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Modular synthesis of bis- and tris-1,2,3-triazoles by permutable sequential azide–aryne and azide–alkyne cycloadditions

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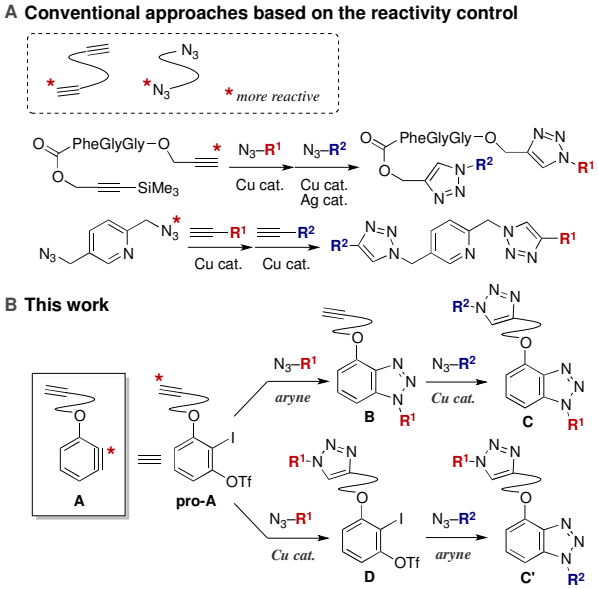
A modular synthetic method for bis- and tris-1,2,3-triazoles that include a benzotriazole structure was developed on the basis of sequential azide–aryne and azide–alkyne cycloadditions. The key to success was efficient halogen–metal exchange reaction-mediated generation of aryne from *ortho*-iodoaryl triflates bearing a base-sensitive terminal alkyne moiety, which was achieved using trimethylsilylmethyl Grignard reagent.

The breakthrough discovery that copper(I) catalyst significantly accelerates the Huisgen cycloadditions[1] between terminal alkyne and azide under mild conditions[2] triggered the explosive diffusion of click chemistry.[3] This method made the connection of molecules quite easy over broad disciplines including materials chemistry and chemical biology.[4] Moreover, the ready accessibility of a number of 1,2,3-triazoles from various azides and alkynes enabled a massive chemical library to be streamlined for high-throughput screening assays in drug discovery researches.[5] The robust triazole skeleton structure has also been recognized as a stable bioisostere of an amide bond due to the physicochemical similarities between them in terms of size, dipole moment, and hydrogen bonding ability, allowing triazoles to serve as good peptide surrogates.[6] These attractive features of triazole have encouraged chemists to synthesize unsymmetrical bistriazoles, which are useful not only for expanding the diversity of the chemical library but also for preparing bifunctional molecules by connecting two different functional molecules.[7,8] In this context, we recently developed a "double-click" reaction using a 1,5-cyclooctadiyne derivative, enabling facile chemical modification of azido-incorporated biomolecules with a small functional azido compound.[9] Herein is introduced an efficient synthetic method for diverse unsymmetrical bistriazoles based on sequential azide–aryne and azide–alkyne cycloadditions, which was achieved using an aryne precursor bearing a terminal alkyne moiety that served as a good diyne equivalent.

Unsymmetrical bistriazoles typically have been prepared by sequential click reactions toward a platform molecule with two alkynes or two azido groups (Scheme 1A).[7a,h] In these methods, the reactivities of the two groups were differentiated by protecting or activating either one of them: the first cyclization was selectively conducted at the more reactive moiety, and then the second cyclization at the remaining side.



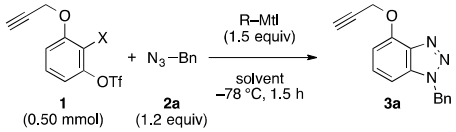
Scheme 1 Synthesis of unsymmetrical bistriazoles by sequential azide–alkyne cycloadditions.

Since 1,2,3-benzotriazole is also a pharmacologically important scaffold,[10] bistriazoles containing this structure are attractive candidates as bioactive compounds. We presumed that this type of bistriazole could be straightforwardly prepared from an aryne[11–14] that bears a terminal alkyne moiety, such as diyne **A**,[15] by consecutive cycloadditions with two azides (Scheme 1B). This approach differs from the previous ones in that the order of the cycloadditions can be reversed if aryne generation and cycloaddition with azide can be performed before and after the triazole formation at the terminal alkyne moiety. To prove the feasibility of this idea,

we designed 2-iodo-3-(propargyloxy)phenyl triflate (**1a**) as an aryne precursor bearing an alkyne moiety. The compound **1a** was readily prepared by the Mitsunobu etherification[16] of propargyl alcohol with known 3-hydroxy-2-iodophenyl triflate,[17] which was easily obtained from resorcinol in three steps. 3-(Propargyloxy)benzyne was supposed to be generated from **1a** by the treatment with an organometallic reagent that triggers the iodo–metal exchange reaction.

Although the reported conditions for aryne generation from *ortho*-iodoaryl triflates were found unsuitable for that purpose from **1a**, we succeeded in finding appropriate conditions after extensive screening for the reaction with benzyl azide (**2a**) (Table 1). An initial attempt under original conditions[13g] using *n*-butyllithium in THF at −78 °C furnished complex mixtures probably due to the competing deprotonation of highly acidic proton at the terminal alkyne (entry 1). Fortunately, another attempt using isopropylmagnesium chloride–lithium chloride complex[13k] afforded desired benzotriazole **3a**, although the yield was not satisfactory (entry 2). We therefore looked for a better Grignard reagent and observed that some reagents significantly increase the reaction efficiency (entries 3–7). In particular, (trimethylsilyl)methylmagnesium chloride with lower nucleophilicity and weaker basicity[19] than the others, provided the best result (entry 7). Under these conditions, the reaction could be performed uneventfully at gram scale, showing the practicality of the method.[18] Bulkiness on the silyl group of the reagent slightly retarded the reaction (entry 8). The use of corresponding lithium reagent instead of Grignard reagent greatly decreased the yield of the cyclized product, indicating the importance of counter cation for this reaction (entry 9). In addition, other solvents such as ether and toluene could be equally used in place of THF (entries 10 and 11). On the other hand, *ortho*-bromoaryl triflate **1b** was essentially inert under the optimized conditions for the iodo substrate **1a** (entry 12).

Table 1 Optimization of azide–aryne cycloaddition



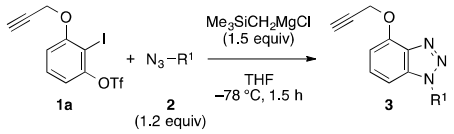
1 (0.50 mmol) 2a (1.2 equiv) 3a

Entry	R–MtI	X	1	Solvent	Yield (%)[a]
1	*n*-BuLi	I	**1a**	THF	ND[b]
2	*i*-PrMgCl·LiCl	I	**1a**	THF	46
3	*n*-BuMgCl	I	**1a**	THF	44
4	MeMgBr	I	**1a**	THF	61
5	*i*-PrMgCl	I	**1a**	THF	82
6	PhMgBr	I	**1a**	THF	70
7	Me_3SiCH_2MgCl	I	**1a**	THF	93
8	$Me_2(Ph)SiCH_2MgCl$	I	**1a**	THF	70
9	Me_3SiCH_2Li	I	**1a**	THF	31
10	Me_3SiCH_2MgCl	I	**1a**	Et_2O	93
11	Me_3SiCH_2MgCl	I	**1a**	toluene	89
12	Me_3SiCH_2MgCl	Br	**1b**	THF	0[c]

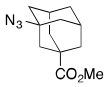
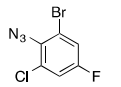
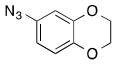
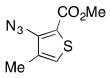
[a]Isolated yields. [b]Product **3a** was not detected (ND), although most of **1a** was consumed. [c]Most of **1b** was recovered.

The low nucleophilicity and weak basicity of the reagent for aryne generation allowed the reaction with a broad range of azides, including those with an electrophilic ester moiety and/or acidic protons (Table 2). The reactions of aryne generated from 1a with alkyl azides such as trimethylsilylmethyl azide (**2b**), *tert*-butyl α-azidoacetate (**2c**), and bulky 1-adamantyl azide (**2d**) smoothly proceeded to afford benzotriazoles **3a**–**3c** in high yields (entries 1–3). Diverse aryl azides bearing either a *para*-electron-donating or -withdrawing group also served as good substrates (entries 4 and 5). To our surprise, the reaction with sterically-hindered 2,6-diisopropylphenyl azide (**2g**) afforded the cycloadduct **3g** in an excellent yield (entry 6). This result might be attributed to the enhanced distortability of the azido group caused by the steric inhibition of resonance, which is similar to the enhanced clickability of **2g** observed in the reaction with a cyclooctyne derivative.[8] Other multisubstituted aryl azides, such as multihalogenated phenyl azide **2h**, 3,4-ethylenedioxyphenyl azide (**2i**), and 2,4-disubstituted 3-azidothiophene **2j**, also sufficiently provided benzotriazoles **3h**–**3j** (entries 7–9).

Table 2 Reactions of aryne generated from **1a** with various azides



1a 2 (1.2 equiv) 3

Entry	N_3–R^1	2	3	Yield (%)[a]
1	$N_3CH_2SiMe_3$	**2b**	**3b**	89
2	$N_3CH_2CO_2t$-Bu	**2c**	**3c**	75
3		**2d**	**3d**	87
4	$N_3C_6H_4$-*p*-OMe	**2e**	**3e**	83
5	$N_3C_6H_4$-*p*-CF_3	**2f**	**3f**	71
6[b]		**2g**	**3g**	92
7		**2h**	**3h**	81
8		**2i**	**3i**	85
9[c]		**2j**	**3j**	79

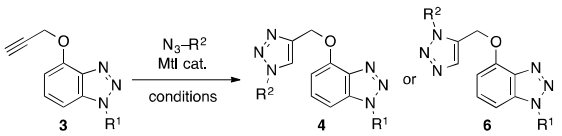
[a]Isolated yields. [b]Reaction was performed using **1a** (1.0 equiv), **2g** (1.5 equiv) and Me_3SiCH_2MgCl (2.0 equiv). [c]Reaction was performed using **1a** (2.1 equiv), **2j** (1.0 equiv) and Me_3SiCH_2MgCl (2.0 equiv).

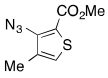
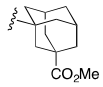
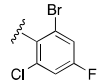
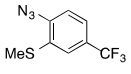
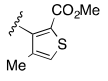
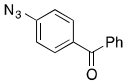
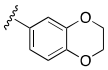
Benzotriazole **3** with the remaining terminal alkyne moiety was applied to metal-catalyzed cyclization with various azides, easily affording bistriazoles bearing a variety of groups often used as pharmacophores (Table 3). Under the copper(I)-catalyzed conditions, 1,4-substituted triazole formation[3,4] proceeded not only with alkyl and aryl azides (entries 1–4) but also with sulfonyl azide (entry 5),[20] efficiently providing bistriazoles **4a**–**4e**. On the other hand, bistriazole **6a** with a 1,5-substituted triazole structure was obtained from the reaction using a ruthenium catalyst,[21] which is favorable for diversifying the bistriazole library (entry 6).

The orthogonality between azide–aryne and azide–alkyne cycloadditions enabled us to reverse the order of the reactions, largely increasing the number of available bistriazoles (Scheme 2). For instance, we could first perform the copper(I)-catalyzed click reaction at the terminal alkyne moiety of **1a** with *p*-anisyl azide (**2e**)

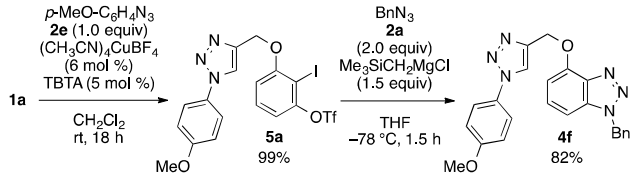
to afford triazole-bearing aryne precursor **5a**. The aryne generation from **5a** and cycloaddition with benzyl azide (**2a**) was feasible under conditions similar to those from **1a,** providing bistriazole **4f** in high yield without any detectable side products originating from undesired intramolecular reactions.

Table 3 Synthesis of bistriazoles by metal-catalyzed azide–alkyne cycloadditions



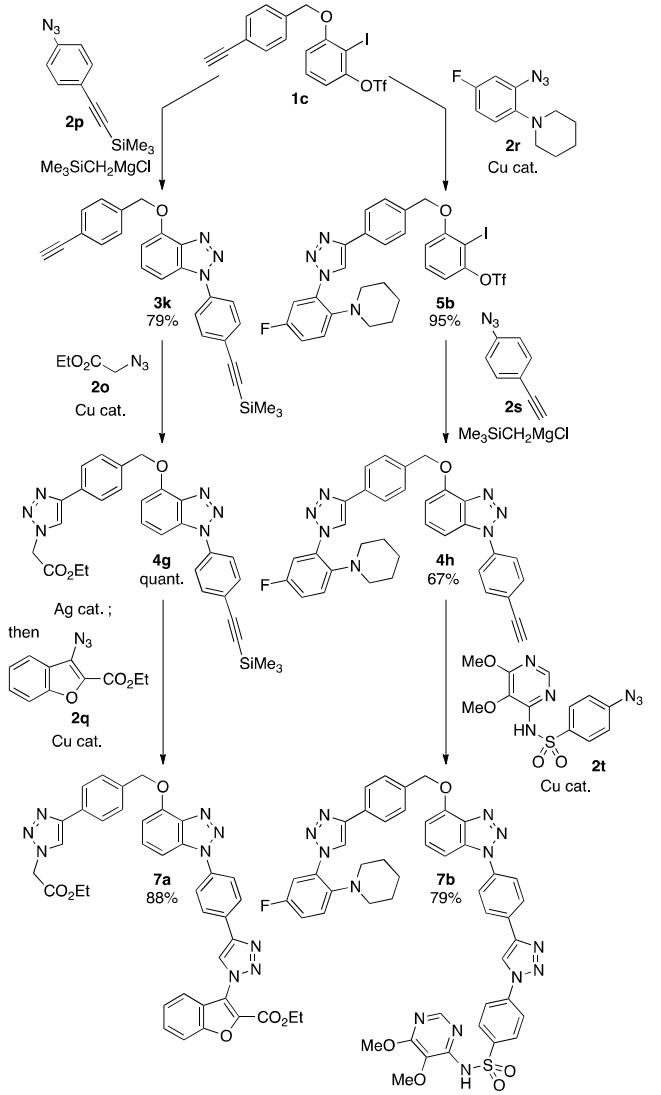
Entry	R^1	3	N_3–R^2	2	Condition[a]	4 or 6	Yield (%)[b]
1	Bn	**3a**		**2j**	A	**4a**	80
2		**3d**	N_3CH_2SPh	**2k**	A	**4b**	86
3		**3h**		**2l**	A	**4c**	69
4		**3j**		**2m**	A	**4d**	80
5		**3i**	N_3SO_2-*p*-Tol	**2n**	B	**4e**	83
6	Bn	**3a**	$N_3CH_2CO_2Et$	**2o**	C	**6a**	70

[a]Condition A: reaction of **3** (1.0 equiv) with **2** (1.0 equiv) in the presence of $(CH_3CN)_4CuBF_4$ (6–7 mol %) and TBTA (5–6 mol %) in *t*-BuOH/H_2O (1/1) at room temperature for 7–64 h. TBTA = tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine. Condition B: reaction of **3** (1.2 equiv) with **2** (1.0 equiv) in the presence of CuI (10 mol %) and 2,6-lutidine (1.2 equiv) in $CHCl_3$ at room temperature for 21 h. Condition C: reaction of **3** (1.2 equiv) with **2** (1.0 equiv) in the presence of $Cp^*RuCl(PPh_3)_2$ (20 mol %) in benzene at 80 °C for 4 h. [b]Isolated yields.



Scheme 2 Bistriazole synthesis by sequential azide–alkyne/azide–aryne cycloadditions.

Two ways of orthogonal conjugation of azides that allowed facile construction of the bistriazole library could be further expanded to the synthesis of tristriazoles with a combination of another bis-reactive junction molecule (Scheme 3). For instance, trimethylsilylmethyl Grignard-triggered azide–aryne cycloaddition using 3-(4-ethynylbenzyl)oxybenzyne precursor **1c** and 4-(trimethylsilylethynyl)phenyl azide (**2p**) provided benzotriazole **3k** including two different alkyne moieties, a terminal and a silyl-protected alkyne. Second cyclization of **3k** with azide **2o** under copper(I)-catalyzed conditions proceeded selectively at the terminal alkyne moiety to afford bistriazole **4g** quantitatively. The modified silver-mediated desilylation[7a] of **4g**, followed by third cyclization with azide **2q** at the bared terminal alkyne furnished tristriazole **7a** in high yield. On the other hand, performing copper(I)-catalyzed cyclization first at the terminal alkyne moiety of **1c** with azide **2r** afforded aryne precursor **5b** in excellent yield. Generation of aryne from **5b** with (trimethylsilyl)methylmagnesium chloride could be conducted in the presence of azide bearing a terminal alkyne moiety such as 4-ethynylphenyl azide (**2s**), which provided bistriazole **4h**. Finally, copper(I)-catalyzed click conjugation at the terminal alkyne moiety of **4h** with azide **2t** afforded tristriazole **7b**. This facile approach to diverse tristriazoles, with several pharmacophoric groups having molecular weights over 500, would facilitate the discovery of druggable molecules like a protein–protein interaction (PPI) inhibitor[22] that interacts with a target having a larger binding pocket.



Scheme 3 Synthesis of tristriazoles by three sequential cycloadditions. See ESI for details of the conditions.

In summary, we established a modular synthetic method for bis- and tris-1,2,3-triazoles based on sequential azide–aryne and azide–alkyne cycloadditions. The key to success was efficient generation of

aryne from *ortho*-iodoaryl triflates bearing a base-sensitive terminal alkyne moiety, which was achieved using trimethylsilylmethyl Grignard reagent. Orthogonality between the cycloadditions is of great advantage for constructing a multitriazole library containing diversified compounds with various pharmacophores in a broad range of molecular weights. Further studies to expand the library by applying the method to the reaction of diyne equivalents with arynophiles and ynophiles other than azides, as well as to explore the scope of aryne generation using trimethylsilylmethyl Grignard reagent are now in progress.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data including copies of NMR spectra. See DOI: 10.1039/c000000x/

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