JOC The Journal of Organic Chemistry

Featured Article

Cu(II)-Catalyzed Oxidative Formation of 5,5'-Bistriazoles

Christopher J. Brassard, Xiaoguang Zhang, Christopher R. Brewer, Peiye Liu, Ronald J Clark, and Lei Zhu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01907 • Publication Date (Web): 14 Oct 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Cu(II)-Catalyzed Oxidative Formation of 5,5'-Bistriazoles

*Christopher J. Brassard, Xiaoguang Zhang, Christopher R. Brewer, Peiye Liu, Ronald J. Clark, Lei Zhu**

Department of Chemistry and Biochemistry, Florida State University, 95 Chieftan Way, Tallahassee, FL 32306-4390, USA

KEYWORDS. CuAAC, copper catalysis, oxidative coupling, 5,5'-bistriazole, TBTA.

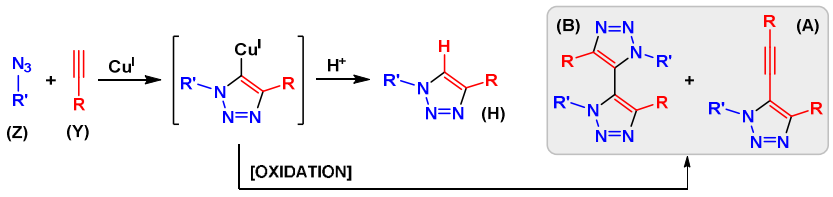
ABSTRACT. Copper(II) acetate under aerobic conditions catalyzes the formation of 5,5'-bis(1,2,3-triazole)s (5,5'-bistriazoles) from organic azides and terminal alkynes. This reaction is an oxidative extension of the widely used copper-catalyzed azide-alkyne 'click' cycloaddition. The inclusions of potassium carbonate as an additive and methanol or ethanol as the solvent, and in most instances an atmosphere of dioxygen, promote the oxidative reaction to afford 5,5'-bistriazole at the expanse of 5-protio-1,2,3-triazole (5-protiotriazole). If needed, tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) as a ligand additive further accelerates the formation of 5,5'-bistriazoles. A convenient procedure to prepare TBTA is also reported to facilitate the adoption of this method by the individuals who wish to make 5,5'-bistriazoles for various purposes. Aromatic azide-derived 5,5'-bistriazoles possess rigid axially chiral structures

with a broad distribution of dihedral angles, which may be explored as chiral ligands in enantioselective catalysis if decorated with proper functional groups.

Introduction

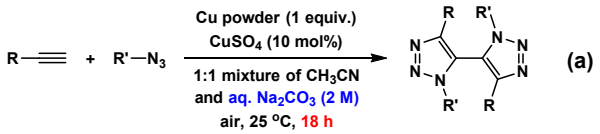
Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) affords 1,4-disubstituted-1,2,3-triazoles ('**H**' in Scheme 1, or '5-protiotriazole').[1,2,3] 5,5'-Bis(1,2,3-triazole)s ('**B**', or '5,5'-bistriazole') and 5-alkynyl-1,2,3-triazoles ('**A**', or '5-alkynyltriazole') are the side products from unintended oxidation (Scheme 1).[4,5] The formation of 5,5'-bistriazole likely results from the oxidative homocoupling of copper(I) triazolide intermediate, a step bearing resemblance to the aromatic Glaser-Hay reaction reported by Do and Daugulis.[6] This hypothesis provides a mechanistic foundation for the selective formation of a 5,5'-bistriazole that puts two azide and two alkyne molecules together in a single step. In addition to providing axially chiral 5,5'-bistriazoles with hopefully an adequate structural diversity for exploring the utility in asymmetric catalysis, this reaction is interesting mechanistically in the context of the widely used CuAAC reactions[5,7-15] and the intensely studied copper-mediated oxidative coupling reactions.[16-19]

Scheme 1. 5,5'-Bistriazole (**B**) and 5-alkynyltriazole (**A**) are side products from CuAAC that likely result from oxidative interception of the Cu(I) triazolide intermediate (bracketed)

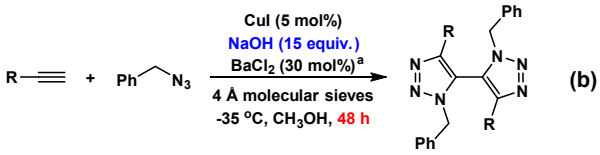


Several methods for preparing 5,5'-bistriazoles via the model of oxidative interception of CuAAC have been reported over the past decade;[20-26] four of which are shown in Scheme 2. These works were also summarized in a review article on the synthesis of broadly defined bistriazoles that include 5,5'-bistriazoles.[27] Angell and Burgess were the first to report the selective formation of 5,5'-bistriazole by the inclusion of a base in a CuAAC method (Scheme 2a).[20] The effect of a base to favor the oxidative reaction was analyzed. Furthermore, the specific effect of carbonate as a bridging ligand for copper centers, in addition to being a base, was postulated. Cuevas-Yañez and coworkers reported the beneficial effect of lowering temperature (-35 °C) in the selective formation of 5,5'-bistriazole (Scheme 2b), at the expense of a long reaction time (48 h).[22] Xu and coworkers' procedure includes an organic amine base (or ligand) in place of an inorganic base for 5,5'-bistriazole synthesis (Scheme 2c),[24] while in the work by Li, Zhang, and coworkers, the strongly basic sodium ethoxide was used (Scheme 2d).[25]

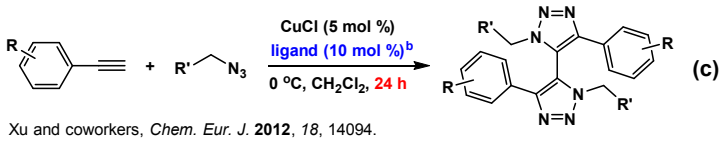
Scheme 2. Selected known methods to prepare 5,5'-bistriazoles.



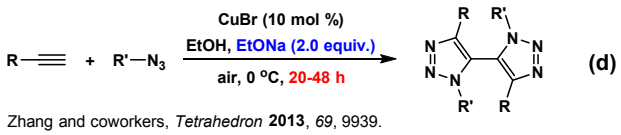
Angell and Burgess, *Angew. Chem. Int. Ed.* **2007**, *46*, 3649.



Cuevas-Yañez and coworkers, *Tetrahedron Lett.* **2011**, *52*, 3514.



Xu and coworkers, *Chem. Eur. J.* **2012**, *18*, 14094.



Zhang and coworkers, *Tetrahedron* **2013**, *69*, 9939.

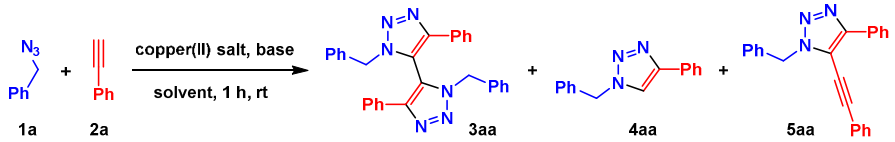
a. $BaCl_2$ was used in the workup;[22] b. polysiloxane-supported amines.

In addition to using a copper catalyst in the +1 oxidation state (in the case of Angell and Burgess' report, copper(I) is presumed to form from the comproportionation of copper powder and copper(II) sulfate[28]), these empirical pioneering works have offered a common denominator for achieving selective 5,5'-bistriazole formation that is the inclusion of a base (blue in Scheme 2). However, the existing methods in general require a relatively long time (12-48 h, red in Scheme 2), and have thus far limited substrate scopes. In particular, 5,5'-bistriazoles derived from aromatic azides have not been reported but for one isolated case.[29]

Results and Discussion

(a) Modifying the CuAAC reaction toward 5,5'-bistriazoles. Herein we report a simple procedure to prepare 5,5'-bistriazoles based on the mechanistic postulate illustrated in Scheme 1 that improves upon the known methods in two aspects: (1) reducing the reaction time from overnight or longer to within 3 h, and (2) expanding the substrate scope to include aromatic azide-derived 5,5'-bistriazoles. Our group has demonstrated that CuAAC can be catalyzed by $Cu(OAc)_2 \cdot H_2O$ without having a reducing agent to deliberately generate a copper(I) species.[30] The absence of a reducing agent renders our method particularly amenable for tweaking to favor the *oxidatively* coupled 5,5'-bistriazoles. Ligand tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) will be included in the procedure if needed due to its known effect of accelerating the triazolyl ring formation step.[31-33] The high cost of TBTA might be viewed as an inconvenience. To alleviate this concern, we developed a cost-effective procedure to prepare TBTA in gram scales within a few hours of total production time, which is described in the Experimental Section.

Table 1. Effect of base, solvent, and copper(II) source on the conversion and selectivity of the reaction between **1a** (benzylazide) and **2a** (phenylacetylene).[a]



Entry	Base	Solvent	Cu(II) salt	conversion[b]	Selectivity (**3aa**/**4aa**/**5aa**)[c]
1	-	MeOH	$Cu(OAc)_2$	15%	0/89/11
2	Li_2CO_3	MeOH	$Cu(OAc)_2$	14%	12/58/30
3	Na_2CO_3	MeOH	$Cu(OAc)_2$	17%	67/20/13
4	**K_2CO_3**	**MeOH**	**$Cu(OAc)_2$**	**> 99%**	**70/8/22**
5	Cs_2CO_3	MeOH	$Cu(OAc)_2$	0	-
6	K_3PO_4	MeOH	$Cu(OAc)_2$	7%	23/9/68
7	TEA	MeOH	$Cu(OAc)_2$	13%	19/64/17
8	DBU	MeOH	$Cu(OAc)_2$	> 99%	3/68/29
9	K_2CO_3	EtOH	$Cu(OAc)_2$	11%	85/4/10
10	K_2CO_3	tBuOH	$Cu(OAc)_2$	0%	-
11	K_2CO_3	MeCN	$Cu(OAc)_2$	43%	38/53/9
12	K_2CO_3	MeOH	$CuCl_2$	98%	69/8/23
13	K_2CO_3	MeOH	$CuSO_4$	87%	67/8/25
14	K_2CO_3	MeOH	$Cu(ClO_4)_2$	90%	66/12/22

a. Reagents and conditions: **1a** (0.55 mmol in 0.25 mL solvent), Cu(II) (0.025 mmol), base (1.0 mmol), and **2a** (0.5 mmol in 0.25 mL solvent), added in this order, 1 h at rt under air; b. the percentage of reacted alkyne, which is the limiting reagent; c. the ratio showing the distribution of converted alkyne into three possible products **3aa**, **4aa**, and **5aa**, based on ^{1}H NMR spectra of crude products. The homocoupled diyne was not observed.

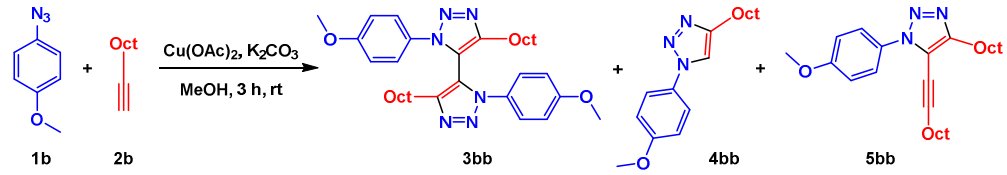
Using the reaction between benzylazide (**1a**) and phenylacetylene (**2a**), which have been the most common pair of substrates for the optimization of 5,5'-bistriazole formation, it was

determined that the inclusions of K_2CO_3 as a base additive, methanol as the solvent, and $Cu(OAc)_2 \cdot H_2O$ in solid form as the catalyst resulted in the selective formation of 5,5'-bistriazole **3aa** (70% selectivity; 54% isolated yield) in 1 h (Table 1, entry 4). K_2CO_3 was reported to have the second best solubility in methanol among the alkali carbonates after Cs_2CO_3.[34] Upon dissolution, K_2CO_3 deprotonates methanol to produce an appropriate amount of methoxide,[35,36] which we postulate to be involved as a ligand for copper in this reaction. This argument is consistent with the report that sodium ethoxide was the choice of base in the 5,5'-bistriazole synthesis by Li, Zhang, and coworkers (Scheme 2d).[25] We tried sodium methoxide as the base in two reactions (see Table S2). Good selectivity values were obtained, consistent with the proposed function of methoxide as a ligand for copper that favors the formation of 5,5'-bistriazole. Yet the reaction became slower with an increasing amount of sodium methoxide. Sodium methoxide was not considered further because K_2CO_3 worked well enough in this work. K_3PO_4 (entry 6) in place of K_2CO_3 resulted in 7% conversion. Organic bases such as TEA (entry 7) or DBU (entry 8) did not deliver satisfactory values of either conversion or selectivity toward 5,5'-bistriazole (**3aa**).

Regarding the solvent, both methanol and ethanol resulted in good selectivity for 5,5'-bistriazole. However, the conversion value in ethanol after 1 h was low (11%, entry 9). The reactions in t-butanol (entry 10) and acetonitrile (entry 11) were sluggish on both conversion and selectivity fronts. The effect of the third variable, the copper(II) source, was studied in methanol. All copper(II) salts tested gave similar marks on conversion and selectivity (entries 4, 12-14). The close reactivity can be explained by the fact that these salts likely rearrange in the presence of carbonate and methoxide to afford similar copper(II) cluster structures. $(CuOH)_2CO_3$, a compound that may bear similarity to the copper(II) species suspected to have formed under the

reported conditions, is competent in oxidative coupling reactions.[37] $Cu(OAc)_2$ was selected for further experiments, which based on our experience gives the most consistent reaction outcome.

Table 2.[a] Effect of TBTA, $NaNO_2$, O_2, and reactant stoichiometry on reaction conversion[b] and selectivity[c].



entry	**1b**/**2b**	Additive	Conversion[b]	Selectivity (**3bb**/**4bb**/**5bb**)[c]
1	1.1/1	None, air	12	-
2	1.1/1	TBTA (5 mol%)[d] air	28	54/34/12
3	1.1/1	TBTA (20 mol%) air	58	40/48/12
4	1.1/1	TBTA (20 mol%), O_2	51	50/35/15
5	1.1/1	TBTA (20 mol%), O_2, $NaNO_2$ (0.5 mmol)	92	39/48/13
6	**2/1**	**TBTA (20 mol%), O_2, $NaNO_2$ (0.5 mmol)**	**> 99**	**61/24/15**
7	1/2	TBTA (20 mol%), O_2, $NaNO_2$ (0.5 mmol)	73	50/40/10

a. Reagents and conditions: the limiting reagent was set at 0.5 mmol. **1b** (variable in 0.25 mL MeOH), $Cu(OAc)_2$ H_2O (0.025 mmol), K_2CO_3 (0.5 mmol), and **2b** (0.5 mmol in 0.25 mL MeOH), added in this order, 3 h at rt; b. the percentage of the reacted limiting reagent; c. the ratio showing the distribution of converted alkyne into three possible products **3bb**, **4bb**, and **5bb**, based on ^1H NMR spectra of crude products; d. the percentage is based off the limiting reagent.

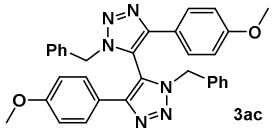
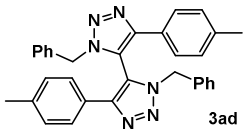
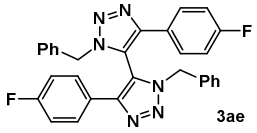
A less reactive pair of substrates, 4-azidoanisole (**1b**) and 1-decyne (**2b**), was used to study how other reaction parameters affect the conversion and selectivity of the 5,5'-bistriazole forming reaction (Table 2).[38] In the absence of **1b**, oxidative homocoupling of alkyne **2b** was not

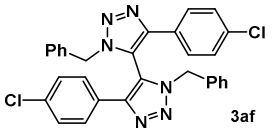
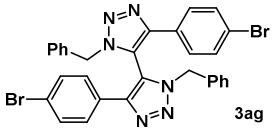
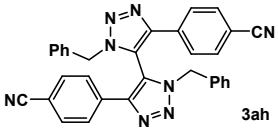
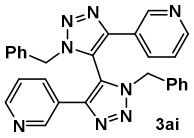
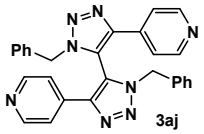
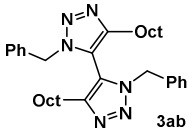
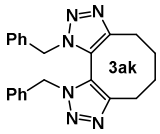
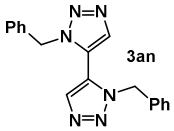
observed under the conditions listed for Table 1, entry 4 in 3 h. The inclusion of 4-azidoanisole (**1b**) resulted in a 12% conversion of **2b** (Table 2, entry 1). Adding ligand TBTA up to 20 mol % helped the conversion, with 40% selectivity to 5,5'-bistriazole (entries 2 and 3). With the understanding that O_2 is the stoichiometric oxidant,[39] an O_2 atmosphere was provided, which increased the selectivity to 5,5'-bistriazole with a drop in conversion (entry 4). The inclusion of $NaNO_2$, which is both an oxidant and a ligand for copper(II), drove the reaction almost to completion (entry 5), with a similar selectivity spread to that of entry 3. By doubling the amount of azide **1b** under the conditions of entry 5, a complete conversion of **2b** was achieved with 61% selectivity toward 5,5'-bistriazole (entry 6, 52% isolated yield for **3bb**). Reversing the stoichiometric ratio (i.e., using an excess of alkyne) slowed down the reaction with a reduction in 5,5'-bistriazole selectivity (entry 7).

Based on the data in Tables 1 and 2, the following reaction parameters were selected for favoring 5,5'-bistriazole formation: (1) 5-10 mol% $Cu(OAc)_2$ as the catalyst; (2) 0.5-2 molar equivalents K_2CO_3 relative to the limiting reagent alkyne as the additive; (3) MeOH or EtOH as the solvent; (4) TBTA as an optional ligand for accelerating the triazolyl ring formation; (5) an O_2 atmosphere for favoring the oxidative reaction; (6) an excess amount of azide to increase the selectivity toward 5,5'-bistriazole; and (7) $NaNO_2$ as an oxidative analog of acetate to push up the conversion and selectivity towards 5,5'-bistriazole, if needed. The decision on whether to include TBTA, O_2, or $NaNO_2$ is made based on the compromise between reaction speed and selectivity under individual circumstances. The effectiveness of this method was tested using various azides and alkynes (Figures S1-2). Using this method, the reactions were completed within 3 h to provide > 50% isolated yields of 5,5'-bistriazole products. The data (Tables 3-5) are described separately based on the nature of the azide component.

(b) Scope of substrates organized by the nature of azides. Benzylazide (**1a**) has been the most studied azide substrate in 5,5'-bistriazole forming reactions.[20,22-25,40] Using the current method, 5,5'-bistriazoles derived from **1a** and *para*-substituted phenylacetylenes readily formed. The selectivity and isolated yields of entries 1-6 in Table 3 are listed in the ascending order of Hammett constant (σ)[41] of the *para*-substituent. Phenylacetylenes equipped with electron-withdrawing *para*-substituents (entries 3-6) require EtOH as the solvent with the assistance of TBTA to afford a complete conversion and good selectivity toward 5,5'-bistriazole within 3 h; the reactions of these substrates in MeOH gave worse selectivity toward 5,5'-bistriazoles. The reactions between **1a** and phenylacetylenes substituted with electron-donating groups (entries 1-2) proceeded smoothly in MeOH without TBTA. We defer to a future mechanistic study to provide an explanation for this empirical electronic correlation with the choice of solvent.

Table 3. 5,5'-Bistriazoles derived from benzylazide.[a]

entry	5,5'-Bistriazole	Selectivity (**3**/**4**/**5**)	Solvent/ ligand	Isolated yield (%)
1	 **3ac**	82/7/11	MeOH/ none	58
2	 **3ad**	75/13/12	MeOH/ none	66
3	 **3ae**	82/14/4	EtOH/ TBTA	63

4	 3af	86/10/4	EtOH/ TBTA	60
5	 3ag	90/6/4	EtOH/ TBTA	72
6	 3ah	77/13/10	EtOH/ TBTA	68
7	 3ai	79/8/13	EtOH/ TBTA	67
8	 3aj	77/18/5	EtOH/ TBTA	62
9[b]	 3ab	80/13/7	MeOH/ none	71
10[c]	 3ak	-	MeOH/ none	17
11[d]	 3an	-	MeOH/ TBTA	17

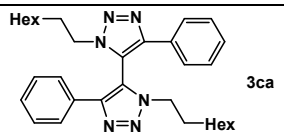
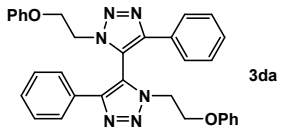
a. Reagents and conditions: benzylazide (1.0 mmol), $Cu(OAc)_2$ (0.025 mmol), TBTA (0.025 mmol if needed), K_2CO_3 (0.5-2 mmol, see the Experimental Section), and alkyne (0.5 mmol) in MeOH or EtOH (0.5 mL) at rt for 3 h; b. azide: 0.5 mmol; alkyne: 1.0 mmol; $Cu(OAc)_2 \cdot H_2O$: 0.050 mmol; c. azide: 2.0 mmol; $Cu(OAc)_2 \cdot H_2O$: 0.1 mmol; under an atmosphere of O_2; d. 6 h, 0 °C – rt.

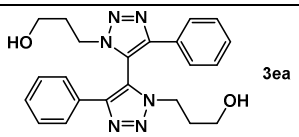
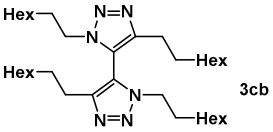
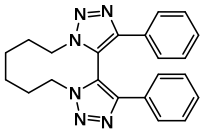
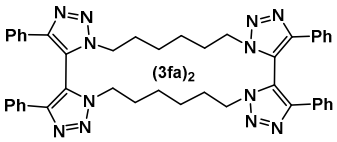
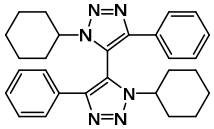
The reactions between benzylazide and 3/4-ethynylpyridine using the combination of TBTA and EtOH resulted in acceptable conversions and selectivity within 3 h (entries 7-8, Table 3).

Benzylazide also reacted well with the aliphatic 1-decyne (entry 9), in MeOH without TBTA. A cyclic 5,5'-bistriazole was prepared from 1,7-octadiyne (entry 10). Ethynyltrimethylsilane was used to react with benzylazide based on the suggestion from a reviewer. This reaction afforded the desilylated 5,5'-bistriazole **3an** (entry 11) in 17% isolated yield. The reaction was extended to 6 h, yet there was evidence based on the ^{1}H NMR that the desilylation was not complete. Furthermore, the desilylated 5-alkynyltriazole could react with benzylazide to afford 4,5'-bistriazole, which might have complicated the analysis of the reaction mixture. Therefore, we did not determine the selectivity values. Compound **3an** was previously reported by Angell and Burgess with 25% isolated yield from a reaction that lasted 18 h.[20]

Aliphatic azide-engaged 5,5'-bistriazole formations are listed in Table 4. Both primary (entries 1-4) and secondary (entry 7) aliphatic azides underwent rapid conversions to 5,5'-bistriazoles with good selectivity. Two macrocyclic 5,5'-bistriazoles (entries 5-6) were obtained from 1,6-bis(azido)hexane in moderate yields. How to selectively produce macrocyclic 5,5'-bistriazoles of arbitrary ring sizes with good isolated yields is an aim of future studies.

Table 4.[a] 5,5'-Bistriazoles derived from aliphatic azides.

entry	5,5'-Bistriazole	Selectivity (**3**/**4**/**5**)	Solvent/ ligand[b]	Isolated Yield (%)
1	 **3ca**	82/10/8	MeOH/ TBTA (0.1)	81
2	 **3da**	87/10/3	EtOH/ TBTA (0.025)	81

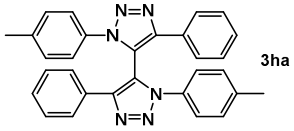
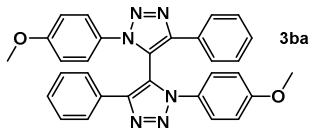
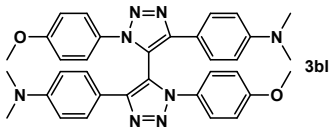
3[c]	 3ea	74/9/17	MeOH/ none	55
4	 3cb	75/11/14	MeOH/ TBTA (0.1)	61
5	 3fa	-	EtOH/ TBTA (0.1)	32
6	 $(3fa)_2$	-	EtOH/ TBTA (0.1)	12
7	 3ga	69/23/8	MeOH/ TBTA (0.025)	53

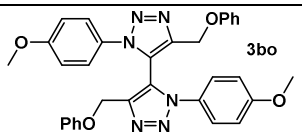
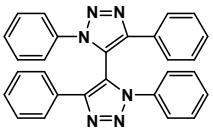
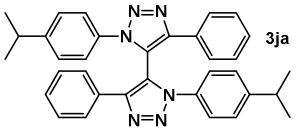
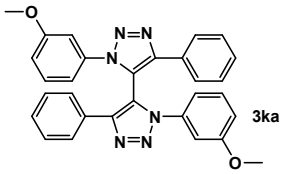
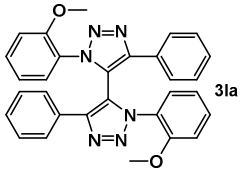
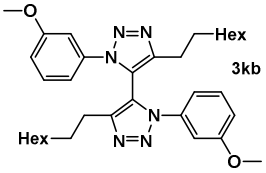
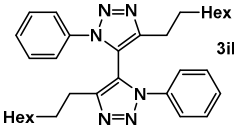
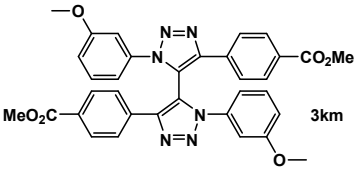
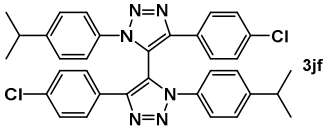
a. Reagents and conditions: azide (0.5-1.0 mmol, see the Experimental Section), $Cu(OAc)_2 \cdot H_2O$ (0.025 mmol), TBTA (0.025-0.10 mmol, if needed); K_2CO_3 (0.25-1.5 mmol, see the Experimental Section), and alkyne (0.5 mmol) in MeOH or EtOH (0.5-1 mL, see the Experimental Section) at rt for 3 h under an atmosphere of O_2; b. mmol in parentheses; c. $NaNO_2$ (0.5 mmol) and an increasing amount of azide (2.5 mmol) were used.

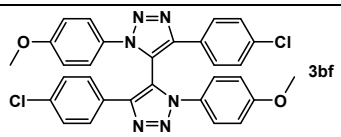
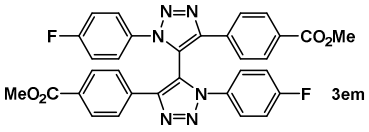
Aromatic azide-involved reactions require the participation of TBTA under an atmosphere of O_2 to reach satisfactory conversions and selectivity favoring 5,5'-bistriazoles (Table 5). On a side note, to the best of our knowledge, this is the first report of copper-catalyzed triazolyl ring formation reaction that was done under an O_2 atmosphere. The conventional wisdom "calls for complete exclusion of oxygen from the reaction medium"[7] because of the requirement of copper in the +1 oxidation state for the cycloaddition step. Yet the rapid triazolyl ring formation observed in this work under an atmosphere of O_2 underscores that the threshold for the copper(I) catalyst can be deceptively low.[42]

The selectivity toward 5,5'-bistriazole of the examples starting with aromatic azides ranges in the 60s-70s%, whereas the 5,5'-bistriazole selectivity values from benzyl (Table 3) and aliphatic (Table 4) azides are higher. MeOH worked well as the solvent when neither alkyne nor aromatic azide substrate bears an electron-withdrawing substituent (entries 1-10, Table 5). All other substrate pairs gave good conversion and selectivity in EtOH. In addition to *para*-substituted azidobenzenes, *meta*- and *ortho*-azidoanisoles also resulted in >50% isolated yields for 5,5'-bistriazoles in four examples (entries 7-9, 11). For a subset of substrates (entries 5, 7, 8, 11) the reactions were run at 0 °C to obtain acceptable isolated yields (i.e., > 50%). The effect of a low temperature for favoring 5,5'-bistriazole formation has been reported by others.[22,24,25] The tradeoff however is the time of the reaction. In the current work, the majority of the reactions do not require a temperature below rt to result in a favorable 5,5'-bistriazole formation with an isolated yield over 50%. Therefore, the effect of temperature was not studied systematically.

Table 5. 5,5'-Bistriazoles derived from aromatic azides.[a]

entry	5,5'-Bistriazole	Selectivity (**3**/**4**/**5**)	Solvent	Isolated Yield (%)
1	 **3ha**	63/12/25	MeOH	59
2	 **3ba**	69/11/20	MeOH	59
3	 **3bl**	69/18/13	MeOH	55

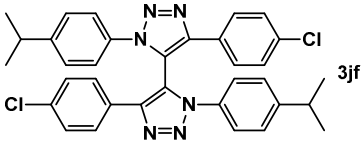
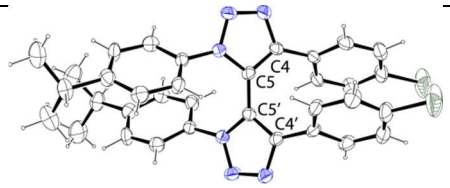
4[b]	 3bo	76/10/14	MeOH	62
5[c]	 3ia	65/12/24	MeOH	56
6	 3ja	65/18/17	MeOH	63
7[c]	 3ka	68/9/23	MeOH	62
8[c]	 3la	66/3/31	MeOH	51
9[d]	 3kb	72/18/10	MeOH	54
10[d, e]	 3ib	65/19/16	MeOH	56
11[c]	 3km	66/29/5	EtOH	52
12	 3jf	72/19/9	EtOH	52

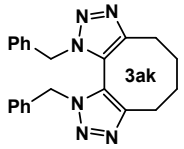
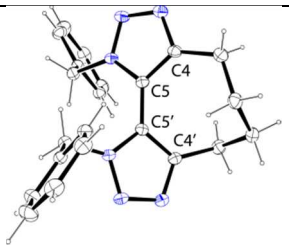
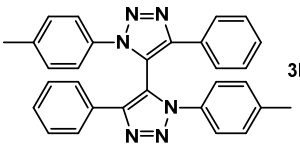
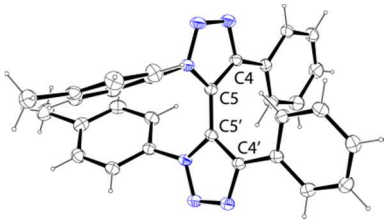
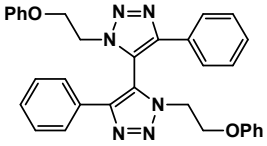
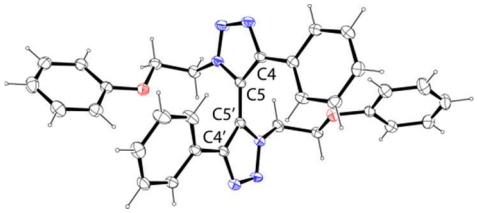
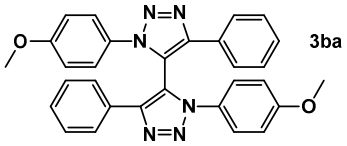
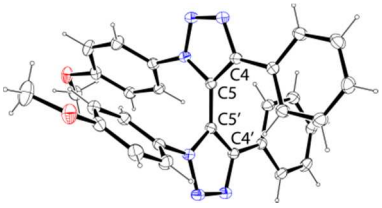
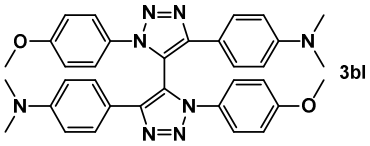
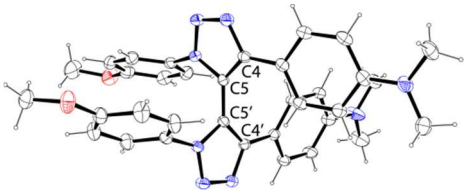
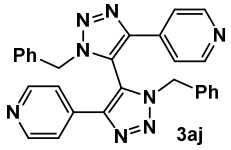
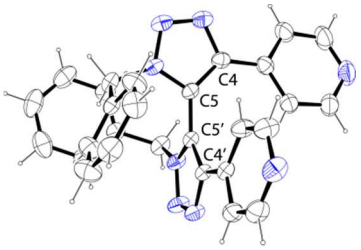
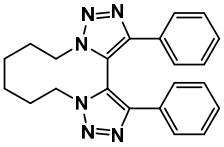
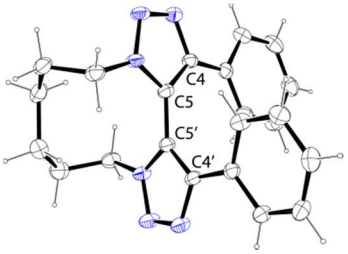
13	 3bf	75/13/12	EtOH	70
14	 3em	74/20/6	EtOH	61

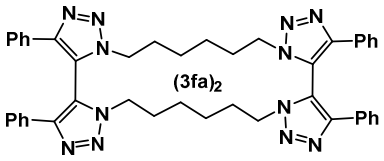
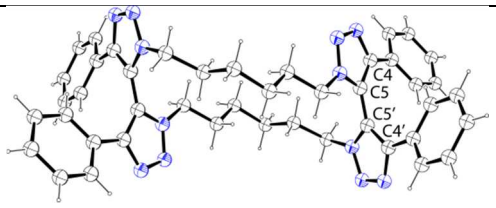
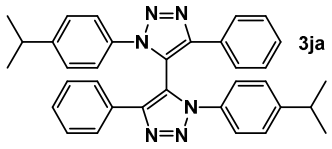
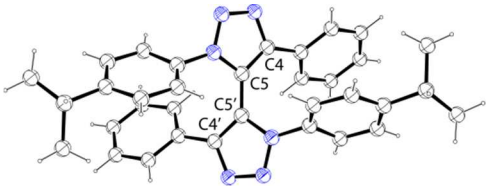
a. Reagents and conditions: azide (1.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.025 mmol), TBTA (0.1 mmol), K_2CO_3 (0.5-2.0 mmol, see the Experimental Section), and alkyne (0.5 mmol) in MeOH or EtOH (0.5 mL) at rt under an O_2 atmosphere for 3 h; b. no TBTA was needed; c. the reaction was run at 0 °C; d. $NaNO_2$ (0.5 mmol) was included; e. azide (2.5 mmol, 5 molar equivalents) was used.

(c) The range of dihedral angles of the axially chiral 5,5'-bistriazoles. The X-ray single crystal structures of ten 5,5'-bistriazoles are shown in Table 6. The dihedral angle along the C5-C5' axis varies from 43° to 130°. The dihedral angle value of BINAP class of ligands is a critical parameter in determining the enantioselectivity of the reactions they are involved in.[43] Tetraaryl-substituted 5,5'-bistriazoles have similarly rigid axially chiral structures with a broader range of dihedral angle distribution than that of BINAPs, which shall introduce new opportunities in developing chiral ligands for asymmetric catalysis.[40]

Table 6. Single crystal structures of 5,5'-bistriazoles and measured dihedral angles (in absolute values in ascending order).

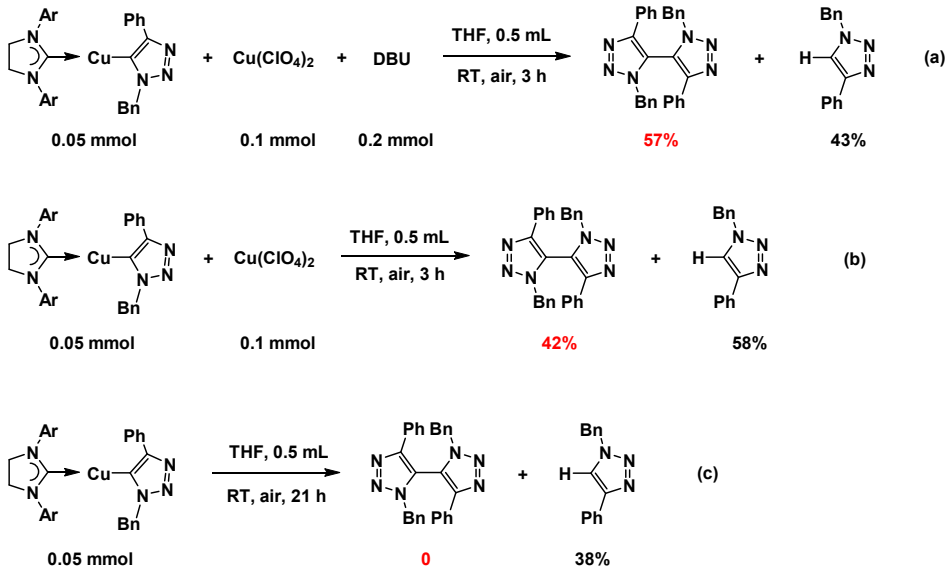
Table	Entry	ChemDraw	Ellipsoid	|Dihedral angle|
5	12	 3jf		43.20

3	10	 3ak		46.16
5	1	 3ha		73.35
4	2	 3da		81.57
5	2	 3ba		83.12
5	3	 3bl		86.21
3	8	 3aj		89.40
4	5	 3fa		95.06

4	6			105.55
5	6			130.89

(d) Mechanistic discussion. As shown in Scheme 1, the triazolide intermediate from the CuAAC reaction could be oxidatively coupled to afford 5,5'-bistriazole. This hypothesis finds precedence in the "aromatic Glaser-Hay" reaction,[6] in which the conjugate base of an aromatic heterocycle is oxidized by copper(II) salts to the homocoupled dimer under aerobic conditions. This comparison offers an explanation to the need of both copper(II) and a strong base for an efficient formation of 5,5'-bistriazole in the current work – copper(II) is the oxidant, while the base minimizes the possibility of triazolide protonation to give 5-protiotriazole. As shown in Scheme 3a, we prepared an N-heterocyclic carbene (NHC)-stabilized copper(I) triazolide based on the procedure by Straub and coworkers,[44] which was treated with $Cu(ClO_4)_2$ and DBU to afford 5,5'-bistriazole as the major product (57%) in 3 h. The rest of the triazolide was turned into 5-protiotriazole. The sources of proton include the moisture in the air and in the solvent. When the base (DBU) was taken away (Scheme 3b), copper(I) triazolide was also fully converted within 3 h with a reduced 5,5'-bistriazole percentage at 42%. Therefore, it can be concluded that the presence of DBU suppressed the 5-protiotriazole formation by making proton less available. Without copper(II) and base under otherwise identical conditions (Scheme 3c), 38% of copper(I) triazolide was converted after 21 h to 5-protiotriazole only.

Scheme 3. The conversion of NHC-Cu(I)-triazolide to 5,5'-bistriazole and 5-protiotriazole[a]



a. Ar = 2,6-diisopropylphenyl; the red numbers under 5,5'-bistriazole are the percentage of the 5,5'-bistriazole from the converted starting material.

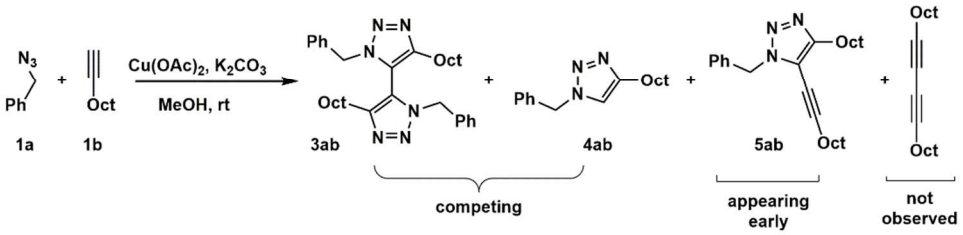
Treating 5-protiotriazoles with either potassium carbonate or alkoxides in the presence of a catalytic or stoichiometric amount of copper(II) salts for the purpose of replicating the "aromatic Glaser-Hay" reaction was however unsuccessful. No trace of 5,5'-bistriazole was observed using several different bases or either catalytic or stoichiometric amount of copper(II) acetate (Scheme S1). Similar lack of reactivity of 5-protiotriazoles in homocoupling was also reported in the previous works on 5,5'-bistriazole synthesis.[20,22,25] The comparison of the observations listed in Schemes 3 and S1 suggest that the activation barrier to reach triazolide is much higher from 5-protiotriazole than from terminal alkyne and azide, under copper-catalyzed conditions.

It was remarked by Angell and Burgess that 5,5'-bistriazole formation under basic conditions "is surprising because it has been stated several times that the pH value is relatively unimportant for copper-mediated cycloadditions to give triazoles".[20] It now can be understood that in those

referred "copper-mediated cycloadditions", sodium ascorbate, or other reducing reagents, was used to mop up any oxidant to keep the level of copper(II) at a minimum. Therefore, oxidative reactions were suppressed regardless of the pH. On the contrary, none of the reported procedures of 5,5'-bistriazole synthesis[12-18] has a reducing reagent such as sodium ascorbate to ensure copper in the +1 oxidation state, which means that the copper(I) catalyst being used in these earlier reports of 5,5'-bistriazole synthesis could be relatively easily oxidized to copper(II), likely by O_2, to allow oxidative coupling to take place, especially when 5-protiotriazole formation is not competitive in the presence of a proton-absorbing strong base. Particularly illuminating is the example described by Oladeinde et al.,[21] in which a typical CuAAC condition of $CuSO_4$/sodium ascorbate results in a 5-protiotriazole as the major product, while switching to a CuI/DIPEA system without protection against oxidant by sodium ascorbate flips the major product to the 5,5'-bistriazole. Copper(II) alone without the assistance of a base would not favor 5,5'-bistriazole because triazolide protonation outcompetes oxidative coupling under those conditions to give 5-protiotriazole as the predominantly favored product.[30]

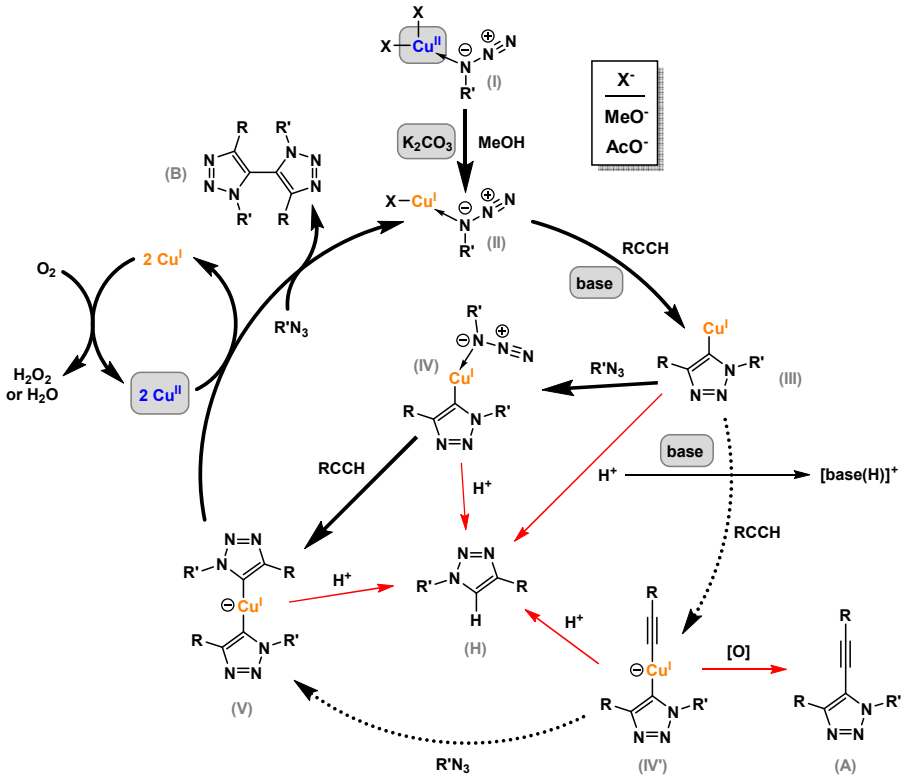
The reaction between benzylazide and 1-decyne (Scheme 4) was monitored using ^{1}H NMR. The conversion values at each time point of the three products are plotted in Figure S4. A few observations yield clues to the mechanism of this reaction: (1) the formation of diyne, the oxidative coupling product of the alkyne, was not observed; (2) 5-alkynyltriazole appeared at the very early stage of the reaction, the production of which did not persist throughout the reaction; (3) 5,5'-bistriazole and 5-protiotriazole compete with each other; and (4) unlike $Cu(OAc)_2$-catalyzed CuAAC reaction that we reported before,[45] the 5,5'-bistriazole formation in the current case does not have a perceptible induction period.

Scheme 4. Reaction between **1a** and **2b**, and observations in the ^{1}H NMR monitoring experiment



Based on the above analysis and observations, one possible model (Scheme 5) is drawn that starts with the formation of a copper(II)/azide complex (**I**). Subsequent *in situ* reduction of **I** to **II** via, for example, alcoholic solvent oxidation,[46] ushers the azide substrate into the catalytic cycle. The steps primarily responsible for 5,5'-bistriazole **B** are marked by bold black arrows, whereas routes leading to side products **H** and **A** are marked by red arrows. Cycloaddition of **II** with alkyne RCCH in the presence of a base to afford copper(I) triazolide (**III**) follows,[47] which recruits either an alkyne (**IV'**) or an azide (**IV** and **V**) to initiate the second triazolide formation.[48,49] The oxidation of copper(I) bistriazolide **V** by copper(II) salts gives **B**,[50] while the resulting copper(I) is recycled back to copper(II) via aerobic oxidation. In this model, only mononuclear copper complexes are drawn; in reality, these complexes might contain bi- or multinuclear copper centers.[51-53] Protonation of a copper(I) triazolide (**III**, **IV**, **IV'**, **V**) may occur to afford the 5-protiotriazole side product **H** (Scheme 5, red arrows inside circle), although the presence of a base reduces the propensity of protonation. Also, intermediate **IV'** may undergo oxidation to form 5-alkynyltriazole **A** (red arrow on lower right of Scheme 5).

Scheme 5. Mechanistic model of 5,5'-bistriazole (**B**) formation[a]



a. The nuclearity of the species is not restricted to monocopper. The major steps that involve copper(II) and base are shaded. Counter ion 'X' is added for the purpose of balancing charges. The likely candidates for X are methoxide (or ethoxide) and acetate. The precise structures of the copper complexes are not known at this point. [O] = oxidation, possibly by copper(II).

The following features of the model in Scheme 5 are consistent with experimental observations: (1) the saturation of copper(II) centers by the azide substrate ensures that any copper(I) acetylide is being rapidly transformed to triazolide. Therefore, alkynylated side product **A** only appears at the early stage of the reaction before the steady state is reached, and the diyne species was not even observed. Several methods for selective formation of 5-alkynyltriazole have been reported.[4,25,54-57] How to favor 5-alkynyltriazole over 5,5'-bistriazole is an interesting mechanistic question to answer in the future. (2) The involvement of the strong base K_2CO_3,

which effectively deprotonates methanol, and to a lesser extent ethanol,[35] increases the rate of the induction reaction to produce the copper(I) catalyst via alcohol oxidation. This model also highlights the requirements of both copper(II) and the carbonate base/ligand (shaded in Scheme 5) in 5,5'-bistriazole formation – copper(II) recruits the azide substrate and acts as the oxidant in the triazolide homocoupling step, while carbonate deprotonates methanol and alkyne, and minimizes 5-protiotriazole formation.

Conclusion

In summary, comparing to the existing methods of 5,5'-bistriazole synthesis, the current method provided high conversion and good selectivity for 5,5'-bistriazole more rapidly with a larger substrate scope that includes aromatic azides. The reported 5,5'-bistriazoles were prepared quickly (< 3 h) and economically with good isolated yields (> 50%). Based on the preliminary mechanistic analysis, the functions of copper(II) salt and carbonate base were defined in a model consistent with the experimental observations. Under a broader mechanistic context, this reaction could also be viewed as the interception of the alkyne oxidative homocoupling pathway by the introduction of an azide. The rigid axially chiral 5,5'-bistriazoles derived from aryl azide and aryl alkyne could conceivably be developed into ligands in assisting asymmetric catalysis.

Experimental Section

(1) Materials and general methods. Reagents and solvents were purchased from various commercial sources and used without further purification unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using precoated TLC plates with silica gel 60 F254. Flash column chromatography was performed using 40−63 μm (230−400 mesh ASTM) silica gel

as the stationary phases. Silica was flame-dried under vacuum to remove adsorbed moisture before use. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz respectively, at 295 K unless otherwise noted. The chemical shifts (δ) are recorded in ppm relative to the residual $CHCl_3$ or CHD_2CN as internal standards. High resolution mass spectra (HRMS) were obtained under electrospray ionization (ESI) using a time-of-flight (TOF) analyzer. Benzylazide purchased from various vendors gave inconsistent results, suggesting that batch-to-batch impurities affect the reaction outcome differently. Therefore, the benzylazide used in this study was prepared from benzylbromide and NaN_3 and rigorous purified. It has been consistently observed that aromatic azides produced from diazotization of aniline derivatives followed by substitution with NaN_3 without solid phase filtration to remove the ^{1}H NMR invisible inorganic impurity gave complete reactions with good selectivity to 5,5'-bistriazoles within 3 h. The rigorously purified aromatic azides react more sluggishly under the same conditions. All the data listed in Table 5 were collected using azides purified via chromatography.

*(2) Convenient synthesis of **TBTA**. (a) The "4-hour procedure"*. Benzylazide (2.0 mL, d = 1.066 g/mL, 16 mmol) was dissolved in *tert*-butanol (7.5 mL) in a 100-mL round-bottom flask equipped with a magnetic stir bar. Tripropargyl amine (712 μL, d = 0.927 g/mL, 5.0 mmol) was subsequently added, and the flask was placed in a water bath at rt. $Cu(OAc)_2 \cdot H_2O$ (36 mg, 0.18 mmol) was added, and the reaction flask was left *uncovered* (to prevent pressure buildup in case of unexpectedly strong heat release) while stirring for 5 min. The flask was then closed with a rubber septum equipped with an argon balloon. The reaction mixture was left stirring for up to 2.5 h, during which a precipitate formed and eventually the reaction mixture gelled. Diethyl ether (20 mL) was added to the flask, and the stirring was kept for another 10-20 min. The product was collected via vacuum filtration. The collected amorphous solid was washed with diethyl ether (15

mL × 3) before air-dried for 30 min. The yield was 2.5 g (94%). The total experiment time was ~ 4 h. The compound is stored in a desiccator at rt for permanent storage. ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 7.66 (s, 3H), 7.35-7.32 (m, 6H), 7.26-7.23 (m, 9H), 5.50 (s, 6H), 3.69 (s, 6H). This compound has been reported.[31]

*(b) A modified **TBTA** synthesis*. Benzylazide (2.0 mL, d = 1.066 g/mL, 16 mmol) was dissolved in *tert*-butanol (20 mL) in a 100-mL round-bottom flask equipped with a magnetic stir bar. Tripropargyl amine (712 μL, d = 0.927 g/mL, 5.0 mmol) was subsequently added, and the flask was placed in a water bath at rt. $Cu(OAc)_2 \cdot H_2O$ (18 mg, 90 μmol) was added, and the reaction flask was left uncovered while stirring for 5 min. The flask was then closed with a rubber septum equipped with an argon balloon. The reaction mixture was left stirring overnight, during which a precipitate formed. Diethyl ether (20 mL) was added to the flask, and the stirring was kept for another 10-20 min. The product was collected via vacuum filtration. The collected amorphous solid was washed with diethyl ether (15 mL × 3) before air-dried for 30 min. The compound can be further dried under vacuum in a desiccator equipped with Drierite. The yield was 2.5 g (94%). The total experiment time was ~ 1 day. The compound is stored in a desiccator for permanent storage. The key modifications are to use more solvent and less copper so that the reaction mixture would not solidify before completion. The cost is more time.

*(c) Procedure for experiments in Table 1 to produce **3aa**.* To a 25-mL round-bottom flask equipped with a magnetic stir bar, benzylazide (73 mg, 0.55 mmol) in 0.25 mL of solvent was added. While stirring at rt, Cu(II) source (0.025 mmol), base/additive (1.0 mmol), and phenylacetylene (51 mg, 0.5 mmol) in 0.25 mL of the solvent were added sequentially. The flask was sealed with a rubber septum, and vented with a needle to air. The reaction mixture was stirred for 1 h at rt, followed by dilution with EtOAc (50 mL). The resulting solution was

transferred to a separation funnel, and the organic layer was washed with a saturated NaCl solution before being dried over anhydrous Na_2SO_4. Following filtration, the solution was concentrated under reduced pressure. ^{1}H NMR of the residue was acquired, based on which the conversion and selectivity from the limited reagent phenylacetylene was calculated. The data are listed in Table 1. Under the conditions shown in entry 4, Table 1, **3aa** was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 5/95) as a white amorphous solid in 54% yield (63 mg). R_f = 0.53 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.44 (d, *J* = 5.0 Hz, 4H), 7.26-7.18 (m, 6H), 7.13 (t, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 4H), 6.80 (d, *J* = 5.0 Hz, 4H), 4.68 (d, *J* = 15.0 Hz, 2H), 4.62 (d, *J* = 15.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 148.0, 133.1, 129.4, 129.2, 129.0, 129.0, 128.9, 128.4, 126.0, 120.0, 52.9; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{30}H_{25}N_6$ 469.2141, found 469.2124. This compound has been reported.[20]

*(d) Procedure for experiments in Table 2 to produce **3bb***. The procedure for the reactions in Table 2 was similar to that of Table 1. 1-Decyne (**2b**) was the limiting reagent at 0.5 mmol. For entry 1, 4-azidoanisole (**1b**, 0.55 mmol, 1.1 molar equivalent) was dissolved in MeOH (0.25 mL). $Cu(OAc)_2 \cdot H_2O$ (0.025 mmol), K_2CO_3 (0.5 mmol), and alkyne **2b** (0.5 mmol) in MeOH (0.25 mL) were added sequentially. For the following entries, the effect of additional changes (TBTA, O_2, $NaNO_2$, azide/alkyne stoichiometry successively) was most reliably observed when a double-quantity reaction mixture was evenly split, while the new component was added to one of the two reaction mixtures. The experimental results were shown as flow charts in Figure S3. The data reported in Table 2 were averages of the duplicated reactions, if applicable. Under the conditions shown in entry 6, Table 2, a white amorphous powder was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 20/80) in 52% yield (74 mg). R_f = 0.34

(dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 6.83 (d, *J* = 7.5 Hz, 4H), 6.75 (d, *J* = 7.5 Hz, 4H), 3.80 (s, 6H), 2.59-2.47 (m, 4H), 1.69-1.57 (m, 4H), 1.32-1.24 (m, 22H), 0.87 (t, *J* = 7.5 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 160.0, 149.2, 129.1, 124.7, 121.4, 114.5, 77.2, 55.7, 31.9, 29.6, 29.4, 29.3, 28.9, 25.4, 22.7, 12.2; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{34}H_{49}N_6O_2$ 573.3914, found 573.3917.

*(e) General procedure and characterization data for the 5,5'-bistriazoles listed in Table 3 (e.g., **3ac**, entry 1).* To a 25-mL round-bottom flask equipped with a stir bar, benzylazide (0.133 g, 1.0 mmol) was added and dissolved in MeOH (0.25 mL). $Cu(OAc)_2 \cdot H_2O$ (5.0 mg, 0.025 mmol, 5 mol % of the limiting reagent alkyne) and K_2CO_3 (0.138 g, 1.0 mmol) were added. 4-Ethynylanisole (66.7 mg, 0.5 mmol) was dissolved in MeOH (0.25 mL), and was added dropwise via a syringe over 10 min to the reaction mixture. The reaction mixture was stirred for 3 h at rt under an atmosphere of air. The reaction mixture was then diluted with EtOAc (50 mL). After solvent removal under reduced pressure, the crude product was purified on a silica column eluted by an increasing proportion of DCM in hexanes (70/30 to 100/0), followed by 1% EtOAc in DCM. R_f = 0.29 (dichloromethane). A white amorphous solid was isolated in 58% yield (78 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 7.35 (d, *J* = 9.0 Hz, 4H), 7.15-7.05 (m, 6H), 6.80 (d, *J* = 7.8 Hz, 4H), 6.72 (d, *J* = 8.4 Hz, 4H), 4.67 (d, *J* = 14.4 Hz, 2H), 4.60 (d, *J* = 15.0 Hz, 2H), 3.75 (s, 6H); ^{13}C{^{1}H} NMR: (125 MHz, $CDCl_3$): δ/ppm 160.0, 147.8, 133.2, 128.8, 128.6, 128.2, 127.2, 121.9, 119.1, 114.4, 55.3, 52.6; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{32}H_{29}N_6O_2$ 529.2352, found 529.2358. This compound has been reported.[25] For compounds in entries 3-8, EtOH was used in place of MeOH, and TBTA (0.013 g, 0.025 mmol, 5 mol % of the limiting reagent alkyne) was added before the addition of the alkyne (0.5 mmol). *Other changes in conditions for the rest of the entries in Table 3 are noted individually*. 5,5'-Bistriazoles were

purified using silica column chromatography eluted by hexanes containing an increasing amount of EtOAc or DCM. If needed, the product can be further purified via trituration using hexanes.

Table 3, entry 2, **3ad**: A reduced amount of K_2CO_3 (0.5 mmol) was used. A white amorphous powder was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 15/85) in 66% yield (82 mg). R_f = 0.53 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.32 (d, *J* = 8.2 Hz, 4H), 7.14 (t, *J* = 7.0 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 4H), 7.00 (d, *J* = 8.5 Hz, 4H), 6.79 (d, *J* = 7.5 Hz, 4H), 4.68 (d, *J* = 14.8 Hz, 2H), 4.57 (d, *J* = 14.8 Hz, 2H), 2.29 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 148.0, 138.9, 133.1, 129.7, 128.8, 128.6, 128.3, 126.5, 125.8, 119.7, 52.6, 21.3; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{32}H_{29}N_6$ 497.2454, found 497.2430. This compound has been reported.[24]

Table 3, entry 3, **3ae**: A white amorphous solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 10/90) in 63% yield (79 mg). R_f = 0.57 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.33 (dd, *J* = 9.0, 5.5 Hz, 4H), 7.15 (t, *J* = 7.0 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 4H), 6.85 (dd, *J* = 9.0, 8.5 Hz, 4H), 6.81 (d, *J* = 7.0 Hz, 4H), 4.74 (d, *J* = 15.0 Hz, 2H), 4.62 (d, *J* = 15.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 163.0 (d, $J(^{13}C\text{-}^{19}F)$ = 248.0 Hz), 147.2, 132.9, 128.9, 128.2, 127.6 (d, $J(^{13}C\text{-}^{19}F)$ = 8.2 Hz), 125.3 (d, $J(^{13}C\text{-}^{19}F)$ = 2.9 Hz), 119.4, 116.0 (d, $J(^{13}C\text{-}^{19}F)$ = 21.7 Hz), 52.9; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{30}H_{23}F_2N_6$ 505.1952, found 505.1958. This compound has been reported.[24]

Table 3, entry 4, **3af**: A white amorphous solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 20/80) in 60% yield (81 mg). R_f = 0.61 (dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 7.29-7.26 (m, 4H), 7.17-7.06 (m, 10H), 6.81 (d, *J* = 7.2 Hz, 4H), 4.76 (d, *J* = 15.0 Hz, 2H), 4.61 (d, *J* = 15.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):

δ/ppm 147.0, 135.1, 132.8, 129.3, 129.0, 128.2, 127.6, 127.0, 119.7, 53.0; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{30}H_{23}Cl_2N_6$ 537.1361, found 537.1366. This compound has been reported.[24]

Table 3, entry 5, **3ag**: A white amorphous solid was isolated via silica column chromatography eluted by dichloromethane/hexanes (60/40 to 90/10) in 72% yield (112 mg). R_f = 0.64 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.28 (d, *J* = 8.5 Hz, 4H), 7.20-7.15 (m, 6H), 7.09 (t, *J* = 7.4 Hz, 4H), 6.80 (d, *J* = 7.6 Hz, 4H), 4.75 (d, *J* = 14.9 Hz, 2H), 4.61 (d, *J* = 14.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 147.0, 132.7, 132.2, 128.9, 128.1, 127.9, 127.1, 123.2, 119.6, 52.9; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{30}H_{23}{}^{79}Br^{81}BrN_6$ 627.0330 found 627.0351.

Table 3, entry 6, **3ah**: A light peach amorphous solid was isolated via silica column chromatography eluted by EtOAc/hexanes (up to 10/90) in 68% yield (88 mg). R_f = 0.29 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.41 (d, *J* = 10.0 Hz, 4H), 7.37 (d, *J* = 10.0 Hz, 4H), 7.16-7.06 (m, 6H), 6.82 (d, *J* = 7.2 Hz, 4H), 4.90 (d, *J* = 15.0 Hz, 2H), 4.60 (d, J = 15.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 146.2, 133.2, 132.8, 132.5, 129.3, 129.1, 128.2, 126.0, 120.4, 118.3, 112.5, 53.3; HRMS (ESI+) (m/z): $[M+CH_3CN+Na]^+$ calcd. for $C_{34}H_{25}N_9Na$ 582.2131, found 582.2120. This compound has been reported.[58]

Table 3, entry 7, **3ai**: A white amorphous solid was isolated via silica column chromatography eluted by EtOAc in dichloromethane (up to 40/60) in 67% yield (78.8 mg). R_f = 0.21 (dichloromethane/EtOAc 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 8.56 (dd, *J* = 2.5, 1.0 Hz, 2H), 8.43 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.55 (ddd, *J* = 8.0, 2.0, 1.5 Hz, 2H), 7.11-7.04 (m, 8H), 6.83 (dd, *J* = 8.0, 1.5 Hz, 4H), 4.95 (d, *J* = 15.0 Hz, 2H), 4.61 (d, *J* = 15.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 149.8, 146.7, 145.5, 132.7, 132.6, 129.2, 129.0, 128.0, 125.2, 123.6, 119.8, 53.2; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{28}H_{23}N_8$ 471.2046, found 471.2042.

Table 3, entry 8, **3aj**: An increased amount of K_2CO_3 (2.0 mmol) was used. The excess of K_2CO_3 was used to deprotonated the HCl salt of the 4-ethynylpyridine substrate. The reaction was run under an atmosphere of O_2. A tan crystalline solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 70/30) in 62% yield (71 mg). R_f = 0.12 (1:1 dichloromethane/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 8.39 (d, *J* = 5.1 Hz, 4H), 7.15-7.08 (m, 10H), 6.83 (d, *J* = 6.8 Hz, 4H), 4.91 (d, *J* = 14.8 Hz, 2H), 4.61 (d, *J* = 14.8 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 150.4, 145.6, 136.1, 132.3, 129.4, 129.1, 128.1, 120.7, 119.5, 53.2; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{28}H_{23}N_8$ 471.2046, found 471.2041; m.p. = 155-156 °C.

Table 3, entry 9, **3ab**: Benzylazide was instead the limiting reagent at 0.5 mmol, while 1-decyne was used at 1.0 mmol. The quantities of $Cu(OAc)_2$ (50 μmol) and K_2CO_3 (0.5 mmol) were also adjusted from those in the General Procedure. A white amorphous solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 15/85) in 71% yield (96 mg). R_f = 0.40 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.29-7.27 (m, 6H), 6.89 (d, *J* = 10.0 Hz, 4H), 4.89 (d, *J* = 15.0 Hz, 2H), 4.56 (d, *J* = 15.0 Hz, 2H), 2.12-2.05 (m, 2H), 1.95-1.89 (m, 2H), 1.43-1.37 (m, 4H), 1.27-1.24 (m, 4H), 1.21-1.17 (m, 10H), 1.16-1.12 (m, 8H), 0.86 (t, *J* = 7.5 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 150.4, 134.2, 129.1, 128.9, 127.9, 120.3, 52.5, 31.9, 29.5, 29.3, 29.2 28.8, 25.0, 22.7, 14.2; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{34}H_{49}N_6$ 541.4019, found 541.4012.

Table 3, entry 10, **3ak**: The alkyne substrate is a diyne. Therefore, the quantities of starting materials and reagents are adjusted to the following: azide (2.0 mmol); $Cu(OAc)_2$ (0.1 mmol); K_2CO_3 (2.0 mmol); MeOH (1.0 mL); and alkyne (0.5 mmol). A white crystalline solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 1/1) in 17% yield

(32 mg). R_f = 0.47 (9:1 dichloromethane/ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 7.27-7.22 (m, 6H), 6.92-6.88 (m, 4H), 5.50 (d, *J* = 15.0 Hz, 2H), 5.15 (d, *J* = 15.0 Hz, 2H), 3.07-3.03 (dd, *J* = 14.4, 7.2 Hz, 2H), 1.89-1.81 (m, 4H), 1.32-1.39 (m, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ/ppm 151.0, 134.2, 129.1, 128.9, 127.2, 121.6, 53.3, 27.8, 24.8; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{22}H_{23}N_6$ 371.1984, found 371.1972; m.p. = 178-179 °C.

Table 3, entry 11, **3an**:[20] To a 25-mL round-bottom flask equipped with a stir bar, benzylazide (133 mg, 1.0 mmol) was added to MeOH (0.25 mL). $Cu(OAc)_2 \cdot H_2O$ (40 mg, 0.2 mmol), TBTA (26 mg, 0.05 mmol), and K_2CO_3 (345 mg, 2.5 mmol) were added sequentially. The reaction mixture was placed in an ice bath. Ethynyltrimethylsilane (98 mg, 1.0 mmol) was dissolved in MeOH (0.25 mL), and was added dropwise into the stirring reaction mixture via a syringe. The reaction mixture was stirred for 6 h as the temperature rose to rt. The reaction mixture was then diluted with EtOAc (50 mL), washed by saturated brine three times. The organic layer was dried over Na_2SO_4 before solvent was removed in vacuo. The crude product was purified on a silica column eluted by a mixture solvent of hexanes/EtOAc = 2/1. The resulting solid was washed with a small amount of diethyl ether. The product was a white amorphous solid in 17% yield (27 mg). R_f = 0.15 (hexanes/EtOAc = 2/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.49 (s, 2H), 7.32-7.28 (m, 6H), 6.94-6.93 (m, 4H), 5.09 (s, 4H).

*(f) General procedure for the 5,5'-bistriazoles listed in Table 4 (e.g., **3ca**, entry 1).* To a 25-mL round-bottom flask equipped with a stir bar, n-octylazide (0.155 g, 1.0 mmol) was added and dissolved in MeOH (0.5 mL). $Cu(OAc)_2 \cdot H_2O$ (5.0 mg, 0.025 mmol), TBTA (53 mg, 0.1 mmol, 20 mol % of the limiting reagent alkyne) and K_2CO_3 (69 mg, 0.5 mmol) were added. phenylacetylene (51 mg, 0.5 mmol) was dissolved in MeOH (0.5 mL), and was added dropwise via a syringe over 10 min to the reaction mixture. The reaction mixture was stirred for 3 h at rt

under an atmosphere of O_2. The reaction mixture was then diluted with EtOAc (50 mL). After solvent removal under reduced pressure, the crude product was purified on a silica gel column eluted by increasing proportion of EtOAc in hexanes (up to 5/95). R_f = 0.81 (dichloromethane). A white amorphous solid was isolated in 81% yield (103.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.59-7.55 (m, 4H), 7.36-7.31 (m, 6H), 3.88 (t, *J* = 7.5 Hz, 4H), 1.61-1.46 (m, 4H), 1.26-1.05 (m, 20H), 0.84 (t, *J* = 7.5 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 147.5, 129.8, 129.4, 129.2, 126.3, 49.2, 31.9, 29.7, 29.1, 29.0, 26.7, 22.8, 14.3; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{32}H_{45}N_6$ 513.3706, found 513.3699. *Changes in conditions of other entries in Table 4 are noted individually*. 5,5'-Bistriazoles were purified using silica column chromatography eluted by hexanes containing an increasing amount of EtOAc or DCM. If needed, the product can be further purified via trituration using hexanes.

Table 4, entry 2, **3da**: Reduced amounts of azide (0.5 mmol) and TBTA (25 μmol) were used. EtOH (0.5 mL) was the solvent. An orange crystalline solid was isolated via silica column chromatography eluted by EtOAc in hexanes (15/85) in 81% yield (107 mg). R_f = 0.36 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.60-758 (m, 4H), 7.33-7.32 (m, 6H), 7.16 (dd, *J* = 8.5, 7.5 Hz, 4H), 6.91 (t, *J* = 7.5 Hz, 2H), 6.51 (d, *J* = 8.0 Hz, 4H), 4.41-4.36 (m, 2H), 4.28-4.18 (m, 4H), 4.00-3.96 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 157.5, 147.3, 129.5, 129.4, 129.3, 129.2, 126.2, 121.6, 121.1, 114.5, 65.5, 48.4; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{32}H_{28}N_6NaO_2$ 551.2171, found 551.2175; m.p. = 165-166 °C.

Table 4, entry 3, **3ea**: Increased amounts of azide (2.5 mmol, 5 molar equivalents) and K_2CO_3 (1.0 mmol) were used. TBTA was not included; instead, $NaNO_2$ (0.5 mmol) was added as an additive. The solvent was MeOH (0.5 mL). A white amorphous solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 50/50) in 55% yield (55 mg). R_f =

0.07 (1:1 dichloromethane/ethyl acetate). ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm 7.47-7.36 (m,10 H), 4.58 (t, *J* = 5.0 Hz, 2H), 4.16 (ddd, *J* = 14, 8.5, 6.5 Hz, 2H), 4.07 (ddd, *J* = 14.5, 9.0, 6.0 Hz, 2H), 3.31(q, *J* = 5.0 Hz, 4H), 1.86-1.69 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ/ppm 146.9, 130.4, 130.2, 129.8, 126.3, 121.2, 58.2, 46.7, 33.0; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{22}H_{25}N_6O_2$ 405.2039, found 405.2034.

Table 4, entry 4, **3cb**: A reduced amount of K_2CO_3 (0.25 mmol) was used. A white amorphous solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 10/90) in 61% yield (89 mg). R_f = 0.80 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 4.04-3.98 (m, 2H), 3.92-3.86 (m, 2H), 2.53-2.47 (m, 2H), 2.41-2.35 (m, 2H), 1.76-1.71 (m, 4H), 1.57-1.62 (m, 4H), 1.20-1.26 (m, 40 H), 0.84 (t, *J* = 7.5 Hz, 12H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 149.2, 120.9, 49.0, 32.0, 31.9, 30.1, 29.7, 29.5, 29.4, 29.3, 29.2, 29.2, 26.8, 25.6, 22.8, 22.8, 14.3, 14.3; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{36}H_{69}N_6$ 585.5584, found 585.5579.

Table 4, entry 5, **3fa**: A reduced amount of (bis)azide (0.5 mmol) and an increased amount of K_2CO_3 (1.5 mmol) were used. The solvent was EtOH (1 mL). A white crystalline solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 25/75) in 32% yield (30 mg). R_f = 0.67 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.55-7.51 (m, 4H), 7.34-7.29 (m, 6H), 4.46 (ddd, *J* = 14.0, 5.0, 1.5 Hz 2H), 3.87 (td, *J* = 13.8 Hz, 4.0 Hz, 2H), 2.28(t, *J* = 15.0 Hz, 2H), 1.63-1.54 (m, 2H), 1.4-1.32 (m, 2H), 0.6-0.51 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 146.5, 129.5, 129.4, 129.1, 126.0, 122.1, 45.3, 28.1, 19.2; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{22}H_{23}N_6$ 371.1984, found 371.1994. m.p. = 213-215 °C.

Table 4, entry 6, **(3fa)$_2$**: A reduced amount of (bis)azide (0.5 mmol) and an increased amount of K_2CO_3 (1.5 mmol) were used. The solvent was EtOH (1 mL). A white crystalline solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 25/75) in 12%

yield (11 mg). R_f = 0.74 (9:1 dichloromethane/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.50-7.46 (m, 8H), 7.37-7.33 (m, 12H), 4.07-4.01 (m, 4H), 3.52-3.46 (m, 4H), 1.63-1.52 (m, 8H), 1.11-0.97 (m, 8H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 147.1, 129.7, 129.6, 129.4, 126.2, 120.5, 49.0, 29.6, 26.9; HRMS (ESI+) (m/z): $[M+Na]^+$ calcd. for $C_{44}H_{44}N_{12}Na$ 763.3710, found 763.3695; m.p. = 328-330 °C.

Table 4, entry 7, **3ga**: Reduced amounts of TBTA (0.025 mmol) and MeOH (0.5 mL) were used. An increased amount of K_2CO_3 (1.0 mmol) was used. A white amorphous powder was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 1/12) in 53% yield (59 mg). R_f = 0.82 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.56-7.54 (m, 4H), 7.34-7.31 (m, 6H), 3.58 (tt, *J* = 12.0, 4.0 Hz, 2H), 2.00 (qd, *J* = 11.8, 3.8 Hz, 2H), 1.88 (qd, *J* = 11.8, 3.8 Hz, 2H), 1.82-1.77 (m, 2H), 1.71-1.62 (m, 2H), 1.61-1.57 (m, 2H), 1.38-1.32 (m, 2H), 1.24-1.07 (m, 4H), 0.89 (qt, *J* = 13.0, 3.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 146.9, 129.8, 129.2, 129.0, 126.5, 120.0, 59.1, 33.8, 32.6, 25.4, 25.3, 24.8; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{28}H_{33}N_6$ 453.2767, found 453.2755.

*(g) General procedure for the 5,5'-bistriazoles listed in Table 5 (e.g., **3ha**, entry 1).* To a 25-mL round-bottom flask equipped with a stir bar, 4-azidotoluene (0.133 g, 1.0 mmol) was added and dissolved in MeOH (0.25 mL). $Cu(OAc)_2 \cdot H_2O$ (5.0 mg, 0.025 mmol), TBTA (53 mg, 0.1 mmol, 20 mol % of the limiting reagent alkyne), and K_2CO_3 (138 mg, 1.0 mmol) were added. phenylacetylene (51 mg, 0.5 mmol) was dissolved in MeOH (0.25 mL), and was added dropwise via a syringe over 30 min to the reaction mixture. The reaction mixture was stirred for 3 h at rt under an atmosphere of O_2. The reaction mixture was then diluted with EtOAc (50 mL). After solvent removal under reduced pressure, the crude product was purified on a silica column eluted by an increasing proportion of EtOAc in hexanes (5:95 to 10:90). R_f = 0.61 (dichloromethane).

Compound **3ha** was isolated as a yellow crystalline solid in 59% yield (68.4 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 7.66-7.63 (m, 4H), 7.33-7.30 (m, 6H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 2H), 2.32 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm: 148.1, 140.0, 133.0, 129.9, 129.4, 129.1, 129.0, 126.3, 123.8, 121.0, 21.1; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{30}H_{25}N_6$ 469.2141, found 469.2142; m.p. = 203-204 °C. *Changes in conditions of other entries in Table 5 are noted individually*. 5,5'-Bistriazoles were purified using silica column chromatography eluted by hexanes containing an increasing amount of EtOAc or DCM. If needed, the product can be further purified via trituration using hexanes.

Table 5, entry 2, **3ba**: A yellow crystalline solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 20/80) in 59% (74.8 mg). R_f = 0.38 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.67-7.65 (m, 4H), 7.35-7.32 (m, 6H), 6.79 (d, *J* = 8.6 Hz, 4H), 6.72 (d, *J* = 7.3 Hz, 4H), 3.78 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 160.3, 148.0, 129.4, 129.1, 129.0, 128.3, 126.3, 125.4, 121.1, 114.4, 55.6; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{30}H_{25}N_6O_2$ 501.2039, found 501.2024; m.p. = 185-186 °C.

Table 5, entry 3, **3bl**: A brown crystalline solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 30/70) in 55% (81 mg). R_f = 0.11 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.69 (d, *J* = 8.6 Hz, 4H), 6.84 (d, *J* = 8.8 Hz, 4H), 6.75 (d, *J* = 8.8 Hz, 4H), 6.71 (d, *J* = 8.7 Hz, 4H), 3.81 (s, 6H), 3.01 (s, 12H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 160.1, 150.6, 148.7, 128.7, 127.2, 125.5, 119.6, 117.3, 114.3, 112.4, 55.6, 40.3; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{34}H_{35}N_8O_2$ 587.2883, found 587.2868; m.p. = 243-245 °C.

Table 5, entry 4, **3bo**: TBTA was not used. A white amorphous powder was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 20/80) in 62% yield (87 mg). R_f =

0.33 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.23 (t, *J* = 8.0 Hz, 4H), 6.94 (t, *J* = 7.2 Hz, 2H), 6.78 (d, *J* = 8.5Hz, 4H), 6.64 (d, *J* = 9.5 Hz, 4H), 6.62 (d, *J* = 9.5 Hz, 4H), 5.27 (s, 4H, a very tight AB system), 3.77 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 160.3, 157.7, 145.2, 129.7, 128.5, 125,2, 123.3, 121.7, 114.7, 114.4, 61.5, 55.7; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{32}H_{29}N_6O_4$ 561.2250, found 561.2248.

Table 5, entry 5, **3ia**: an increased amount (2.0 mmol) of K_2CO_3 was used. The reaction was kept at 0 °C. A white amorphous powder isolated via silica column chromatography eluted by EtOAc in hexanes (up to 5/95) in 56% yield (62 mg). R_f = 0.75 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.66-7.64 (m, 4H), 7.35-3.31(m, 8H), 7.22 (t, *J* = 10.0 Hz, 4H), 6.86 (d, *J* = 10.0 Hz, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 148.4, 135.6, 129.9, 129.6, 129.4, 129.3, 126.6, 124.1, 121.1; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{28}H_{21}N_6$ 441.1828, found 441.1827.

Table 5, entry 6, **3ja**: A white crystalline solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 1/40) in 63% yield (83.2 mg). R_f = 0.72 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.62-7.60 (m, 4H), 7.31-7.29 (m, 6H), 7.04 (d, *J* = 8.5 Hz, 4H), 6.75 (d, *J* = 8.5 Hz, 4H), 2.87 (sept, *J* = 6.5 Hz, 2H), 1.21(d, *J* = 6.5 Hz, 12H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ/ppm 150.7, 148.1, 133.2, 129.5, 129.1, 129.0, 127.4, 126.5, 123.8, 121.1, 33.9, 24.0, 23.9; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{34}H_{33}N_6$ 525.2767, found 525.2753; m.p. = 204-205 °C.

Table 5, entry 7, **3ka**: The reaction was run at 0 °C. An orange amorphous solid was isolated via silica column chromatography eluted by EtOAc/hexanes (up to 1/8) in 62% (77 mg). R_f = 0.47 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.70-7.67 (m, 4H), 7.35-7.32 (m, 6H), 7.13 (t, *J* = 8.1 Hz, 2H), 6.87 (dd, *J* = 8.5, 5.0 Hz, 2H), 6.46 (d, *J* = 7.5 Hz, 2H), 6.38 (t, *J* =

2.2 Hz, 2H), 3.54 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 160.2, 148.3, 136.3, 130.1, 129.3, 129.2, 126.4, 121.1, 116.5, 115.9, 109.1, 55.4; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{30}H_{25}N_6O_2$ 501.2039, found 501.2048.

Table 5, entry 8, **3la**: An off-white amorphous powder was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 10/90) in 51% yield (64 mg). R_f = 0.32 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.77-7.75 (m, 4H), 7.32 (ddd, *J* = 9.5, 7.5, 1.5 Hz, 2H), 7.25-7.23(m, 6H), 6.77-6.74 (m, 4H), 6.59 (dd, *J* = 8.0, 2.0 Hz, 2H), 3.18 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 153.0, 146.7, 131.4, 129.9, 128.6, 128.5, 128.2, 126.5, 124.3, 123.2, 120.5, 111.5, 55.0; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{30}H_{24}N_6NaO_2$ 523.1858, found 523.1867.

Table 5, entry 9, **3kb**: a reduced amount of K_2CO_3 (0.5 mmol) was used. $NaNO_2$ (0.5 mmol) was included. A light yellow amorphous powder was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 10/90) in 54% yield (77.6 mg). R_f = 0.43 (dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 7.12 (t, *J* = 8.1 Hz, 2H), 6.85 (ddd, *J* = 7.0, 2.0, 0.5 Hz, 2H), 6.42 (t, *J* = 2.1Hz, 2H), 6.38 (ddd, *J* = 6.5, 1.5, 0.5 Hz, 2H), 3.66 (s, 6H), 2.69-2.63 (m, 2H), 2.60-2.53 (m, 2H), 1.75-1.67 (m, 2H), 1.66-1.58 (m, 2H), 1.37-1.31 (m, 4H), 1.30-1.23 (m, 16H), 0.87 (t, *J* = 7.1 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ/ppm 160.3, 149.3, 137.0, 130.1, 121.4, 115.4, 115.1, 108.9, 55.4, 31.9, 29.7, 29.4, 29.3, 29.0, 25.4, 22.7, 14.1; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{34}H_{49}N_6O_2$ 573.3917, found 573.3920.

Table 5, entry 10, **3ib**: An increased amount of azide (2.5 mmol, 5 molar equivalents) was used. The amount of K_2CO_3 was dropped to 0.5 mmol, and $NaNO_2$ (0.5 mmol) was included. A white amorphous solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 4/96) in 56% yield (71 mg). R_f = 0.78 (dichloromethane). ^{1}H NMR (500 MHz,

$CDCl_3$): δ/ppm 7.32 (t, *J* = 7.5Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 4H), 6.87 (d, *J* = 10.0 Hz, 4H), 2.63-2.50 (m, 4H), 1.74-1.56 (m, 4H), 1.33-1.24 (m, 20H), 0.87 (t, *J* = 7.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 149.6, 136.1, 129.6, 129.3, 123.4, 121.4, 32.1, 29.8, 29.5, 29.5, 29.1, 25.6, 22.9, 14.4; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{32}H_{45}N_6$ 513.3706, found 513.3710.

Table 5, entry 11, **3km**: A reduced amount of TBTA (0.05 mmol) and an increased amount of K_2CO_3 (1.5 mmol) were used. The solvent was EtOH (0.5 mL). The reaction was run at 0 °C. A yellow amorphous powder was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 1/5) in 52% yield (80 mg). R_f = 0.13 (dichloromethane). ^1H NMR (500 MHz, $CDCl_3$): δ/ppm 7.99 (d, *J* = 8.0 Hz, 4H), 7.73 (d, *J* = 7.5 Hz, 4H), 7.14 (t, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.42 (d, *J* = 7.5 Hz, 2H), 6.37 (s, 2H), 3.90 (s, 6H), 3.58 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 166.5, 160.3, 147.1, 136.1, 133.4, 130.7, 130.6, 130.5, 130.3, 126.2, 121.6, 116.5, 115.7, 109.4, 55.5, 52.5, 52.4; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{34}H_{29}N_6O_6$ 617.2149, found 617.2149.

Table 5, entry 12, **3jf**: The solvent was EtOH (0.5 mL). A white crystalline solid was isolated via silica column chromatography eluted by dichloromethane in hexanes (30/70 to 100/0) in 52% yield (77.2 mg). R_f = 0.80 (dichloromethane). ^1H NMR (500 MHz, $CDCl_3$): δ/ppm 7.53 (d, *J* = 8.8 Hz, 4H), 7.28 (d, *J* = 8.8 Hz, 4H), 7.05 (d, *J* = 8.2 Hz, 4H), 6.73 (d, *J* = 8.5 Hz, 4H), 2.88 (sept, *J* = 7.0 Hz, 2H), 1.22 (d, *J* = 8.0 Hz, 12H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 151.0, 146.9, 135.2, 133,0, 129.4, 127.8, 127.6, 127.5, 123.7, 120.8, 33.9, 23.9, 23.8; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{34}H_{31}Cl_2N_6$ 593.1987, found 593.2015; m.p. = 233-234 °C.

Table 5, entry 13, **3bf**: The solvent was EtOH (0.5 mL). A yellow amorphous solid was isolated via silica column chromatography eluted by EtOAc in hexanes (up to 15/85) in 70% yield (104 mg). R_f = 0.54 (dichloromethane). ^1H NMR (500 MHz, $CDCl_3$): δ/ppm 7.58 (d, *J* =

8.6 Hz, 4H), 7.31 (d, J = 8.6 Hz, 4H), 6.75 (d, J = 9.1 Hz, 4H) 6.73 (d, J = 9.1 Hz, 4H), 3.79 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 160.5, 146.9, 135.3, 129.5, 128.1, 127.7, 127.4, 125.4, 120.9, 114.6, 55.7; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{30}H_{23}{}^{35}Cl_2N_6O_2$ 569.1260, found 569.1254.

Table 5, entry 14, **3em**: The solvent was EtOH (0.5 mL). A light yellow amorphous powder was isolated via silica column chromatography eluted by EtOAc in dichloromethane (up to 3/97) in 61% yield (90 mg). R_f = 0.74 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.99 (d, J = 7.9 Hz, 4H), 7.70 (d, J = 7.8 Hz, 4H), 6.97 (dd, J = 9.0, 8.0 Hz, 4H), 6.86 (dd, J = 9.5, 4.5 Hz, 4H), 3.91 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ/ppm 166.4, 163.1, (d, $J(^{13}C\text{-}^{19}F)$ = 208.2 Hz), 147.3, 133.0, 131.3 (d, $J(^{13}C\text{-}^{19}F)$ = 2.5 Hz), 131.0, 130.6, 126.2, 125.8 (d, $J(^{13}C\text{-}^{19}F)$ = 7.5 Hz), 121.3, 116.9 (d, $J(^{13}C\text{-}^{19}F)$ = 18.7 Hz) ,52.4; HRMS (ESI+) (m/z): $[M+H]^+$ calcd. for $C_{32}H_{23}F_2N_6O_4$ 593.1749, found 593.1735.

AUTHOR INFORMATION

Corresponding Author

lzhu@chem.fsu.edu

ACKNOWLEDGMENT

This work was supported by the National Science Foundation (CHE1213574).

Supporting Information. Synthetic procedures and characterizations of new compounds; .cif files of x-ray single crystal structures; and method of ^{1}H NMR reaction monitoring experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES

(1) Tornøe, C. W.; Meldal, M. In *Peptides 2001, Proc. Am. Pept. Symp.*; American Peptide Society and Kluwer Academic Publishers: San Diego, 2001, p 263.

(2) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

(3) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(4) Gerard, B.; Ryan, J.; Beeler, A. B.; Porco Jr., J. A. *Tetrahedron* **2006**, *62*, 6405.

(5) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302.

(6) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052.

(7) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

(8) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51.

(9) Finn, M. G.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1231.

(10) *Click Triazoles*; Košmrlj, J., Ed.; Springer, 2012; Vol. 28.

(11) Diéz-González, S. *Catal. Sci. Technol.* **2011**, *1*, 166.

(12) Dervaux, B.; Prez, F. E. D. *Chem. Sci.* **2012**, *3*, 959.

(13) Alonso, F.; Moglie, Y.; Radivoy, G. *Acc. Chem. Res.* **2015**, *48*, 2516.

(14) Hassan, S.; Müller, T. J. J. *Adv. Synth. Catal.* **2015**, *357*, 617.

(15) Haldón, E.; Nicasio, M. C.; Pérez, P. J. *Org. Biomol. Chem.* **2015**, *13*, 9528.

(16) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.

(17) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(18) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062.

(19) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234.

(20) Angell, Y.; Burgess, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 3649.

(21) Oladeinde, O. A.; Hong, S. Y.; Holland, R. J.; Maciag, A. E.; Keefer, L. K.; Saavedra, J. E.; Nandurdikar, R. S. *Org. Lett.* **2010**, *12*, 4256.

(22) González, J.; Pérez, V. M.; Jiménez, D. O.; Lopez-Valdez, G.; Corona, D.; Cuevas-Yañez, E. *Tetrahedron Lett.* **2011**, *52*, 3514.

(23) Kwon, M.; Jang, Y.; Yoon, S.; Yang, D.; Jeon, H. B. *Tetrahedron Lett.* **2012**, *53*, 1606.

(24) Zheng, Z.-J.; Ye, F.; Zheng, L.-S.; Yang, K.-F.; Lai, G.-Q.; Xu, L.-W. *Chem. Eur. J.* **2012**, *18*, 14094.

(25) Li, L.; Fan, X.; Zhang, Y.; Zhu, A.; Zhang, G. *Tetrahedron* **2013**, *69*, 9939.

(26) Goyard, D.; Chajistamatiou, A. S.; Sotiropoulou, A. I.; Chrysina, E. D.; Praly, J.-P.; Vidal, S. *Chem. Eur. J.* **2014**, *20*, 5423.

(27) Zheng, Z.-J.; Wang, D.; Xu, Z.; Xu, L.-W. *Beilstein J. Org. Chem.* **2015**, *11*, 2557.

(28) Wang, Q.; Chan, T. R.; Higraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192.

(29) To the best of our knowledge, a bis(azido)-substituted ferrocene was reported to afford a bistriazole as an isolated example. See Hoyo, A. M. d.; Latorre, A.; Díaz, R.; Urbano, A.; Carreño, M. C. *Adv. Synth. Catal.* **2015**, *357*, 1154.

(30) Kuang, G.-C.; Michaels, H. A.; Simmons, J. T.; Clark, R. J.; Zhu, L. *J. Org. Chem.* **2010**, *75*, 6540.

(31) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853.

(32) Michaels, H. A.; Zhu, L. *Chem. Asian J.* **2011**, *6*, 2825.

(33) Barsoum, D. N.; Brassard, C. J.; Deeb, J. H. A.; Okashah, N.; Sreenath, K.; Simmons, J. T.; Zhu, L. *Synthesis* **2013**, *45*, 2372.

(34) Stenger, V. A. *J. Chem. Eng. Data* **1996**, *41*, 1111.

(35) Platonov, A. Y.; Evdokimov, A. N.; Kurzin, A. V.; Maiyorova, H. D. *J. Chem. Eng. Data* **2002**, *47*, 1175.

(36) The more soluble Cs_2CO_3 has to be controlled at a proper quantity to deliver a good selectivity for 5,5'-bistriazole, usually with a longer reaction time than what K_2CO_3 could manage (see Table S1).

(37) Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842.

(38) The experiments were done to ensure that the effects of individual factors were reliably recorded. See Figure S3 in the SI.

(39) The reactions under an atmosphere of argon give primarily 5-protiotriazoles, Table S3.

(40) Laborde, C.; Wei, M.-M.; Lee, A. v. d.; Deydier, E.; Daran, J.-C.; Volle, J.-N.; Poli, R.; Pirat, J.-L.; Manoury, E.; Virieux, D. *Dalton Trans.* **2015**, *44*, 12539.

(41) Montalti, M.; Credi, A.; Prodi, L.; Gandolfi, M. T. In *Handbooks of Photochemistry*; 3rd ed.; CRC Taylor and Francis: 2006, p 624.

(42) Zhu, L.; Brassard, C. J.; Zhang, X.; Guha, P. M.; Clark, R. J. *Chem. Rec.* **2016**, *16*, 1501.

(43) Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. *Acc. Chem. Res.* **2007**, *40*, 1385.

(44) Nolte, C.; Mayer, P.; Straub, B. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 2101.

(45) Kuang, G.-C.; Guha, P. M.; Brotherton, W. S.; Simmons, J. T.; Stankee, L. A.; Nguyen, B. T.; Clark, R. J.; Zhu, L. *J. Am. Chem. Soc.* **2011**, *133*, 13984.

(46) Brotherton, W. S.; Michaels, H. A.; Simmons, J. T.; Clark, R. J.; Dalal, N. S.; Zhu, L. *Org. Lett.* **2009**, *11*, 4954.

(47) The cycloaddition step is usually depicted as the reaction between copper(I) acetylide and an azide (e.g., see ref. #5). In our case, an azide/copper complex reacts with an alkyne in the presence of a base to afford triazolyl ring (see ref. #42). The azide/copper

interaction occurs before copper(I) acetylide formation so that the oxidative coupling side reaction involving acetylide is minimized.

(48) Intermediate **IV'** bears resemblance to the aryl(alkynyl)cuprate species studied by Knochel and coworkers. See: Dubbaka, S. R.; Kienle, M.; Mayr, H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 9093. Potassium ion should be the counter cation.

(49) The depicted mononuclear bis(triazolyl)cuprate **V** could be considered as a diarylcuprate ion that is balanced by potassium ion.

(50) The intermediate in the last step could involve oxidation of copper(I) to copper(III) followed by reductive elimination, or the displacement of copper(I) by two copper(II) followed by inner-sphere electron transfer similar to that postulated for the Glaser coupling to afford 5,5'-bistriazole.

(51) Goj, L. A.; Blue, E. D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Petersen, J. L. *Organometallics* **2006**, *25*, 4097.

(52) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.

(53) Qi, X.; Bai, R.; Zhu, L.; Jin, R.; Lei, A.; Lan, Y. *J. Org. Chem.* **2016**, *81*, 1654.

(54) Yang, D.; Fu, N.; Liu, Z.; Li, Y.; Chen, B. *Synlett* **2007**, 278.

(55) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Synlett* **2012**, *23*, 2179.

(56) Yamamoto, K.; Bruun, T.; Kim, J. Y.; Zhang, L.; Lautens, M. *Org. Lett.* **2016**, *18*, 2644.

(57) Wang, W.; Wei, F.; Ma, Y.; Tung, C.-H.; Xu, Z. *Org. Lett.* **2016**, *18*, 4158.

(58) Cerda-Pedro, J. E. d. l.; Rojas-Lima, S.; Santillan, R.; López-Ruiz, H. *J. Mex. Chem. Soc.* **2015**, *59*, 130.

SYNOPSIS (Word Style “SN_Synopsis_TOC”).