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Visible-Light-Mediated 1,7-Enyne Bicyclizations for Synthesis of Cyclopenta[*c*]quinolines and Benzo[*j*]phenanthridines

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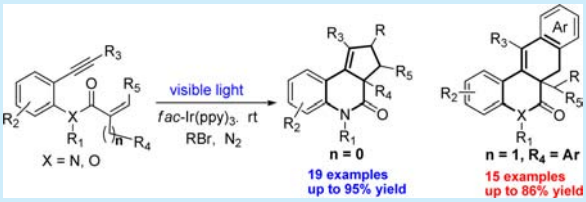
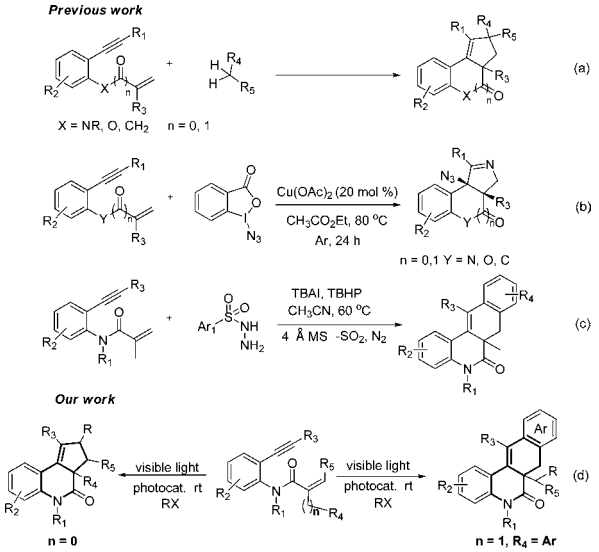
Supporting Information

ABSTRACT: A photocatalytic process for 1,7-enyne bicyclizations with α-bromo diethyl malonate has been established via synergistic domino bicyclizations. This protocol provides an efficient and practical method for the synthesis of various cyclopenta[*c*]quinolines and benzo[*j*]phenanthridines under operational simplicity and mild reaction conditions.



Complex polycyclic hydrocarbons, as the important structural motifs, can be found in numerous natural products.[1] The radical triggered bicyclization method for synthesis of the polycyclic compounds with biomedical and chemical activities have attracted special attention from chemists.[2] Owing to both unsaturated moieties, 1,n-enynes play an important role in the development of substrate-specific domino cyclization reactions that achieve highly functionalized hydrocarbons via radical-triggered tandem additions across the C−C double bond and the C−C triple bond of 1,n-enynes in a one-pot strategy.[3] Among these, 1,7-enynes were found to be viable substrates for providing various fused five-membered carbocyclic compounds (Scheme 1a).[4] A copper-catalyzed radical [2 + 2 + 1] annulation of 1,n-enynes to synthesize pyrroline compounds has also been found by Li's group (Scheme 1b).[5a] At the same time, Guigen Li's laboratory has devoted effort to the development of catalytic arylsulfonyl radical triggered 1,7-enyne bicyclizations (Scheme 1c).[5b]

Scheme 1. Reported 1,7-Enyne Bicyclizations and Our Strategy



Nowadays, the visible light photoredox catalysis strategy has represented a uniquely powerful and straightforward tool for synthetic transformations in organic chemistry, due to its attractive properties such as excellent functional group tolerance, environmentally friendly, safety, and availability.[6] Over the past decades, considerable work on the application of α-bromo ester in various visible-light-induced chemical transformations have been developed by Stephenson,[7] MacMillan,[8a] and others.[8b,c] Despite the previous advances on the bicyclizations of 1,n-enynes, room still exists for developing a visible-light-mediated pathway to construct the polycyclic compounds with milder reaction conditions. In this regard, in this paper we disclose our strategy for synthesis of both cyclopenta[*c*]quinolines and benzo[*j*]phenanthridines through alkyl radical addition/1,5-H shift as well as alkyl radical addition/radical cyclization pathway respectively from 1,7-enynes in the presence of a photoredox catalyst (Scheme 1d).

Initially, our investigation was carried out by using 1,7-enyne (**1a**) as a model substrate and α-bromo diethyl malonate **2** as an oxidant in the presence of *fac*-Ir(ppy)$_3$ (0.005 mmol) under visible light irradiation (blue LEDs) (Table 1). We speculated that the sequential addition of the diethyl malonate radical generated in the reaction to the C−C double bond and alkyne group might lead to the bicyclization reaction of 1,7-enyne **1a**. Gratifyingly, the desired cyclopenta[*c*]quinoline (**3a**) was afforded in 50% yield, when the reaction was treated with K_2CO_3 as a base in DMSO for 72 h at room temperature (Table 1, entry 1). The optimization of the reaction conditions was then conducted by the examination of solvents, such as DMF, CH_2Cl_2, CH_3CN, and THF, which suggested CH_2Cl_2 or CH_3CN was the ideal chioce (Table 1, entries 2−5). Compared with 2,6-lutidine as the additive, other bases such as *t*-BuOK,

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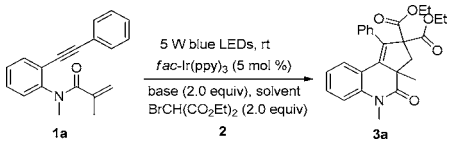
Table 1. Screening of Optimal Reaction Conditions[a]



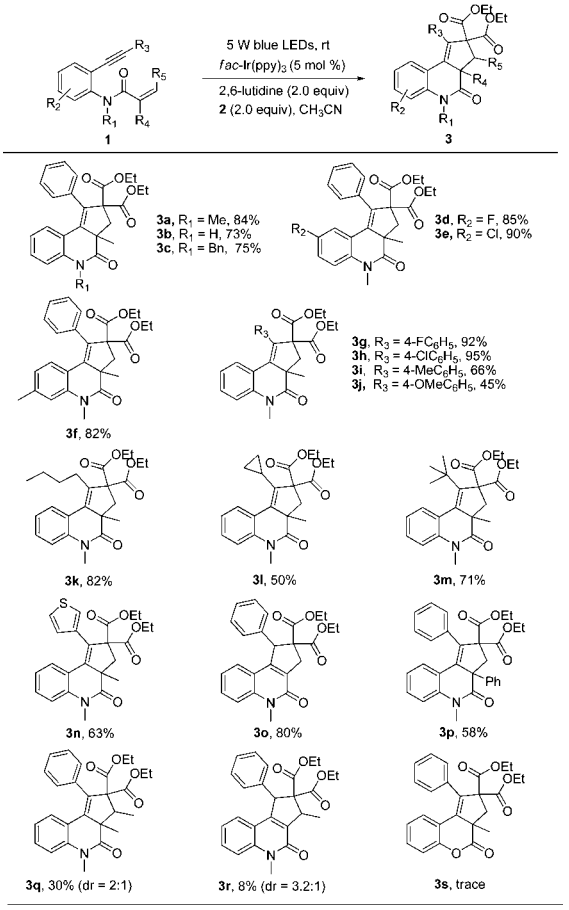
entry	catalyst	solvent	base	yields (%)[b]
1	*fac*-Ir(ppy)$_3$	DMSO	K_2CO_3	50
2	*fac*-Ir(ppy)$_3$	DMF	K_2CO_3	56
3	*fac*-Ir(ppy)$_3$	CH_2Cl_2	K_2CO_3	72
4	*fac*-Ir(ppy)$_3$	CH_3CN	K_2CO_3	70
5	*fac*-Ir(ppy)$_3$	THF	K_2CO_3	54
6	*fac*-Ir(ppy)$_3$	CH_2Cl_2	*t*-BuOK	8
7	*fac*-Ir(ppy)$_3$	CH_2Cl_2	NaOH	46
8	*fac*-Ir(ppy)$_3$	CH_2Cl_2	2,6-lutidine	78
9	*fac*-Ir(ppy)$_3$	CH_2Cl_2	K_2HPO_4	45
10	***fac*-Ir(ppy)$_3$**	**CH_3CN**	**2,6-lutidine**	**84**
11[c]	*fac*-Ir(ppy)$_3$	CH_3CN	2,6-lutidine	0
12	–	CH_3CN	2,6-lutidine	0

[a]Reaction conditions: **1a** (0.1 mmol), *fac*-Ir(ppy)$_3$ (0.005 mmol), base (0.2 mmol), **2** (0.2 mmol), solvent (anhydrous, 1 mL), 5 W blue LED light, rt, under a N_2 atmosphere. [b]Isolated yield. [c]In the dark.

NaOH, K_2CO_3, and K_2HPO_4 led to lower yields (Table 1, entries 6−9). Considering the volatility of CH_2Cl_2, we explored our reaction using CH_3CN as the solvent and 2,6-lutidine as the base which led to the highest yield (Table 1, entry 10). Further experiments demonstrated that either *fac*-Ir(ppy)$_3$ or light was essential for the reaction (Table 1, entries 11−12).

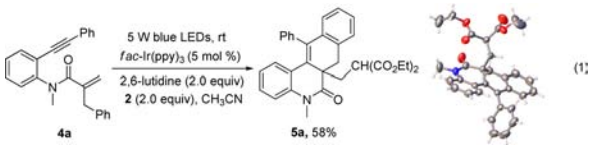
With the optimal reaction conditions in hand, the scope of this visible-light-mediated bicyclization reaction of 1,7-enyne **1** was investigated and the results were listed in Scheme 2. First, we evaluated the substitution effect of the nitrogen atom. It showed that substrates with a N-Me group, a free N−H group, or a N-Bn group were suitable for constructing cyclopenta[*c*]-quinolines in moderate to good yields (Scheme 2, **3a**−**3c**). Different substituents, such as F, Cl, and Me, on the aromatic ring of the aniline moiety were well tolerated in the standard reaction conditions to afford the corresponding products in excellent yields (Scheme 2, **3d**−**3f**). Electronic-withdrawing or -donating substituents, including F, Cl, Me, and MeO, on the aromatic ring at the terminal alkyne, all smoothly led to the corresponding products (Scheme 2, **3g**−**3j**) in which the electron-deficient aryl groups (**3g** and **3h**) had higher reactivity than the electron-rich aryl groups (**3i** and **3j**). Even if using the aliphatic alkynes, such as a bulky *tert*-butyl or a cyclopropyl group, the reactions were still performed very well (Scheme 2, **3k**−**3m**). In the case of the thiophen-3-yl-containing alkyne, 1,7-enyne **1n** was successfully converted to **3n** in 63% yield. Interestingly, α-unsubstituted substrate **1o** was also tolerant of the reaction conditions, forming the product **3o** in 80% yield with a double bond shift. For 1,7-enyne **1p**, which has a Ph group on the α position of the acrylamide moiety, the reaction occurred smoothly in moderate yield to deliver the expected product **3p**. Remarkably, 1,7-enynes **1q** and **1r**, which had a Me group at the terminal position of the double bond, showed low reactivity for the formation of the corresponding products (Scheme 2, **3q**−**3r**). It seems that the reaction conditions are not ideal for the substrate of acrylate **1s**. Notably, when using a substrate with a benzyl group at the α position of the double bond, such as 1,7-enyne **4a**, a fused six-membered benzo[*j*]-phenanthridine (**5a**) was obtained instead of the cyclopenta-

Scheme 2. Scope of 1,7-Enynes 1[a,b]



[a]Reaction conditions: **1** (0.1 mmol), *fac*-Ir(ppy)$_3$ (0.005 mmol), 2,6-lutidine (0.2 mmol), **2** (0.2 mmol), CH_3CN (anhydrous, 1 mL), 5 W blue LED light, rt, under a N_2 atmosphere. [b]Isolated yield.

[*c*]quinoline (eq 1). As a bonus, the structure of **5a** was further illustrated by X-ray crystallographic analysis.[11a]



The conversion of **4a** to **5a** provides an easy access to a highly functionalized polycyclic structure with chemical and bioactive importance, which prompts us to explore it in detail. Further efforts therefore had been made to improve the yield of the desired product **5a**. Finally, we chose K_2HPO_4 as the base and DMSO as the solvent to investigate the scope of 1,7-enynes **4**. As shown in Scheme 3, substrates with the N-Me group and free N−H group were successfully transformed to the desired benzo[*j*]phenanthridines in moderate to good yields (Scheme 3, **5a**−**5b**). The optimal conditions were found to be suitable for a variety of 1,7-enynes with different substituents, namely F, Cl, or Me, on the aromatic ring of the aniline moiety (Scheme 3, **5c**−**5e**). The aromatic ring tethered to the alkyne substituted with an electron-donating or -withdrawing group, such as *p*-Cl- or *p*-OMe, has no effect on the reaction, giving the corresponding products in good yields (Scheme 3, **5f**−**5g**). Notably, the alkyne tethered with alkyl or thiophenyl groups

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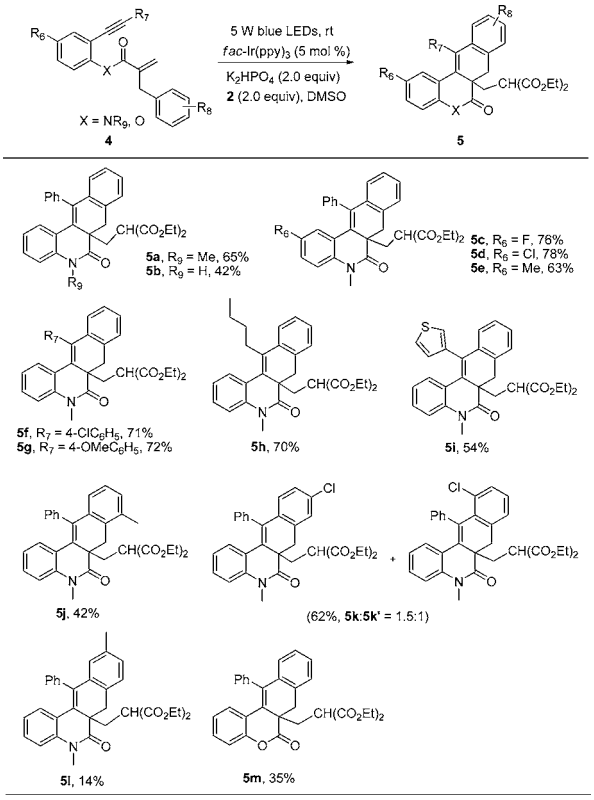
Scheme 3. Scope of 1,7-Eynes 4[a,b]



[a]Reaction conditions: **4** (0.1 mmol), *fac*-Ir(ppy)$_3$ (0.005 mmol), K_2HPO_4 (0.2 mmol), **2** (0.2 mmol), DMSO (anhydrous, 1 mL), 5 W blue LED light, rt, under a N_2 atmosphere. [b]Isolated yield.

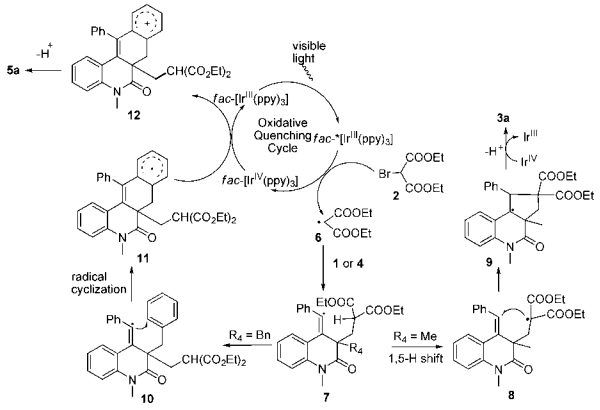
was also tolerant of the reaction conditions to afford the desired products **5h** and **5i** in 70% and 54% yields, respectively. The substituent on the benzyl ring affected the reaction which led to the expected product in decreased yield (Scheme 3, **5j** and **5l**). When the *meta*-position of the benzyl ring was substituted with a Cl group, two isomers of **5k** and **5k**′ were afforded in a ratio of 1.5:1. It was worth noting that the reaction conditions were also suitable for the acrylate substrate, such as **4m**, to deliver the polycyclic lactone product **5m** in 35% yield.

Due to the importance of the fluorine substituent on the small molecules for the agrochemical, pharmaceutical, and materials industries,[9] we then conducted the reaction with fluorine oxidants to prepare di- and/or trifluoromethylated products. As shown in eq 2, the corresponding products **5n** and

5o were obtained in synthetically useful yields when ethyl bromodifluoroacetate and Tognis' reagent were employed in the reaction of 1,7-enyne **4a**. Their structures were identified by X-ray crystallographic analysis.[11b]

Based on the above results and literature,[7,8,10] a plausible mechanism for the formation of the products **3** and **5** was proposed in Scheme 4. Initially, [*fac*-^{III}Ir(ppy)$_3$] was induced to

Scheme 4. Possible Mechanism



the excited state [*fac*-^{III}Ir(ppy)$_3$]* by visible light. Then, [*fac*-^{III}Ir(ppy)$_3$]* was oxidized by α-bromo diethyl malonate **2** to generate a relatively stable radical **6** and bromine ion along with *fac*-Ir^{IV}(ppy)$_3$. Subsequently, the radical **6** was captured by the C−C double bond in 1,7-enyne **1** or **4** followed by cyclization with the C−C triple bond to afford the radical intermediate **7**. When R_4 was a Me group, a 1,5-H shift occurred to form the more stable radical intermediate **8** which was cyclized to form intermediate **9**. After oxidization by *fac*-Ir^{IV}(ppy)$_3$ and loss of a proton, intermediate **9** was converted to the final product **3a**. On the other hand, for R_4 = Bn, cyclization of the radical intermediate **10** occurred to offer intermediate **11** which was then oxidized by *fac*-Ir^{IV}(ppy)$_3$ to form the key cation **12**. Finally, the product **5a** was obtained after loss of a proton.

In conclusion, we have developed a visible-light-mediated 1,7-enyne bicyclization reaction with α-bromo diethyl malonate **2** for the synthesis of a wide range of cyclopenta[*c*]quinolines and benzo[*j*]phenathridines. This novel photocatalytic strategy has attracted special attention due to its operational simplicity, excellent functional group tolerance, and high yields under mild conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03662.

Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)
X-ray crystal structure data for **5a** (CIF)
X-ray crystal structure data for **5n** (CIF)
X-ray crystal structure data for **5o** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) (a) CCDC 1442497 contains the supplementary crystallographic data for **5a**. (b) CCDC 1443412 and 1443411 contain data for **5n** and **5o**. All data can be acquired free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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