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# Synthesis of 5-iodo-1,2,3-triazole from organic azide and terminal alkyne – ligand acceleration effect, substrate scope, and mechanistic insight

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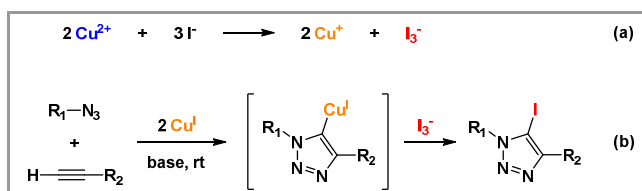
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**Abstract:** A method to prepare 5-iodo-1,2,3-triazole directly from organic azide and terminal alkyne mediated by *in situ* generated copper(I) and iodinating agents is reported. This work is an extension from our previous report (Brotherton, W. S. et al. *J. Org. Chem.* **2012**, *77*, 6443-6455). The major methodological advance of the current procedure is to achieve high conversion and iodo/proto selectivity of a broad substrate scope without using an excess amount of alkyne, which was required in the previous method. The use of an accelerating ligand is key to the success of reactions involving unreactive azides or alkynes. New mechanistic insights are provided, including the confirmation of 1-iodoalkyne formation as a key intermediate step under the established conditions.

**Key words:** azide, copper, ligand acceleration, 1-iodoalkyne, 5-iodo-1,2,3-triazole.

## Introduction

5-Iodo-1,2,3-triazole is a key intermediate of the three-component reaction sequence of azide, alkyne, and a matching partner of a palladium-catalyzed cross-coupling process.<sup>1,2</sup> The state-of-art method for preparing 5-iodo-1,2,3-triazoles with a wide substrate scope and mild reaction conditions was reported by Hein, Fokin, and coworkers, which entails the activation of a terminal alkyne to 1-iodoalkyne before the copper(I)-catalyzed cycloaddition with an azide.<sup>2</sup> The separate step of converting a terminal alkyne to 1-iodoalkyne may be eliminated. To this end several other methods have been developed before and after Hein and Fokin's work, by which 5-iodo-1,2,3-triazole can be reached directly from conjugating terminal alkyne and azide.<sup>3-5</sup> The utilities of these direct conjugation methods are however limited by their inclusion of either corrosive iodinating or oxidizing agents, such as iodine chloride (ICl)<sup>3</sup> and *N*-bromosuccinimide (NBS)<sup>4</sup>. Furthermore, the substrate scopes and the efficiencies of these methods in terms of reaction time and conversion are yet to rival those of Hein and Fokin's method.<sup>2</sup>



**Scheme 1** (a) A balanced ionic equation of *in situ* production of copper(I) and triiodide from copper(II) and iodide, which (b) mediate the coupling reaction between azide and alkyne to afford 5-iodo-1,2,3-triazole. The ligands and counter ions associated with copper are omitted. The +2 and +1 oxidation states of copper are colored blue and orange, respectively.

Our group has developed a method to prepare 5-iodo-1,2,3-triazole starting from terminal alkyne and azide mediated by *in situ* generated copper(I) species and triiodide ions.<sup>6</sup> The key mechanistic postulate is depicted in Scheme 1. Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O reacts with NaI to rapidly afford copper(I) species and triiodide ion, which catalyzes the cycloaddition of azide and alkyne, and iodates the cuprous triazolide intermediate, respectively, to afford 5-iodo-1,2,3-triazole.<sup>6</sup> A similar procedure was reported concurrently by Årstad and coworkers, in which <sup>125</sup>I from Na<sup>125</sup>I was applied as a radioactive tracer via the 5-iodo-1,2,3-triazole formation that has found use in nuclear imaging applications.<sup>7</sup>

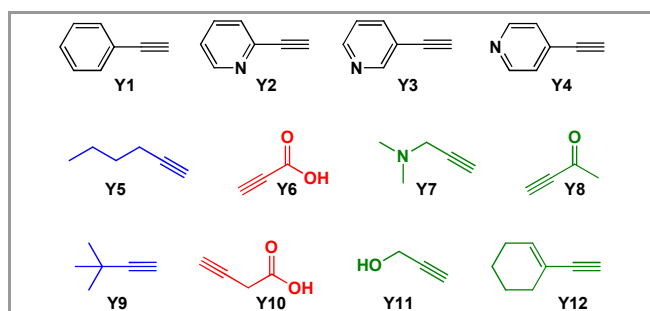
Azides that are capable of chelating a copper ion at the alkylated nitrogen position (chelating azides)<sup>8,9</sup> work well under our initially reported procedure. Other azides lacking the chelating ability appear to have inadequate reactivity, and often need an excess amount of alkyne and/or the assisting ligand *N,N*-tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA),<sup>10</sup> (in two cases) to reach full completion.<sup>6</sup> Herein, we report the optimized method of 5-iodo-1,2,3-triazole synthesis directly from azide and alkyne, the efficiency of which is improved over that of our previous procedure in terms of time, conversion, selectivity, and substrate scope.

The highlights of the current work include the following: (1) ligand assistance is demonstrated in an expanded collection of substrates, which greatly increases the substrate scope of this reaction. (2) The need for an excess amount of alkyne to convert unreactive azide is eliminated, thus enhancing the practicality of this method. (3) The reaction time is

shortened from 12 h to within 6 h. In addition to the improvements in the synthetic method, we have investigated the effects of various alkali iodides on both the conversion and selectivity, and the likely involvement of *in situ* formed 1-iodoalkyne as a key intermediate. The conclusions of these studies collectively enrich the knowledge base on the mechanistic front of this reaction.

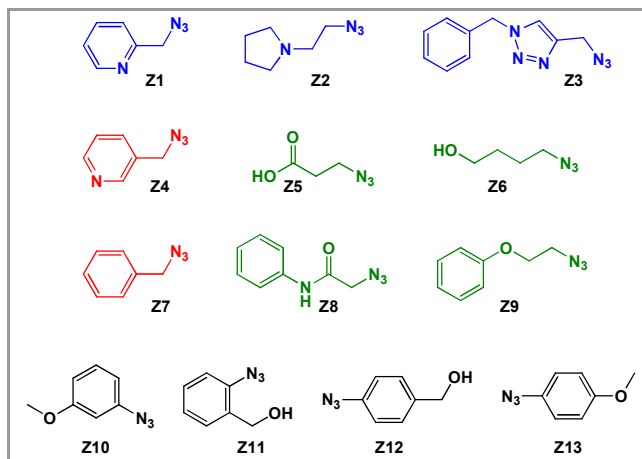
## Results and Discussion

**(a) Choices of azides and alkynes.** The selections of azides and alkynes are shown in Figures 1 and 2, respectively. We aim to cover a wide range of functional groups, and to have adequate data to be able to comment on reactivities of different classes of compounds under the developed conditions with confidence. Among the alkynes, both aliphatic and aromatic substrates are included. The effect of exchangeable protons on iodo/proto selectivity is studied using **Y6**, **Y10** (two carboxylic acids),<sup>11</sup> and **Y11** (an alcohol). Methylketone **Y8** is included to determine whether the iodoform reaction may compete with the 5-iodo-1,2,3-triazole formation.

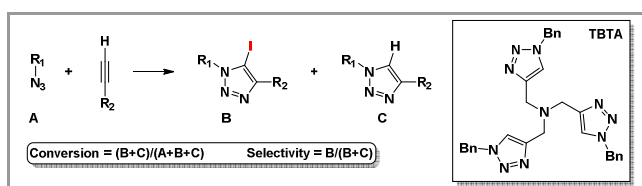


**Figure 1** Aromatic (black), aliphatic (blue), carboxyl-containing (red), and other functional group-containing (green) alkynes.

Among the selected azides, chelating azides **Z1-Z3** are expected to be highly reactive, based on our previous observations on 2-picolylazide **Z1**.<sup>6</sup> **Z4** and **Z7** represent benzylic azides, which are also recognized as reasonably facile substrates. This may be due to the interaction between the aryl ring and the copper(I) bound to the alkylated nitrogen of the azido group.<sup>12</sup> Aromatic azides **Z10-Z13** are included, as well as aliphatic azides (**Z5-Z6**, **Z8-Z9**) that contain different functional groups including carboxyl (**Z5**) and hydroxyl (**Z6**).



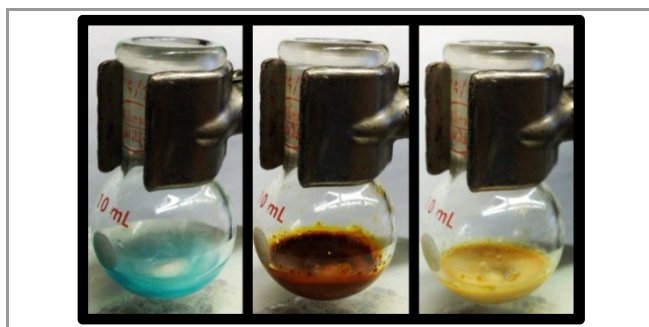
**Figure 2** Chelating (blue), benzylic (red), aromatic (black), and functional group-containing aliphatic (green) azides.



**Scheme 2** Conditions: azide (A): 0.2 mmol; alkyne: 0.22 mmol; THF or CH<sub>3</sub>CN: 1 mL; Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O: 0.4 mmol; TEA or DBU: 0.2 mmol; NaI, KI, or LiI: 0.8 mmol; rt, up to 6 h. TBTA: 10 mol % (if needed).

**(b) Reaction conditions and isolation procedure.** The reaction conditions are listed in the caption of Scheme 2.<sup>13</sup> In a typical experiment, the azide is first dissolved in THF (or CH<sub>3</sub>CN). The additions of Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and NaI (or KI, LiI) in solid forms follow, after which the reaction mixture turns into muddy brown, indicative of I<sub>2</sub>/I<sub>3</sub><sup>-</sup> formation (Figure 3, middle). If needed, the accelerating ligand TBTA is added at this point. TEA (or DBU) and alkyne are added in this order, and the reaction mixture is left stirring at rt. Azide could also be added after alkyne without a noticeable difference in reaction efficiency. The disappearance of the azide, which is the limiting reagent, is monitored by thin-layer chromatography (TLC). The fading of the dark brown color of the initial reaction mixture usually accompanies the reaction progress (Figure 3).

In most cases the reaction proceeds to full conversion within 6 h. Stoichiometric amount of alkyne<sup>14</sup> is effective in the current procedure. This is a noteworthy improvement over our previously reported procedure in which inefficient reactions were compensated by using an excess amount of alkyne (2.5 equiv.).<sup>6</sup> The ability to run the reactions at an equal molar ratio of azide and alkyne within a few hours enhances the practicality of this method.



**Figure 3** The colors of the reaction mixture of  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (0.4 mmol) in THF (1 mL) (left), immediately following the addition of NaI (0.8 mmol), TEA (0.2 mmol), and propargyl alcohol (0.22 mmol) (middle), and 20 min after the addition benzyl azide (0.2 mmol) (right).

After a complete conversion is reached, ethyl acetate and aqueous ammonia (28-30%) are added to dilute the reaction mixture. A deep blue color immediately appears as the copper(I) species are converted to tetraammine copper(II) ions under the aerobic conditions and are sequestered to the aqueous phase.<sup>15</sup> If a substrate contains a carboxyl group, a saturated solution of  $\text{NH}_4\text{Cl}$  is used in place of aqueous ammonia. After two more extractions using saturated brine followed by drying, the ethyl acetate layer is concentrated to afford the crude product. The conversion and selectivity data in Tables 1-2, as defined in Scheme 2, were calculated based on the analysis of  $^1\text{H}$  NMR spectra of the crude products. In cases where both conversion and iodo/proto selectivity are high, the product is isolated via either a short silica column or a trituration procedure. The isolated yields are listed in Tables 1-2.

(c) Reactions not requiring an accelerating ligand.

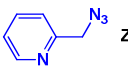
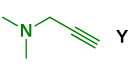
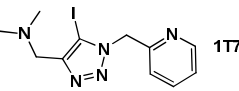
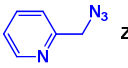
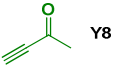
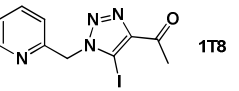
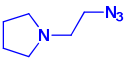
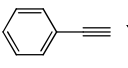
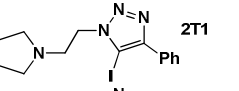
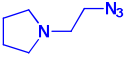
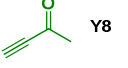
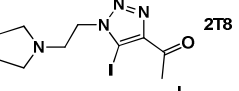
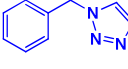
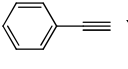
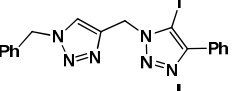
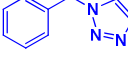
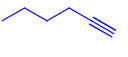
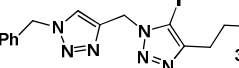
The reactions that do not require an accelerating

ligand to proceed are shown in Table 1. It becomes evident that all entries of Table 1 involve either chelating (blue) or benzylic (red) azides, which possess high reactivity under the developed conditions. All reactions but one (entry 7) proceed to completion within 6 h. The reaction between **Z4** and **Y1** takes 24 h to complete (entry 7), but it is greatly accelerated by the addition of TBTA (see the next section). Both TEA and DBU work well as the base; but TEA appears to afford faster conversion than DBU. LiI, NaI, and KI are all applicable as the iodide source with minor reactivity differences, which is briefly elaborated in a later section.

Products in entries 1 (**1T7**), 3 (**2T1**), and 7 (**4T1**) were reported in our previous work.<sup>6</sup> Under the current conditions, the reaction times of entries 1 and 3 were reduced from 6 h to 30-90 min. The isolated yield of **4T1** (89%, entry 7) is much higher than the previously reported number (49%). In the presence of TBTA (10 mol %, Table 2, entry 1), the yield of **4T1** is increased further to 95% while the reaction time is shortened to 2.5 h. These entries represent the improvement of the current method over the earlier version.<sup>6</sup>

Most reactions show exclusive selectivity favoring 5-iodo-1,2,3-triazole over its 5-proto counterpart. 2-Ethynylpyridine (**Y2**), *N,N*-dimethylpropargylamine (**Y7**) and 3-butyn-2-one (**Y8**)-involved reactions show less than ideal iodo/proto selectivity. These three alkynes tend to undergo the typical copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) rapidly, probably due to the ability of their 1,2,3-triazole products to act as bidentate accelerating ligands for the CuAAC route. This is a hypothesis that shall be tested in a future project.

**Table 1** Examples of 5-iodo-1,2,3-triazole formation without ligand acceleration.<sup>a</sup>

entry	azide	alkyne	product	Solvent/base/iodide	Conversion <sup>b</sup> (time) selectivity <sup>b</sup>	Isolated yield
1	 <b>Z1</b>	 <b>Y7</b>	 <b>1T7</b>	THF/TEA/LiI	100% (0.5 h) 85%	44%
2	 <b>Z1</b>	 <b>Y8</b>	 <b>1T8</b>	THF/DBU/KI	100% (3 h) 80%	53%
3	 <b>Z2</b>	 <b>Y1</b>	 <b>2T1</b>	THF/TEA/NaI	100% (1.5 h) 100%	69%
4	 <b>Z2</b>	 <b>Y8</b>	 <b>2T8</b>	THF/TEA/LiI	100% (1.5 h) 88%	31% <sup>c</sup>
5	 <b>Z3</b>	 <b>Y1</b>	 <b>3T1</b>	THF/DBU/KI	100% (4 h) 100%	86%
6	 <b>Z3</b>	 <b>Y5</b>	 <b>3T5</b>	THF/DBU/KI	100% (6 h) 100%	87%

7				THF/TEA/NaI	100% (24 h) 100%	89%
8				THF/TEA/NaI	100% (25 min) 100%	85%
9				THF/DBU/KI	98% (3 h) 84%	65%
10				THF/DBU/KI	100% (3 h) 100%	72%
11				THF/DBU/KI	100% (1 h) 78%	60%
12				THF/DBU/KI	94% (3 h) 100%	65%
13				THF/DBU/KI	100% (3.5 h) 100%	57%

a. Reaction conditions: azide (0.2 mmol), alkyne (0.22 mmol), solvent (1 mL),  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (0.4 mmol), alkali iodide (0.8 mmol), and base (0.2 mmol). The selections of solvent, base, and alkali iodide are shown in column 5 from the left. b. Conversion and iodo/proto selectivity, as defined in Scheme 2, were calculated from  $^1\text{H}$  NMR spectra of the crude products after extraction. c. Compound **7T8** is not stable on silica column or in  $\text{CDCl}_3$ .

**(d) TBTA-accelerated reactions.** The acceleratory effect of ligand TBTA was suggested by a reviewer of our earlier paper,<sup>6</sup> which included two reactions aided by TBTA after the revision. The current data demonstrates the scope of TBTA-accelerated reactions under the conditions depicted in Scheme 2. The slow reaction in Table 1 (entry 7) is significantly accelerated by the addition of 10 mol % TBTA (entry 1, Table 2). All aromatic azides fail to convert to 5-iodo-1,2,3-triazoles without TBTA within 6 h, but they proceed smoothly to completion with high iodo/proto selectivity in the presence of TBTA (10 mol %). A few functionalized aliphatic azides (**Z5**, **Z6**, **Z8**, and **Z9**), which have little reactivity without ligand acceleration, also convert readily to the 5-iodo-1,2,3-triazole products in the presence of TBTA (10 mol %). The iodo/proto selectivity is high even of hydroxylated and carboxylated substrates (entries 2, 3, 6, 8, 12, 13, 14, and 17). For reactions involving carboxyl-containing substrates, saturated  $\text{NH}_4\text{Cl}$

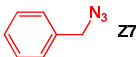
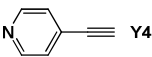
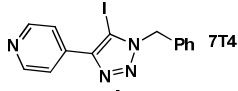
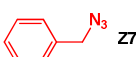
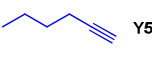
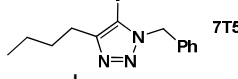
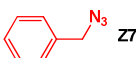
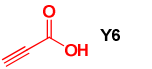
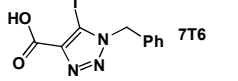
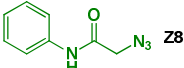
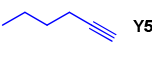
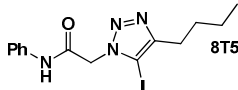
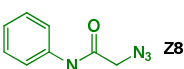
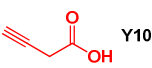
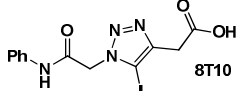
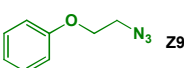
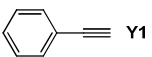
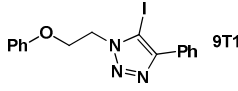
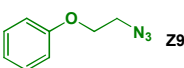
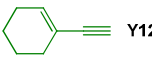
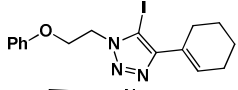
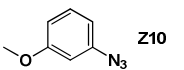
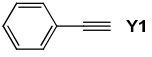
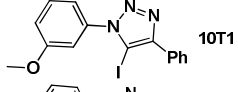
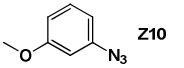

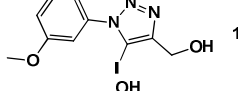
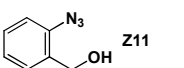
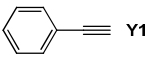
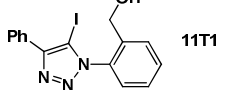
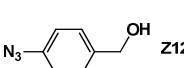
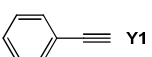
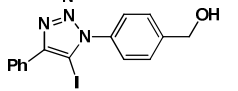
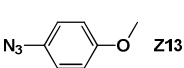
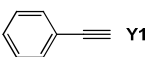
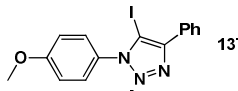
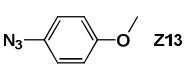
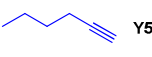
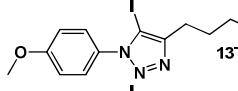
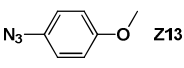

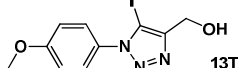
solution is used in the extraction step in place of aqueous ammonia so that the carboxylic acid product is neutralized and sequestered to the organic solvent.

We reported the syntheses of **4T1** (entry 1) and **9T1** (entry 9) previously.<sup>6</sup> However the isolated yields were only moderate (49% and 58%, respectively) in 12 h while excess of alkyne had to be used. In the current work with the aid of TBTA (10 mol %), over 95% yield was achieved within 3 h in both cases using equal molar ratio of azide and alkyne (10 mol % excess of alkyne was used for the convenience of reaction progress monitoring via TLC).

The reactions that require TBTA to achieve a high conversion mostly afford 5-iodo-1,2,3-triazole exclusively. For the couple of cases with less than 100% iodo/proto selectivity, we feel that the data pool is too small for us to attribute this observation to any structural features of the substrates.

Table 2 Reactions aided significantly by TBTA (10 mol %).<sup>a</sup>

entry	azide	alkyne	product	Solvent/base/iodide	Conversion <sup>b</sup> (time) selectivity <sup>b</sup>	Isolated yield
1				THF/DBU/NaI	100% (2.5 h) 100%	95%
2				THF/TEA/KI	100% (6 h) 100%	64%
3				THF/DBU/KI	100% (2.5 h) 100%	73%

4				THF/TEA/KI	100% (6 h) 100%	75%
5				THF/TEA/KI	100% (1 h) 100%	70%
6				THF/TEA/LiI	100% (6 h) 100%	64%
7				THF/DBU/KI	100% (6 h) 89%	76%
8				THF/TEA/LiI	75% (6 h) 100%	75%
9				THF/TEA/NaI	100% (3 h) 100%	99%
10				THF/TEA/KI	71% (6 h) 94%	53%
11				THF/TEA/KI	100% (1 h) 100%	93%
12				THF/TEA/KI	80% (3 h) 100%	72%
13				THF/TEA/LiI	90% (24 h) 100%	77%
14				CH <sub>3</sub> CN/TEA/NaI	100% (12 h) 100%	55%
15				THF/TEA/KI	80% (1 h) 100%	49%
16				THF/TEA/KI	80% (6 h) 100%	75%
17				THF/TEA/KI	94% (6.5 h) 100%	75%

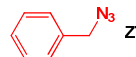
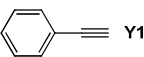
a. Reaction conditions: azide (0.2 mmol), alkyne (0.22 mmol), solvent (1 mL), Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (0.4 mmol), TBTA (0.02 mmol, 10 mol %), alkali iodide (0.8 mmol), and base (0.2 mmol). The selections of solvent, base, and alkali iodide are shown in column 5 from the left. b. Conversion and iodo/proto selectivity, as defined in Scheme 2, were calculated from <sup>1</sup>H NMR spectra of the crude products after extraction.

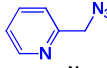
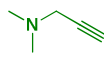
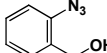
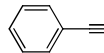
(e) *Effect of alkali iodides.* The reactivity differences among LiI, NaI, KI, and CsI in three sets of reactions were investigated. The data are shown in Table 3. Benzyl azide (**Z7**) and phenylacetylene (**Y1**, table 3, entry 1) constitute a typical substrate pair without special functional groups. 2-Picolylazide (**Z1**) and *N,N*-dimethylpropargylamine (**Y7**, table 3, entry 2) represent reactive substrate pairs that undergo fast conversions *without* ligand acceleration. Entry 3 includes a pair of unreactive substrates (**Z11** and **Y1**) that require the aid of TBTA. CsI is the most

unproductive iodide source in all three reactions. LiI and NaI afford consistently high conversions, which is attributed to their high solubility in THF.

Another notable observation is that the reactive substrate pair (entry 2) undergoes rapid conversion, but with impaired iodo/proto selectivity. This is a manifestation of the classical reactivity/selectivity relationship. In this reaction, rapid conversion pathways to both 5-iodo-1,2,3-triazole and 5-proto-1,2,3-triazole are competing to afford a relatively low selectivity.

Table 3 The alkali cation effect.<sup>a</sup>

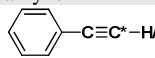
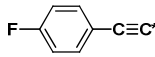
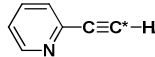
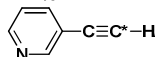
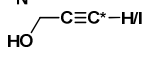
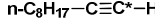
entry	azide	alkyne	conversion (time), selectivity (LiI)	conversion (time), selectivity (NaI)	conversion (time), selectivity (KI)	conversion (time), selectivity (CsI)
1			76±12% (3 h) 100±0%	81±20% (3 h) 100±0%	51±11% (3 h) 87±5.0%	0% (3 h) N.A.

2			100% (30 min) 87±10%	100% (30 min) 85±5.5%	100% (30 min) 78±11%	100% (30 min) 40±5.7%
3			59±12% (6 h) 89±9.5%	62±3.6% (6 h) 88±11%	43±12% (6 h) 85±13%	0% (6 h) N.A.

a. Reaction conditions: added in this order are alkyne (0.22 mmol), THF (1 mL),  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (0.4 mmol), alkali iodide (0.8 mmol), TBTA (0.02 mmol, 10 mol % only in entry 3), and azide (0.2 mmol). Stir at rt for 3 h (entry 1), 30 min (entry 2), or 6 h (entry 3). b. Conversion and iodo/proto selectivity as defined in Scheme 2 were calculated based on  $^1\text{H}$  NMR spectra of the crude products. Average values and standard deviations of triplicated experiments are reported.

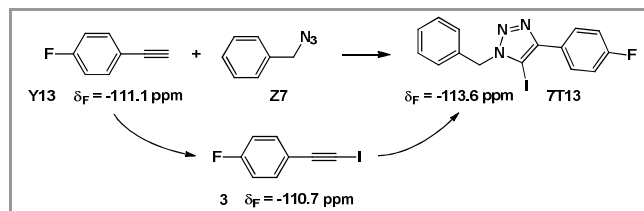
### (f) Mechanistic discussion

Table 4 1-Iodoalkyne formation characterized by  $^{13}\text{C}$  NMR chemical shift.<sup>a</sup>

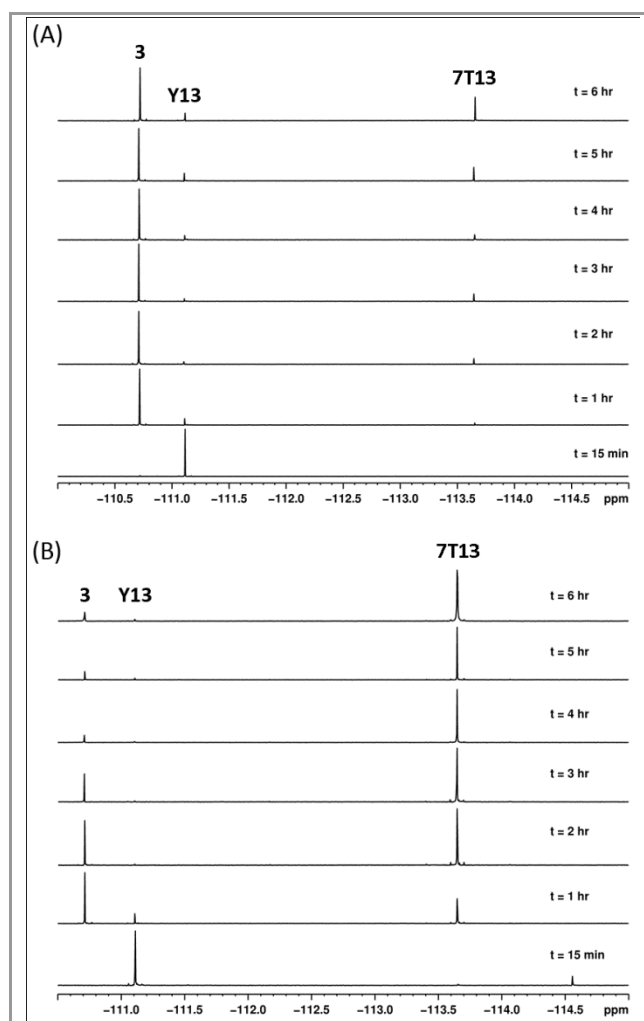
entry	alkyne	$\delta_{\text{C}^*(\text{H})}/\text{ppm}$	$\delta_{\text{C}^*(\text{I})}/\text{ppm}$
1		77.4	6.33
2		77.1	6.33
3		77.2	10.03
4		80.8	8.93
5		73.9	2.92
6		68.2	-7.47

a. Reaction conditions: added in this order are alkyne (0.22 mmol), THF (1 mL),  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (0.4 mmol), KI (0.8 mmol), and TEA (0.2 mmol). Stir at rt for 20 min. The reaction mixture was filtered through Celite.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) spectra of 1-iodoalkynes were acquired after solvent removal.

The rapid fading of brown color of the reaction mixture is an indication that the reaction is progressing well. But in a few cases, the complete color fading precedes the completion of the reaction. These observations led us to surmise that the formation of 1-iodoalkyne may have occurred before the participation of azide in the order of events. We found that a full conversion of phenylacetylene to 1-iodo-2-phenylethyne occurs within 20 min in the absence of an azide under otherwise same conditions. After filtering the reaction mixture through Celite<sup>16</sup> and solvent removal,  $^{13}\text{C}$  NMR spectrum was taken. The chemical shift of  $\text{C}^*$  in the alkyne undergoes a large upfield shift, diagnostic of 1-iodoalkyne formation (Table 4). The conversion of propargyl alcohol to 3-iodoprop-2-yn-1-ol occurs even without  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  ( $\text{I}_2$  was used in place of KI),<sup>17</sup> although the reaction is less efficient. Therefore, the formation of 1-iodoalkyne is facile in the presence of a base (e.g. TEA) and an iodinating source (e.g.  $\text{I}_2$ ). Consequently, under the conditions of 5-iodo-1,2,3-triazole synthesis, 1-iodoalkyne may form prior to entering the catalytic cycle en route to 5-iodo-1,2,3-triazole. The addition of TBTA has little effect on the efficiency of 1-iodoalkyne formation under the conditions described in the caption of Table 4, suggesting that TBTA is instead responsible for the acceleration of one or more elementary steps involving the copper(I) catalyst and the azide.



**Scheme 3 A**  $^{19}\text{F}$  NMR assay to capture the 1-iodoalkyne intermediate **3**. The chemical shifts are referenced to  $\alpha, \alpha, \alpha$ -trifluorotoluene in  $\text{CDCl}_3$ . Reaction conditions: azide **Z7** (0.4 mmol), alkyne **Y13** (0.4 mmol), THF (2 mL),  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (0.8 mmol), KI (1.6 mmol), and TEA (0.4 mmol). The reaction was repeated with the inclusion of TBTA (0.04 mmol, 10 mol %).



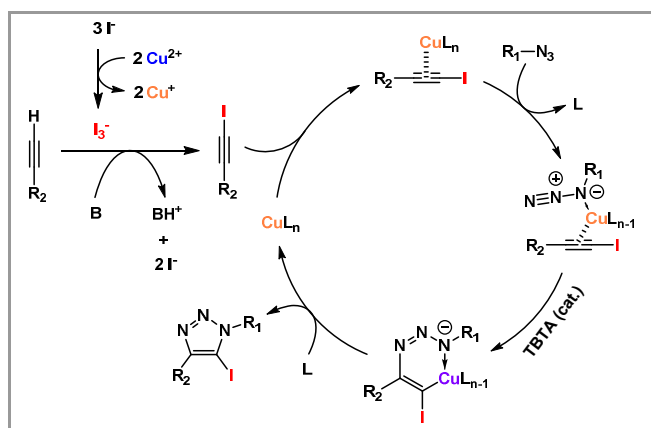
**Figure 4** Progress of reactions shown in Scheme 3 (A) without and (B) with TBTA (10 mol %). Aliquots of reaction mixture were drawn at prescribed intervals and  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) spectra were acquired.



Although  $^{13}\text{C}$  NMR spectroscopy is diagnostic in characterizing the 1-iodoalkyne intermediate, the inability for integration and lengthiness of acquisition render it ineffective in following the reaction progress.  $^1\text{H}$  NMR is fast and quantitative. However, the difference between alkyne and 1-iodoalkyne in  $^1\text{H}$  NMR is often small, and the alkynyl C-H signal is often obscured by solvent residue peaks.  $^{19}\text{F}$  NMR spectroscopy<sup>18</sup> has neither of the shortcomings of  $^{13}\text{C}$  NMR, and shall afford clean enough spectra to make unambiguous assignments and quantification of different species formed in a reaction.

The reaction between fluorinated alkyne **Y13** and benzyl azide (**Z7**) was monitored by  $^{19}\text{F}$  NMR spectroscopy (Scheme 3). Aliquots of the reaction mixture were drawn at prescribed intervals. After quenching  $\text{I}_2/\text{I}_3^-$  using a solution of sodium thiosulfate and running the organic fraction through a pad of Celite in a Pasteur pipet, the sample was concentrated and redissolved in  $\text{CDCl}_3$ . The  $^{19}\text{F}$  NMR spectra of the aliquots were acquired over the course of the reaction without TBTA (Figure 4A). At the 1-h mark, the majority of alkyne **Y3** was converted to 1-iodoalkyne **3**, while the 5-iodo-1,2,3-triazole product **7T13** began to form. At the 6-h mark the experiment was terminated and 28% conversion was achieved.

In the presence of 10 mol % TBTA, the conversion of **Y13** and **Z7** to product **7T13** was significantly accelerated, reaching 95% after 4 h (Figure 4B). The rapid formation of 1-iodoalkyne **3** was not affected by the inclusion of TBTA, and alkyne **Y13** was barely noticeable after 2 h. It is notable that the sample collected at the 15-min mark contained a small portion of 5-proto-1,2,3-triazole side product ( $\delta_{\text{F}} = -114.5$  ppm), which likely formed during the aliquot workup. From Figure 4B, it is evident that a large amount of alkyne starting material is still present 15 min into the reaction, which may undergo the traditional TBTA-accelerated CuAAC reaction during the aqueous workup to afford 5-proto-1,2,3-triazole. However, after conversion to the 1-iodoalkyne was completed ( $t = 1$  h) this side product was no longer observed.



**Scheme 4** Outline of a mechanism that involves the 1-iodoalkyne intermediate. The catalytic cycle component is adapted from the work by Hein, Fokin, and coworkers.<sup>2</sup> B: base. Orange, blue, and

purple represent +1, +2, and +3 oxidation states of copper, respectively. A dative bond from the alkylated nitrogen of the azide, which bears a formal negative charge, to  $\text{Cu}^{\text{III}}$  center in the intermediate is used for electron-bookkeeping purposes. With chelating azide or otherwise reactive substrates, TBTA may not be required.

Based on the rapid conversion of alkyne **Y13** to 1-iodoalkyne **3** observed in the  $^{19}\text{F}$  NMR experiments (Figure 4), we conclude that the mechanism outlined in Scheme 4, the catalytic component of which was first proposed by Hein, Fokin, and coworkers,<sup>2</sup> is most appropriate. *In situ* generated  $\text{I}_3^-$  iodinate alkyne to 1-iodoalkyne with the assistance of a base. Copper(I) subsequently catalyzes the conjugation step between 1-iodoalkyne and azide. Based on the comparison of the kinetic profiles of reactions in the absence and presence of TBTA as shown in Figure 4, it appears that TBTA specifically accelerates the azide/1-iodoalkyne cycloaddition step, presumably by activating the copper(I) species in similar ways that TBTA benefits the traditional CuAAC reactions.<sup>8, 10, 19</sup> Throughout this mechanistic pathway, the carbon-iodine bond remains intact. This pathway accounts for the high iodo/proto selectivity and is more plausible than the alternative route outlined in Scheme 1b, which was also considered by Hein, Fokin and coworkers<sup>2</sup>, others,<sup>3, 5</sup> and us.<sup>6</sup>

Although not implausible, it is hard to defend the cuprous triazolide intermediate in Scheme 1b given the observed high iodo/proto selectivity without rigorous removal of water (i.e., crystalline water contained in  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ ). If for any reason the 1-iodoalkyne is formed slowly or is unstable, copper(I) acetylide formation would occur competitively to channel the reaction to the typical CuAAC pathway, thus lowering the iodo/proto selectivity.

**(g) Recommended procedure.** The  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  used in this work is dried at 40–70 °C in a vacuum oven for overnight to remove adsorbed moisture (not crystalline water), and subsequently stored in a dry keeper. The recommended procedure begins with the dissolution of the azide in THF to afford a 0.2 M solution. The additions of LiI (4 molar equiv.),  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (2 molar equiv.), TEA (1 molar equiv.), and the alkyne (1 molar equiv.) follow sequentially. If a non-chelating azide is used, it is recommended that the ligand TBTA (10 mol %) be included to ensure the conversion in a timely manner, usually no longer than 6 h. As a full conversion is established by the TLC trace, the reaction mixture is partitioned between ethyl acetate and aqueous ammonia, which removes copper salts quickly and cleanly. After one or two extractions with saturated NaCl solution and drying, the crude product obtained after solvent removal may be subjected to column chromatography or a trituration procedure to afford the analytically pure material.

The following variations may be made without compromising the reaction efficiency. (1) The azide

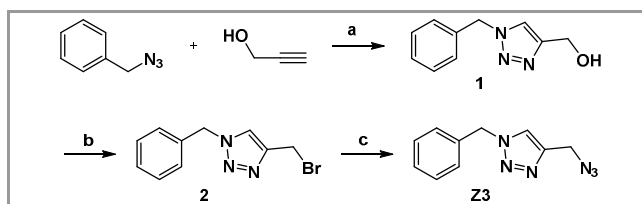
may be added at the end following the alkyne. (2) Acetonitrile is another effective solvent, in particular when the substrates have limited solubility in THF. (3) TEA may be substituted by DBU. (4) NaI and KI, which are less expensive than LiI, under most circumstances are equally effective. (5) The workup procedure is dependent on the structure of the product. For example, if a carboxylic acid is being isolated, a saturated  $\text{NH}_4\text{Cl}$  or an EDTA solution of an appropriate pH value shall be used in place of aqueous ammonia.

## Conclusion

The coupling of organic azide and terminal alkyne in the presence of  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  and alkali iodide affords 5-iodo-1,2,3-triazole under mild conditions. With the addition of accelerating ligand TBTA (10 mol %), this procedure tolerates a board array of functional groups including carboxyl, hydroxyl, and many others. Both aliphatic and aromatic azides and alkynes readily convert to 5-iodo-1,2,3-triazole products with high to exclusive iodo/proto selectivity. Among alkali iodides, LiI and NaI afford consistently high conversion and iodo/proto selectivity. The intermediacy of 1-iodoalkyne in this sequence of reactions is directly observed using a  $^{19}\text{F}$  NMR assay, and is consistent with a mechanism that entails the initial formation of 1-iodoalkyne where the C-I bond remains intact throughout the cyclization steps to afford 5-iodo-1,2,3-triazole. This mechanistic pathway best accounts for the observed high iodo/proto selectivity.<sup>2</sup> The minor 5-proto-1,2,3-triazole occasionally observed is attributed to the conventional copper(I)-catalyzed azide-alkyne “click” cycloaddition, which becomes competitive when the substrate structures favor this route, or when the 1-iodoalkyne is formed slowly or is unstable.

**Warning! Low molecular weight organic azides and copper(II) perchlorate hexahydrate used in this study are potentially explosive. Appropriate protective measures shall always be taken when handling these compounds.** Reagents and solvents were purchased from various commercial sources and used without further purification unless otherwise stated. Benzyl azide was purchased from Alfa Aesar at 94% purity, which most likely contributed to the across-the-board lower than expected (based on conversion) isolated yields for reactions involving benzyl azide.  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  was placed in a vacuum oven at 40–70 °C for overnight and stored in a dry keeper before use. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with silica gel 60 F254 or with aluminum oxide 60 F254 neutral. Flash column chromatography was performed using

40–63  $\mu\text{m}$  (230–400 mesh ASTM) silica gel or alumina (80–200 mesh, pH 9–10) as the stationary phases. Silica and alumina gel were flame-dried under vacuum to remove adsorbed moisture before use.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 500 (or 300) and 125 (or 75) MHz, respectively.  $^{19}\text{F}$  NMR spectra were acquired on a 400 MHz spectrometer at 376 MHz. The chemical shifts ( $\delta$ ) are recorded in ppm relative to the residual  $\text{CHCl}_3$  or  $\text{CHD}_2\text{CN}$  as internal standards.



**Scheme 5** Synthesis of azide **Z3**. Conditions and reagents: a)  $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$  (5 mol %),  $t\text{BuOH}$ , rt, 16 h; b)  $\text{PBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 4 h; c)  $\text{NaN}_3$ ,  $\text{DMF}$ , 50 °C, 16 h.

## Compound 1<sup>20</sup>

To an argon-charged round-bottom flask, benzyl azide (80.7 mg, 0.606 mmol), propargyl alcohol (37 mg, 0.67 mmol) and *tert*-butanol (0.5 mL) were added sequentially followed by the addition of an aqueous solution of  $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$  (75  $\mu\text{L}$  of a 0.4 M solution, 5 mol % against benzyl azide). The reaction mixture was stirred at rt for 16 h, and then separated on a silica column eluted with  $\text{CH}_3\text{OH}$  (0–5%) in  $\text{CH}_2\text{Cl}_2$  to afford compound **1** (a white amorphous solid, 106 mg, 93%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 7.45 (s, 1H), 7.39–7.35 (m, 3H), 7.28–7.26 (m, 2H), 5.50 (s, 2H), 4.75 (s, 2H), 2.30 (s(b), 1H).

## Compound 2

To an argon-charged round-bottom flask containing compound **1** (388 mg, 2.05 mmol),  $\text{CH}_2\text{Cl}_2$  (5.0 mL) and phosphorus tribromide (1.10 g, 4.09 mmol) were added sequentially. The reaction mixture was stirred at rt for 4 h, and then quenched with  $\text{H}_2\text{O}$  (2 mL). The reaction was extracted by  $\text{CH}_2\text{Cl}_2$ , and the organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under vacuum. The reaction mixture was separated on a silica column eluted with ethyl acetate (30%) in  $\text{CH}_2\text{Cl}_2$  to afford compound **2** (a white amorphous solid, 382 mg, 74%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 7.48 (s, 1H), 7.40–7.38 (m, 3H), 7.29–7.26 (m, 2H), 5.52 (s, 2H), 4.55 (s, 2H).

## Azide **Z3**

To an argon-charged round-bottom flask compound **2** (56 mg, 0.23 mmol),  $\text{DMF}$  (2.0 mL), and sodium azide (297 mg, 4.57 mmol) were added sequentially. The reaction mixture was stirred at 50 °C overnight. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with saturated  $\text{NH}_4\text{Cl}$  solution

(50 mL × 3). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to give **Z3** (a white amorphous solid, 290 mg, 39%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm 7.45 (s, 1H), 7.39-7.37 (m, 3H), 7.29-7.26 (m, 2H), 5.54 (s, 2H), 4.47 (s, 2H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ/ppm 143.1, 134.3, 129.3, 129.0, 128.2, 122.2, 54.4, 45.7.

HRMS (CI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>11</sub>N<sub>6</sub> 215.1045, found 215.1042.

**Compound 7T7 (Table 1, Entry 11).** *This is a representative procedure (method 1) to prepare 5-iodo-1,2,3-triazoles shown in Table 1, in which TBTA ligand was not required.*

Benzyl azide (**Z7**, 27.0 mg, 0.20 mmol) was dissolved in THF (1.0 mL) in a 10-mL round-bottom flask equipped with a magnetic stirring bar. To this solution KI (132.8 mg, 0.80 mmol) and Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (148.2 mg, 0.40 mmol) were added. After the solution was stirred for 3-5 min, DBU (30.0 mg, 0.20 mmol) and *N,N*-dimethylpropargylamine (**Y7**, 18.3 mg, 0.22 mmol) were added sequentially. The reaction mixture was stirred at rt for up to 6 h. The reaction mixture was diluted with ethyl acetate (50 mL) and aqueous ammonia (28-30%, 25 mL), before transferred to a separatory funnel. The organic layer was washed with saturated brine (25 mL × 2), separated, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure to produce the crude product, the <sup>1</sup>H NMR spectrum of which afforded the conversion and selectivity data reported in Table 1. The crude product was purified on a silica gel column using CH<sub>2</sub>Cl<sub>2</sub> as the eluent with increasing amount of ethyl acetate (0-30%) to afford an off-white amorphous solid (48 mg, 60%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm 7.35-7.32 (m, 3H), 7.26-7.23 (m, 2H), 5.60 (s, 2H), 3.53 (s, 2H), 2.29 (s, 6H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ/ppm 148.8, 134.4, 128.9, 128.5, 127.7, 80.9, 54.2, 53.9, 45.3.

HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>16</sub>IN<sub>4</sub> 343.04196, found 343.04157.

**Compound 1T7<sup>6</sup> (Table 1, Entry 1)** was prepared using method 1 in 30 min. TEA and LiI were used in place of DBU and KI, respectively. The isolated yield was 44% (a white amorphous solid, 30.0 mg).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 8.58 (d, J = 4.2 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.23 (t, J = 5.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 5.75 (s, 2H), 3.56 (s, 2H), 2.30 (s, 6H).

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ/ppm: 154.6, 149.8, 149.1, 137.3, 123.3, 121.5, 81.7, 55.8, 54.2, 45.4.

HRMS: (CI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>15</sub>IN<sub>5</sub> 344.03725, found 344.03645

**Compound 1T8 (Table 1, Entry 2)** was prepared using method 1 in 6 h (an off-white amorphous solid, 35 mg, 53%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm 8.60-8.58 (m, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.26 (s, 1H), 7.00 (d, J = 7.8 Hz, 1H), 5.80 (s, 2H), 2.74 (s, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ/ppm 192.2, 153.4, 149.9, 147.5, 137.2, 123.4, 121.6, 82.8, 55.4, 27.7.

HRMS (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>10</sub>H<sub>9</sub>IN<sub>4</sub>ONa 350.97187, found 350.97127.

**Compound 2T1<sup>6</sup> (Table 1, Entry 3)** was prepared using method 1 in 1.5 h. TEA and NaI were used in place of DBU and KI, respectively. The isolated yield was 75% (a white amorphous solid, 55 mg).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.93 (d, J = 6.9 Hz, 2H), 7.49-7.39 (m, 3H), 4.60 (t, J = 7.5 Hz, 2H), 3.03 (t, J = 7.4 Hz, 2H), 2.64 (t, J = 6.5 Hz, 4H), 1.81 (s, 4H).

**Compound 2T8 (Table 1, Entry 4)** was prepared using method 1 in 1.5 h. TEA and LiI were used in place of DBU and KI, respectively. The isolated yield was 31% (an off-white amorphous solid, 21 mg).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 4.56 (t, J = 7.2 Hz, 2H), 2.98 (t, J = 7.2 Hz, 2H), 2.70 (s, 3H), 2.59 (m, 4H), 1.78 (m, 4H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ/ppm: 192.4, 147.2, 82.3, 55.2, 54.5, 49.8, 27.8, 23.8.

HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>15</sub>OIN<sub>4</sub> 334.02909, found 334.02841.

**Compound 3T1 (Table 1, Entry 5)** was prepared using method 1 in 4 h (an off-white amorphous solid, 76 mg, 86%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm 7.91 (d, J = 8.4 Hz, 2H), 7.48-7.36 (m, 6H), 7.26-7.24 (m, 3H), 5.79 (s, 2H), 5.50 (s, 2H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ/ppm 150.2, 142.3, 134.3, 130.2, 129.3, 129.2, 129.1, 128.8, 128.7, 128.3, 127.5, 123.3, 54.5, 46.6.

HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>15</sub>IN<sub>6</sub>Na 465.03006, found 465.02860.

**Compound 3T5 (Table 1, Entry 6)** was prepared using method 1 in 6 h (a white amorphous solid, 73 mg, 87%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm 7.41 (s, 1H), 7.37-7.35 (m, 2H), 7.26-7.22 (m, 3H), 5.67 (s, 2H), 5.49 (s, 2H), 2.63 (t, J = 7.2 Hz, 2H), 1.69-1.59 (m, 2H), 1.39-1.30 (m, 2H), 0.92 (t, J = 7.2 Hz, 2H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ/ppm 152.5, 142.4, 134.3, 129.3, 129.0, 128.2, 123.1, 78.7, 54.4, 46.3, 31.1, 25.9, 22.4, 13.9.

HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>20</sub>IN<sub>6</sub> 423.07941, found 423.07844.

**Compound 4T11 (Table 1, Entry 8)** was prepared using method 1 in 15 min. TEA and NaI were used in

place of DBU and KI, respectively. The isolated yield was 85% (an off-white amorphous solid, 54 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 8.67 (s, 1H), 8.60 (d,  $J = 4.5$  Hz, 1H), 7.60 (d,  $J = 7.8$  Hz, 1H), 7.30 (dd,  $J = 12.6, 3.1$  Hz, 1H), 5.62 (s, 2H), 4.72 (d,  $J = 5.6$  Hz, 2H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) 151.3, 149.3, 148.9, 135.4, 131.2, 123.9, 84.2, 54.8, 50.8.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_9\text{H}_{10}\text{IN}_4\text{O}$  316.98993, found: 316.99071.

**Compound 7T2 (Table 1, Entry 9)** was prepared using method 1 in 3 h (a white amorphous solid, 47 mg, 65%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 8.63 (d,  $J = 4.2$  Hz, 1H), 8.12 (d,  $J = 7.8$  Hz, 1H), 7.74 (td,  $J = 7.8, 1.2$  Hz, 1H), 7.22–7.29 (m, 6H), 5.67 (s, 2H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 149.9, 149.1, 148.7, 136.7, 134.5, 129.0, 128.6, 127.9, 123.2, 121.9, 77.5, 54.3.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{12}\text{IN}_4$  363.01066, found 363.01111.

**Compound 7T3 (Table 1, Entry 10)** was prepared using method 1 in 3 h (60 mg, 72%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 9.21 (s, 1H), 8.63 (d,  $J = 4.2$  Hz, 1H), 8.25 (d,  $J = 7.8$  Hz, 1H), 7.43–7.34 (m, 5H), 7.26 (s, 1H), 5.69 (s, 2H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 149.6, 148.3, 147.8, 134.9, 134.2, 129.1, 128.8, 128.0, 126.7, 123.6, 77.7, 54.6.

HRMS (CI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{12}\text{IN}_4$  363.0107, found 363.0101.

**Compound 7T8 (Table 1, Entry 12)** was prepared using method 1 in 3 h (a white amorphous solid, 42 mg, 65%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 7.37–7.30 (m, 5H), 5.65 (s, 2H), 2.71 (s, 3H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 192.4, 147.6, 133.8, 129.2, 129.0, 128.2, 81.9, 54.3, 27.8.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_{11}\text{IN}_3\text{O}$  327.99468, found 327.99360.

**Compound 7T9 (Table 1, Entry 13)** was prepared using method 1 in 3.5 h (a white amorphous solid, 40 mg, 57%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 7.33–7.32 (m, 5H), 5.59 (s, 2H), 1.46 (s, 9H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 157.2, 134.6, 128.8, 128.3, 127.8, 74.0, 54.1, 31.8, 29.5.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{17}\text{IN}_3$  342.04675, found 342.04656.

**Compound 6T1 (Table 2, Entry 3)** *This is a representative procedure (method 2) to prepare 5-iodo-1,2,3-triazoles shown in Table 2, in which TBTA ligand (10 mol %) was required.*

4-Azidobutanol (**Z6**, 23.0 mg, 0.20 mmol) was dissolved in THF (1.0 mL) in a 10-mL round-bottom flask equipped with a magnetic stirring bar. To this solution KI (132.8 mg, 0.80 mmol),  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (148.2 mg, 0.40 mmol), and TBTA (10.6 mg, 0.020 mmol) were added. After the solution was stirred for 3–5 min, DBU (30.0 mg, 0.20 mmol) and phenylacetylene (**Y1**, 22.5 mg, 0.22 mmol) were added sequentially. The reaction mixture was stirred at rt for up to 6 h, until it was diluted with ethyl acetate (50 mL) and aqueous ammonia (28–30%, 25 mL), and transferred to a separatory funnel. The organic layer was washed with saturated brine (25 mL  $\times$  2), separated and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure to afford the crude product. The conversion and selectivity data reported in Table 2 was calculated as defined in Scheme 2 from the  $^1\text{H}$  NMR spectrum of the crude product. The crude product was purified on a silica gel column using  $\text{CH}_2\text{Cl}_2$  as the eluent with increasing amount of ethyl acetate (0–20%) to afford an amorphous white solid (62 mg, 73%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 7.93 (d,  $J = 6.6$  Hz, 2H), 7.50–7.4 (m, 3H), 4.52 (t,  $J = 7.2$  Hz, 2H), 3.77–3.70 (m, 2H), 2.14–2.03 (m, 2H), 1.72–1.63 (m, 2H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 149.8, 130.3, 128.7, 128.6, 127.5, 76.4, 62.0, 50.7, 29.3, 26.5.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_{15}\text{IN}_3\text{O}$  344.02598, found 344.02580.

**Compound 4T1<sup>6</sup> (Table 2, Entry 1)** was prepared using method 2 in 2.5 h. NaI was used in place of KI. The isolated yield was 95% (a white amorphous solid, 69 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 8.71 (s, 1H), 8.61 (d,  $J = 3.9$  Hz, 1H), 7.92 (d,  $J = 6.9$  Hz, 2H), 7.64 (d,  $J = 8.1$  Hz, 1H), 7.47–7.38 (m, 3H), 7.32–7.30 (m, 1H), 5.70 (s, 2H).

**Compound 5T5 (Table 2, Entry 2)** was prepared using method 2 in 6 h. TEA was used in place of DBU. The isolated yield was 64% (a yellow amorphous solid, 56 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 4.61 (t,  $J = 7.2$  Hz, 2H), 3.07 (t,  $J = 7.2$  Hz, 2H), 2.66 (t,  $J = 7.2$  Hz, 2H), 1.70–1.60 (m, 2H), 1.43–1.33 (m, 2H), 0.93 (t,  $J = 7.2$  Hz, 3H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 152.3, 78.9, 46.3, 31.2, 29.9, 25.8, 22.5, 14.0, 1.2.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_9\text{H}_{15}\text{IN}_3\text{O}_2$  324.02089, found 324.02085.

**Compound 7T4 (Table 2, Entry 4)** was prepared using method 2 in 6 h. TEA was used in place of DBU. The isolated yield was 75% (a white amorphous solid, 74 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm 8.70 (d,  $J = 6.0$  Hz, 2H), 7.94 (t,  $J = 4.8$  Hz, 2H), 7.37–7.30 (m, 5H), 5.7 (s, 2H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  150.2, 147.2, 137.8, 133.9, 129.0, 128.7, 127.8, 121.1, 78.0, 54.5.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{12}\text{IN}$  363.01066, found 363.01026.

**Compound 7T5 (Table 2, Entry 5)** was prepared using method 2 in 1 h. The limiting reagent benzyl azide was used at 0.4 mmol. All other reagents were doubled accordingly. TEA was used in place of DBU. The isolated yield was 70% (96 mg, a beige amorphous solid).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  7.35-7.33 (m, 3H), 7.26-7.24 (m, 2H), 5.57 (s, 2H), 2.65 (t,  $J = 7.2$  Hz, 2H), 1.72-1.62 (m, 2H), 1.41-1.33 (m, 2H), 0.93 (t,  $J = 7.2$  Hz, 3H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ): 152.5, 134.5, 128.9, 128.4, 127.8, 78.2, 54.2, 31.1, 25.9, 22.3, 13.9.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{17}\text{IN}_3$  342.04671, found 342.04605.

**Compound 7T6 (Table 2, Entry 6)** was prepared using method 2. TEA and LiI were used in place of DBU and KI, respectively. Saturated  $\text{NH}_4\text{Cl}$  (pH ~ 5) was used in place of aqueous ammonia for extraction. The isolated yield was 64% (a white amorphous solid, 45 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  7.37-7.34 (m, 3H), 7.30-7.26 (m, 2H), 5.66 (s, 2H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  133.7, 129.0, 128.8, 127.9, 101.8, 90.3, 55.6.

MS (EI) ( $m/z$ ):  $[\text{M}-\text{CO}_2\text{H}]^+$  calcd for  $\text{C}_9\text{H}_7\text{IN}_3$  284.0, found 284.1. Molecular ion was not found using EI, CI, and ESI ionization methods.

**Compound 8T5 (Table 2, Entry 7)** was prepared using method 2 in 6 h (a white amorphous solid, 59 mg, 76%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  7.65 (s(b), 1H), 7.44 (d,  $J = 7.8$  Hz, 2H), 7.32 (t,  $J = 7.2$  Hz, 2H), 7.15 (t,  $J = 7.8$  Hz, 1H), 5.22 (s, 2H), 2.71 (t,  $J = 7.2$  Hz, 2H), 1.76-1.66 (m, 2H), 1.45-1.35 (m, 2H), 0.95 (t,  $J = 7.8$  Hz, 3H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  164.1, 151.2, 138.9, 129.4, 124.3, 119.6, 84.4, 53.2, 31.3, 25.6, 22.0, 14.2.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{18}\text{IN}_4\text{O}$  385.05253, found 385.05206.

**Compound 8T10 (Table 2, Entry 8)** was prepared using method 2 in 6 h. TEA and LiI were used in place of DBU and KI, respectively. Saturated  $\text{NH}_4\text{Cl}$  (pH ~ 5) was used in place of aqueous ammonia for extraction. The isolated yield was 75% (a yellow oil, 60 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta/\text{ppm}$  10.56 (s, 1H), 7.59 (d,  $J = 9.0$  Hz, 2H), 7.34 (t,  $J = 6.0$  Hz, 2H), 7.12 (t,  $J = 9.0$  Hz, 1H), 5.33 (s, 2H), 3.62 (s, 2H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ):  $\delta/\text{ppm}$  170.6, 163.5, 145.5, 138.4, 128.9, 123.8, 119.2, 86.0, 52.9, 32.1.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{12}\text{H}_{11}\text{IN}_4\text{NaO}_3$  408.97735, found 408.97657.

**Compound 9T1<sup>6</sup> (Table 2, Entry 9)** was prepared using method 2 in 3 h. TEA and NaI were used in place of DBU and KI. The isolated yield was 99% (a white amorphous solid, 78 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ): 7.93 (dd,  $J = 8.4, 1.5$  Hz, 2H), 7.40-7.31 (m, 3H), 7.29 (d,  $J = 7.5$  Hz, 2H), 6.97 (t,  $J = 7.4$  Hz, 1H), 6.89 (d,  $J = 8.8$  Hz, 2H), 4.87 (t,  $J = 5.8$  Hz, 2H), 4.48 (t,  $J = 5.7$  Hz, 2H).

**Compound 9T12 (Table 2, Entry 10)** was prepared using method 2 in 6 h. TEA was used in place of DBU. The isolated yield was 53% (an off-white amorphous solid, 42 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 7.26 (d,  $J = 7.5$  Hz, 2H), 6.96 (t,  $J = 7.4$  Hz, 1H), 6.87 (dd,  $J = 7.8, 1.0$  Hz, 2H), 6.42 (t,  $J = 1.9$  Hz, 1H), 4.78 (t,  $J = 5.9$  Hz, 2H), 4.41 (t,  $J = 5.8$  Hz, 2H), 2.55-2.51 (m, 2H), 2.25-2.19 (m, 2H), 1.81-1.75 (m, 2H), 1.74-1.63 (m, 2H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ )  $\delta/\text{ppm}$ : 158.1, 151.5, 129.7, 129.0, 128.2, 121.6, 114.7, 76.4, 66.2, 49.7, 27.5, 25.6, 22.8, 22.1.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{19}\text{IN}_3\text{O}$  396.05728, found 396.05703.

**Compound 10T1 (Table 2, Entry 11)** was prepared using method 2 in 1 h. TEA was used in place of DBU. The limiting reagent azide **Z10** was used at 0.4 mmol. All other reagents were doubled accordingly. The isolated yield was 93% (141 mg, a white amorphous solid).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  8.01 (d,  $J = 8.4$  Hz, 1H), 7.54-7.42 (m, 5H), 7.16-7.10 (m, 3H), 3.89 (s, 3H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  160.2, 150.5, 138.0, 130.2, 130.2, 128.8, 128.7, 117.9, 118.8, 116.3, 112.2, 55.8.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{13}\text{IN}_3\text{O}$  378.01033, found 378.01095.

**Compound 10T11 (Table 2, Entry 12)** was prepared using method 2 in 3 h. TEA was used in place of DBU. The isolated yield was 72% (48 mg, a white amorphous solid).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  7.46 (t,  $J = 7.8$  Hz, 1H), 7.20-7.04 (m, 3H), 4.83 (d,  $J = 6.6$  Hz, 2H), 3.87 (s, 3H), 2.30 (t,  $J = 6.0$  Hz, 1H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ): 160.4, 151.4, 137.8, 130.3, 118.3, 116.4, 111.8, 80.0, 56.9, 55.9.

HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{10}\text{H}_{10}\text{IN}_3\text{O}_2\text{Na}$  353.97154, found 353.97106.

**Compound 11T1 (Table 2, Entry 13)** was prepared using method 2 in 24 h. TEA and LiI were used in place of DBU and KI, respectively. The isolated yield was 77% (a white amorphous solid, 58 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 8.05 (dd,  $J = 8.4, 1.5$  Hz, 2H), 7.73 (d,  $J = 6.7$  Hz, 1H), 7.63 (td,  $J = 7.6,$

1.2 Hz, 1H), 7.55-7.45 (m, 4H), 7.40 (d, J = 6.8 Hz, 1H), 4.39 (d, J = 6.2 Hz, 2H), 2.49 (t, J = 6.4 Hz, 1H).

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ/ppm: 148.4, 139.5, 134.2, 130.8, 130.3, 128.8, 128.5, 128.0, 127.8, 127.7, 127.0, 84.4, 58.5.

HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>13</sub>IN<sub>3</sub>O 378.01033, found 378.01160.

**Compound 12T1 (Table 2, Entry 14)** was prepared using method 2 in 6 h. CH<sub>3</sub>CN, TEA, and NaI were used in place of THF, DBU, and KI, respectively. The isolated yield was 55% (a light orange amorphous solid, 42 mg).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ/ppm: 7.95 (dd, J = 6.2, 1.4 Hz, 2H), 7.57-7.53 (m, 6H), 7.47 (t, J = 5.7 Hz, 1H), 5.45 (t, J = 5.9 Hz, 1H), 4.64 (d, J = 5.8 Hz, 2H).

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ/ppm: 149.1, 145.0, 135.4, 130.4, 128.7, 128.5, 127.2, 127.1, 126.4, 83.7, 62.3.

HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>13</sub>IN<sub>3</sub>O 378.01033, found 378.01097.

**Compound 13T1 (Table 2, Entry 15)** was prepared using method 2 in 1 h. TEA was used in place of DBU. The limiting reagent azide **Z13** was used at 0.4 mmol. All other reagents were doubled accordingly. The isolated yield was 49% (74 mg, a white amorphous solid).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm 8.01 (d, J = 8.4 Hz, 2H), 7.53-7.43 (m, 5H), 7.07 (d, J = 8.4 Hz, 2H), 3.91 (s, 3H).

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): 160.3, 148.8, 130.4, 129.8, 128.7, 128.5, 128.1, 127.2, 114.5, 83.8, 55.6.

HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>13</sub>IN<sub>3</sub>O 378.01033, found 378.00982.

**Compound 13T5 (Table 2, Entry 16)** was prepared using method 2 in 6 h. TEA was used in place of DBU. The isolated yield was 75% (an off-white amorphous solid, 54 mg).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.42 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 3.88 (s, 3H), 2.73 (t, J = 7.9 Hz, 2H), 1.79-1.69 (m, 2H), 1.47-1.37 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ/ppm: 160.6, 152.4, 130.1, 127.4, 114.4, 79.9, 55.7, 31.2, 26.1, 22.4, 13.9.

HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>17</sub>IN<sub>3</sub>O 358.04162, found 358.04165.

**Compound 13T11 (Table 2, Entry 17)** was prepared using method 2 in 6.5 h. TEA was used in place of DBU. The isolated yield was 75% (49 mg, a white amorphous solid).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm 7.42 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 4.81 (d, J = 6.6 Hz, 2H), 3.90 (s, 3H), 2.15 (t, J = 7.8 Hz, 1H).

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ/ppm 160.2, 151.0, 129.7, 127.6, 114.5, 85.5, 55.6, 55.0.

HRMS (CI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>11</sub>O<sub>2</sub>IN<sub>3</sub> 331.98963, found 331.98965.

**Compound 7T13** was prepared using method 2 in 6 h. TEA was used in place of DBU. The isolated yield was 71% (a white amorphous solid, 55 mg).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm 7.94-7.89 (m, 2H), 7.38-7.32 (m, 5H), 7.18-7.12 (m, 2H), 5.67 (s, 2H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ/ppm 163.9, 161.9, 149.5, 134.2, 129.4, 129.3, 129.0, 128.6, 127.9, 126.4, 126.3, 115.7, 115.5, 76.3, 54.5.

HRMS (EI) (*m/z*): [M]<sup>+</sup> calcd for C<sub>15</sub>H<sub>11</sub>FN<sub>3</sub>I 378.9982, found 378.9978.

**<sup>19</sup>F NMR experiment.** Benzyl azide (**Z7**, 53 mg, 0.4 mmol), THF (2 mL), Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (296 mg, 0.8 mmol), KI (264 mg, 1.6 mmol), and if needed, TBTA (21 mg, 0.04 mmol) were added sequentially to a glass vial with a stir bar and the reaction mixture was allowed to stir for ~ 5 min. TEA (40 mg, 0.4 mmol) and 4-fluoro-1-ethynylbenzene (**Y13**, 48 mg, 0.4 mmol) were then added and the reaction mixture was allowed to stir at rt. Aliquots of the reaction mixture (~ 0.1 mL) were taken at different reaction times and diluted with ethyl acetate before being added to a test tube containing a solution of sodium thiosulfate to quench I<sub>2</sub>. The organic layer was then removed and ran through a Celite pad to remove copper before being concentrated under reduced pressure and dissolved in CDCl<sub>3</sub>. One drop of α,α,α-trifluorotoluene was added as a reference standard (-63.72 ppm). All spectra were acquired at 376 MHz at rt.

**Supporting Information.** Copies of <sup>1</sup>H and <sup>13</sup>C NMR data of compounds reported in this article are available online at <http://www.thieme-connect.com/ejournals/toc/synthesis>.

## Acknowledgment

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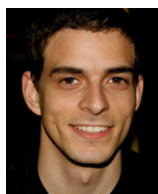
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- (13) In a few cases, the scale was doubled, as indicated in the experimental section.
- (14) 10 Mol % excess of alkyne was used for the convenience of monitoring azide as the limiting reagent.
- (15) The oxidant is O<sub>2</sub>, not perchlorate or its derivatives, based on the following experiments: when aqueous ammonia (28-30%) is added to an ethyl acetate suspension of Cu<sup>I</sup>Cl, the water phase immediately turns deep blue, thus precluding the relevance of perchlorate in the oxidation of copper(I). When Cu<sup>I</sup>Cl is added to a stirred mixture of ethyl acetate and aqueous ammonia that has been purged with argon for 10 min, the solution turns from clear to a pale light blue. The minimal blue coloration could be attributed to minor oxidation of copper(I) by the residue O<sub>2</sub> in the solution. Two to three min after argon purging is terminated, the solution turns to a deep blue color, suggesting facile aerobic oxidation of the majority of, if not all, copper(I) to tetraammine copper(II) ions.
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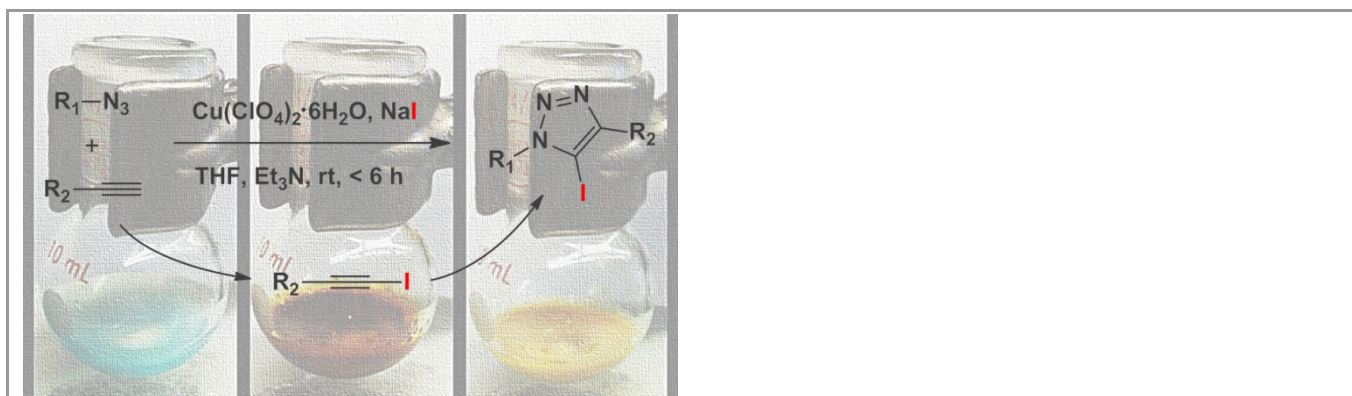
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### 5-Iodo-1,2,3-Triazole Synthesis



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