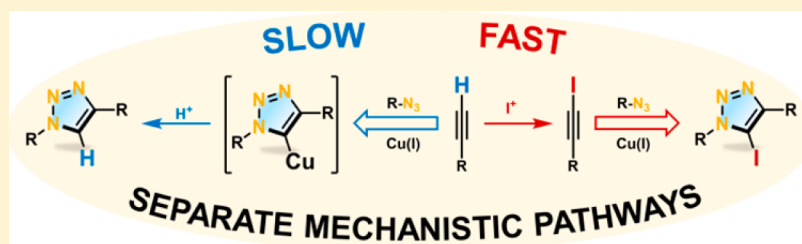# Mechanism of Copper(I)-Catalyzed 5-Iodo-1,2,3-triazole Formation from Azide and Terminal Alkyne

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S *Supporting Information*

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 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 of the iodoalkyne is consumed. Using ¹H NMR to follow a homogeneous iodotriazole forming reaction, the rapid formation of an iodoalkyne is shown to dictate the selectivity of an iodotriazole over a protiotriazole. To ensure the exclusive production of iodotriazole, the complete conversion of an alkyne to an 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 (Figure 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(ClO₄)₂·6H₂O, which quickly affords the CuI catalyst for the subsequent cyclo-addition, *and* the electrophilic I₂ or I₃⁻ as the source of the iodo substituent.[23] This method avoids the preformation of an 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) result-ing 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 iodo-triazoles.

The postulated mechanisms of iodotriazole formation from either an iodoalkyne or a terminal alkyne are summarized in Figure 2. One unclarified issue is whether a copper(I) triazolide (E) intermediate is involved. Hein, Fokin, and co-workers described two possible routes starting from an iodoalkyne.[21,25] One entails a cycloaddition between an 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]
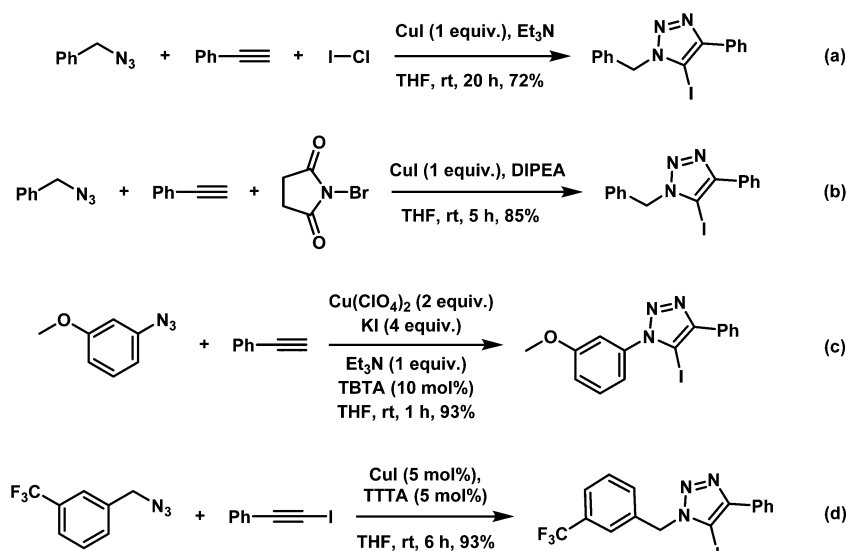
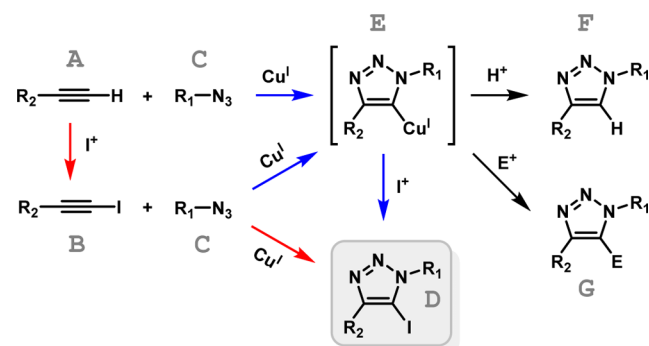**Figure 1.** Selective methods for preparing iodotriazoles.

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 an iodoalkyne (**4**) from an 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.

■ 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
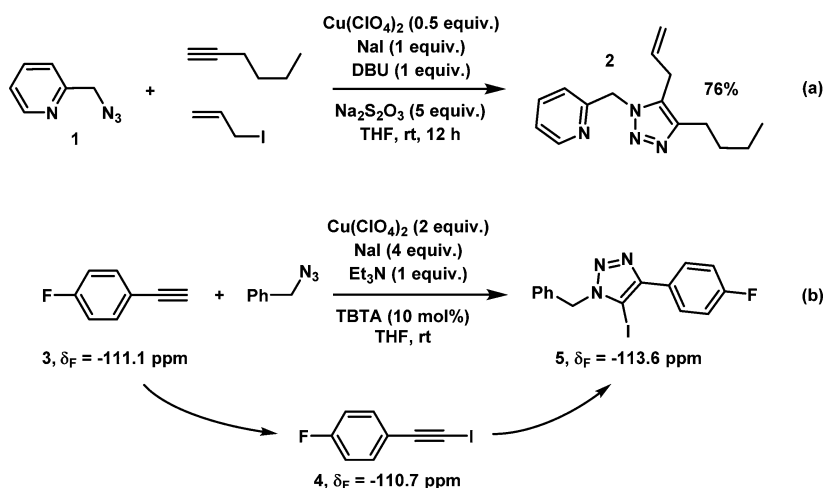

Figure 3. Observations supporting (a) copper(I) triazolide,[19] and (b) iodoalkyne intermediates.[20]
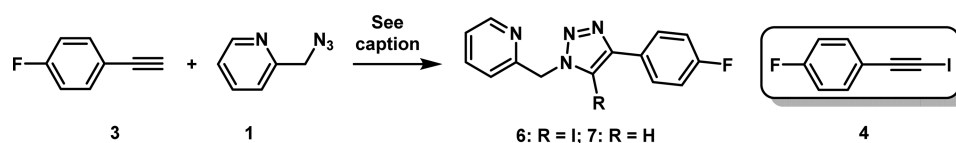
Figure 4. A homogeneous reaction between azide **1** and alkyne **3** to afford iodotriazole **6** was monitored by ^{1}H NMR in real time. Protiotriazole **7** is the side product. Reagents: azide **1** (10 mM), alkyne **3** (10 mM), TEA (0−60 mM), LiI (20−45 mM), Cu(ClO$_4$)$_2$·6H$_2$O (0−30 mM), in CD$_3$CN (0.5 mL).

3b).[20] While this method provided evidence of the iodoalkyne intermediate, revelations on other aspects of the reaction, in particular the changes of nonfluorinated 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 *homogeneous* 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.

Stock solutions of each reaction component were prepared in CD$_3$CN. 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 homogeneous, 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 oweing to its excellent reactivity and solubility in CD$_3$CN. 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.

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$_4$)$_2$·6H$_2$O (10 mM), and TEA (4 mM) were dissolved in CD$_3$CN. The amount of Cu(ClO$_4$)$_2$·6H$_2$O as the stoichiometric oxidant is enough to convert 50% of the alkyne to an iodotriazole, leaving the other half to afford a 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 an iodoalkyne is sensitively dependent on [TEA]. The conversion of an alkyne to

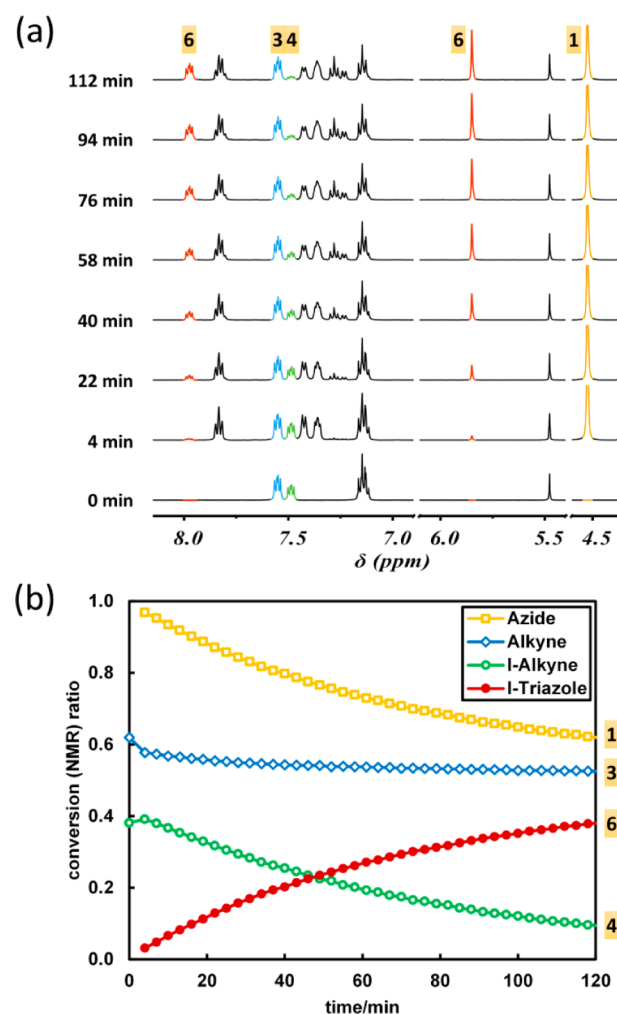**Figure 5.** (a) Time-evolution of the ^{1}H NMR spectrum of a reaction shown in Figure 4. The reactants were dissolved in CD$_3$CN (0.5 mL) in the following order: TEA (20 mM), DCM (2.5 mM, internal standard), LiI (40 mM), alkyne **3** (10 mM, blue), and Cu(ClO$_4$)$_2$·6H$_2$O (20 mM). Azide **1** (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**]).

iodoalkyne, but not necessarily the rate, also depends on [TEA]. As soon as iodoalkyne **4** was fully consumed after ~50 min, 50% of alkyne **3** had been converted to iodotriazole **6**, which is the maximum possible amount of iodotriazole
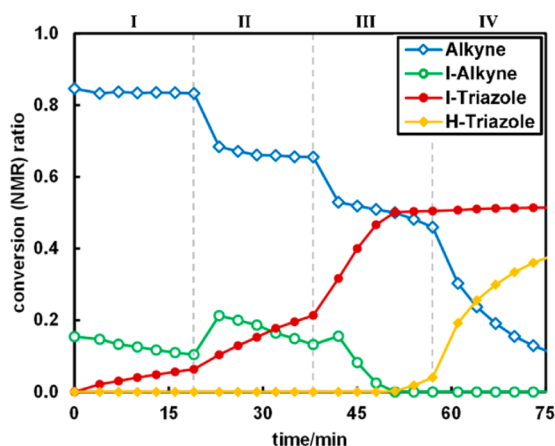
Figure 6. Effect of TEA on the outcome of the reaction. Blue open diamonds, alkyne **3**; green open circles, iodoalkyne **4**; garnet filled circles, iodotriazole **6**; and gold filled diamonds, protiotriazole **7**. Initial concentrations: alkyne **3** (10 mM), LiI (40 mM), TEA (4.0 mM), and $Cu(ClO_4)_2 \cdot 6H_2O$ (10 mM). Azide **1** (10 mM) was added after the first datum point was taken. [TEA] was increased to 10, 13, and 17 mM at the end of sections I, II, and III, respectively.

Figure 7. 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.

production under the given conditions. At this point, the formation of protiotriazole **7** commenced, which was significantly accelerated by the last addition of the 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 the 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 an iodoalkyne will be elaborated in subsection 4.

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) (eq 1). The ^{1}H 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 eq 1 is an equilibrium with a substantial amount of copper in the +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
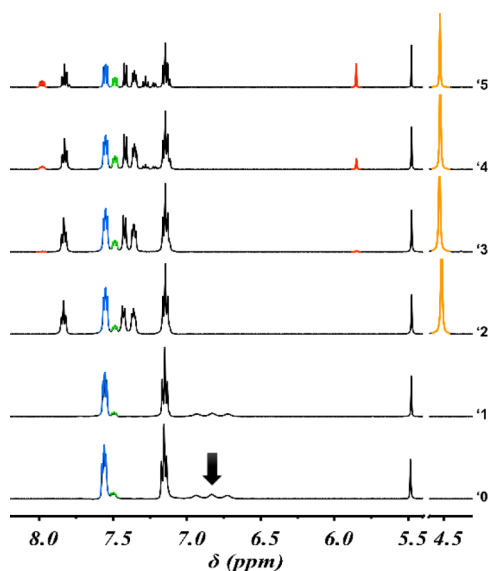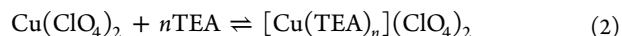
(eq 2, Figure S2), the observation of which marks a condition unsuitable for iodotriazole formation.

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

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

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 $CuClO_4$ (eq 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 (eq 3). Therefore, CuI, rather than acetonitrile-solvated copper(I), presumably catalyzes the iodotriazole formation.

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

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 of the iodoalkyne is

consumed, the iodoalkyne formation needs to be maximized in order to achieve a high iodo/protio selectivity.

4. Iodo/Protio Selectivity Depends on the Efficiency of Iodoalkyne Formation. The conversion from an iodoalkyne to an iodotriazole precedes that of an alkyne to a protiotriazole (Figure 6). Therefore, the efficient iodoalkyne formation appears to be the prerequisite for a selective synthesis of an iodotriazole over a protiotriazole. The factors that contribute to the iodoalkyne formation were studied (Figure 8a). In the absence of azide **1**, mixing alkyne **3** (10
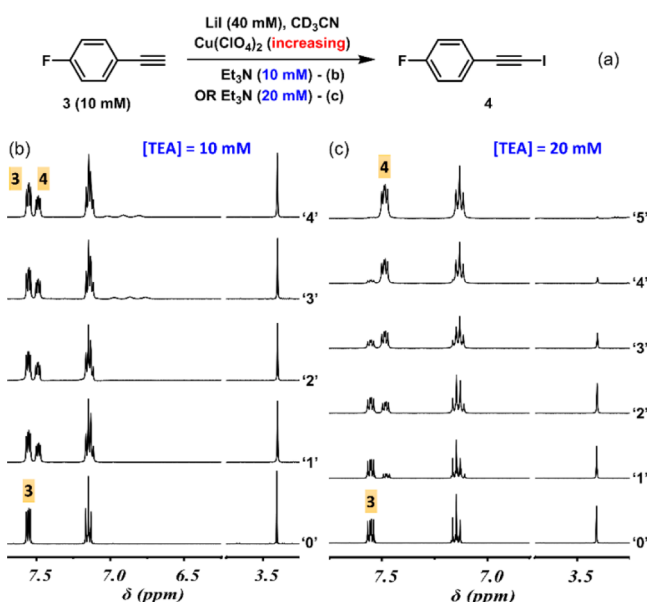

Figure 8. (a) Iodoalkyne **4** formation from alkyne **3** (10 mM) in the presence LiI (40 mM), Et₃N (10 or 20 mM), and Cu(ClO₄)₂·6H₂O (0−25 mM). (b) [TEA] = 10 mM and [Cu(ClO₄)₂ 6H₂O] at '0', '1', '2', '3', and '4' were 0, 5, 10, 15, and 19 mM, respectively. (c) [TEA] = 20 mM and [Cu(ClO₄)₂ 6H₂O] at '0', '1', '2', '3', '4', and '5' were 0, 4, 10, 16, 21, and 25 mM, respectively.

mM), LiI (40 mM), Cu(ClO₄)₂·6H₂O (5 mM), and TEA (10 mM) in CD₃CN resulted in the instantaneous formation of iodoalkyne **4** (Figure 8b, spectrum '1') at the 40% level.[41] The addition of more Cu(ClO₄)₂·6H₂O (Figure 8b, spectra '2'−'4') failed to result in a further increase in iodoalkyne production. The ¹H NMR spectra acquired when [Cu(ClO₄)₂·6H₂O] 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(ClO₄)₂·6H₂O] 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.
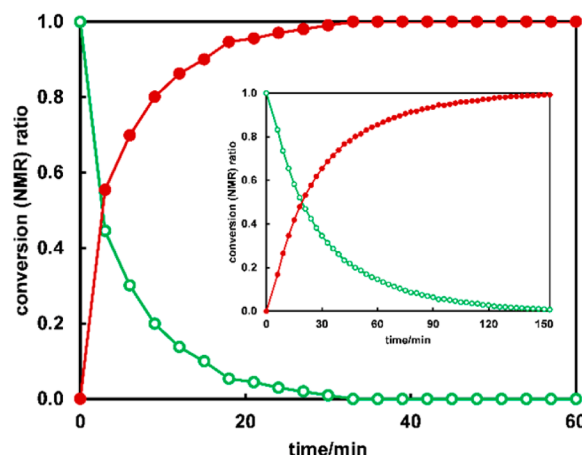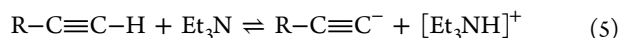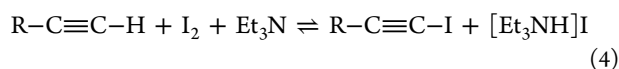

Figure 9. Full conversion to iodoalkyne **4** (green open circles) leads to the complete selectivity for iodotriazole **5** (garnet filled circles). Concentrations: alkyne **3** (10 mM), LiI (40 mM), Cu(ClO₄)₂·6H₂O (25 mM), and TEA (25 mM). Azide **1** (10 mM) was added after the first spectrum was taken. Inset: alkyne **3** (10 mM), Cu(ClO₄)₂·6H₂O (2 mM), LiI (15 mM), I₂ (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 a terminal alkyne followed by electrophilic iodination (eq 4). The deprotonation step is depicted in eq 5. In addition to being a base, TEA also activates I₂ via the TEAI⁺ intermediate (eq 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 I₂ 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.

$$R-C\equiv C-H + I_2 + Et_3N \rightleftharpoons R-C\equiv C-I + [Et_3NH]I \tag{4}$$

$$R-C\equiv C-H + Et_3N \rightleftharpoons R-C\equiv C^- + [Et_3NH]^+ \tag{5}$$

$$I_2 + Et_3N \rightleftharpoons [Et_3NI]^+ + I^- \tag{6}$$

In our iodotriazole synthesis, Cu(ClO₄)₂·6H₂O has been used as the stoichiometric oxidant that converts iodide to iodine (or triiodide), which reacts with the alkyne to afford the iodoalkyne. If iodine (I₂) was offered as the stoichiometric oxidant, then the reaction could be rendered catalytic in Cu(ClO₄)₂·6H₂O. The reaction shown in the inset of Figure 9 indeed proceeded smoothly in the presence of 20 mol % Cu(ClO₄)₂·6H₂O and 0.8 mol equiv of I₂, which is the first example of copper-*catalyzed* iodotriazole formation from a *terminal alkyne*.[43] TEA and LiI were added at 3.0 and 1.5 mol equiv, 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
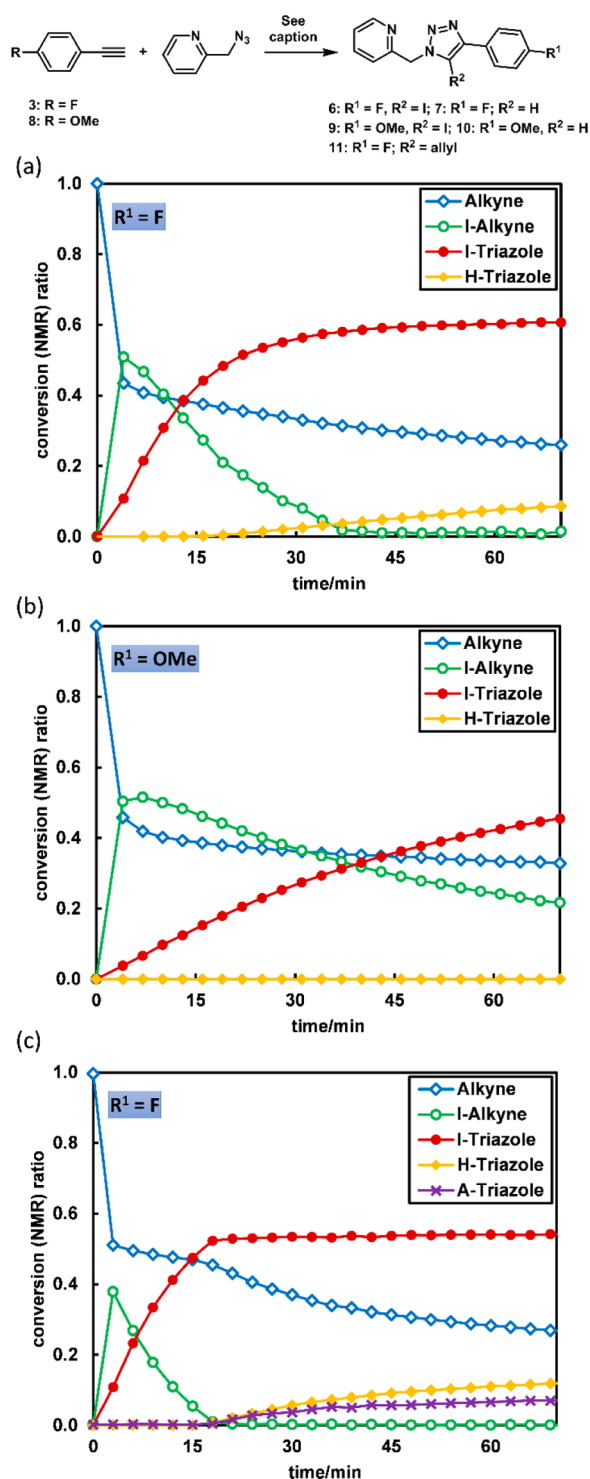
3: R = F
8: R = OMe

6: R¹ = F, R² = I; 7: R¹ = F; R² = H
9: R¹ = OMe, R² = I; 10: R¹ = OMe, R² = H
11: R¹ = F; R² = allyl

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$_4$)$_2$·6H$_2$O (10 mM), and TEA (20 mM) in CD$_3$CN.

reducing the copper loading so that both iodo- and protiotriazole products could form. In the experiments, all reaction components other than Cu(ClO$_4$)$_2$·6H$_2$O were dissolved in CD$_3$CN in an NMR tube, and an initial NMR spectrum was taken before Cu(ClO$_4$)$_2$·6H$_2$O was added to start the reaction. Therefore, unlike the data presented in previous
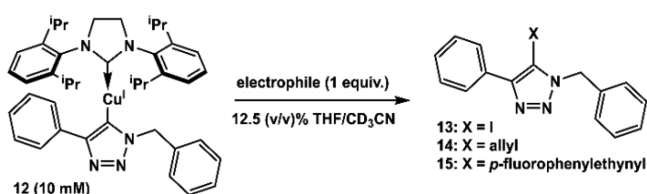
sections, no *in situ* preformation of iodoalkyne was deliberately done.

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-fold. A 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 the iodoalkyne appears insensitive to the substituent on the alkyne. Therefore, the iodoalkyne formation step is not turnover 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 turnover limiting and is favored by an electron-deficient iodoalkyne. Presumably, backbonding of copper(I) to the 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, an allyl iodide was introduced into the reaction mixture that produced the data in Figure 10a. In comparison 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 coproduction 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 the iodotriazole is (almost) over in a separate reaction pathway.

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 co-workers,[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 co-workers.[21] Allyl iodide turned out to be a more competent electrophile in the reaction with copper(I) triazolide **12**, reaching a 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

Table 1. Electrophile Trapping of [Cu^I(NHC)(Triazolide)] 12[a]

13: X = I
14: X = allyl
15: X = p-fluorophenylethynyl

Entry	Electrophile	Time	13 (%)	14 (%)	15 (%)
1	F—⬡—≡—I	3 h	3	-	2
2	F—⬡—≡—I	26 h	64	-	21
3	⟋⟍I	3 h	-	58	-
4	⟋⟍I + F—⬡—≡—I	3 h	24	54	2
5	⟋⟍I + I—I	5 min	100	0	-

[a]Conditions: Compound **12** (10 mM) and electrophile (10 mM each) in CD$_3$CN with 12.5% (v/v) THF at rt. The yields were calculated from the ^{1}H NMR spectra of the reaction mixtures.

allyltriazole **14** formed simultaneously with the latter having a higher rate (Figure 11).[49] This kinetic profile is in stark contrast
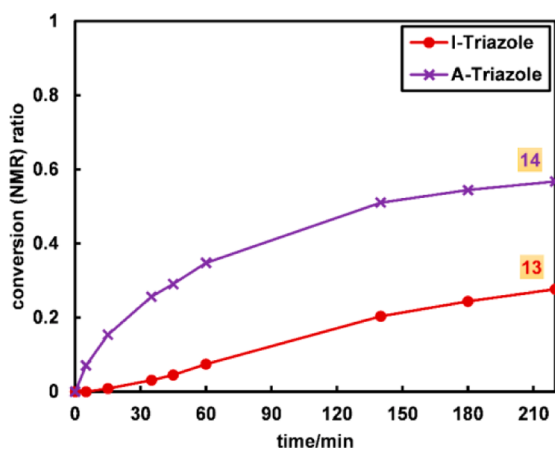

Figure 11. Reaction progress of entry #4 in Table 1 monitored by ^{1}H NMR. Concentrations: [Cu^I(NHC) (triazolide)] (**12**, 10 mM), iodoalkyne **4** (10 mM), and allyl iodide (10 mM) in CD$_3$CN with 12.5% (v/v) THF at rt.

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 the 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.

8. Mechanistic Proposal. The iodotriazole formation mechanism as shown in Figure 12 starts from the rapid reduction of Cu(ClO$_4$)$_2$·6H$_2$O 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 the alkyne to iodoalkyne (depicted in the gray box), which is completed within the time of preparing an NMR sample, sends the iodoalkyne into the catalytic cycle on right to produce the iodotriazole. Based on our previous work, an accelerating ligand such as tris[(1-benzyl-1*H*-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 an 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 a terminal alkyne or an iodoalkyne, the reaction bypasses the copper(I) triazolide intermediate by proceeding in a separate pathway via a rapid formation of an iodoalkyne followed by the copper(I)-catalyzed cycloaddition with an azide.

CONCLUSIONS

Azides and alkynes undergo copper(I)-catalyzed cycloadditions in the presence of an electrophilic iodinating agent to afford iodotriazoles, while a 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 an iodoalkyne or on the copper(I) triazolide intermediate within the catalytic cycle to afford an iodotriazole. This work provides evidence to support the former scenario, in which the iodoalkyne forms rapidly from an alkyne in the presence of an iodinating agent. The iodoalkyne then undergoes cycloaddition with an azide to afford an 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 an iodotriazole in a reaction starting from a terminal alkyne, conditions need to be applied to ensure full *in situ* conversion of the alkyne to the 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 toward certain electrophiles, including I$_2$ to afford an iodotriazole. However, in reality it is bypassed on the reaction coordinate that starts from a terminal alkyne.

EXPERIMENTAL SECTION

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.

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$_4$)$_2$·6H$_2$O was dried in a vacuum oven at 40 °C before use. Stock solutions of each reaction component were prepared in advance except Cu(ClO$_4$)$_2$·6H$_2$O, which was prepared immediately prior to mixing because of its
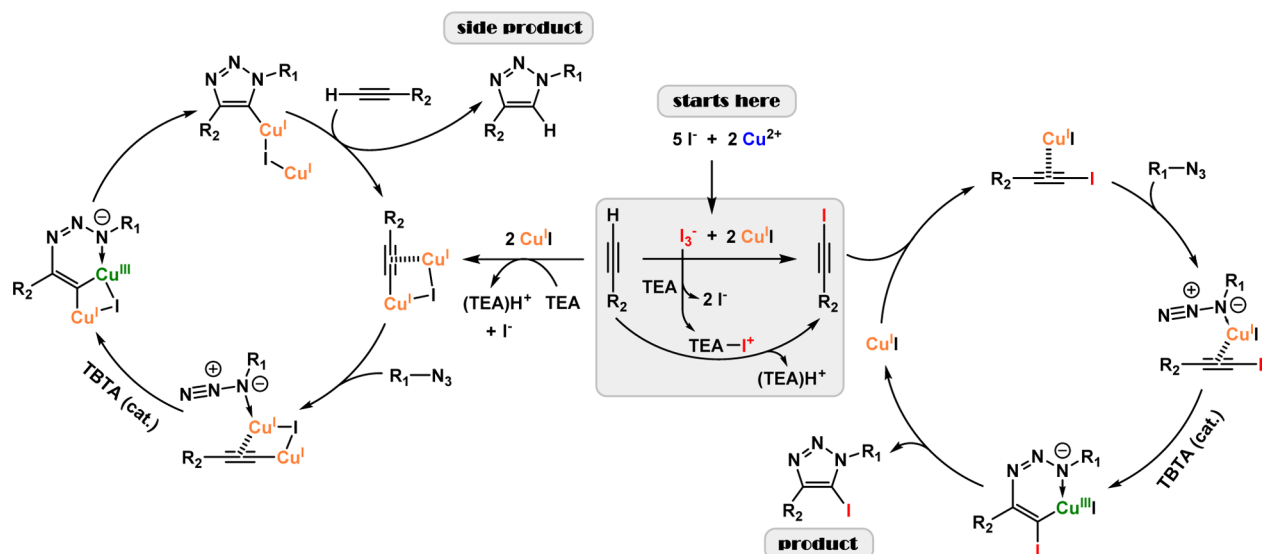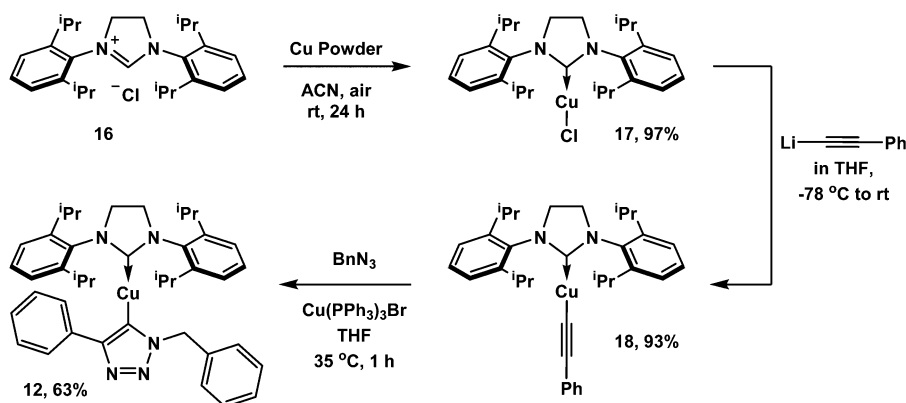
Figure 12. Proposed mechanism of iodotriazole formation under the conditions shown in the caption of Figure 4. Copper in oxidation states +1, + 2, and +3 are color-coded orange, blue, and green, respectively.

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

tendency to lose efficacy in acetonitrile. ^{1}H 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$_2$S$_2$O$_3$ (158 mg, 1.0 mmol), and Cu(ClO$_4$)$_2$·6H$_2$O (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$_2$Cl$_2$ to remove the inorganic materials. Solvent removal followed by purification on a silica column eluted with CH$_2$Cl$_2$ 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$_3$CN) 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$_3$CN) 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.

[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) (Scheme 1). The reaction was stirred vigorously at rt for 10 min and 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 (Scheme 1). 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) and 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 redissolved 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$_6$D$_6$) 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 ref 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$_3$)$_3$Br (36 mg, 0.04 mmol) were suspended in dry THF (10 mL) (Scheme 1). 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$_2$Cl$_2$) 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$_2$Cl$_2$) 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$_5$Cu, 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$_3$CN were prepared in advance for all reaction components except Cu(ClO$_4$)$_2$·6H$_2$O, because of its tendency to lose efficacy in acetonitrile. The Cu(ClO$_4$)$_2$·6H$_2$O 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$_3$CN before adding Cu(ClO$_4$)$_2$·6H$_2$O (50 μL, 200 mM). The first NMR spectrum taken was marked as time "0". After the initial scan was collected, 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$_3$CN were 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$_4$)$_2$·6H$_2$O (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 h 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$_3$CN before adding Cu(ClO$_4$)$_2$·6H$_2$O (25 μL, 200 mM). An initial NMR was taken, which 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. 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 for 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$_4$)$_2$·6H$_2$O were conducted similarly.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01536.

Additional figures and ^{1}H/^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(40) Under the same conditions, a nonchelating 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$_4$)$_2$·6H$_2$O 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 reoxidizing 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 ^{1}H NMR spectrum depends on the ratio of TEA and Cu(ClO$_4$)$_2$·6H$_2$O. As TEA is more than twice as much as Cu(ClO$_4$)$_2$·6H$_2$O, 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 the terminal alkyne required a stoichiometric amount of copper salt (e.g., refs 16−20, 27).

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