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Click Chemistry

Copper(I)-Catalyzed Cycloaddition of Bismuth(III) Acetylides with Organic Azides: Synthesis of Stable Triazole Anion Equivalents**

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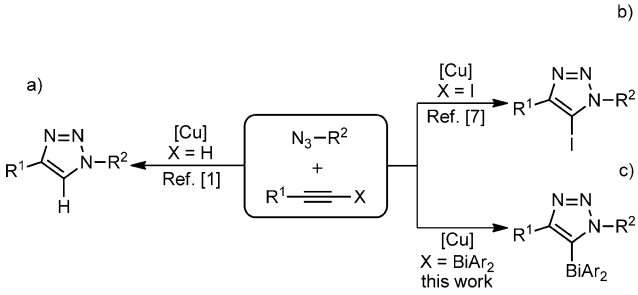
The copper(I)-catalyzed azide–alkyne cycloaddition[1] (CuAAC; Scheme 1 a) is now widely used as a reliable method for covalently connecting diverse building blocks.[2] The experimental simplicity of the reaction and the robust nature of 1,2,3-triazole products have enabled numerous applications of this process in synthetic and medicinal chemistry,[3] bioconjugations,[4] material science,[5] and polymer chemistry.[6] The recent discovery that 1-iodoalkynes also readily react with organic azides, regiospecifically producing 5-iodo-1,2,3-triazoles (Scheme 1 b),[7] further expanded the utility of this copper-catalyzed reaction.

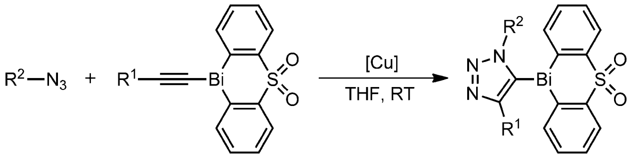


Scheme 1. Various copper(I)-catalyzed routes to substituted 1,2,3-triazoles.

Although 5-iodo-1,2,3-triazoles can be efficiently and directly prepared using this method, their subsequent functionalization is not always straightforward, often resulting in the formation of proto-dehalogenated products, although some exceptions can be noted.[7,8] With this in mind, we envisioned the use of a preformed metalated acetylide that could both promote the cycloaddition reaction and form a stable 5-metalated triazole. Direct functionalization of the 5-position of the triazole could be accomplished from this metalated intermediate, thus bypassing inefficient transmetalation steps and eliminating the undesired proto-dehalogenation side reaction.

Reactions of bromoalkynes, as well as gold and aluminum acetylides as active cycloaddition partners in the CuAAC have been recently reported.[9] However, the synthetic utility of these acetylides is limited by their own instability, low reactivity with organic azides, high cost, and instability of the resulting triazolides. Thus, we set out to utilize a stable acetylide which would surmount all of the above limitations (Scheme 1 c). Ideally it would be reactive with azides under copper catalysis and would produce stable, yet sufficiently reactive triazolide products which additionally could be versatile precursors for the construction of fully substituted 1,2,3-triazoles.

Herein, we report that 1-bismuth(III) acetylides, a bench-stable, easily accessible, and nontoxic class of σ-acetylides,[10] undergo an efficient cycloaddition with organic azides in the presence of a copper catalyst to form 5-bismuth(III) triazolides (Scheme 2). The reaction exhibits a broad substrate scope, proceeds under mild reaction conditions (at ambient temperature), and delivers stable bismuth(III) triazolides in reliably high yields. These unique and previously unreported metalated triazolides undergo several mild and chemoselective reactions in the absence of transition metals, thus forming various 5-substituted triazoles inaccessible by other means.



Scheme 2. Copper(I)-catalyzed synthesis of 5-bismuth(III)-triazolides. THF = tetrahydrofuran.

Although organobismuth chemistry is well described in the chemical literature,[11] only a handful of stable 1-bismuth(III) acetylides have been reported.[12] The rarity of these bismuth compounds is likely a result of their low hydrolytic stability, difficult preparation, and most importantly, a general lack of utility. Nevertheless, Akiba and co-workers demonstrated that oxygen or nitrogen ligands proximal to the metal center greatly increase the stability of bismuth(III) complex regardless of the electronic nature of the attached carbon ligand (sp^2 or sp^3).[13] Building on this observation, Suzuki and co-workers reported an elegant use of diphenyl sulfone as a ligand for bismuth(III), and allowed preparation of a hydrolytically stable bismuth(III) acetylide.[12d]

To explore the reactivity of various bismuth(III) acetylides, a common precursor, 10-iodophenothiabismine 5,5-dioxide (Scheme 3), was synthesized in large batches

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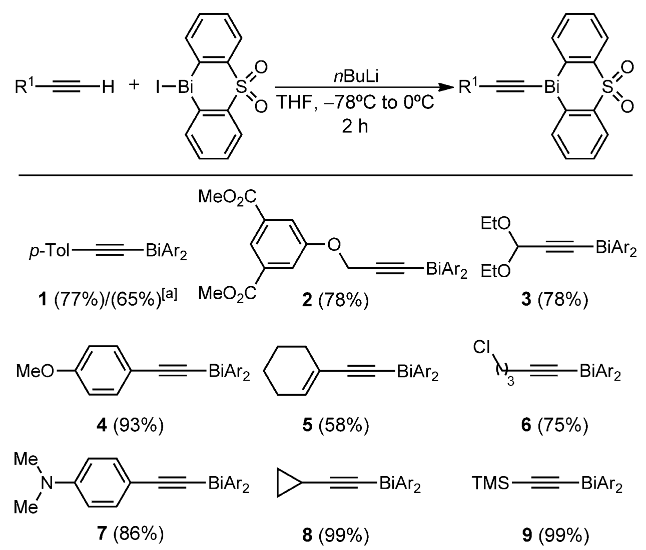


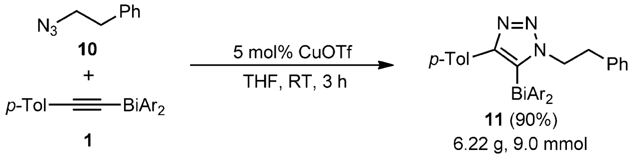
Scheme 3. Synthesis of bismuth(III) acetylides by reaction with lithium acetylides. General reaction conditions: alkyne (2.18 mmol), bismuth(III) iodide (1.00 g, 1.81 mmol), *n*BuLi (2.18 mmol), THF (25 mL), −78 to 0 °C, 2 h. Values within parentheses represent yields of isolated products. [a] The reaction was performed on 15 mmol scale. $BiAr_2$ = phenothiabismine 5,5-dioxide, TMS = trimethylsilyl.

(> 20 g) from commercially available starting materials in two steps and in an overall 68 % yield. Following a slightly modified procedure of Suzuki and co-workers, the diphenyl sulfone bismuth(III) acetylide **1** was easily prepared by reaction with lithiated 4-ethynyl toluene (generated in situ). As already mentioned, **1** is a bench-stable, free-flowing powder that shows no degradation after several months (> 8) of storage open to air and moisture.

Examining the scope of the synthesis of bismuth(III) acetylides (Scheme 3) revealed that the methyl ester **2**, olefin **5**, alkyl chloride **6**, *N*,*N*-disubstituted aniline **7**, and trimethylsilyl acetylene **9** were all compatible with the reaction conditions. In all cases, the triazolide products (**1**–**9**) were free-flowing white powders, stable to hydrolysis and oxidation, and were formed in good to excellent yield. Also of note, they were isolated simply by aqueous workup, trituration, and filtration.

With the diverse array of bismuth acetylides at our disposal, we examined their copper-catalyzed cycloaddition with organic azides. An initial survey of experimental conditions, which included a broad range of copper(I)/(II) salts, solvents, and ligands, showed that the reaction of **1** and the azide **10** (Scheme 4) formed mixtures of both the 5-H and 5-bismuth triazolides. Notably, formation of the 5-H triazole was completely suppressed only when the electronically deficient copper(I) catalyst, CuOTf, was used in the absence of other ligands. Under these optimized reaction conditions, the cycloaddition of **1** and **10** proceeded at ambient temperature in a THF solution with 5 mol % CuOTf, thus yielding the 5-bismuth(III) triazolide **11** as the sole product (Scheme 4).

This catalytic system was applied to a series of structurally and functionally diverse azides and 1-bismuth(III) acetylides (Scheme 5). In all cases, the 5-bismuth(III)-1,2,3-triazoles



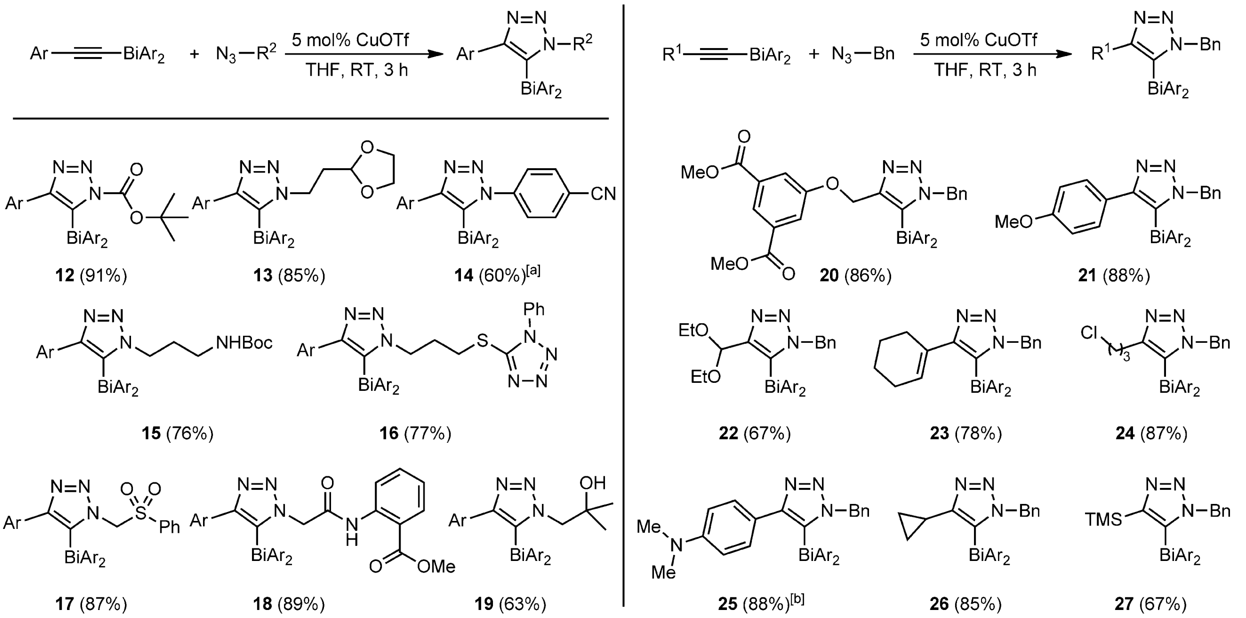
Scheme 4. Optimized synthesis of the bismuth triazolide **11**. Tf = trifluoromethanesulfonyl.

(**12**–**27**) were obtained as exclusive products in good to excellent yield at ambient temperature. Many functional groups were compatible with the synthesis of these triazolides, including esters (**18**, **20**), acetals (**13**, **22**), a nitrile (**14**), a carbamate (**15**), an amide (**18**), a free alcohols (**19**), a tertiary amine (**25**), and a substituted silane (**27**). Furthermore, these products were typically isolated by aqueous workup, trituration with a nonpolar solvent, and filtration. This process was easily performed on larger scales. The triazolide **11** was prepared on a 10 mmol scale, thus delivering over six grams of the product in 90 % yield (Scheme 4).

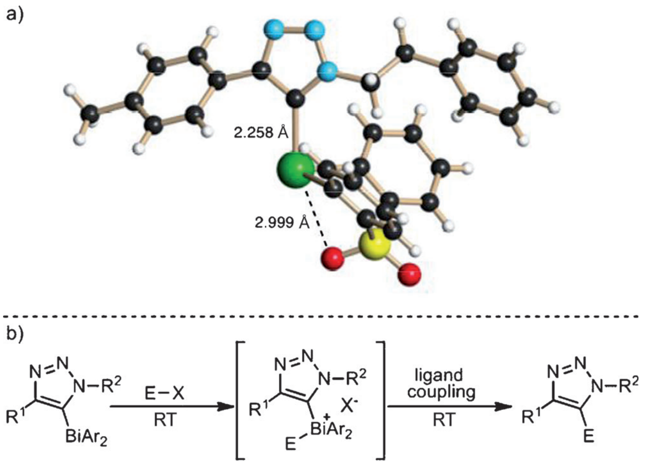
To better understand the bonding in this congested heterocyclic system, we obtained the single-crystal X-ray structure of **11** (Scheme 6 a). Of note in this complex is the long bismuth–triazole bond (C-5, 2.258 Å) and the relatively short intramolecular bismuth–oxygen bond (S-O, 2.999 Å). This complex, likely a result of the tethered diphenyl sulfone ligand, exists in a constrained trigonal pyramidal geometry. We hypothesize that the strong bismuth–oxygen interaction stabilizes the complex yet renders it more nucleophilic than traditional triaryl bismuth complexes.[14] With this in mind, we reasoned that reaction of this complex with different electrophiles would chemo- and regioselectively decorate the triazole by the formation of a bismuthonium complex[14] with subsequent ligand coupling (or self-decomposition),[15] thus leading to the selective formation of the fully substituted 1,2,3-triazole (Scheme 6 b).

Initial exploration of this reactivity manifold performed on **11** verified our hypothesis, thus giving various fully substituted 1,2,3-triazoles (**28**–**33**; Scheme 7). We found that carbonyl electrophiles such as acyl chlorides, diphosgene, and oxalyl chloride worked efficiently, thus giving the triazoles **28**, **29 a,b**, and **30** respectively, at room temperature and without the need of transition-metal catalysts.[16] In the case of diphosgene and oxalyl chloride, an additional oxygen- or nitrogen-based nucleophile was reacted with the resulting intermediate, thus forming ester- and amide-based products (**29 a**, **29 b**, and **30**). These reactions were found to achieve the highest efficiency in the presence of an amine base (TEA, DIPEA, DMAP, etc.). We speculate that these additives act both as ligands for the bismuth center and, in some cases (i.e. DMAP), can further activate the electrophile. When used in the correct proportions, these amines tempered the reactivity and delivered consistent yields of the fully substituted triazoles. Interestingly, when higher concentrations of the amines were employed, the addition of the electrophile could be fully suppressed, thus giving credence to the role of the amine as a ligand for the bismuth center.

A noteworthy dichotomy arose when **11** was reacted with various chlorinated sulfur-based electrophiles. For example,



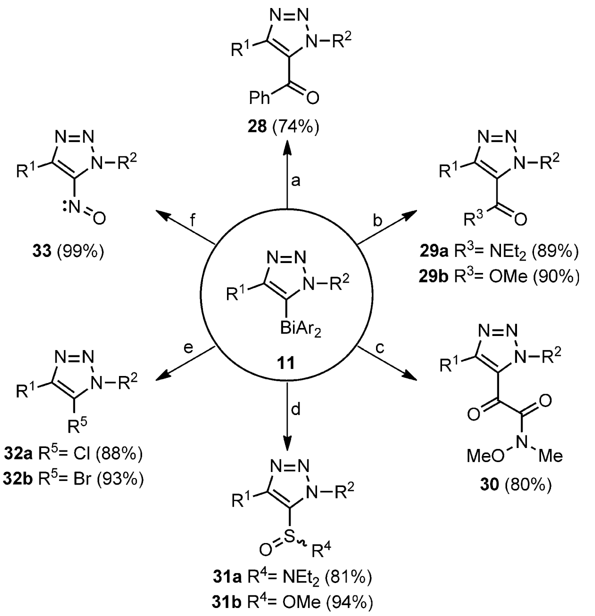
Scheme 5. Substrate scope for the formation of bismuth (III) triazolides from 1-bismuth(III) acetylides and organic azides. General reaction conditions: 1-bismuth(III) acetylide (1 mmol), azide (1 mmol), CuOTf (5 mol%), THF (3 mL), RT, 3 h. Values within parentheses represent yields of isolated products. [a] Used 10 mol% CuOTf. [b] For solubility purposes the reaction was performed in DMF (3 mL). Ar = *p*-tol, $BiAr_2$ = phenothiabismine 5,5-dioxide, Bn = benzyl.



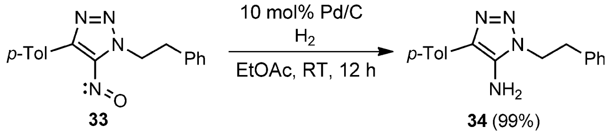
Scheme 6. a) Crystal structure of **11**, highlighting the short (2.999 Å) bismuth–oxygen intramolecular bond. b) Formation and decomposition of a bismuthonium complex (in brackets) to yield 5-substituted triazoles.

treatment with thionyl chloride and subsequent quenching with diethylamine gave the sulfinic amide **31a** in 81% yield at room temperature. This method was expanded to form the sulfinic ester **31b** in 94% yield. However, when **11** was reacted with sulfuryl chloride, the 5-chlorotriazole **32a** was formed in 88% yield. Reaction with bromine (Br_2) gave similar results, thus yielding the 5-bromotriazole **32b** in 93% yield. The formation of **32a** and **32b** likely involves a redox process, wherein an unstable bismuth(V) intermediate is formed with a subsequent facile reductive elimination at ambient temperature to give the 5-halotriazole.

Most interestingly, **11** reacted with nitrosonium tetrafluoroborate at room temperature to quantitatively produce the nitroso triazole **33** as a stable green solid. As an example of the versatile reactivity of this derivative,[17] it was readily reduced to the corresponding amino triazole **34**, also in



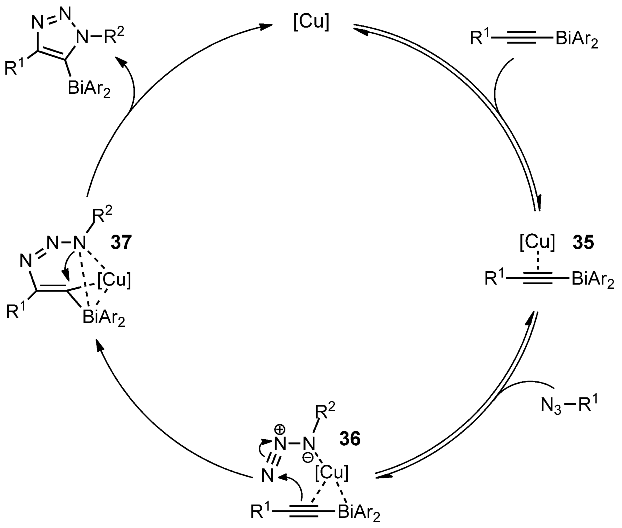
Scheme 7. Conversion of **11** into various 5-substituted-1,2,3-triazoles at room temperature. a) PhCOCl (4 equiv), DMAP (1 equiv), TEA (4 equiv), CH_2Cl_2, RT, 12 h; b) diphosgene (2 equiv), DMAP (1 equiv), TEA (4 equiv), NucH (20 equiv), CH_2Cl_2, RT, 1 h; c) oxalyl chloride (2 equiv), DIPEA (3 equiv), NucH (20 equiv), CH_2Cl_2, RT, 30 min; d) $SOCl_2$ (2 equiv), DIPEA (2 equiv), NucH (20 equiv), CH_2Cl_2, RT, 30 min; e 1) SO_2Cl_2 (2 equiv), TEA (2 equiv), CH_2Cl_2, RT, 30 min; e 2) Br_2 (1.2 equiv), CH_2Cl_2, RT, 5 min; f) nitrosonium tetrafluoroborate (2 equiv), CH_2Cl_2, air, RT, 12 h. See the Supporting Information for experimental details.



Scheme 8. Reduction of the nitroso **33** into the amino triazole **34**. See the Supporting Information for experimental details.

quantitative yield (Scheme 8). Further synthetic uses of these nitroso heterocycles (e.g. **33**) are easily envisioned and will be reported in due course.

The outline of the mechanistic proposal of this transformation is shown in Scheme 9. Supported by previous mechanistic investigations of reactions of 1-iodoalkynes[7] and preformed copper(I) acetylides,[18] we hypothesize that the active cycloaddition complex **35** is formed through a weak and reversible π interaction of the copper(I) catalyst with bismuth(III) acetylide. Coordination of the azide reveals the vinylidene-like reactivity of complex **36**, in which the first covalent bond between the electrophilic terminal nitrogen of the azide and now nucleophilic β-carbon of the acetylide is formed, producing intermediate **37**. The coordination environment of the copper center determines the fate of this heterodinuclear complex: electron-rich ligands favor elimination of bismuth (forming the 5-H triazoles upon the hydrolysis of the copper triazolide), whereas the electron-deficient copper(I) triflate gives only bismuth(III) triazolides. The reactivity of bismuth and other main group elements in this transformation is currently being examined both experimentally and computationally and should shed light on the nature of the fleeting metal–metal interactions in these short-lived but critically important complexes.



Scheme 9. Proposed catalytic cycle for the copper(I)-catalyzed cycloaddition of bismuth(III) acetylides and organic azides.

The copper(I)-catalyzed synthesis of bismuth(III) triazolides from 1-bismuth(III) acetylides and organic azides described here is a rapid, selective, and high-yielding method for the preparation of uniquely stable heterocyclic scaffolds. Additionally, the reaction of bismuth(III) triazolides with various electrophiles allows the efficient production of fully substituted 1,2,3-triazoles inaccessible by other means. Further mechanistic investigations of this reaction and development of its synthetic applications are currently underway in our laboratory. Moreover, activation of stable bismuth(III) acetylides using copper(I) catalysts and their subsequent reaction with appropriate electrophilic partners is being explored as a general synthetic tool.

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