Visible-Light Photocatalysis

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Tandem Cyclizations of 1,6-Enynes with Arylsulfonyl Chlorides by Using Visible-Light Photoredox Catalysis**

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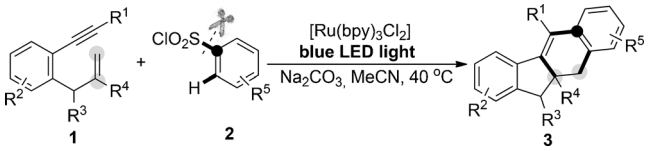
The tandem cyclization strategy is of continuing interest in the field of organic chemistry because it is a uniquely powerful tool for the synthesis of polysubstituted polycyclic compounds.[1–3] One typical transformation is the cyclization of enynes, in particular the cyclization of 1,6-enynes because this transformation offers unparalleled efficiency, atom economy, and operational simplicity in the assembly of synthetically versatile polycyclic compounds, and still remains an important challenge. Generally, there are two basic methods for 1,6-enyne cyclizations: through metal catalysis or a radical reaction (thermal[2g] or photochemical cyclizations).[2,3] However, many enyne cyclizations are carried out at relatively high reaction temperatures, and the photochemical cyclizations often involve irradiation with ultraviolet light; moreover, the substrate scope of these reactions is restricted to endiynes and enyne allenes.[3] Common enynes can not absorb either ultraviolet or visible light efficiently, thereby limiting their applications in organic synthesis.

Recently, visible-light photoredox catalysis has attracted great interest in organic synthesis community because visible light is environmentally benign, mild, easy to handle, infinitely available, and has promising applications in industry.[4–6] However, despite progress in this area, the in situ generation of aryl radicals for C–C(aryl) bond formation by visible light photoredox catalysis is quite rare.[5] Efforts from the groups of Deronzier,[5a–e] Sanford,[5f] and König[5g–i] have been devoted to investigating aryldiazonium salts as a source of aryl radicals for the C–H arylation. Very recently, we found that arylsulfonyl chlorides could also be utilized as aryl radical precursors for the sequential arylation of alkynes and carbocyclization with benzylic C(sp^3)–H bonds.[5j,7] We hypothesized that standard enynes could not absorb visible light efficiently, but they may serve as a platform to trap radicals. Herein, we report a new tandem cyclization of 1,6-enynes with arylsulfonyl chlorides; this tandem cyclization is triggered by visible-light photoredox catalysis and involves the use of 1,6-enynes as radical acceptors, thus allowing the formation of a diverse range of 10*a*,11-dihydro-10*H*-benzo[*b*]fluorene architectures[8] in one step (Scheme 1). This work represents the first example of 1,6-enyne cyclization by using the visible-light photoredox catalysis strategy. Most importantly, we show that arylsulfonyl chlorides play two roles: they provide an *ortho*-C(aryl)–H bond to participate in the tandem cyclization and on cleavage of the SO_2Cl group aryl radicals are formed.



Scheme 1. Tandem cyclization of alkynes with alkenes and $ArSO_2Cl$. bpy = bipyridine.

We initially explored the tandem cyclization reaction of methyl 2-(hydroxy(2-(phenylethynyl)phenyl)methyl)acrylate (**1a**) with 4-nitrobenzene-1-sulfonyl chloride (**2a**), [Ru(bpy)$_3$Cl$_2$]·6H$_2$O, Na_2CO_3, and 36 W compact fluorescent light in MeCN at 40 °C: The desired 10*a*,11-dihydro-10*H*-benzo[*b*]fluorene **3aa** was formed, albeit in low yield, after 12 h (Table 1, entry 1).[9] Interestingly, the yield of **3aa** was dramatically enhanced to 79% when the reaction was performed with 5 W blue LED light (entry 2). Extensive screening of bases revealed that the use of an inorganic base (Na_2CO_3 or NaOAc) facilitated the reaction, but the use an organic base (Et_3N) impeded it (entries 2–4). In addition, the amount of base also affected the reaction: The yield of **3aa** was lowered to 64% when 2 equivalents of Na_2CO_3 were used (entry 5). The reaction could proceed in the absence of base, but the yield was decreased (entry 6). Next, both solvent and reaction temperature were investigated (entries 2 and 7–11): The reaction in MeCN at 40 °C gave the best results (entry 2). The amount of Ru catalyst affected the reaction yield (entries 12 and 13): The reaction in the presence of 10 mol% of Ru gave the identical results to those in the presence of 5 mol% Ru, whereas the reaction with 2 mol% of Ru led to a low yield of product **3aa**. Two other visible-light photoredox catalysts, [Ir(ppy)$_3$] and Eosin Y, were also tested (entries 14 and 15). With [Ir(ppy)$_3$], a good yield was still achieved (entry 14). Notably, the current reaction could be successfully carried out under transition-metal-free conditions: In the presence of Eosin Y, the desired 10*a*,11-dihydro-

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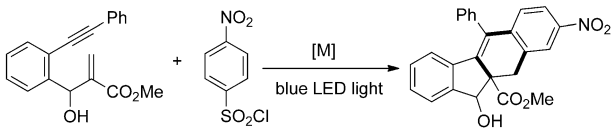
Table 1: Screen of reaction conditions.[a]

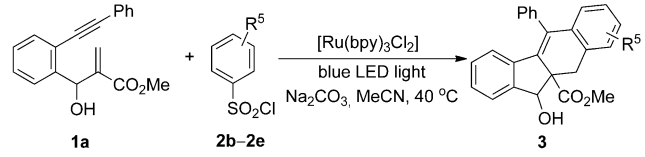


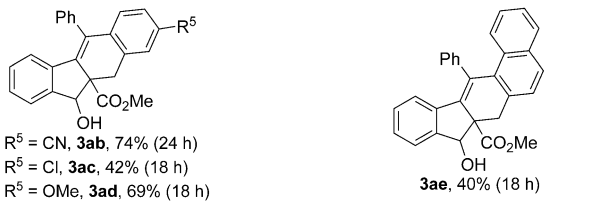
Entry	[M] [mol%]	Base [equiv]	Solvent	*T* [°C]	Yield [%][b]
1[c]	$[Ru(bpy)_3Cl_2]$ (5)	Na_2CO_3 (1)	MeCN	40	12
2	$[Ru(bpy)_3Cl_2]$ (5)	Na_2CO_3 (1)	MeCN	40	79
3	$[Ru(bpy)_3Cl_2]$ (5)	NaOAc (1)	MeCN	40	55
4	$[Ru(bpy)_3Cl_2]$ (5)	Et_3N (1)	MeCN	40	18
5	$[Ru(bpy)_3Cl_2]$ (5)	Na_2CO_3 (2)	MeCN	40	64
6	$[Ru(bpy)_3Cl_2]$ (5)	–	MeCN	40	31
7	$[Ru(bpy)_3Cl_2]$ (5)	Na_2CO_3 (1)	toluene	40	5
8	$[Ru(bpy)_3Cl_2]$ (5)	Na_2CO_3 (1)	NMP	40	trace
9	$[Ru(bpy)_3Cl_2]$ (5)	Na_2CO_3 (1)	CH_2Cl_2	40	11
10	$[Ru(bpy)_3Cl_2]$ (5)	Na_2CO_3 (1)	MeCN	25	48
11	$[Ru(bpy)_3Cl_2]$ (5)	Na_2CO_3 (1)	MeCN	60	70
12	$[Ru(bpy)_3Cl_2]$ (2)	Na_2CO_3 (1)	MeCN	40	20
13	$[Ru(bpy)_3Cl_2]$ (10)	Na_2CO_3 (1)	MeCN	40	76
14	$[Ir(ppy)_3]$ (5)	Na_2CO_3 (1)	MeCN	40	80
15	Eosin Y (5)	Na_2CO_3 (1)	MeCN	40	66
16	–	Na_2CO_3 (1)	MeCN	40	0
17[d]	$[Ru(bpy)_3Cl_2]$ (5)	Na_2CO_3 (1)	MeCN	40	0

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (2 equiv), [M], base and solvent (anhydrous, 2 mL) with 5 W blue LED light for 12 h under argon atmosphere. ppy = phenylpyridine. For side products, see Ref. [9]. [b] Yield of the isolated product. [c] 36 W compact fluorescent light used instead of 5 W blue LED light. [d] Without additional light.

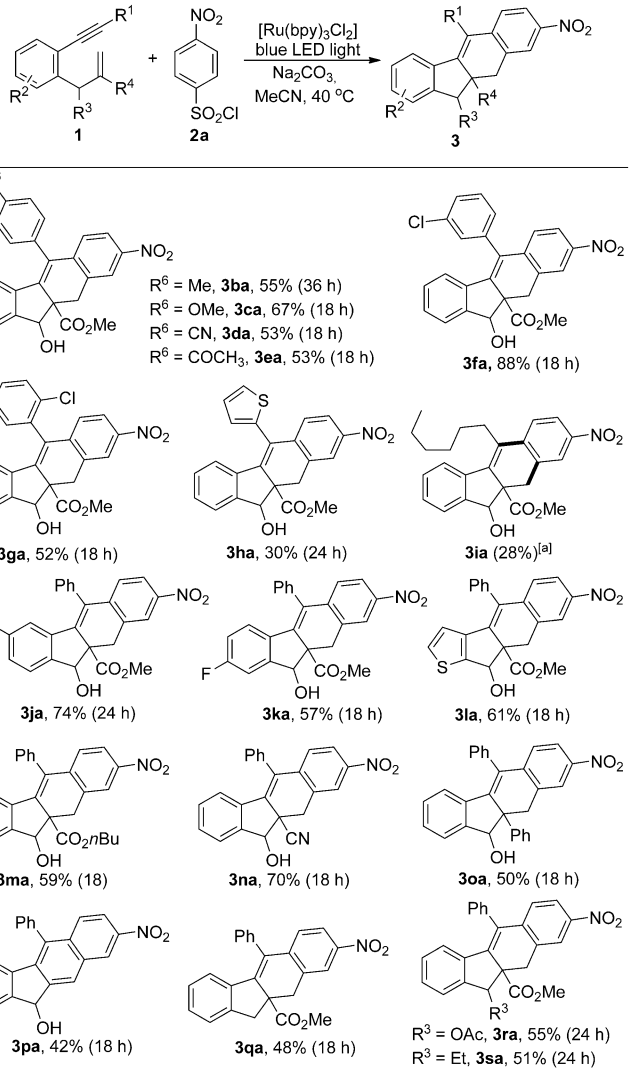
10*H*-benzo[*b*]fluorene **3aa** was furnished in 66% yield (entry 15). However, the reaction did not take place in the absence of either the visible-light photoredox catalysts (entry 16) or additional visible light (entry 17).

Encouraged by these results, we applied the above visible-light photocatalysis protocol to a range of both 1-allyl-2-ethynylbenzenes **1** and arylsulfonyl chlorides **2** to investigate the scope (Scheme 2 and Scheme 3). The scope of arylsulfonyl chlorides **2** was initially explored in the presence of substrate **1a**, $[Ru(bpy)_3Cl_2]$, Na_2CO_3, and 5 W blue LED light (Scheme 2). Gratifyingly, a variety of arylsulfonyl chlorides **2**, having either electron-withdrawing or electron-donating aryl groups, were viable in the reaction, although the electron-withdrawing arylsulfonyl chlorides displayed higher reactivity





Scheme 2. Screen of the arylsulfonyl chlorides **2**.



Scheme 3. Tandem cyclization of 1-allyl-2-ethynylbenzenes **1** with 4-nitrobenzene-1-sulfonyl chloride (**2a**). Reaction conditions: **1** (0.3 mmol), **2a** (2 equiv), $[Ru(bpy)_3Cl_2]$ (5 mol%), Na_2CO_3 (1 equiv), and anhydrous MeCN (2 mL) with 5 W blue LED light at 40°C under argon atmosphere. For side products, see Ref. [9]. [a] Methyl 2-formyl-3-hexyl-4-(4-nitrophenyl)-1,2-dihydronaphthalene-2-carboxylate (**4ia**) was isolated in 35% yield.

than the electron-donating arylsulfonyl chlorides. 4-Cyanobenzene-1-sulfonyl chloride reacted with **1a** to afford the desired 10*a*,11-dihydro-10*H*-benzo[*b*]fluorene **3ab** in 74% yield, and the reaction of 4-methoxybenzene-1-sulfonyl chloride lead to the tandem cyclization product (**3ad**) in 69% yield. Pleasingly, a Cl group on the aryl ring was tolerated under the standard reaction conditions (see product **3ac**). For naphthalene-1-sulfonyl chloride the desired polycyclic ring product **3ae** was formed in 40% yield.

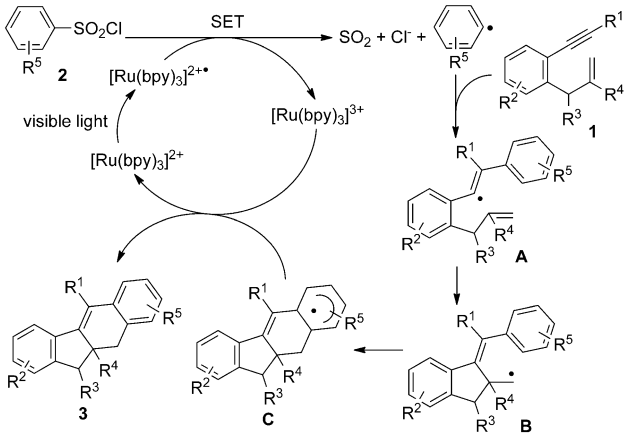
We next explored the scope of the 1-allyl-2-ethynylbenzenes **1** in the reaction with 4-nitrobenzene-1-sulfonyl chloride (**2a**) and the $[Ru(bpy)_3Cl_2]/Na_2CO_3$/5 W blue LED light system (Scheme 3). The current reaction conditions were general to a wide range of 1-allyl-2-ethynylbenzenes **1**. Screening revealed that several substituents, such as Me,

MeO, CN, $COCH_3$, and Cl, on the aryl ring of the terminal alkyne were well-tolerated (see products **3ba**–**3ga**). For example, when substrate **1b** was treated with sulfonyl chloride **2a**, $[Ru(bpy)_3Cl_2]$, Na_2CO_3, and 5 W blue LED light 10*a*,11-dihydro-10*H*-benzo[b]fluorene **3ba** was obtained in 55% yield. With cyano- or acetyl-substituted substrates, a moderate yield was achieved (products **3da** and **3ea**). Interestingly, Cl-substituted substrates were also compatible with the standard reaction conditions and displayed high reactivity, thus providing products which can be additionally modified at the halogenated position (see products **3fa** and **3ga**). Thiophen-2-yl-substituted alkyne was also suitable for the tandem cyclization reaction (see product **3ha**). Notably, aliphatic alkyne successfully underwent 5-*exo*-cyclization to give **3ia**, albeit in a low yield and with acccompanying formation of the 6-*exo*-cyclization product **4ia**.

Interestingly, substrates with Me and F substituents on the aryl ring of the 1-allyl-2-ethynylarene moiety were compatible with the standard conditions (products **3ja** and **3ka**). The current reaction could be used to construct a heterocycle-containing polycyclic system: The reaction of methyl 2-(hydroxy(2-(phenylethynyl)thiophen-3-yl)methyl)acrylate gave **3la** in 61% yield, thus making this method useful for the preparation of heterocycle-containing pharmaceuticals and natural products. Substituents at the 2-position of the terminal alkene moiety were tolerated under the standard reaction conditions: Both CO_2nBu- and CN-substituted alkenes, for instance, underwent the tandem cyclization smoothly, to provide the corresponding products **3ma** and **3na** in 59% and 70% yields, respectively and the cyclization involving the phenyl-substituted alkene occured in moderate yield (see product **3oa**). Gratifyingly, a monosubstituted alkene also underwent the tandem cyclization reaction, to provide 8-nitro-5-phenyl-11*H*-benzo[*b*]fluoren-11-ol **(3pa)**, a deprotonation product. Lastly, it is noteworthy that a hydroxy group is not necessary for the reaction: When the hydroxy group replaced by a H atom, an OAc group, or an Et group the corresponding 10*a*,11-dihydro-10*H*-benzo[*b*]fluorenes **3qa**–**3sa** were synthesized in moderate yields.

Notably, the reaction could proceed using the nonmetal visible-light photoredox catalyst, Eosin Y (entry 15 in Table 1), thus suggesting that Ru and Ir act only as visible-light photoredox catalysts, and do not participate in the cyclization steps. The formation of product **4ia** implies that the selectivity of the addition of in situ generated aryl radicals is determined by the substituents at the terminal alkynes. In addition, the structure of product **3aa**, confirmed by the X-ray single-crystal diffraction analysis, indicates that in-situ generated aryl radicals firstly attack the carbon–carbon triple bond.[10]

A possible mechanism, outlined in Scheme 4, is proposed on the basis of the results described above and literature reports.[4,5] An aryl radical (Ar·) is firstly formed by a single-electron transfer (SET) from the excited state $[Ru(bpy)_3]^{2+\cdot}$ to an arylsulfonyl chloride, and subsequent addition of the aryl radical (Ar·) to the carbon–carbon triple bond in substrate **1** results in radical intermediate **A**. Radical intermediate **A** undergoes the cyclization reaction with the alkene to yield radical intermediate **B**. Intramolecular cyclization of **B** with an arene ring gives rise to radical intermediate **C**. Finally, oxidation of **C** by $[Ru(bpy)_3]^{3+}$ and subsequent deprotonation take place to furnish 10*a*,11-dihydro-10*H*-benzo[*b*]fluorene **3** and regenerate the active $[Ru(bpy)_3]^{2+}$ species.



Scheme 4. Possible mechanism.

In summary, we have successfully executed a 1,6-enyne cyclization that involves arylsulfonyl chlorides and is triggered by visible-light photoredox catalysis to construct functionalized 10a,11-dihydro-10*H*-benzo[b]fluorenes, a ubiquitous component of many natural products, biomolecules, optoelectronic materials, and devices.[8] Most importantly, this present protocol provides a new example of visible-light photoredox catalysis, extends the scope of enyne cyclizations and represents a new synthetic utilization of arylsulfonyl chlorides. Further development and applications of this mild tandem cyclization transformation in organic synthesis are currently underway in our laboratory.

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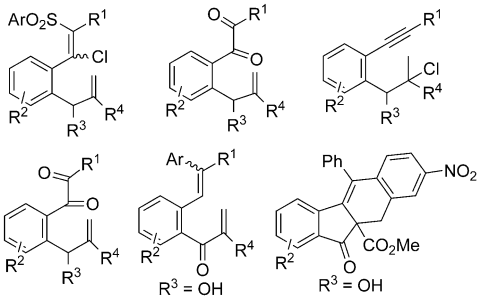
[9] Some side products (see below) were observed in less than 5% yields, as determined by GC-MS and LC-MS analysis.



[10] The structure of product **3aa** was unambiguously confirmed by the X-ray single-crystal diffraction analysis. The detailed data are summarized in Supporting Information.

