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Synthesis of 5-Iodo-1,4-disubstituted-1,2,3-triazoles Mediated by in Situ Generated Copper(I) Catalyst and Electrophilic Triiodide Ion

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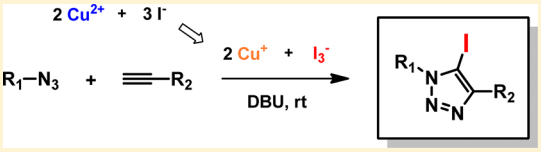
Supporting Information

ABSTRACT: Mixing copper(II) perchlorate and sodium iodide solutions results in copper(I) species and the electrophilic triiodide ions, which collectively mediate the cycloaddition reaction of organic azide and terminal alkyne to afford 5-iodo-1,4-disubstituted-1,2,3-triazoles. One molar equivalent of an amine additive is required for achieving a full conversion. Excessive addition of the amine compromises the selectivity for 5-iodo-1,2,3-triazole by promoting the formation of 5-proto-1,2,3-triazole. Based on preliminary kinetic and structural evidence, a mechanistic model is formulated in which a 5-iodo-1,2,3-triazole is formed via iodination of a copper(I) triazolide intermediate by the electrophilic triiodide ions (and possibly triethyliodoammonium ions). The experimental evidence explains the higher reactivity of the in situ generated copper(I) species and triiodide ion in the formation of 5-iodo-1,2,3-triazoles than that of the pure forms of copper(I) iodide and iodine.



INTRODUCTION

The copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC)[1,2] affords 1,2,3-triazoles under a vast array of conditions in high yields. It has, since its discovery, become one of the most applied organic reactions in this century in many areas of research.[3,4] Expansion of CuAAC into the synthesis of 5-iodo-1,2,3-triazoles (5-iodotriazole in the following text) and, by further elaboration, 1,4,5-trisubstituted 1,2,3-triazoles, has recently garnered much interest.[5] 5-Iodotriazole was observed as a byproduct in CuAAC reactions where copper(I) iodide (CuI) was used as a catalyst.[6,7] Wu et al.[8] reported the first synthesis of 5-iodotriazole through a "one-pot" reaction strategy (Scheme 1A). Based on the mechanism of the CuAAC reaction proposed by Fokin et al.,[1,4] Wu and co-workers suggested that the copper(I) triazolide intermediate could be trapped by the electrophilic iodine monochloride (ICl) to afford 5-iodotriazole. Other one-pot methods have since been developed on the basis of the same mechanistic hypothesis to prepare 5-iodotriazoles (e.g., see Scheme 1B), and other 1,4,5-trisubstituted triazoles.[9−11]

More recently, Hein, Fokin, and co-workers reported the synthesis of 5-iodotriazole from the CuI-catalyzed cycloaddition of 1-iodoalkyne and organic azide (iCuAAC)[13] in the presence of an assisting ligand such as tris((1-benzyl-1*H*-1,2,3-triazolyl)-methyl)amine (TBTA) or tris((1-*tert*-butyl-1*H*-1,2,3-triazolyl)-methyl)amine (TTTA, Scheme 1C).[12] With low catalyst loadings (5 mol %) and short reaction times (6 h), 5-iodotriazoles were produced in good yields (73−99%). Further optimization led to a "one-pot" method that entailed the sequential formations of 1-iodoalkyne and 5-iodotriazole.[13]

We are motivated to prepare 5-iodotriazoles by their promises as substrates of palladium-catalyzed cross-coupling reactions[12−14] and subjects to study halogen bonding[15,16] in the context of supramolecular chemistry.[17] As demonstrated by others, 5-iodotriazoles could couple with arylboronic acids, alkenes, and terminal alkynes via Suzuki, Heck, and Sonogashira reactions, respectively.[12,14] Functionalization of 5-iodotriazolyl-containing macrocycles via palladium-catalyzed means was also achieved.[18] Additionally, Rowan and co-workers applied a palladium-mediated approach to fusing two 5-iodotriazolyl moieties, which afforded compounds of extended aromaticity.[19] On the supramolecular chemistry front, 5-iodotriazolium has become an attractive component in aiding anion recognition.[17,20]

Our investigation in 5-iodotriazole synthesis started with the observation that the CuI-catalyzed cycloaddition of 2-picolyl azide with 1-iodoalkynes gave 5-iodotriazoles without an *extra* assisting ligand, which was considered essential in the original report by Fokin et al. A "one-pot" method was subsequently developed that allowed for the formation of 5-iodotriazoles from terminal alkynes without the separate synthesis of the 1-iodoalkyne substrates. In our method, copper(I) catalyst and the electrophilic triiodide ion (I_3^-) are formed in situ via the reduction of copper(II) salts by NaI (Scheme 2, right). The copper(I) species catalyzes the iCuAAC reaction, while I_3^- (and likely also triethyliodoammonium ion), rather than iodine (I_2), iodinates the copper(I) triazolide intermediate to afford a 5-iodotriazole. This in situ approach to producing copper(I) species mirrors the Fokin/Sharpless CuAAC conditions where the copper(I) catalyst emerges via the reduction of $CuSO_4$ by sodium ascorbate (Scheme 2, left). A mechanistic model is presented based on the kinetic and structural evidence.

RESULTS AND DISCUSSION

"Assisting Ligand-Free" Synthesis. 1-Iodoalkynes were prepared following a procedure described in the literature.[21] The reaction between 2-picolyl azide and 1-iodo-2-phenylethyne

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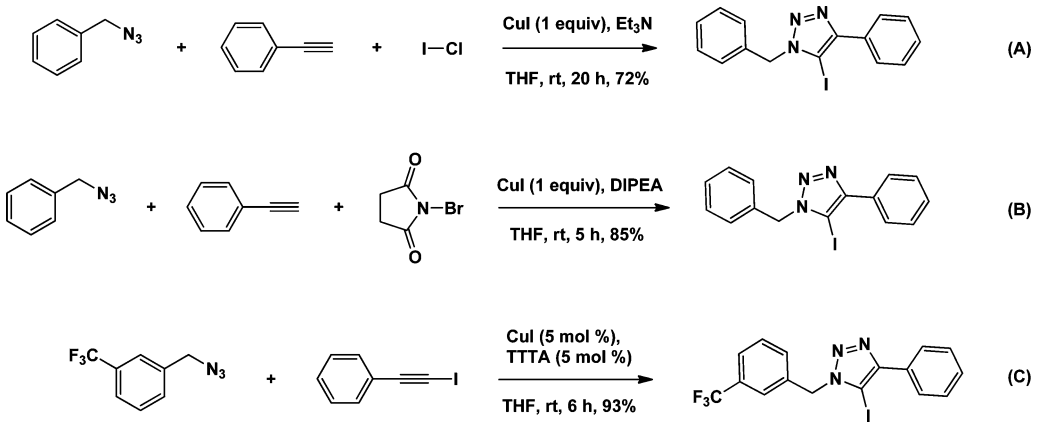
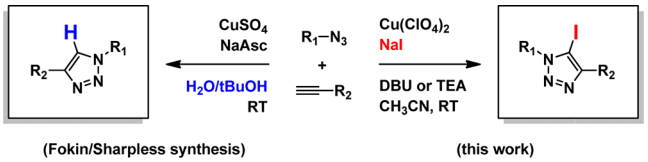
Scheme 1. Selected Methods To Prepare 5-Iodotriazoles: (A) Reaction Reported by Wu et al.[8] in Which ICl is the Iodinating Agent; (B) Reaction Reported by Zhang et al.[9] in Which the Iodinating Agent Results from the Reaction of NBS and CuI; (C) Reaction Reported by Hein, Fokin, et al.[12]



Scheme 2. Methods of in Situ Copper(I) Generation, Which Leads to the Formation of 5-Prototriazoles (Left) and 5-Iodotriazoles (Right), Respectively



(**1a**) under the catalysis of CuI in THF, with no *additional* assisting ligand, proceeded to completion in 90% yield of 5-iodotriazole **1** in 4 h (Scheme 3). Under these conditions, Hein, Fokin, and co-workers reported no reaction starting with other azides in the absence of an amine ligand such as triethylamine (TEA) or TTTA.[12] In our case, the chelating[22] 2-picolyl azide and/or product **1** might act as "build-in" assisting ligands. $Cu(OAc)_2$, which mediates the CuAAC reactions involving 2-picolyl azide exceptionally well,[22,23] showed a moderate reactivity under otherwise identical conditions to afford 5-iodotriazole **1** in 41% after 2 days.

Under the same conditions, the reactions between several other 1-iodoalkynes and 2-picolyl azide afforded 5-iodotriazoles in moderate to good yields (55−84%, Table 1). The reactions involving 4-(iodoethynyl)anisole (**2a** in entry 2, Table 1) and 3-iodo-*N*,*N*-dimethylpropargylamine (**6a** in entry 6, Table 1) did not go to completion. No 5-iodotriazole product was isolated using 4-iodoethynyl-*N*,*N*-dimethylaminobenzene (**7a**). The three inefficient 1-iodoalkynes (**2a**, **6a**, and **7a**) are relatively electron-rich and, hence, are weak iodinating agents in trapping the copper(I) triazolide intermediate in the Cu/I exchange step to afford 5-iodotriazole.[12] The limited scope of 1-iodoalkyne substrates in conjunction with the occasional difficulty in handling 1-iodoalkynes[7] prompted us to explore alternative methods to access 5-iodotriazoles starting from stable terminal alkynes.

Multicomponent Reaction To Generate 5-Iodotriazoles. In the previously reported methods for preparing 5-iodotriazoles, a corrosive iodinating agent, such as ICl,[8] or additional synthesis of unstable 1-iodoalkynes[12] is required. Herein, we report a simple and economical method for the selective formation of 5-iodotriazoles starting from organic azide and terminal alkyne, mediated by in situ generated copper(I) catalyst and iodinating reagent from readily available copper(II) salts and NaI.[25]

(a) In Situ Generation of CuI and I_2 (and I_3^-). More than half a century ago, Kauffman and Pinnell[26] found that copper(II) sulfate reacts with potassium iodide to afford copper(II) iodide (eq 1), which decomposes immediately to yield CuI and I_2 (eq 2).

$$CuSO_4 + 2KI \rightarrow K_2SO_4 + CuI_2 \quad (1)$$

$$2CuI_2 \rightarrow 2CuI + I_2 \quad (2)$$

$$I_2 + I^- \rightleftharpoons I_3^- \quad (3)$$

Inspired by this work, copper(II) perchlorate and sodium iodide (NaI) were used to generate CuI and I_2, in which CuI catalyzes the cycloaddition of azide and alkyne, while I_2 may intercept the copper(I) triazolide intermediate to afford a 5-iodotriazole. In the presence of surplus I^-, I_3^- forms (eq 3), which is also an electrophilic iodinating agent, for instance, in iodoform reactions. Reactions 1−3 complete within seconds after mixing the reactants, which can be considered instantaneous. The production of I_2 and I_3^-, as well as the reduction of copper(II), can be monitored conveniently using absorption spectroscopy (Figure S1, Supporting Information).

In the 5-iodotriazole formation reactions described in this paper, 2 molar equiv of copper(II) salt (0.4 mmol in the captions of Tables 1−5) were used relative to the limiting agent azide (0.2 mmol) because the molar ratio between copper(II) and I_2 (or I_3^-) is 2:1 as shown in eqs 1−3, and 1 molar equiv of I_2 or I_3^- is needed for the formation of 5-iodotriazole. NaI (4 molar equiv relative to the azide) was used, which ensures that all of the formed I_2 would be converted to I_3^- (eq 3), a potent iodinating reagent. The reaction stoichiometry is later depicted in the proposed mechanistic cycle (Scheme 4).

(b) Effect of a Base Additive. We selected 2-picolyl azide as the organic azide component in the initial investigation of the variables of the reaction conditions, because the self-acceleratory effect of 2-picolyl azide significantly shortens the conversion time. The scope of organic azides under the optimized conditions is shown in Table 6 and is elaborated in associated discussions.

The formation of 5-iodotriazole **1** from 2-picolyl azide and phenylacetylene in THF in the presence of $Cu(ClO_4)_2$ and NaI (Table 2, entry 1) was observed after 6 h in a low yield (19%).

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Scheme 3. Reaction of 2-Picolyl Azide with 1-Iodo-2-phenylethyne (1a) To Afford Compound 1

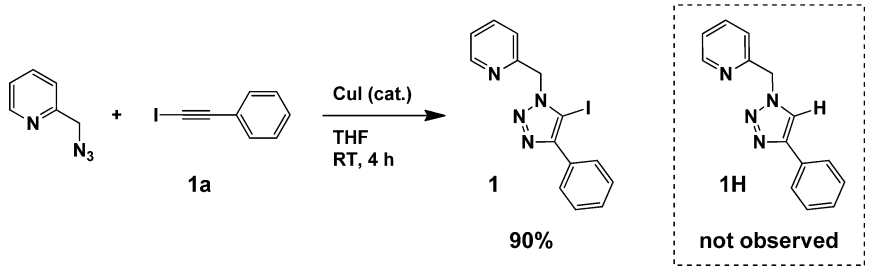
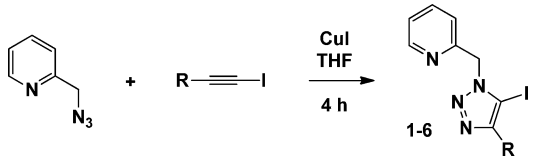


Table 1. "Ligand-Free"[24] Synthesis of 5-Iodotriazoles Using 2-Picolyl Azide and 1-Iodoalkynes[a]



entry	1-iodoalkyne	5-iodotriazole	isolated yield (%)
1	1a	**1**	90
2	2a	**2**	62[b]
3	3a	**3**	77
4	4a	**4**	84
5	5a	**5**	73
6	6a	**6**	55[b]
7	7a	-	NR[c]

[a]Reaction conditions: 2-picolyl azide (0.4 mmol), 1-iodoalkyne (0.5 mmol), CuI (5 mol %), THF (2 mL), rt, 4 h. [b]Reaction did not go to completion. [c]NR: no reaction.

With the addition of 1 equiv of triethylamine (TEA, entry 3), the yield increased to 97%. Excessive inclusion of TEA led to the formation of the undesired 5-proto-1,2,3-triazole (5-prototriazole in the following text) **1H** (entry 4).[28] No other side products were observed in these reactions. At 1 molar equiv, diethylamine (entry 5), DMAP (entry 7),[29] and DBU (entry 8) showed results comparable to those of TEA. The inorganic base Na_2CO_3 showed selectivity for **1** over **1H** with a moderate conversion (68%, entry 9). Mixing Na_2CO_3 with 0.5 equiv of TEA resulted in a complete conversion and selectivity for 5-iodotriazole **1** (entry 10).

It appears that an amine base is required for achieving a high conversion. The excessive addition of the amine may lead to the accumulation of its conjugated acid from deprotonating the alkyne reactant. The conjugate acid ammonium ion as a protonating agent competes with the iodinating reagent for the copper(I) triazolide intermediate, thus compromising the iodo/proto (**1**/**1H** in Table 2) selectivity. In addition to being a base, the amine additive may act as a nucleophilic catalyst to activate I_2 to the more electrophilic iodinating reagent triethyliodoammonium ion, as suggested by Heaney et al.,[30] and triiodide (eq 4). The addition of TEA into an CH_3CN solution of I_2 results in the formation of I_3^- as observed in the absorption spectra (Figure S2A, Supporting Information) and downfield shifts of TEA hydrogen peaks in ^1H NMR (Figure S2B, Supporting Information), supporting the occurrence of the reaction shown in eq 4.

$$Et_3N + 2I_2 \rightleftharpoons Et_3\overset{+}{N} - I + I_3^- \quad (4)$$

(e) Solvent Effect. Various solvents were evaluated in the reaction shown in Table 3 using TEA as the additive. The selectivity for 5-iodotriazole over 5-prototriazole (iodo/proto selectivity) was observed in all solvents. The reactions in noncoordinating solvents (toluene and CH_2Cl_2, entries 1 and 3, respectively)[31] were sluggish. The ability of solvent to stabilize copper(I) oxidation state affects the outcome of the reaction. For example, copper(I) ion in water has a high propensity to disproportionate,[32] which likely contributed to the low isolated

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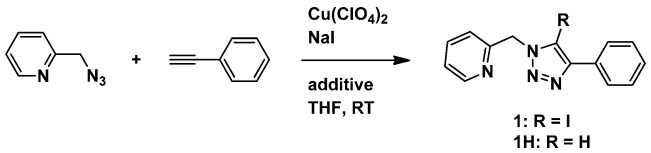
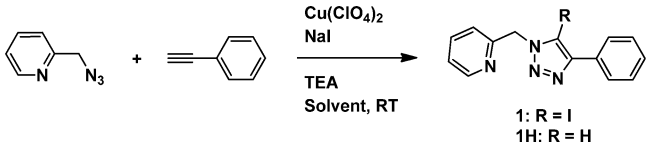
Table 2. Additive Effect on the Synthesis of 5-Iodotriazole 1[a]



entry	additive (pK_a)[b]	equiv	1/1H	isolated yield of 1 (%)
1	none		1:0	19[d]
2	TEA (9.0)	0.5	3.5:1	68[d]
3	TEA (9.0)	1.0	1:0	97
4	TEA (9.0)	1.5	9:1	84
5	Et_2NH (9–10)[e]	1.0	1:0	91
6	pyridine (3.4)	1.0	3.5:1	79
7	DMAP (9.2)	1.0	1:0	96
8	DBU (12)	1.0	1:0	90
9	Na_2CO_3 (10)[f]	1.0	1:0	68[d]
10	TEA/Na_2CO_3	0.5/5.0	1:0	96

[a]2-Picolyl azide (0.2 mmol), phenylacetylene (0.23 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.4 mmol), NaI (0.8 mmol), THF (1 mL), rt, 6 h. [b]pK_a of the conjugate acid in DMSO[27] is shown in parentheses. [c]Iodo/proto selectivity: product ratio ([1]/[1H]) determined by ^1H NMR. [d]Reaction did not go to completion. [e]Estimated to be 9–10. The value is not listed in the Evans pK_a table.[27] [f]pK_a in water.

Table 3. Solvent Effect on the Formation of 5-Iodotriazole 1[a]



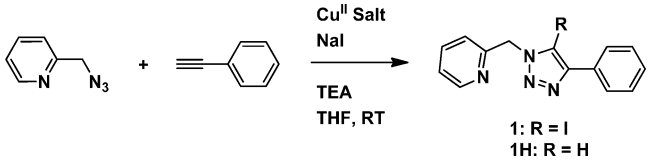
entry	solvent	1/1H[b]	isolated yield of 1 (%)
1	toluene	2:1	58
2	EtOAc	1:0	74
3	CH_2Cl_2	1:0	44[c]
4	THF	1:0	97
5	acetone	1:0	90
6	CH_3CN	1:0	93
7	DMF	1:0	86
8	2-propanol	13:1	40[c]
9	methanol	1:0	68[c]
10	water	2:1	23[c]

[a]2-Picolyl azide (0.2 mmol), phenylacetylene (0.23 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.4 mmol), NaI (0.8 mmol), TEA (0.2 mmol), solvent (1 mL), rt, 6 h. [b]Product ratio was determined by ^1H NMR. [c]Reaction did not go to completion.

yield in water (entry 10). In acetone (entry 5) and CH_3CN (entry 6),[33] copper(I) is stabilized. Consequently, high isolated yields were achieved.

(d) Reactivity of Copper(II) Salt. Various copper(II) salts were treated with NaI to convert to copper(I) with different catalytic activities (Table 4). Copper(II) perchlorate[34] and copper(II) triflate (Table 4, entries 1 and 5), which contain weakly coordinating anions, resulted in facile conversion and excellent iodo/proto selectivity. The in situ generated copper(I) catalyst and iodinating reagent were more reactive than the pure forms of CuI and I_2 (entry 6). The low reactivity of the CuI/I_2 combination in the syntheses of 5-iodotriazoles has also been observed by others.[8,9]

Table 4. Effect of Copper(II) Salt in the Formation of 5-Iodotriazole 1[a]



entry	copper source	1/1H[b]	isolated yield of 1 (%)
1	$Cu(ClO_4)_2$	1:0	97
2	$CuSO_4$	4.5:1	87
3	$CuCl_2$	16:1	82
4	$Cu(OAc)_2$	4:1	70
5	$Cu(CF_3SO_3)_2$	13:1	89
6[c]	CuI/I_2	13:1	55[d]

[a]2-Picolyl azide (0.2 mmol), phenylacetylene (0.23 mmol), copper(II) salt (0.4 mmol), NaI (0.8 mmol), TEA (0.2 mmol) THF (1 mL), rt, 6 h. [b]Product ratio determined by ^1H NMR. [c]CuI (0.2 mmol), I_2 (0.2 mmol). [d]Reaction did not go to completion.

(e) Scope of Terminal Alkyne. A number of terminal alkynes were subjected to the optimized conditions, which include $Cu(ClO_4)_2$ as the copper(II) source, TEA or DBU as the amine additive, and THF or CH_3CN as the solvent in reactions with 2-picolyl azide (Table 5). The reactions proceeded to give 5-iodotriazole exclusively, with the exceptions of entries 2 and 4, in which iodo/proto selectivities were 4:1 and 3:2, respectively. Compound **6** (entry 4) was produced from *N,N*-dimethylpropargylamine in 51% yield, which is comparable with that afforded from the 1-iodoalkyne substrate (Table 1, entry 6). The iodo/proto selectivity of entry 5 was not hindered by the hydroxyl-containing alkyne substrate (propargyl alcohol), indicating that the iodination outcompetes the protonation of the copper(I) triazolide intermediate by an alcohol. Notably, compound **9** (entry 7) was isolated in 84% yield, while the related reaction using 1-iodoalkyne (Table 1, entry 7) failed to occur. Using 2 equiv of 2-picolyl azide in the presence of 1,3-diethynylbenzene gave the bisiodotriazole compound **12** (entry 10), which is similar to a recently reported molecule prepared via a 1-iodoalkyne intermediate.[19] A comparable isolated yield was achieved using the current method, which avoided the synthesis of 1-iodoalkyne, and consequently shortened the reaction time.

(f) X-ray Single-Crystal Structure of 5-Iodotriazole 1. Single crystals of compound **1** suitable for X-ray diffraction were obtained upon cooling a hot CD_3CN solution of **1** to room temperature (Figure 1). The dihedral angle between the planes of 5-iodotriazolyl and phenyl moieties is 20.1°. The crystal packing reveals several $\pi-\pi$ interactions that vertically stack the molecules. An intermolecular interaction between the pyridyl nitrogen and the iodo substituent of an adjacent molecule was observed (Figure 1), with a N1–I1 distance of 2.879 Å and an N1–I1–C1 angle of 168.43°. This interaction can be classified as "halogen bonding", where a halogen atom on an electron-deficient aromatic ring interacts with the lone pair electrons of an electronegative atom in a similar manner to hydrogen bonding.[16] There is also a secondary interaction between the N2 nitrogen and the iodo-substituent (N2–I1: 3.800 Å), which forces the pyridyl group slightly off the plane of the 5-iodotriazolyl, and the C2–N1–I1 angle (105°) from the expected 120°. To our knowledge, this is the first observation of halogen bonding in the solid-state structures of 5-iodotriazoles

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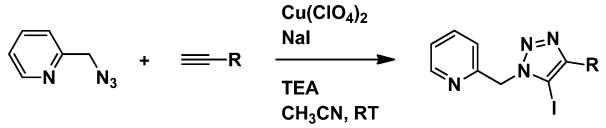
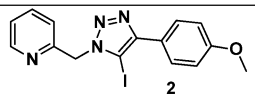
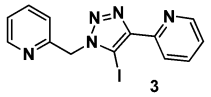
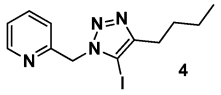
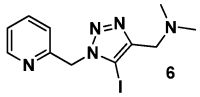
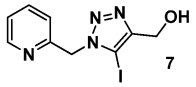
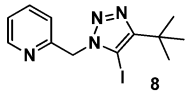
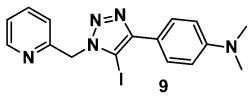
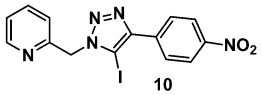
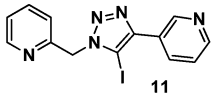
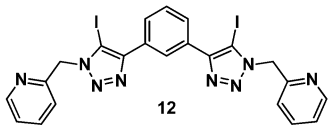
Table 5. 5-Iodotriazole Synthesis Applying Various Terminal Alkyne Molecules[a]



entry	product structure	isolated yield (%)
1	 2	83
2	 3	74
3	 4	97
4	 6	51
5	 7	78
6	 8	88
7	 9	84
8	 10	93
9	 11	75
10[b]	 12	53

[a]2-Picolyl azide (0.2 mmol), alkyne (0.23 mmol), $Cu(ClO_4)_2·6H_2O$ (0.4 mmol), NaI (0.8 mmol), TEA (0.2 mmol), CH_3CN (1 mL), rt, 6 h. [b]2-Picolyl azide (0.45 mmol), alkyne (0.2 mmol), TEA (0.4 mmol), $Cu(ClO_4)_2·6H_2O$ (0.8 mmol), NaI (1.6 mmol), CH_3CN (1 mL), rt, 6 h.

(halogen bonding involving a 5-iodotriazolium in the solid state was reported in ref 17).[18,35]

(g) Scope of Organic Azide. The scope of organic azide in the formation of 5-iodotriazole was investigated in the reactions with phenylacetylene (Table 6). In these reactions, DBU was found to work more consistently than TEA to afford the 5-iodotriazole molecules. Benzyl azide (entry 1) and 3-trifluoromethylbenzyl azide[12] (entry 2) showed high reactivity under the developed conditions. Most other azides under the same conditions led to the formation of a small amount of 5-iodotriazole product, 1,4-diphenylbuta-1,3-diyne, as the result of alkyne oxidative homocoupling (OHC)[36] and the recovery of the remaining azide reactant after 12 h. Presumably in these cases, the 5-iodotriazole formation is slow enough to allow the OHC reaction to be competitive. To mitigate the effect of the alkyne OHC reaction, the amount of phenylacetylene was doubled, which drove the reaction to completion in most cases.[37] The 5-iodotriazole was the sole product with few exceptions. *N*-(2-Azidoethyl)pyrrolidine (entry 6, Table 6) gave a significant amount of 5-prototriazole (~ 30%). It was described previously that an excess amount of TEA (Table 2, entry 4) in the reaction leads to the formation of 5-prototriazole. In this case, a tertiary amino group is part of the azide substrate.

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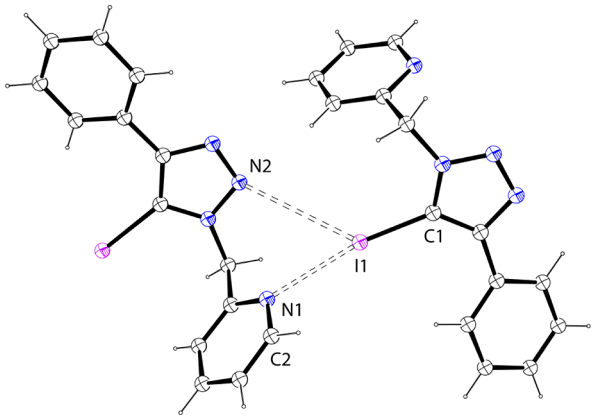

Figure 1. ORTEP view (30% ellipsoids) of compound **1**. Intermolecular interactions between 5-iodo group and N1/N2 on the adjacent molecule are marked by dashed bonds.

In addition to examples of aromatic (entry 3), benzylic (entries 1, 2, 8, 10), and aliphatic azides (all other entries), a number of common functional groups are represented in Table 6 (the inclusion of entries 9−12 was suggested by a reviewer). Tertiary amino (entry 6) and ester (entry 9) groups were tolerated. An isomer of 2-picolyl azide, 3-picolyl azide, proceeded to completion, albeit with a lower isolated yield (49%). The inclusion of amide (entry 11) and carboxylic acid (entry 12) groups in the azide structure resulted in no conversion, while the azides were fully recovered. The addition of a catalytic amount (10 mol %) of the known acceleratory ligand TBTA, also suggested by a reviewer, led to full conversions of the azides and respectable isolated yields in both cases after 6 h (entries 11 and 12). A substantive investigation of acceleratory ligand effect in 5-iodotriazole synthesis using the reported method is currently underway.

(h) Reaction Mechanism. Under the developed conditions, the reaction to form compound **1** was monitored via ^{1}H NMR in CD_3CN. After the last component (alkyne) was added to the reaction mixture, an aliquot of which was diluted with CD_3CN in an NMR tube to afford a homogeneous solution. The ^{1}H NMR spectra of the reaction mixture were acquired at prescribed intervals over time (Figure 2). The methylene proton peaks are color-coded in Figure 2 to highlight the change from 2-picolyl azide (blue) to 5-iodotriazole **1** (red). Only the formation of compound **1** was observed without evidence that the reaction proceeded through a 5-prototriazole intermediate (i.e., **1H**). Control experiments verified that **1H** could not be iodinated under the reaction conditions.

The published mechanistic models of 5-iodotriazole formation from either terminal alkyne[8] or 1-iodoalkyne[12,30] share much in common with that of the CuAAC reaction proposed by Fokin, Sharpless, and co-workers.[1,38] In one model that invokes the formation of copper(I) acetylide,[39] the elementary steps track those of the CuAAC until the formation of copper(I) triazolide, which is intercepted by an iodinating reagent such as ICl,[8] 1-iodoalkyne,[12] or triethyliodoammonium ion.[30]

The mechanistic model that accounts for our observations is depicted in Scheme 4. Under the reported conditions, the copper(II) salt reacts with NaI to give copper(I) species, I_2, and I_3^-, when NaI exceeds 1 molar equiv relative to copper(II). Both the copper(II) reduction and I_3^- formation steps can be monitored using absorption spectroscopy and are considered instantaneous (Figure S1, Supporting Information). Deprotonation of alkyne by a base, such as DBU or TEA, follows the π-complex formation between the alkyne and copper(I)[4] to afford the copper(I) acetylide **I**. Similar to CuAAC reaction, the acetylide formation step is rate-determining (or more precisely "kinetically significant", if other elementary steps also affect the rate), because in the absence of a base the conversion is poor (Table 2, entry 1). Subsequent azide coordination prompts the formation of the dinuclear vinylidene-like intermediate **III**, which undergoes a reductive ring contraction to reach the copper(I) triazolide **IV**. An electrophilic iodinating reagent, I_3^- as shown in Scheme 4, captures the copper(I) triazolide to afford 5-iodotriazole **V**. An excess amount of TEA (B) may contribute to a high concentration of triethylammonium (B−H$^+$ in Scheme 4) upon alkyne deprotonation in the system, which competes with I_3^- for copper(I) triazolide to afford the byproduct 5-prototriazole (**V′**).

From the proposed model, we conclude that the degree of *conversion* of the reactants is determined by the reactivities of the base (B) and the copper(I) catalyst, while the iodo/proto *selectivity* depends on the relative strengths of iodinating reagents and available protonating sources (i.e., B−H$^+$). Therefore, both conversion and selectivity are sensitive to the base: a high concentration of base helps conversion but lowers the iodo/proto selectivity. Under the current procedure, 1 molar equiv of the base relative to the limiting reagent azide appears to be optimal for both conversion and selectivity.

In an attempt to characterize the species formed from a mixture of 2-picolyl azide, $Cu(ClO_4)_2$, and NaI in CH_3CN, tetrakis(acetonitrile)copper(I) perchlorate[40] was isolated (Figure S4, Supporting Information). The back-donation of electrons from copper(I) to CH_3CN protects copper(I) from oxidation to copper(II).[41] Ligand exchanges with CH_3CN would allow tetrakis(acetonitrile)copper(I) perchlorate to serve as a precursor to other copper(I) complexes.[42] The observation of the tetrakis(acetonitrile)copper(I) perchlorate suggests that under the reported in situ conditions, in addition to the freshly formed CuI, other solvated or ligated copper(I) species may also be present to catalyze the reaction, likely with a higher activity than the pure form, coordinatively saturated CuI.

The observation of tetrakis(acetonitrile)copper(I) perchlorate led us to investigate the nature of the formed I_2. The CH_3CN solution of I_2 shows three absorption bands at 294, 367 (shoulder), and 467 nm (blue trace in Figure 3).[43−45] Addition of NaI to the I_2 solution reduces the intensity of the 467 nm band and enhances those of the 294 and 367 nm bands (red trace), thus reporting a shift of the equilibrium toward I_3^- (eq 3, also see Figure S1A, Supporting Information).[44,46,47] The absorption spectrum of the mixture of $Cu(ClO_4)_2$ and NaI in 1:2 molar ratio in CH_3CN contains two bands at 294 and 367 nm with no appearance of a copper(II) d−d transition band in the 700 nm range (green trace). The absence of the 467 nm band suggests that I_2 exists in the form of I_3^- in the reaction mixture.

An X-ray single-crystal structure of tetrabutylammonium triiodide was obtained under conditions similar to those applied in the reported reactions. Mixing copper(II) perchlorate with Bu_4NI, which is capable of replacing NaI in the reaction depicted in Table 2, entry 3, to afford compound **1**, in CH_3OH gave CuI as an off-white precipitate that was filtered off. Slow evaporation of the filtrate led to the formation of dark red single crystals, which were solved to be tetrabutylammonium triiodide[48] (Figure 4).

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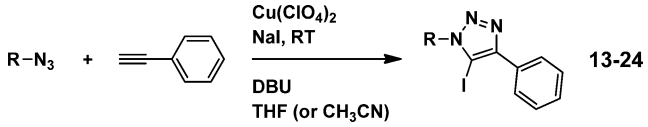
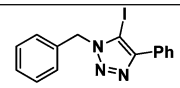
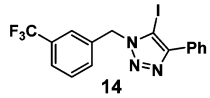
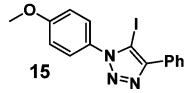
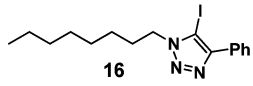
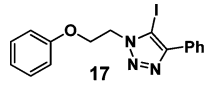
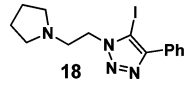
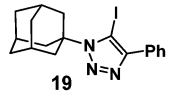
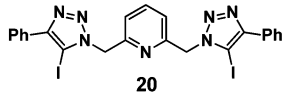
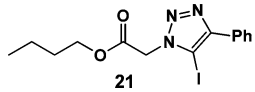
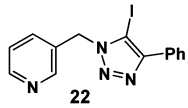
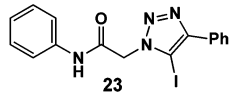
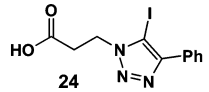
Table 6. 5-Iodotriazole Synthesis Applying Various Organic Azides[a]



entry	product	isolated yield (%)
1	 13	93
2	 14	93
3	 15	70[b]
4	 16	98
5	 17	58[b,c]
6	 18	65[b]
7	 19	trace[b,c]
8[d]	 20	69
9	 21	95
10	 22	49
11	 23	80[d]
12	 24	62[d]

[a]Azide (0.2 mmol), phenylacetylene (0.23 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.4 mmol), NaI (0.8 mmol), DBU (0.2 mmol), THF or CH_3CN (1 mL), rt, 12 h. [b]Same as condition (a) except the amount of phenylacetylene (0.5 mmol). [c]Reaction did not go to completion. [d]A catalytic amount of *N*,*N*,*N*-tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA, 0.02 mmol) was added. Reaction time: 6 h. No conversion was observed in the absence of TBTA.

The use of I_3^- as an iodinating reagent in the iodination of acetone is well-known.[49,50] It is probable in the present case that I_3^- is more reactive than I_2 in iodinating the copper(I) triazolide intermediate. To assess the relative reactivities of I_3^- and I_2, two reactions were investigated involving 2-picolyl azide, phenylacetylene, CuI (0.5 equiv), and DBU in CH_3CN, where

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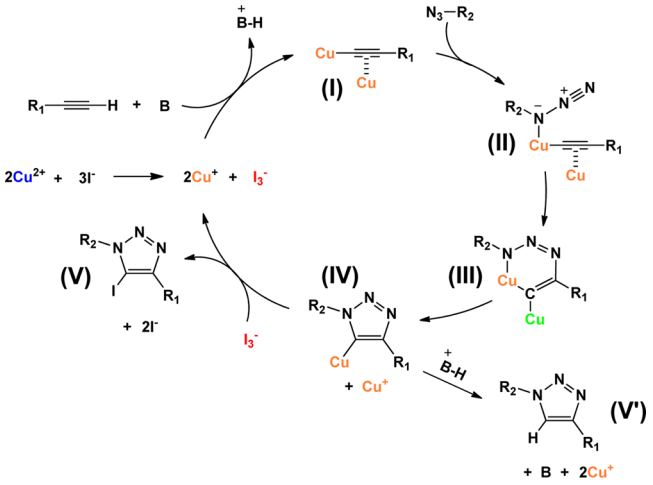
Scheme 4. Mechanistic Model of the One-Pot Conditions To Generate 5-Iodotriazole[a]

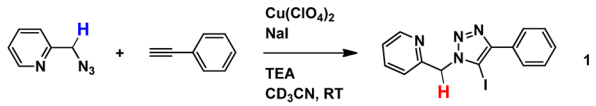


[a]Key: blue, copper(II); orange, copper(I); green, copper(III). B: base, i.e., TEA. We note that in addition to I_3^-, other iodinating species, such as triethyliodoammonium, may also participate in the reaction.

one contained Bu_4NI_3 and the other I_2. The reaction with I_2 did not complete after 20 h (29% 2-picolyl azide remains as determined by ^{1}H NMR) and showed a mixture of **1** and **1H** (68% and 3%, respectively). The reaction involving Bu_4NI_3 reached completion exclusively to **1**. These results suggest that I_3^- is a better electrophile than I_2 under the reported conditions, based on the improved iodo/proto selectivity when Bu_4NI_3 was used. It is unclear why I_3^- led to a better conversion than I_2. Our current hypothesis, which needs to be tested in the near future, is that I_3^- may interact with CuI to form a more potent catalyst.

The reactions to afford 5-iodotriazole **1** under the optimized conditions with different concentrations of NaI were followed by ^{1}H NMR (Figure 5A). The initial rates[51] were determined, by which the apparent kinetic order of NaI was estimated to be 4.4 (Figure 5B). The abnormally high kinetic order of NaI is consistent with the kinetic significance of I_3^-. The poor linearity of the correlation perhaps is a manifestation of the varying distribution of I^-, I_2, and I_3^- at different NaI concentrations. A complete kinetic investigation will be carried out to determine the kinetic involvements of other components in the reaction.

(i). One-Pot Synthesis of 5-Allyl-1,4-disubstituted-1,2,3-triazole ***25****.* On the basis of the mechanistic picture in Scheme 4, an electrophile other than I_3^- shall also trap the copper(I) triazolide intermediate **IV** to complete the C5-functionalization. To test this hypothesis, the loadings of $Cu(ClO_4)_2$ and NaI were reduced, while the electrophilic allyl iodide was introduced to the reaction mixture of 2-picolyl azide and 1-hexyne. The formation of 2-((5-allyl-4-butyl-1,2,3-triazol-1-yl)-methyl)pyridine (**25**) was observed at 15 mol % $Cu(ClO_4)_2$ loading in CH_3CN. The reaction did not reach completion after 12 h and showed a mixture of the 5-iodotriazole product (**1**) and **25**. Increasing the $Cu(ClO_4)_2$ loading to 0.5 equiv improved the conversion but also promoted the formation of **1**. In the Kauffman and Pinnell synthesis of CuI from copper(II) salts and NaI, I_2 was eliminated by sodium thiosulfate.[26] The addition of sodium thiosulfate to the reaction mixture containing



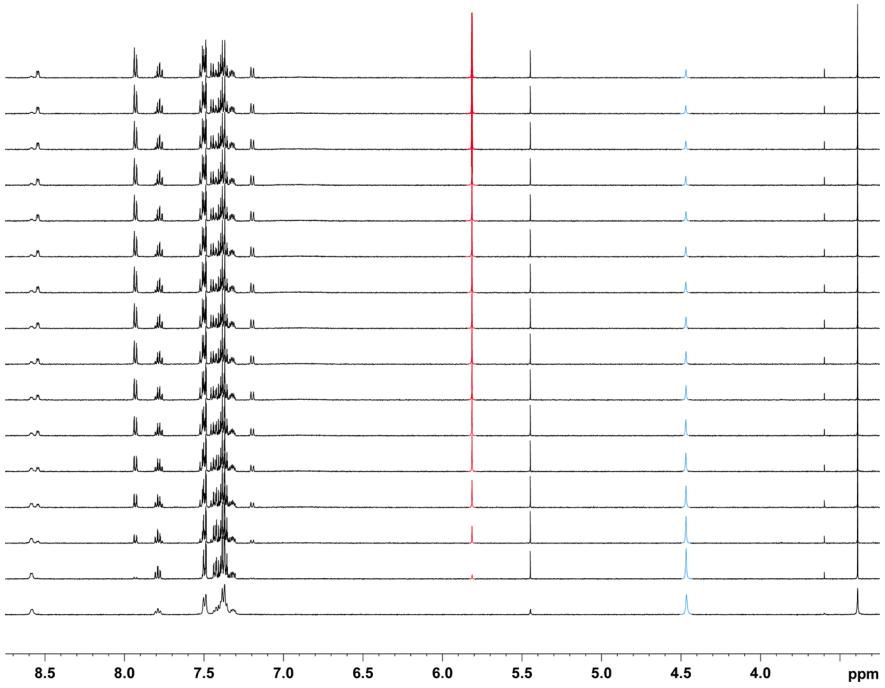


Figure 2. ^{1}H NMR (500 MHz, CD_3CN) spectra of 2-picolyl azide (5.2 mM) with phenylacetylene (9.4 mM) in the presence of $Cu(ClO_4)_2 \cdot 6H_2O$ (10 mM), NaI (21 mM), and TEA (5.7 mM), taken at every 50 min. The methylene proton peaks of 2-picolyl azide and iodotriazole **1** are marked blue and red, respectively.

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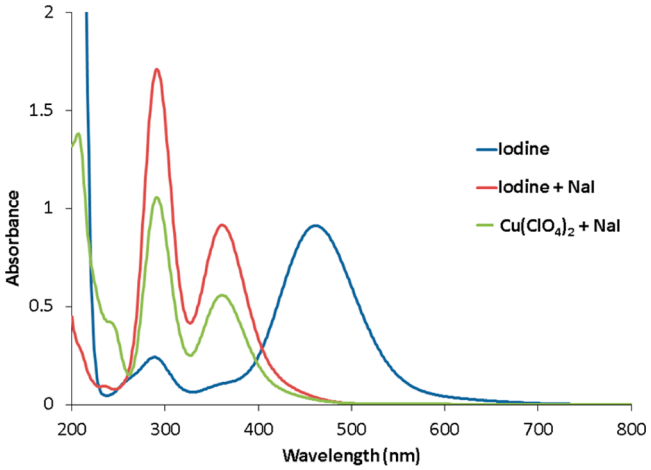


Figure 3. Absorption spectra of solutions of I_2 (1.1 mM, blue), mixture of I_2 (38 μM) and NaI (38 μM, red), and reaction mixture of $Cu(ClO_4)_2$ (40 μM) and NaI (80 μM, green) in CH_3CN.

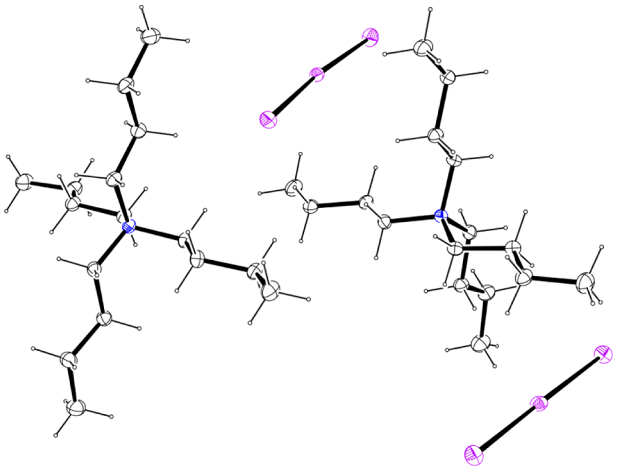
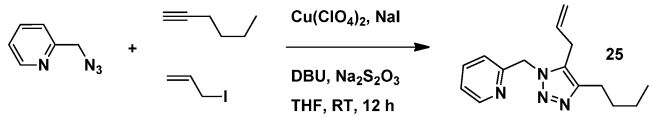


Figure 4. ORTEP view (30% ellipsoids) of tetrabutylammonium triiodide. Carbon atoms are shown in black, nitrogen in blue, and iodine in purple.

0.5 equiv of $Cu(ClO_4)_2$ drove the reaction to completion in 12 h (Scheme 5). 5-Iodotriazole **1** still formed as a minor component, which can be separated chromatographically to give an isolated yield of compound **25** at 76%.[52] 5-Allylation by trapping the copper(I) triazolide have been reported by others under CuI- or CuBr-mediated, but otherwise similar, conditions.[8,10] Notable improvements in the current work include the reduced use of allyl iodide and the copper (pre)catalyst, relatively short reaction time, and tolerance of air exposure, compared to the existing methods.

Scheme 5. One-Pot, Multicomponent Synthesis of 5-Allyl-1,2,3-triazole 25[a]



[a]Key: 2-picolyl azide (0.20 mmol), NaI (0.20 mmol), $Na_2S_2O_3$ (1.0 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.10 mmol), DBU (0.20 mmol), allyl iodide (0.33 mmol), and 1-hexyne (0.23 mmol) in THF (1 mL), rt, 12 h.

CONCLUSION

In summary, we have shown that 5-iodo-1,4-disubstituted-1,2,3-triazoles can be prepared from the CuI-mediated cycloaddition reaction of 2-picolyl azide and 1-iodoalkynes without the addition of an assisting ligand. To circumvent the synthesis of 1-iodoalkynes, a one-pot, multicomponent procedure has been developed where a copper(II) salt is reduced by NaI to generate in situ the copper(I) catalyst and the iodinating source, I_3^-. The in situ generated copper(I) catalyst and I_3^- are more reactive than the pure forms of CuI and I_2, respectively, likely because (1) the in situ copper(I) species is better solvated and hence undergoes more efficient ligand exchange than the pure form of CuI and (2) I_3^- ion is a stronger electrophilic iodinating agent than I_2. The reaction also requires 1 equiv of an amine additive, which may act as a nucleophilic catalyst to deliver the iodinating reagents, in addition to deprotonating the alkyne substrate. The resulting conjugate acid is considered to be an efficient proton donor, which, at a relatively high concentration, protonates copper(I) triazolide to compete with iodination. Extending from this work, more systematic mechanistic investigations are planned to elucidate the functions of various components, including accelerating ligands, in determining the conversion and iodo/proto selectivity of the reaction, based on which the conditions for C5 functionalization can be optimized, and the scope be expanded.

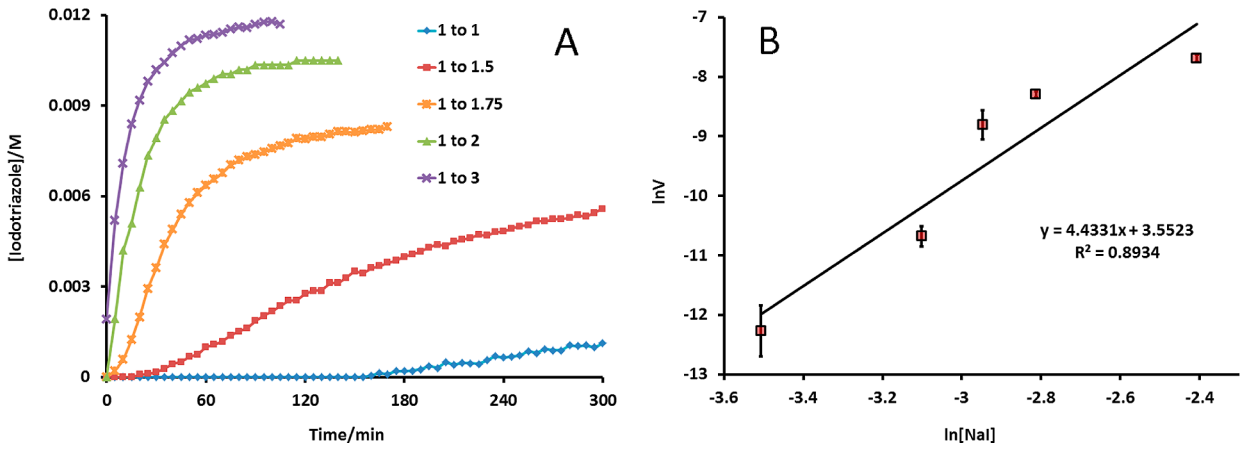


Figure 5. (A) Time courses of compound **1** formation at various ratios of $[Cu(ClO_4)_2]/[NaI]$ shown in the legend. Conditions: [2-picolyl azide] = 15 mM; [phenylacetylene] = 17 mM; [TEA] = 15 mM; $[Cu(ClO_4)_2]$ = 30 mM. (B) Plot of ln *V* (initial rate) vs ln[NaI]. The slope yields the kinetic order of NaI.

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EXPERIMENTAL SECTION

Materials and General Methods. Warning! Low molecular weight organic azides and copper(II) perchlorate 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 used without further purification unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed using precoated TLC plates with silica gel 60 F254 or with aluminum oxide 60 F254 neutral. Flash column chromatography was performed using 40−63 μm (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}H and ^{13}C NMR spectra were recorded at 500 (or 300) and 125 (or 75) MHz, respectively, at 295 K unless otherwise noted. The chemical shifts (δ) are recorded in ppm relative to the residual $CHCl_3$ or CHD_2CN as internal standards. Synthesis of 1-iodoalkynes followed a previously reported procedure.[21] All 1-iodoalkynes synthesized in this work were previously reported: 1-(iodoethynyl)benzene,[53,54] 4-(iodoethynyl)-anisole,[54,55] 2-(iodoethynyl)pyridine,[54] 1-iodohexyne,[56] 3-iodo-*N*,*N*-dimethylpropargylamine,[12] and [(3-iodo-2-propynyl)oxy]benzene.[57]

"Assisting Ligand-Free" Conditions To Prepare 5-Iodotriazoles. A freshly prepared solution of 1-iodo-2-phenylethyne (114 mg, 0.50 mmol) in THF (2 mL) was mixed with 2-picolyl azide (0.40 mmol, 54 mg). A catalytic amount of CuI (<2 mg) was added, and the reaction mixture was stirred at rt for 4 h. Following completion, the mixture was loaded on a short silica column using CH_2Cl_2. The column was eluted with CH_2Cl_2 containing an increasing amount of ethyl acetate up to 50% v/v to yield the pure compound.

Synthesis of *n*-Butyl Azidoacetate. *n*-Butanol (741 mg, 10 mmol) was dissolved in toluene (15 mL) in a round-bottom flask equipped with a magnetic stir bar. The flask was seated in a water bath at rt before chloroacetyl chloride (1.13 g, 10 mmol) and diisopropylethylamine (1 mL) were added dropwise sequentially. After the addition, the reaction mixture was stirred at rt for 3 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with deionized water (3 × 50 mL) and brine (50 mL) sequentially. The organic layer was separated and dried over Na_2SO_4. Upon solvent removal, *n*-butyl chloroacetate was dissolved in CH_3CN (20 mL). NaN_3 (3.25 g, 50 mmol) was subsequently added along with catalytic amounts of 18-crown-6 and Bu_4NI. The reaction mixture was stirred at rt for 48 h before CH_3CN was removed under reduced pressure using a rotatory evaporator. The residue was diluted in CH_2Cl_2, which was washed with brine (3 × 50 mL) in a separation funnel. The organic layer was separated and dried over Na_2SO_4. Upon solvent removal, the residue was eluted through a short silica column using CH_2Cl_2 (100 mL). *n*-Butyl azidoacetate (1.40 g) was isolated upon solvent removal in 89% yield over two steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 4.22 (t, J = 6.0 Hz, 2H), 3.83 (s, 2H), 1.64 (pent, J = 6.0 Hz, 2H), 1.40 (sext, J = 6.0 Hz, 2H), 0.95 (t, J = 6.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm: 168.5, 65.7, 50.3, 30.5, 19.0, 13.6. MS (EI) (m/z): $[M]^+$ calcd for $C_6H_{11}N_3O_2$ 157.0851, found 157.0839.

Synthesis of 2-Azido-*N*-phenylacetamide. Aniline (931 mg, 10 mmol) was dissolved in toluene (15 mL) in a round-bottom flask equipped with a magnetic stirring bar. Chloroacetyl chloride (1.13 g, 10 mmol) and diisopropylethylamine (1 mL) were added dropwise sequentially. After the addition, the reaction mixture was stirred at rt for 2 h. Subsequently, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with deionized water (3 × 50 mL) and brine (50 mL) sequentially. The organic layer was separated and dried over Na_2SO_4. Upon solvent removal, the recovered 2-chloro-*N*-phenylacetamide was mixed with NaN_3 (3.25 g, 50 mmol) in CH_3CN (20 mL) in a round-bottom flask with a stirring bar. Catalytic amounts of 18-crown-6 and Bu_4NI were added, and the mixture was stirred at rt for 45 h. The reaction was then diluted with CH_2Cl_2 (70 mL), transferred to a separation funnel, and washed with brine (3 × 50 mL). The organic layer was dried over Na_2SO_4. Upon solvent removal, the residue was eluted using CH_2Cl_2 (100 mL) through a short silica column to afford 2-azido-*N*-phenylacetamide (1.58 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.00 (bs, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.16 (t, J = 7.2 Hz, 1H), 4.16 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm: 164.8, 136.9, 129.3, 125.2, 120.3, 53.1. MS (EI) (m/z): $[M]^+$ calcd for $C_8H_8ON_4$ 176.0698, found 176.0686.

Synthesis of 3-Picolyl Azide. 3-Picolyl chloride hydrogen chloride (430 mg, 3.0 mmol) and NaN_3 (846 mg, 12.9 mmol) were mixed in CH_3CN (15 mL) in a round-bottom flask equipped with a magnetic stirring bar. DIPEA (390 mg, 3.0 mmol) and catalytic amounts of 18-crown-6 and Bu_4NI were added sequentially. The reaction mixture was stirred at rt for 19 h before ethyl acetate (90 mL) was added. The white precipitate was filtered off, and the solution was washed with basic brine (pH = 11). The organic layer was dried over Na_2SO_4. 3-Picolyl azide (109 mg, 81%) was obtained after solvent removal. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.59 (s, 2H), 7.68 (d, J = 7.8 Hz, 1H), 7.36−7.32 (m, 1H), 4.40 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm: 149.6, 149.2, 135.7, 131.1, 123.6, 52.0.

Representative Procedure for the One-Pot Synthesis of 5-Iodotriazole. 2-Picolyl azide (27 mg, 0.20 mmol) was dissolved in THF (1 mL, comparable yields were obtained in CH_3CN) in a 10-mL round-bottom flask equipped with a magnetic stirring bar. To this solution were added NaI (120 mg, 0.80 mmol) and $Cu(ClO_4)_2{\cdot}6H_2O$ (148 mg, 0.40 mmol). The reaction was stirred for ∼3−5 min before DBU (30 μL, 0.20 mmol) and phenylacetylene (25 μL, 0.23 mmol) were added. The stirring continued at rt for 6 h before the reaction mixture was diluted with ethyl acetate (50 mL) and washed sequentially with a 28−30% w/w NH_4OH solution (25 mL) and brine (2 × 25 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product as a light yellow powder, which was purified on a silica column eluted with CH_2Cl_2 with an increasing amount of ethyl acetate up to 50% v/v as a white powder in 97% yield (70 mg).

For other azides, up to 0.5 mmol of alkyne may be needed for the limit reagent azide (0.2 mmol) to fully convert. The completion of a reaction, which may take less than 6 h, usually is associated with the complete fading of the dark brown color of the initial reaction mixture. For the syntheses of compounds **23** and **24**, a catalytic amount of TBTA (0.02 mmol) was added before the addition of DBU and phenylacetylene.

Compound ***1***. Isolated as an off-white solid in 97% yield (70 mg). Mp: 150−152 °C. ^{1}H NMR (500 MHz, CD_3CN): δ/ppm 8.52 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.95−7.91 (m, 2H), 7.77 (td, J = 7.7, 1.8 Hz, 1H), 7.54−7.48 (m, 2H), 7.44 (tt, J = 7.4, 1.6 Hz, 1H), 7.33−7.29 (m, 1H), 7.18 (d, J = 7.8 Hz, 1H), 5.80 (s, 2H). ^{13}C NMR (125 MHz, CD_3CN, 323 K) δ/ppm 155.8, 151.1, 150.8, 138.4, 132.1, 129.8, 129.8, 128.6, 124.4, 123.1, 79.8, 56.7. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{14}H_{12}N_4I$ 363.0107, found 363.0116.

Compound ***2***. Isolated as an off-white solid in 83% yield (65 mg). Mp: 98−106 °C. ^{1}H NMR (500 MHz, CD_3CN, 333 K): δ/ppm 8.53 (d, J = 4.4 Hz, 1H), 7.87 (dt, J = 9.0, 2.5 Hz, 2H), 7.75 (td, J = 7.7, 1.8 Hz, 1 H), 7.29 (dd, J = 7.6, 4.9 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 7.05 (dt, J = 8.9, 2.6 Hz, 2H), 5.77 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, CD_3CN, 333 K) δ/ppm 161.5, 156.0, 151.1, 150.8, 138.4, 130.1, 124.6, 124.4, 123.2, 115.4, 78.9, 56.8, 56.4. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{15}H_{14}N_4IO$ 393.0212, found 393.0219.

Compound ***3***. Isolated as a light yellow solid in 74% yield (54 mg). Mp: 145−147 °C. ^{1}H NMR (500 MHz, CD_3CN): δ/ppm 8.66 (bs, 1H), 8.52 (d, J = 4.9 Hz, 1H), 8.11 (bs, 1H), 7.87 (t, J = 7.6 Hz, 1H), 7.76 (td, J = 7.7, 1.9 Hz, 1H), 7.35 (bs, 1H), 7.32−7.27 (m, 1H), 7.18 (d, J = 7.9 Hz, 1H), 5.83 (s, 2H). ^{13}C NMR (125 MHz, CD_3CN, 323 K) δ/ppm 155.8, 151.3, 150.8, 150.1, 149.6, 138.3, 138.0, 124.4, 124.3, 123.0, 122.7, 80.5, 56.5. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{13}H_{11}N_5I$ 364.0059, found 364.0065.

Compound ***4***. Isolated as a yellow oil in 97% yield (66 mg). ^{1}H NMR (500 MHz, CD_3CN, 323 K): δ/ppm 8.52 (d, J = 3.8 Hz, 1H), 7.73 (td, J = 7.7, 1.8 Hz, 1H), 7.28 (dd, J = 5.0, 7.6 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 5.68 (s, 2H), 2.66 (t, J = 7.5 Hz, 2H), 1.71−1.63 (m, 2H), 1.43−1.34 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, CD_3CN, 323 K) δ/ppm 155.0, 153.2, 150.7, 138.2, 124.2, 122.9, 80.9, 56.4, 32.0, 26.7, 23.0, 14.2. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{12}H_{16}N_4I$ 343.0420, found 343.0410.

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Compound **5**. Isolated as a beige solid in 73% yield (117 mg). Mp: 94−96 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 8.59 (d, J = 4.8 Hz, 1H), 7.65 (td, J = 7.7, 1.8 Hz, 1H), 7.33−7.27 (m, 2H), 7.24 (dd, J = 7.8, 5.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 2H), 6.98 (t, J = 7.3 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 5.76 (s, 2H), 5.16 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm 158.4, 154.1, 149.8, 148.1, 137.4, 129.6, 123.4, 121.7, 121.5, 115.2, 81.7, 61.9, 55.8. HRMS (EI+) (m/z): $[M]^+$ calcd for $C_{15}H_{13}N_4IO$ 392.0134, found 392.0124.

Compound **6**. Isolated as a pale yellow gum in 55% (76 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 8.56 (d, J = 4.8 Hz, 1H), 7.62 (td, J = 7.8, 1.8 Hz, 1H), 7.21 (dd, J = 7.2, 5.0 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 5.74 (s, 2H), 3.55 (s, 2H), 2.29 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm 154.4, 149.7, 148.9, 137.2, 123.2, 121.4, 81.9, 55.6, 54.0, 45.2. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{11}H_{15}N_5I$ 344.0372, found 344.0372.

Compound **7**. Isolated as a white powder in 78% yield (49 mg). Mp: 114−120 °C. ^{1}H NMR (500 MHz, CD_3CN, 323 K): δ/ppm 8.52 (d, J = 4.6 Hz, 1H), 7.75 (td, J = 7.7, 1.8 Hz, 1H), 7.30 (dd, J = 7.7, 5.0 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 5.71 (s, 2H), 4.60 (s, 2H). ^{13}C NMR (125 MHz, CD_3CN, 323 K) δ/ppm 155.8, 152.5, 150.7, 138.3, 124.4, 123.1, 81.9, 57.0, 56.4. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_9H_{10}N_4IO$ 316.9899, found 316.9904.

Compound **8**. Isolated as a white solid in 88% yield (60 mg). Mp: 117−118 °C. ^{1}H NMR (500 MHz, CD_3CN, 323 K): δ/ppm 8.52 (d, J = 4.6 Hz, 1H), 7.73 (td, J = 7.7, 1.8 Hz, 1H), 7.28 (dd, J = 7.6, 5.0 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 5.70 (s, 2H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, CD_3CN, 323 K) δ/ppm 158.1, 156.2, 150.7, 138.3, 124.2, 122.9, 76.7, 56.5, 32.7, 30.2. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{12}H_{16}N_4I$ 343.0420, found 343.0417.

Compound **9**. Isolated as a dark solid in 84% (68 mg). Mp: 143−145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 8.61 (d, J = 3.8 Hz, 1H), 7.88 (dt, J = 9.0, 2.5 Hz, 2H), 7.65 (td, J = 7.3, 1.7 Hz, 1H), 7.24 (dd, J = 7.1, 5.2 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.80 (dt, J = 8.9, 2.4 Hz, 2H), 5.81 (s, 2H), 3.01 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm 154.8, 150.8, 150.7, 149.8, 137.4, 128.4, 123.2, 121.6, 118.2, 112.2, 75.8, 55.9, 40.6. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{16}H_{17}N_5I$ 406.0529, found 406.0517.

Compound **10**. Isolated as a light yellow solid in 93% yield (76 mg). Mp: 174−175 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.62 (d, J = 4.2 Hz, 1H), 8.33 (d, J = 9.0 Hz, 2H), 8.23 (d, J = 9.0 Hz, 2H), 7.71 (dt, J = 1.8, 7.8 Hz, 1H), 7.31−7.26 (m, 1H), 7.06 (d, J = 7.8 Hz, 1H). ^{1}H NMR (500 MHz, CD_3CN): δ/ppm 8.53 (d, J = 4.5 Hz, 1H), 8.33 (dt, J = 9.1, 2.3 Hz, 2H), 8.25 (dt, J = 9.1, 2.2 Hz, 2H), 7.78 (td, J = 7.7, 1.8 Hz, 1H), 7.32 (dd, J = 7.4, 5.2 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 5.83 (s, 2H). ^{13}C NMR (125 MHz, CD_3CN, 323 K) δ/ppm 155.7, 151.0, 149.3, 149.2, 138.5, 138.5, 129.3, 125.2, 124.6, 123.4, 81.4, 57.0. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{14}H_{11}N_5IO_2$ 407.9957, found 407.9954.

Compound **11**. Isolated as a white powder in 75% yield (54 mg). Mp: 136−137 °C. ^{1}H NMR (500 MHz, CD_3CN): δ/ppm 9.14 (s, 1H), 8.61 (d, J = 4.2 Hz, 1H), 8.52 (d, J = 4.7 Hz, 1H), 8.27 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.78 (td, J = 7.7, 1.8 Hz, 1H), 7.45 (ddd, J = 8.0, 4.9, 0.7 Hz, 1H) 7.33−7.29 (m, 1H), 7.22 (d, J = 7.9 Hz, 1H), 5.81 (s, 2H). ^{13}C NMR (125 MHz, CD_3CN, 323 K) δ/ppm 155.4, 150.6, 150.5, 149.1, 148.4, 138.2, 135.5, 127.8, 124.6, 124.3, 123.0, 80.9, 56.5. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{13}H_{11}N_5I$ 364.0059, found 364.0056.

Compound **12**. Isolated as an off-white solid in 53% (68 mg). Mp: 175−178 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.62 (d, J = 1.8 Hz, 2H), 8.04 (dd, J = 1.8, 7.8 Hz, 2H), 7.69 (dt, J = 1.8, 7.8 Hz, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.28−7.24 (m, 2H), 6.98 (d, J = 8.4 Hz, 2H), 5.86 (s, 4H). ^{13}C NMR (125 MHz, CD_3CN, 333 K) δ/ppm 155.9, 150.9, 150.8, 138.4, 132.6, 130.4, 128.7, 127.2, 124.4, 123.2, 80.0, 56.9. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_8I_2Na$ 668.9480, found 668.9473.

Compound **13**.[8] Isolated as a white solid in 93% yield (67 mg). ^{1}H NMR (500 MHz, CD_3CN): δ/ppm 7.95−7.85 (m, 2H), 7.55−7.46 (m, 2H), 7.46−7.31 (m, 4H), 7.30−7.25 (m, 2H), 5.70 (s, 2H).

Compound **14**.[12] Isolated as a white solid at 93% yield (80 mg). ^{1}H NMR (300 MHz, CD_3CN): δ/ppm 7.96−7.88 (m, 2H), 7.70−7.40 (m, 7H), 5.77 (s, 2H).

Compound **15**. Isolated as a white solid in 70% yield (52 mg). Mp: 208−210 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 323 K): δ/ppm 8.06−8.00 (m, 2H), 7.53−7.40 (m, 5H), 7.08 (dt, J = 8.9, 2.9 Hz, 2H), 3.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 328 K) δ/ppm 161.3, 150.4, 130.7, 130.5, 128.9, 128.8, 128.2, 128.0, 114.8, 78.4, 55.9. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{15}H_{13}N_3IO$ 378.0103, found 378.0114.

Compound **16**.[8] Isolated as a light yellow solid in 98% yield (77 mg). ^{1}H NMR (500 MHz, CD_3CN): δ/ppm 7.92−7.87 (m, 2H), 7.53−7.46 (m, 2H), 7.45−7.40 (m, 1H), 4.44 (t, J = 7.2 Hz, 2H), 1.96−1.86 (m, 2H), 1.40−1.22 (m, 10H), 4.44 (t, J = 7.2 Hz, 3H).

Compound **17**. Isolated as a white powder in 58% yield (46 mg). Mp: 137−142 °C. ^{1}H NMR (500 MHz, CD_3CN): δ/ppm 7.91−7.87 (m, 2H), 7.52−7.47 (m, 2H), 7.42 (tt, J = 7.4, 1.5 Hz, 1H), 7.30−7.24 (m, 2H), 6.95 (tt, J = 7.4, 1.0 Hz, 1H), 6.91−6.87 (m, 2H), 4.83 (t, J = 5.3 Hz, 2H), 4.50 (t, J = 5.3 Hz, 2H). ^{13}C NMR (125 MHz, CD_3CN, 323 K) δ/ppm 159.4, 150.7, 132.0, 130.7, 129.8, 129.7, 128.7, 122.5, 115.9, 80.0, 67.4, 51.3. HRMS (EI+) (m/z): $[M]^+$ calcd for $C_{16}H_{14}N_3IO$ 391.0182, found 391.0174.

Compound **18**. Isolated as a light brown solid in 65% yield (48 mg). Mp: 132−133 °C. ^{1}H NMR (500 MHz, CD_3CN): δ/ppm 7.92−7.88 (m, 2H), 7.52−7.47 (m, 2H), 7.43 (tt, J = 7.4, 1.7 Hz, 1H), 4.55 (t, J = 6.6 Hz, 2H), 2.97 (t, J = 6.6 Hz, 2H), 2.58−2.53 (m, 4H), 1.74−1.69 (m, 4H). ^{13}C NMR (125 MHz, CD_3CN, 323 K) δ/ppm 150.5, 132.2, 129.8, 129.7, 128.6, 79.1, 56.1, 55.0, 51.2, 24.7. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{14}H_{18}N_4I$ 369.0576, found 369.0573.

Compound **20**. Isolated from a short silica column eluted by CH_2Cl_2 containing an increasing amount of ethyl acetate up to 100% v/v as an off-white solid in 69% yield (89 mg). Mp: 215−216 °C. ^{1}H NMR (500 MHz, DMSO-d_6, 333 K): δ/ppm 7.90−7.82 (m, 5H), 7.50−7.35 (m, 6H), 7.19 (d, J = 7.7 Hz, 2H), 5.79 (s, 4H). ^{13}C NMR (125 MHz, DMSO-d_6, 333 K) δ/ppm 154.2, 148.5, 138.0, 130.4, 128.1, 127.8, 126.7, 120.7, 81.4, 54.4. HRMS (EI+) (m/z): $[M]^+$ calcd for $C_{23}H_{17}N_7I_2$ 644.9635, found 644.9630.

Compound **21**. Isolated as an off-white amorphous solid in 95% yield (73 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.96 (dd, J = 1.2, 3.6 Hz, 2H), 7.51−7.41 (m, 3H), 5.27 (s, 2H), 4.24 (t, J = 6.6 Hz, 2H), 1.64 (pent, J = 7.2 Hz, 2H), 1.36 (sext, J = 7.8 Hz, 2H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm: 165.8, 150.3, 130.1, 128.8, 127.6, 78.0, 66.5, 51.8, 30.5, 19.1, 13.8. HRMS (ESI+) (m/z): $[M + H]^+$ calcd for $C_{14}H_{17}N_3IO_2$ 386.0365, found 386.0359.

Compound **22**. Isolated as an off-white amorphous solid in 49% yield (35 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ/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). ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm: 150.5, 150.1, 149.4, 135.8, 130.3, 130.1, 128.9, 128.7, 127.5, 124.1, 52.0. HRMS (ESI+) (m/z): $[M + H]^+$ calcd for $C_{14}H_{12}N_4I$ 363.0107, found 363.0107.

Compound **23**. Isolated as an off-white amorphous solid in 80% yield (65 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.97 (d, J = 7.2 Hz, 2H), 7.60 (bs, 1H), 7.51−7.46 (m, 5H), 7.34 (t, J = 7.8 Hz, 2H), 7.18 (t, J = 7.8 Hz, 1H), 5.34 (s, 2H). ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 10.6 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 7.54 (t, J = 7.9 Hz, 2H), 7.44 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 8.4 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 5.47 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm: 163.6, 148.6, 138.4, 130.6, 129.0, 128.8, 128.4, 126.8, 123.9, 119.3, 83.0, 53.2. HRMS (ESI+) (m/z): $[M + H]^+$ calcd for $C_{16}H_{14}N_4IO$ 405.0212, found 405.0198.

Compound **24**. The crude product after extraction was triturated with diethyl ether (3 × 10 mL) to afford an off-white amorphous solid in 62% yield (43 mg). The solubility of **24** is too low in the solvents that we use to allow for the acquisition of a satisfactory ^{13}C NMR spectrum. Therefore, only ^{1}H NMR and HRMS data are reported. ^{1}H NMR (500 MHz, CD_3OD) δ/ppm: 7.85 (d, J = 8.2 Hz, 2H), 7.48 (t, J = 7.4 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H), 4.72 (t, J = 7.0 Hz, 2H),

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3.07 (t, J = 7.0 Hz, 2H). HRMS (ESI+) (m/z): $[M + H]^+$ calcd for $C_{11}H_{11}N_3IO_2$ 343.9896, found 343.9907.

Procedure for the One-Pot Synthesis of Compound 25. 2-Picolyl azide (27 mg, 0.20 mmol) was dissolved in THF (1 mL). To this solution were added NaI (30 mg, 0.20 mmol), $Na_2S_2O_3$ (158 mg, 1.0 mmol), and $Cu(ClO_4)_2{\cdot}6H_2O$ (37 mg, 0.10 mmol). The reaction mixture was stirred for ~5 min before DBU (30 μL, 0.20 mmol), allyl iodide (30 μL, 0.33 mmol), and 1-hexyne (26 μL, 0.23 mmol) were added. The stirring was continued at rt for 12 h. Upon completion, the reaction mixture was eluted through a short silica column using CH_2Cl_2 to remove inorganic materials. Solvent removal followed by purification on a silica column eluted with CH_2Cl_2 containing an increasing amount of ethyl acetate up to 50% v/v afforded a pale yellow oil in 76% yield (39 mg). ^{1}H NMR (500 MHz, CD_3CN): δ/ppm 8.50 (d, J = 4.3 Hz, 1H), 7.73 (td, J = 7.8, 1.8 Hz, 1H), 7.28 (dd, J = 7.8, 5.1 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 5.75−5.65 (m, 1H), 5.2 (s, 2H), 4.97 (dq, J = 10.2, 1.6 Hz, 1H), 4.86 (dq, J = 17.2, 1.6 Hz, 1H), 3.39 (dt, J = 6.0, 1.7 Hz, 2H) 2.57 (t, J = 7.6 Hz, 2H), 1.60−1.52 (m, 2H), 1.36−1.27 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, CD_3CN) δ/ppm 156.1, 150.6, 146.6, 138.4, 134.2, 132.4, 124.2, 123.2, 117.4, 53.8, 32.6, 27.2, 25.3, 23.1, 14.2. HRMS (EI+) (m/z): $[M]^+$ calcd for $C_{15}H_{20}N_4$ 257.1766, found 257.1763.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray data of compound **1**, Bu_4NI_3, and $[Cu(CH_3CN)_4]ClO_4$ (CIF), and additional figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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