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Visible-Light-Driven Dearomatization Reaction toward the Formation of Spiro[4.5]deca-1,6,9-trien-8-ones

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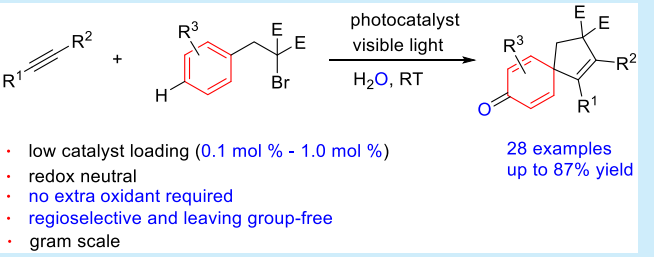
ABSTRACT: A visible-light-driven regioselective dearomative cyclization between 2-benzyl-2-bromomalonate and alkynes under mild conditions leading to the formation of spiro[4,5]-decanes has been developed. In the presence of H_2O, a variety of 2-benzyl-2-bromomalonates smoothly undergo 5-exo-dig radical dearomative cyclization with alkynes to afford the corresponding spiro[4,5]decanes in moderate to good yield in a step-economical manner under oxidant-free conditions.

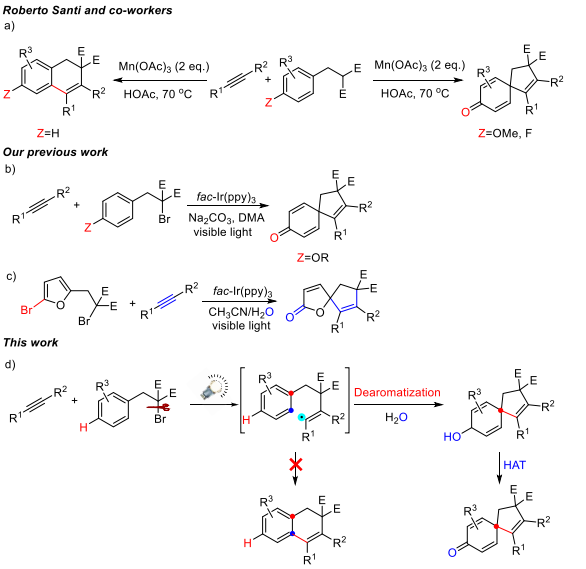


Spiro[4,5]decane skeletons are found in many synthetic and natural molecules that exhibit diverse biological activities,[1] such as anticancer,[1a] antivirus,[1d] and antibacterial properties.[1b] Thus the development of step-economical methods for efficient access to the spiro-cycle with a sterically hindered quaternary carbon center from readily accessible starting materials is of great importance. Dearomative cyclization reactions of arenes have developed into a straightforward and powerful strategy to construct these molecular scaffolds,[2] including acid-catalyzed cyclization,[3] transition-metal-catalyzed cyclization,[4] electrophilic cyclization,[5] and radical cyclization.[1f,6] In 1994, Santi developed an efficient coupling of diethyl benzyl malonates and alkynes for the synthesis of spiro[4,5]decatriene and tetrahydronaphthalene derivatives using a stoichiometric amount of $Mn(OAc)_3$. The regioselectivity greatly depended on the substituents on the aromatic unit, and the main product, spiro[4,5]decatriene, was obtained only when the substrates bore 4-F or 4-OMe (Scheme 1a).[6b]

Remarkably, visible-light-driven photoredox catalysis has evolved into an effective and impactful synthetic tool, which has paved new ways for the exploitation of radical approaches owing to its sustainable and green features.[7] Among them, many elegant examples of intra- or intermolecular dearomative cyclization protocols for the azaspirocycles under the irradiation of visible-light have been reported.[8] Our group has recently achieved an efficient intermolecular dearomative cyclization of 2-bromo-1,3-dicarbonyl compounds and alkynes for the synthesis of spiro[4,5]decane skeletons by using a photoredox catalyst (Scheme 1b).[9] Then, we developed new access to the synthesis of spirocycle skeletons by applying H_2O as an external oxygen source via C−Br bond cleavage under mild reaction conditions (Scheme 1c).[10]

However, most of the aforementioned accomplishments have been limited to the substrates bearing some para substituents, such as hydroxyl, alkoxyl, or halogen, on the aromatic ring. From the synthetic point of view, substrates bearing no substituents on the aromatic ring have the advantages of atom economy and step economy. As such, the development of direct and simple methods for the general synthesis of these spirocarbocycles form readily available starting materials still remains a highly demanding task. Herein

Scheme 1. Radical Spirocyclization onto an Aromatic Ring for the Synthesis of Spiro[4,5]decane Derivatives



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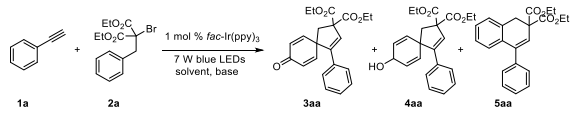
we report a visible-light-driven regioselective dearomative cyclization of 2-benzyl-2-bromomalonate with alkynes in the presence of H_2O to give the corresponding spiro[4,5]decanes via the intermediate spiro[4.5]deca-1,6,9-trien-8-ol, followed by hydrogen abstraction and oxidation (Scheme 1d).

To substantiate the aforementioned reaction design, we embarked on the investigation with the reaction of phenylacetylene **1a** and diethyl 2-benzyl-2-bromomalonate **2a** in the presence of *fac*-Ir(ppy)$_3$ (1 mol %) in a mixture solvent (DMA/H_2O 1:1) under 7 W blue LED irradiation. Gratifyingly, the reaction took place at room temperature, and the desired product, spiro[4,5]decane **3aa**, was isolated in 52% yield along with the 6-endo-dig cyclization byproduct **5aa** in 32% yield (Table 1, entry 1). Next, we investigated the influence of the amount of water for the reaction (Table 1, entries 1−4). To our delight, the isolated yield of **3aa** could be increased to 85% when a mixed solvent of DMA/H_2O with a 5:1 (v/v) ratio was used (Table 1, entry 2). Subsequently, solvent screenings showed that DMA was superior to other solvents (Table 1, entries 5−8). To our surprise, when MeOH was used as the solvent, the yield of byproduct **5aa** was increased as high as 72% (Table 1, entry 7). Intriguingly, the yield of **5aa** was further increased to 85%, and no desired product **3aa** was observed when the reaction was performed in MeCN (Table 1, entry 8). We inferred that different solvents might affect the regioselectivity by favoring the types of radical cyclization (5-exo-dig vs 6-endo-dig). A range of various bases, such as Na_2CO_3, K_2CO_3, Li_2CO_3, $NaHCO_3$, and 2,6-lutidine, were added, and **3aa** was observed in verified yield. In these cases, the intermediate spiro[4.5]deca-1,6,9-trien-8-ol **4aa** was also present by ^{1}H NMR (Table 1, entries 9−13). Moreover, reducing the amount of **2a** also lead to the decreased yield of target product **3aa** (Table 1, entries 14 and 15). Control experiments disclosed that both the photosensitizer and visible light were indispensable in this transformation (Table 1, entries 17 and 18). Finally, the experiments with on/off light suggested that the chain propagation is not a main mechanistic pathway. (See the Supporting Information.)

Table 1. Optimization of Reaction Conditions[a]



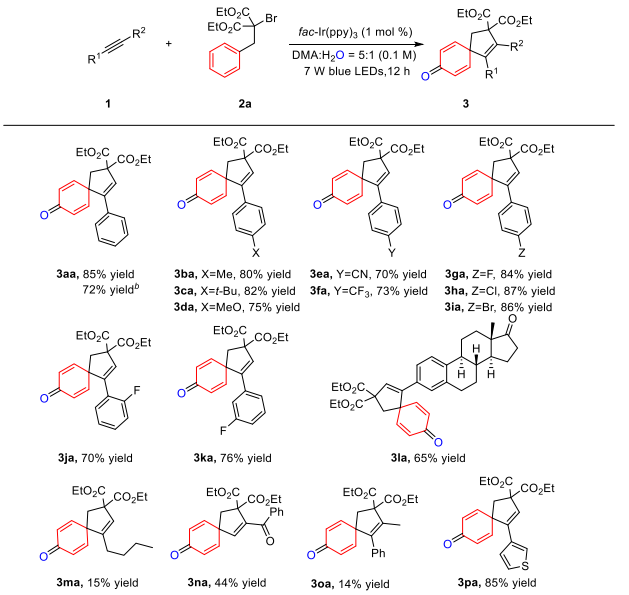
entry	solvent	3aa yield (%)[b]	4aa yield (%)[b]	5aa yield (%)[b]
1	DMA/H_2O 1:1	52	0	32
2	DMA/H_2O 5:1	86 (85)[c]	0	11
3	DMA/H_2O 10:1	78	3	16
4	DMA/H_2O 30:1	63	4	18
5	DMF/H_2O 5:1	68	0	25
6	THF/H_2O 5:1	54	0	46
7	MeOH/H_2O 5:1	16	0	72
8	CH_3CN/H_2O 5:1	0	0	85
9[d]	DMA/H_2O 5:1	81	7	11
10[e]	DMA/H_2O 5:1	71	14	11
11[f]	DMA/H_2O 5:1	77	4	11
12[g]	DMA/H_2O 5:1	71	11	11
13[h]	DMA/H_2O 5:1	68	14	13
14[i]	DMA/H_2O 5:1	34	19	35
15[j]	DMA/H_2O 5:1	62	13	17
16[k]	DMA/H_2O 5:1	85	1	13
17[l]	DMA/H_2O 5:1	0	0	0
18[m]	DMA/H_2O 5:1	0	0	0

[a]Conditions: **1a** (30.6 mg, 0.3 mmol), **2a** (197.5 mg, 0.6 mmol), catalyst (4.2 mg, 1 mol %), solvent (3 mL), irradiation with 7 W blue LEDs at rt for 12 h. [b]^{1}H NMR yields were reported using benzyl ether as an internal standard. [c]Isolated yield. [d]Na_2CO_3 (1.2 equiv) was added. [e]K_2CO_3 (1.2 equiv) was added. [f]Li_2CO_3 (1.2 equiv) was added. [g]$NaHCO_3$ (1.2 equiv) was added. [h]2,6-Lutidine (1.2 equiv) was added. [i]1.2 equiv. **2a**. [j]1.5 equiv. **2a**. [k]2.5 equiv. **2a**. [l]Without photocatalyst. [m]Reaction was carried out in the dark.

With the optimized conditions in hand, we first examined the scope of alkynes for this visible-light-driven dearomative cyclization reaction (Scheme 2). Gratifyingly, a broad spectrum of aryl acetylenes bearing diverse substituents, electron-donating and electron-withdrawing, smoothly underwent the transformation to produce the corresponding spiro[4.5]deca-1,6,9-trien-8-ones in fair to good yield (Scheme 2, **3aa**−**ia**). To our delight, the substituents at the ortho or meta position for the aromatic ring did not significantly affect the reaction efficiency, and the target products were obtained in moderate yield (Scheme 2, **3ja**−**ka**). Remarkably, the aryl alkyne with an estrone skeleton was also well accommodated in this transformation to give the corresponding product **3la**, which may be applied in the late-stage functionalization of pharmaceutical molecules. In addition, our protocol could be applied to aliphatic alkyne, albeit in lower yield (Scheme 2, **3ma** and **3na**). Finally, the product **3pa** could be obtained in 85% yield when the heteroaryl acetylene (thiophene) was used as the reaction partner. To showcase the scalability of this method, a 5.0 mmol scale reaction of **1a** and **2a** was also carried out under the optimized conditions to give the target product **3aa** in 78% yield with a catalyst loading of 0.1 mol %.

Next, the scope of 2-bromo-1,3-dicarbonyls (**2**) was explored. We found that the reaction outcome could be easily

Scheme 2. Substrates Scope of Alkynes[a]



[a]Conditions: **1** (0.3 mmol), **2a** (197.5 mg, 0.6 mmol), *fac*-Ir(ppy)$_3$ (4.2 mg, 1 mol %), DMA/H_2O 5:1 (3 mL), irradiation with 7 W blue LEDs at rt for 12 h; isolated yields. [b]**1a** (510.68 mg, 5.0 mmol), **2a** (3.29 g, 10 mmol), *fac*-Ir(ppy)$_3$ (7.0 mg, 0.1 mol %), DMA/H_2O 5:1 (50 mL), irradiation with 7 W blue LEDs at rt for 36 h.

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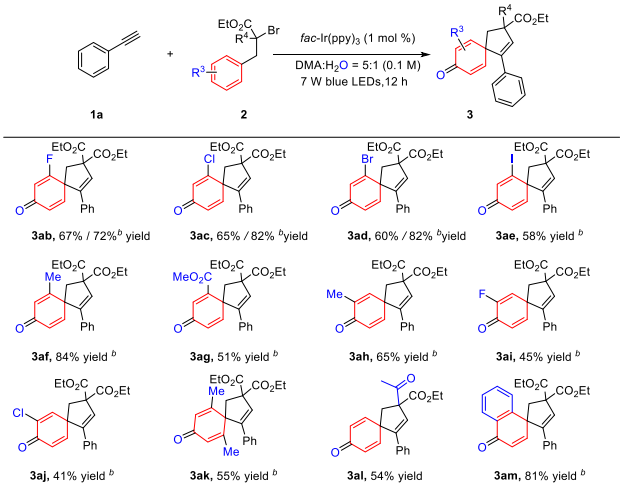
influenced by the nature of the phenyl substituents (Scheme 3). As expected, the substrate with ortho-halogens (F, Cl, Br)

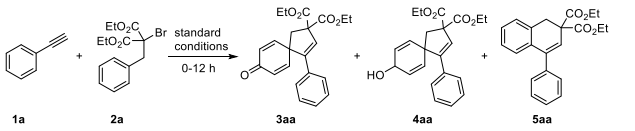
Scheme 3. Substrate Scope of 2-Bromo-carbonyl Compounds[a]



[a]Conditions: **1a** (30.6 mg, 0.3 mmol), **2** (0.6 mmol), *fac*-Ir(ppy)$_3$ (4.2 mg, 1 mol %), DMA/H_2O 5:1 (3 mL), irradiation with 7 W blue LEDs at rt for 12 h; isolated yields. [b]Na_2CO_3 (38.2 mg, 0.36 mmol) was added.

afforded the desired spirocycles under the optimized reaction conditions in 60−67% yield. Interestingly, the intermediate spiro[4.5]deca-1,6,9-trien-8-ol (**4**) was isolated in 24−39% yield instead of the dihydronaphthalene byproduct **5**, which may be ascribed to the decreased nucleophilicity of the position meta to an electron-withdrawing group. However, the yields of the corresponding products were improved by adding 1.2 equiv of Na_2CO_3 (Scheme 3, **3ab**−**ad**). When the substrate **2e** with an *ortho*-iodo group was treated with **1a**, **3ae** was obtained in 58% yield, and the dehalogenation product (**3aa**) was also isolated in 13% yield. Meanwhile, the electron-donating methyl substituent could deliver the corresponding product **3af** in high yield. However, the electron-withdrawing ester group on the phenyl ring produced a poor yield of the product **3ag**. Furthermore, moderate yields were still achieved from the substrates with a *meta*-methyl, -fluorine or -chloro group (Scheme 3, **3ah**−**aj**). Compared with **1f** (84% yield for **3af**), the substrate **1k**, which was functionalized with two *ortho*-methyl groups, afforded only a moderate yield of **3ak** (55%) due to the steric hindrance. In addition, **2l** proved to be a viable substrate that gave the corresponding product **3al** in 54% yield. Moreover, the substrate with a naphthalene ring was also applicable to this system, delivering the desired product **3am** in 81% yield.

To gain insight into this protocol, a time−yield profile of the coupling of phenylacetylene **1a** and diethyl 2-benzyl-2-bromomalonate **2a** utilizing the optimized conditions was recorded by ^1H NMR spectroscopy in Figure 1. The substrates were rapidly consumed to form spiro[4.5]deca-1,6,9-trien-8-ol **4aa** in 43% yield in 2.0 h, along with the desired product **3aa** and the byproduct **5aa** in 35 and 11% yield, respectively. Then, spiro[4.5]deca-1,6,9-trien-8-ol **4aa** gradually converted into spiro[4,5]decane **3aa** in 12 h, which indicated that **4aa** was the key reaction intermediate.



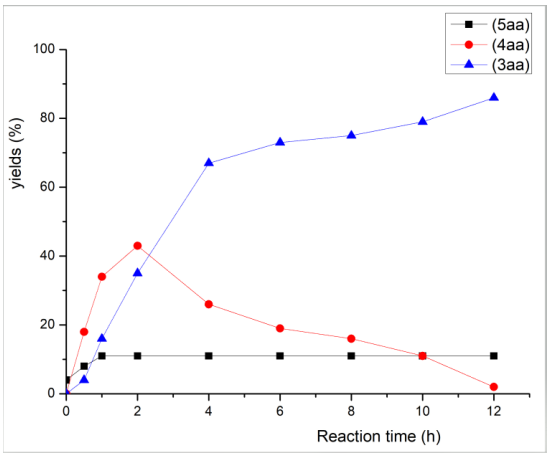
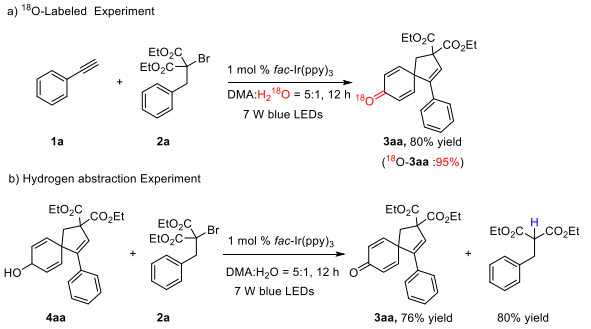


Figure 1. Time−concentration profile of the model reaction.

To further probe into the mechanism, a series of verification experiments were performed, as shown in Scheme 4. First, in

Scheme 4. Verification Experiments



the presence of $H_2{}^{18}O$, the photocatalytic intermolecular dearomative cyclization of phenylacetylene **1a** and diethyl 2-benzyl-2-bromomalonate **2a** afforded the ^{18}O-labeling product **3aa** in 80% yield, suggesting that the oxygen atom of the carbonyl group should come from $H_2{}^{18}O$ (Scheme 4a). In addition, the reaction of spiro[4.5]deca-1,6,9-trien-8-ol **4aa** and **2a** under optimized conditions yielded product **3aa** and diethyl 2-benzylmalonate,which reveals that the following oxidation of alcohol **4aa** to ketone **3aa** might undergo a hydrogen abstraction (Scheme 4b).

On the basis of the control experiments and related reports,[9] we thus proposed a possible mechanism for this photocatalytic regioselective dearomative cyclization (Scheme 5). First, 2-benzyl-2-bromomalonate **2a** can be reduced by the excited Ir^{III}* species to generate the radical **A**. Subsequently, **A** reacted with phenylacetylene **1a** to produce the spirocycle intermediate **C** via an intramolecular 5-exo-dig radical cyclization sequence. The spirocycle radical **C** could be oxidized by an Ir^{IV} metal complex to carbocation **D**. Then, the carbocation **D** reacted with H_2O to afford the spiro[4.5]deca-1,6,9-trien-8-ol **4aa**, which underwent a hydrogen abstraction by the radical intermediate **A** to give the radical intermediate **E**. Finally, the

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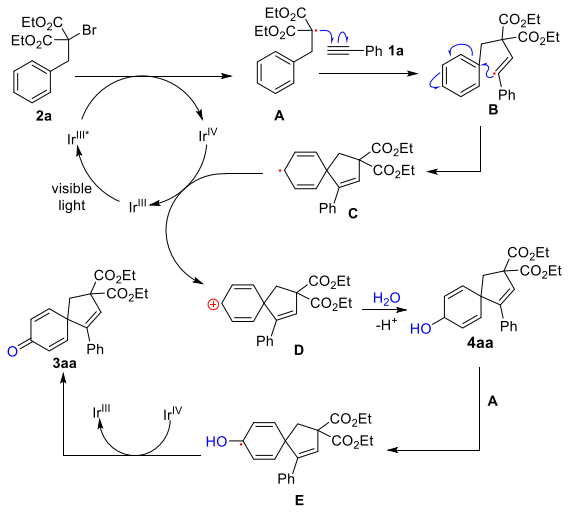
Scheme 5. Proposed Mechanism



intermediate **E** underwent another single-electron transfer with an Ir^{IV} metal complex to produce desired product **3aa**.

In conclusion, we have developed an efficient visible-light-driven dearomative 5-exo-dig radical cyclization between 2-benzyl-2-bromomalonate and alkynes in the presence of H_2O, affording the spirocarbocycle structures in a step-economical manner under mild conditions. The application of relay photoredox catalysis to other dearomatization reactions is currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04283.

Preparation of substrates, general procedure, characterization data, and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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