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Copper Catalyzed Photoredox Synthesis of α-Keto Esters, Quinoxaline, Naphthoquinone: Controlled Oxidation of Terminal Alkynes to Glyoxals

Deb Kumar Das,[‡] V. Kishore Kumar Pampana[‡] and Kuo Chu Hwang*

Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, Republic of China.
E-mail: kchwang@mx.nthu.edu.tw; Fax: (+886) 35711082.
[‡]These authors contributed equally.

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ABSTRACT:

Herein, we report a facile visible light induced copper catalyzed controlled oxidation of terminal C≡C alkynes to *α*-keto esters and quinoxalines *via* formation of phenylglyoxals as stable intermediate, under mild conditions by using molecular O_2 as a sustainable oxidant. The current copper catalysed photoredox method is simple, highly functional group compatible with a broad range of electron rich, electron poor aromatic alkynes as well as aliphatic alcohols (1º, 2º and 3º alcohols), providing an efficient route for preparation of *α*-keto esters (43 examples), quinoxaline as well as naphthoquinone with higher yields than literature reported thermal processes.Furthermore, the synthetic utility of the products has been depicted by the synthesis of two biologically active molecules, i.e., E-coli DHPS inhibitor, and CFTR activator using the current photoredox process. In addition, we applied this methodology for one pot synthesis of a heterocyclic compound (quinoxaline, an FLT3 inhibitor) by trapping the intermediate phenylglyoxal with *O*-phenylenediamine. The intermediate phenylglyoxal can also be isolated and further react with an internal alkyne to form naphthoquinone. This process can be readily scaled up to a gram scale.

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INTRODUCTION

Photoredox catalysis has proven to be a powerful tool for the construction of new chemical bonds that has attracted research attention from all around the world.[1] Photoredox copper-based complexes have been shown to be an inexpensive, potent catalytic system for various organic transformations.[2] In recent years, the direct introduction of two vicinal functional groups into terminal alkynes *via* activation of C≡C triple bond becomes a very attractive process to achieve valuable synthons, bioactive natural products, and their synthetic analogues.[3,4] In particular, catalyzed oxidation of C≡C triple bonds by transition metal complexes in the presence of molecular O_2 plays an important role in chemical industry.[5] However, it remains very challenging to avoid over oxidation of C≡C triple bonds to generate over-oxidized products.[6] Our group has recently reported various visible light-mediated copper(I)-catalysed cross-coupling, and C-H annulations reactions.[7] It has been demonstrated that copper(I) phenylacetylide is the key photo catalyst involved in this visible light induced coupling reactions.[7] It was shown that photo-irradiation of copper(I) phenylacetylide in presence of molecular oxygen can generate Cu(II)-phenylacetylide and superoxide radical anion *via* single electron transfer (SET) process.[7d] The generated superoxide radical anion coordinates to copper ligand complex, and is responsible for controlled oxidation of C≡C triple bond of terminal alkyne.[7d]Similarly, we envisaged that a terminal alkyne can be transformed into valuable *α*-keto esters *via* controlled oxidation. *α*-Keto ester analogues are considered to be valuable precursors and intermediates for various pharmaceuticals and bioactive molecules.[8] Due to their vast potential,[8] many research groups have put significant efforts into the synthesis of these compounds in recent years.[9] Recently, Jiao et al. reported photoredox catalyzed synthesis of *α*-keto esters *via* oxidation of *α*-aryl halo derivatives using expensive ruthenium catalyst under sunlight irradiation (Scheme 1a).[10a]

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Thereafter, the same group described aerobic oxidative esterification reaction of 1,3-diones *via* C-C bond cleavage at high temperatures (Scheme 1b)[10b] that results in unwanted esters as byproducts. Later on, Song et al. demonstrated oxidative esterification of acetophenones at high temperatures.[11] Despite significant progress, common major limitations of literature strategies include the use of expensive catalysts[9a,d,f,11] pre-synthesized starting substrates,[9b,h,11]the need of additives or base,[9d-g,10a,11] requirement of stoichiometric amounts of oxidants,[9a] formation of ester byproducts,[10b] harsh reaction conditions, [9 b-c,e-g,10b,11] poor or no yield of product when 2º or 3º alcohols were used.[9a-e,10b,11]Therefore, there is a strong need to develop an efficient modality for the construction of α-keto esters that can conquer the above-mentioned limitations. In this communication, we report a visible-light-induced copper catalyzed synthesis of α-keto esters from reaction of a variety of alkynes and aliphatic alcohols under mild conditions using O_2 as oxidant (Scheme1c).

(Scheme 1)

The significance of the present work includes: (a) this is the first example of oxidation of terminal alkynes to α-keto esters under visible light at room temperature under mild condition; (b) low toxic, inexpensive CuI was used as catalyst and abundant O_2 as an oxidant, (c) controlled oxidation of C≡C triple bond to phenylglyoxals, thus no formation of ester or homo-coupling byproducts, and (d) broad substrate scope and compatibility with a wide range of aromatic alkynes and 1º, 2º, or 3º alcohols. To the best of our knowledge, the use of terminal alkynes as a key starting material for the synthesis of α-keto esters under visible light has yet to be reported.

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RESULTS AND DISCUSSION

When a mixture of phenyl acetylene **1a** (0.5mmol), MeOH **2a** (2 mL), copper iodide (CuI, 5 mol%), and 2-picolinic acid (1.0 equiv.) as a ligand in CH_3CN (4 mL) in presence of molecular O_2 was irradiated under blue LEDs at room temperature for 12h, it furnished the desired α-keto ester (**3a**) with a yield of 86% (Table 1, entry 1). When CuI was replaced by other CuX catalysts (X=Cl, Br), the desired product, **3a**, was not formed (Table 1, entry 2). The halide anion effect was attributed to the larger size and polarizability and better leaving ability of iodide ion in organic solvents as compared to other halide anions that facilitates easy formation of copper complex for this reaction. Removal of copper catalyst or ligand failed to produce **3a** (Table 1, entries 3 & 4). When the amount of ligand loading was decreased to 5 or 10 mol%, the conversion of phenyl acetylene to desired α-keto ester (**3a**) was low and either reaction failed or gave very trace amount of desired product (Table 1, entries 5 & 6). Reaction with 50 mol % of 2-picolinic acid as ligand provided the product **3a** in 71% yield (Table 1, entry 7). Whereas, increasing the amount of ligand to 2.0 equivalents gave α-keto ester in 85% yield (Table 1, entry 8). The yield was similar when 1.0 equivalent of ligand was used (Table 1, entry 1). Increasing or decreasing the amount of ligand failed to increase the yield of the desired product, thus it can be concluded that optimal amount of the 2-picolinic acid ligand is 1.0 equiv. Replacing the ligand with di-picolinic acid does not affect the yield of **3a** (Table 1, entry 9), whereas in case of 2-amino pyridine as ligand, we observed a complete inhibition of **3a** (Table 1, entry 10). Yield of **3a** remains the same in neat MeOH, but tends to decrease in THF and toluene (Table 1, entries 11-13). Reactions under ambient white light irradiation produced **3a** with 82% yield (Table 1, entry 15). Removal of either O_2 or either light leads to no product formation, indicating their crucial roles in the current protocol (Table 1, entries 16 & 17).

(Table 1)

Having established the optimal reaction conditions, we then investigated the scope and applicability of this reaction using different 1º, 2º and 3º alcohols as substrates for the synthesis of substituted α-keto esters (Table 2). Reactions were performed with various primary alcohols like ethanol (**2b**), *n*-propanol (**2c**), *n*-butanol (**2d**) and 2-methylpropan-1-ol (**2e**), and the desired product (**3b-e)** was obtained in good yields at room temperature (Table 2). The current photochemical process also works well for primary alcohol like 2-methoxyethanol (**2f**) and benzyl alcohol (**2g**) providing α-keto esters (**3f** and **3g)** in good to excellent to yields under similar reaction conditions (Table 2).

(Table 2)

Interestingly, cyclopropanemethanol (**2h**) and tetrahydrofurfuryl alcohol (**2i)** reacted well with **1a** to produce **3h**, and **3i** in 84% and 68% yields, respectively, without cyclic ring opening. Next, **1a** reacts with 2^o alcohols (**2j-2l**) smoothly to afford corresponding α-keto esters (**3j-3l**) in good yields. Slightly strained or labile alcohols (**2h, 2i, 2k, 2l**) worked well in this protocol, without

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producing any cleavage products, which are not possible using earlier thermal processes. Besides, **1a** reacts with alicyclic 2^{o} alcohols (**2m-2o**) to afford desired products (**3m–3o)** in good yields (Table 2). Unfortunately, this protocol does not work for the aromatic alcohols, such as phenol, which was attributed to the fact that phenol was oxidized to *p*-benzoquinones in the presence of copper and O_2.[7a,12] Reaction of **1a** with tertiary butanol (**2p**), provided α-keto ester **3p** in 70% yield (**Table 2**). It is worth to note that transformation of terminal alkynes to α-keto esters using tertiary alcohols has no precedent literature reports. Unfortunately, this protocol does not work for the aliphatic amines. Both primary and secondary amines, such as *n*-propyl amine and piperidine, were used as nucleophiles for the present system, but no α-ketoamide product was observed. Next, a competitive reaction of phenyl acetylene (**1a)** with equal moles of 1º, 2º and 3º alcohols, such as MeOH (**2a**), isopropanol (**2j**) and tertiary butanol (**2p**) under standard conditions was surveyed, which afforded α-keto ester **3a** as major product in 73% yield derived from 1º alcohol i.e., MeOH. Product **3j** derived from 2º alcohol was formed in trace quantity with no any α-keto ester **3p** resulting from tertiary butanol. From nucleophilic attach to the glyoxal aldehyde, 3º alcohol is expected to be better than 2º alcohol, and then 1º alcohol. This observed result clearly indicates that steric hindrance plays a more important role than electronic factor, which leads to predominance of primary alcohol in the coupling reaction.

Next, the substrate scope of aryl alkynes was examined with different aliphatic alcohols under the standard conditions (Table 3). The electron neutral and halo-(Cl, F, and I) substituted phenyl acetylenes readily react with aliphatic alcohols to afford corresponding *α*-keto esters (**4b–4j**) with good to excellent yields as depicted in Table 3. Aryl alkynes with strong electron withdrawing and donating (CF_3, CN, nitro, acetyl, ester, sulfone, methoxy) groups showed excellent tolerance in the current photoredox protocol to give corresponding *α*-keto esters (**4k−4t**) in good yields (Table 3). Copper-catalyzed aerobic oxidative coupling reactions involving electron rich substituted terminal alkynes suffer from homo-coupling as byproduct.[7d]However, in the current process no homo-coupling product was observed. Notably, the present photoredox process works well for reaction of 1,3-dialkynes to generate 1,3-α-diketo ester products **4u** and **4v** in good yields when using methanol as the solvent. The synthesis of 1,3-diketo esters is either difficult[8b,d,13] or not achievable by previously reported thermal processes. However, in contrast, it was easily achieved with the current photoredox process.

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(Table 3)

Note that when tertiary butanol was coupled with 1,3-dialkyne, only mono α-keto ester **4w** was obtained in 81% yield, where the absence of di-substituted *α*-keto ester might be due to steric hindrance effect from the bulky tertiary butyl group in the S_N2 reaction. Notably heterocyclic alkynes 2-ethynylthiophenes, 3-ethynylthiophenes and 3-ethynylpyridine, which are usually sensitive to oxidative conditions, also effectively react with 1^o, 2^o and 3^o alcohols to generate the desired *α*-keto esters (**4x**-**4z, 4va**) in moderate to good yields. However, heterocyclic alkynes ethynyl indole and ethynyl pyrimidine failed to give desired *α*-keto esters under the current protocol. This protocol was successful in producing α-keto ester, **4wa**, in 83% yield when heteroaryl alkyne 5-ethynyl-1,3-benzodioxole was used under similar conditions. Unfortunately, aliphatic terminal alkynes did not work for this protocol and failed to produce corresponding *α*-keto ester as products. The reason for the failure of aliphatic alkynes is most probably due to the lower acidity of aliphatic terminal alkynes as compared to aromatic ones, thus making the step of formation of copper phenylacetylide from aliphatic alkynes slower than aromatic alkynes.

Finally, the application of the current visible light-initiated Cu(I)-catalyzed strategy was demonstrated for the expedient synthesis of compounds with biological activity, such as 1-benzyl-3-(3-nitrophenyl)quinoxalin-2(1*H*)-one **6n** (a CFTR activator)[8a] and bis oxime ester **5t** (an E-*coli* DHPS inhibitor)[8c]. Phenylquinoxalinone**6n** could be synthesized in 3 steps in 44% overall yield (Scheme 2), which is greener and better than the literature reported method (4 steps with overall yields of 32%). (Scheme S1 and S2, ESI†).[8a]

(Scheme 2)

Next, bis oxime ester **5t** was prepared in 2 steps in 60% overall yield (Scheme 2), which is also better and greener than literature reported process (4 steps, 25% overall yield) using pre-synthesized starting substrates.[8c] In addition, the current process can be readily scaled up to a gram scale (1.029 g of 3-Nitro phenyl acetylene); 1.16 g of **4n** was obtained (79% yield) after irradiation with blue LEDs for 12 h at room temperature (ESI†) and further we have evaluated and compared green chemistry metrics (Fig. S5 and S6, ESI†).[7d] The structures of **4n** and **6n** were confirmed by single-crystal X-ray diffraction (Fig. S7 and S8, ESI†). In addition, compounds **4u, 4v**, and **4x** can be used as precursors for synthesizing biologically active molecules (Scheme S7, ESI†).

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Synthesis of Quinoxaline *via* double condensation of 1,2-phenylenediamines with phenylglyoxals in the presence of catalyst is a well-established concept in organic synthesis.[14a] Hashmi et al. reported gold and silver bi-metal co-catalyzed synthesis of quinoxaline derivatives from terminal alkynes which involved oxidation of phenyl acetylene to phenyl glyoxals using external oxidant pyridine N-oxide (4 equiv.)[14b] (Scheme S6, ESI†). Recently, it was shown quinoxaline derivatives can be synthesized by copper-catalyzed oxidative reaction of phenylglyoxal with *o*-phenylenediamines.[14c] Inspired by the above literature reports, we hypothesized controlled oxidation of phenyl acetylene will generate phenylglyoxal as a possible intermediate in the present copper catalyzed photoredox process. Thus trapping of phenylglyoxal intermediate with 1,2-phenylenediamines may lead to one-pot synthesis of pharmacologically active 2-phenyl quinoxaline by using cheaper Cu catalyst and abundant molecular O_2 as an oxidant. So, under the same reaction condition, we added 1.0 equiv. of 4,5-dimethylbenzene-1,2-diamine (**7**) to the reaction solution and irradiated with visible light for 12h at room temperature (**Scheme 3**). Not surprisingly, we obtained the corresponding 6,7-dimethyl-2-phenylquinoxaline (**8**), which is a biologically active FLT3 inhibitor),[15] in 65% yield as a product in this unprecedented photoredox copper catalyzed one pot process (**Scheme 3**). We did not observe formation of 3-phenylquinoxalin-2-ol as a product in the current photoredox method, which was previously reported as a key product under a strong basic condition.[7g] The difference in the formation of products was attributed to the differences in the reaction condition and thus different reaction mechanisms (Mechanistic comparison, Scheme S7, ESI†).

(Scheme 3)

To provide detail insights regarding the reaction mechanism, we carried out several control experiments, as shown in Scheme 4. First, pre-synthesized copper(I)-phenylacetylide**1a′** was used to react with MeOH, in the absence of CuI under similar reaction condition, which produced the desired *α*-keto ester (**3a**) with 40% yield after 12 h of irradiation (eq 1, **Scheme 4**).

(Scheme 4)

The reduced yield can be attributed to the fact that the isolated Cu(I)-phenylacetylide powder exists in highly aggregated forms.[7d,16] The result implies that in situ-generated Cu(I)-phenylacetylide is most probably the key light-absorbing photocatalyst involved in this oxidative coupling reaction. Next, we performed a short-time reaction of 3 h, under the optimal condition,

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and we were delighted to isolate phenylglyoxal**13** as a stable intermediate in 62% yield (eq 2, Scheme 4). Phenylglyoxals are important precursors in organic synthesis, and can be used to construct various biologically active heterocyclic compounds.[14b,17]In the literature, very few methods are available for the synthesis of glyoxal derivatives.[14b] The most common method for the synthesis of phenylgloxal involves SeO_2 mediated oxidation of substituted methyl ketones under harsh reaction conditions.[18] Recently, photoredox oxidation of brominated acetophenones to phenylglyoxal was reported using expensive ruthenium photocatalyst.[19] That method, however, cannot use commercially available phenylacetylene as the starting substrate. In contrast, synthesis of phenylglyoxal was easily achieved in short time in our current study under mild reaction conditions using inexpensive copper to catalyze photoredox process and commercially available arylalkynes as starting substrates. After isolation of phenylglyoxal, we conducted some key control experiments with **13** for better understanding of the reaction mechanism. First, reaction of phenylglyoxal with MeOH was carried out in the presence of light and O_2, but in the absence of CuI catalyst, which leads to no formation of α-keto ester **3a** (eq 3, **Scheme 4**). When phenylglyoxal reacts with the solvent MeOH in the presence of 5mol% CuI catalyst, light and O_2, but the absence of the 2-picolinic acid ligand, only a trace amount of **3a** was formed (eq 4, **Scheme 4**). When the control reaction was performed in the presence of CuI catalyst, 2-picolinic acid, O_2, and blue light irradiation, **3a** was produced in 90% yield (eq 5, **Scheme 4**). If the same reaction was carried out in a N_2 atmosphere, no formation of 3a was observed (eq. 6, **Scheme 4**). From the above control experiments (eq 3-6, **Scheme 4**), it is very clear that CuI catalyst, 2-picolinic acid ligand, O_2, and blue light irradiation all are very crucial factors for the formation of the α-keto ester product **3a**.

Selective oxidation of terminal alkynes to glyoxal, free from the subsequent over oxidation to glyoxalic acid, is a very challenging reaction in synthetic chemistry.[6] In our current protocol, selective oxidation of phenyl acetylene to phenyl glyoxal was achieved successfully and no phenyl glyoxalic acid resulting from over oxidation was observed. Thus, when phenyl glyoxalic acid **15** was used to react with MeOH under the same condition, we did not observe the product **3a**, which clearly suggests that over oxidization of glyoxal to glyoxalic acid[20] did not occur in the current reaction condition (eq 7, Scheme 4). 2-Picolinic acid plays a crucial role in avoiding the formation of homocoupling product from copper phenylacetylide (which is a common side product in reaction involving terminal alkynes in presence of copper catalyst) and it directs the

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system to activate terminal C≡C bond *via* controlled oxidation to phenylglyoxal. It is documented in the literature that nitrogen containing ligands can reduce the formation of polymeric byproducts and Glaser alkyne-alkyne homocoupling products.[21a] Hence the optimal amount of ligand is found to be 1.0 equivalent due to the above mentioned facts. Formation of polymeric form of Cu(II) bis-picolinate (single crystal X-ray Fig. S9, ESI†) might be one of the reason for the decrease in the yield when reaction was carried out with 5 and 10 mol% of 2-picolinic acid as ligand. Also due to amphoteric nature of 2-picolinic acid[21b], it can help maintain the acidic pH of the reaction mixture, thus avoiding the over-oxidation of phenyl glyoxal to glyoxalic acid. Therefore, excess amount of 2-picolinic acid (i.e., 1 eqv.) ligand, instead of catalytical amount, is required to achieve optimal product yield. Next, phenylglyoxal **13**, isolated from the current photoredox process could readily react with internal alkyne for the synthesis of 1,2-naphthoquinone **16**, *via* oxidative annulation reaction[22] (eq 8, **Scheme 4**). Further, reaction of phenylglyoxal **13** with MeOH was carried out under O_2 in the absence of light i.e., dark condition, which leads to no formation of α-keto ester **3a** (eqns 9 & 10, **Scheme 4**). This result clearly demonstrates that light irradiation is required for the transformation of phenyl glyoxal to α-keto ester product. Most probably, the transformation of phenyl glyoxal to α-keto ester product requires the help of copper superoxide radical, which cannot be generated in the absence of light irradiation. The superoxide radical anion was generated under visible light irradiation of Cu(I)-phenylacetylide, and is responsible for controlled aerobic oxidation of phenyl glyoxal to α-ketoesters.

Finally, isotopic labeling experiment was carried out in presence of $^{18}O_2$ (98%), instead of $^{16}O_2$ air, under the standard conditions (**Scheme 5**). ^{18}O labeled α-keto esters **3f** were obtained, with a ratio of $^{18}O^{18}O$-**3f**: $^{18}O^{16}O$-**3f**: $^{16}O^{16}O$-**3f** = 63.4: 26.4: 10.2 (Scheme S9 ESI†). These results unambiguously indicate that the oxygen atoms in the α-keto ester products mainly originate from the molecular O_2. The $^{18}O^{16}O$-**3f** product was most probably formed *via* a partial exchange with moisture in air or during the silica gel column purification process.[19] It should be noted that the compounds containing 1,2-diketo groups are active, and the oxygen of carbonyl can be exchanged *via* hemiketal with the oxygen of water in air.[5b,23]

(Scheme 5)

Based on the above control experiments and our previous studies,[7c,d] a plausible mechanism was proposed and shown in **Scheme 6**. Photoexcitation of in situ-generated Cu(I)-phenylacetylide (**1a'**) (UV-visible spectrum, Fig. S6, ESI†) generates a long lived (τ= 15.9 μs) triplet excited

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state Cu(I)-phenylacetylide (9)[7c,d] with partial charge separation occurring *via* ligand to metal charge transfer (LMCT).[7c-d] Thus photoexcited Cu(I)-phenylacetylide then donates an electron to molecular O_2 (i.e., a SET process) to generate a superoxide radical anion ($O_2^{\bullet-}$) and an electron deficient Cu(II)-phenylacetylide (**10**),[7c,d] which was confirmed by EPR measurements by using 5,5-dimethyl-1-pyrrolineN-oxide (DMPO) as a selective superoxide spin trapping reagent (Fig. S2, ESI†). Next, coordination of 2-picolinic acid (L) to Cu(II)-phenylacetylide and subsequent reaction to molecular O_2 results in the formation of copper(III)-superoxo complex **11**.[7c,24] Isomerization rearrangement of the resulting Cu(III)-peroxo complex (**11**)occurs with concurrent formation of a C–O bond to form the intermediate (**12**),[23] Subsequent O–O bond cleavage of the intermediate (**12**)produces 2-oxo-2-phenylacetaldehyde (**13**) and $Cu^{II}(pic)_2$ was eliminated as a blue ppt (Fig. S1 & S9, ESI†).[25] Further, a nucleophilic attack on (**13**) by alcohol (**2**) on electron deficient carbonyl group affords hemiacetal intermediate (**14**),[9c,11] which further undergoes copper catalysed aerobic oxidation[26] to produce α-keto esters (**3**). When 4,5-dimethylbenzene-1,2-diamine (**7**) was present in the reaction mixture, it traps the in situ-generated phenylglyoxal**13***via* intermolecular double condensation reaction to produce 6,7-dimethyl-2-phenylquinoxaline (**8**) in a one-pot manner, as shown in Scheme 6.

(Scheme 6)

In the presence of 4,5-dimethylbenzene-1,2-diamine, formation of *α*-keto esters was suppressed, due to the fact that *o*-phenylene diamine acts as a better nucleophile (N is less electronegative than O) to phenylglyoxal than alcohol (**2**), thus favouring the formation of 2-phenyl quinoxaline (**8**), instead of formation of hemiacetal (**14**).

CONCLUSION

In summary, we have developed an unprecedented visible light induced copper catalyzed process for the controlled aerobic oxidation of terminal C≡C triple bond to phenylglyoxal at room temperature, followed by esterification, for the synthesis of α-keto esters that evades the need of base, expensive catalyst, strong oxidants, elevated temperatures and other harsh reaction conditions. The reaction proceeds easily with excellent functional group tolerance towards electron donating and withdrawing terminal alkynes. Moreover, it is compatible with 1^o, 2^o, 3^o alcohols and slightly strained or labile alcohols, which is not possible or difficult in thermal processes. The utility of this protocol has also been successfully applied for the synthesize two

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biologically active molecules, i.e., 1-benzyl-3-(3-nitrophenyl) quinoxalin-2(1*H*)-one (a CFTR activator) and bis oxime ester (an E-*coli* DHPS inhibitor) in a gram scale with fewer steps and higher total yields than the literature reported processes. We have also demonstrated one pot synthesis of pharmacologically active heterocyclic compound i.e., 2-phenyl quinoxaline (a FLT3 inhibitor) *via* an unprecedented photoredox copper catalyzed process, as well as synthesis of naphthoquinone using phenylglyoxal isolated from the current photoredox process.

AUTHOR INFORMATION

Corresponding Author

*** Email: kchwang@mx.nthu.edu.tw**

Author Contributions

‡ D.K.D and V.K.K.P contributed equally for this work.

Conflicts of interest

There are no conflicts to declare.

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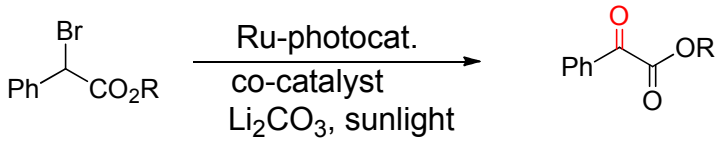
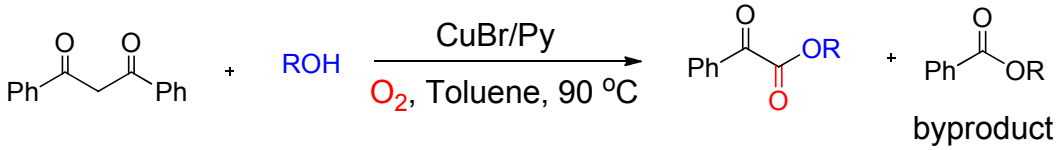
Scheme 1. Different synthetic approaches toward α-keto esters.

Previous Work

a) $Ru(bpy)_3Cl_2$ catalyzed oxidation of α-aryl halogen derivatives under sunlight



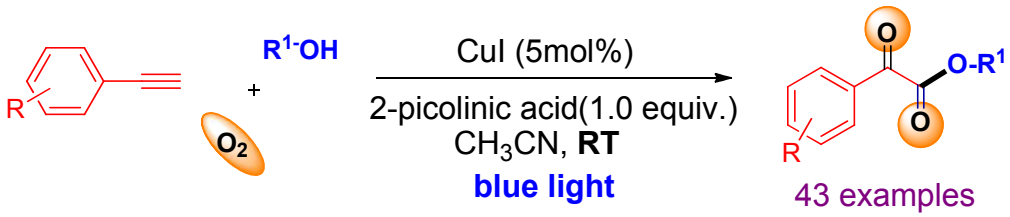
b) Cu-catalyzed aerobic oxidative esterification reaction of 1,3-diones



Previous reports failed with 3° alcohols and gave poor yields with 2° alcohols.

Current work **Visible light initiates the reaction**

c) Photoredox copper catalyzed synthesis of α-keto esters under blue light



43 examples

- Controlled oxidation of terminal C≡C triple bond.
- O_2 (1 atm) as oxidant
- Works very well with 1°, 2° & 3° alcohols at RT with excellent yields.
- No formation of byproducts with broad substrate scope

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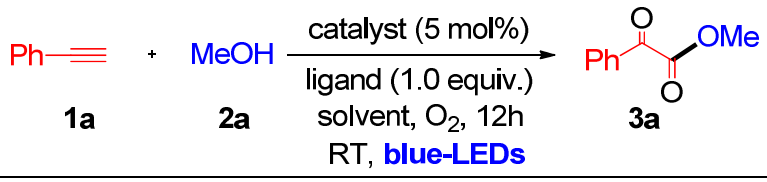
Table 1. Optimization of reaction condition[a]



1a **2a** **3a**

entry	Cu [catalyst]	ligand	solvent	yield%[b]
1	**CuI**	**2-picolinic acid**	**CH_3CN**	**86**
2[c]	Other Copper salts	2-picolinic acid	CH_3CN	n.r
3	**none**	2-picolinic acid	CH_3CN	n.r
4	CuI	**none**	CH_3CN	0
5[d]	CuI	2-picolinic acid	CH_3CN	0
6[e]	CuI	2-picolinic acid	CH_3CN	<5
7[f]	CuI	2-picolinic acid	CH_3CN	71
8[g]	CuI	2-picolinic acid	CH_3CN	85
9	CuI	dipicolinic acid	CH_3CN	82
10	CuI	2-aminopyridine	CH_3CN	**0**
11[h]	**CuI**	**2-picolinic acid**	**none**	**86**
12	CuI	2-picolinic acid	THF	65
13	CuI	2-picolinic acid	Toluene	36
14[i]	CuI	2-picolinic acid	MeOH	76
15[j]	CuI	2-picolinic acid	MeOH	82
16[k]	CuI	2-picolinic acid	MeOH	n.r
17[l]	CuI	2-picolinic acid	MeOH	n.r

[a]Reaction conditions: **1a** (0.50 mmol), MeOH (2 mL), CH_3CN (4 mL), ligand (0.5 mmol) and catalyst (0.05 mmol), the reaction mixture was irradiated with blue LEDs (40 mW/cm^2 at 460 nm) at RT for 12h under O_2 (1atm). [b]Isolatedyields. [c]Other copper salts such as CuX (X = Cl, Br). [d]5 mol % of 2-picolinic acid was used. [e]10 mol% of 2-picolinic acid were used. [f]50 mol % of 2-picolinic acid was used. [g]2.0 equiv. of 2-picolinic acid were used. [h]MeOH (4 mL) was used both as reactant and solvent. [i]Under 1 atm. air. [j]Under ambient white light irradiation (12h, 8 mW/cm^2 at 460 nm). [k]At room temperature and in the dark. [l]Under N_2 atmosphere. n.r. = no reaction.

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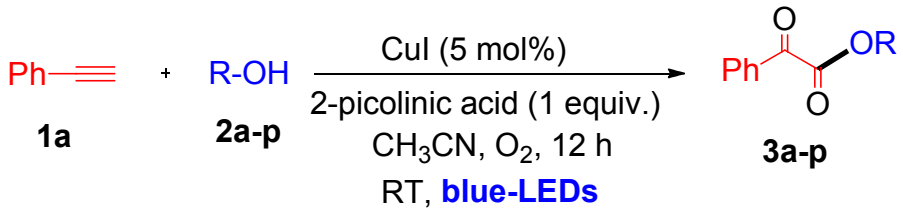
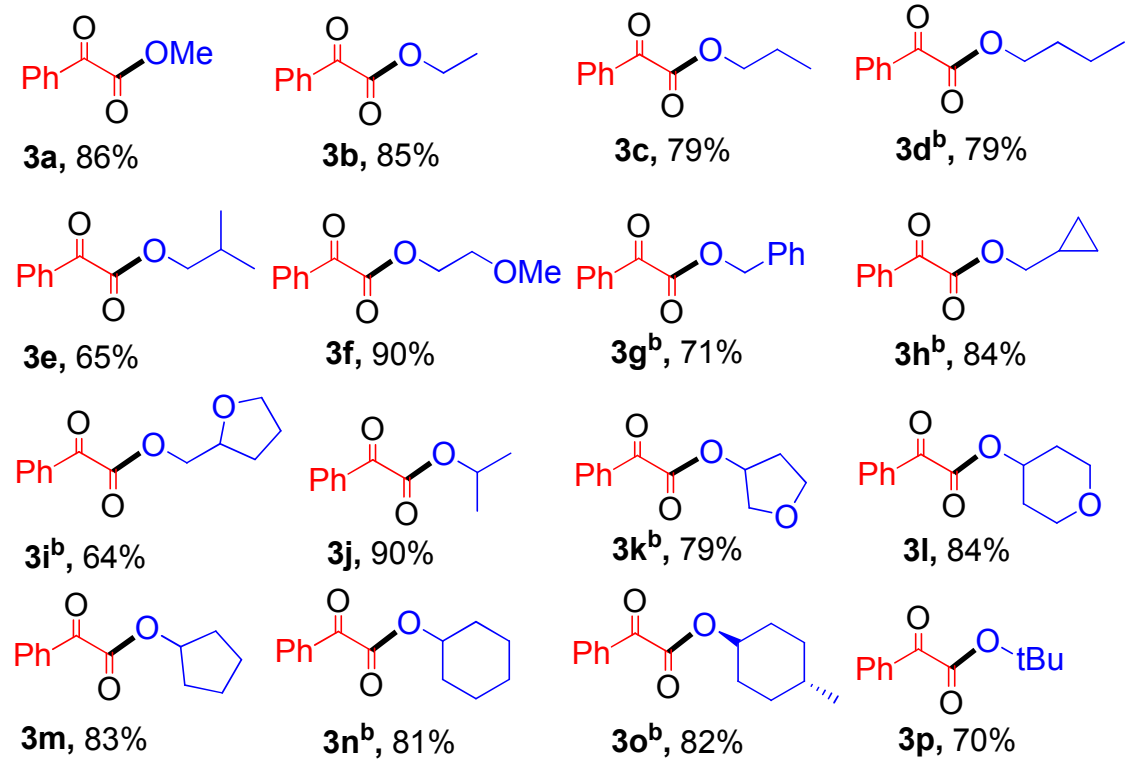
Table 2. Substrate scope of alcohols[a]





[a]Standard conditions. [b]2 mmol of ROH in 4 mL of CH_3CN, isolated yields.

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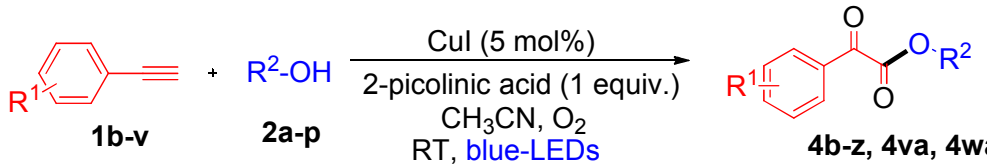
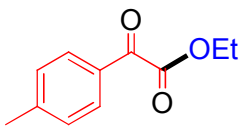
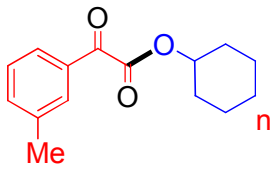
Table 3. Substrate scope of aryl terminal alkynes[a]

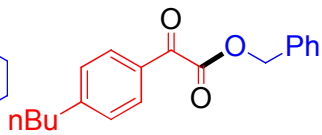




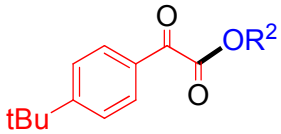
4b, 87%, 12h



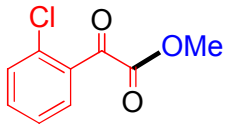
4c[b], 86%, 12h



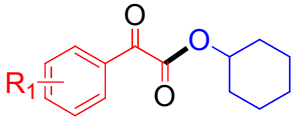
4d[b], 74%, 12h



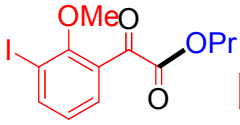
4e, R^2 = Me, 90%, 12h
4f, R^2 = ^{t}Bu, 70%, 12h



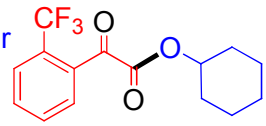
4g, 77%,12h



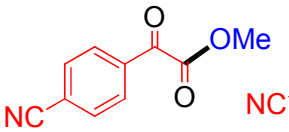
4h[b], R^1=4-Cl, R^2 = Cy,78%,12h
4i[b], R^1=4-F, R^2 = Cy 72%,12h



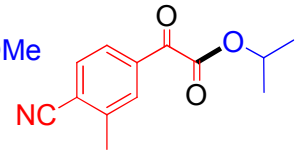
4j, 84%, 12h



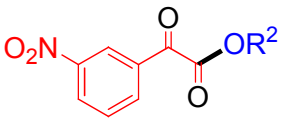
4k[b], 72%, 12h



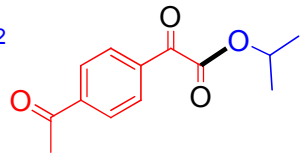
4l, 82%, 9h



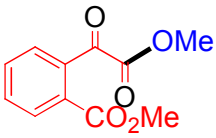
4m, 84%, 9h



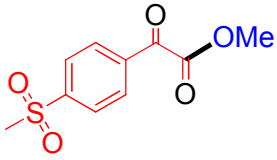
4n, R^2 = Me, 84%, 9h
4o, R^2 = ^{t}Bu, 61%, 9h



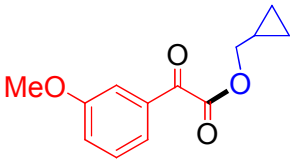
4p, 86 %, 9h



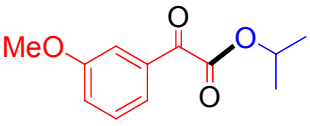
4q, 78%, 12h



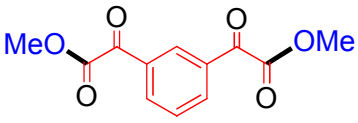
4r, 84%, 12h



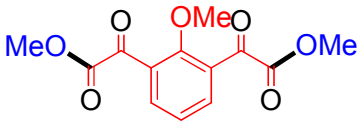
4s[b], 88%, 12h



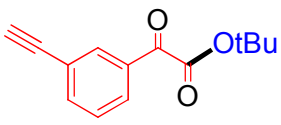
4t, 92%, 12h



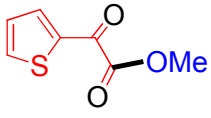
4u, 93%, 12h



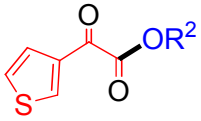
4v, 94%, 12h



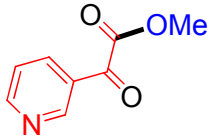
4w, 81%, 12h



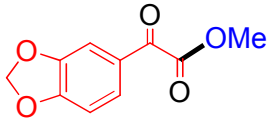
4x, 89%, 12h



4y, R^2=*i*-Pr, 78%, 12h
4z, R^2=tBu, 40%, 12h



4va, 80%, 12h



4wa, 83%, 12h

[a]Standard conditions. [b]2 mmol of R-OH in 4 mL of CH_3CN.

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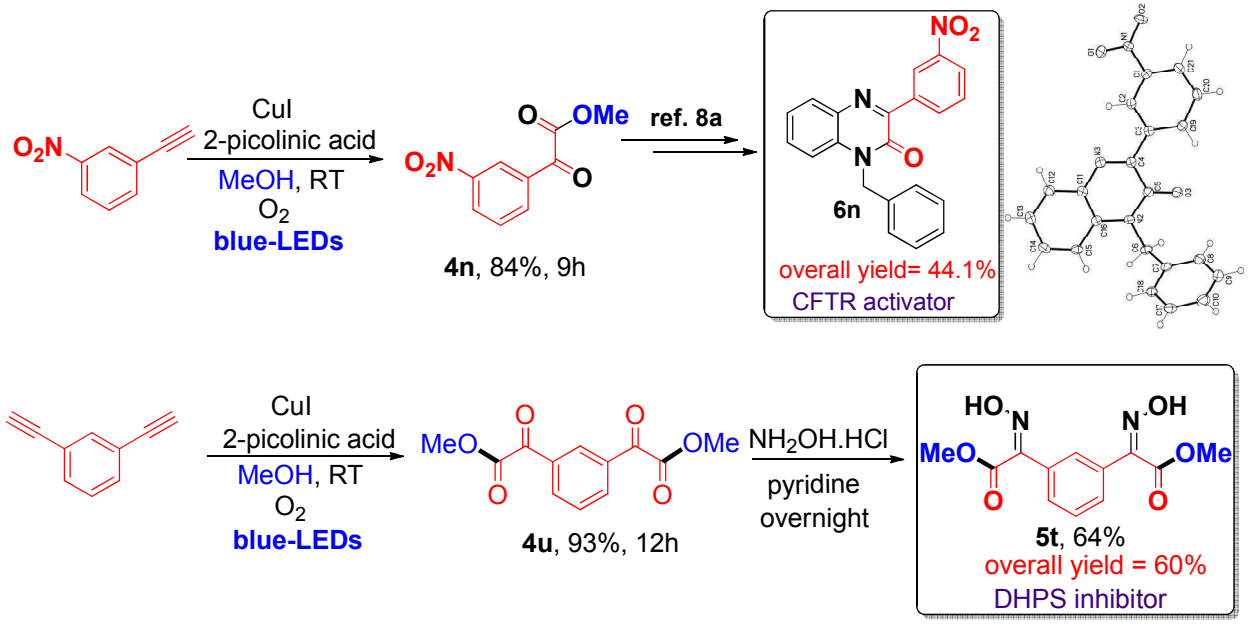
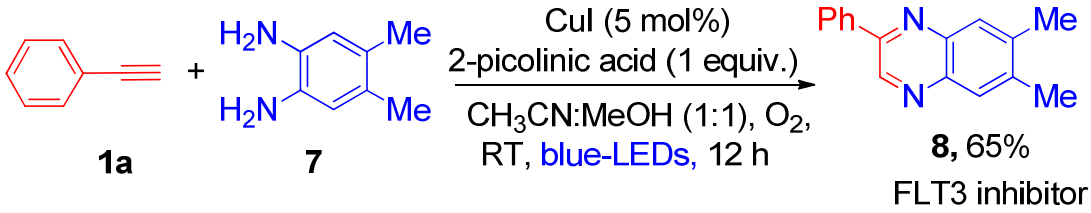
Scheme 2. Synthesis of biologically active phenylquinoxalinone, 6n (CFTR activator) and bis oxime ester, 5t (DHPS inhibitor).



Scheme 3. One pot synthesis of 2-phenyl quinoxaline (a FLT3 inhibitor) by in-situ trapping phenylglyoxal using commercially available substrate, 1,2-phenylenediamine.



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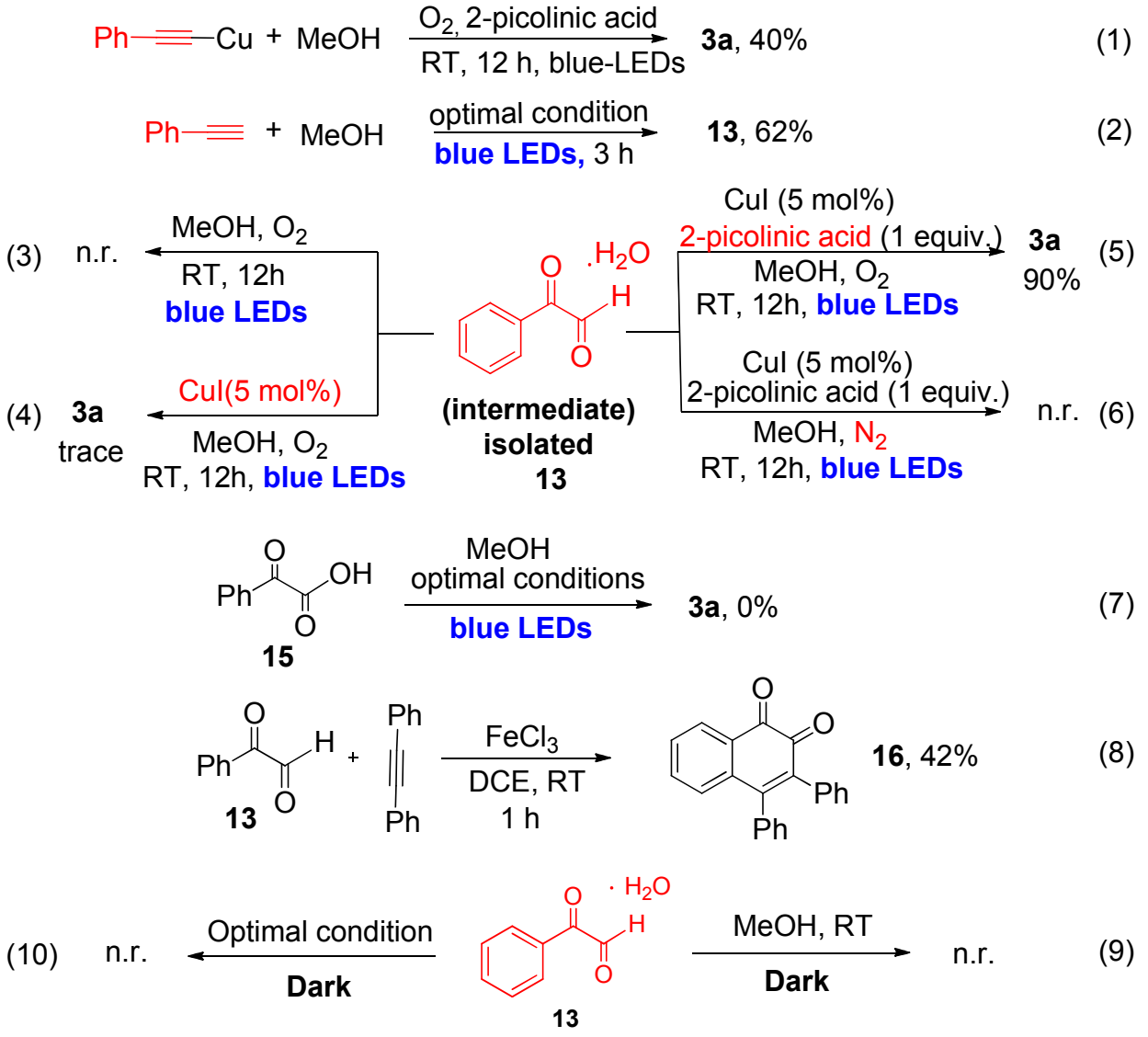
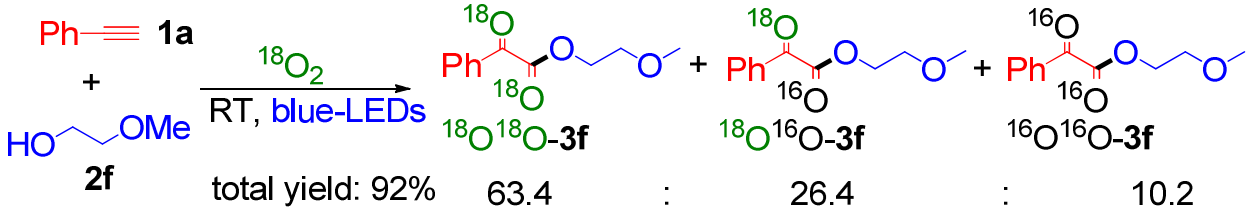
Scheme 4. Mechanistic control studies.



Scheme 5. Isotopic labelling experiment.



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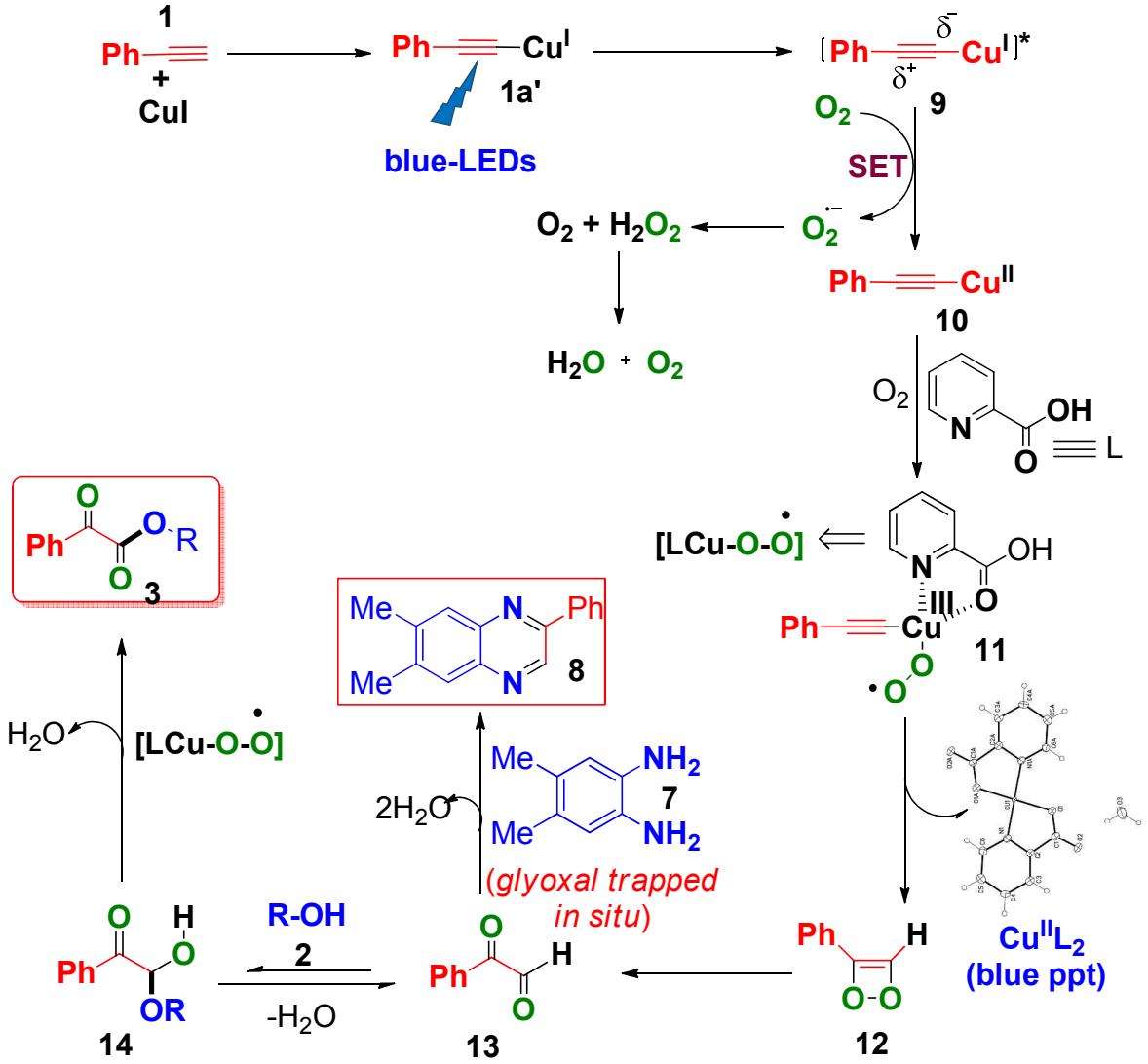
Scheme 6. Plausible mechanism for the formation of α-keto esters.



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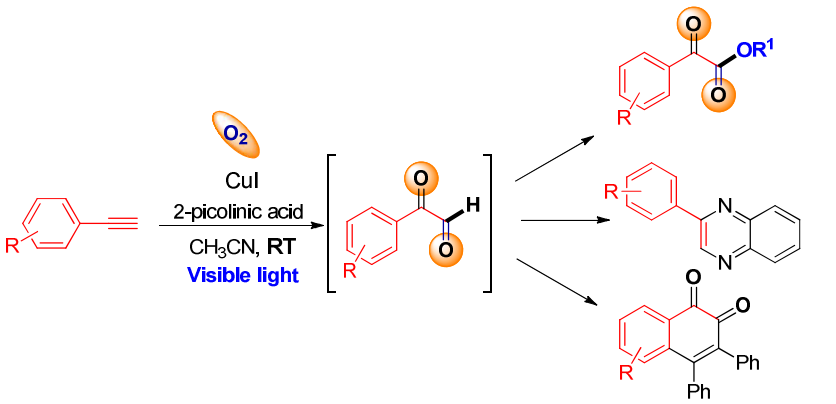

Controlled oxidation of terminal C≡C triple bond. O_2 (1atm) as oxidant and reagent