Synthesis of 5-Iodo-1,2,3-triazoles from Organic Azides and Terminal Alkynes: Ligand Acceleration Effect, Substrate Scope, and Mechanistic Insights

David N. Barsoum, Christopher J. Brassard, Jason H. A. Deeb, Najeah Okashah, Kesavapillai Sreenath, J. Tyler Simmons, Lei Zhu*

Department of Chemistry and Biochemistry, Florida State University, 95 Chieftan Way, Tallahassee, FL 32306-4390, USA
Fax +1(850)6448281; E-mail: lzhu@chem.fsu.edu

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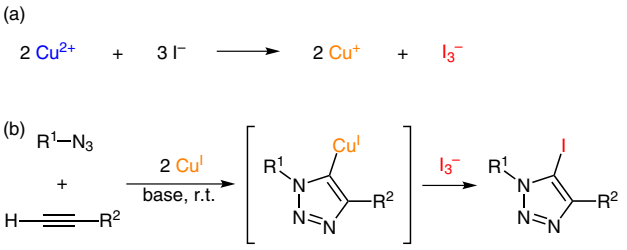
Abstract: An improved method has been developed for the preparation of 5-iodo-1,2,3-triazoles directly from organic azides and terminal alkynes by a reaction mediated by copper(I) and iodinating agents generated in situ. The major methodological advance of the current procedure is that it provides a high conversion and good iodo/proto selectivity with a broad range of substrates without using an excess of the alkyne, which was required in the previous method. The use of an accelerating ligand is essential to the success of reactions involving unreactive azides or alkynes. New mechanistic insights are provided, including the confirmation that a 1-iodoalkyne is formed as a key intermediate under the established conditions for the reaction.

Key words: azides, alkynes, copper, catalysis, heterocycles, cyclizations, triazoles, halogenation, iodine

1 Introduction

5-Iodo-1,2,3-triazoles are key intermediates in three-component reaction sequences involving azides, alkynes, and matching partners from a palladium-catalyzed cross-coupling process.[1,2] A state-of-the-art method for preparing 5-iodo-1,2,3-triazoles with a wide substrate scope under mild reaction conditions was reported by Hein, Fokin, and co-workers;[2] this method entails the activation of a terminal alkyne by formation of a 1-iodoalkyne that undergoes copper(I)-catalyzed cycloaddition with an azide (Scheme 1). The separate step of converting the terminal alkyne into a 1-iodoalkyne can be eliminated. To this end, several methods have been developed, before and after Hein and Fokin's work, by which 5-iodo-1,2,3-triazoles can be prepared directly from conjugating terminal alkynes and azides.[3–5] The usefulness of these direct conjugation methods is, however, limited because they involve corrosive iodinating agents, such as iodine chloride,[3] or oxidizing agents, such as *N*-bromosuccinimide.[4] Furthermore, the substrate scopes of these methods and their efficiencies in terms of reaction time and conversion do not yet rival those of Hein and Fokin's method.[2]

Our group has developed a method for preparing 5-iodo-1,2,3-triazoles from azides and terminal alkynes that is mediated by copper(I) species and triiodide ions generated in situ (Scheme 1).[6] The postulated mechanism is shown in Scheme 1. Copper(II) perchlorate hexahydrate reacts rapidly with sodium iodide to give copper(I) species and triiodide ions; the former catalyzes the cycloaddition of the azide and the terminal alkyne, and the latter iodinates the cuprous triazolide intermediate to give the corresponding 5-iodo-1,2,3-triazole.[6] A similar procedure was reported concurrently by Årstad and co-workers, who used ^{125}I from $Na^{125}I$ as a radioactive tracer in 5-iodo-1,2,3-triazoles for nuclear imaging applications.[7]



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

Azides that are capable of chelating a copper ion at the alkylated nitrogen position (chelating azides)[8,9] work well under our initially reported procedure. Other azides lacking this chelating ability appear to have inadequate reactivity, and often require an excess of the alkyne or, in two cases, the presence of an assisting ligand {tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA)}[10] to reach completion.[6] Here, we report an optimized method for the synthesis of 5-iodo-1,2,3-triazoles directly from an azide and an alkyne, which is more efficient than our previous procedure in terms of time, conversion, selectivity, and substrate scope.

The highlights of our current work are: (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 of the alkyne to convert unreactive azides is eliminated, enhancing the practicality of this method; and (3) the reaction time is reduced from twelve to six hours. In addition to achieving these improvements in the synthetic method, we have investigated the effects of various alkali iodides on both the conversion and selectivity, and we have examined the

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Biographical Sketches

Lei Zhu received his BS in chemistry from Peking University (P. R. of China) in 1997. He subsequently entered New York University (USA) for his graduate studies in chemistry under the mentorship of Professor James Canary. After defending his PhD dissertation in January 2003, Lei joined Professor Eric Anslyn's group at the University of Texas at Austin (USA) as a postdoctoral fellow. Upon completing his postdoctoral appointment, Lei began his independent career as an assistant professor in the Department of Chemistry and Biochemistry at Florida State University (USA) in August 2005 and was promoted to associate professor in 2011.

David N. Barsoum is attending Florida State University (USA) where he will obtain his BS in biochemistry in the fall of 2013. He has been working with Dr. Lei Zhu since January 2012. He enjoys merging art with chemistry, and he plans to continue research in graduate school in 2014.

Christopher J. Brassard is originally from Leominster, MA (USA). In 2001 he received his BS in biochemistry from Worcester Polytechnic Institute, Worcester, MA (USA). Upon completing his degree, he gained a full-time position with ArQule Inc., an oncology-based drug-discovery company. While he was there, he earned his Master's degree in chemistry from Northeastern University in Boston (USA). In 2011, he was accepted to the PhD program at Florida State University (USA), where he is conducting research under the guidance of Dr. Lei Zhu.

Jason H. A. Deeb is currently striving to earn his BS in biochemistry at Florida State University (USA). His fascination with the synthesis of organic compounds brought him to the Zhu group, and his research under the guidance of Dr. Lei Zhu began in May of 2012. After his projected graduation in 2014, he plans to obtain an MD and he believes that the knowledge that he has gained of organic compounds will aid him in his quest to understand the chemistry of the human brain.

Najeah Okashah is currently pursuing her BS in biochemistry at Florida State University (USA), and she will complete her degree in the spring of 2014. She has been working with Dr. Lei Zhu since June 2012. After her graduation, she is planning on continuing to do research and on pursuing an MD or PhD.

Kesavapillai Sreenath received his BSc (2000) and MSc degrees (2002) in chemistry from Kerala University (India). In 2010, he obtained his PhD from Kerala University under the supervision of Dr. Karical R. Gopidas. His research focuses on fluorescent molecules for bioimaging applications and on transition-metal-catalyzed organic reactions.

J. Tyler Simmons grew up in New Brockton, AL (USA), and received his BS in chemistry from Troy University (USA) in May 2008. Later that year, he joined the graduate program in chemistry at Florida State University (USA) and began his dissertation research under the guidance of Dr. Lei Zhu. Tyler's research is focused on copper-catalyzed organic reactions and on the development of fluorescent indicators for mapping biological zinc ions.

probable involvement of 1-iodoalkynes, formed in situ, as key intermediates. The conclusions of these studies collectively improve our knowledge of the mechanism of this reaction.

2 Results and Discussion

2.1 Choices of Azides and Alkynes

The alkynes and azides that we used are shown in Figure 1 and Figure 2, respectively. Our aim was to cover a wide range of functional groups and to generate sufficient data to be able to comment with confidence on the reactivities of various classes of compounds under our developed conditions. Both aliphatic and aromatic alkynes were examined. The effect of exchangeable protons on the iodo/proto selectivity was studied by using the carboxylic acids **Y6** and **Y10**[11] and the alcohol **Y1**. The methyl ketone **Y8** was included to determine whether the iodoform reaction competes with the formation of the 5-iodo-1,2,3-triazole.

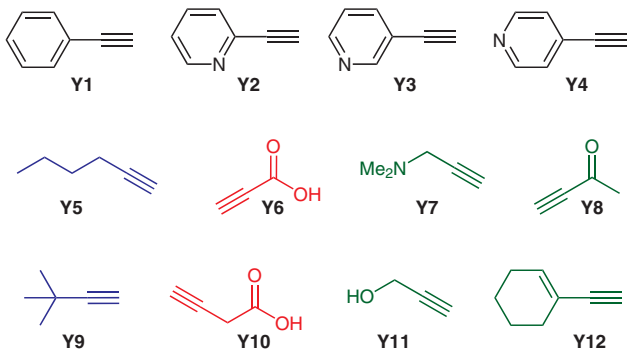


Figure 1 Aromatic (black), aliphatic (blue), carboxylated (red), and other functionalized alkynes (green).

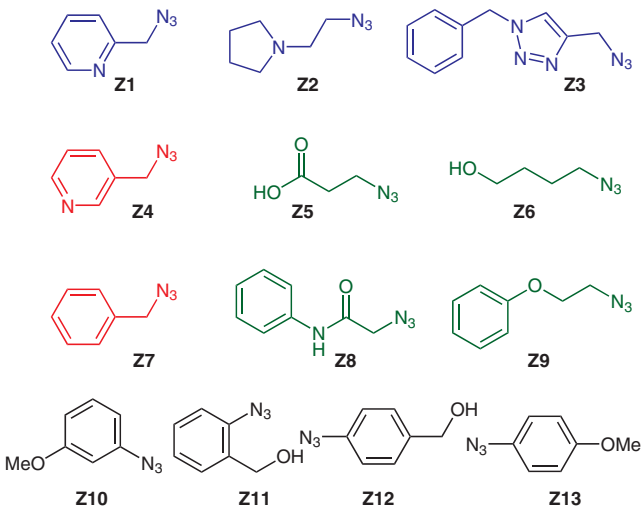


Figure 2 Chelating (blue), benzylic (red), aromatic (black), and functionalized aliphatic azides (green).

Among the azides that we examined, the chelating azides **Z1**–**Z3** were expected to be highly reactive on the basis of our previous observations on 2-(azidomethyl)pyridine (**Z1**).[6] **Z4** and **Z7** are benzylic azides that are also reasonably reactive substrates, possibly as a result of interaction between the aryl ring and copper(I) bound to the alkylated nitrogen of the azido group.[12] Aromatic azides **Z10**–**Z13** were included, as well as aliphatic azides (**Z5**, **Z6**, **Z8** and **Z9**) containing various functional groups, including carboxyl (**Z5**) and hydroxy groups (**Z6**).

2.2 Reaction Conditions and Isolation Procedures

The reaction conditions are listed in the caption to Scheme 2.[13] In a typical experiment, a solution of the azide in tetrahydrofuran or acetonitrile was treated by addition of solid copper(II) perchlorate hexahydrate and sodium, potassium, or lithium iodide. The reaction mixture then turned muddy brown, indicating the formation of I_2/I_3^- (Figure 3, center). If needed, the accelerating ligand TBTA was added at this stage. Triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the alkyne were added sequentially, and the mixture was stirred at room temperature. The azide could also be added after alkyne without any noticeable difference in the efficiency of the reaction. The disappearance of the azide, the limiting reactant, was monitored by thin-layer chromatography. Progress of the reaction was usually accompanied by fading of the dark-brown color of the initial reaction mixture (Figure 3).

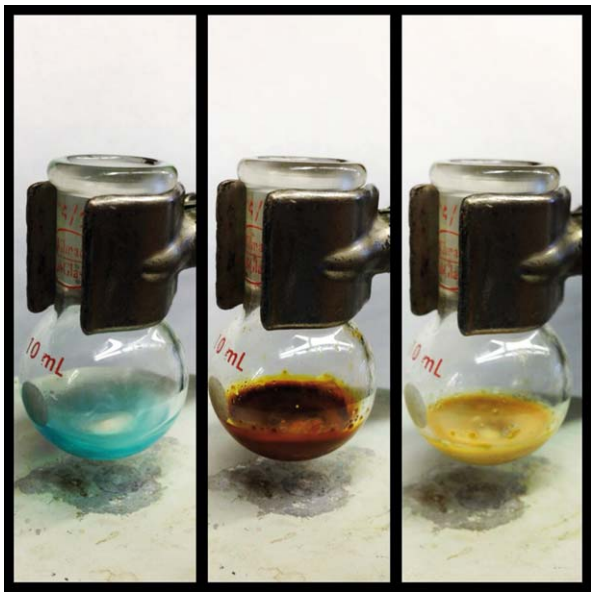
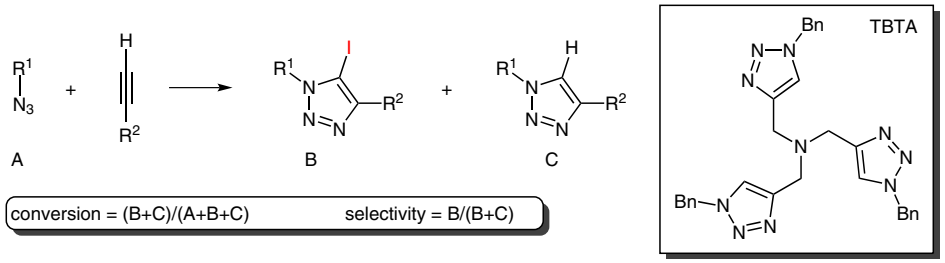


Figure 3 The colors of a reaction mixture of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.4 mmol) in THF (1 mL) in the initial state (left); immediately following the addition of NaI (0.8 mmol), Et_3N (0.2 mmol), and propargyl alcohol (0.22 mmol) (center); and 20 min after the addition of BnN_3 (0.2 mmol) (right).



Scheme 2 *Reaction conditions*: azide (A; 0.2 mmol); alkyne (0.22 mmol); THF or MeCN (1 mL); $Cu(ClO_4)_2 \cdot 6H_2O$ (0.4 mmol); Et_3N or DBU (0.2 mmol); NaI, KI, or LiI (0.8 mmol); r.t.; ≤6 h. TBTA was added (10 mol%) if required.

In most cases, the reaction proceeded to full conversion within six hours. Stoichiometric amounts of alkyne[14] were effective in the current procedure. This is a notable improvement over our previously reported procedure in which the use of an excess of the alkyne (2.5 equiv) was necessary to compensate for the low reactivity of certain substrates.[6] The ability to perform the reactions with equimolar amounts of the azide and the alkyne within a few hours greatly enhances the practicality of this method.

When the reaction was complete, ethyl acetate and 28–30% aqueous ammonia were added to dilute the reaction mixture. A deep-blue color immediately appeared as the copper(I) species were converted into tetraamine copper(II) ions under the aerobic conditions and sequestered to the aqueous phase.[15] For substrates containing a carboxyl group, a saturated solution of ammonium chloride was used instead of aqueous ammonia. After two more extractions with saturated brine, followed by drying, the ethyl acetate layer was concentrated to afford the crude product. The conversion and selectivity data are shown in Tables 1 and 2, and defined in Scheme 2, were calculated on the basis of ^{1}H NMR spectroscopic analysis of the crude products. In cases in which both the conversion and the iodo/proto selectivity were high, the product was isolated either by chromatography on a short column of silica gel or by a trituration procedure. The isolated yields are listed in Tables 1 and 2.

2.3 Reactions Not Requiring an Accelerating Ligand

The reactions that did not require an accelerating ligand to proceed are shown in Table 1. It is evident that all the entries of Table 1 involve either chelating (blue) or benzylic (red) azides that possess high reactivities under the developed conditions. All the reactions except one (entry 7) proceeded to completion within six hours. The reaction between 3-(azidomethyl)pyridine (**Z4**) and ethynylbenzene (**Y1**) took 24 hours to complete (entry 7), but was greatly accelerated by the addition of TBTA (see section 2.4). Both triethylamine and DBU worked well as the base, but triethylamine appeared to afford faster conversions than did DBU. Lithium, sodium, and potassium iodides could all be used as the iodine source with minor differences in reactivity, as discussed briefly in section 2.5.

Table 1 Examples of 5-Iodo-1,2,3-triazole Formation without Ligand Acceleration[a]

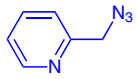
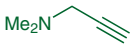
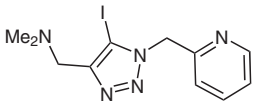
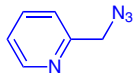
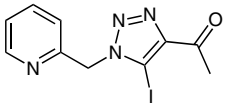
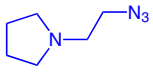
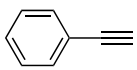
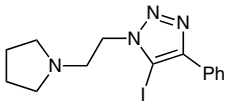
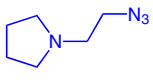
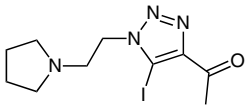
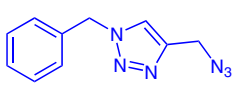
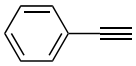
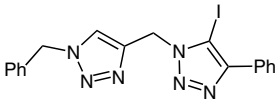
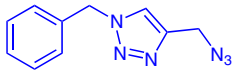
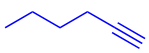
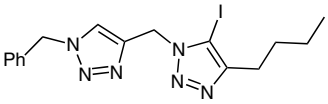
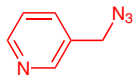
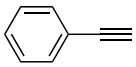
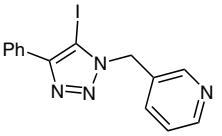
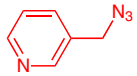
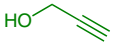
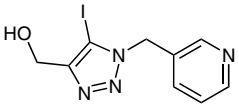
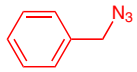
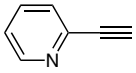
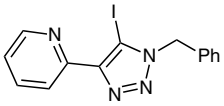
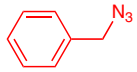
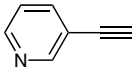
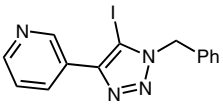
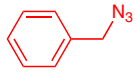
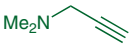
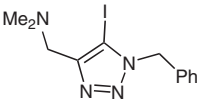
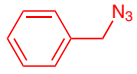
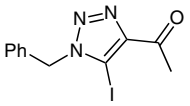
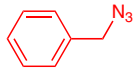
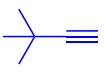
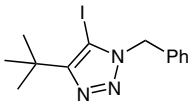
Entry	Azide	Alkyne	Product	Base	Iodide	Conversion[b] (%)	Time	Selectivity[b] (%)	Yield[c] (%)
1	 **Z1**	 **Y7**	 **1T7**	Et_3N	LiI	quant	0.5 h	85	44
2	 **Z1**	 **Y8**	 **1T8**	DBU	KI	quant	3 h	80	53
3	 **Z2**	 **Y1**	 **2T1**	Et_3N	KI	quant	1.5 h	100	69
4	 **Z2**	 **Y8**	 **2T8**	Et_3N	LiI	quant	1.5 h	88	31[d]

Table 1 Examples of 5-Iodo-1,2,3-triazole Formation without Ligand Acceleration[a] (continued)

Entry	Azide	Alkyne	Product	Base	Iodide	Conversion[b] (%)	Time	Selectivity[b] (%)	Yield[c] (%)
5	 **Z3**	 **Y1**	 **3T1**	DBU	KI	quant	4 h	100	86
6	 **Z3**	 **Y5**	 **3T5**	DBU	KI	quant	6 h	100	87
7	 **Z4**	 **Y1**	 **4T1**	Et_3N	NaI	quant	24 h	100	89
8	 **Z4**	 **Y11**	 **4T11**	Et_3N	NaI	quant	25 min	100	85
9	 **Z4**	 **Y2**	 **7T2**	DBU	KI	98	3 h	84	65
10	 **Z7**	 **Y3**	 **7T3**	DBU	KI	quant	3 h	100	72
11	 **Z7**	 **Y7**	 **7T7**	DBU	KI	quant	1 h	78	60
12	 **Z7**	 **Y8**	 **7T8**	DBU	KI	94	3 h	100	65
13	 **Z7**	 **Y9**	 **7T9**	DBU	KI	quant	3.5 h	100	57

[a] Reaction conditions: azide (0.2 mmol), alkyne (0.22 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.4 mmol), alkali metal iodide (0.8 mmol), base (0.2 mmol), THF (1 mL).
[b] The conversion and iodo/proto selectivity, as defined in Scheme 2, were calculated from ^1H NMR spectra of the crude products after extraction.
[c] Isolated yield.
[d] Compound **2T8** was not stable on a silica gel column or in $CDCl_3$.

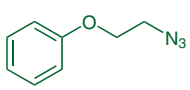
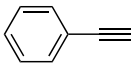
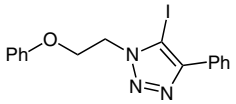
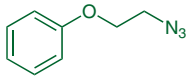
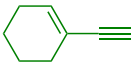
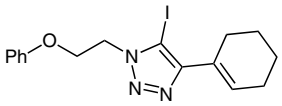
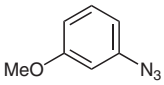
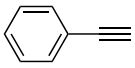
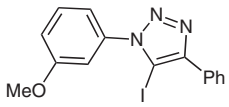
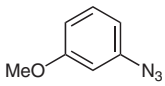
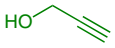
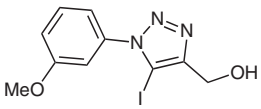
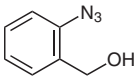
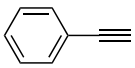
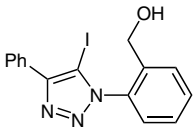
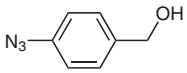
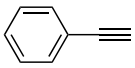
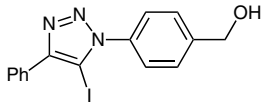
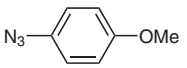
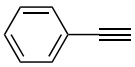
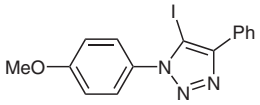
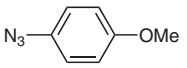
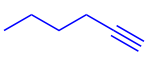
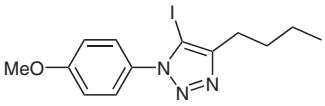
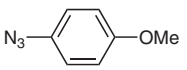
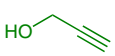
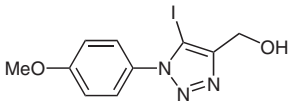
The products in entries 1 (**1T7**), 3 (**2T1**), and 7 (**4T1**) were reported in our previous work.[6] However, under the current conditions, the reaction times for entries 1 and 3 were reduced from 6 hours to 30–90 min. The isolated yield of **4T1** (89%, entry 7) was much higher than that previously reported (49%). In the presence of 10 mol% TBTA (Table 2, entry 1), the yield of **4T1** was increased further to 95% and the reaction time was reduced to 2.5 hours. These entries represent improvements in the current method over the earlier version.[6]

Most reactions show exclusive selectivity toward 5-iodo-1,2,3-triazoles over their 5-proto counterpart. However, the reactions involving 2-ethynylpyridine (**Y2**), *N*,*N*-dimethylpropargylamine (**Y7**), or but-3-yn-2-one (**Y8**) showed suboptimal iodo/proto selectivity. These three alkynes tend to undergo the typical copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) rapidly, probably because of the ability of the corresponding 1,2,3-triazole products to act as bidentate accelerating ligands for the CuAAC route. We will test this hypothesis in a future project.

Table 2 Reactions Aided Significantly by TBTA (10 mol%)[a]

Entry	Azide	Alkyne	Product	Solvent	Base	Iodide	Conv.[b] (%)	Time (h)	Selectivity[b] (%)	Yield[c] (%)
1	**Z4**	**Y1**	**4T1**	THF	DBU	NaI	quant	2.5	100	95
2	**Z5**	**Y5**	**5T5**	THF	Et_3N	KI	quant	6	100	64
3	**Z6**	**Y1**	**6T1**	THF	DBU	KI	quant	2.5	100	73
4	**Z7**	**Y4**	**7T4**	THF	Et_3N	KI	quant	6	100	75
5	**Z7**	**Y5**	**7T5**	THF	Et_3N	KI	quant	1	100	70
6	**Z7**	**Y6**	**7T6**	THF	Et_3N	LiI	quant	6	100	64
7	**Z8**	**Y5**	**8T5**	THF	DBU	KI	quant	6	89	76
8	**Z8**	**Y10**	**8T10**	THF	Et_3N	LiI	75	6	100	75

Table 2 Reactions Aided Significantly by TBTA (10 mol%)[a] (continued)

Entry	Azide	Alkyne	Product	Solvent	Base	Iodide	Conv.[b] (%)	Time (h)	Selectivity[b] (%)	Yield[c] (%)
9	 **Z9**	 **Y1**	 **9T1**	THF	Et_3N	NaI	quant	3	100	99
10	 **Z9**	 **Y12**	 **9T12**	THF	Et_3N	KI	71	6	94	53
11	 **Z10**	 **Y1**	 **10T1**	THF	Et_3N	KI	quant	1	100	93
12	 **Z10**	 **Y11**	 **10T11**	THF	Et_3N	KI	80	3	100	72
13	 **Z11**	 **Y1**	 **11T1**	THF	Et_3N	LiI	90	24	100	77
14	 **Z12**	 **Y1**	 **12T1**	MeCN	Et_3N	NaI	quant	12	100	55
15	 **Z13**	 **Y1**	 **13T1**	THF	Et_3N	KI	80	1	100	49
16	 **Z13**	 **Y5**	 **13T5**	THF	Et_3N	KI	80	6	100	75
17	 **Z13**	 **Y11**	 **13T11**	THF	Et_3N	KI	94	6.5	100	75

[a] Reaction conditions: azide (0.2 mmol), alkyne (0.22 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.4 mmol), TBTA (0.02 mmol, 10 mol%), alkali metal iodide (0.8 mmol), base (0.2 mmol), solvent (1 mL).

[b] The conversion and iodo/proto selectivity, as defined in Scheme 2, were calculated from the ^1H NMR spectra of the crude products after extraction.

[c] Isolated yield.

2.4 TBTA-Accelerated Reactions

The acceleratory effect of the ligand TBTA was suggested by a reviewer of our earlier paper,[6] which, after revision, included two reactions aided by TBTA. The current results demonstrate the scope of TBTA-accelerated reactions under the conditions shown in Scheme 2. The slow reaction of 3-(azidomethyl)pyridine (**Z4**) with ethynylbenzene (**Y1**) (Table 1, entry 7) was significantly accelerated by the addition of 10 mol% TBTA (Table 2, entry 1). In the absence of TBTA, the conversion of aromatic azides into 5-iodo-1,2,3-triazoles in less than 6 hours failed, but these reactions proceeded 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, were also readily converted into the 5-iodo-1,2,3-triazole products in the presence of TBTA (10 mol%). The iodo/proto selectivity was high, even with hydroxylated or carboxylated substrates (entries 2, 3, 6, 8, 12–14, and 17). For reactions involving carboxylated substrates, saturated ammonium chloride solution was used in the extraction step instead of aqueous ammonia, so that the carboxylic acid product was neutralized and sequestered into the organic solvent.

We have reported syntheses of **4T1** (entry 1) and **9T1** (entry 9) previously.[6] However, the isolated yields were only moderate (49% and 58%, respectively) in 12 hours, and an excess of the alkyne had to be used. In the current work, with the aid of TBTA (10 mol%), yields of over 95% were achieved within three hours in both cases from close-to-equimolar amounts of the azide and alkyne (a 10 mol% excess of the alkyne was used for convenience in monitoring the progress of the reaction by thin-layer chromatography).

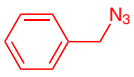
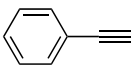
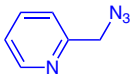
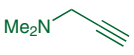
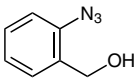
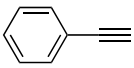
The reactions that required TBTA to achieve a high conversion generally gave the corresponding 5-iodo-1,2,3-triazole exclusively. For the two cases that showed less than 100% iodo/proto selectivity, we feel that the data pool is too small for us to attribute this observation to any structural feature of the substrates.

2.5 Effects of Alkali Iodides

The differences in reactivity between lithium, sodium, potassium, and cesium iodide in three sets of reactions were investigated (Table 3). Benzyl azide (**Z7**) and ethynylbenzene (**Y1**) were used as a typical pair of substrates without special functional groups (Table 3, entry 1), 2-(azidomethyl)pyridine (**Z1**) and *N*,*N*-dimethylpropargylamine (**Y7**) as a pair of reactive substrates that undergo rapid conversion *without* ligand acceleration (entry 2), and (2-hydroxymethyl)phenyl azide (**Z11**) and ethynylbenzene (**Y1**) as a pair of unreactive substrates that require the aid of TBTA (entry 3). Cesium iodide was the least productive iodide source in all three reactions. Lithium and sodium iodides gave consistently high conversions, probably as a result of their high solubilities in tetrahydrofuran.

Another notable observation is that the pair of reactive substrates (entry 2) underwent rapid conversion, but with impaired iodo/proto selectivity. This is a manifestation of the classical reactivity/selectivity relationship. In this reaction, the rapid conversion pathways to the 5-iodo-1,2,3-triazole and to the 5-proto-1,2,3-triazole compete, resulting in relatively low selectivity.

Table 3 The Alkali Cation Effect[a,b]

Entry	Azide	Alkyne	Conv., (time), selectivity (LiI)	Conv., (time), selectivity (NaI)	Conv., (time), selectivity (KI)	Conv., (time), selectivity (CsI)
1	 **Z7**	 **Y1**	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	 **Z1**	 **Y7**	100% (30 min) 87 ± 10%	100% (30 min) 85 ± 5.5%	100% (30 min) 78 ± 11%	100% (30 min) 40 ± 5.7%
3	 **Z11**	 **Y1**	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 order) alkyne (0.22 mmol), THF (1 mL), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.4 mmol), alkali metal iodide (0.8 mmol), TBTA (0.02 mmol, 10 mol%; entry 3 only), azide (0.2 mmol), r.t., 3 h (entry 1), 30 min (entry 2), or 6 h (entry 3).
[b] The conversion and iodo/proto selectivity, as defined in Scheme 2, were calculated from ^{1}H NMR spectra of the crude products. Average values and standard deviations for triplicate experiments are reported.

2.5 Mechanistic Discussion

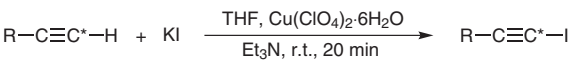
Rapid fading of the brown color of the reaction mixture is an indication that the reaction is progressing well. In a few cases, however, complete fading of the color preceded completion of the reaction. These observations led us to surmise that the formation of a 1-iodoalkyne may have occurred before the participation of azide. We found that ethynylbenzene is fully converted into (iodoethynyl)benzene within 20 minutes in the absence of an azide, under otherwise identical conditions. After filtering the reaction mixture through Celite[16] and removing the solvent, we recorded the ^{13}C NMR spectrum. The chemical shift of C* in the alkyne undergoes a large upfield shift, diagnostic of the formation of the 1-iodoalkyne (Table 4). The conversion of propargyl alcohol into 3-iodoprop-2-yn-1-ol occurs even in the absence copper(II) perchlorate hexahydrate (diiodine was used instead of potassium iodide),[17] although the reaction was less efficient. Therefore, 1-iodoalkynes are readily formed in the presence of a base such as triethylamine and an iodinating source such as diiodine. Consequently, under the conditions for synthesis of 5-iodo-1,2,3-triazoles, a 1-iodoalkyne might form before entering the catalytic cycle en route to 5-iodo-1,2,3-triazole. The addition of TBTA has little effect on the efficiency of formation of the 1-iodoalkyne under the conditions shown in the footnote to 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.

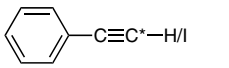
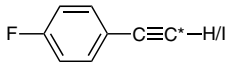
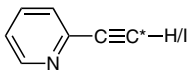
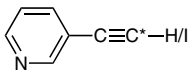
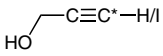
Although ^{13}C NMR spectroscopy is diagnostic in characterizing the 1-iodoalkyne intermediate, the inability to perform integration and the lengthiness of acquisition of the spectrum render it ineffective in following the progress of the reaction. ^{1}H NMR, on the other hand, is fast and quantitative. However, the differences in the ^{1}H NMR spectra of alkynes and 1-iodoalkynes are often small, and the alkynyl C–H signal is often obscured by solvent-residue peaks. ^{19}F NMR spectroscopy[18] has neither of the shortcomings of ^{13}C NMR, and it affords sufficiently clean spectra to permit unambiguous assignments and quantification of various species formed in a reaction.

The reaction between fluorinated alkyne **Y13** and benzyl azide (**Z7**) was monitored by ^{19}F NMR spectroscopy (Scheme 3). Aliquots of the reaction mixture were withdrawn at prescribed intervals. After I_2/I_3^- had been quenched by using a solution of sodium thiosulfate and the organic fraction had been passed through a pad of Celite in a Pasteur pipette, the sample was concentrated and redissolved in $CDCl_3$. The ^{19}F NMR spectra of the aliquots were acquired over the course of the reaction without TBTA [Figure 4 (A)]. At the one-hour mark, the majority of alkyne **Y3** had been converted into 1-iodoalkyne **3**, and the 5-iodo-1,2,3-triazole product **7T13** had begun to form. At the six-hour mark the experiment was terminated, at which point the conversion was 28%.

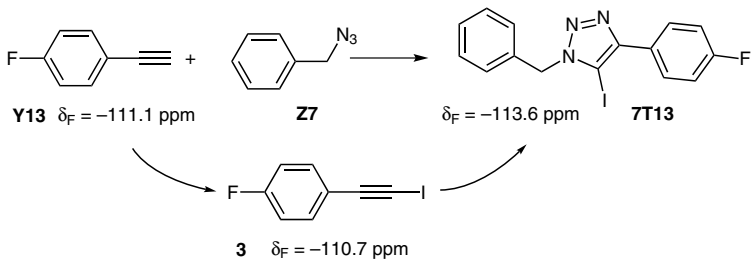
Conversion of **Y13** and **Z7** into product **7T13** was significantly accelerated in the presence of 10 mol% TBTA, reaching 95% after four hours [Figure 4 (B)]. The rapid formation of 1-iodoalkyne **3** was not affected by the presence of TBTA, and alkyne **Y13** was barely detectable after two hours. It is noteworthy that the sample collected at

Table 4 1-Iodoalkyne Formation Characterized from the ^{13}C NMR Chemical Shift[a]



Entry	Alkyne	$\delta_{C*(H)}$ (ppm)	$\delta_{C*(I)}$ (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	n-C_8H_{17}–C≡C*–H/I	68.2	−7.47

[a] Reaction conditions: (added in order) alkyne (0.22 mmol), THF (1 mL), $Cu(ClO_4)_2·6H_2O$ (0.4 mmol), KI (0.8 mmol), Et_3N (0.2 mmol), r.t., 20 min. The mixture was filtered through Celite and ^{13}C NMR (125 MHz, $CDCl_3$) spectra of the 1-iodoalkynes were acquired after solvent removal.



Scheme 3 A ^{19}F NMR assay to capture the 1-iodoalkyne intermediate **3**. The chemical shifts are referenced to $PhCF_3$ in $CDCl_3$. *Reagents and conditions*: azide **Z7** (0.4 mmol), alkyne **Y13** (0.4 mmol), THF (2 mL), $Cu(ClO_4)_2·6H_2O$ (0.8 mmol), KI (1.6 mmol), Et_3N (0.4 mmol). The reaction was repeated with the inclusion of TBTA (0.04 mmol, 10 mol%).

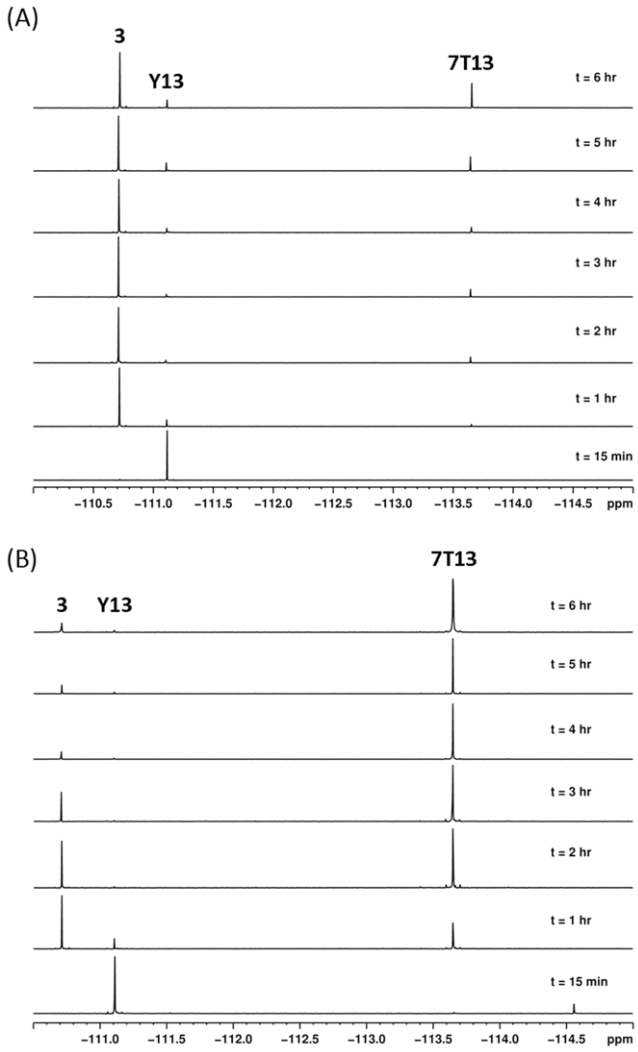
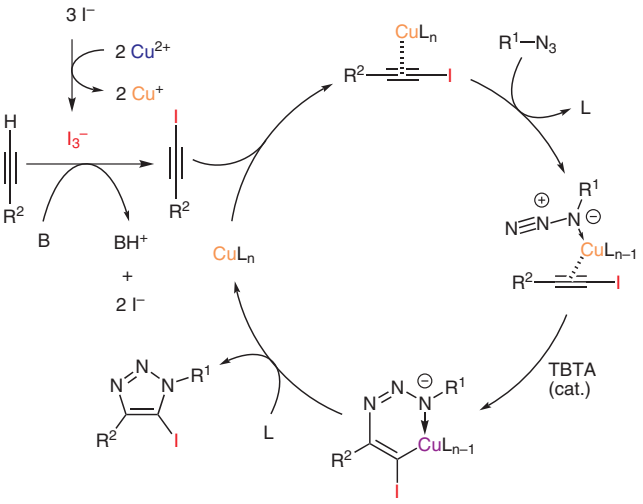


Figure 4 The progress of the reactions shown in Scheme 3: (A) without and (B) with TBTA (10 mol%). Aliquots of reaction mixture were drawn at prescribed intervals and ^{19}F NMR (376 MHz, $CDCl_3$) spectra were acquired.

the 15-minute mark contained a small amount of the5-proto-1,2,3-triazole side product ($\delta_F = -114.5$ ppm), which was probably formed during workup of the sample. From Figure 4 (B), it is evident that a large amount of alkyne starting material is still present 15 minutes into the reaction, and this might undergo a conventional TBTA-accelerated CuAAC reaction during the aqueous workup to afford the 5-proto-1,2,3-triazole. However, when conversion into the 1-iodoalkyne was complete after one hour, this side product was no longer observed.

On the basis of the rapid conversion of alkyne **Y13** into 1-iodoalkyne **3** observed in the ^{19}F NMR experiments (Figure 4), we conclude that the most appropriate mechanism is that outlined in Scheme 4, the catalytic component of which was first proposed by Hein, Fokin, and co-workers.[2] I_3^- generated in situ iodinates the alkyne to form the 1-iodoalkyne with the assistance of the base. Copper(I) subsequently catalyzes the conjugation step between the 1-iodoalkyne and the azide. On the basis of the comparison of the kinetic profiles for the reactions in the absence and presence of TBTA (Figure 4), it appears that TBTA specifically accelerates the azide/1-iodoalkyne cycloaddition step, presumably by activating the copper(I) species in similar way to that in which TBTA assists conventional CuAAC reactions.[8,10,19] The carbon−iodine bond remains intact throughout this mechanistic pathway. This pathway accounts for the high iodo/proto selectivity and is more plausible than the alternative route outlined in Scheme 1 (b), which has also been considered by Hein, Fokin, and co-workers,[2] by others,[3,5] and by us.[6]



Scheme 4 Outline of a mechanism involving a 1-iodoalkyne intermediate. The catalytic cycle component is adapted from the work by Hein, Fokin, and co-workers[2] (B = base). Orange, blue, and purple colors represent the +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 the Cu^{III} center in the intermediate is used for the purposes of electron bookkeeping. With a chelating azide or other reactive substrate, TBTA may not be required.

Although it is not implausible, it is hard to defend the presence of the cuprous triazolide intermediate in Scheme 1 (b), given the observed high iodo/proto selectivity without rigorous removal of water [there is crystalline water present in $Cu(ClO_4)_2 \cdot 6H_2O$]. If, for any reason, the 1-iodoalkyne is formed slowly or is unstable, formation of a copper(I) acetylide would occur competitively, channeling the reaction toward the typical CuAAC pathway and lowering the iodo/proto selectivity.

2.7 Recommended Procedure

The copper(II) perchlorate hexahydrate that was used in this work was dried at 40−70 °C in a vacuum oven overnight to remove adsorbed moisture (but not crystalline water), and subsequently stored in a dry keeper. The recommended procedure begins with dissolution of the azide in tetrahydrofuran to give a 0.2 M solution. LiI (4 equiv), $Cu(ClO_4)_2 \cdot 6H_2O$ (2 equiv), triethylamine (1 equiv), and the alkyne (1 equiv) are then added sequentially. If a non-chelating azide is used, we recommend that the ligand TBTA (10 mol%) is included to ensure that the conver-

sion occurs in a timely manner, usually no longer than six hours. When thin-layer chromatography indicates that conversion is complete, the reaction mixture is partitioned between ethyl acetate and aqueous ammonia to remove copper salts quickly and cleanly. After one or two extractions with saturated brine, followed by drying, the crude product obtained after solvent removal can be purified by column chromatography or by a trituration procedure to afford the analytically pure material.

The following variations may be made without compromising the efficiency of the reaction: (1) The azide can be added at the end, following the alkyne. (2) Acetonitrile is another effective solvent, in particular when the substrates have limited solubility in tetrahydrofuran. (3) Triethylamine can be replaced with DBU. (4) Sodium and potassium iodide, which are less expensive than LiI, are equally effective under most circumstances. (5) The workup procedure is dependent on the structure of the product. For example, if a carboxylic acid is being isolated, a saturated solution of ammonium chloride or an EDTA solution with an appropriate pH value shall be used instead of aqueous ammonia.

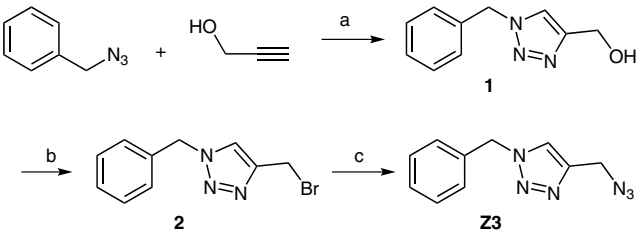
3 Conclusion

Coupling of an organic azide with a terminal alkyne in the presence of copper(II) perchlorate and an alkali metal iodide under mild conditions gives the corresponding 5-iodo-1,2,3-triazole. With the addition of the accelerating ligand TBTA (10 mol%), this procedure can tolerate a wide variety of functional groups, including carboxyl or hydroxy groups. Aliphatic and aromatic azides and alkynes can be readily converted into 5-iodo-1,2,3-triazoles with high to exclusive iodo/proto selectivity. Among alkali metal iodides, lithium and sodium iodide both afford consistently high conversions and iodo/proto selectivities. The intermediacy of a 1-iodoalkyne in this sequence of reactions was directly observed by ^{19}F NMR, and is consistent with a mechanism that involves the initial formation of a 1-iodoalkyne and in which the carbon–iodine bond remains intact throughout the cyclization steps to afford the 5-iodo-1,2,3-triazole. This mechanistic pathway best accounts for the observed high iodo/proto selectivity.[2] The minor 5-proto-1,2,3-triazole product that is occasionally observed is attributed to the conventional copper(I)-catalyzed azide–alkyne click cycloaddition reaction, which can compete when the substrate structures favor this route, or when the 1-iodoalkyne is formed slowly or is unstable.

CAUTION! Low-molecular-weight organic azides and copper(II) perchlorate hexahydrate used in this study are potentially explosive. Appropriate protective measures should always be taken when handling these compounds.

Reagents and solvents were purchased from various commercial sources and were used without further purification unless otherwise stated. BnN_3 of 94% purity was purchased from Alfa Aesar, which probably contributed to the lower-than-expected isolated yields from all reactions involving this reactant. $Cu(ClO_4)_2·6H_2O$ was dried in a vacuum oven at 40–70 °C overnight and stored in a dry keeper before use. Analytical TLC was performed on plates precoated with silica gel 60 F254 or neutral aluminum oxide 60 F254. Flash column chromatography was performed by using 40–63 μm (230–400 mesh ASTM) silica gel or alumina (80–200 mesh, pH 9–10) as the stationary phases. Before use, silica gel and alumina were flame-dried under vacuum to remove adsorbed moisture. ^1H NMR spectra were recorded at 500 or 300 MHz on Bruker and Varian spectrometers, respectively. ^{13}C NMR spectra were recorded at 125 or 75 MHz on Bruker and Varian spectrometers, respectively.^{19}F NMR spectra were recorded at 376 MHz on a 400-MHz Bruker spectrometer. The chemical shifts (δ) are reported in ppm relative to the residual $CHCl_3$ or CHD_2CN as internal standards.

4-(Azidomethyl)-1-benzyl-1*H*-1,2,3-triazole (*Z*3)
Triazole ***Z*3** was prepared according to Scheme 5.



Scheme 5 Synthesis of azide ***Z*3**. *Reagents and conditions*: (a) $Cu(OAc)_2·H_2O$ (5 mol%), *t*-BuOH, r.t., 16 h; (b) PBr_3, CH_2Cl_2, r.t., 4 h; (c) NaN_3, DMF, 50 °C, 16 h.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methanol (1)[20]
BnN_3 (80.7 mg, 0.606 mmol), $HC{\equiv}CCH_2OH$ (37 mg, 0.67 mmol), and *t*-BuOH (0.5 mL) were added sequentially to an argon-filled round-bottom flask. A 0.4 M aq soln of $Cu(OAc)_2·H_2O$ (75 μL, 5 mol% on BnN_3) was then added, and the mixture was stirred at r.t. for 16 h. The mixture was then separated by column chromatography (silica gel, 0–5% MeOH–CH_2Cl_2) to give a white amorphous solid; yield; 106 mg (93%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.39–7.35 (m, 3 H), 7.28–7.26 (m, 2 H), 5.50 (s, 2 H), 4.75 (s, 2 H), 2.30 (br s, 1 H).

1-Benzyl-4-(bromomethyl)-1*H*-1,2,3-triazole (2)
A round-bottom flask was charged with triazole **1** (388 mg, 2.05 mmol), CH_2Cl_2 (5.0 mL), and PBr_3 under argon (1.10 g, 4.09 mmol), and the mixture was stirred at r.t. for 4 h. The reaction was then quenched with H_2O (2 mL), and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude product was purified by chromatography (silica gel, 30% EtOAc–CH_2Cl_2) to give a white amorphous solid; yield; 382 mg (74%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1 H), 7.40–7.38 (m, 3 H), 7.29–7.26 (m, 2 H), 5.52 (s, 2 H), 4.55 (s, 2 H).

4-(Azidomethyl)-1-benzyl-1*H*-1,2,3-triazole (*Z*3)
Compound **2** (56 mg, 0.23 mmol), DMF (2.0 mL), and NaN_3 (297 mg, 4.57 mmol) were added sequentially to an argon-filled round-bottom flask, and the mixture was stirred at 50 °C overnight. The mixture was then diluted with EtOAc (50 mL) and washed with sat. aq NH_4Cl (3 × 50 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum to give a white amorphous solid; yield: 290 mg (39%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.39–7.37 (m, 3 H), 7.29–7.26 (m, 2 H), 5.54 (s, 2 H), 4.47 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.1, 134.3, 129.3, 129.0, 128.2, 122.2, 54.4, 45.7.

HRMS (CI): *m/z* [M + H]$^+$ calcd for $C_{10}H_{11}N_6$: 215.1045; found: 215.1042.

[(1-Benzyl-5-iodo-1*H*-1,2,3-triazol-4-yl)methyl]dimethylamine (7T7; Table 1, Entry 11); Typical Procedure Not Requiring TBTA Ligand

BnN_3 (**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 stirrer bar. To this soln, KI (132.8 mg, 0.80 mmol) and $Cu(ClO_4)_2·6H_2O$ (148.2 mg, 0.40 mmol) were added, and the mixture was stirred for 3−5 min. DBU (30.0 mg, 0.20 mmol) and $Me_2NCH_2C{\equiv}CH$ (**Y7**; 18.3 mg, 0.22 mmol) were then added sequentially and the mixture was stirred at r.t. for up to 6 h. The mixture was then diluted with EtOAc (50 mL) and 28−30% aq NH_3 (25 mL) then transferred to a separatory funnel. The organic layer was washed with sat. brine (2 × 25 mL), separated, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a crude product. The conversion and selectivity reported in Table 1 were calculated from the ^{1}H NMR spectrum of the crude product. The crude product was purified by chromatography (silica gel, 0−30% gradient EtOAc−CH_2Cl_2) to give an off-white amorphous solid; yield: 48 mg (60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35−7.32 (m, 3 H), 7.26−7.23 (m, 2 H), 5.60 (s, 2 H), 3.53 (s, 2 H), 2.29 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.8, 134.4, 128.9, 128.5, 127.7, 80.9, 54.2, 53.9, 45.3.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{16}IN_4$: 343.04196; found: 343.04157.

{[5-Iodo-1-(pyridin-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl]methyl}dimethylamine (1T7;[6] Table 1, Entry 1)

This was prepared by the typical procedure in 30 min using Et_3N and LiI instead of DBU and KI, respectively. White amorphous solid; yield: 30.0 mg (44%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 4.2 Hz, 1 H), 7.64 (t, *J* = 7.8 Hz, 1 H), 7.23 (t, *J* = 5.4 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 5.75 (s, 2 H), 3.56 (s, 2 H), 2.30 (s, 6 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 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]$^+$ calcd for $C_{11}H_{15}IN_5$: 344.03725; found: 344.03645.

2-[(1-Acetyl-5-iodo-1*H*-1,2,3-triazol-4-yl)methyl]pyridine (1T8; Table 1, Entry 2)

This was prepared by the typical procedure in 6 h as an off-white amorphous solid; yield: 35 mg (53%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60−8.58 (m, 1 H), 7.68 (t, *J* = 7.2 Hz, 1 H), 7.26 (s, 1 H), 7.00 (d, *J* = 7.8 Hz, 1 H), 5.80 (s, 2 H), 2.74 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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]$^+$ calcd for $C_{10}H_9IN_4ONa$: 350.97187; found: 350.97127.

5-Iodo-1-phenyl-4-(2-pyrrolidin-1-ylethyl)-1*H*-1,2,3-triazole (2T1; Table 1, Entry 3)[6]

This was prepared by the typical procedure in 1.5 h using Et_3N and NaI instead of DBU and KI, respectively. White amorphous solid; yield: 55 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 6.9 Hz, 2 H), 7.49−7.39 (m, 3 H), 4.60 (t, *J* = 7.5 Hz, 2 H), 3.03 (t, *J* = 7.4 Hz, 2 H), 2.64 (t, *J* = 6.5 Hz, 4 H), 1.81 (s, 4 H).

1-Acetyl-5-iodo-4-(2-pyrrolidin-1-ylethyl)-1*H*-1,2,3-triazole (2T8; Table 1, Entry 4)

This was prepared by the typical procedure in 1.5 h, using Et_3N and LiI instead of DBU and KI, respectively. Off-white amorphous solid; yield: 21 mg (31%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.56 (t, *J* = 7.2 Hz, 2 H), 2.98 (t, *J* = 7.2 Hz, 2 H), 2.70 (s, 3 H), 2.59 (m, 4 H), 1.78 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.4, 147.2, 82.3, 55.2, 54.5, 49.8, 27.8, 23.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{10}H_{15}OIN_4$: 334.02909; found: 334.02841.

1-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-5-iodo-4-phenyl-1*H*-1,2,3-triazole (3T1; Table 1, Entry 5)

This was prepared by the typical procedure in 4 h as an off-white amorphous solid; yield: 76 mg (86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.4 Hz, 2 H), 7.48−7.36 (m, 6 H), 7.26−7.24 (m, 3 H), 5.79 (s, 2 H), 5.50 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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 + Na]$^+$ calcd for $C_{18}H_{15}IN_6Na$: 465.03006; found: 465.02860.

1-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-4-butyl-5-iodo-1*H*-1,2,3-triazole (3T5; Table 1, Entry 6)

This was prepared by the typical procedure in 6 h as a white amorphous solid: yield: 73 mg (87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (s, 1 H), 7.37−7.35 (m, 2 H), 7.26−7.22 (m, 3 H), 5.67 (s, 2 H), 5.49 (s, 2 H), 2.63 (t, *J* = 7.2 Hz, 2 H), 1.69−1.59 (m, 2 H), 1.39−1.30 (m, 2 H), 0.92 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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]$^+$ calcd for $C_{16}H_{20}IN_6$: 423.07941; found: 423.07844.

[5-Iodo-1-(pyridin-3-ylmethyl)-1*H*-1,2,3-triazol-4-yl]methanol (4T11; Table 1, Entry 8)

This was prepared by the typical procedure in 15 min using Et_3N and NaI instead of DBU and KI, respectively. Off-white amorphous solid; yield: 54 mg (85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (s, 1 H), 8.60 (d, *J* = 4.5 Hz, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.30 (dd, *J* = 12.6, 3.1 Hz, 1 H), 5.62 (s, 2 H), 4.72 (d, *J* = 5.6 Hz, 2 H).

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

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_9H_{10}IN_4O$: 316.98993, found: 316.99071.

2-(1-Benzyl-5-Iodo-1*H*-1,2,3-triazol-4-yl)pyridine (7T2; Table 1, Entry 9)

This was prepared by the typical procedure in 3 h as a white amorphous solid; yield: 47 mg (65%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 4.2 Hz, 1 H), 8.12 (d, *J* = 7.8 Hz, 1 H), 7.74 (td, *J* = 7.8, 1.2 Hz, 1 H), 7.22−7.29 (m, 6 H), 5.67 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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* [M + H]$^+$ calcd for $C_{14}H_{12}IN_4$: 363.01066; found: 363.01111.

3-(1-Benzyl-5-iodo-1*H*-1,2,3-triazol-4-yl)pyridine (7T3; Table 1, Entry 10)

This was prepared by the typical procedure in 3 h as a white amorphous solid: yield: 60 mg (72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.21 (s, 1 H), 8.63 (d, *J* = 4.2 Hz, 1 H), 8.25 (d, *J* = 7.8 Hz, 1 H), 7.43−7.34 (m, 5 H), 7.26 (s, 1 H), 5.69 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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* [M + H]$^+$ calcd for $C_{14}H_{12}IN_4$: 363.0107; found: 363.0101.

1-(1-Benzyl-5-iodo-1*H*-1,2,3-triazol-4-yl)ethanone (7T8; Table 1, Entry 12)
This was prepared by the typical procedure in 3 h as a white amorphous solid; yield: 42 mg (65%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.30 (m, 5 H), 5.65 (s, 2 H), 2.71 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.4, 147.6, 133.8, 129.2, 129.0, 128.2, 81.9, 54.3, 27.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_{11}IN_3O$: 327.99468; found: 327.99360.

1-Benzyl-4-*tert*-butyl-5-iodo-1*H*-1,2,3-triazole (7T9; Table 1, Entry 13)
This was prepared by the typical procedure in 3.5 h as a white amorphous solid; yield: 40 mg (57%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33−7.32 (m, 5 H), 5.59 (s, 2 H), 1.46 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.2, 134.6, 128.8, 128.3, 127.8, 74.0, 54.1, 31.8, 29.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{17}IN_3$: 342.04675; found: 342.04656.

4-(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)butan-1-ol (6T1; Table 2, Entry 3); Typical Procedure Requiring TBTA Ligand
$HO(CH_2)_4N_3$ (**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 stirrer bar. KI (132.8 mg, 0.80 mmol), $Cu(ClO_4)_2·6H_2O$ (148.2 mg, 0.40 mmol), and TBTA (10.6 mg, 0.020 mmol) were added, and the soln was stirred for 3−5 min. DBU (30.0 mg, 0.20 mmol) and PhC≡CH (**Y1**, 22.5 mg, 0.22 mmol) were then added sequentially and the mixture was stirred at r.t. for up to 6 h. It was then diluted with EtOAc (50 mL) and 28−30% aq NH_3 (25 mL), and transferred to a separatory funnel. The organic layer was washed with sat. brine (2 × 25 mL), separated, and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product. The conversion and selectivity reported in Table 2 were calculated from the ^{1}H NMR spectrum of this crude product. The crude product was then purified by chromatography (silica gel, 0−20% gradient EtOAc−CH_2Cl_2) to give a white amorphous solid; yield: 62 mg (73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 6.6 Hz, 2 H), 7.50−7.40 (m, 3 H), 4.52 (t, *J* = 7.2 Hz, 2 H), 3.77−3.70 (m, 2 H), 2.14−2.03 (m, 2 H), 1.72−1.63 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.8, 130.3, 128.7, 128.6, 127.5, 76.4, 62.0, 50.7, 29.3, 26.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{15}IN_3O$: 344.02598; found: 344.02580.

3-[(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]pyridine (4T1; Table 2, Entry 1)[6]
This was prepared by the typical method in 2.5 h. NaI was used instead of KI. White amorphous solid; yield: 69 mg (95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (s, 1 H), 8.61 (d, *J* = 3.9 Hz, 1 H), 7.92 (d, *J* = 6.9 Hz, 2 H), 7.64 (d, *J* = 8.1 Hz, 1 H), 7.47−7.38 (m, 3 H), 7.32−7.30 (m, 1 H), 5.70 (s, 2 H).

3-(4-Butyl-5-iodo-1*H*-1,2,3-triazol-1-yl)propanoic Acid (5T5; Table 2, Entry 2)
This was prepared by the typical method in 6 h using Et_3N instead of DBU. Yellow amorphous solid; yield: 56 mg (64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.61 (t, *J* = 7.2 Hz, 2 H), 3.07 (t, *J* = 7.2 Hz, 2 H), 2.66 (t, *J* = 7.2 Hz, 2 H), 1.70−1.60 (m, 2 H), 1.43−1.33 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.3, 78.9, 46.3, 31.2, 29.9, 25.8, 22.5, 14.0, 1.2.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_9H_{15}IN_3O_2$: 324.02089; found: 324.02085.

4-(1-Benzyl-5-iodo-1*H*-1,2,3-triazol-4-yl)pyridine (7T4; Table 2, Entry 4)
This was prepared by the typical method in 6 h using Et_3N instead of DBU. White amorphous solid; yield: 74 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.70 (d, *J* = 6.0 Hz, 2 H), 7.94 (t, *J* = 4.8 Hz, 2 H), 7.37−7.30 (m, 5 H), 5.7 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.2, 147.2, 137.8, 133.9, 129.0, 128.7, 127.8, 121.1, 78.0, 54.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{12}IN$: 363.01066; found: 363.01026.

1-Benzyl-4-butyl-5-iodo-1*H*-1,2,3-triazole (7T5; Table 2, Entry 5)
This was prepared by the typical method in 1 h, but using 0.4 mmol of the limiting reactant, BnN_3; quantities of all other reagents were doubled accordingly. Et_3N was used instead of DBU. Beige amorphous solid; yield: 96 mg (70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35−7.33 (m, 3 H), 7.26−7.24 (m, 2 H), 5.57 (s, 2 H), 2.65 (t, *J* = 7.2 Hz, 2 H), 1.72−1.62 (m, 2 H), 1.41−1.33 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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* [M + H]$^+$ calcd for $C_{13}H_{17}IN_3$: 342.04671; found: 342.04605.

1-Benzyl-5-iodo-1*H*-1,2,3-triazole-4-carboxylic Acid (7T6; Table 2, Entry 6)
This was prepared by the typical method using Et_3N and LiI instead of DBU and KI, respectively. Sat. aq NH_4Cl (pH ~5) was used instead of aq NH_3 for extraction. White amorphous solid; yield: 45 mg (64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.34 (m, 3 H), 7.30−7.26 (m, 2 H), 5.66 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 133.7, 129.0, 128.8, 127.9, 101.8, 90.3, 55.6.

HRMS (EI): *m/z* [M − CO_2H]$^+$ calcd for $C_9H_7IN_3$: 284.0; found: 284.1. No molecular ion was found by EI, CI, or ESI ionization methods.

2-(4-Butyl-5-iodo-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (8T5; Table 2, Entry 7)
This was prepared by the typical method in 6 h as a white amorphous solid; yield: 59 mg (76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (br s, 1 H), 7.44 (d, *J* = 7.8 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.15 (t, *J* = 7.8 Hz, 1 H), 5.22 (s, 2 H), 2.71 (t, *J* = 7.2 Hz, 2 H), 1.76−1.66 (m, 2 H), 1.45−1.35 (m, 2 H), 0.95 (t, *J* = 7.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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* [M + H]$^+$ calcd for $C_{14}H_{18}IN_4O$: 385.05253; found: 385.05206.

[1-(2-Anilino-2-oxoethyl)-5-iodo-1*H*-1,2,3-triazol-4-yl]acetic Acid (8T10; Table 2, Entry 8)
This was prepared by the typical method in 6 h using Et_3N and LiI instead of DBU and KI, respectively. Sat. aq NH_4Cl (pH ~5) was used instead of aq NH_3 for extraction. Yellow oil; yield: 60 mg (75%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.56 (s, 1 H), 7.59 (d, *J* = 9.0 Hz, 2 H), 7.34 (t, *J* = 6.0 Hz, 2 H), 7.12 (t, *J* = 9.0 Hz, 1 H), 5.33 (s, 2 H), 3.62 (s, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.6, 163.5, 145.5, 138.4, 128.9, 123.8, 119.2, 86.0, 52.9, 32.1.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{11}IN_4NaO_3$: 408.97735; found: 408.97657.

5-Iodo-1-(2-phenoxyethyl)-4-phenyl-1*H*-1,2,3-triazole (9T1; Table 2, Entry 9)[6]
This was prepared by the typical method in 3 h using Et_3N and NaI instead of DBU and KI, respectively. White amorphous solid; yield: 78 mg (99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 8.4, 1.5 Hz, 2 H), 7.40−7.31 (m, 3 H), 7.29 (d, *J* = 7.5 Hz, 2 H), 6.97 (t, *J* = 7.4 Hz, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 4.87 (t, *J* = 5.8 Hz, 2 H), 4.48 (t, *J* = 5.7 Hz, 2 H).

4-Cyclohex-1-en-1-yl-5-iodo-1-(2-phenoxyethyl)-1*H*-1,2,3-triazole (9T12; Table 2, Entry 10)
This was prepared by the typical method in 6 h using Et_3N instead of DBU. Off-white amorphous solid; yield: 42 mg (53%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 7.5 Hz, 2 H), 6.96 (t, *J* = 7.4 Hz, 1 H), 6.87 (dd, *J* = 7.8, 1.0 Hz, 2 H), 6.42 (t, *J* = 1.9 Hz, 1 H), 4.78 (t, *J* = 5.9 Hz, 2 H), 4.41 (t, *J* = 5.8 Hz, 2 H), 2.55−2.51 (m, 2 H), 2.25−2.19 (m, 2 H), 1.81−1.75 (m, 2 H), 1.74−1.63 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 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* [M + H]$^+$ calcd for $C_{16}H_{19}IN_3O$: 396.05728; found: 396.05703.

5-Iodo-1-(3-methoxyphenyl)-4-phenyl-1*H*-1,2,3-triazole (10T1; Table 2, Entry 11)
This was prepared by the typical method in 1 h, but using Et_3N instead of DBU with 0.4 mmol of the limiting reactant azide **Z10**; quantities of all other reagents were doubled accordingly. White amorphous solid; yield: 141 mg (93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 1 H), 7.54−7.42 (m, 5 H), 7.16−7.10 (m, 3 H), 3.89 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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* [M + H]$^+$ calcd for $C_{15}H_{13}IN_3O$: 378.01033; found: 378.01095.

[5-Iodo-1-(3-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methanol (10T11; Table 2, Entry 12)
This was prepared by the typical method in 3 h using Et_3N instead of DBU. White amorphous solid; yield: 48 mg (72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (t, *J* = 7.8 Hz, 1 H), 7.20−7.04 (m, 3 H), 4.83 (d, *J* = 6.6 Hz, 2 H), 3.87 (s, 3 H), 2.30 (t, *J* = 6.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.4, 151.4, 137.8, 130.3, 118.3, 116.4, 111.8, 80.0, 56.9, 55.9.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{10}H_{10}IN_3O_2Na$: 353.97154; found: 353.97106.

[2-(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl]methanol (11T1; Table 2, Entry 13)
This was prepared by the typical method in 24 h using Et_3N and LiI instead of DBU and KI, respectively. White amorphous solid; yield: 58 mg (77%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 8.4, 1.5 Hz, 2 H), 7.73 (d, *J* = 6.7 Hz, 1 H), 7.63 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.55−7.45 (m, 4 H), 7.40 (d, *J* = 6.8 Hz, 1 H), 4.39 (d, *J* = 6.2 Hz, 2 H), 2.49 (t, *J* = 6.4 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 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]$^+$ calcd for $C_{15}H_{13}IN_3O$: 378.01033; found: 378.01160.

[4-(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl]methanol (12T1; Table 2, Entry 14)
This was prepared by the typical method in 6 h using MeCN, Et_3N, and NaI instead of THF, DBU, and KI, respectively. Light-orange amorphous solid; yield: 42 mg (55%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (dd, *J* = 6.2, 1.4 Hz, 2 H), 7.57−7.53 (m, 6 H), 7.47 (t, *J* = 5.7 Hz, 1 H), 5.45 (t, *J* = 5.9 Hz, 1 H), 4.64 (d, *J* = 5.8 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 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]$^+$ calcd for $C_{15}H_{13}IN_3O$: 378.01033; found: 378.01097.

5-Iodo-1-(4-methoxyphenyl)-4-phenyl-1*H*-1,2,3-triazole (13T1; Table 2, Entry 15)
This was prepared by the typical method in 1 h, but using Et_3N instead of DBU and 0.4 mmol of the limiting reactant, azide **Z13**; all other reagents were doubled accordingly. White amorphous solid; yield: 74 mg (49%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 2 H), 7.53−7.43 (m, 5 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 3.91 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 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]$^+$ calcd for $C_{15}H_{13}IN_3O$: 378.01033; found: 378.00982.

4-Butyl-5-iodo-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (13T5; Table 2, Entry 16)
This was prepared by the typical method in 6 h using Et_3N instead of DBU. Off-white amorphous solid; yield: 54 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 9.0 Hz, 2 H), 7.03 (d, *J* = 9.0 Hz, 2 H), 3.88 (s, 3 H), 2.73 (t, *J* = 7.9 Hz, 2 H), 1.79−1.69 (m, 2 H), 1.47−1.37 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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]$^+$ calcd for $C_{13}H_{17}IN_3O$: 358.04162; found: 358.04165.

[5-Iodo-1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methanol (13T11; Table 2, Entry 17)
This was prepared by the typical method in 6.5 h using Et_3N instead of DBU. White amorphous solid; yield: 49 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 9.0 Hz, 2 H), 7.05 (d, *J* = 9.0 Hz, 2 H), 4.81 (d, *J* = 6.6 Hz, 2 H), 3.90 (s, 3 H), 2.15 (t, *J* = 7.8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.2, 151.0, 129.7, 127.6, 114.5, 85.5, 55.6, 55.0.

HRMS (CI): *m/z* [M + H]$^+$ calcd for $C_{10}H_{11}O_2IN_3$: 331.98963; found: 331.98965.

1-Benzyl-4-(4-fluorophenyl)-5-iodo-1*H*-1,2,3-triazole (7T13)
This was prepared by the typical method in 6 h using Et_3N instead of DBU. Amorphous white solid; yield: 55 mg (71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94−7.89 (m, 2 H), 7.38−7.32 (m, 5 H), 7.18−7.12 (m, 2 H), 5.67 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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]$^+$ calcd for $C_{15}H_{11}FN_3I$: 378.9982; found: 378.9978.

^{19}F NMR Experiment

BnN_3 (**Z7**, 53 mg, 0.4 mmol), THF (2 mL), $Cu(ClO_4)_2 \cdot 6H_2O$ (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 containing a stirrer bar, and the mixture was stirred for ~5 min. Et_3N (40 mg, 0.4 mmol) and 4-fluoro-1-ethynylbenzene (**Y13**, 48 mg, 0.4 mmol) were then added, and the mixture was stirred at r.t. Aliquots of the mixture (~0.1 mL) were taken at various reaction times. The samples were diluted with EtOAc then added to a test tube containing aq $Na_2S_2O_3$ to quench the I_2. The organic layer was removed, passed through a Celite pad to remove Cu, and concentrated under reduced pressure. The residue was dissolved in $CDCl_3$ and one drop of $PhCF_3$ was added as a reference standard (−63.72 ppm). All spectra were acquired at 376 MHz at r.t.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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