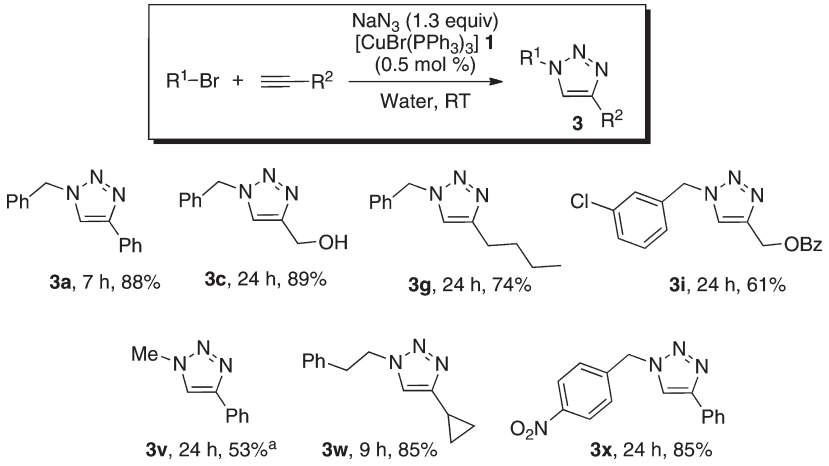
Ultimately, water was found to be the best solvent for this three-component transformation, as it had been for the reactions from isolated azides. Interestingly, no inhibitory effect was observed whith water as reaction media, even when an aqueous saturated solution of NaBr was employed. Satisfyingly, the reaction from organic halides in the presence of NaN_3 proceeded smoothly in aqueous media at room temperature without requiring higher catalytic loadings when compared to the reactions from the preisolated azides (Scheme 3). Good to high yields were obtained of pure triazoles with no purification step required. In general, reactions were allowed to proceed for 24 h, although shorter reaction times were shown to be sufficient in the case of triazoles **3a** and **3w**, for instance. To the best of our knowledge these results represent the lowest catalyst loading used so far for this three-component transformation.[31]

In conclusion, careful optimization of the reaction conditions allowed for the use of $[CuBr(PPh_3)_3]$ **1** in the preparation of diverse 1,2,3-triazoles under very mild reaction conditions and low catalytic loadings. Specifically, the preparation of triazoles bearing glyco-substituents proved the broad applicability of our Click conditions. Also, the robustness of the present catalytic system allowed its application to the three-component preparation of triazoles with the lowest copper loading reported so far.

It is important to note that most of the reported applications of complex **1** in cycloaddition reactions do not completely meet the strict Click criteria. This fact does not dismiss the importance of such studies, since this might be caused by the inherent sensitive nature of the starting materials or the products formed. Still, the present Click catalytic system, along with the fact that **1** is commercially available or can be easily prepared from $CuBr_2$ and PPh_3, make us expect this compound to become the catalyst of choice for an increasing number of Click applications.

dx.doi.org/10.1021/jo200085j |*J. Org. Chem.* 2011, 76, 2367–2373

Scheme 3. [CuBr(PPh$_3$)$_3$]-Catalyzed Formation of Triazoles from *in Situ* Generated Azides



[a] From MeI.

EXPERIMENTAL SECTION

All reagents were used as received. Unless otherwise stated, all reactions were carried out in air and using technical solvents without any particular precautions to exclude moisture or oxygen. Columns chromatography and TLC were performed on silica gel, using UV light and a phosphomolybdic acid dip to visualize the products. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 or 500 MHz spectrometers at room temperature. Chemical shifts (δ) are reported in ppm with respect to tetramethylsilane (^{1}H NMR) or fluorobenzene (^{19}F NMR) as internal standards. The assignment of certain NMR signals was supported by 2D NMR experiments. Mass spectra (MS) were recorded using EI, ESI, or CI techniques. All reported yields are isolated yields and in the catalytic studies are the average of at least two runs.

Complex [CuBr(PPh$_3$)$_3$] **1** was prepared in 80% yield from the reaction of CuBr$_2$ and PPh$_3$ in boiling methanol for 15 min in air.[32] All organic azides were prepared following the reported procedures.[33]

New Spectroscopic Data for Organic Azides. *1-Azidomethyl-3-chlorobenzene.* From 1-bromomethyl-3-chlorobenzene (1.31 mL, 10 mmol) and following the Alvarez procedure[33a] (18 h, rt), 1.34 g of the title compound was isolated as a pale yellow oil after extraction (80%). ^{1}H NMR data for the title compound were consistent with the previously reported data:[34] ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.4 (C, C^{Ar}), 134.7 (C, Cl−C^{Ar}), 130.1 (CH, CH^{Ar}), 128.5 (CH, CH^{Ar}), 128.2 (CH, CH^{Ar}), 126.2 (CH, CH^{Ar}), 54.1(CH$_2$, *C*H$_2$N$_3$).

1-Azidohexane. From 1-bromohexane (2.81 mL, 20 mmol) and following the Alvarez procedure[33a] (18 h, rt), 1.92 g of the title compound was isolated as a colorless oil after extraction (76%). ^{1}H NMR data for the title compound was consistent with the previously reported data:[35] ^{13}C NMR (100 MHz, CDCl$_3$) δ 51.5 (CH$_2$,*C*H$_2$N$_3$), 31.3 (CH$_2$), 28.8 (CH$_2$), 26.4 (CH$_2$), 22.5 (CH$_2$), 14.0 (CH$_3$).

(A) General Procedure for the [3 + 2] Cycloaddition of Azides and Terminal Alkynes. In a vial fitted with a screw cap were loaded azide (0.5 mmol), alkyne (0.5 mmol), and [CuBr(PPh$_3$)$_3$] **1** (2.3 mg, 0.5 mol %). The reaction was allowed to proceed at room temperature and monitored by ^{1}H NMR analysis of aliquots. After total consumption of the starting azide or no further conversion, the reaction product was simply dissolved in ethyl acetate and concentrated or alternatively collected by filtration and washed with pentane. In all examples, the crude products were estimated to be greater than 95% pure by ^{1}H and ^{13}C NMRs. Reported yields are isolated yields and are the average of at least two independent runs.

(B) General Procedure for the [3 + 2] Cycloaddition of In Situ Generated Azides and Terminal Alkynes. The procedure described above was followed using an alkyl halide (0.5 mmol), NaN$_3$ (42 mg, 0.65 mmol), and an alkyne (0.5 mmol) in water (1 mL).

*1-Benzyl-4-phenyl-1H-1,2,3-triazole (**3a**).* (A) Using the general procedure from 62 μL of benzyl azide and 55 μL of phenylacetylene, and after 3 h of reaction, 0.116 g of the title compound was isolated as a white solid after evaporation of ethyl acetate (99%). (B) Using the general procedure from 59 μL of benzyl bromide and 55 μL of phenylacetylene and after 7 h of reaction, 0.104 g of the title compound was isolated as an off-white solid (88%). Spectroscopic data were consistent with previously reported data for this compound.[30]

*Benzoic Acid 1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl Ester (**3b**).* (A) Using the general procedure from 62 μL of benzyl azide and 72 μL of benzoic acid prop-2-ynyl ester, and after 30 min of reaction, 0.142 g of the title compound was isolated as a white solid after evaporation of ethyl acetate (97%). Spectroscopic data were consistent with previously reported data for this compound.[36]

*(1-Benzyl-1H-[1,2,3]triazol-4-yl)methanol (**3c**).* (A) Using the general procedure from 62 μL of benzyl azide and 29 μL of prop-2-yn-1-ol, and after 8 h of reaction, 92 mg of the title compound was isolated as a yellow solid after evaporation of ethyl acetate (97%). (B) Using the general procedure from 59 μL of benzyl bromide and 29 μL of prop-2-yn-1-ol and after 24 h of reaction, 84 mg of the title compound was isolated as an off-white solid (89%). Spectroscopic data were consistent with previously reported data for this compound.[37]

*1-Benzyl-4-cyclopropyl-1H-[1,2,3]triazole (**3d**).* (A) Using the general procedure from 62 μL of benzyl azide and 42 μL of ethynylcyclopropane, and after 5 h of reaction, 97 mg of the title compound was isolated as a white solid after evaporation of ethyl acetate (97%). Spectroscopic data were consistent with previously reported data for this compound.[38]

*2-(1-Benzyl-1H-[1,2,3]triazol-4-yl)pyridine (**3e**).* (A) Using the general procedure from 62 μL of benzyl azide and 51 μL of 2-ethynylpyridine, and after of 30 min of reaction, 0.116 g of the title compound was isolated as an off-white solid after evaporation of ethyl acetate (98%). Spectroscopic data were consistent with previously reported data for this compound.[39]

*1-Benzyl-4-(3-chloropropyl)-1H-[1,2,3]triazole (**3f**).* (A) Using the general procedure from 62 μL of benzyl azide and 53 μL of 5-chloro-1-pentyne, and after 6 h of reaction, 0.106 g of the title compound was isolated as a light brown solid after washing with pentane (88%). Spectroscopic data were consistent with previously reported data for this compound:[40] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41−7.32 (m, 3H, 2 H^{Ar} + NC*H*=), 7.29−7.22 (m, 3H, H^{Ar}), 5.50 (s, 2H, PhC*H*$_2$), 3.56

dx.doi.org/10.1021/jo200085j |*J. Org. Chem.* 2011, 76, 2367–2373

(t, 2H, J = 6.4 Hz, $CH_2CH_2CH_2Cl$), 2.88 (t, 2H, J = 7.4 Hz, $CH_2CH_2CH_2Cl$), 2.21−2.09 (m, 2H, $CH_2CH_2CH_2Cl$); HRMS calcd for $C_{12}H_{15}N_3Cl$ 236.0955, found 236.0952 ($[M + H]^+$).

*1-Benzyl-4-butyl-1H-[1,2,3]triazole (**3g**).* (A) Using the general procedure from 62 μL of benzyl azide and 57 μL of 1-hexyne, and after of 8 h of reaction, 90 mg of the title compound was isolated as an off-white solid after evaporation of ethyl acetate (84%). (B) Using the general procedure from 59 μL of benzyl bromide and 57 μL of 1-hexyne, and after 24 h of reaction, 80 mg of the title compound was isolated as an off-white solid (74%). Spectroscopic data were consistent with previously reported data for this compound.[10]

*1-Benzyl-4-(trimethylsilyl)-1H-1,2,3-triazole (**3h**).* (A) Using the general procedure from 62 μL of benzyl azide and 71 μL of trimethylsilylacetylene, and after 4 h of reaction, 79 mg of the title compound was isolated as an off-white solid after evaporation of ethyl acetate (68%). Spectroscopic data were consistent with previously reported data for this compound.[30]

*Benzoic Acid 1-(3-Chlorobenzyl)-1H-[1,2,3]triazol-4-ylmethyl Ester (**3i**).* (A) Using the general procedure from 84 mg of 1-azidomethyl-3-chlorobenzene and 72 μL of benzoic acid prop-2-ynyl ester, and after 30 min of reaction, 0.160 g of the title compound was isolated as an off-white solid after evaporation of ethyl acetate (97%). (B) Using the general procedure from 65 μL of 3-chlorobenzyl bromide and 72 μL of benzoic acid prop-2-ynyl ester, and after 24 h of reaction, 0.100 g of the title compound was isolated as an off-white solid (61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.00 (m, 2H, H^{Ar}), 7.64 (s, 1H, H^{Ar}), 7.59−7.52 (m, 1H, H^{Ar}), 7.59−7.52 (m, 1H, H^{Ar}), 7.46−7.39 (m, 2H, H^{Ar}), 7.37−7.27 (m, 3H), 7.19−7.14 (m, 1H, H^{Ar}), 5.50 (s, 2H, CH_2), 5.46 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C, C=O), 143.4 (C, =CCH_2OBz), 136.3 (C, C^{Ar}), 135.0 (C, C^{Ar}), 133.2 (CH, CH^{Ar}), 130.4 (CH, CH^{Ar}), 129.72 (CH, CH^{Ar}), 129.67 (CH, CH^{Ar}), 129.1 (CH, CH^{Ar}), 128.4 (CH, CH^{Ar}), 128.2 (CH, CH^{Ar}), 126.1 (CH, CH^{Ar}), 123.9 (CH, NCH=), 58.0 (CH_2, CH_2O), 53.5 (CH_2, $PhCH_2$); HRMS calcd for $C_{17}H_{15}N_3O_2Cl$ 328.0853, found 328.0854 ($[M + H]^+$).

*1-(4-Nitrobenzyl)-1H-[1,2,3]triazole-4-carboxylic Acid Ethyl Ester (**3j**).* (A) Using the general procedure from 89 mg of 1-azidomethyl-4-nitrobenzene and 58 μL of propynoic acid ethyl ester, and after of 1 h of reaction, 0.131 g of the title compound was isolated as an off-white solid after evaporation of ethyl acetate (96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, 2H, J = 8.7 Hz, H^{Ar}), 8.07 (s, 1H, NCH=C), 7.44 (d, 2H, J = 8.7 Hz, H^{Ar}), 5.71 (s, 2H, $ArCH_2$), 4.43 (q, 2H, J = 7.1 Hz, $C(O)CH_2CH_3$), 1.41 (t, 3H, J = 7.1 Hz, $C(O)CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4 (C, C=O), 148.3 (C, O_2N-C^{Ar}), 141.1 (C, =CCO_2Et), 140.7 (C, C^{Ar}), 128.7 (CH, CH^{Ar}), 127.5 (CH, CH^{Ar}), 124.5 (CH, CH=CCO_2Et), 61.5 (CH_2, OCH_2CH_3), 53.2 (CH_2, $ArCH_2$), 14.7 (CH_3); HRMS calcd for $C_{12}H_{12}N_4O_4$ 277.0937, found 277.0926 ($[M + H]^+$).

*1-(3,5-Bis-trifluoromethylbenzyl)-4-phenyl-1H-[1,2,3]triazole (**3k**).* (A) Using the general procedure from 135 mg of 1-azidomethyl-3,5-bis-trifluoromethylbenzene and 55 μL of phenylacetylene, and after of 6 h of reaction, 0.149 g of the title compound was isolated as an off-white solid after evaporation of ethyl acetate (80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H, NCH=), 7.86−7.81 (m, 2H, H^{Ar}), 7.80−7.76 (m, 2H, H^{Ar}), 7.47−7.40 (m, 2H, H^{Ar}), 7.39−7.32 (m, 1H, H^{Ar}), 5.71 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9 (C, CH=C−Ph), 137.3 (C, C^{Ar}), 132.7 (q, J = 33.8 Hz, CF_3), 130.0 (C, C^{Ar}), 128.9 (CH, CH^{Ar}), 128.5 (CH, CH^{Ar}), 128.0 (CH, CH^{Ar}), 125.8 (CH, CH^{Ar}), 123.1−122.8 (m, $C-CF_3$), 121.5 (CH, CH^{Ar}), 119.5 (CH, NCH=), 53.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.9 (s); m/z (ESI) 372 ($[MH]^+$, 100), 195 (5); HRMS calcd for $C_{17}H_{12}N_3F_6$ 372.0935, found 372.0947 ($[M + H]^+$).

*4-Cyclopropyl-1-(1-phenylethyl)-1H-[1,2,3]triazole (**3l**).* (A) Using the general procedure from 74 mg of (1-azidoethyl)benzene and 42 μL of ethynylcyclopropane, and after 4 h of reaction, 78 mg of the title compound was isolated as an off-white solid after evaporation of ethyl acetate (73%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.29 (m, 3H, H^{Ar}), 7.28−7.23 (m, 2H, H^{Ar}), 7.11 (s, 1H, NCH=), 5.76 (q, 1H, J = 7.1 Hz, PhCH), 1.95 (d, 3H, J = 7.1 Hz, CH_3), 1.93−1.87 (m, 1H, $CH^{cyclopropyl}$), 0.94−0.87 (m, 2H, CH_2), 0.84−0.79 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2 (=C-cyclopropyl), 140.1 (C, C^{Ar}), 128.9 (CH, CH^{Ar}), 128.3 (CH, CH^{Ar}), 126.4 (CH, CH^{Ar}), 118.3 (NCH=), 58.9 (CH, PhCH), 21.2 (CH_3), 7.6 ($CH^{cyclopropyl}$), 6.7 (CH_2); HRMS calcd for $C_{13}H_{16}N_3$ 214.1344, found 214.1333 ($[M + H]^+$).

*1-Phenethyl-4-phenyl-1H-[1,2,3]triazole (**3m**).* (A) Using the general procedure from 74 mg of (2-azidoethyl)benzene and 55 μL of phenylacetylene, and after of 24 h of reaction, 0.118 g of the title compound was isolated as an off-white solid after evaporation of ethyl acetate (95%). Spectroscopic data were consistent with previously reported data for this compound.[30]

*1-(1-Hexyl-1H-[1,2,3]triazol-4-yl)cyclohexanol (**3o**).* (A) Using the general procedure from 64 mg of 1-azidohexane and 62 mg of 1-ethynylcyclohexanol, and after 4 h of reaction, 0.118 g of the title compound was isolated as an off-white solid after filtering and washing with pentane (94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H, NCH=), 4.32 (t, 2H, J = 7.3 Hz, CH_2N), 2.27 (s, 1H, OH), 2.07−1.82 (m, 6H), 1.82−1.67 (m, 2H), 1.67−1.50 (m, 3H), 1.44−1.23 (m, 8H), 0.88 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6 (C, CH=C), 119.6 (CH, CH=C), 69.6 (CH_2), 50.3 (CH_2), 38.2 (CH_2), 31.1 (CH_2), 30.2 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 22.0 (CH_2), 13.9 (CH_3); HRMS calcd for $C_{14}H_{26}N_3O$ 252.2076, found 252.2072 ($[MH]^+$).

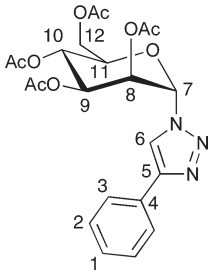
*6-(4-Phenyl[1,2,3]triazol-1-yl)hexanenitrile (**3p**).* (A) Using the general procedure from 69 mg of 6-azidohexanenitrile and 55 μL of phenylacetylene, and after 2 h of reaction, 0.115 g of the title compound were isolated as an off-white solid after evaporation of ethyl acetate (95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.81 (m, 2H, H^{Ar}), 7.76 (s, 1H, NCH=), 7.49−7.40 (m, 2H, H^{Ar}), 7.37−7.31 (m, 1H, H^{Ar}), 4.43 (t, 2H, J = 7.0 Hz, CH_2N), 2.36 (t, 2H, J = 7.0 Hz, CH_2CN), 2.08−1.97 (m, 2H, CH_2), 1.79−1.67 (m, 2H, CH_2), 1.59−1.48 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8 (C, CH=C−Ph), 130.5 (C, C^{Ar}), 128.8 (CH, C^{Ar}), 128.1 (CH, C^{Ar}), 125.6 (CH, C^{Ar}), 119.5 (CH or CH=C−Ph), 119.3 (C, CN), 49.8 (CH_2, CH_2-N), 29.5 (CH_2), 25.5 (CH_2), 24.7 (CH_2), 17.0 (CH_2); HRMS calcd for $C_{14}H_{17}N_4$ 241.1453, found 241.1459 ($[MH]^+$).

*1-(9H-Fluoren-9-yl)-4-phenyl-1H-[1,2,3]triazole (**3q**).* (A) Using the general procedure from 0.103 g of 9-azido-9H-fluorene and 55 μL of phenylacetylene, and after of 4 h of reaction, 0.131 g of the title compound was isolated as a light red solid after evaporation of ethyl acetate (80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.78 (m, 2H), 7.75−7.69 (m, 2H), 7.54−7.47 (m, 4H), 7.38−7.26 (m, 6H), 6.86 (s, 1H, CH−N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1 (C, CH=C−Ph), 141.1 (C, C^{Ar}), 140.5 (C, C^{Ar}), 130.3 (C, C^{Ar}), 129.9 (CH, CH^{Ar}), 128.7 (CH, CH^{Ar}), 128.3 (CH, CH^{Ar}), 128.1 (CH, CH^{Ar}), 125.6 (CH, CH^{Ar}), 125.3 (CH, CH^{Ar}), 120.5 (CH, CH^{Ar}), 117.2 (CH, NCH=), 64.5 (CH, CHN); HRMS calcd for $C_{21}H_{16}N_3$ 310.1344, found 310.1343 ($[M + H]^+$).

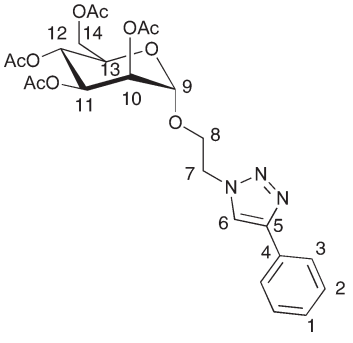
*Dimethyl(1-phenyl-1H-[1,2,3]triazol-4-ylmethyl)amine (**3r**).* (A) Using the general procedure from 59 mg of azidobenzene and 54 μL of dimethylprop-2-ynylamine, and after of 4 h of reaction, 0.100 g of the title compound was isolated as a brown solid after evaporation of ethyl acetate (99%). Spectroscopic data were consistent with previously reported data for this compound.[41]

*Acetic Acid 4,5-Diacetoxy-2-acetoxymethyl-6-(4-phenyl-1H-[1,2,3]-triazol-1-yl)tetrahydropyran-3-yl ester (**3s**).* (A) Using the general procedure from 186 mg of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl azide, 55 μL of phenyl acetylene, and 9.2 mg of **1** (2 mol %), and after 24 h of reaction, 0.230 g of the title compound was isolated as a white solid

after evaporation of ethyl acetate (97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H, H^6), 7.88−7.84 (m, 2H, H^3), 7.48−7.43 (m, 2H, H^2), 7.40−7.35 (m, 1H, H^1), 6.07 (d, 1H, J = 2.7 Hz, H^7), 6.03−6.01 (m, 1H, H^8), 6.00−5.96 (m, 1H, H^9), 5.39 (t, 1H, J = 8.9 Hz, H^{10}), 4.39 (dd, 1H, J = 5.5; 12.5 Hz, H^{12}), 4.09 (dd, 1H, J = 2.6; 12.5 Hz, H^{12}), 3.98−3.93 (m, 1H, H^{11}), 2.19 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.072 (s, 3H, CH_3), 2.066 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C, C=O), 169.7 (C, C=O), 169.6 (C, C=O), 169.2 (C, C=O), 148.4 (C, C^5), 129.7 (C, C^4), 128.9 (CH, C^3), 128.7 (CH, C^1), 125.9 (CH, C^2), 119.7 (CH, C^6), 83.6 (CH, C^7), 72.2 (CH, C^{11}), 68.8 (CH, C^9), 68.3 (CH, C^8), 66.1 (CH, C^{10}), 61.6 (CH_2, C^{12}), 20.71 (CH_3), 20.66 (2C, CH_3), 20.6 (CH_3); HRMS calcd for $C_{22}H_{26}N_3O_9$ 476.1669, found 476.1656 [$(M + H)^+$].



*Acetic Acid 4,5-Diacetoxy-2-acetoxymethyl-6-[2-(4-phenyl[1,2,3]-triazol-1-yl)ethoxy]tetrahydropyran-3-ylEster (**3t**).* (A) Using the general procedure from 0.105 g (0.25 mmol) of 2′-azidoethyl-2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside and 28 μL (0.25 mmol) of phenylacetylene, 0.128 g of the title compound was isolated as a foamy white solid after evaporation of ethyl acetate (97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H, H^6), 7.91−7.86 (m, 2H, H^3), 7.46−7.38 (m, 2H, H^2), 7.35−7.29 (m, 1H, H^1), 5.27−5.12 (m, 3H, H^7+H^{10}), 4.87−4.81 (m, 1H, H^9), 4.70−4.67 (m, 1H, H^8), 4.66−4.57 (m, 1H, H^8), 4.20−4.04 (m, 2H, H^{12} + $1H^{14}$), 3.98−3.85 (m, 2H, H^{13} + $1H^{14}$), 3.22−3.12 (m, 1H, H^{11}), 2.13 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.72 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C, C=O), 169.9 (C, C=O), 169.5 (C, C=O), 147.8 (C, C^5), 130.3 (C, C^4), 128.7 (CH, C^3), 129.1 (CH, C^1), 125.7 (CH, C^2), 121.0 (CH, C^6), 96.7 (CH, C^9), 69.0 (CH, C^{13}), 68.72 (CH, C^{10}), 68.70 (CH, C^{11}), 65.6 (CH_2, C^7), 65.2 (CH, C^{12}), 61.9 (CH_2, C^{14}), 49.7 (CH_2, C^8), 20.7 (CH_3), 20.60 (CH_3), 20.56 (CH_3), 20.1 (CH_3); HRMS calcd for $C_{24}H_{30}N_3O_{10}$ 520.1931, found 520.1931 [$(M + H)^+$].



*1-(2′,3′,4′,6′,-Tetra-O-acetyl-α-D-mannopyranosyloxyethyl)-4-(2″,-3″,4″,6″-tetra-O-acetyl-α-D-mannopyranosyloxymethyl)-1H-[1,2,3]-triazole (**3u**).* (A) Using the general procedure from 0.105 g of 2′-azidoethyl-2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside and 97 mg of α-D-mannopyranoside-2-propyn-1-yl-2,3,4,6-tetraacetate in toluene (0.5 mL), 0.179 g of the title compound was isolated as a foamy white solid after evaporation of toluene (89%). Spectroscopic data for the title compound were consistent with the previously reported one.[13]

*1-Methyl-4-phenyl-1H-[1,2,3]triazole (**3v**).* (B) Using the general procedure from 32 μL of methyl iodide and 55 μL of phenylacetylene, and after 24 h of reaction, 42 mg of the title compound was isolated as an off-white solid (53%). Spectroscopic data were consistent with previously reported data for this compound.[30]

*4-Cyclopropyl-1-phenethyl-1H-[1,2,3]triazole (**3w**).* (B) Using the general procedure from 68 μL of (2-bromoethyl)benzene and 42 μL of cyclopropylacetylene, and after 9 h of reaction, 95 mg of the title compound was isolated as an off-white solid (89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.23 (m, 3H, H^{Ar}), 7.18−7.07 (m, 2H, H^{Ar}), 6.97 (s, 1H, NC*H*=), 4.52 (t, 2H, J = 7.4 Hz, CH_2N), 3.18 (t, 2H, J = 7.4 Hz, ArCH_2), 1.97−1.87 (m, 1H, C*H*), 0.97−0.88 (m, 2H, $CH_2^{cyclopropyl}$), 0.82−0.73 (m, 2H, $CH_2^{cyclopropyl}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0 (C, NCH=*C*), 137.2 (C, C^{Ar}), 128.7 (CH, CH^{Ar}), 128.7 (CH, CH^{Ar}), 127.0 (CH, CH^{Ar}), 119.9 (CH, NCH=), 51.4 (CH_2, CH_2N), 36.8 (CH_2, PhCH_2), 7.6 (CH, $CH^{cyclopropyl}$), 6.6 (CH_2, $CH_2^{cyclopropyl}$); HRMS calcd for $C_{13}H_{16}N_3$ 214.1344, found 214.1342 [$(M + H)^+$].

*1-(4-Nitrobenzyl)-4-phenyl-1H-[1,2,3]triazole (**3x**).* (B) Using the general procedure from 0.108 g 4-nitrobenzyl bromide and 55 μL of phenylacetylene, and after 9 h of reaction, 0.119 g of the title compound was isolated as an off-white solid (85%). Spectroscopic data were consistent with previously reported data for this compound.[30]

General Procedure for the [3 + 2] Cycloaddition of Azides and Terminal Alkynes at Low Catalyst Loading. In a vial fitted with a screw cap, the required amount of a freshly prepared solution 0.25 mM of $[CuBr(PPh_3)_3]$ **1** in dichloromethane was introduced and the solvent evaporated under a flux of compressed air. Then, azide (0.5 mmol) and alkyne (0.5 mmol) were loaded. The reaction was allowed to proceed at room temperature and monitored by ^{1}H NMR analysis of aliquots.

■ ASSOCIATED CONTENT

Supporting Information. NMR data for reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +44 (0)207594 9699. Fax: +44 (0)207594 5804. E-mail: s.diez-gonzalez@imperial.ac.uk.

■ ACKNOWLEDGMENT

EPSRC and Imperial College London are acknowledged for financial support of this work. Dr. King Kuok (Mimi) Hii is also acknowledged for her selfless support and guidance.

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