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Visible Light-driven Copper Photoredox-catalyzed Multicomponent Coupling of Arylamines, Terminal Alkynes, and Alcohols via HAT Process

Arunachalam Sagadevan, V. Kishore Kumar Pampana, and Kuo Chu Hwang*

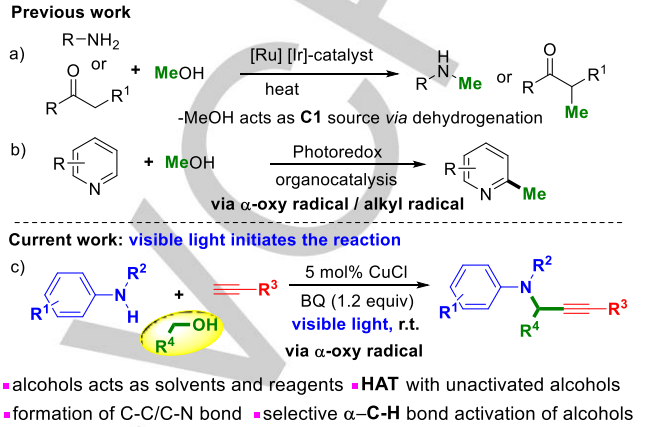
Abstract: The first successful example of 3-component coupling of *N*-alkylanilines, terminal alkynes, and alcohols was achieved at R.T. *via* a visible light-mediated copper-catalyzed photoredox-hydrogen atom transfer (HAT) process. This method allows preparation of propargylamines *via* unique selective α-*C*-*H* bond activation of unactivated alkylalcohols. Preliminary studies indicate that a formation of α-oxy radical is operative. 53 examples were presented. This approach allows facilitates rapid access to biologically important propargylamines from abundant methanol feedstock.

Visible-light photoredox catalysis has emerged in recent years as a powerful and sustainable platform to access new chemical reactions *via* single electron transfer (SET) with organic substrates.[1] In this context, the photoredox SET process can enable rapid generation of radical intermediates (*via* selective activation of inert organic substrates) under mild reaction conditions that employ challenging C(sp^3)-H bond activation of organic feedstocks, leading to the development of new bond construction (*C*-*C*/*C*-*N*).[1b,2] From a sustainability point of view, direct utilization of commercial solvents as substrates for new chemical transformation using low energy visible light irradiation at R.T. is a grand challenge in modern synthetic chemistry.[2]

Environmentally benign simple alcohol, such as MeOH and EtOH, is an abundant feedstock from renewable biomass resources, and is frequently used as solvents and substrates for various chemical transformations, including, a) industrial production of aldehydes, acids, esters, ethers, etc.,[3] b) used as inexpensive energy storage (H_2) materials,[4] and (c) used as alkylating agents (**Scheme 1a**).[5] Apart from classical two-electron oxidation reactions of methanol, SET process coupling with HAT from unactivated alcohols (e.g. MeOH) to make C1 synthon for C(sp^3)-H bond functionalization is important.[2,6] In 2015, Macmillan group reported an efficient way to use alcohols as alkylating agent for heteroarene *C*-*H* functionalization via generation of an α-oxy radical /alkyl radical by means of visible light photoredox catalysis (**Scheme 1b**).[7] Apart from this unprecedented discovery, an alternative platform with combination of copper and light may promote new prospect on α-*C*-*H* bond activation of methanol that could be developed for challenging bond construction with arylamines and terminal alkynes (*via* α-oxy radical) in the presence of inexpensive catalyst (e.g., copper) under visible light irradiation at low temperatures, which is highly desirable and is hitherto unknown.

Owing to its earth abundance and inexpensiveness, the use of copper-complexes as photoredox catalysts has become a rapidly growing research area in organic synthesis, and has been successfully employed in numerous cross-coupling reactions.[8] In this regard, we have recently demonstrated a variety of visible-light-initiated copper-catalyzed coupling reactions.[9] Herein, we report a discovery of the first visible light-induced 3-component couplings of *N*-alkylanilines, terminal alkynes, and alcohols to prepare propargylamines through a SET process, followed by unexpected selective α-*C*-*H* bond activation of unactivated alkyl alcohols via HAT process (i.e. not by direct oxidation of alcohol to aldehyde) at R.T. using an inexpensive catalyst (5 mol% CuCl), benzoquinone as an oxidant without use of other ligands and bases (**Scheme 1c**).

Propargylamines are important precursors for preparation of N-containing heterocycles, biologically active compounds, and natural products.[10] Thus, in recent years, numerous methods



Scheme 1. Transition metal-catalyzed activation of methanol.

have been developed for the preparation of propargylamines,[11] including; transition metal-catalyzed 3-component-couplings.[11a] Despite indisputable advances, nearly all reactions require aldehyde (toxic, a known human carcinogen) as one of the 3-component-coupling partners. One of the remaining challenges for preparation of propargylamines is to develop methods employing renewable resources via high atom economic C−H bond transformations, which would be of immense synthetic value from the environmental point of view. Hence, the development of new methodologies exploiting readily available alcohols as solvents as well as reagents, especially under visible light irradiation, would be of great importance in contemporary organic synthesis.

Inspired by our previous work (where 1° arylamines were used as substrates and indoles are the major products),[9b] we were delighted to find that when 2° arylamines were used as substrates, propargylamines become the dominant products. Visible light irradiation of N-ethylaniline (**1a**), phenylacetylene (**2a**), and benzoquinone (BQ) with 5 mol% CuCl in CH_3OH furnished propargylamine **3a** in 74 % and indole in 18% yield (Table 1, entry 1).[9b,12] Upon increasing the substrate concentrations (*via* reducing solvent volume) was found to boost up the **3a** yield to 84% (Table 1, entry 2) with concurrent suppression of indole formation to trace amount (vide infra).[12] Different catalysts were screened, including CuCl, CuBr and $CuCl_2$; CuCl provides the highest yield (entry 2, Table 1). In the solvent screening studies, MeOH alone provided the best yield of **3a**. However, the addition of other solvents with MeOH (1:1) leads to poor yields (entries 5-7). Control experiments (entries 11-14) revealed that visible light, CuCl and BQ are essential for the current 3-component coupling reaction. Notably, thermal heating (at 65 °C) in dark did not produce **3a**. Meanwhile, ambient white light irradiation can also initiate the reaction but with a lower **3a** yield (entry 10). When 10 mol% of BQ was used, decrease in the **3a** yield was observed (entry 13). Importantly, the use of electron-rich 2-methyl-BQ, instead of BQ, can improve **3a** yield slightly to 86%, most probably due to its stronger hyperconjugative effect.[13] In contrast, electron-withdrawing 2-Cl-BQ leads to a lower yield (72%). BQ, rather than 1-Me-BQ, was adopted in all later studies due to its cheaper price and common availability.

Under the optimal condition (Table 1, entry 2), we examine the

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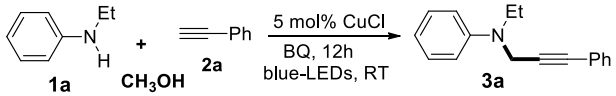
Table 1. Optimization of reaction condition.[a]



Entry	[Cu]-catalyst	Solvent	Yield [%][b]
1[c]	CuCl	MeOH	74
2	**CuCl**	**MeOH**	**84**
3	CuBr	MeOH	82
4	$CuCl_2$	MeOH	79
5	CuCl	CH_3CN-MeOH	62
6	CuCl	MeOH-THF	37
7[d]	CuCl	MeOH-H_2O	76
8[e]	CuCl (2-Me BQ)	MeOH	86
9[f]	CuCl (2-Cl BQ)	MeOH	72
10[g]	CuCl (ambient light)	MeOH	58
11[h]	CuCl (dark at 65 °C)	MeOH	0
12[i]	CuCl (without BQ)	MeOH	n.r
13[j]	CuCl (10 mol% BQ)	MeOH	14
14[k]	none	MeOH	n.r

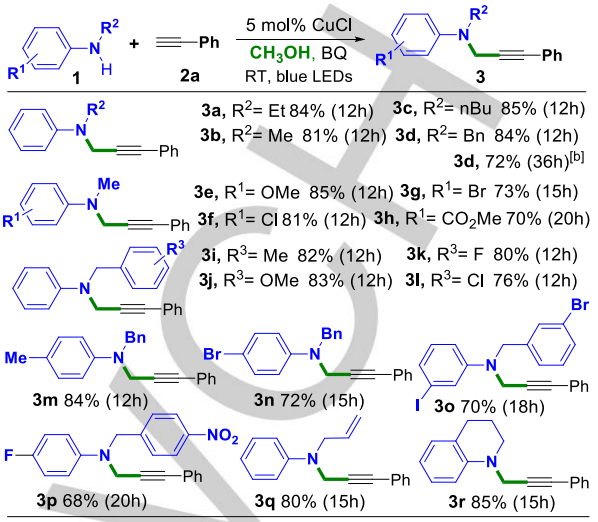
a. Unless otherwise noted, reaction conditions are as follows; **1a (**0.5 mmol)**, 2a (**0.55 mmol)**,** BQ (0.6 mmol), [Cu] catalyst (5 mol%), solvent (4 mL). The mixture was irradiated with blue LEDs (40 mW/cm^2 at 460 nm) for 12 h under N_2 (1 atm.). b. Yield of isolated product. C. 7 mL of methanol. d. 0.5 mL water was added. e. 2-Methyl-BQ was used, instead of BQ. f. 2-Chloro-BQ was used, instead of BQ. g. Reaction irradiated with an ambient white light bulb for 30 h (8 mW/cm^2 at 460 nm). h. Reaction conducted in the dark at 65 °C. i. In the absence of BQ. j. 10 mol % BQ was used k. In the absence of [Cu] catalyst. n.r. = no reaction.

substrate scope of substituted *N*-alkylanilines (Table 2). A wide range of *N*-alkyl/benzyl anilines can be used in the 3-component coupling reaction to generate corresponding propargylamines in good yields. As compared to electron donating and neutral groups, electron withdrawing groups on both benzene ring and *N*-atom of substrates lead to slightly lower propargylamines yields (**3g, 3h, & 3n-3p,** 68-73%), presumably in part because of electron rich *N*-alkylanilines could undergo complexation with Cu^{II}-phenylacetylide more effectively to produce aminyl radical cation (via infra)[14] and then furnish the propargylamines in high yields (**3a-3f & 3i-3m,** 76 to 85% yield). Notably, halogen-substituted *N*-alkyl/benzyl anilines also selectively underwent 3-component coupling to generate propargylamines (**3f, 3g, 3l, 3n & 3o**). Note that the competitive Sonogashira reaction did not occur at all.[9d] Moreover substituted *N*-benzyl-anilines (**1i-1p**) and *N*-allyl-aniline (**1q**) is effectively involved in the methanol C-H activation reaction and affords propargylamines (**3i-3p & 3q**) in very good yields without having side reactions at the benzyl CH_2 position and the C=C bond. In case of a tetrahydroquinoline substrate (**2r**), the expected product **3r** was formed in 85% yield; however, tetrahydro-isoquinoline and 2° aliphatic amines were found to be unsuccessful substrates in the current strategy due to coupling reaction of 2° aliphatic amines with BQ[15] in the dark and precipitatoin of the photocatalyst **2a'** (in polymeric form). Furthermore, synthetic application of propargylamine (**3b**) was implemented for the preparation of biologically/synthetically potent compounds, such as isoxazole, pyrazole, and E-β-aminoacryaldehyde (see, details Scheme S3 in S.I).

Next, the scope of alkynes was evaluated with N-alkyl/benzyl aniline (**1**) under the optimal condition. As shown in Table 3, aryl alkynes with various functional groups could couple with *N*-alkyl/benzyl anilines to furnish corresponding propargylamines in high yields. Aryl alkynes bearing Me, tBu, Et, and halogen substituents (F, Cl, & Br) also performed well (**4b-4g, 4k & 4l,** 71-85% yield). Notably, aryl alkynes bearing electron withdrawing groups (-CF_3, -Ac & -NO_2) were found to be competent substrates (**4h-4j, 4m & 4n,** 63-71% yield). Other than aryl alkynes, thiophene alkynes, and n-octyl alkynes also performed well in this transformation (**4o-4q,** 72-79% yield).

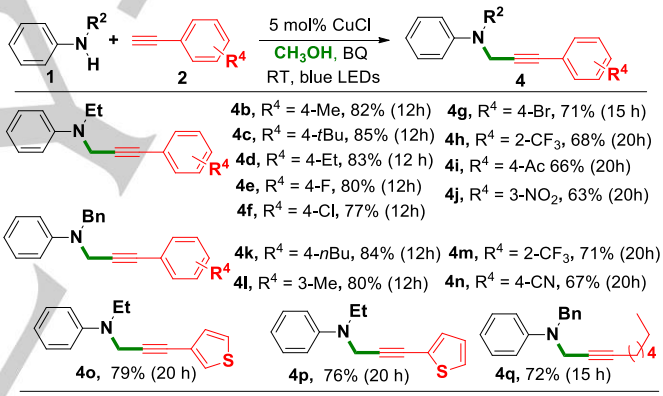
Finally, the scope of alcohol substrates was explored. Various alcohols were employed in this transformation, furnishing the corresponding propargylamines in moderate to good yields (52-

Table 2. Substrate scope of N-alkyl/benzyl anilines.[a]



[a] Standard condition. Isolated yield after purification by column chromatography. [b] The reaction was performed on a 5 mmol scale.

Table 3. Substrate scope of terminal alkynes.[a]



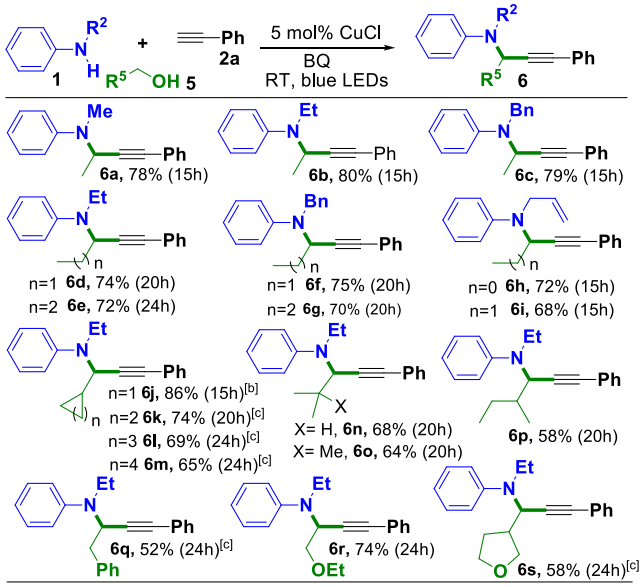
[a] Standard condition. Isolated yield after purification by column chromatography on silica gel.

86%, Table 4). Importantly, long chain alcohols (e.g., *n*-propanol and *n*-butanol) showed exceptional regioselectivity and underwent a HAT process selectively at the α-*C*-*H* bond position. Mechanistically, dehydrogenation of ethanol is known to be easier than methanol (ΔH = +68 vs. +84 kJ mol^{-1}).[16] However, in the current system, methanol affords propargylamines in higher yields than long-chain aliphatic alcohols, which provides a clue regarding the involvement of α-oxy radical intermediate (*via* a HAT process with alcohols) rather than the occurrence of direct dehydrogenation of alcohols to aldehydes. Moreover, cycloalkyl carbinols selectively provided propargylamines in good yields (**6j-6m**). Particularly, cyclopropane carbinol reacted more effectively and produced **6j** in 70% along with 16% of **6e** through a minor pathway of strain-driven cleavage of cyclopropane ring (see eqn. 5). Aliphatic alcohol with branched methyl groups also selectively generates desired propargylamines in good yields (**6n-6p,** 58-68%) without a reaction at other remote active methyne *C*-*H* bonds (**6n** & **6p**). Interestingly, 2-phenyl ethanol, 2-ethoxy-ethanol, and tetrahydro-3-furanmethanol also afforded propargylamines (**6q-6s,** 52-74% yield) by selective HAT at the α-*C*-*H* bond site next to hydroxyl group rather than weak benzylic/-ether site *C*–*H* bond. Secondary alcohols do not work in the current protocol, most probably due to its increased steric hindrance.[7]

To gain mechanistic insight, varioius control experiments were

performed (eqn. 1-6). Pre-synthesized copper(I) phenylacetylide **2a'** was used in the reaction (without CuCl and **2a**) and afforded 3a in 52% yield after 30 h irradiation (eqn. 1). This control reaction suggests that in situ-generated Cu(I)-phenylacetilyde

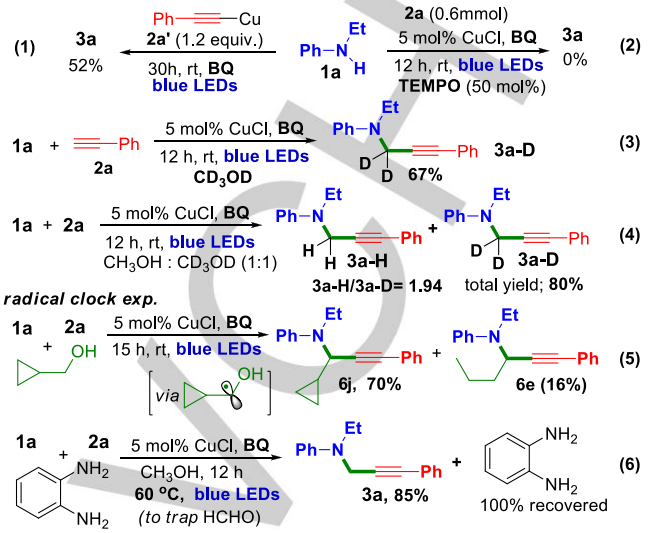
Table 4. Substrate scope of various alcohols.[a]



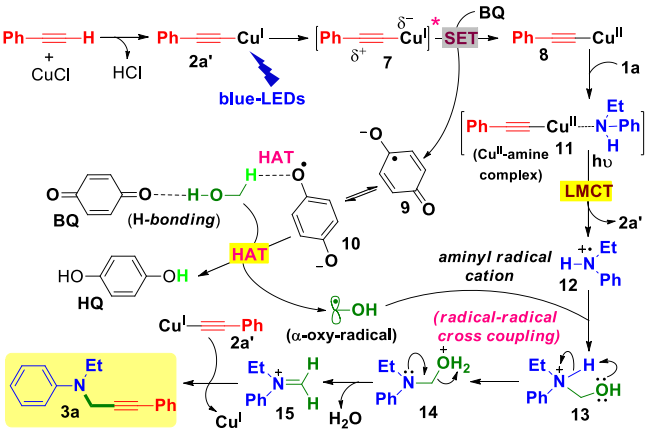
[a]Standard condition. Isolated yield after purification by column chromatography on silica gel. [b] Mixture of **6j** (70%) and **6e** (16%) was obtained. [c] 1.0 mL alcohol in 2 mL CH_3CN.

might be the key light-absorbing photocatalyst.[9] The presence of 50 mol% of TEMPO-completely quenches the reaction (eqn. 2), suggesting involvement of radical intermediates in the reaction. In addition, when CD_3OD was used, **3a-D** was obtained in 67% yield. Moreover, the intermolecular crossover experiment was carried out in a CH_3OH-CD_3OD (1:1) co-solvent, **3a-H** and **3a-D** were obtained in 1.94:1 ratio with a total yield of 80%. The value of 1.94 for kinetic isotope effect is consistent with a larger barrier (or a stronger C-D bond) for the formation of α-oxy radical from CD_3OD (eqns. 3 & 4). Furthermore, when cyclopropane carbinol was used in the reaction, products **6j** (70%) and **6e** (16%) were obtained in a 4.4:1 ratio (eq. 5), implying that the reaction proceeds through intermediacy of α-oxy cyclopropylcarbinyl radical (*via* a HAT process), which involves a minor pathway as strain-driven cleavage of cyclopropane ring to primary carbon-radical, followed by H-abstraction from OH proton of hydroquinone (k= ~3.0 x 10^5 M^{-1} s^{-1})[17] to form an aldehyde[6] and subsequently coupling[11a] with **1a** and Cu(I)-phenylacetylide **2a'** (see details in S.I.). However, other reaction pathways cannot be ruled out exclusively without further experimental evidence. An additional control experiment was carried out intending to trap any possible formaldehyde intermediate (if any, *via* oxidation of MeOH) using o-phenylenediamine under photoirradiation at 60 ºC.[18] However, no diamine-formaldehyde cyclized product was observed, only 85% **3a** was formed (eqn. 6). This control experiment unambiguously excludes the possibility of the current reaction going through formaldehyde formation pathway. The above control experiments support the conclusion that propargylamine was formed *via* a unique consecutive SET-HAT process, rather than oxidation of methanol to formaldehyde. Based on fluorescence quenching experiments (photochemically excited Cu^I-phenylacetylide was quenched by BQ), and redox potential values of Cu(I)-phenylacetylide (E_{redox}= -2.048 V_{SCE} in CH_3CN)[9b] and BQ (-0.92 V_{SCE}),[9b,19] SET from photoexcited triplet copper(I)-phenylacetylide to BQ is exothermic and can occur spontaneously.

Based on the above mechanistic results and our previous investigation,[9] a reaction mechanism was proposed in **Scheme 2**. Visible-light irradiation of *in-situ* generated Cu(I)-phenylacetylide **2a'** generates a long-lived Cu(I)-phenylacetylide **7** triplet excited state (τ= 15.95 μs).[9b] As photoexcited Cu^I-phenylacetylide **7** can function as an electron donor and transfer an electron to BQ to generate a persistent BQ radical anion **9** as well as the intermediate Cu(II)-phenylacetylide **8**.[9b] Then, the



electrophilic BQ radical anion **9** or **10** further undergoes a HAT from the α-*C*-*H* bond of methanol to generate an α-oxy radical and hydroquinone.[20] The relative bond dissociation energy (BDE) of methanol α-*C*-*H* bond (91.8~96 kcal mol^{-1})[21,22] vs. phenolic O-H bond (86~90 kcal mol^{-1}),[21] is thermodynamically slightly unfavourable. However, it was reported in the literature that intermolecular hydrogen bonding interaction of OH group of alcohol with hydrogen bond acceptor molecule can weaken the α-*C*-*H* bond of alcohol MeOH (by ~10-12 kcal mol^{-1}).[22c] In the current system, hydrogen bonding interaction between BQ and OH group of methanol[20b,23] can weaken the α-*C*-*H* bond of MeOH (*via* polar effects in the transition state)[6a,22] and thereby renders selective HAT from α-C-H of methanol possible, leading to generation of α-oxy radical by electrophilic radical anion **9** or **10**.[20] The occurrence of a HAT process was supported by outcome of various mechanistic control experiments (see, eq. (2), (3) & (4)). In contrast to 1º arylamines (anilines), secondary arylamines have larger steric hindrance and better electron donation ability,[24] thus, it more propensity to undergo complexation at the Cu(II) site of **8** to generate Cu^{II}-amine complex **11**[25] and allowing for the propargylamine product formation rather than going to the indole pathway[9b,12] (see



Scheme 2. Proposed reaction mechanism.

mechanistic comparison in Scheme S7, S.I.). Upon photoexcitation of the complex **11**, ligand to metal charge transfer (LMCT) occurs, leading to formation of aminyl radical cation **12** and stable Cu(I)-phenylacetylide **2a'**[14,26] Subsequently, the nucleophilic α-oxy radical[7] would then undergo radical-

radical cross-coupling with electrophilic aminyl radical cation **12**[27] to afford the complex **13**. At this juncture, complex **13** would undergo intramolecular proton transfer to eliminate H_2O, thereby furnishing iminium species **15,** followed by addition of **2a'** would lead the product **3a** with concomitant regeneration of CuCl catalyst.

In summary, we have developed the first literature example of visible light-mediated CuCl-catalyzed A^3-coupling among secondary N-alkyl anilines, terminal alkynes, and alcohols for facile synthesis of propargylamine (53 examples) under a very mild condition at RT. Experimental evidences indicate that the coupling reaction occurs via a unique consecutive SET-HAT process and the formation of a transient α-oxy radical, by α-C-H bond activation of unactivated alkyl alcohols via HAT process (i.e. not by direct oxidation of alcohol to aldehyde). From a synthetic perspective, this protocol offers an efficient synthetic route for the preparation of biologically important propargylamines from abundant methanol feedstock, obviating the use of any ligands and toxic chemicals.

Experimental Section

Experimental details can be found in the supporting information.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: photochemistry, copper, single electron transfer, methanol, propargylamine

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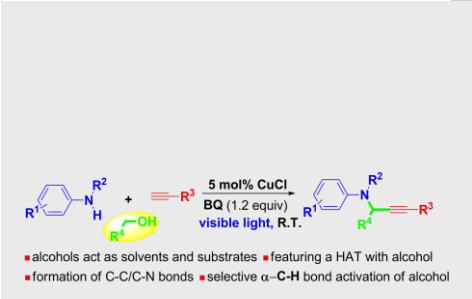
Methanol C-H bond Activation by HAT-process**:** A visible-light copper photoredox-catalyzed process can enable the HAT process with alcohols (formation of α-oxy radical) to accomplish the propargylamines via three-component coupling reactions at room temperature. This transformation represents a sustainable and atom economical approach to the preparation of biologically important propargylamines from abundant methanol feedstock.



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