Communication

Visible Light Copper Photoredox-catalyzed Aerobic Oxidative Cou-pling of Phenol and Terminal alkynes: Regioselctive Synthesis of functionalized Ketones via C#C triple bond cleavage

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Visible Light Copper Photoredox-catalyzed Aerobic Oxidative Coupling of Phenol and Terminal alkynes: Regioseletive Synthesis of Functionalized Ketones via C≡C Triple Bond Cleavage

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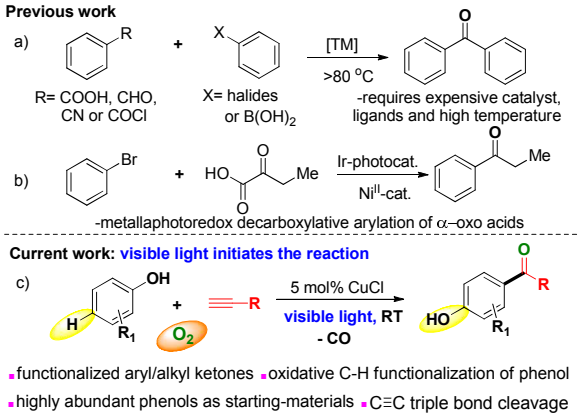
Supporting Information Placeholder

ABSTRACT: Direct oxidative coupling of phenols and terminal alkynes was achieved at room temperature by a visible light-mediated copper-catalyzed photoredox process. This method allows regioselective synthesis of hydroxyl-functionalized aryl and alkyl ketones from simple phenols and phenylacetylene via C≡C triple bond cleavage. 47 examples were presented. From a synthetic perspective, this protocol offers an efficient synthetic route for the preparation of pharmaceutical drugs, such as, pitofenone and fenofibrate.

The development of new chemical transformations by employing simple and readily available starting materials using low energy visible light irradiation is of great importance in synthetic chemistry. In this regard, visible light-activated photoredox catalysis (Ru- or Ir-) are proven to be a powerful platform for the design and development of valuable new chemical reactions through participation of unique single electron transfer pathways.[1] With respect to earth abundance, and inexpensiveness, copper-based photoredox catalysis has become a rapidly growing area of research in organic synthesis and has been successfully shown to facilitate various coupling reactions using specific copper complexes [Cu(dap)Cl][2] or a combination of simple CuCl with substrates (in-situ generated photocatalysts).[3] In connection to this topic, our group has recently reported that visible-light activated copper-catalyzed process for C-C/C-N cross-coupling and C-H annulation reactions.[4] We anticipate that photoexcited copper(I) acetylide can involve a single electron transfer process with oxidants (e.g., O_2 or benzoquinone) and stimulate the essential coupling reaction upon visible light irradiation. Herein, we report the discovery of the first visible light mediated aerobic oxidative coupling of simple phenols with terminal alkynes to prepare the hydroxyl functionalized aryl/alkyl ketones through SET process to O_2 under very mild conditions using a simple and inexpensive catalyst (5% CuCl, without use of external oxidants and bases; see Scheme **1c**).

Ketones are versatile intermediates and important structural motifs in pharmaceuticals, natural products, numerous photosensitizers, and advanced organic materials.[5] Consequently, previous efforts have been devoted to developing synthetic methods for synthesizing ketones, as follows, a) organometallic additions to Weinerb amides/acyl halides;[6] b) direct arylation of aldehyde by aryl halides/aryl boronic acids;[7] and c) metal-catalyzed decarboxylative addition of benzoic acid to nitriles;[8] d) Cu/Pd-catalyzed decarboxylative addition of α-oxocarboxylates to aryl halides, (scheme **1a**).[9] Despite the utility of such processes, common drawbacks include: a) generally suffer from tedious preparation of starting materials and, sometimes, poor stabilities; b) usage of expensive catalysts and requirement of high temperature; and c) more importantly, all reported processes are limited to preparation of simple aryl/alkyl ketones without additional functionalities.

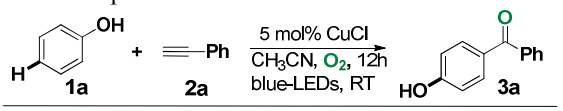
Scheme 1. Transition-metal-catalyzed synthesis of ketones



Recently, the MacMillan group reported an efficient method to synthesize ketones through direct decarboxylative arylation of α-oxo acids by merging phototredox and nickel catalysis (scheme **1b**).[10] Despite this important advances, direct oxidative coupling of readily available phenols with terminal alkynes to prepare functionalized ketones via C≡C triple bond cleavage remains unexplored. The topic of C≡C triple bond cleavage is fundamentally challenging, but provides great opportunity to construct targeted molecules through unusual routes.[11] Moreover, owing to their natural availability, low toxicity and low cost, the utilization of unactivated phenols (polymeric forms in lignin and coal) as starting materials is an economically attractive alternative to existing organic halides as cross coupling partners.[12] More importantly, aryl/alkyl ketone bearing a hydroxyl group is one of the most versatile intermediates for organic transformations[13] and direct synthesis of pharmaceutical drugs, such as, tamoxifen, estrogen receptor modulator, and others.[14] The current work presents the first literature method for single-step regioselective synthesis of hydroxyl substituted aryl/alkyl ketones (see **Scheme 1c**), which is complementary to well-known organic name reactions, such as, the Fries rearrangement[15] (i.e. conversion of phenolic ester to hydroxyl-aryl ketones with mixture of ortho and para products by heating in the presence of Lewis acids or uv-light).

Inspired by our previous work,[4a] we found that in the absence of arylamines and the presence of O_2, aryl ketone (**3a**) could be formed via direct oxidative coupling of benzoquinone (BQ)/hydroquinone (HQ) and terminal alkynes via C≡C cleavage under photoirradiation (Table 1, entries 1 & 2).

Table 1. Optimization of reaction condition.[a]



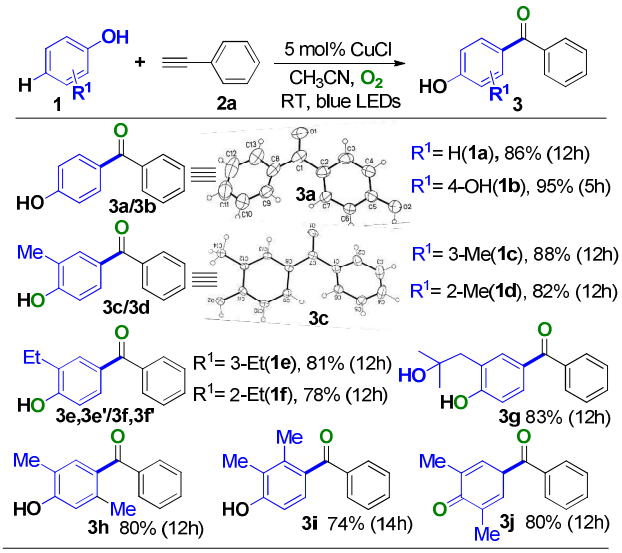
Entry	[Cu] Catalyst	Solvent	Yield [%][b]
1[c]	CuCl (BQ used as SM)	CH_3CN	87 (7hr)
2[d]	CuCl (HQ used as SM)	CH_3CN	95 (5hr)
3	**CuCl**	**CH_3CN**	**86**
4[e]	CuCl (without **2a**)	CH_3CN	90 (BQ)
5	CuBr	CH_3CN	85
6	$CuCl_2$	CH_3CN	82
7	CuCl	CH_3CN-MeOH	70
8	CuCl	CH_3OH	80
9	CuCl	DMF	45
10	CuCl	THF	15
11[f]	CuCl	CH_3CN-H_2O	83
12[g]	CuCl	CH_3CN	84
13[h]	CuCl	CH_3CN	65
14[i]	CuCl	CH_3CN	60 (BQ)
15[j]	none	CH_3CN	n.r
16[k]	CuCl	CH_3CN	0

[a]Unless otherwise noted, reaction conditions are as follows; **1a** (0.5 mmol), **2a** (0.55 mmol), [Cu] catalyst (5 mol%) solvent (7 mL). The mixture was irradiated with blue LEDs (power density: 40 mW/cm^2 at 460 nm) for 10 h in an O_2 (1 atm.). [b]Yield of the isolated product. [c]benzoquinone (BQ) used as substrate. [d]hydroquinone (HQ) used as substrate. [e] reaction conducted without **2a**. [f]0.5 mL water was added. [g]In the presence of air (1 atm.). [h]Reaction irradiated with an ambient white light bulb for 17 h (power density: 8 mW/cm^2 at 460 nm). [i]Reaction conducted in the dark at 80 °C (60% BQ obtained). [j]In the absence of [Cu] catalyst. [k]In the absence of O_2. n.r. = no reaction.

Interestingly, using phenol as the starting material in the presence of **2a**, O_2, and CuCl (5 mol%) under visible light irradiation affords the desired aryl ketone (**3a**) with an 86% yield (entry 3). Nevertheless, in the absence of **2a**, 90% of BQ (as a stable intermediate) was obtained via oxidation of phenol (entry 4). Indeed, electron rich phenols can be oxidized to benzoquinones by Cu(I) or Cu(II)-salt and O_2.[16] Upon visible light irradiation phenol (**1a**) is readily oxidized to BQ (Table 1, entry 4 & 14). The reason could be attributed to the fact that Cu(I) salt readily interacts with O_2 to form Cu-superoxo or -peroxo complexes.[16] Photo-irradiation of such Cu-complexes can further promote oxidation of phenol to generate BQ. Various copper catalysts were examined. CuX (X=Cl or Br) and $CuCl_2$ were found to be the most effective catalysts (Table 1, entries 3 & 5-6). In the solvent screening, CH_3CN provided the highest yield among all. The addition of water (0.5 mL) does not affect the product yield (entries 7-11). In the presence of air, the product yield decreases slightly to 84% (Table 1, entry 12). Further investigation establishes that CuCl, O_2, and visible light all are required for the current reaction. Note that in dark thermal conditions (at 80 °C), 60% of BQ was obtained, but no aryl ketone was generated (Table 1, entries 14-16).

Under optimized conditions (Table 1, entry 3), various electron rich phenols were demonstrated to undergo oxidative coupling with phenylacetylene (**2a**) to form the hydroxyl-aryl ketones (Table 2). Particularly, 4-hydoxy-phenol (hydroquinone, **1b**) effectively couples with **2a** to generate **3a** with a 95% yield after 5 h blue LED irradiation. In the case of mono-substituted phenols (**1c-1d & 1g**), regioselective coupling of **2a** with Me/tBu-substituted BQ at their free carbonyl site generates aryl ketones (**3c-3g**). However, the reactions of **1e** & **1f** generate a mixture of regioisomers (inseparable). Notably, formation of t- butyl substituted hydroxyl aryl ketone involves intramolecular 1,5 H abstraction by Cu-superoxo and phenoxy radicals to afford **3g** (see details in S.I.). Interestingly, when 3,5-dimethyl phenol (**1j**) was used as a substrate, it could be oxidized to its corresponding benzoquinone and then couples with **2a** exclusively in meta position to the methyl group to generate the quinone type product **3j** instead of hydroxyl-aryl ketone (Table 2). This is probably due to the steric hindrance of the Me-substitution group.

Table 2. Substrate scope of phenols[a]



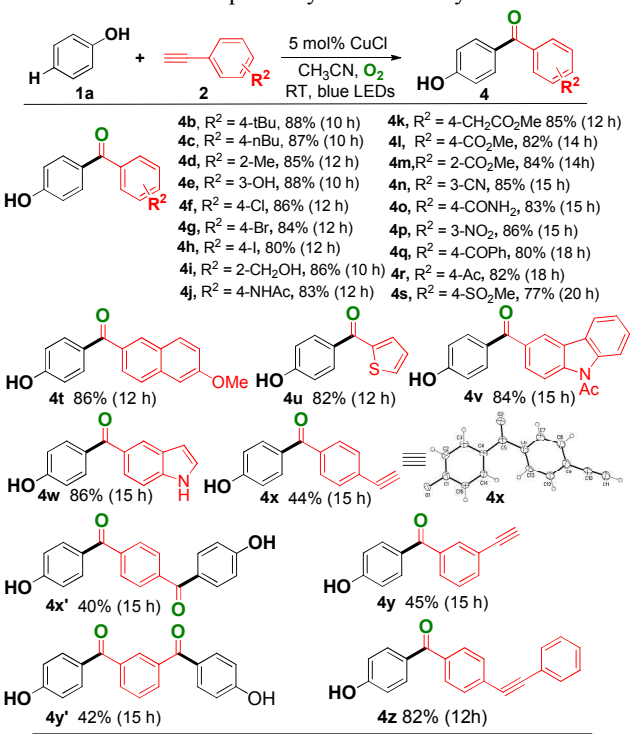
[a]Standard condition. Isolated yield after purification by column chromatography on silica gel.

Next, the substrate scopes of aryl alkynes were examined with coupling partner phenol (**1a**) under the optimized condition. Table **3** shows that aryl alkynes with various functional groups could couple with functionalized phenols to regioselectively furnish their corresponding hydroxyl-aryl ketones in high yields. Halo-substituted (Cl, Br, and I) and 3-OH, and 2-CH_2OH substituted aryl alkynes could also smoothly react with phenols to generate the aryl ketones in good yields (80 – 88%). The additional hydroxyl functionality is useful for further synthetic modifications.[17] Notably, aryl alkynes bearing moderate to strong electron withdrawing groups (**2j-2s**) could also successfully proceed with the current oxidative coupling reactions (**4j-4s**). Moreover, heteroaryl alkynes (**2u-2w**), 1,4/1,3-diynes (2x & 2y) and substituted internal alkynes (2z) are also well tolerated and can couple with phenols to generate their corresponding ketones in high yields (**4u-4z**). Table 4 shows that aliphatic terminal alkynes, including, cyclohexyl, cyclohexenyl, linear chain alkynes (pentyl, hexyl and octyl), and other liner chain alkynes (**5a-5i**) could also react smoothly to generate the desired ketones in good yields (**6a-6i**). The structures of **3a**, **3c**, and **4x** were confirmed by single-crystal x-ray diffraction. Copper-catalyzed aerobic oxidative coupling reactions involving terminal alkynes always suffer from homocoupling by-product formation,[16] but in the current process no homocoupling product was observed.

Finally, the application of this new reaction was demonstrated for the rapid preparation of pharmaceutical drugs, such as, pitofenone (an antispasmodic drug),[14a] and fenofibrate (fibrate class of cholesterol reducing drug).[18] These two important medicinal drugs could be synthesized using the new process in two steps (72~76% total yields) (**Scheme 2**), which is far better than other existing literature multi-step methods (4 steps with total yields of

37% for pitofenone and 71% for fenofibrate).[14a,19] In addition, compounds **3a**, **3c**, **4h**, **6h**, and **6i** can be used as precursors for synthesizing corresponding hydroxyl aryl ketones pharmaceutical drugs (Details in S.I.).

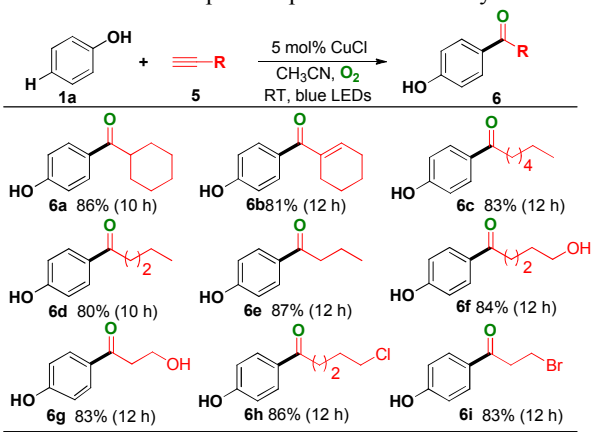
Table 3. Substrate scope of aryl terminal alkynes[a]



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

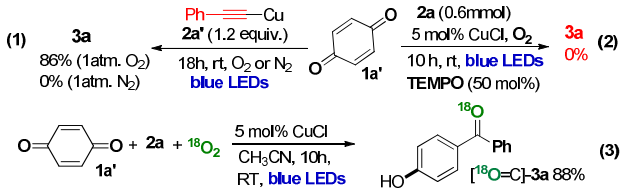
To gain mechanistic insights, various control experiments were carried out (Eq. 1 – 3). BQ (**1a'**) was used as a substrate and conducted some key control experiments for the formation of aryl ketones under standard conditions. First, pre-synthesized copper(I) phenylacetylide **2a'** was used to react with BQ **1a'** in the absence of CuCl, which generates the desired ketone (**3a**) with an 86% yield after 18 h irradiation (Eq. 1).

Table 4. Substrate scope of aliphatic terminal alkynes[a]



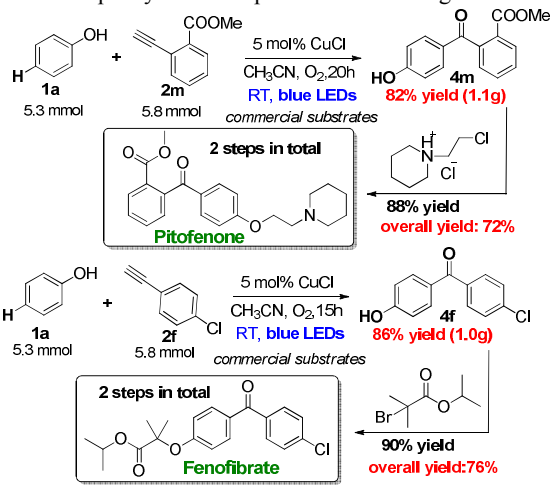
[a]Standard condition. Isolated yield after purification by column chromatography on silica gel.

Thus, this control reaction suggests that in situ-generated Cu(I)-phenylacetylide might be the key light-absorbing photocatalyst. When the above reaction was carried out under an N_2 atmosphere, instead of an O_2 atmosphere, no aryl ketone (**3a**) was produced (Eq. 1). Furthermore, when the reaction of BQ **1a'** with **2a** was carried out in the presence of TEMPO (50 mol%), the formation of aryl ketone (**3a**) was completely inhibited (see Eq. 2), suggesting that radical intermediates might be involved in the reaction. Finally, when the reaction was carried out in the presence of $^{18}O_2$ (98%), ^{18}O product (97% ^{18}O in carbonyl oxygen) was obtained exclusively (Eq. 3), indicating that the oxygen atom in the ketone products originated from O_2. Based on these control experiments, we speculated that a SET process may occur between photoexcited Cu(I)-phenylacetylide and O_2, instead of BQ. Indeed, O_2 has lower redox potential (-0.78 V_{SCE}) when compared to BQ (-0.98 V_{SCE}).[20] Both the redox potentials of O_2 and BQ are sufficiently lower than for electronically excited Cu(I)-phenylacetylide (-2.048 V_{SCE} in CH_3CN).[4a,b,c] Therefore, the SET process from the photoexcited triplet copper(I) phenylacetylide to O_2 is exothermic and can occur spontaneously.



Based on the above mechanistic results and our previous investigation,[4] a reaction mechanism was proposed and shown in **Scheme 3**. Visible-light irradiation of in-situ generated Cu(I)-phenylacetylide (**2a'**) generates a long-lived excited state of Cu(I)-phenylacetylide **7**, which then undergoes a SET process to donate an electron to O_2 and generates the intermediates Cu(II)-phenylacetylide **8** as well as superoxide radical anion, as evidenced by EPR experiments (see S.I.). Indeed, by considering the redox potential of **2a'** (-2.048 V_{SCE} in CH_3CN)[4a,b,c] and strong electron affinity of O_2, a facile SET process most probably occurs between the photoexcited triplet Cu(I)-phenylacetylide and O_2. Concurrently, phenol (**1a**) was oxidatively converted to BQ **1a'** by the Cu(II)-superoxo intermediate.[16]

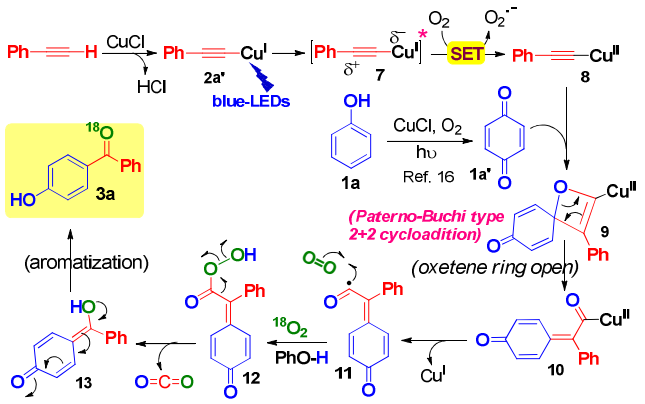
Scheme 2. Rapid synthesis of pharmaceutical drugs



Next, Paterno-Buchi type [2+2] cycloaddition of Cu(II)-phenylacetylide **8** with BQ (**1a'**) generates the labile Cu(II)-oxetene ring **9**,[21] which then rearranges to generate the Cu^{II}-coordinated quinone methide **10**, followed by rapid fragment to generate the acyl radical intermediate **11** and Cu^{I}.[16,10] Subsequent dark reactions with molecular oxygen O_2 and abstraction of a phenolic proton lead to the formation of peracid **12**[16,22] that then

undergoes radical cleavage to extrude the CO_2 and generates the hydroxyl substituted quinone methide **13**. Keto-enol tautomerism (via aromatization) then leads to the formation of aryl ketone (**3a**). By using a ferrioxalate actinometer as a reference for comparison,[23] the quantum yield for the formation of aryketone **3a** was determined to be 0.7525, suggesting that no chain process was involved in the current photoredox reactions (see S.I. for details for quantum yield measurements).

Scheme 3. Proposed reaction mechanism



In summary, we have demonstrated a novel new chemistry to regioselectively synthesizes hydroxyl functionalized aryl ketones via visible light-induced CuCl-catalyzed oxidative coupling of phenol and terminal alkynes at room temperature. The coupling reaction occurs via the SET process with O_2 and C≡C triple cleavage, followed by Paterno-Buchi type [2+2] cycloaddition reaction. Overall, 47 examples were demonstrated. This new chemistry is easily operated using simple and readily available starting materials under mild conditions, and is also applicable for rapid and efficient preparation of pharmaceutical drugs, such as, pitofenone and fenofibrate (2 steps with overall yields of 72 – 76%, which are far better than other processes reported in the literature (4 steps, 37 and 71% total yields for pitofenone and fenofibrate, respectively).

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data are available free of charge via the Internet at http://pubs.acs.org.

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Notes: The authors declare no competing financial interests.

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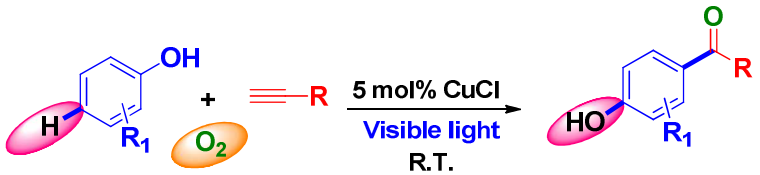
SYNOPSIS TOC (Word Style “SN_Synopsis_TOC”).



- functionalized aryl/alkyl ketones
- oxidative C-H functionalization of phenol
- highly abundant phenols as starting materials
- C≡C triple bond cleavage