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De Novo Synthesis of Polysubstituted Naphthols and Furans Using Photoredox Neutral Coupling of Alkynes with 2-Bromo-1,3-dicarbonyl Compounds

Heng Jiang, Yuanzheng Cheng, Yan Zhang,* and Shouyun Yu*

State Key Laboratory of Analytical Chemistry for Life Science and Institute of Chemical
Biology and Drug Innovation, School of Chemistry and Chemical Engineering,
Nanjing University, Nanjing, 210093, China

yushouyun@nju.edu.cn; njuzy@nju.edu.cn

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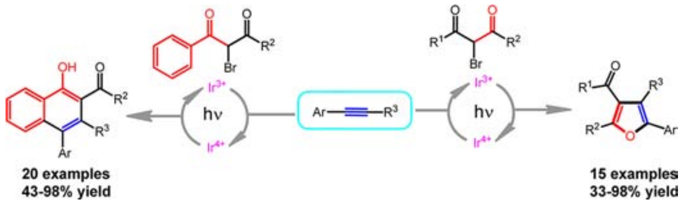
ABSTRACT



A conceptually new strategy has been described for the mild, practical, and environmentally friendly preparation of naphthols and furans using a visible-light promoted photoredox neutral approach. These reactions between accessible electron-deficient bromides and commercially available alkynes could be carried out at room temperature in good-to-excellent chemical yields without any external stoichiometric oxidants.

Redox reactions constitute one of the most fundamental chemical transformations in organic synthesis.[1] In addition to redox functional group interconversions, redox carbon–carbon bond formation has received increasing attention, especially oxidative coupling.[2] However, atom economy of these transformations is often questionable when using additional oxidants. Lacking of safe, economic, chemoselective, and environmentally acceptable oxidative or reductive reagents also restricts their applications in industrial processes.[3] In contrast, neutral redox processes can address these problems due to the absence of stoichiometric redox reagents. As a consequence, intense studies are now focused on neutral redox reactions in both the academic and industrial communities.[4]

Polysubstituted aromatic compounds, especially heterocycles, are frequently encountered in pharmaceuticals and natural products.[5] The preparation of these compounds *via* the direct substitution of aromatic rings often suffers from poor regioselectivity, harsh conditions, or tedious steps.[6] The *de novo* synthesis of polysubstituted aromatic compounds from prefunctionalized precursors under mild

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conditions provides one of the major solutions to this problem.[7]

Visible-light photoredox catalysis, which takes advantage of the redox potential of the photocatalyst under irradiation, has recently emerged as a powerful tool for promoting useful organic transformations.[8] This strategy has also been employed to construct several valuable heterocyclic compounds,[9] including indoles, benzothiophenes, benzothiazoles, tetrahydroimidazoles, and isoxazolidines. To the best of our knowledge, benzene rings and furans have not been synthesized using this technology. Herein, we would like to present our efforts in the *de novo* synthesis of polysubstituted naphthols and furans *via* the photoredox approach under mild conditions.

Compared with alkenes, which have been frequently used to couple with electron-deficient bromides under photoredox catalysis,[10] alkynes have seldom been employed in these transformations.[11] It can be envisioned that several aromatic rings can be achieved using α-bromo-*β*-ketocarbonyls and alkynes as coupling partners, as shown in Figure 1. Coupling of an alkyne with the radical **I** generated from α-bromo-*β*-ketones by visible-light mediated reduction could lead to the formation of sp^2 carbon-based radical species **II** or **III**. When aryl ketones are employed, the radical **II** can go through oxidative homolytic aromatic substitution (HAS)[12] to generate the naphthol motif.[13] Instead, when an alkyl ketone is used, the radical **III** could attack the carbonyl group to give the furan framework.[14] As a neutral redox transformation, stoichiometric external oxidants can be avoided.

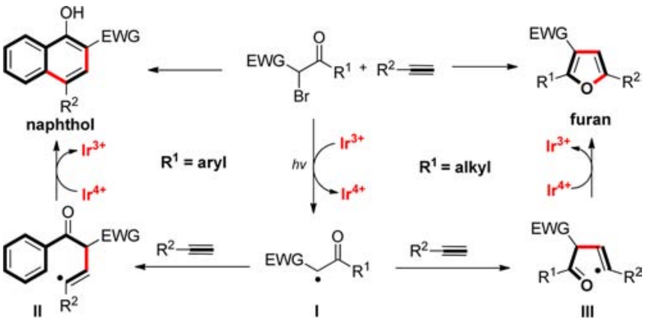

Figure 1. Rationale for redox neutral coupling of alkynes with electron-deficient bromides.

This idea was first examined using aryl ketobromide **1a** and phenylacetylene **2a** as model substrates (Table 1). When a solution of **1a** and **2a** in CH_3CN was irradiated by a 13 W white LED in the presence of photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) and Na_2HPO_4 for 12 h, the desired naphthol **3a** was isolated in 75% yield (entry 1). EtOH and CH_2Cl_2 did not give improved results (entries 2−3). To our delight, a 96% yield was achieved when DMSO was used as solvent (entry 4). The yield was slightly increased to 98% using DMF as solvent (entry 5). $NaHCO_3$ and K_3PO_4 were less effective for this transformation (entries 6−7). Several other photocatalysts, such as $Ir(ppy)_3$ (**II**), $Ru(bpy)_3(PF_6)_2$ (**III**), and fluorescein dye, were not superior to $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (entries 8−10). Control experiments verified the necessity of a base, irradiation, and a photocatalyst (entries 11−13).

To explore the scope of this transformation, a variety of alkynes were tested, as shown in Figure 2. All the substituted phenylacetylenes tested so far have worked quite

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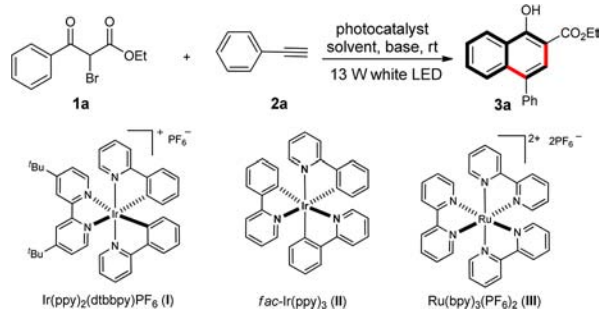
Table 1. Reaction Condition Optimization[a]



entry	catalyst	base	solvent	yield (%)[b]
1	**I**	Na_2HPO_4	CH_3CN	75
2	**I**	Na_2HPO_4	EtOH	63
3	**I**	Na_2HPO_4	CH_2Cl_2	59
4	**I**	Na_2HPO_4	DMSO	96
5	**I**	**Na_2HPO_4**	**DMF**	**98**
6	**I**	$NaHCO_3$	DMF	55
7	**I**	K_3PO_4	DMF	35
8	**II**	Na_2HPO_4	DMF	89
9	**III**	Na_2HPO_4	DMF	29
10	fluorescein	Na_2HPO_4	DMF	47
11	**I**	None	DMF	36
12	none	Na_2HPO_4	DMF	No
13[c]	**I**	Na_2HPO_4	DMF	No

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), base (0.24 mmol), and catalyst (0.002 mmol, 1.0 mol %) in indicated solvent (2.0 mL) were irradiated by 13 W white LED at rt for 12 h. [b] Isolated yield. [c] No irradiation.

well giving the corresponding naphthols **3a**–**3f** in good-to-excellent yields. Naphthalene-derived alkynes could also go through this transformation smoothly to provide binaphthene derivatives **3g** and **3h** in 83% and 71% yields respectively. Aliphatic alkynes were also suitable coupling partners, but with less efficiency than their aromatic counterparts. The corresponding naphthols **3i**–**3l** were isolated in 52–75% yields. Tetrasubstituted naphthol **3m** could also be prepared using this strategy in 43% yield when 1-phenyl-1-propyne was coupled with 5.0 equiv of bromide **1a**.

Various aryl ketobromides were then explored. *tert*-Butyl 2-bromo-3-oxo-3-phenylpropanoate **1b** worked quite well to give **3n** in excellent yield (95%). 2-Bromide-1,3-diones **1c** and **1d** were also appropriate substrates to afford naphthols **3o** and **3p** in satisfactory yields. It is also worth mentioning that various aryl groups, such *m*-MeO-phenyl, 3-furyl, and 2-naphthyl, were compatible in this transformation with high regioselectivity to give phenol derivatives **3q**–**3s** respectively. Phenol derivatives **3t** was also achieved in 72% yield from ethyl 2-bromo-3-(naphthalen-1-yl)-3-oxopropanoate (**1h**).

Based on these observations and literature precedents,[8,12] a possible, but not exclusive, catalytic cycle is proposed for this transformation, as shown in Figure 3. First, the photocatalyst Ir^{3+} complex is irradiated to the excited state Ir^{3+*} and oxidatively quenched by **1a** with generation of the Ir^{4+} complex and radical species **4** respectively. Radical **4** can then add onto alkyne **2a** to generate the vinyl radical intermediate **5**, which can engage in intramolecular homolytic aromatic substitution (HAS)[12] to provide radical intermediate **6**. This can be oxidized by Ir^{4+} to form cation intermediate **7** and regenerate Ir^{3+}. Ultimately, naphthol **3a** can be formed by deprotonation and tautomerization assisted by base.

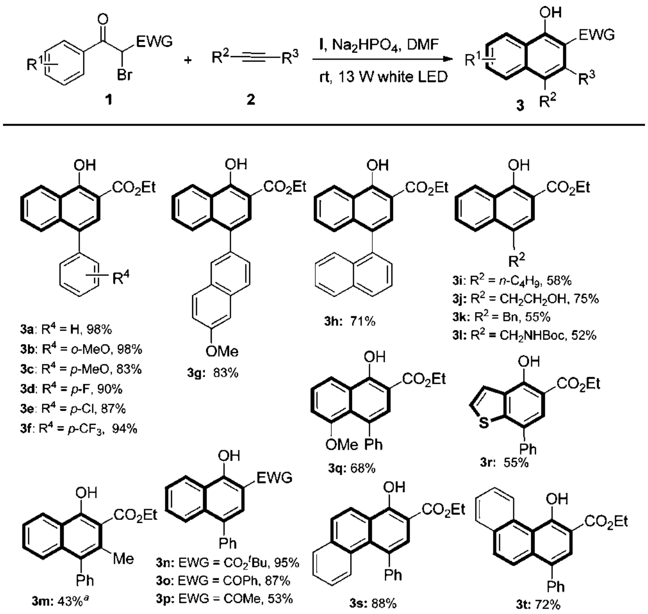


Figure 2. Scope of coupling of bromides with alkynes. All reactions carried out under optimized conditions. The yields were isolated yields. [a]5.0 equiv of bromide **1a** was used, and the reaction time was prolonged to 48 h.

The success with naphthols inspired us to explore the possibility of preparing furans using a similar strategy. Consequently, 2-bromocyclohexane-1,3-dione (**8a**) and phenylacetylene (**2a**) were chosen for further investigation (Figure 4). Coupling of bromide **8a** with phenylacetylene (**2a**) afforded furan **9a** when the optimized conditions for naphthols were applied, but only in 22% yield. A change in the solvent from DMF to EtOH led to an acceptable yield (60%) being obtained (for the detailed condition screening, see the Supporting Information). Mechanistically, the radical intermediate **11** was generated *via* a similar pathway to that by which intermediate **5** was formed. Furan **9a** was produced by addition of radical **11** onto the carbonyl group,[14d,15] oxidation of radical **12**, and deprotonation of oxonium cation **13** in the presence of a base.

To find out the scope of this transformation, the reactivity of phenylacetylenes possessing various groups was then studied systematically. As shown in Figure 5, it was found that electron-rich phenylacetylenes gave the desired furans with satisfactory to excellent yields (**9b**, **9d**, **9e**). Acceptable yields were obtained from 54% to 61%

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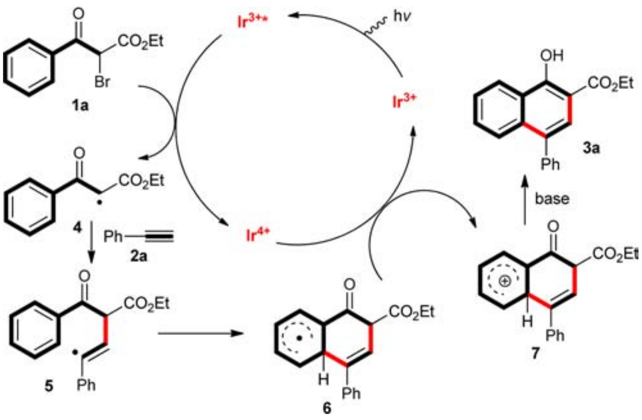

Figure 3. Proposed mechanism for formation of the naphthols.

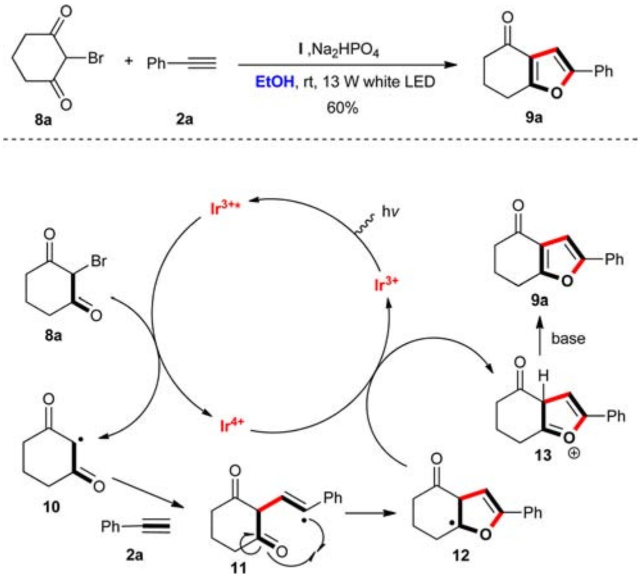

Figure 4. Coupling of phenylacetylene with 2-bromocyclohexane-1,3-dione.

(**9f**–**9h**) when weak electron-withdrawing groups, such as *p*-Ph, *m*-MeO, and *p*-F, were attached to the benzene ring. Strong electron-withdrawing groups, such as *p*-Cl, *p*-Br, and *p*-CF$_3$, slowed down this transformation significantly and reduced the yields to 33–43% (**9i**–**9k**). *o*-MeO-phenylacetylene worked less efficiently (**9c**, 80% yield) than its *para* counterpart due to the additional steric effect. 6-Methoxy-2-naphthylacetylene could undergo this transformation smoothly to provide the desired product **9l** in 81% yield. Alkyl and aryl groups in the 5-position of **8a** had no obvious influence on the reaction efficiency, and excellent yields were obtained (98% for **9m** and 92% for **9n**).

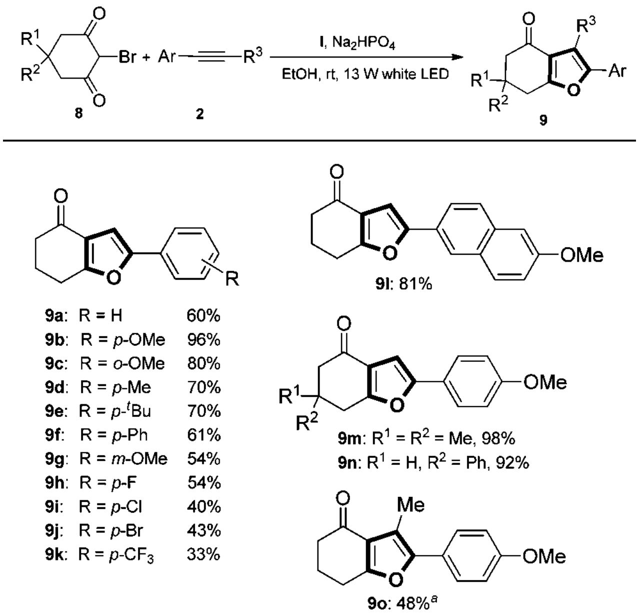

Figure 5. Scope of coupling of bromides with alkynes. All reactions carried out under optimized conditions. The yields were isolated yields. ^{a}4.0 equiv of bromide **8a** were used, and the reaction time was prolonged to 48 h.

Remarkably, the tetrasubstituted furan (**9o**) could be also prepared in 48% yield when the internal alkyne was employed coupled with 4.0 equiv of the bromide **8a**.

In summary, we have developed a mild and efficient synthetic approach to functionalized naphthols and furans using photoredox coupling of alkynes with 2-bromo-1,3-dicarbonyl compounds. These reactions, which are of broad substrate scope, can be carried out at room temperature and afforded good-to-excellent chemical yields of products under environmentally friendly conditions, without use of any external stoichiometric oxidants. Application of inexpensive and readily available electron-deficient bromides and alkynes as raw materials should also benefit the future development of industrial processes. Further exploration of these transformations and mechanistic details are underway.

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Supporting Information Available. Full experimental procedures, characterization data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.