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Mechanism of Copper(I)-Catalyzed 5-Iodo-1,2,3-triazole Formation from Azide and Terminal Alkyne

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ABSTRACT. 5-Iodo-1,2,3-triazole (iodotriazole) can be prepared from a copper(I)-catalyzed reaction between azide and terminal alkyne in the presence of an iodinating agent, with 5-protio-1,2,3-triazole (protiotriazole) as the side product. The increasing utilities of iodotriazoles in synthetic and supramolecular chemistry drive the efforts in improving their selective syntheses based on a sound mechanistic understanding. A routinely proposed mechanism takes the cue from the copper(I)-catalyzed azide-alkyne cycloaddition, which includes copper(I) acetylide and triazolide as the early and the late intermediates, respectively. Instead of being protonated to afford protiotriazole, an iodinating agent presumably intercepts the copper(I) triazolide to give iodotriazole. The current work shows that copper(I) triazolide can be iodinated to afford iodotriazoles. However, when the reaction starts from a terminal alkyne as under the practical

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circumstances, 1-iodoalkyne (iodoalkyne) is an intermediate while copper(I) triazolide is bypassed on the reaction coordinate. The production of protiotriazole commences after almost all iodoalkyne is consumed. Using ^{1}H NMR to follow a homogenous iodotriazole forming reaction, the rapid formation of iodoalkyne is shown to dictate the selectivity of iodotriazole over protiotriazole. To ensure the exclusive production of iodotriazole, the complete conversion of alkyne to iodoalkyne has to, and can be achieved at the early stage of the reaction.

Introduction

5-Iodo-1,2,3-triazoles (iodotriazoles) have found increasing utilities in multicomponent synthesis,[1-9] halogen bonding-based anion recognition,[10-13] and radiolabeling of probes and drugs in biomedical research.[14,15] An iodotriazole can be synthesized from a copper(I)-catalyzed cycloaddition between an organic azide with either a terminal alkyne in the presence of an electrophilic iodinating agent (Figures 1a-c),[16-20] or a 1-iodoalkyne (iodoalkyne, Figure 1d).[21,22] The method that our group reported (Figure 1c)[19] is initialized by the reaction between an alkali metal iodide and $Cu(ClO_4)_2 \cdot 6H_2O$, which quickly affords the CuI catalyst for the subsequent cycloaddition, *and* the electrophilic I_2 or I_3^- as the source of the iodo substituent.[23] This method avoids the preformation of iodoalkyne and the direct use of the often corrosive electrophilic iodinating agents in the earlier methods, and has since been applied in producing iodotriazoles as synthetic intermediates[24] or anion receptors.[11-13] In these iodotriazole-forming reactions, 5-protio-1,2,3-triazole (protiotriazole) resulting from the more conventional copper(I)-catalyzed azide-alkyne cycloaddition is the somewhat persistent side product. This mechanistic study was

motivated in part by the need of increasing iodo/protio selectivity in the synthesis of iodotriazoles.

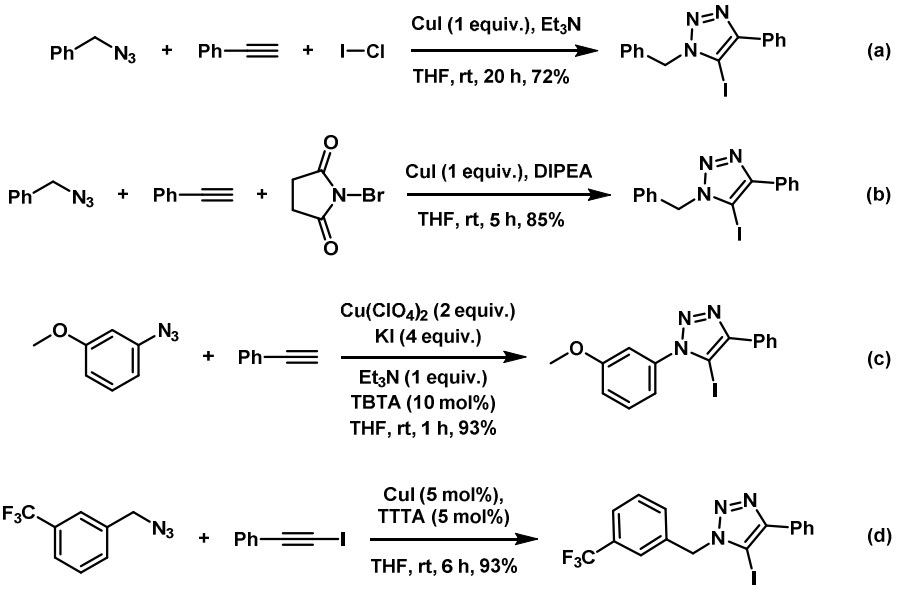


Figure 1. Selective methods for preparing iodotriazoles.

The postulated mechanisms of iodotriazole formation from either iodoalkyne or terminal alkyne are summarized in Figure 2. One unclarified issue is whether a copper(I) triazolide (E) intermediate is involved. Hein, Fokin, and coworkers described two possible routes starting from iodoalkyne.[21,25] One entails a cycloaddition between iodoalkyne and azide without breaking the C-I bond (B/C→D, red route in Figure 2); the other requires a copper(I) triazolide intermediate (B/C→E→D blue route). Most reports on reactions starting from a terminal alkyne accepted the electrophilic iodination of a copper(I) triazolide intermediate as a necessary step (A/C→E→D, blue route),[15-18,26,27] including our own initial work.[19] Mechanisms including similar steps of

electrophilic addition to a copper(I) triazolide have been proposed to explain the formations of 5-chloro-,[28] 5-phosphonate,[29] and 5-amino-1,2,3-triazoles.[30]

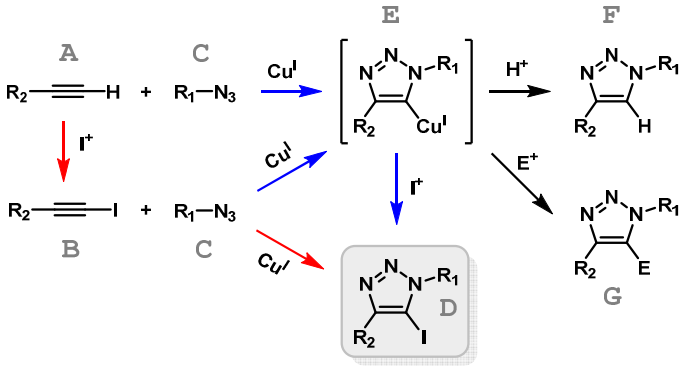


Figure 2. Postulated paths to take terminal alkyne A and azide C to iodotriazole D, and related products F and G. E^+ = electrophile; I^+ = potential iodinating agent, in this work I_2 or iodoalkyne.

Some discussions on the mechanistic aspects of the iodotriazole formation have appeared in literature[26,31-33] in the context of the two proposals (either including or excluding copper(I) triazolide) depicted in Figure 2.[21,25] However, evidence that could unambiguously distinguish the two mechanisms has yet to emerge. We previously reported that (a) the addition of allyl iodide in the reaction mixture affords the 5-allylated product **2** (Figure 3a), which supports the involvement of a copper(I) triazolide,[19] and (b) ^{19}F NMR shows the formation of iodoalkyne (**4**) from alkyne prior to the appearance of iodotriazole **5** (Figure 3b).[20,34] The principal purpose of this paper is to piece together these observations and to provide a coherent mechanistic picture of copper(I)-catalyzed iodotriazole formation. The key question to ask is whether the copper(I) triazolide is a required intermediate in the mechanistic sequence, or is an off-cycle species that

forms only under suboptimal conditions. The dependence of the reaction efficiency, in terms of conversion and iodo/protio selectivity, on the reaction variables will also be characterized.

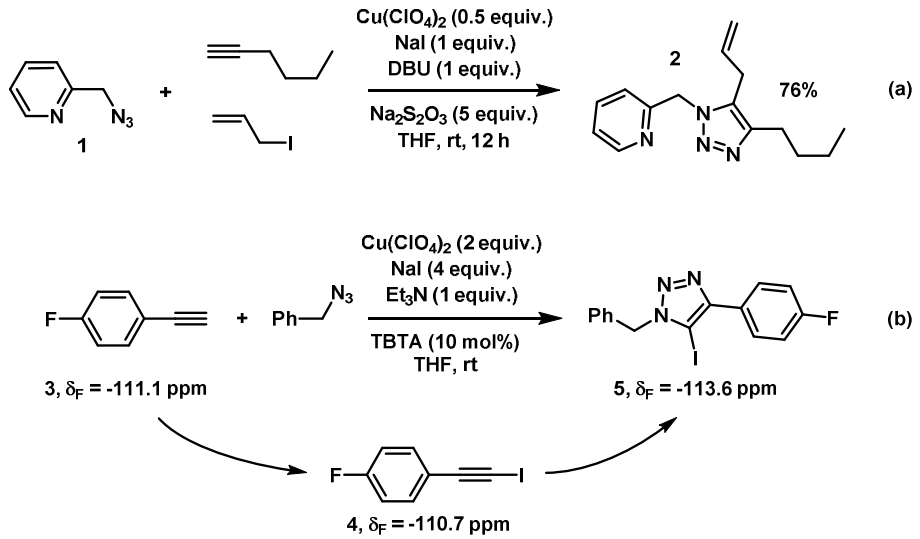


Figure 3. Observations supporting (a) copper(I) triazolide,[19] and (b) iodoalkyne intermediates.[20]

Results and Discussion

1. Using ^{1}H NMR to Monitor the Reaction in Real Time.[35] In our previous study, aliquots of the mixture from the *heterogeneous* reaction starting from 1-ethynyl-4-fluorobenzene were quenched before subjecting to ^{19}F NMR analysis (Figure 3b).[20] While this method provided evidence of the iodoalkyne intermediate, revelations on other aspects of the reaction, in particular the changes of non-fluorinated species, were limited. In the current work, ^{1}H NMR spectroscopy was used to follow the changes of all organic components in an iodotriazole-forming *homogenous* reaction. The conditions listed in the caption of Figure 4 were adapted from our previously reported method[19,20] and were modified appropriately to answer specific

questions regarding (a) reaction conversion, (b) iodo/protio selectivity, and (c) how to distinguish two mechanistic pathways.

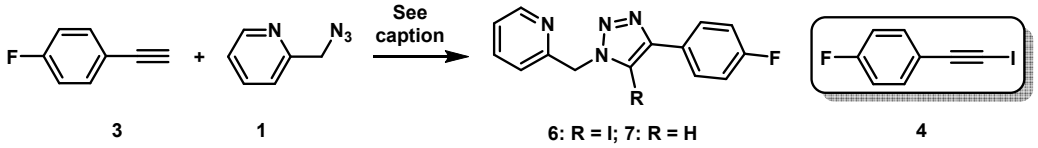


Figure 4. A homogeneous reaction between azide **1** and alkyne **3** to afford iodotriazole **6** was monitored by ^{1}H NMR in real time. Protiotriazole **7** is the side product. Reagents: azide **1** (10 mM), alkyne **3** (10 mM), TEA (0-60 mM), LiI (20-45 mM), $Cu(ClO_4)_2 \cdot 6H_2O$ (0-30 mM), in CD_3CN (0.5 mL).

Stock solutions of each reaction component were prepared in CD_3CN. Metal-chelating 2-picolyl azide[36-38] **1** was used due to its fast reaction rate under ligand-free conditions, so that millimolar concentrations of substrates could afford a significant conversion[39] in a homogenous, therefore, ^{1}H NMR manageable environment (Figure 5).[40] 1-Ethynyl-4-fluorobenzene **3** was the alkyne of choice, whereas LiI was the iodide source owning to its excellent reactivity and solubility in CD_3CN. The time-evolved ^{1}H NMR spectra of an example reaction are shown in Figure 5a. The relative conversion (disappearance of reactants and appearance of products) of each species over time was calculated using the formulas listed in the caption of Figure 5. The conversion values over time are plotted in Figure 5b.

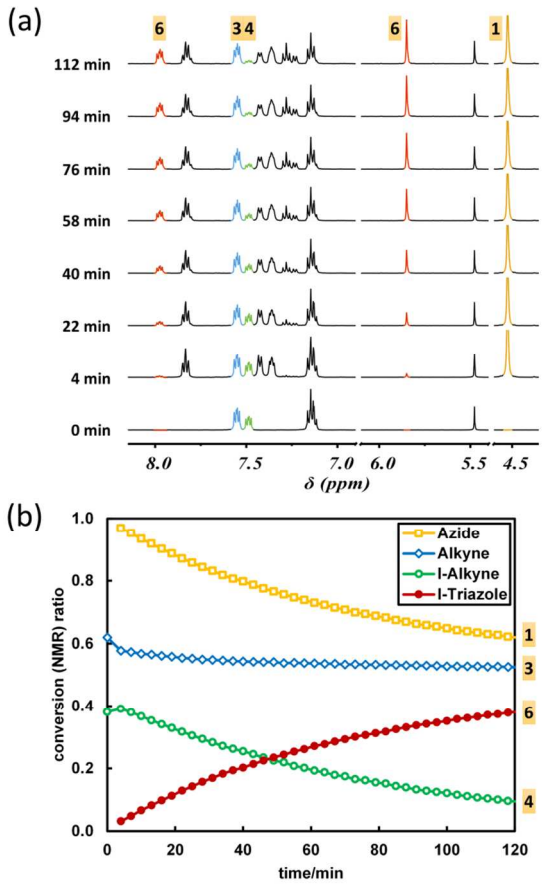


Figure 5. (a) Time-evolution of the ^{1}H NMR spectrum of a reaction shown in Figure 4. The reactants were dissolved in CD_3CN (0.5 mL) in the following order: TEA (20 mM), DCM (2.5 mM, internal standard), LiI (40 mM), alkyne **3** (10 mM, blue), and $Cu(ClO_4)_2 \cdot 6H_2O$ (20 mM). Azide **1** (10 mM, gold) was added after the first spectrum was taken. Iodoalkyne **4**: green; iodotriazole **6**: garnet. All other peaks in black were not used to determine conversions. (b) Reaction profile showing the relative changes of different reaction participants over time, calculated from the raw integration values based on the following formulas: azide (gold squares) = [**1**]/([**1**] + [**6**] + [**7**]); alkyne (blue diamonds) = [**3**]/([**3**] + [**4**] + [**6**] + [**7**]); iodoalkyne (green open circles) = [**4**]/([**3**] + [**4**] + [**6**] + [**7**]); iodotriazole (garnet filled circles) = [**6**]/([**3**] + [**4**] + [**6**] + [**7**]); and protiotriazole (not observed in this example) = [**7**]/([**3**] + [**4**] + [**6**] + [**7**]).

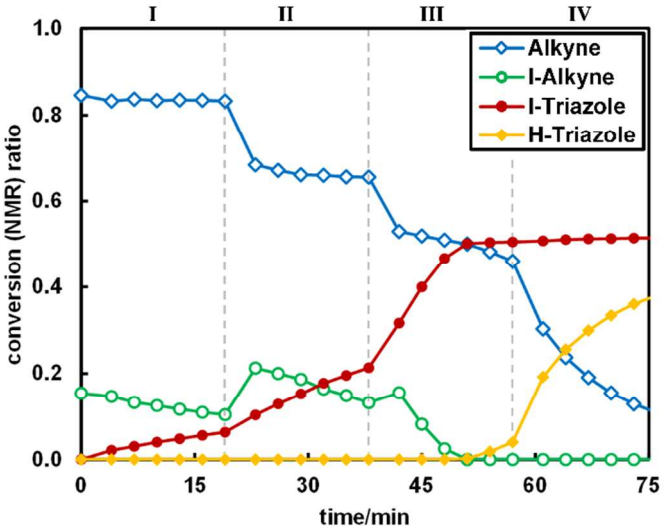


Figure 6. The effect of TEA on the outcome of the reaction. Blue open diamonds - alkyne **3**, green open circles – iodoalkyne **4**, garnet filled circles – iodotriazole **6**, and gold filled diamonds – protiotriazole **7**. Initial concentrations: alkyne **3** (10 mM), LiI (40 mM), TEA (4.0 mM), and $Cu(ClO_4)_2 \cdot 6H_2O$ (10 mM). Azide **1** (10 mM) was added after the first datum point was taken. [TEA] was increased to 10, 13, 17 mM at the end of sections I, II, and III, respectively.

2. TEA Accelerates the Formation of Iodotriazole, Which Precedes that of Protiotriazole. In an experiment designed for studying the role of TEA, alkyne **3** (10 mM), LiI (40 mM), $Cu(ClO_4)_2 \cdot 6H_2O$ (10 mM), and TEA (4 mM) were dissolved in CD_3CN. The amount of $Cu(ClO_4)_2 \cdot 6H_2O$ as the stoichiometric oxidant is enough to convert 50% alkyne to iodotriazole, leaving the other half to afford protiotriazole. Therefore, the information on the competitive formation of iodo- and protiotriazoles could be acquired. ^{1}H NMR revealed that 18% iodoalkyne **4** (green open circles, Figure 6) formed after mixing the reaction components except the azide. The addition of 2-picolyl azide **1** (10 mM, not shown) led to the formation of iodotriazole **6** (garnet filled circles) at the expense of iodoalkyne **4**, while the concentration of alkyne **3** (blue

open diamonds) was unaltered. The effect of TEA on the reaction was studied by periodic introduction of TEA aliquots into the reaction. At the 16-min mark, the concentration of TEA was brought up to 10 mM (section II), which prompted an immediate conversion from alkyne **3** to iodoalkyne **4**, and further on to iodotriazole **6** with a higher rate than the first leg of the reaction. The next addition of TEA took place at the 43-min mark (section III), which caused a similarly steep drop in alkyne **3**. However, the jump in iodoalkyne **4** was not close in magnitude to that of the previous segment, because the conversion rate of the incipiently formed iodoalkyne **4** to iodotriazole **6** was much greater than that in the last period.

The observations up to this point suggest that the rate of iodotriazole formation from iodoalkyne is sensitively dependent on [TEA]. The conversion of alkyne to iodoalkyne, but not necessarily the rate, also depends on [TEA]. As soon as iodoalkyne **4** was fully consumed at ~ 50-min mark, 50% of alkyne **3** had been converted to iodotriazole **6**, which is the maximum possible amount of iodotriazole production under the given conditions. At this point, the formation of protiotriazole **7** commenced, which was significantly accelerated by the last addition of TEA aliquot at the 58-min mark (section IV). The delayed formation of protiotriazole **7** suggests that the productions of iodo- and protiotriazoles are governed by two independent processes, rather than competing in the same catalytic cycle.

The kinetic dependence on [TEA] of both iodotriazole and protiotriazole formation can be understood by the necessity of alkyne deprotonation in the early stages of the reactions. Beyond the function of a base, TEA may act as a supporting ligand for solvating copper catalyst and may accelerate ligand exchange in the catalytic cycle to assist in the cycloaddition step. The significant beneficial effect of TEA on the formation of iodoalkyne will be elaborated in Subsection 4.

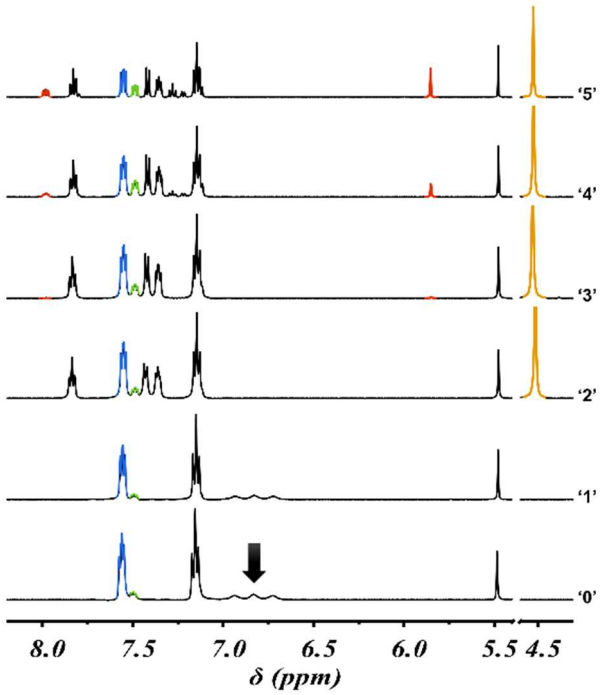


Figure 7. The effect of LiI on the outcome of the reaction. Spectrum '0': the mixture of alkyne **3** (10 mM, blue), LiI (20 mM), $Cu(ClO_4)_2 \cdot 6H_2O$ (20 mM), and TEA (20 mM). Spectrum '1': Azide **1** (10 mM, gold) was added in the reaction mixture. Spectra '2' – '4': [LiI] was increased to 36, 50, 62 mM, respectively. Spectrum '5': the reaction 18 min after spectrum '4' was taken. Iodoalkyne **4**: green; iodotriazole **6**: garnet.

3. Excess LiI is Needed to Maintain High Reactivity of the Copper(I) Catalyst. The effect of LiI on the efficiency of iodotriazole formation was studied by increasing [LiI] over the course of a reaction. The initial [LiI] was equal to $[Cu(ClO_4)_2 \cdot 6H_2O]$, which was the minimum amount of LiI to fully reduce copper(II) (equation 1). The ^1H NMR of the mixture excluding azide **1** is spectrum '0' in Figure 7. In addition to the peaks of TEA, alkyne **3** (blue), and a small amount of iodoalkyne **4** (green), there was a broad triplet at 6.7-6.9 ppm (pointed to by an arrow). The addition of azide **1** (10 mM) did not alter the spectrum (Figure 7, spectrum '1'). The azide

signals were completely unseen, suggesting that the chelating azide **1** formed paramagnetic copper(II) complexes[36,38] that are likely in a rapid equilibrium with its copper(I) counterparts, thus broadening the proton peaks of azide **1** down to the baseline. The addition of LiI eliminated the broad triplet at 6.7-6.9 ppm; and simultaneously the azide signals appeared (spectrum '2'). This observation suggests that added LiI reduced the remaining copper(II), thus restoring the azide signals in the spectrum. In this case, the reaction depicted in equation 1 is an equilibrium with a substantial amount of copper in +2 oxidation state, rather than a complete irreversible reaction as we had presumed.[23] The broad triplet is attributed to a copper(II) complex of TEA (equation 2, Figure S2), and the observation of which marks a condition unsuitable for iodotriazole formation.

$$2Cu(ClO_4)_2 + 2LiI \rightleftharpoons 2CuClO_4 + 2LiClO_4 + I_2 \quad (1)$$

$$Cu(ClO_4)_2 + \mathrm{n}TEA \rightleftharpoons [Cu(TEA)_n](ClO_4)_2 \quad (2)$$

The second addition of LiI narrowed the bandwidths of the azide peaks, and appeared to have initiated the formation of iodotriazole **6** (garnet in spectrum '3', Figure 7). The last addition of LiI, which favors the formation of CuI from the acetonitrile-solvated $CuClO_4$ (equation 3), further increased the rate of iodotriazole formation (spectrum '4'). The conversion values of various components as a function of time is shown in Figure S3. These observations suggest that in order to have a meaningful production of iodotriazole, the amount of LiI needs to be more than enough to reduce all copper(II) to CuI (equation 3). Therefore, CuI, rather than acetonitrile-solvated copper(I), presumably catalyzes the iodotriazole formation.

$$CuClO_4 + LiI \rightleftharpoons CuI + LiClO_4 \quad (3)$$

At fixed concentrations of LiI and TEA, the incremental addition of $Cu(ClO_4)_2 \cdot 6H_2O$ over the course of a reaction led to the ultimate inhibition of the cycloaddition that affords iodotriazole

(Figure S4), due to the growth of inactive copper species including copper(II). Therefore, [$Cu(ClO_4)_2 \cdot 6H_2O$] needs to be adequate to produce enough iodoalkyne for selective iodotriazole formation, yet not too high that the formation of inactive copper complexes is favored.

The results in this subsection provided guidance for improving the efficiency and selectivity of iodotriazole formation. (a) Adequate amounts of TEA and LiI are needed to maintain copper in its catalytically active form; (b) the inhibitory effect of $Cu(ClO_4)_2 \cdot 6H_2O$ suggests that its concentration should be scaled back if a more convenient stoichiometric oxidant could be included; (c) because protiotriazole formation starts after all iodoalkyne is consumed, the iodoalkyne formation needs to be maximized in order to achieve a high iodo/protio selectivity.

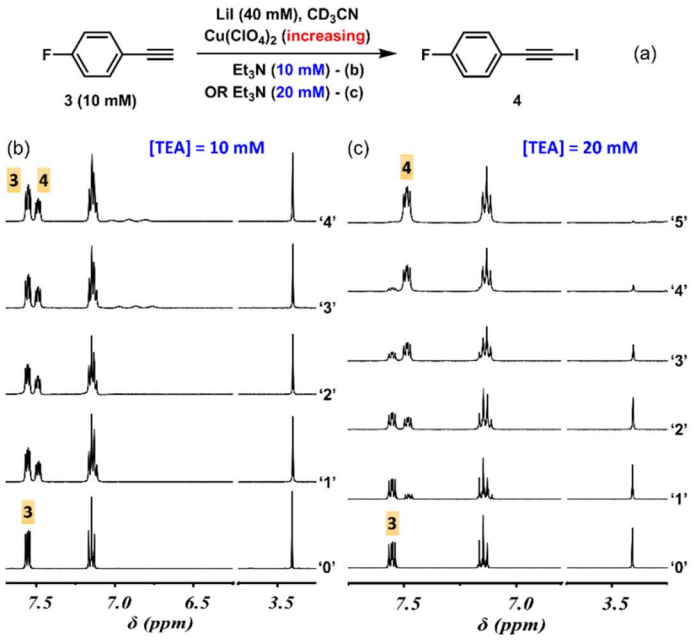


Figure 8. (a) Iodoalkyne **4** formation from alkyne **3** (10 mM) in the presence LiI (40 mM), Et_3N (10 or 20 mM), and $Cu(ClO_4)_2$ $6H_2O$ (0-25 mM). (b) [TEA] = 10 mM and [$Cu(ClO_4)_2$ $6H_2O$] at 0', '1', '2', '3', and '4' were 0, 5, 10, 15, and 19 mM, respectively. (c) [TEA] = 20 mM and [$Cu(ClO_4)_2$ $6H_2O$] at 0', '1', '2', '3', '4', and '5' were 0, 4, 10, 16, 21, 25 mM, respectively.

4. Iodo/Protio Selectivity Depends on the Efficiency of Iodoalkyne Formation. The conversion from iodoalkyne to iodotriazole precedes that of alkyne to protiotriazole (Figure 6). Therefore, the efficient iodoalkyne formation appears to be the prerequisite for a selective synthesis of iodotriazole over protiotriazole. The factors that contribute to the iodoalkyne formation were studied (Figure 8a). In the absence of azide **1**, mixing alkyne **3** (10 mM), LiI (40 mM), $Cu(ClO_4)_2 \cdot 6H_2O$ (5 mM), and TEA (10 mM) in CD_3CN resulted in the instantaneous formation of iodoalkyne **4** (Figure 8b, spectrum '1') at 40% level.[41] The addition of more $Cu(ClO_4)_2 \cdot 6H_2O$ (Figure 8b, spectra '2'-'4') failed to result in further increase in iodoalkyne production. The ^1H NMR spectra acquired when $[Cu(ClO_4)_2 \cdot 6H_2O]$ was higher than 10 mM showed the broad triplet in 6.7-6.9 ppm (Figure 8b, spectra '3' and '4'), revealing the presence of the inhibitive Cu(II)/TEA complex (Figure S2).[42]

When [TEA] was increased to 20 mM (Figure 8c), or higher up to 0.1 M (Figure S5), increasing $[Cu(ClO_4)_2 \cdot 6H_2O]$ facilitated the iodoalkyne formation linearly to completion. Under such conditions, the selectivity of iodotriazole formation was expected to be maximized as the terminal alkyne was no longer present. As shown in Figure 9, at 25 mM TEA, full conversion from alkyne **3** to iodoalkyne **4** was reached (green open circle at time '0'). The addition of 2-picolyl azide **1** at this point led to the rapid production of iodotriazole **6** (garnet filled circles). Over 50% of iodoalkyne **4** (green open circles) was converted to iodotriazole **6** even before the first ^1H NMR spectrum was taken after the addition of azide **1**. The complete conversion to iodotriazole **6** was over within 30 min. No protiotriazole **7** was observed.

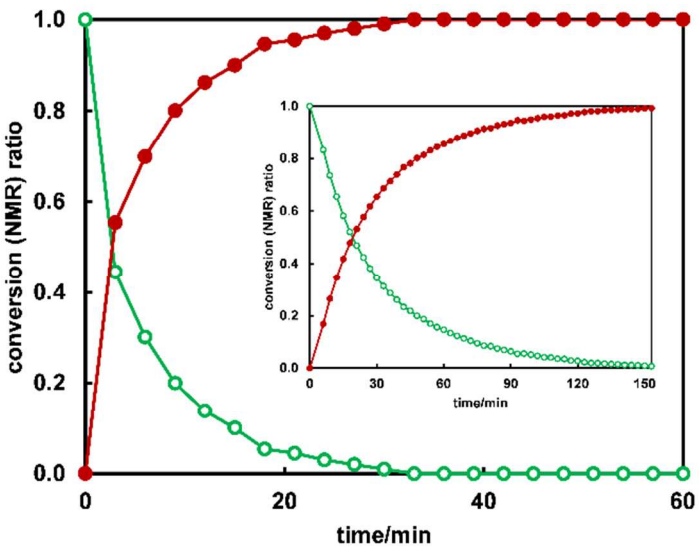


Figure 9. Full conversion to iodoalkyne **4** (green open circles) leads to the complete selectivity for iodotriazole **5** (garnet filled circles). Concentrations: alkyne **3** (10 mM), LiI (40 mM), $Cu(ClO_4)_2 \cdot 6H_2O$ (25 mM), and TEA (25 mM). Azide **1** (10 mM) was added after the first spectrum was taken. Inset: alkyne **3** (10 mM), $Cu(ClO_4)_2 \cdot 6H_2O$ (2 mM), LiI (15 mM), I_2 (8 mM), and TEA (30 mM). Azide **1** (10 mM) was added after the first spectrum was taken.

The initial iodoalkyne formation appears to proceed through deprotonation of terminal alkyne followed by electrophilic iodination (equation 4). The deprotonation step is depicted in equation 5. In addition to being a base, TEA also activates I_2 via the $TEAI^+$ intermediate (equation 6).[19,26] In conjunction with the accelerating effect of TEA on the cycloaddition step as described in the previous subsection, we believe that TEA has three functions in this reaction: (a) deprotonating the alkyne as a base; (b) activating I_2 as a nucleophilic catalyst to enhancing the efficiency of iodoalkyne formation; and (c) protecting CuI from aggregating during the reaction, thus maintaining the catalytic potency of the copper(I) catalyst.

$$R - C \equiv C - H + I_2 + Et_3N \rightleftharpoons R - C \equiv C - I + [Et_3NH]I \qquad (4)$$

$$R - C \equiv C - H + Et_3N \rightleftharpoons R - C \equiv C^- + [Et_3NH]^+ \quad (5)$$

$$I_2 + Et_3N \rightleftharpoons [Et_3NI]^+ + I^- \quad (6)$$

In our iodotriazole synthesis $Cu(ClO_4)_2 \cdot 6H_2O$ has been used as the stoichiometric oxidant that converts iodide to iodine (or triiodide), which reacts with alkyne to afford iodoalkyne. If iodine (I_2) was offered as the stoichiometric oxidant, then the reaction could be rendered catalytic in $Cu(ClO_4)_2 \cdot 6H_2O$. The reaction shown in the inset of Figure 9 indeed proceeded smoothly in the presence of 20 mol% $Cu(ClO_4)_2 \cdot 6H_2O$ and 0.8 molar equivalent of I_2, which is the first example of copper-*catalyzed* iodotriazole formation from *terminal alkyne*.[43] TEA and LiI were added at 3.0 and 1.5 molar equivalents, respectively, which ensured that the iodoalkyne formation was complete and the copper(I) catalyst for the cycloaddition was competent. A lower amount of either component would have decreased either the conversion or the iodo/protio selectivity, or both, of the catalytic reaction significantly.

5. More Electron-Deficient Alkyne Reacts Faster. The kinetic profiles of two reactions involving fluorinated alkyne **3** or methoxylated alkyne **8** were compared to show the electronic effect on the reactivity and iodo/protio selectivity (Figures 10a,b). The reaction conditions were modified by reducing the copper loading so that both iodo- and protiotriazole products could form. In the experiments, all reaction components other than $Cu(ClO_4)_2 \cdot 6H_2O$ were dissolved in CD_3CN in an NMR tube, and an initial NMR spectrum was taken before $Cu(ClO_4)_2 \cdot 6H_2O$ was added to start the reaction. Therefore, unlike the data presented in previous sections, no *in situ* preformation of iodoalkyne was deliberately done.

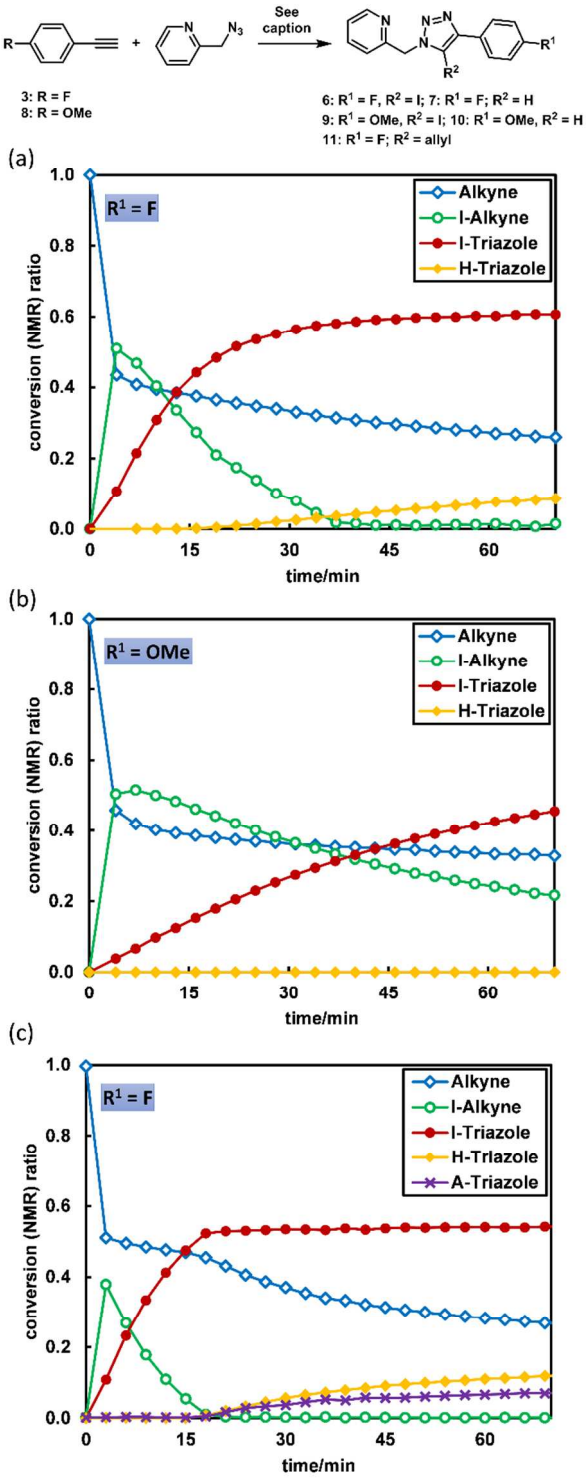


Figure 10. Reaction progress monitored by ^{1}H NMR. Alkyne = **3** in (a), 4-ethynylanisole (**8**) in (b); and **3** in (c). Allyl iodide (10 mM) was also included in (c). Concentrations: azide **1** (10 mM), alkyne (10 mM), LiI (40 mM), $Cu(ClO_4)_2 \cdot 6H_2O$ (10 mM), and TEA (20 mM) in CD_3CN.

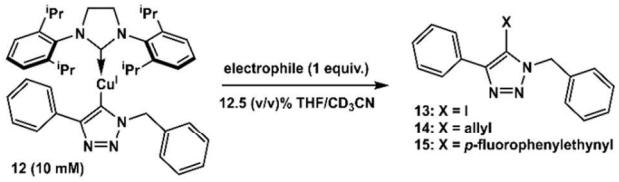
Alkyne **3** was quickly converted to iodoalkyne **4**, the consumption of which (green open circles, Figure 10a) coincided with the production of iodotriazole **6** (garnet filled circles). The appearance of protiotriazole **7** (gold filled diamonds) lagged behind, but took over the latter half of the reaction after iodoalkyne **4** was consumed. The time-evolved ^{1}H NMR spectra of this reaction are shown in Figure S6a. Starting with alkyne **8** with the electron-richer methoxy substituent (Figure 10b), the rapid production of iodoalkyne was not affected. Rather, the initial rate of iodotriazole formation dropped by 4 folds. Protiotriazole was not observed during the allotted time.

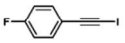
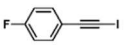
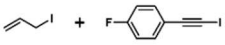
Preliminary conclusions could be drawn based on the dependence of the reaction on the electronic property of the alkyne. The production of iodoalkyne appears insensitive to the substituent on the alkyne. Therefore, the iodoalkyne formation step is not turn-over limiting in this reaction. The electron-deficient iodoalkyne reacts faster with azide **1** in the cycloaddition step than its electron-richer, methoxylated counterpart, to afford iodotriazole **6** and protiotriazole **7** sequentially. This observation suggests that the cycloaddition step is turn-over limiting, and is favored by an electron-deficient iodoalkyne. Presumably, backbonding of copper(I) to iodoalkyne,[33,44,45] which should be favored by an electron-withdrawing substituent, accelerates the cycloaddition step.[46]

6. Allyltriazole Forms after Iodotriazole, Simultaneously with Protiotriazole. To provide more details in the allylation reaction depicted in Figure 3a, allyl iodide was introduced into the reaction mixture that produced the data in Figure 10a. Comparing to the reaction progress data in Figure 10a, iodotriazole **6** reached a similar conversion in 20 min (Figure 10c; the spectra are shown in Figure S6b). The production of protiotriazole **7** (gold filled diamonds) picked up at this point. Allyltriazole **11** (purple crosses in Figure 10c) appeared together with protiotriazole **7**. The

delayed co-production of protiotriazole **7** and allyltriazole **11** supports the mechanism that both compounds are formed via a copper(I) triazolide intermediate, *after* the reaction to produce iodotriazole is (almost) over in a separate reaction pathway.

Table 1. Electrophile trapping of [Cu^{I}(NHC)(triazolide)] **12**[a]



Entry	Electrophile	Time	13 (%)	14 (%)	15 (%)
1		3 h	3	-	2
2		26 h	64	-	21
3		3 h	-	58	-
4		3 h	24	54	2
5		5 min	100	0	-

a. Conditions: Compound **12** (10 mM) and electrophile (10 mM each) in CD_3CN with 12.5% (v/v) THF at rt. The yields were calculated from the ^1H NMR spectra of the reaction mixtures.

7. Copper(I) Triazolide is a Viable Substrate to be Iodinated. The reactivity of a copper(I) triazolide in iodination to afford iodotriazole was also investigated. Following a modified synthesis (see Scheme 1 in the Experimental Section) by Straub and coworkers,[47] an *N*-heterocyclic carbene (NHC) supported copper(I) triazolide **12** was prepared (Table 1). In the presence of iodoalkyne **4**,[48] copper(I) triazolide **12** was slowly converted to iodotriazole **13** (Table 1, entries 1 and 2), while the alkynylated triazole **15** was observed as the minor product. This reaction demonstrated that an iodoalkyne could be an (surprisingly reluctant) electrophilic iodination source for the NHC-supported copper(I) triazolide **12** to afford an iodotriazole – part

of the less favored of the two mechanistic models proposed by Hein, Fokin, and coworkers.[21] Allyl iodide turned out to be a more competent electrophile in the reaction with copper(I) triazolide **12**, reaching 58% yield (based on ^{1}H NMR) of allyltriazole **14** after 3 h (entry 3). The low reactivity of iodoalkyne in the reaction with copper(I) triazolide **12** was further demonstrated in the experiment while both iodoalkyne **4** and allyl iodide competed for coupling with the triazolide (entry 4). The time-course experiment showed that both iodotriazole **13** and allyltriazole **14** formed simultaneously with the latter having a higher rate (Figure 11).[49] This kinetic profile is in stark contrast to that in Figure 10c, in which allyltriazole did not appear until the iodotriazole formation phase was almost over. Therefore, the comparison between kinetic profiles in Figures 10c and 11 further supports the conclusion that when the iodotriazole formation reaction starts from terminal alkyne and azide in the presence of an iodinating agent, the copper(I) tirazolide becomes an incompetent intermediate that is bypassed on the reaction coordinate altogether. In the last experiment (entry 5), the strongly electrophilic molecular iodine easily outcompeted allyl iodide to deliver iodotriazole **13** within minutes.

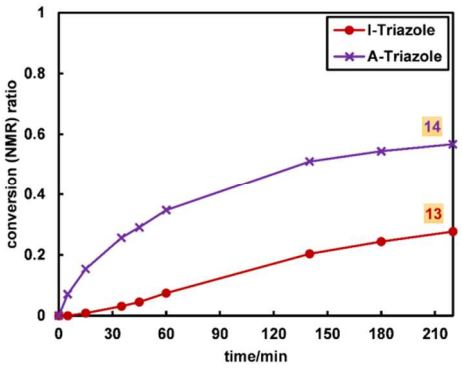


Figure 11. Reaction progress of entry #4 in Table 1 monitored by ^{1}H NMR. Concentrations: [Cu^I(NHC)(triazolide)] (**12**, 10 mM), iodoalkyne **4** (10 mM), and allyl iodide (10 mM) in CD_3CN with 12.5% (v/v) THF at rt.

8. Mechanistic Proposal. The iodotriazole formation mechanism as shown in Figure 12 starts from the rapid reduction of $Cu(ClO_4)_2 \cdot 6H_2O$ by an alkali metal iodide (e.g., LiI). With an adequate amount of iodide, the resulting CuI is the catalyst for the subsequent cycloaddition reaction, while molecular iodine (I_2) or triiodide ions (I_3^- as shown) act as the iodinating agent. The rapid, TEA-aided conversion of alkyne to iodoalkyne (depicted in the grey box), which is completed within the time of preparing an NMR sample, sends iodoalkyne into the catalytic cycle on right to produce iodotriazole. Based on our previous work, an accelerating ligand such as tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA)[50] might be needed for the cycloaddition step,[20] if the azide is not self-accelerating via chelating copper. The cycloaddition between a terminal alkyne and an azide – the typical 'click' reaction to produce protiotriazole, occurs much slower and operates through a separate catalytic cycle that involves a copper(I) triazolide intermediate (left, Figure 12). Electrophiles such as allyl iodide may compete with the proton source to react with copper(I) triazolide to afford 5-substituted triazoles. Therefore, both mechanistic pathways proposed by Hein et al.,[21] which include either the cycloaddition between iodoalkyne and azide, or the iodination of a copper(I) triazolide intermediate, are verifiable. However, under various reported experimental conditions in which the reaction starts from either terminal alkyne or iodoalkyne, the reaction bypasses the copper(I) triazolide intermediate by proceeding in a separate pathway via a rapid formation of iodoalkyne followed by the copper(I)-catalyzed cycloaddition with an azide.

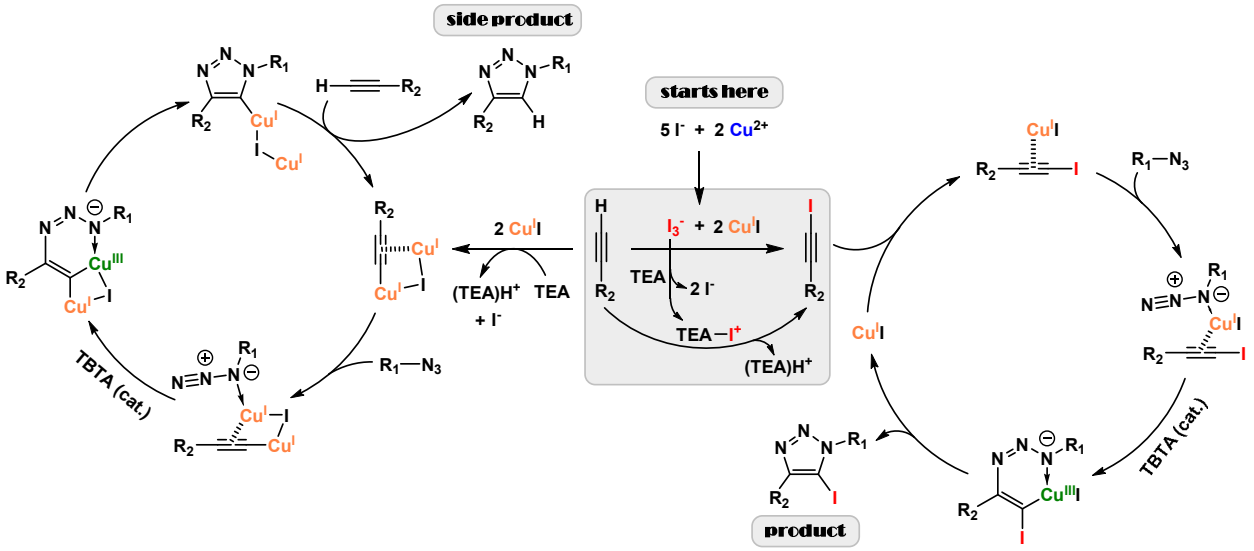


Figure 12. Proposed mechanism of iodotriazole formation under the conditions shown in the caption of Figure 4. Copper in oxidation states +1, +2, and +3 are color-coded orange, blue, and green, respectively.

Conclusions

Azide and alkyne undergo copper(I)-catalyzed cycloaddition in the presence of an electrophilic iodinating agent to afford iodotriazole, while protiotriazole is the undesired but sometimes persistent side product. Two mechanisms have been proposed for the iodotriazole formation, in which iodination occurs either on the alkyne outside of the catalytic cycle to afford iodoalkyne, or on the copper(I) triazolide intermediate within the catalytic cycle to afford iodotriazole. This work provides evidence to support the former scenario, in which the iodoalkyne forms rapidly from alkyne in the presence of an iodinating agent. Iodoalkyne then undergoes cycloaddition with an azide to afford iodotriazole. The protiotriazole side product is produced via a different pathway that operates after the iodotriazole formation is almost completed. This information leads to the recommendation that in order to achieve exclusive selectivity of iodotriazole in a

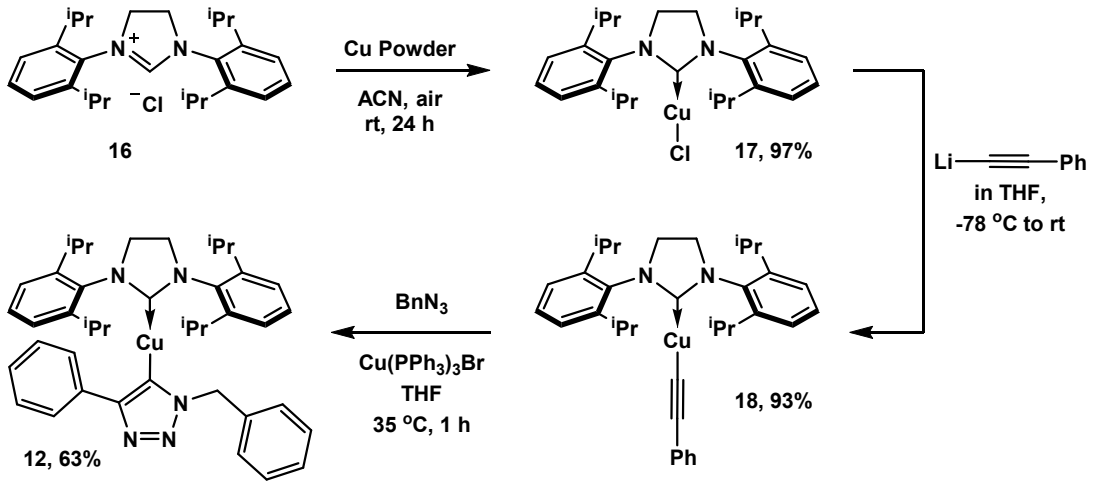
reaction starting from a terminal alkyne, conditions need to be applied to ensure full *in situ* conversion of alkyne to iodoalkyne. Specific to our reported method, the optimized conditions shall include adequate quantities of the nucleophilic base TEA and the iodide source LiI. Copper(I) triazolide is confirmed to be reactive towards certain electrophiles, including I_2 to afford iodotriazole. However, in reality it is bypassed on the reaction coordinate that starts from terminal alkyne.

Experimental Section

1. Materials and General Methods. Reagents and solvents were purchased from various commercial sources and were used without further purification unless otherwise stated. $Cu(ClO_4)_2 \cdot 6H_2O$ was dried in a vacuum oven at 40 °C before use. Stock solutions of each reaction component were prepared in advance except $Cu(ClO_4)_2 \cdot 6H_2O$, which was prepared immediately prior to mixing because of its tendency to lose efficacy in acetonitrile. ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz respectively. All chemical shifts were reported in δ units relative to tetramethylsilane. High resolution mass spectra (HRMS) were obtained using a time-of-flight analyzer. The identity of compounds **1**,[36] **4**,[20] **6**,[19] **7**,[47] **9**,[19] **10**,[37] **13**,[19] **14**,[16] **16**,[19] **17**,[51] and **18**[52] were verified by comparing with reported data. These compounds were prepared when needed by following reported procedures.

2. Synthesis and Characterization of New Compounds. Compound **11** was prepared by following a reported procedure.[19] 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-ethynyl-4-fluorobenzene (28 mg,

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 the 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 12% yield (7.0 mg). ^{1}H NMR (500 MHz, CD_3CN) δ/ppm 8.52 (bs, 1H), 7.75 (td, J = 7.5 Hz, 2.0 Hz, 1H), 7.73-7.69 (m, 2H), 7.29 (t, J = 6.5 Hz, 1H), 7.22-7.18 (m, 3H), 5.88-5.80 (m, 1H), 5.62 (s, 2H), 5.04 (dt, J = 10.5 Hz, 1.0 Hz, 1H), 4.86 (dt, J = 17.5 Hz, 1.5 Hz, 1H), 3.62 (dt, J = 5.5 Hz, 2 Hz, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ/ppm. 163.7 (d, $^1J_{CF}$ = 242 Hz), 156.4, 150.8, 138.6, 134.1, 132.7, 130.2 (d, $^3J_{CF}$ = 7.5 Hz), 129.5, 124.5, 123.4, 118.1, 116.9 (d, $^2J_{CF}$ = 21.2 Hz), 54.5, 28.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}FN_4$: 295.1359; found 295.1359.



Scheme 1. Synthesis of [Cu^I(NHC)(triazolide)] **12**.

[Cu^I(NHC)Cl] (17).[51] To a flame-dried round-bottom flask equipped with a magnetic stirring bar, compound **16** (2.0 g, 4.68 mmol) was added followed by Cu powder (1.5 g, 23.4 mmol) and acetonitrile (50 mL). The reaction was stirred vigorously at rt for 10 min, then at 55 °C for 24 h.

The hot reaction mixture was filtered through a silica pad to remove excess copper powder and the solvent was removed under vacuum to provide a white solid. The yield was 2.2 g (97%, 4.5 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm 7.40 (t, J = 7.5 Hz, 2H), 7.25 (d, J = 7.7 Hz, 4H), 4.02 (s, 4H), 3.10-3.02 (m, 4H), 1.37 (d, J = 6.5 Hz, 12H), 1.34 (t, J = 6.5 Hz, 12H).

[Cu^I(NHC)(Ph-C≡C)] (18).[52] To a dry Schlenk flask charged with argon and equipped with a magnetic stirring bar, compound **17** (2.21 g, 4.52 mmol) was suspended in dry THF (50 mL) and cooled to -78 °C in a dry ice/acetone bath. To this, a lithium phenylacetylide solution in THF (6.2 mL, 1.0 M in THF, 6.2 mmol) was added dropwise over 5 min. The cold bath was then removed and the reaction mixture was stirred vigorously for 2 h as it slowly warmed to rt. The solvent was removed in vacuo on the Schlenk line to provide a gummy yellow solid. DCM (40 mL) was added to the crude product, and the solution was filtered through a Celite plug (slurry packed in DCM) then washed with additional DCM (3 × 25 mL). The filtrate was concentrated under vacuum on the Schlenk line to give a yellow solid, which was re-dissolved in a minimal amount of DCM and combined with hexanes (100 mL). The flask was capped and placed in a freezer for approximately 1 h. The precipitate was filtered, washed with hexanes and dried under high vacuum to afford a pale yellow powder. The yield was 2.32 g (93%, 4.18 mmol). ^{1}H NMR (500 MHz, C_6D_6) δ/ppm 7.42 (d, J = 7.0 Hz, 2H), 7.17-7.14 (m, 2H), 7.04 (d, J = 8.0 Hz, 4H), 6.82 (t, J = 7.5 Hz, 2H), 6.76 (t, J = 7.5 Hz, 1H), 3.12 (s, 4H), 2.99-2.94 (m, 4H), 1.48 (d, J = 6.1 Hz, 12H), 1.17 (d, J = 6.9 Hz, 12H).

[Cu^I(NHC)(triazolide)] (12). This procedure is modified from that reported in reference #47. To a dry Schlenk flask charged with argon and equipped with a magnetic stirring bar, compound **18** (0.43 g, 0.77 mmol) and $Cu(PPh_3)_3Br$ (36 mg, 0.04 mmol) was suspended in dry THF (10 mL). Benzyl azide (145 μL, 1.16 mmol) was added and the reaction mixture was stirred

vigorously for 3 h. The solvent was removed in vacuo and the crude product was triturated with toluene. The solid was dissolved in DCM and filtered through a Celite plug (slurry in DCM). Hexanes were added to the filtrate and the solution was placed in a freezer for approximately 1 h. The precipitate was collected and dried in vacuo, to afford a white amorphous solid. The yield was 340 mg (64%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ/ppm 7.44 (t, J = 7.8 Hz, 4H), 7.25 (d, J = 8.0 Hz, 4H), 7.18-7.17 (m, 3H), 6.97 (tt, J = 8.0, 1.5 Hz, 1H), 6.90 (t, J = 8.0 Hz, 2H), 6.64 (dd, J = 3.9, 1.6 Hz, 2H), 4.50 (s, 2H), 4.05 (s, 4H), 3.16–3.07 (m, 4H), 1.32 (d, J = 6.9 Hz, 12H), 1.19 (d, J = 6.9 Hz, 12H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ/ppm 205.2, 155.2, 152.8, 147.5, 139.2, 136.4, 135.2, 130.5, 128.7, 128.4, 127.2, 127.1, 125.4, 125.3, 125.2, 55.9, 29.4, 25.6, 24.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{42}H_{51}N_5Cu$: 688.3440; found 688.3425.

3. Procedures of Using ^{1}H NMR to Monitor Reaction Progress. A Representative Procedure of the in situ ^{1}H NMR Assay (azide was added last). Stock solutions in CD_3CN were prepared in advance for all reaction components except $Cu(ClO_4)_2 \cdot 6H_2O$, because of its tendency to lose efficacy in acetonitrile. The $Cu(ClO_4)_2 \cdot 6H_2O$ solution was prepared immediately prior to the experiment to limit this effect. TEA (50 μL, 200 mM), DCM (25 μL, 50 mM, internal standard), 1-ethynyl-4-fluorobenzene (25 μL, 200 mM), and LiI (100 μL, 200 mM) were added to the NMR tube sealed with a rubber septum sequentially using airtight glass syringes. The mixture was diluted with 225 μL of CD_3CN before adding $Cu(ClO_4)_2 \cdot 6H_2O$ (50 μL, 200 mM). The first NMR spectrum taken was marked as time "0". After collecting the initial scan, 2-picolyl azide (25 μL, 200 mM) was injected into the sample. This injection served as the start time for the reaction. All the concentrations listed in the procedure are stock solution concentrations of individual reaction participants. The final concentrations of all reaction components after mixing of this experiment

are listed in the caption of Figure 5. NMR spectra were collected every 3 min over the course of the reaction for 1.5 h on average.

A Representative Procedure of the in situ ^{1}H NMR Assay (copper(II) perchlorate was added last). TEA (25 μL, 200 mM), DCM (25 μL, 50 mM), 1-ethynyl-4-fluorobenzene (25 μL, 200 mM), LiI (100 μL, 200 mM), and 2-picolyl azide (25 μL, 200 mM) were added to a rubber septum-sealed NMR tube sequentially using glass syringes. Then 250 μL of CD_3CN was injected into the NMR tube. An initial scan of the mixture was taken which served as time "0". Immediately prior to the spectral acquisition, $Cu(ClO_4)_2 \cdot 6H_2O$ (50 μL, 200 mM) was injected into the sample. This injection served as the start time for the reaction. The final concentrations of all the reaction components are listed in the caption of Figure 10. NMR spectra were collected every 3 min over the course of the reaction for 1.5 on average.

The Procedure to Study the Effect of TEA on the Outcome of the Reaction. TEA (10 μL, 200 mM), DCM (25 μL, 50 mM, internal standard), 1-ethynyl-4-fluorobenzene (25 μL, 200 mM), and LiI (100 μL, 200 mM) were added to a rubber septum-sealed NMR tube sequentially using glass syringes. The mixture was diluted with 265 μL of CD_3CN before adding $Cu(ClO_4)_2 \cdot 6H_2O$ (25 μL, 200 mM). An initial NMR was taken, which marked as time "0". After collecting the initial scan, 2-picolyl azide (25 μL, 200 mM) was injected into the sample. This injection served as the start time for the reaction. The concentrations of all reaction components at the start of the reaction are listed in the caption of Figure 6. Six NMR scans were then collected from the sample every 3 min. Immediately after the sixth scan, TEA (15 μL, 200 mM) was injected into the NMR tube and the reaction was again scanned six times. The process was repeated two more cycles with sequential additions of TEA (10 μL × 2 at 200 mM). The NMR experiments to study the effects of LiI and $Cu(ClO_4)_2 \cdot 6H_2O$ were conducted similarly.

Supporting Information. Additional figures and $^{1}H/^{13}C$ NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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(39) The concentrations of azide and alkyne (10 mM each) in the current work are the lowest to date to achieve full conversion to iodotriazole.

(40) Under the same conditions, a non-chelating azide such as benzyl azide is unable to initiate iodotriazole formation within the same time period (i.e., 2 h), unless an accelerating ligand TBTA is involved in the reaction (Figure S1).

(41) If $Cu(ClO_4)_2 \cdot 6H_2O$ were the sole oxidant, the theoretical iodoalkyne yield would be 25%. The observation of 40% iodoalkyne formation suggests that O_2 (likely dissolved in the solvent) participated in the reaction in re-oxidizing copper(I).

(42) The formation of the inhibitive Cu(II)/TEA complex as identified by the broad triplet just short of 7 ppm on the ^1H NMR spectrum depends on the ratio of TEA and $Cu(ClO_4)_2 \cdot 6H_2O$. As TEA is more than twice as much as $Cu(ClO_4)_2 \cdot 6H_2O$, the broad triplet starts to disappear (Figure S2), and the reactivity of the Cu(II)/TEA/LiI system to produce iodoalkyne appears to be restored.

(43) Previously only the reaction starting from iodoalkyne was *catalyzed* by a copper(I) salt (e.g., ref. #21). All examples starting from terminal alkyne required stoichiometric amount of copper salt (e.g., refs #16-20, 27).

(44) Thompson, J. S.; Bradley, A. Z.; Park, K.-H.; Dobbs, K. D.; Marshall, W. *Organometallics* **2006**, *25*, 2712.

(45) Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 7558.

(46) Or, as a reviewer pointed out that the azide could be a nucleophile, while π-activated iodoalkyne is the electrophile. We agree that this scenario is likely, and possibly operating in a concerted pathway, as recently suggested in Ref. #33.

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

(48) Armatore, C.; Blart, E.; Genet, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829. The resulting iodoalkyne has to be rigorously purified to remove any possible contamination of highly reactive iodinating agents.

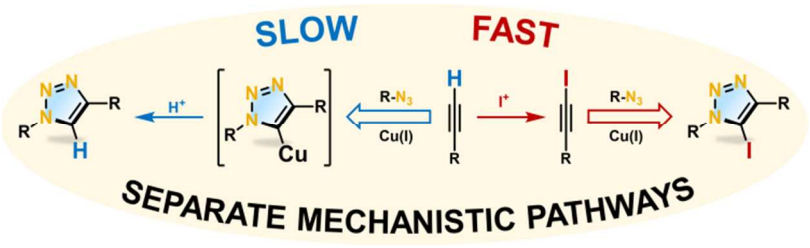
(49) In this case the iodotriazole formation appeared to have been accelerated by the presence of allyl iodide. The presence in the reaction mixture of the alkynylated triazole **15** and an uncharacterized allyl derivative (Figure S7) will be investigated at a future time.

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

(51) Liu, B.; Ma, X.; Wu, F.; Chen, W. *Dalton Trans.* **2015**, *44*, 1836.

(52) Warrell, B. T.; Matik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457.

SYNOPSIS.


SLOW
FAST
H+
R-N3
Cu(I)
I+
R-N3
Cu(I)
Cu
SEPARATE MECHANISTIC PATHWAYS