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# Photoinduced Copper-Catalyzed Regioselective Synthesis of Indoles: Three-Component Coupling of Arylamines, Terminal Alkynes, and Quinones

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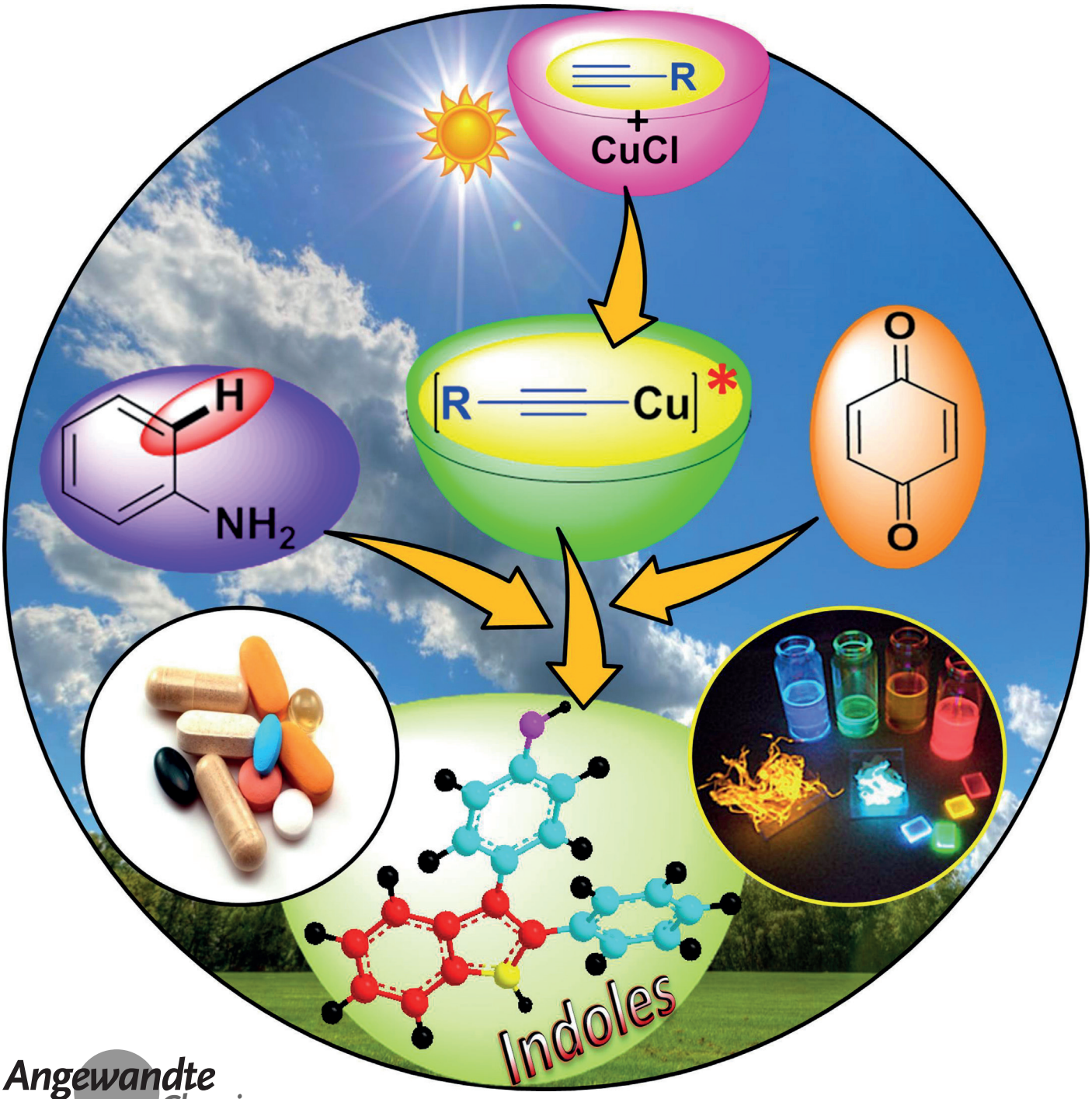
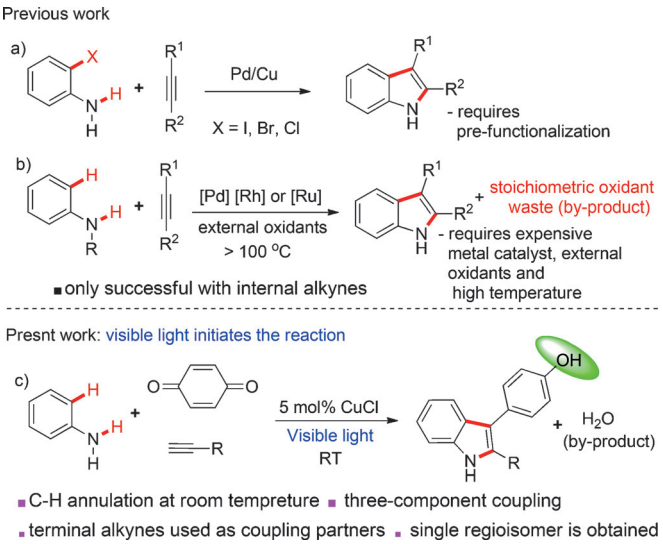


***Abstract:*** *The first successful example of a visible-light-induced copper-catalyzed process for C–H annulation of arylamines with terminal alkynes and benzoquinone is described. This three-component reaction allows use of a variety of commercial terminal alkynes as coupling partners for the one-step regioselective synthesis of functionalized indoles. Moreover, the current process represents a sustainable and atom-economical approach for the preparation of complex indoles from easily accessible starting materials under visible-light irradiation, without the need for expensive metals and harsh reaction conditions.*

The indole scaffold is an important structural component of numerous natural products, pharmaceutical drugs, and organic materials.[1] Over the last 100 years, an array of powerful approaches have been developed for the synthesis of the indole moiety, including the classical Fischer indole synthesis.[2] Among them, palladium/copper-catalyzed aniline–alkyne cyclizations are the predominent methods for constructing indoles.[3] However, these methods mostly require prefunctionalized anilines (Scheme 1 a). To address this challenge, researchers have recently focused on exploiting the C–H annulation of easily accessible arylamines without a C–X bond.[4] Thus far, expensive metal catalysts such as palladium, ruthenium, and rhodium complexes play a central role in the preparation of indoles by C–H annulation of internal alkynes with aryl amines (Scheme 1 b).[5] Despite the increased attention, common disadvantages of all these methods include: a) the requirement of stoichiometric amounts of oxidants, such as, $Cu(OAc)_2$, AgOAc, $PhI(OAc)_2$, and *t*BuOOH, thus leading to the generation of undesired waste, b) the need for high-reaction temperatures, c) the fact that the reaction works only with internal alkynes, and d) generation of unsymmetrical aryl indoles as a mixture of regioisomers. Recently, copper complexes have been successfully employed as an inexpensive catalyst/mediator for oxidative C–H alkynylation of arenes/heretoarenes,[6] as well as for intra- and intermolecular coupling reactions through C–H functionalization.[7] Despite the many advantages, a copper-catalysis strategy for C–H annulation of arylamines with terminal or internal alkynes remains unexplored for either photochemical or thermal (dark) conditions. Thus, further the discovery of new types of copper-catalyzed C–H annulations using unactivated terminal alkynes as a coupling partner, especially under low-energy visible-light irradiation, remains unexplored.

Visible-light-activated photoredox catalysis has recently emerged as a novel activation mode and an alternative to thermal metal-catalyzed reactions.[8] Moreover, photoinitiated copper redox catalysis has been shown to be an inexpensive and potentially useful method for alkyne–azide cycloaddition (CuAAC) reactions,[9] C–C cross-couplings,[10]




***Scheme 1.*** Transition-metal-catalyzed indole synthesis.

and various C–N, C–S, and C–O cross-coupling reactions.[11] We have recently reported a visible-light-induced CuCl-catalyzed process for efficient C–C and C–N cross-coupling reactions.[12] We envisioned that these visible-light-mediated couplings may proceed through the initial photoexcitation of copper(I) acetylides.[12a,d] Herein we report the discovery of the first visible-light-induced three-component coupling (TCC) of aniline, alkynes, and benzoquinone to assemble indoles through a C–H annulation under mild reaction conditions (room temperature) by using a simple and inexpensive process (5% CuCl, without the use of external oxidants; Scheme 1 c). The current process is unprecedented, and is complementary to well-known copper-catalyzed $A^3$-coupling reactions (amine, alkyne, and aldehyde).[13] Furthermore, installation of a phenol functional group on the indole ring is attractive because the phenol motif not only allows a broad range of transformations, including Ullmann C–O couplings,[14] electrophilic aromatic substitutions (alkylation and acylation), and other processes/transformations,[15] but also facilitates stronger β-binding affinity toward estrogen receptors (ER) than does an unfunctionlized phenyl ring.[16] The current work represents the very first literature method for single-step regioselective synthesis of 3-*p*-hydroxyphenyl-substituted indoles (Scheme 1 c).

In an initial study (Table 1), we were delighted to find that visible-light irradiation of aniline (**1a**), phenylacetylene (**2a**), and benzoquinone (**3a**) in $CH_3CN/CH_3OH$ (1:1 v/v) in the presence of CuCl (5 mol%) at 25 °C for 6 hours furnished the corresponding indole **4a** in 55% yield[17] (Table 1, entry 1). After optimization, we found that in $CH_3OH$, the product yield is improved to 85% (entry 2), and the presence of water (0.5 mL) does not affect the reaction (entry 8). However, other solvents were examined and poor yields were obtained (entries 5–7). Different copper catalysts were screened, and CuX (X = Cl or Br) turns out to be the most effective catalyst (entries 2 and 3). Control experiments show that, in the absence of either light, CuCl ,or benzoquinone, no reaction occurs (entries 10–12). Meanwhile, the reaction can be

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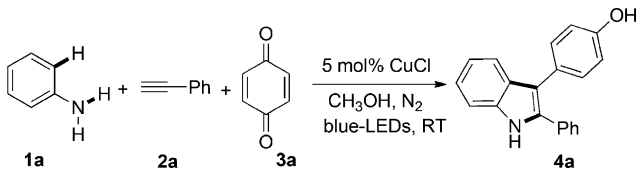
***Table 1:*** Optimization of reaction conditions.[a]




| Entry | [Cu] Catalyst | Solvent | Yield [%][b] |
|---|---|---|---|
| 1 | CuCl | $CH_3CN$/MeOH (1:1) | 55 |
| 2 | CuCl | MeOH | 85 |
| 3 | CuBr | MeOH | 85 |
| 4 | $CuCl_2$ | $CH_3CN$/MeOH (1:1) | 0 |
| 5 | CuCl | $CH_3CN$ | 10 |
| 6 | CuCl | EtOH | 76 |
| 7 | CuCl | DMF | trace |
| 8[c] | CuCl | MeOH/$H_2O$ | 74 |
| 9[d] | CuCl | MeOH | 60 |
| 10[e] | CuCl | MeOH | 0 |
| 11[f] | none | MeOH | n.r |
| 12[g] | CuCl | MeOH | n.r |

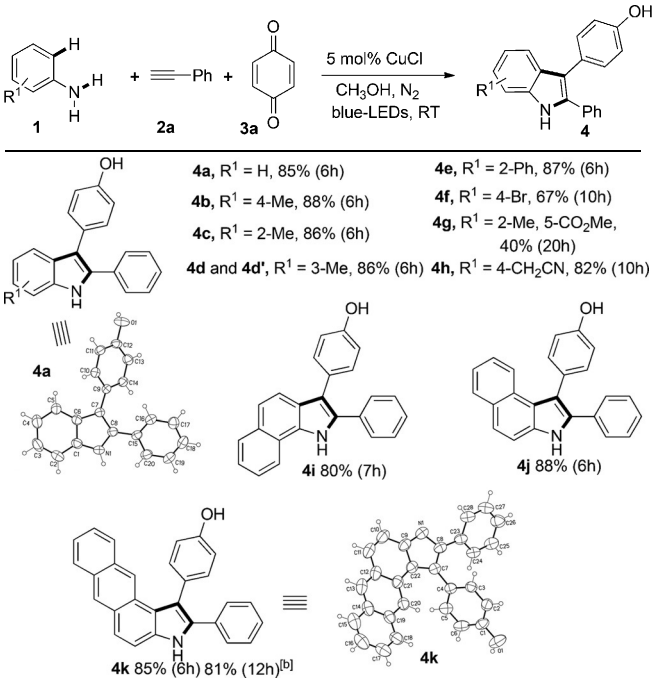
[a] Unless otherwise noted, reaction conditions are as follows; **1a** (0.5 mmol), **2a** (0.55 mmol), **3a** (0.6 mmol), [Cu] catalyst (5 mol%), and solvent (7 mL). The mixture was irradiated with blue LEDs (power density: 40 mW cm$^{-2}$ at 460 nm) for 6 h in a $N_2$ atmosphere. [b] Yield of the isolated product. [c] 0.5 mL water was added. [d] Reaction irradiated with an ambient white light bulb for 15 h (power density: 8 mW cm$^{-2}$ at 460 nm). [e] Reaction conducted in the dark at 60 °C. [f] In the absence of [Cu] catalyst. [g] In the absence of benzoquinone (**3a**). n.r. = no reaction, DMF = *N*,*N*-dimethylformamide.

conducted using other light sources (ambient white light; entry 9), however blue LEDs provided better yields.

By using the optimal reaction conditions (Table 1, entry 2), we explored the scope of the reaction with various substituted anilines (Table 2). In most of cases, both electron-rich and electron-neutral anilines proceed smoothly to afford the corresponding indole products (**4a**–**e**; 85 to 88% yield). However, the reaction of a *meta*-substituted aniline (**1d**) resulted in the formation of a mixture of regioisomers (inseparable). It was found that the current protocol was well tolerated by a wide range of substrates, such as, 1-naphthyl amine, 2-naphthyl amine, and 2-amino-anthracene, and facilitates the expedient synthesis of complex indoles (**4i**–**k**). Notably, a halo-substituted aniline selectively underwent the C–H annulation (**4f**), and the competitive Sonogashira reaction[12a,18] does not occur. Moreover, anilines containing ester and benzylnitrile moieties could also be employed to generate indole scaffolds in good to moderate yields (**4g,h**). In addition, the current process can be readily scaled up to a gram scale (0.96 g); 1.56 grams of **4k** (81% yield) can be obtained after 12 hours of irradiation with blue LEDs at room temperature (see Scheme S1 in the Supporting Information).

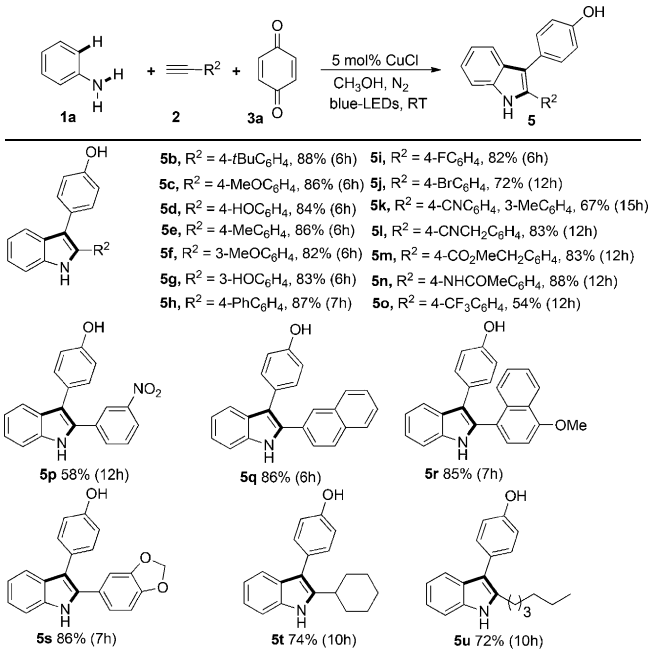
Next, the scope with respect to the terminal alkynes was examined under the optimized reaction conditions. As shown in Table 3, a wide range of phenylacetylenes, including both elecrton-rich and electron-deficient groups, are amenable to the current protocol (**5b**–**h**, 82 to 88%; **5k**–**p**, 54-88% yield). Notably, the indole **5d** has good binding affinities to the estrogen receptor (ER).[19] In addition, aryl alkynes bearing halo-substituents (**2i,j**) can readily react with **1a** and **3a** to

***Table 2:*** Scope of arylamines (**1**).[a]




[a] Standard reaction conditions. Yield of product isolated after purification by column chromatography on silica gel. [b] The reaction was performed on a 5 mmol (0.96 g) scale (a preparative scale).

***Table 3:*** Scope of terminal alkynes (**2**).[a]




[a] Standard reaction conditions. Yield of the product isolated after purification by column chromatography on silica gel.

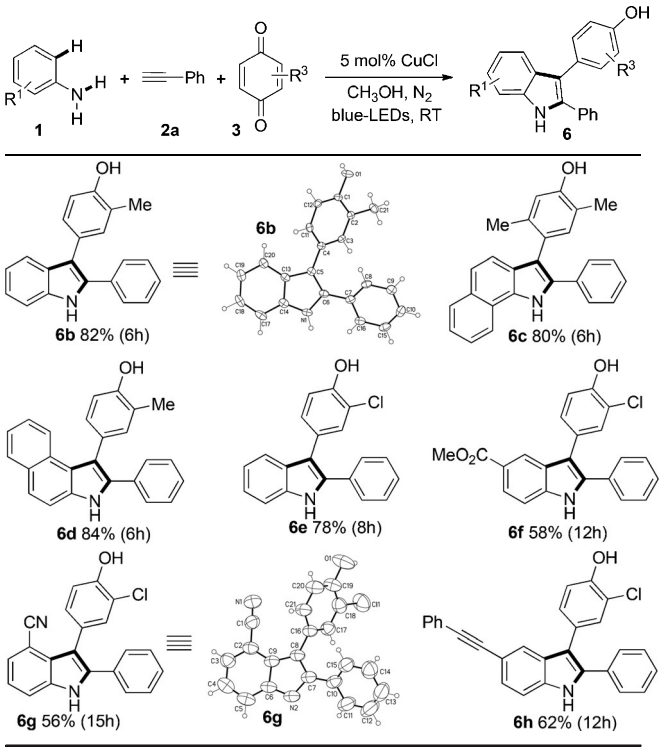
yield the desired indoles (**5i,j**). In general, copper-catalyzed oxidative C–H annulation reactions involving terminal alkynes often suffer from homocoupling by-product formation.[6] In the current three-component C–H annulation

reactions, no alkyne homocoupling product was observed. Besides aryl alkynes, other terminal alkynes, including bulky naphthalenyl, heteroaryl, cyclohexyl, and octyl alkynes, also underwent the reaction to furnish the desired indoles in good yields (**5q**–**u**). Notably, terminal alkynes, which are challenging coupling partners for rhodium-, palladium-, nickel-, and ruthenium-catalyzed indole synthesis,[5] proved to be amenable to the current system.

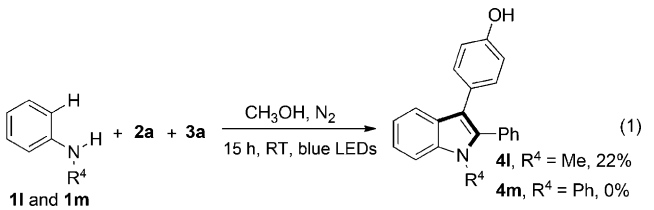
As shown in Table 4, substituted benzoquinones (**6b**–**h**) also successfully underwent the reaction to provide indole products in good yields (56–84% yields). It is notable that unsymmetrical benzoquinones, such as 2-methyl benzoquinone (**3b**) and 2-chloro benzoquinone (**3e**), selectively underwent the C–H annulation reaction to deliver a single regioisomer (**6b, 6d**, and **6e**–**h**).

***Table 4:*** Scope of benzoquinones (**3**).[a]

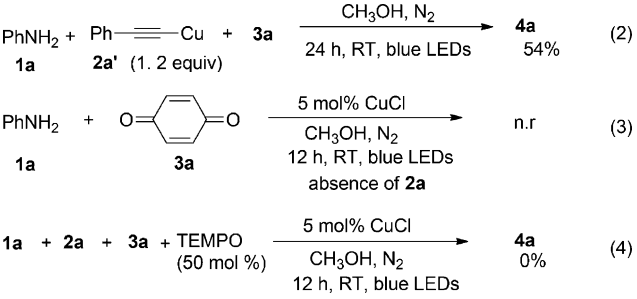



[a] Standard reaction conditions. Yield of the product isolated after purification by column chromatography on silica gel.

The structures of **4a**, **4k**, **6b**, and **6g** were confirmed by single-crystal X-ray diffraction.[20] A selected example of *N*-methyl aniline (**1l**) coupled with **2a** and **3a** to afford the target indole (**4l**) in a lower yield of 22% [Eq. (1)], but *N*-phenyl aniline (**1m**) does not work in the current system.




To study the reaction mechanism, a set of control experiments were carried out [Eq. (2)–(4)]. First, we synthesized the copper(I) phenylacetylide **2a′**[21] and investigated its reaction with **1a** and **3a** under standard reaction conditions. The copper(I) phenylacetylide **2a′** (1.2 equiv) reacted with **1a** to afford the indole product **4a** in 54% upon isolation [Eq. (2)]. Notably, copper-catalyzed 1,3 nucleophilic addition of aryl amines to benzoquinone is already known in the literature.[7b] However, in the absence of **2a** under the standard reaction conditions, the reaction of **1a** with **3a** does not occur [Eq. (3)]. This result indicates that in situ generated copper(I) phenylacetylide might be the key light-absorbing catalyst. Furthermore, the reaction of **1a**, **2a**, and **3a** in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was examined under the standard reaction condition. The formation of **4a** was completely inhibited [Eq. (4)], thus suggesting that a radical process might be involved in the reaction. Finally, we found that benzoquinone quenches the excited state of the copper(I) phenylacetylide (**7**), as indicated by luminescence quenching experiments (see Figure S7 in the Supporting Information).




Moreover, the presence of 1 mM benzoquinone reduces the lifetime of **7** from 15.95 μs to 11.05 μs (see Figure S8 in the Supporting Information). Since copper is not a heavy metal and does not have strong spin-orbital coupling character, most organocopper metal complexes stay at the singlet excited state upon photoexcitation, and thus have short excited-state lifetimes, typically shorter than 1 μs. However, some photoexcited copper metal complexes do undergo intersystem crossing to become triplet excited states. As a result of spin-forbidden transition, the triplet excited-state metal complexes have long excited-state lifetimes, ranging from 1 microsecond to milliseconds.[22] These results suggest that the photoexcited triplet **7** would undergo single-electron transfer (SET) to benzoquinone, and thus would have formed the benzoquinone radical anion **9** (see Scheme 2), and the copper(II) phenylacetylide **8**. The presence of **9** and a copper-(II) species were further confirmed by EPR measurements under standard reaction conditions at 77 K. However, no EPR signal was observed in either the dark or in the absence of CuCl or benzoquinone (see Figures S1–S6 in the Supporting Information). Moreover, we have compared the redox potentials of copper(I) acetylide and quinones. Based on cyclic voltammetry (CV), the redox potential of **2a′** was determined to be $-2.048\ V_{SCE}$ in $CH_3CN$ (see Figure S11 in the Supporting Information). The excitation and emission profiles of in situ generated **2a′** are shown in Figure 1. A bandgap energy of $E^{00} = 2.52$ eV was obtained from the

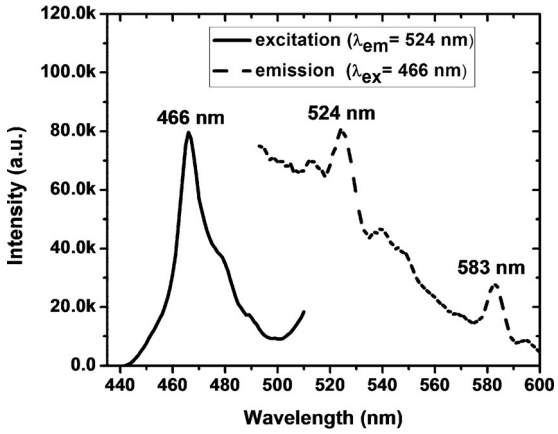
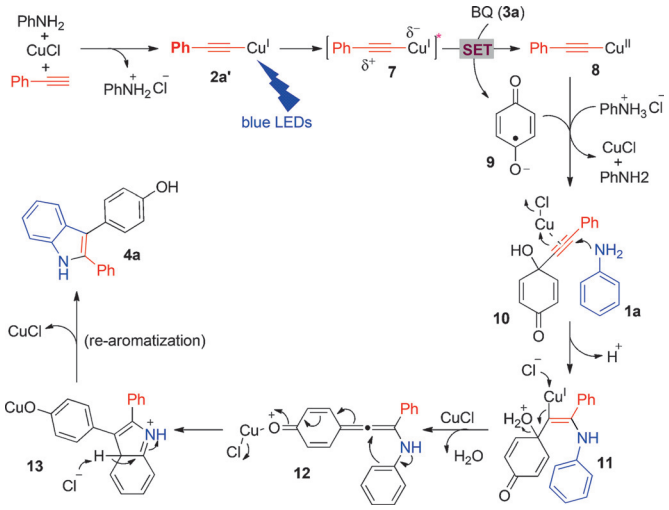



***Figure 1.*** Excitation and emission spectra of in situ generated **2a′** in $CH_3OH$.

intersection of **2a′** emission and excitation profiles. This redox potential is sufficiently higher than that (−0.92 $V_{SCE}$) for 1,4-benzoquinone.[23] Therefore, SET from a photoexcited triplet copper(I) phenylacetylide to benzoquinone is exothermic and can occur spontaneously.

Based on the above mechanistic data, a plausible mechanism is proposed in Scheme 2. Initially, photoirradiation of in situ generated **2a′**[24] by blue LEDs (see UV-visible absorption spectra in Figure S10 in the Supporting Information) produces the long-lived triplet photoexcited **7** ($\tau$ = 15.95 μs) by ligand to metal charge transfer (LMCT).[12d,25] Then, the singlet excited state of copper(I) phenylacetylide undergoes facile intersystem crossing to the triplet excited state,[12b,26] and then undergoes a SET process with benzoquinone (BQ; **3a**) to afford the benzoquinone radical anion **9** and the copper(II) phenylacetylide **8**, as evidenced by EPR measurements (see Figures S1 and S3 in the Supporting Information). The radical anion **9** (benzoquinone radical anion) has the propensity to attack onto the $Cu^{II}$-phenylacetylide **8** to regenerate the copper(I) catalyst[11a,12b] and furnish the copper(I)-coordinated alkyne complex **10**. It is known that free CuCl could coordinate to the disubstituted alkyne moiety through a π-alkyne complex,[27] thereby enhancing its electrophilicity. The resulting electron-deficient triple bond then undergoes nucleophilic attack by aniline (at the β-carbon atom) to provide the complex **11**, thus leading to formation of the complex **12**. Friedel–Crafts-type cyclization of **12** generates the intermediate **13**,[28] and finally affords the desired indole product (**4a**) by the liberation of the catalyst CuCl through re-aromatization process.




***Scheme 2.*** A proposed reaction mechanism.

In conclusion, we have developed a novel visible-light mediated CuCl-catalyzed three-component coupling of anilines, terminal alkynes, and benzoquinones, thus leading to facile one-step regioselective synthesis of functionalized indoles at room temperature. Overall, 39 examples are described with substrates having a wide range of functional groups, including, halides, methoxy, alkyl, ester, nitro, cyano, acetanilide, etc. The current method can be readily scaled up to a preparative (1–2 g) scale. This transformation represents the first example of a copper-catalyzed C–H annulation of arylamines with terminal alkynes and provides substituted indoles as a single regioisomer. From a synthetic point of view, the current method represents a sustainable and atom-economical approach to construct indoles from easily accessible starting materials under visible-light irradiation, without the need for expensive metals and external oxidants or additives.

## Experimental Section

General procedure**:** A dry test tube (20 mL) containing 5 mol% CuCl was evacuated and purged with dry $N_2$ gas. And then 7 mL of dry $CH_3OH$ was added by syringe, followed by aniline (0.5 mmol) and the terminal acetylene (0.55 mmol). A yellow suspension was formed and then benzoquinone (0.60 mmol) added was added. The reaction mixture was irradiated with blue LEDs (40 mW $cm^{-2}$ at 460 nm) at room temperature (25–28°C) until completion of the reaction (monitored by TLC). The reaction mixture was diluted with 40% ethyl acetate in *n*-hexane and stirred for 10 min. The mixture was filtered through Celite and silica gel pads, and washed with ethyl acetate. The filtrate was concentrated and the residue was purified by column chromatography on silica gel to collect the indole product.

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