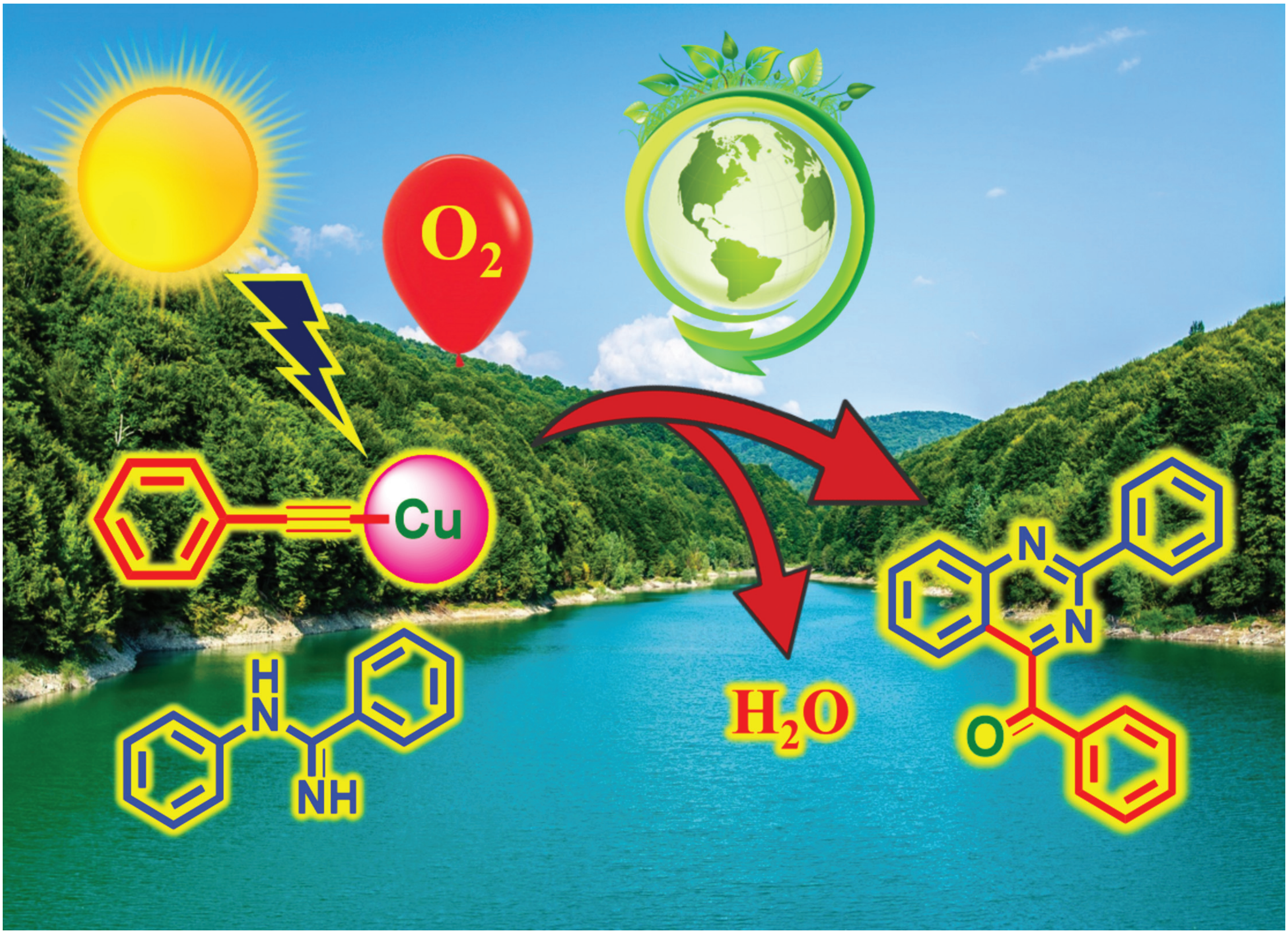

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Photoredox synthesis of functionalized quinazolines *via* copper-catalyzed aerobic oxidative C_{sp^2}–H annulation of amidines with terminal alkynes

We are presenting a simple, inexpensive CuCl catalyzed C–H annulation of amidines with terminal alkynes to form functionalized quinazolines at room temperature. This photochemical method is a mild process, highly efficient, and practically applicable to the synthesis of anticancer agents.

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Photoredox synthesis of functionalized quinazolines *via* copper-catalyzed aerobic oxidative C_{sp^2}–H annulation of amidines with terminal alkynes†

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We have developed a visible light-induced photo-redox copper-catalyzed oxidative C_{sp^2}–H annulation (Friedel–Crafts-type cyclization) of amidines with terminal alkynes at room temperature to synthesize functionalized quinazolines. We report copper(I)-phenylacetylide catalyzed photo-oxidative C_{sp^2}–H annulation of amidines at RT, which is very challenging and complementary to the conventional transition metal-catalyzed thermal annulation reactions. We have demonstrated the application of this method by synthesizing anti-cancer compounds. Moreover, green chemistry metrics (the *E*-factor is ~1.9 times better than that of the reported thermal method) and Eco-Scale (scales 55.4, which shows an acceptable synthesis) evaluations show that this method is eco-friendly and environmentally feasible.

Over the past few decades, transition metal-catalyzed (TMC) C–H functionalization/C–H annulation has emerged as a sustainable and powerful method in organic synthesis, with extensive applications in chemical biology, materials sciences and pharmaceutical chemistry.[1] In this instance, expensive noble metal catalysts, such as palladium, ruthenium, and rhodium complexes, have played major roles in C–H functionalization *via* metal-chelated C–H insertion (activation).[2] Owing to its abundance on the Earth and inexpensiveness, copper catalysts are particularly attractive for C–H alkenylation, alkynylation, and amination of arenes *via* two-electron or single electron processes (SET).[2] Despite this, thermal TMC C–H annulation reactions share some common drawbacks, such as; (a) the use of expensive precious metal catalysts; (b) tedious processes and the use of toxic reagents; (c) the use of excess amounts of oxidants, such as peroxides, Selectfluor, $PhI(OAc)_2$, MnO_2, and $K_2S_2O_8$, thus leading to the generation of undesired waste (with a high *E*-factor), and (d) harsh reaction conditions. Thus, the development of simple copper-catalyzed C–H annulation reactions using molecular oxygen as an oxidant at room temperature and under low energy visible light irradiation is highly desirable and very challenging.

The use of visible light photo-redox catalysis (PRC) in organic synthesis has dramatically upsurged in recent years. Recently, copper complexes have emerged as an inexpensive and appealing complement to expensive conventional PRC (*i.e.*, Ru or Ir-complexes)[3] for various organic cross-couplings (C–C, C–N) and C–H functionalization reactions under visible light irradiation. In this regard, our group has demonstrated the visible light-induced and inexpensive Cu(I) phenylacetylide (*in situ* generated photocatalyst)-catalyzed C–C, C–N/O coupling reactions and C–H annulation reactions.[4] Besides, copper photocatalysis has been proven to follow the principles of green chemistry.[3b,d,4] Most of the literature reported that photocatalysis reactions use expensive transition metal-containing photocatalysts, along with specially designed ligands, and an excess amount of organic oxidants, which leads to an increase in the amount of waste and the cost of the reaction. Thus, the use of all these reactants adversely affects the ecology, the environment, or the ecosystem. Therefore, it is important to develop an external photocatalyst-free green synthetic process which follows the guidelines of green chemistry.

Herein, we report the visible light-initiated copper-catalyzed oxidative C_{sp^2}–H annulation of amidines with terminal alkynes to form 2,4-disubstituted quinazolines using molecular O_2 as an oxidant at RT (Scheme 2, eqn (b)). In the current discovery, the copper ion forms a complex with the coupling partner (terminal alkyne) rather than the substrate (amidines), which is opposite to the traditional TMC thermal annulation reactions (Scheme 1, eqn (1a) and (1b)).

Quinazolines are a vital class of fused heterocycles as they are widely present in natural products and synthetic pharmaceutical compounds and thus have been extensively investigated for therapeutic activities[5] such as anticancer,[5a,d,6] antiviral[7] and antitubercular activities.[8] Therefore, the synthesis of

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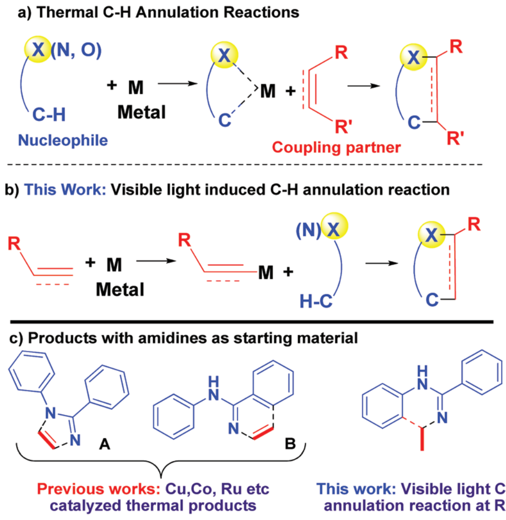
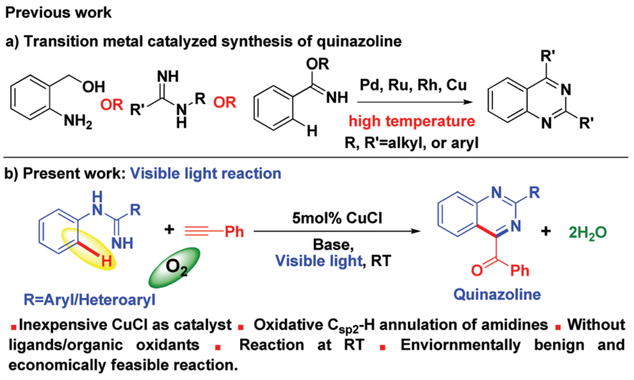


Scheme 1 Transition metal-catalyzed C–H annulation reactions.



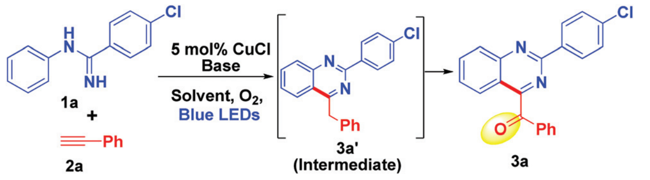
Scheme 2 Transition metal-catalyzed synthesis of quinazolines.

quinazolines has grabbed great attention for years, and various powerful methods have been developed, including transition metal[9,10] and metal-free[11] catalyzed thermal reactions. Despite all these indisputable advances, thermal metal/metal-free catalyzed methods have common drawbacks, such as (a) the use of expensive metal catalysts; (b) high temperature and harsh reaction conditions; (c) the use of excess ligands and organic oxidants; (d) generation of toxic byproducts and huge amounts of reaction waste, thus adding a heavy burden to the environment.

Given the fact that amidines have been widely used as starting materials in metal-catalyzed thermal reactions to construct heterocycles, Neuville's group reported the thermal-mediated copper(II)-catalyzed regioselective addition of terminal alkynes to aniline nitrogen, followed by the 5-*endo-dig* cyclization process to generate imidazoles[12a] (not quinazolines) (Scheme 1c, **A**), while L. Ackerman's group reported the synthesis of isoquinolines from amidines and diazo[12b] compounds, where only one NH was involved in the cyclisation[12a,c] (Scheme 1c, **B**). In contrast, our work uses amidines to form quinazolines under visible light irradiation. The significant features of our finding include: (a) the synthesis of 2,4-disubstituted quinazolines at RT by simultaneous C–C and C=N bond formation; (b) products are applicable for the further synthesis of anticancer compounds in few steps; (c) the reaction uses simple CuCl as a catalyst and O_2 as an oxidant under mild reaction conditions without the need for complicated ligands; (d) a simple reaction setup, and water was produced as the only by-product; (e) the green metrics and Eco-Scale evaluations signify that the current photochemical process is simple, cost-effective and environmentally benign.

In the initial experiment, 4-chloro-*N*-phenylbenzimidamide (**1a**) and phenylacetylene (**2a**) were used as the standard substrates (Table 1). Initially, the reaction of **1a** with **2a** in the presence of CuCl (5 mol%), K_2CO_3 (1.2 equiv.), and O_2 in MeOH afforded the product **3a** in 64% yield upon 18 h irradiation (entry 1, Table 1). Next, solvents such as ACN, DCM, DCE, and THF were screened. However, only trace amounts of products were formed in these solvents. Thus, mixed solvents were employed for further optimization. Surprisingly, the reaction in an ACN–MeOH (1 : 1) co-solvent formed the intermediate **3a′** and product **3a** in 22% and 41% yield, respectively. The above

Table 1 Optimization of reaction conditions[a]



Entry	[Cu] catalyst	Base	Solvent	Yield[b] [%]
1	CuCl	K_2CO_3	MeOH	64 (18 h)
2	CuCl	K_2CO_3	ACN : MeOH (1 : 1)	41 (22) (18 h)
3	CuCl	K_2CO_3	DCM : MeOH (1 : 1)	58 (18) (18 h)
4	CuCl	K_2CO_3	DCM : MeOH (1 : 1)	66
5	CuCl	K_2CO_3	DCM : MeOH (2 : 1)	76
6	CuBr	K_2CO_3	DCM : MeOH (2 : 1)	68
7	CuCl	Cs_2CO_3	DCM : MeOH (2 : 1)	71
8	CuCl	Na_2CO_3	DCM : MeOH (2 : 1)	70
9	CuCl	^{t}BuOK	DCM : MeOH (2 : 1)	64
10[c]	CuCl	K_2CO_3	DCM : MeOH (2 : 1)	53
11[d]	CuCl	K_2CO_3	DCM : MeOH (2 : 1)	73
12[e]	CuCl	K_2CO_3	DCM : MeOH (2 : 1)	27 (14)
13[f]	None	K_2CO_3	DCM : MeOH (2 : 1)	n.r.
14[g]	CuCl	None	DCM : MeOH (2 : 1)	0
15[h]	CuCl	K_2CO_3	DCM : MeOH (2 : 1)	n.r.
16[i]	CuCl	K_2CO_3	DCM : MeOH (2 : 1)	0

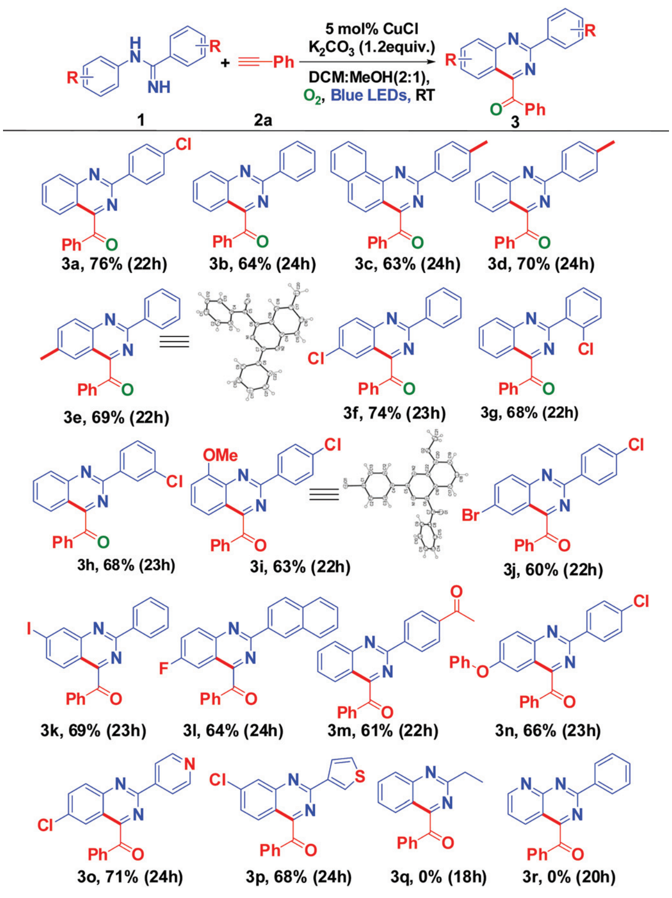
[a] Unless otherwise noted, reaction conditions are as follows; **1a** (0.2 mmol), **2a** (0.4 mmol), [Cu] catalyst (5 mol%), base (1.2 equiv.), and solvent (6 mL). The mixture was irradiated with blue LEDs (power density: 40 mW cm^{-2} at 460 nm) for 22 h in O_2 (1 atm). All light reactions were conducted in an air-conditioned room with a cooling fan around blue-LED's to maintain the reaction temperature within 25–28 °C. [b] Yield of the isolated product. The value in brackets denotes the yield of intermediate **3a′**. [c] 0.5 mL of water was added. [d] In the presence of air (1 atm.). [e] Reaction irradiated with an ambient white light bulb for 40 h (power density: 8 mW cm^{-2} at 460 nm). [f] In the absence of the [Cu] catalyst. [g] In the absence of the base. [h] In the absence of O_2. [i] Reaction conducted in the dark at 60 °C. n.r. = no reaction.

results indicate that the intermediate **3a′** upon further photoirradiation will be transformed to the product **3a**.

Further investigation revealed that the solvent composition and irradiation time played a crucial role in the formation of product **3a** in good yield (entries 3–5, Table 1). The product **3a** was obtained in a good yield of 76% in DCM : MeOH (2 : 1) upon 22 h irradiation. Among the bases examined, K_2CO_3 was found to be more efficient for the formation of **3a** (entries 7–9). Further optimization investigations demonstrate that CuCl, K_2CO_3, O_2, and visible light are essential for the formation of the product in good yield (entries 13–16, Table 1). In all the above reactions, ∼10–15% of the alkyne homocoupling product[4g] was observed.

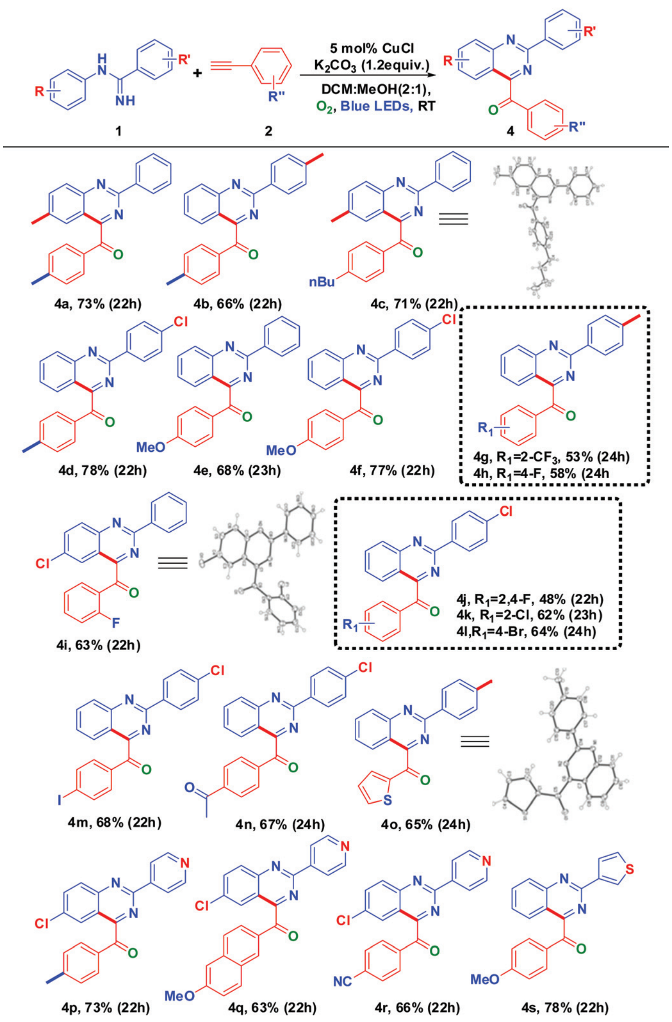
Under the optimized conditions, we then investigated the scope of amidine derivatives and terminal aromatic alkynes (Tables 2 and 3). Various aryl/heteroaryl amidine and aryl/hetero aryl alkyne derivatives with electron neutral, donating and withdrawing groups, including halogen (I, Br, Cl, and F) substituted groups, were all well tolerated by the current oxidative annulation reaction to form quinazoline products (**3a–3p** and **4a–4s**) in moderate to good yields. Notably, substrate (**1p**) selectively forms the product (**3p**) without forming other isomers. However, substrates, such as *N*-phenylpropionimidamide (**1q**) and *N*-(pyridin-2-yl) benzimidamide (**1r**), did not work in the current protocol. The reason for these incompatible substrates is not clear. The structures of **3e**, **3i**, **4c**, **4i**, and **4o** were confirmed by single crystal X-ray diffraction.[21]

Table 2 Substrate scope of *N*-arylbenzimidamide[a]



[a] Standard reaction conditions. Isolated yields after purification by column chromatography on silica gel.

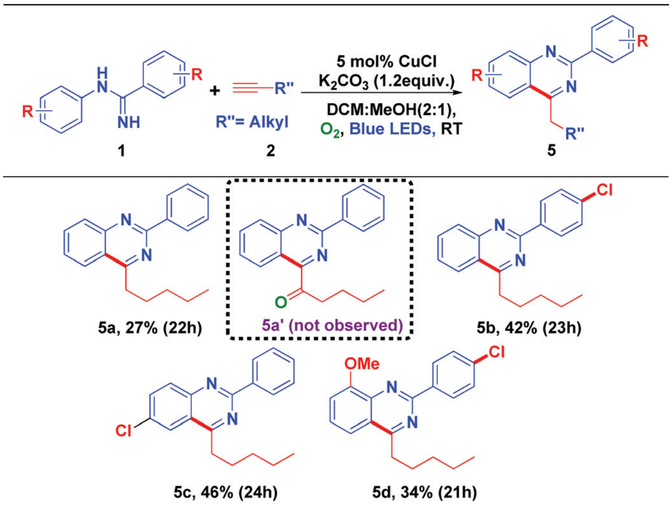
Table 3 Substrate scope of *N*-arylbenzimidamide with terminal alkynes[a]



[a] Standard reaction conditions. Isolated yields after purification by column chromatography on silica gel.

Subsequently, we turned our attention to the variation of amidines with aliphatic terminal alkynes (Table 4). To our surprise, when **1b** reacted with 1-hexyne under standard reaction conditions, we observed the product 4-pentyl-2-phenylquinazoline (**5a**) in a low yield of 31%, instead of oxidized product **5a′**. Also, other amidine derivatives (**1a**, **1f**, and **1i**) reacted with long-chain aliphatic terminal alkynes to generate the products **5b–5d** in low yields. Unfortunately, other aliphatic terminal alkynes did not work well with the photo-oxidative annulation reaction. The reason for the formation of unoxidized products (**5a–5d**) could be well explained based on the Cu-superoxo chemistry. CuCl reacts with O_2 to form Cu-superoxo, which

Table 4 Substrate scope of *N*-arylbenzimidamide with aliphatic terminal alkynes[a]

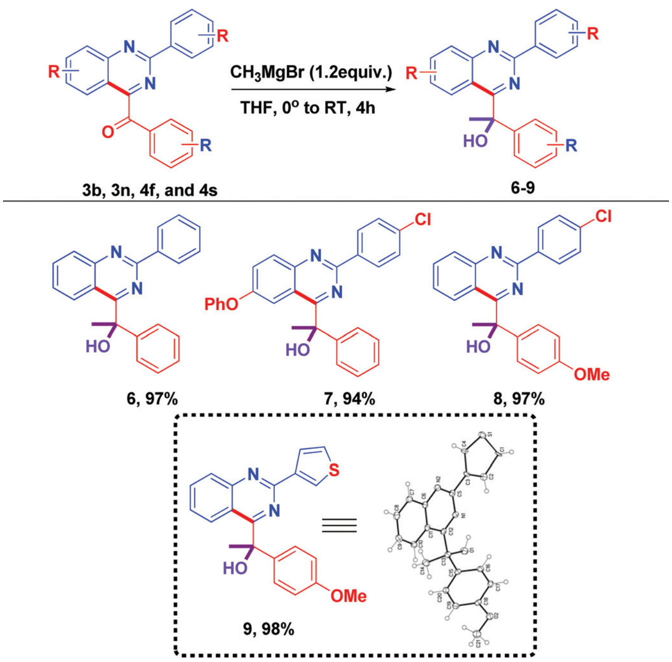


[a] Standard reaction conditions. Isolated yields after purification by column chromatography on silica gel.

further oxidizes the benzylic CH_2 (intermediate **3a′**) to form the oxidized product.[13] The C–H bond dissociation energy for the benzylic CH_2 (~90.0 kcal mol^{-1}) is less than that of the aliphatic chain $–CH_2$ (~100.0 kcal mol^{-1}).[14] Thus, the further oxidation of benzylic CH_2 is thermodynamically favored.

Furthermore, to demonstrate the application of this photo-oxidative C_{sp^2}–H annulation reaction, some anti-cancer compounds were prepared by late-stage functionalization of compounds (**3b**, **3n**, **4f**, and **4s**). Compounds **3b**, **3n**, **4f**, and **4s** were subjected to further reaction with methyl magnesium bromide to form the products **6**, **7**, **8**, and **9**, respectively, in excellent yields (Table 5). Compounds **8** and **9** are known to have excellent anti-proliferative (anti-cancer) activities.[15] The IC_{50} values[15] are 0.40 μM and 0.035 μM for compounds **8** and **9**, respectively. It is important to note that these anti-cancer compounds were prepared in a total of 3 steps using the current photoredox protocol (starting from commercially available substrates), which is far better than the reported 6-step thermal reactions[16] (see the ESI†).

Table 5 Synthesis of anti-cancer compounds[a]



[a] Standard reaction conditions. Isolated yields after purification by column chromatography on silica gel.

Table 6 Evaluation of green chemistry metrics for the synthesis of **3a**

$$\text{Atom economy (\%) (AE)} = \frac{\text{Molecular mass of desired product}}{\text{Molecular mass of all reactants}} \text{ x } 100$$

$$\text{Reaction mass efficiency (\%) (RME)} = \frac{\text{Mass of desired product}}{\text{Mass of all reactants}} \text{ x } 100$$

Reactant 1	4-chloro-*N*-phenylbenzimidamide	1.15g	5.0 mmol	FW 230.69
Reactant 2	Phenylacetylene	1.0g	9.8 mmol	FW 102.13
Base	K_2CO_3 (1.2equiv.)	0.83g	6.0 mmol	FW 138.2
Solvent	DCM (15mL,19.95g) MeOH (7.5mL,5.94g)	25.89g	----	----
Auxiliary	----	----	----	----
Recycled Solvent	DCM+MeOH	8.11g	----	----
Product	(2-(4-chlorophenyl)quinazolin-4-yl)(phenyl)methanone	0.98g	2.84 mmol	FW 344.79

Product yield = 56.8%

$$\text{E-factor} = \frac{1.15 + 1.0 + 0.83 + 25.89 - (0.98+8.11)}{0.98\text{g}} = 20.18 \text{ Kg waste/ 1 Kg product}$$

$$\text{Atom economy} = \frac{344.79}{348.82} \text{ x } 100 = 98.8\%$$

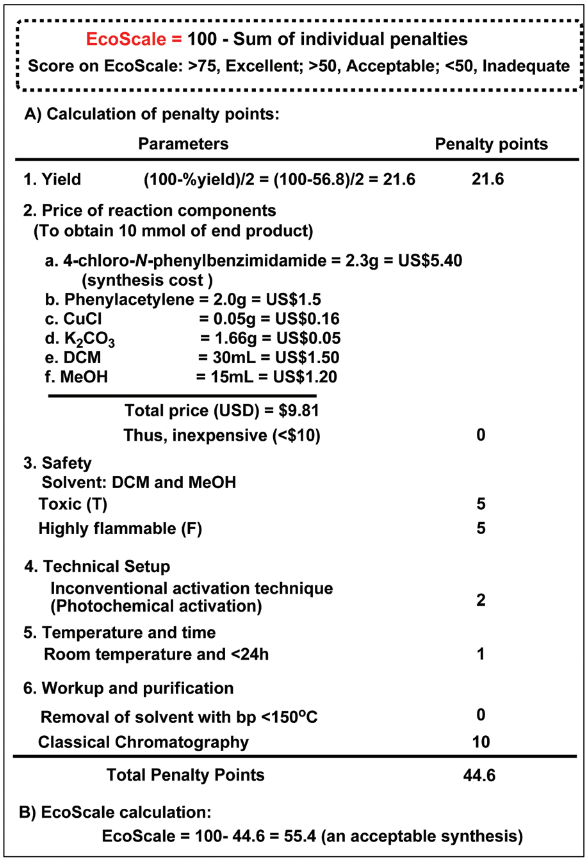
Atom efficiency = 56.8% x 98.8% /100= 56.1%

$$\text{Carbon efficiency} = \frac{21}{13 + 8} \text{ x } 100 = 100\%$$

$$\text{Reaction mass efficiency} = \frac{0.98\text{g}}{1.15\text{g} + 1.0\text{g}} \text{ x } 100 = 45.6\%$$

Finally, to demonstrate the practicality and efficiency of this photo-oxidative annulation reaction, a gram reaction was performed. The reaction of 4-chloro-*N*-phenylbenzimidamide (**1a**, 1.15 g, 5.0 mmol) with **2a** (9.8 mmol) in the presence of CuCl, K_2CO_3, and O_2 under photoirradiation for 24 h was performed to generate 0.98 g of product **3a** (56.8% yield). We have also evaluated the green chemistry metrics,[4c,f,h,13] and the Eco-Scale[13] value for this photo-oxidative annulation reaction on a preparative scale for the synthesis of **3a**. The green chemistry metric evaluation for the current green process has an *E*-factor of 20.18, 98.8% atom economy, 56.1% atom efficiency, 100% carbon efficiency and 45.6% reaction mass efficiency (Table 6). The Eco-Scale value for the current photo-oxidative annulation reaction is 55.4 on the scale of 100, which indicates an acceptable green synthesis process (Table 7). In addition, we have also calculated (3.0 mmol scale reaction) and compared the green chemistry metrics of the current photochemical reaction and literature reported thermal method[9a] for the synthesis of

Table 7 Eco Scale calculation for the synthesis of **3a**



EcoScale = 100 - Sum of individual penalties

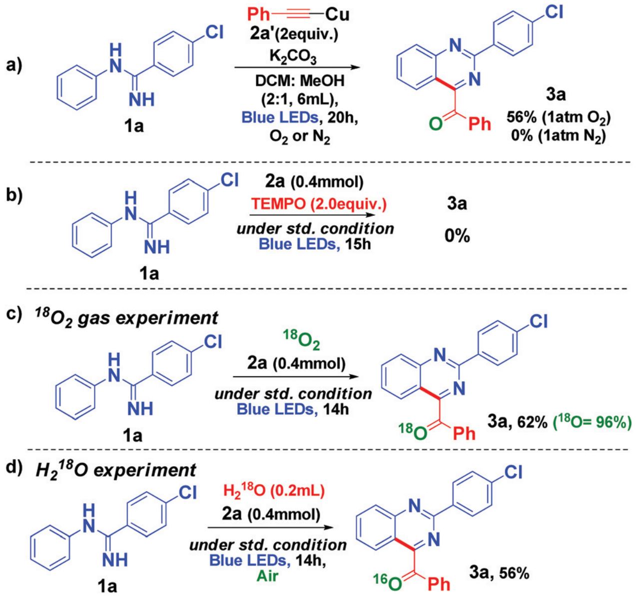
Score on EcoScale: >75, Excellent; >50, Acceptable; <50, Inadequate

A) Calculation of penalty points:

Parameters	Penalty points
1. Yield (100-%yield)/2 = (100-56.8)/2 = 21.6	21.6
2. Price of reaction components (To obtain 10 mmol of end product)	
a. 4-chloro-*N*-phenylbenzimidamide = 2.3g = US\$5.40 (synthesis cost)	
b. Phenylacetylene = 2.0g = US\$1.5	
c. CuCl = 0.05g = US\$0.16	
d. K_2CO_3 = 1.66g = US\$0.05	
e. DCM = 30mL = US\$1.50	
f. MeOH = 15mL = US\$1.20	
Total price (USD) = \$9.81	
Thus, inexpensive (<\$10)	0
3. Safety Solvent: DCM and MeOH	
Toxic (T)	5
Highly flammable (F)	5
4. Technical Setup Inconventional activation technique (Photochemical activation)	2
5. Temperature and time Room temperature and <24h	1
6. Workup and purification	
Removal of solvent with bp <150°C	0
Classical Chromatography	10
Total Penalty Points	44.6

B) EcoScale calculation:

EcoScale = 100- 44.6 = 55.4 (an acceptable synthesis)



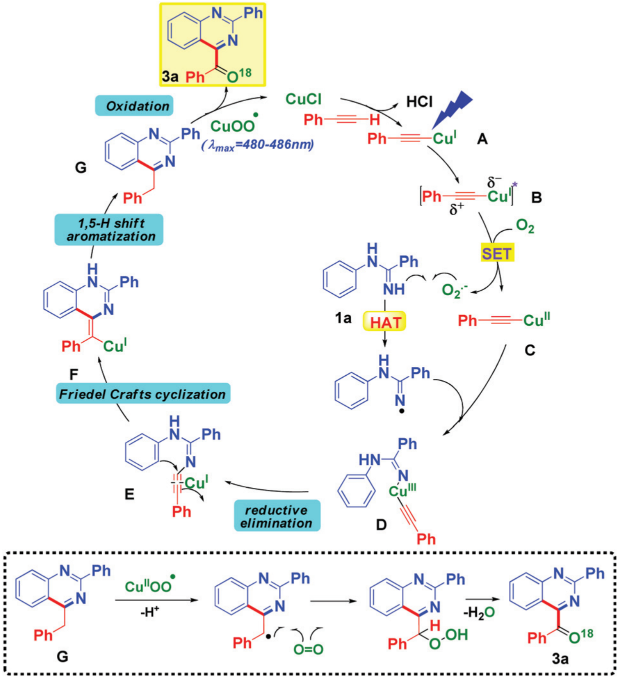
Scheme 3 Mechanistic investigations.

compound **4e**. Their green chemistry metrics values are tabulated in Table S3 (see detailed evaluation in the ESI†). The results show that the green chemistry metrics values of the current photochemical protocol are better than those for the literature reported thermal method, especially, the *E*-factor (an important physical parameter of green synthetic chemistry) of the current photochemical process is ~1.9 times better than that of the thermal method.[9a] Besides, we have also evaluated the Eco-Scale for the current photochemical method and a literature reported thermal method[9a] for the synthesis of compound **4e**. The Eco-Scale value of the current photochemical method is within an acceptable level, and is better than that of the literature procedure, the Eco-Scale value of which is at an inadequate level (see detailed evaluation in the ESI†). Thus, the current synthetic organic reaction is simple, ecofriendly, and highly efficient.

To obtain mechanistic insights into the current photo-oxidative annulation reaction, various control reactions were performed (Scheme 3). First, the reaction of **1a** was carried out with pre-synthesized Cu(I)-phenylacetylide (**2a′**) powder in the absence of CuCl and in the presence of a base for 20 h under photo-irradiation, which led to the formation of product **3a** in 56% yield. This decrease in yield is due to the polymeric form (and thus poor dispersion) of the Cu(I)-phenylacetylide (**2a′**) solid. This suggests that the *in situ* generated Cu(I)-phenylacetylide might be the key light-absorbing photocatalyst responsible for this annulation reaction. When the above reaction was carried out under an N_2 atmosphere, no product (**3a**) was obtained (Scheme 3, eqn (a)). Next, when the standard reaction was conducted in the presence of a radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine1-oxyl) for 15 h, no product (**3a**) was obtained, indicating that the current annulation reaction is likely to proceed *via* a radical pathway (Scheme 3, eqn (b)). Also, to detect the source of the O-atom in the product, reactions were carried out in the presence of $^{18}O_2$ gas (instead of $^{16}O_2$) (Scheme 3, eqn (c)) and in the presence of 0.2 mL of $H_2{}^{18}O$ (Scheme 3, eqn (d)) for 14 h under standard reaction conditions. The results indicated that the O-atom in the product is solely from the molecular oxygen (O_2).

Based on these above mechanistic investigations and our previous mechanistic studies,[4] a possible reaction mechanism is depicted in Scheme 4. Under visible light irradiation, *in situ* generated Cu(I)-phenylacetylide (**A**) (λ_{max} = 472 nm) absorbs blue light and becomes photochemically excited triplet state **B** (a long-lived triplet lifetime, $\tau = 15.95$ μs).[4,17] This photoexcited state B then undergoes a SET process by donating an electron to molecular O_2 and generates a Cu(II) complex, **C**, as well as a superoxide anion radical.[18] EPR experiments[19] confirm the formation of the superoxide anionic radical (see the ESI†). Also, the formation of complexes **A**, **B**, and **C** was supported by theoretical calculation studies reported by W. Thiel *et al.*[20]

In the next stage, the basic nature of the copper-superoxo radical anion has propensity to abstract acidic NH proton **1a** to form a nitrogen-centered radical, which further reacts with Cu(II)-phenylacetylide complex **C** and forms Cu^{III}-complex species **D**. This intermediate Cu^{III}-complex **D** undergoes reductive elimination and generates Cu(I)-coordinated ynamine inter-



Scheme 4 Proposed reaction mechanism.

mediate **E**. Intermediate **E** then undergoes Friedel–Crafts-type cyclization (6-*exo-dig* cyclization) to form cyclized intermediate **F** and subsequent aromatization to form compound **G**, which upon photo-oxidation by Cu(II) superoxo (λ_{abs} = 486 nm)[13] forms product **3b**.

Conclusions

In summary, we have developed a photo-oxidative copper-catalyzed C_{sp^2}–H annulation of amidines with terminal alkynes to form functionalized quinazolines at RT, which achieves simultaneously C–C and C=N bond formation and shows a totally different reaction mechanism from conventional transition metal-catalyzed thermal annulation reactions. Overall, 46 examples were presented. This reaction could achieve a gram scale synthesis of functionalized quinazolines using a simple reaction setup, commercially available substrates, low energy visible light, inexpensive CuCl as a catalyst, and O_2 as an oxidant under mild reaction conditions. Water is the only byproduct in the reactions. This method is also applicable for the synthesis of anticancer compounds in overall 3 steps from simple commercially available starting materials, far better than a total of 6 steps in literature reported methods. Moreover, the current protocol does not require the use of any expensive, toxic external photocatalyst or organic oxidants, and thus is simple and cost-efficient. In addition, the current method does not produce any harmful byproducts which are toxic to the environment or the ecosystem. Also, green chemistry metric calculation shows that the *E*-factor for the current green organic reaction is ~1.9 times better than that of the reported thermal method. Eco-Scale evaluation for this synthetic C–H annulation reaction scales 55.4 on the scale of 0–100 and indicates that it is an acceptable organic synthesis from the safety, cost, and environmental points of view.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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