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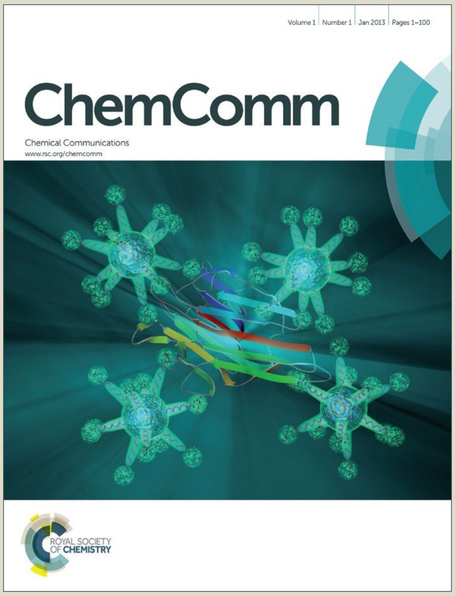

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Visible-light-induced chemoselective radical/oxidative addition domino process to access α-chloro and α-alkoxy aryl ketones

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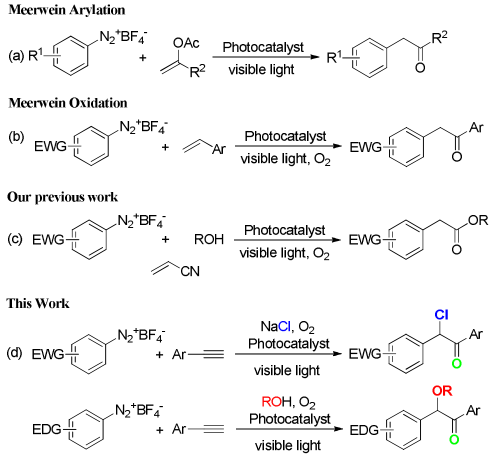
A visible-light-induced radical-triggered chemoselective domino process to access α,α-*di*-functionalized ketones under mild conditions has been developed. This protocol provides a direct approach to synthesize α-chloro or α-alkoxy aryl ketones based on the electronic properties of the substrates. The reaction can tolerate a variety of functional groups to afford the corresponding products in moderate to good yields.

α-Functionalized ketones such as α-halo,[1] α-alkoxy[2] and α-amino[3] ketones are versatile building blocks for pharmaceutical and natural product synthesis. Traditional approaches to access these compounds are via halogenation of ketones[4] or their alcohol precursors[5] followed by attack with different nucleophiles.[5b,6] Alternatively, hydroxybromination of styrenes[7] and hypervalent iodine (III)-mediated oxidative rearrangement of vinyl halides,[8] silyl enol ethers[9] as well as α-diazo ketones[10] are also useful routes to α-functionalized ketones. However, these methods usually requires the use of toxic reagents, excess of oxidants or metal catalysts. Thus, a simple and environmentally friendly way to synthesize these products is still highly desirable.

Recently, visible-light-induced radical oxidation of vinylarenes or alkynes has received much attention. The König, cai, Yadav and our group successfully prepared 1,2-diarylated ethanones,[11,12a] β-ketophosphine oxides,[12b] β-keto sulfoxides[13] and α-aryl esters[14] utilizing this strategy. However, only *mono*-functionalized keto-derivatives at α-position have been achieved (using arylation as example, Scheme 1, (a-c)). The synthesis of α,α-*di*-functionalized ketones, however, has not been reported yet. The challenge for α,α-*di*-functionalization process lies in how to generate and trap the radical intermediate or its corresponding oxidized electrophilic cations. Nevertheless, this issue has been less studied since current research mainly focused on the 1,2-difunctionalization of double bonds via an ATRA (atom-transfer radical addition)-type mechanism.[15] We envisioned whether triple bond could undergo such ATRA process with oxygen by radical rearrangement. If possible, the α,α-*di*-functionalized ketones could be delivered. Given the importance of functionalized ketones, and in continuation of our interest in photoredox catalysis, herein, we report a visible-light-induced chemoselective radical/oxidative addition domino process to access α-chloro and α-alkoxy aryl ketones (Scheme 1, (d)).



Scheme 1 Photocatalytic approaches for functionalization of alkenes and alkynes.

Our initial efforts focused on using Cl^- to trap the ion intermediate which was generated by the reaction of aryl diazonium salt (**1a**) and phenylacetylene (**2a**) under oxygen using visible-light catalysis (Table 1). Pleasingly, a 63% yield of product **3aa** was obtained in the presence of $Ru(bpy)_3Cl_2$ (3 mol%) and HCl (2.2 equiv) in methanol after irradiation with a 5 W blue LED for 8 h (entry 1). Other photocatalysts such as $Ir(ppy)_3$ and Rhodamine B showed less catalytic activities (entries 2 and 3). Switching the catalysts to Eosin Y and Eosin B provided the comparable yields with $Ru(bpy)_3Cl_2$ (entries 4 and 5, 64% and 60%, respectively). Thus, the cheap and

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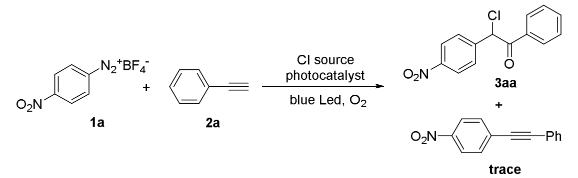
nonmetallic Eosin Y was selected as the ideal photocatalyst. Furthermore, increasing the amount of Eosin Y to 6 mol% led to a decreased yield (entry 6). Other Cl sources such as NaCl and NCS (*N*-chlorosuccinimide) were also checked. Notably, when NaCl was used as the Cl source, the reaction proceeded smoothly to deliver the desired product **3aa** in 62% yield (entry 7); while no reaction was observed in the presence of NCS (entry 8). This indicated that the reaction may proceed through a nucleophilic attack of chloride anion (see the mechanism). The choice of solvent had a significant impact on the reaction. Trace amounts of desired products were obtained in DMF and DMSO. Reactions in THF, acetonitrile and 1,4-dioxane afforded relatively lower yields (entries 11~13). Other control experiments were also performed. No reaction took place in the absence of a photocatalyst or visible light (entries 14 and 15). Reaction under air provided a lower yield of **3aa** (46%). Slightly increasing the amount of **2a** and NaCl did not affect the reaction (entries 17 and 18). However, changing the concentration of **1a** afforded decreased yields (entries 19 and 20). In addition, trace amount of by-product 1-nitro-4-(phenylethynyl)benzene was also observed, indicating a cross-coupling reaction between **1a** and **2a** occurred in this reaction.

Table 1. Optimization of reaction conditions.[a]

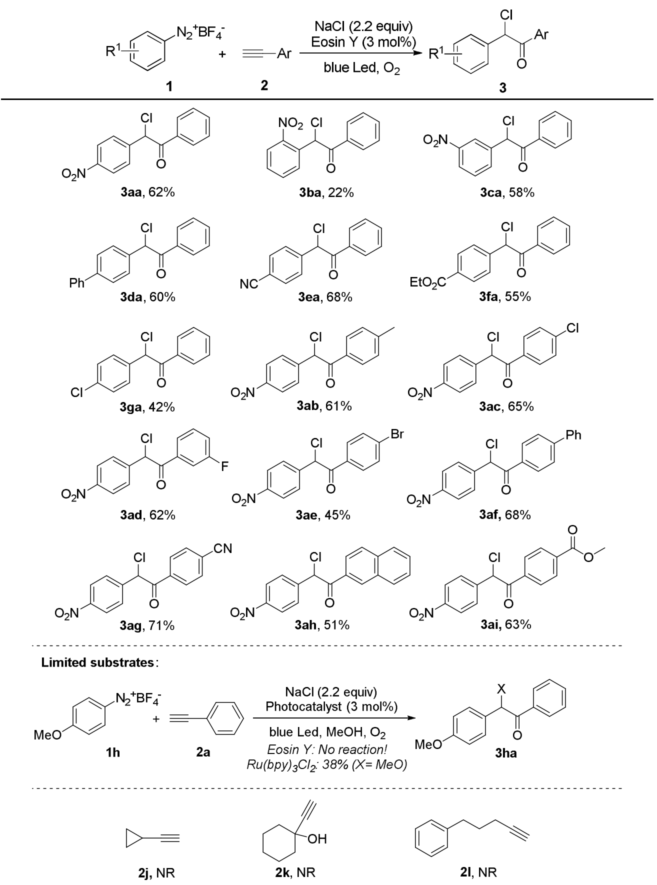


Entry	Catalyst (mol%)	Cl source	Solvent	Yield (%)[b]
1	$Ru(bpy)_3Cl_2$ (3)	HCl	MeOH	63
2	$Ir(ppy)_3$ (3)	HCl	MeOH	38
3	Rhodamine B(3)	HCl	MeOH	42
4	Eosin Y (3)	HCl	MeOH	64
5	Eosin B(3)	HCl	MeOH	60
6	Eosin Y (6)	HCl	MeOH	45
7	Eosin Y (3)	NaCl	MeOH	62
8	Eosin Y (3)	NCS	MeOH	NR[c]
9	Eosin Y (3)	NaCl	DMF	trace
10	Eosin Y (3)	NaCl	DMSO	trace
11	Eosin Y (3)	NaCl	THF	32
12	Eosin Y (3)	NaCl	CH_3CN	55
13	Eosin Y (3)	NaCl	1,4-dioxane	40
14	Eosin Y (3)	NaCl	MeOH	NR[d]
15	Eosin Y (3)	NaCl	MeOH	NR[e]
16	Eosin Y (3)	NaCl	MeOH	46[f]
17	Eosin Y (3)	NaCl	MeOH	62[g]
18	Eosin Y (3)	NaCl	MeOH	62[h]
19	Eosin Y (3)	NaCl	MeOH	46[i]
20	Eosin Y (3)	NaCl	MeOH	42[j]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.1 equiv), Cl source (2.2 equiv), and photocatalyst in indicated solvent (2 mL) were irradiated with a 5 W blue LED under oxygen at room temperature for 8 h. [b] Isolated yields. [c] No reaction. [d] Reaction without photocatalyst. [e] Reaction without light. [f] Reaction under open air. [g] **2a** (2 equiv) was used. [h] NaCl (4.4 equiv) was used. [i] 0.5 M of **1a**. [j] 0.1 M of **1a**.

With these results in hand, the scope and generality of the present method was then examined (Table 2). As shown from the table, aryl diazonium salts containing functional groups such as NO_2, Ph, CN, ester, and Cl were well tolerated under the standard conditions, affording the desired products **3** in moderate yields, except substrate **1b**, which gave the corresponding product in only 22% yield owing to the hindrance effect. It was worth noting that substrate **1h** with a strong electron-donating group (MeO) was unsuitable for the present reaction conditions, providing trace amount of desired product. Surprisingly, a methoxylated product **3ha** (38%) was obtained by switching the photocatalyst to $Ru(bpy)_3Cl_2$. We envisioned that it may provide a new direct route to access α-alkoxy aryl ketones using electron-rich aryl diazonium salts. Different aromatic alkynes were evaluated as well. Most of the substrates showed good activities regardless of electron-withdrawing or -donating groups (45~71%). The aliphatic alkynes such as **2j**, **2k**, and **2l,** however, were inert toward this transformation.

Table 2. Reaction scope.[a]



[a] Reaction conditions: **1** (0.5mmol), **2** (1.1 equiv) and NaCl (2.2 equiv) in MeOH (2 mL) were irradiated with a 5 W blue LED under oxygen at room temperature for 8 h. Isolated yields.

The above results from table 2 prompted us to optimize the reaction conditions for preparation of α-alkoxy aryl ketones. After adjusting the reaction conditions (see ESI), a 48% yield of product **4a** was obtained in the presence of $Ru(bpy)_3Cl_2$ (2 mol%) in a mixed solvent system ($MeOH/CH_3CN$, 1:3) after irradiation with a 5 W blue LED for 8 h. Aryl diazonium salts containing functional groups such as methoxyl, fluoro, and

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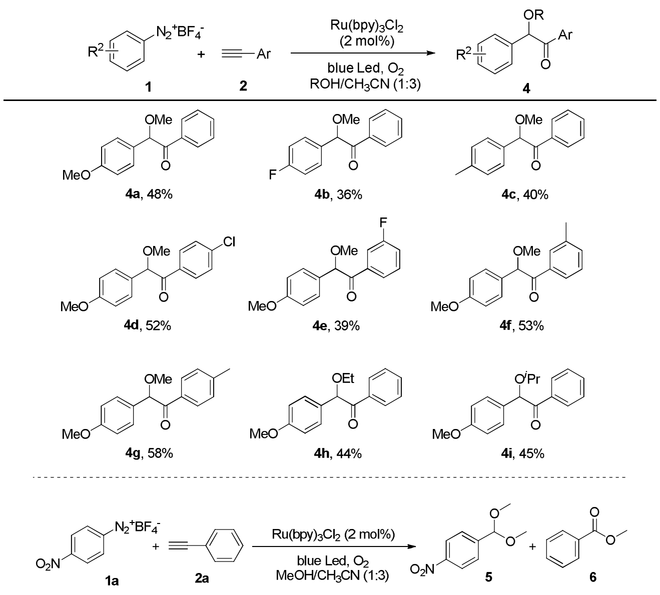
methyl were tolerated, affording the corresponding products in moderate yields. For substrate **1a**, no desired α-alkoxylated product was detected but decomposed products **5** and **6** were isolated. Aromatic alkynes also showed good compatibilities. Again, aliphatic alkynes were still inert toward the present reaction conditions. Reactions of other simple alcohols such as ethanol and isopropanol also proceeded smoothly to give the corresponding products in moderate yields (**4h**, 44%; **4i**, 45%). We also tried other nucleophiles such as H_2O, HCOOH or CH_3COOH, however, no desired products were detected.

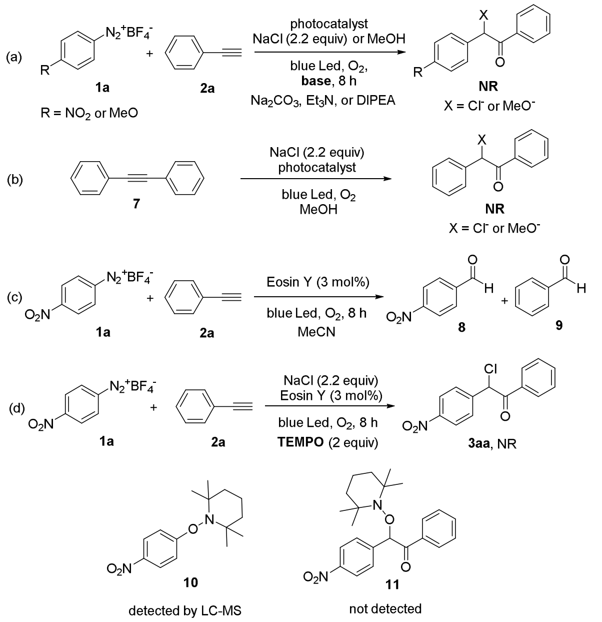
Table 3. Photocatalyzed the synthesis of α-alkoxy aryl ketones.[a]



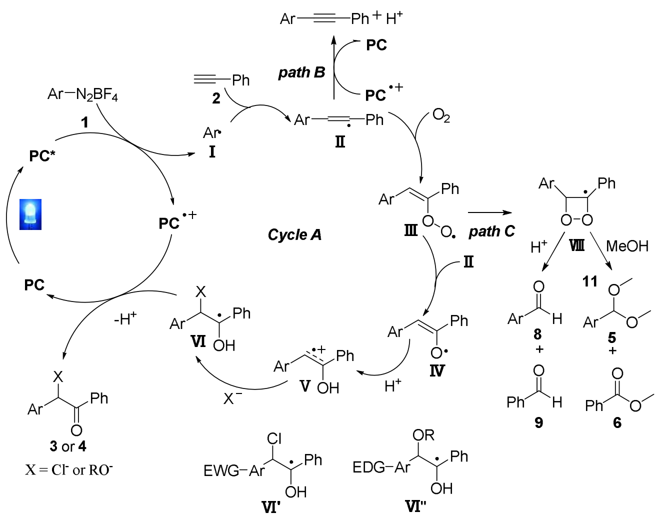
[a] Reaction conditions: **1** (0.5mmol), **2** (1.1 equiv), $Ru(bpy)_3Cl_2$ (2 mol%), in an alcohol (0.5 mL) and CH_3CN (1.5 mL) were irradiated with a 5 W blue LED under oxygen at room temperature for 8 h. Isolated yields.

Following control experiment was carried out to gain some insight into the mechanism (Scheme 2). Initially, it was observed that the reaction was completely inhibited when base (such as Na_2CO_3, Et_3N, and DIPEA) was added to the reaction mixture, which suggested that H^+ may play an important role in this reaction (scheme 2(a)). It was also worth noting that the reaction solution showed weakly acidic (pH = 5~6). No product was obtained when **7** was used as the substrate under the standard reaction conditions (scheme 2(b)). When the reaction carried out without any nucleophiles, no desired products were observed. Insteadly, 4-nitrobenzaldehyde and benzaldehyde was obtained (scheme 2(c)). This C-C bond cleavage process may proceed via the scission of dioxetane radical intermediate (see mechanism, path c). Moreover, when 2 equiv of radical scavenger, 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), was added to the reaction mixture under standard conditions, the transformation was completely inhibited. Meanwhile, an adduct of 4-nitrophenyl radical with TEMPO **10** was detected by LC-MS. However, we did not observed the adduct **11** at the current stage (scheme 2(d)).

Although the detailed mechanism remains unclear at this stage, a plausible mechanism is proposed on the basis of previous reports and experimental results (Scheme 3). Initially, the photocatalyst (PC) is excited under irradiation with visible light, which performs a single electron transfer (SET) to generate aryl radical I from aryl diazonium salt **1**.[16] Subsequent addition of I to aryl alkyne **2** generates the radical II, which reacts with molecular oxygen to give peroxy radical III.[17] Then reaction between intermediate II and III delivers radical IV,[17] which further abstracts a H^+ to form olefin radical cation V.[18] Then nucleophilic trapping of intermediate V by Cl^- or RO^- affords the corresponding intermediate VI. Subsequent SET oxidation of intermediate VI via 1,2- hydrogen atom shift furnishes the product **3** or **4**.[19]



Scheme 2 Control experiments.



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Scheme 3 Proposed mechanism.

The H^+ in this process may be generated by cross-coupling reaction between **1a** and **2a** as reported by König group (Scheme 3, path B).[20] The high chemoselectivity in such a radical-triggered domino process may be attributed to the strong substituent effect. Electron-withdrawing group substituted intermediates Ⅴ preferentially undergoes nucleophilic reaction with chloride ion to give products **3**, while electron-donating substituted ones tend to react with alcohols to give products **4**. It is noticed that, the redox potential of the photocatalysts also plays an important role in this reaction. Due to the electronic effect of the substituents, photocatalyst with relatively higher oxidation potential is necessary at the final SET process for the electron-donating groups substituted intermediates Ⅵ'' compared with electron-withdrawing groups substituted intermediates Ⅵ'. The oxidation potential of Eosin Y is only about 0.78 V ($E_{1/2}^{M+/M}$ = + 0.78 V vs SCE),[21] resulting in that Ⅵ'' cannot be easily oxidized by Eosin Y, but can be oxidized by $[Ru(bpy)_3]^{2+}$ ($E_{1/2}$ $^{M+/M}$ = + 1.29 V vs SCE).[22] On the other hand, Eosin Y is capable of oxidizing the electron-withdrawing groups substituted intermediates Ⅵ', leading to the formation of products **3**. Moreover, the decomposed products **5**, **6** and **8**, **9** may be generated through path C.[23] Due to the high tension of four-membered ring intermediates, only electron-withdrawing groups substituted intermediates Ⅶ can undergo intramolecular nucleophilic reaction to give intermediates Ⅷ. Further hydrogenolysis or alcoholysis of Ⅷ affords **5**, **6** and **8**, **9** respectly.[23]

In summary, we have developed a visible-light-induced radical-triggered chemoselective domino process to access α,α-*di*-functionalized ketones. This protocol provides a direct approach to synthesize α-chloro or α-alkoxy aryl ketones based on the electronic properties of the substrates. A series of substrates survived the reaction conditions to give the corresponding products in moderate to good yields. Notably, the prepared α-chloro aryl ketones can be further modified to access other useful compounds.

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