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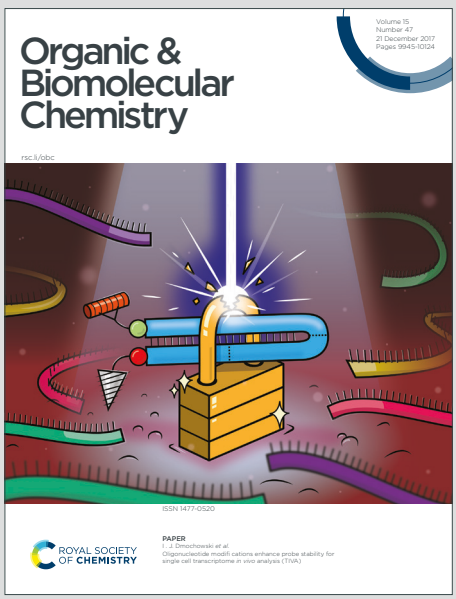

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ARTICLE

Photo-Mediated Synthesis of Halogenated Spiro[4,5]trienones of *N*-Aryl Alkynamides with $PhI(OCOCF_3)_2$ and KBr/KCl

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A novel and convenient photo-mediated halogenated spirocyclization of *N*-(*p*-methoxyaryl)propiolamides has been developed. The photolysis of phenyliodine bis(trifluoroacetate) (PIFA) as an iodination reagent led to iodinated ipsocyclization under the irradiation of a xenon lamp, while the brominated ipsocyclization or chlorinated ipsocyclization were achieved by irradiating the mixture of PIFA with KBr/KCl under a blue LED. The present protocol simply utilizes light as the safe and clean energy source, and without the aid of external photocatalyst providing various 3-halospiro[4,5]trienones in good to excellent yields (up to 93%).

Introduction

Spirocycles, including spiro[4,5]decatrienones, are essential kind of skeletons in many natural products and pharmaceuticals (Figure 1).[1] Among the various spirocycles, the azaspiro[4,5]trienones are crucial and interesting because of their remarkable biological activities[2] and diverse synthetic applications.[3] The considerable efforts have been devoted to develop novel and efficient synthesis of the core spirocyclic structure.[4]

Generally, the spiro[4,5]trienone structures can be constructed via the oxidative *spiro*-cyclization of phenol derivatives,[5] electrophilic *ipso*-cyclization,[6] transition-metal-mediated intramolecular nucleophilic *ipso*-cyclization,[7] and the radical coupling *ipso*-cyclization.[8]

It is worth noting that halogen functionalities are good synthetic intermediates for further transformation to functional materials. In 2005, Larock[9] firstly reported a method that *N*-(*p*-methoxyphenyl)-3-phenylpropiolamide converted to spiro[4,5]trienone with 2 equiv of I_2. In 2008, Li[10] reported a method for the synthesis of halogenated spiro[4,5]trienones from *N*-(*p*-methoxyaryl)propiolamides with CuX (X= I, Br, SCN) and electrophilic fluoride reagents (Scheme 1, eq 1). In 2012, the same group[11] disclosed halogenated spiro[4,5]trienones by the electrophilic spirocyclization of *N*-arylpropiolamides with NXS (Scheme 1, eq 2). Recently, Qiu[12] reported the synthesis of brominated spiro[4,5]trienones from *N*-arylpropiolamides using $ZnBr_2$ as bromine source and oxone as oxidant at room temperature (Scheme 1, eq 3). Meanwhile, Du[13] developed a metal-free oxidative protocol for iodinated spiro[4,5]trienone skeletons from *N*-(*p*-fluoroaryl)propiolamides by using PIFA and $BF_3{\bullet}Et_2O$ (Scheme 1, eq 4). However, there are few reports on the application of hypervalent iodine(III) for construction of iodinated heterocycles, in which the iodo moiety originated from the hypervalent iodine reagent.[14] Furthermore, a kind of iodine(III)-based halogenating reagent generated in situ by hypervalent iodine(III) with inorganic halides, has attracted wide attention.[15] Therefore, the development of simple, mild, environmentally friendly method to access halogenated spiro[4,5]trienones is still highly desirable.

In recent years, organic transformations under visible light irradiation with photocatalyst-free have captured much attention.[16] In 2017, Mahiuddin[17] reported a visible light-induced selenylative spirocyclization of *N*-arylpropiolamides at room temperature in oxygen atmosphere without external photocatalyst (Scheme 1, eq 5). Herein we report an efficient and clean synthesis of halogenated spiro[4,5]trienones based on photo-induced photocatalyst-free radical-cyclization-dearomatization process of *N*-(*p*-methoxyaryl) propiolamides at room temperature (Scheme 1, eq 6). This strategy involves a connection of the halogen radical with the electron-deficient carbon-carbon triple bond to generate the halogenated spiro[4,5]trienones skeletons.

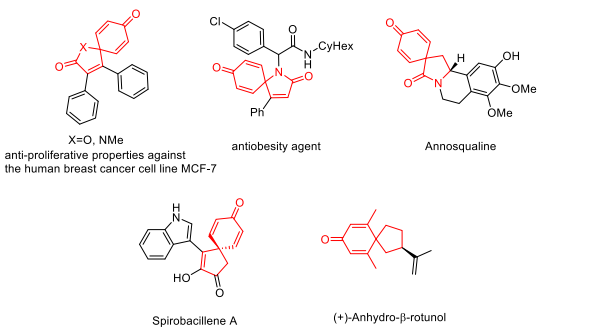

Fig. 1 Structure of representative spirocyclic bio-active compounds.

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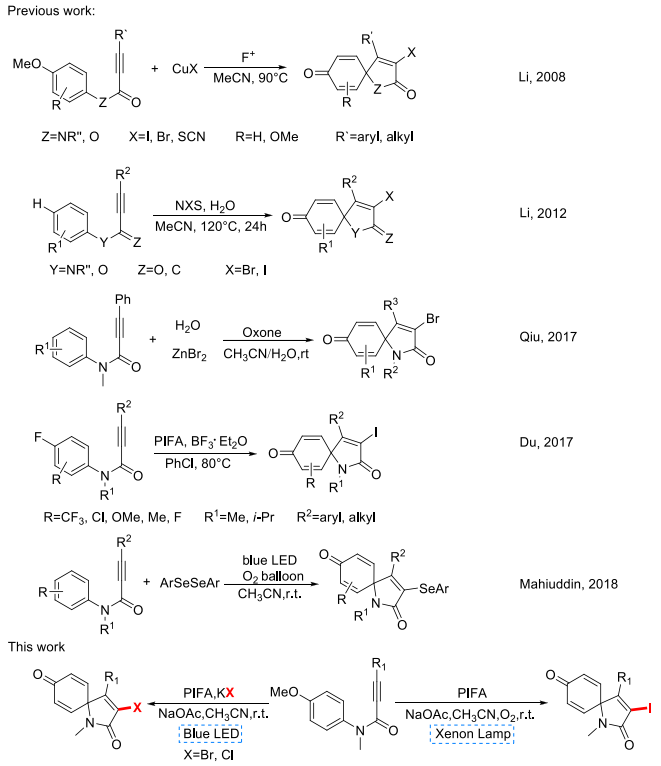


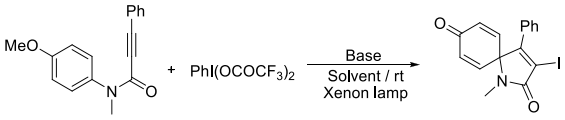
Scheme 1 The Intramolecular Spiro-cyclization of Alkynes.

Results and discussion

In 2018, Qing[18] developed the visible light-induced decarboxylative trifluoromethylation of (hetero)arenes using $C_6F_5I(OCOCF_3)_2$ as the trifluoromethylating reagent. Inspired by this work, we initially postulated an intramolecular cyclization reaction of *N*-(*p*-methoxyaryl)propiolamide (**1a**) in the presence of PIFA to afford 3-trifluoromethyl spiro[4,5]trienones. The reaction was carried out with **1a** and PIFA in the presence of Na_2HPO_4 in MeCN at room temperature under the irradiation of a Xenon lamp for 12 h. However, iodinated spiro[4,5]trienone was detected in 33% yield without expected 3-trifluoromethyl spiro[4,5]trienone (Table 1,entry 1). Encouraged by this result, increasing the amount of PIFA to 2 equiv gave **2a** in overall 51% yield (Table 1, entry 2). In an attempt to improve the reaction efficiency, a variety of solvents were tested, and MeCN gave the best yield (Table 1, entries 3-4). Varying the amount of Na_2HPO_4 revealed that 2.0 equiv Na_2HPO_4 was preferable (Table 1, entries 5-7). With the addition of TBHP or BPO, the yields decreased obviously (Table 1, entries 8-9). Notably, without irradiation of a Xenon lamp the spirocyclization reaction did not occur (Table 1, entry10). Screening of other bases, such as K_2CO_3, NaOAc, $NaHCO_3$ and Cs_2CO_3, the NaOAc gave the highest yield of 80% (Table 1, entries 11-14). Prolonged irradiation time to 18 h ledto higher yield (Table 1, entry 15). Notably, the use of oxygen atmosphere in lieu of air improved the reaction efficacy and the product **2a** was isolated in 93% yield (Table 1, entry 16). Therefore, the optimized conditions for this process were defined as the use of **1a** (1 equiv) with PIFA (2 equiv), and NaOAc (2 equiv) in MeCN at room temperature in oxygen atmosphere under the irradiation of a Xenon lamp for 18 h.

With the optimized reaction conditions in hand, the scope of this iodinated spirocyclization method was investigated (Table 2). Firstly, a series of aryl substituents at the terminal alkynes were examined. Bearing both electron-donating (**2b**-**2d**) and electron-withdrawing (**2e**-**2m**) groups at the para-position of the phenyl ring gave the corresponding products in good yields. Additionally, steric factors also influenced on the iodinated spirocyclization process (**2j**-**2l**), and the spirocyclization reaction could not occur in the case of *ortho*-bromo substitution of the phenyl connected with the alkyne. Gratifyingly, the method was extended to heteroaromatic alkyne leading to **2n** in 56% yield. Unfortunately, treatment of terminal alkyne (R_1=H) with PIFA failed to construct product **2o**. Besides, the substrate with free N-H (R_2=H) of arylpropiolamide only gave a trace amount of the desired product **2p**. It was unfortunately that only trace target product **2q** was obtained when a methyl was substituted on the alkyne.

Table 1. Optimization of the Iodinated Spirocyclization Reaction Conditions[a]



1a 2a

Entry	Solvent	Additive (equiv.)	Base (equiv.)	Time (h)	yield[b] (%)
1[c]	MeCN		Na_2HPO_4 (4.0)	12	33
2	MeCN		Na_2HPO_4 (4.0)	12	51
3	CH_2Cl_2		Na_2HPO_4 (4.0)	12	49
4	PhMe		Na_2HPO_4 (4.0)	12	45
5	MeCN		Na_2HPO_4 (3.0)	12	64
6	MeCN		Na_2HPO_4 (2.0)	12	72
7	MeCN		-	12	32
8	MeCN	TBHP	Na_2HPO_4 (2.0)	12	21
9	MeCN	BPO	Na_2HPO_4 (2.0)	12	54
10[d]	MeCN		Na_2HPO_4 (2.0)	12	N.D.
11	MeCN		K_2CO_3 (2.0)	12	65
12	MeCN		NaOAc (2.0)	12	80
13	MeCN		$NaHCO_3$ (2.0)	12	69
14	MeCN		Cs_2CO_3 (2.0)	12	17
15	MeCN		NaOAc (2.0)	18	84
16[e]	MeCN		NaOAc(2.0)	18	93
17[f]	MeCN		NaOAc(2.0)	18	N.D.

[a]All reactions were performed in a Schlenk tube around condensate water with **1a** (1.0 equiv, 0.2 mmol), PIFA (2.0 equiv), base in solvent (2 mL) at room temperature under the irradiation of a Xenon lamp. [b]Isolated yields. [c]1 equiv of PIFA. [d]Without irradiation. [e]In oxygen atmosphere. [f]With the irradiation of blue LED.

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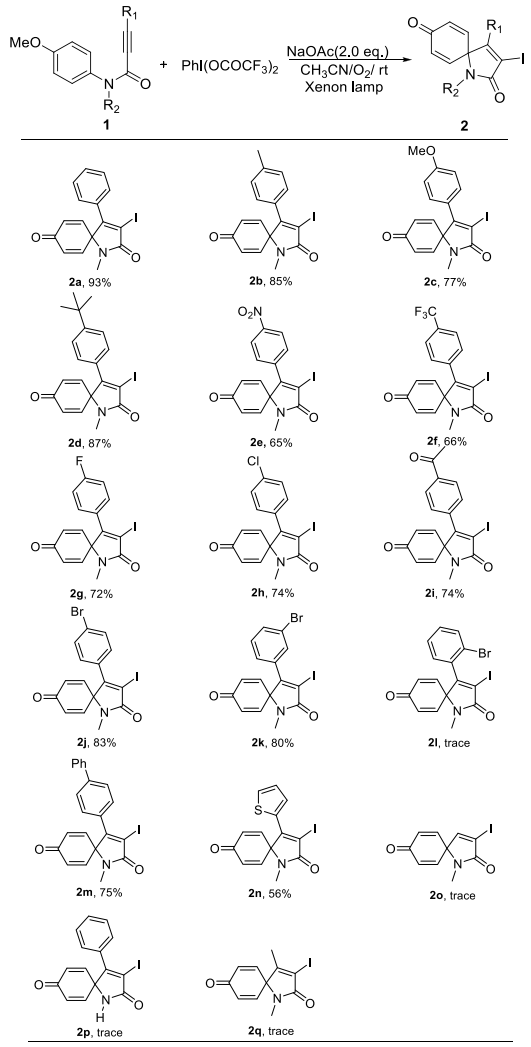
Table 2. Substrate Scope of Iodinated Spiro[4,5]trienones[a]

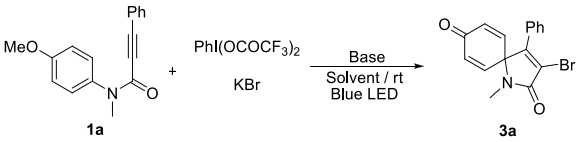


[a]All reactions were performed in a Schlenk tube around condensate water with **1** (1.0 equiv, 0.2 mmol), PIFA (2 equiv), NaOAc (2 equiv) in CH_3CN (2 mL) at room temperature in oxygen atmosphere under the irradiation of a Xenon lamp for 18 h.

Encouraged by the good results of iodination spirocyclization, we turned our attention to the reaction of brominated and chlorinated spirocyclization of *N*-(*p*-methoxyaryl)propiolamides. In 2017, Hu[19] reported Ru^{III} photoredox catalyzed oxidative C–H chlorination of aromatic compounds using NaCl as the chlorine source and $Na_2S_2O_8$ as the oxidant. In 2019, Nagib and Fuchs[15e] developed site-selective hetero(aryl) C–H functionalization strategy by in situ generation of non-symmetric iodanes from $PhI(OAc)_2$ and the anions of acids, salts, and acyl halides. Herein we investigated a photo-induced brominated spirocyclization and chlorinated spirocyclization with PIFA and KBr/KCl as sources of halogen radical. Initially, we used *N*-(*p*-methoxyaryl)propiolamide **1a**, as a model, 1.0 equiv of PIFA and 2.0 equiv of KBr in CH_2Cl_2 under irradiation of a 15W blue LED, and the desired brominated spiro[4,5]trienone was obtained in 88% yield (Table 3, entry 1). For the control experiment, without irradiation, the yield of **3a** was drastically reduced to 46% (Table 3, entry 2). Subsequently, screening the amount of PIFA, KBr, solvent and irradiation time, the optimized conditions of brominated spirocyclization were achieved as using **1a** (1 equiv) with PIFA (1.5 equiv), KBr (2.0 equiv) and NaOAc (2 equiv) in MeCN at room temperature under irradiation of a 15W blue LED for 2h. Gratifyingly, the reaction of substrate **1a** with PIFA and KCl processed smoothly under irradiation of a blue LED, affording the corresponding chlorinated spiro[4,5]trienone **3b** in 76% yield.

With the optimized reaction conditions in hand, the scopes of the brominated spiro[4,5]trienones and chlorinated spiro[4,5]trienones were investigated as shown in Table 4. It showed good tolerance for a series of aryl substituents at the alkynes. When R_1 was 4-methoxyphenyl, the reaction gave the corresponding chlorinated spiro[4,5]trienones (**3c**) in good yield. Extensive screening revealed that electron-deficient groups at the *para*-position of the phenyl ring were well-tolerated, affording the desired products in moderate yields (**3d**-**3j**). Furthermore, the heteroaromatic alkyne gave the desired products **3k** and **3l** in 62% and 54% yields, respectively. Particularly, with phenyl 3-phenylpropiolate, the reaction proceeded smoothly as well, to afford **3m** in good yields. Notably, the substrate with free N-H (R_2=H) of arylpropiolamide, which was not easy to halogenation spirocyclization under metal catalyst[8g, 20] or visible-light-catalyzed conditions,[8o] served well for the synthesis of free N-H brominated spiro[4,5]trienone (**3n**) under the optimal conditions. Unfortunately, none of cyclization products **3o** and **3p** was observed when terminal alkyne (R_1=H) was utilized in this process.

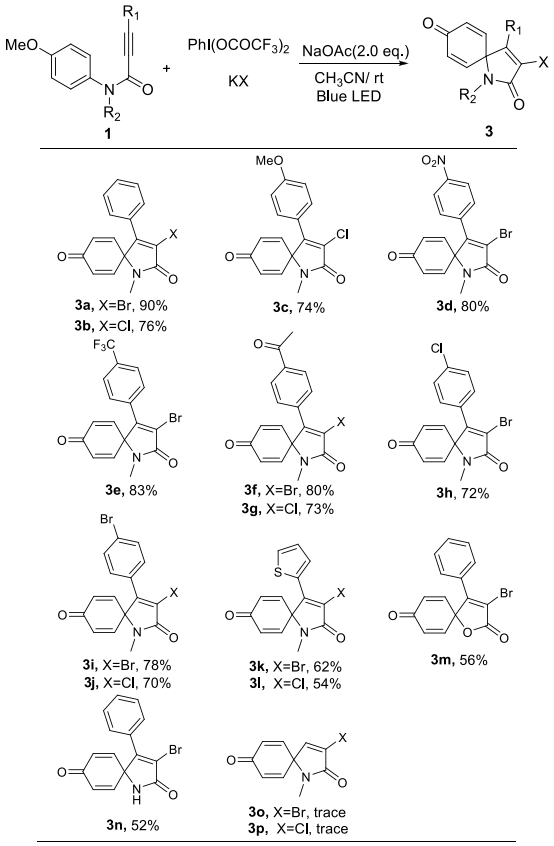
Table 3. Optimization of the Brominated Spirocyclization Reaction Conditions[a]



Entry	PIFA (equiv)	KBr (equiv)	Solvent	Time (h)	Yield[b](%)
1	1.0	2.0	CH_2Cl_2	18	88
2	1.0	1.0	CH_2Cl_2	18	65
3	1.5	2.0	CH_2Cl_2	18	90
4	2.0	2.0	CH_2Cl_2	18	92
5	-	2.0	CH_2Cl_2	18	N.D.
6	1.5	2.0	CH_3CN	18	94
7	1.5	2.0	DMF	18	64
8	1.5	2.0	THF	18	57
9	1.5	2.0	CH_3CN	12	94
10	1.5	2.0	CH_3CN	6	92
11	1.5	2.0	CH_3CN	3	90
12	1.5	2.0	CH_3CN	2	90
13[c]	1.5	2.0	CH_3CN	2	45
14[d]	1.5	2.0	CH_3CN	2	92

[a]All reactions were performed in a Schlenk tube with **1a** (1.0 equiv, 0.2 mmol), PIFA, KBr, NaOAc (2,0 equiv) in solvent (2 mL) at room temperature under the irradiation of a 15 W blue LED. [b]Isolated yields. [c]Without irradiation. [d]Under the irradiation of a Xenon lamp.

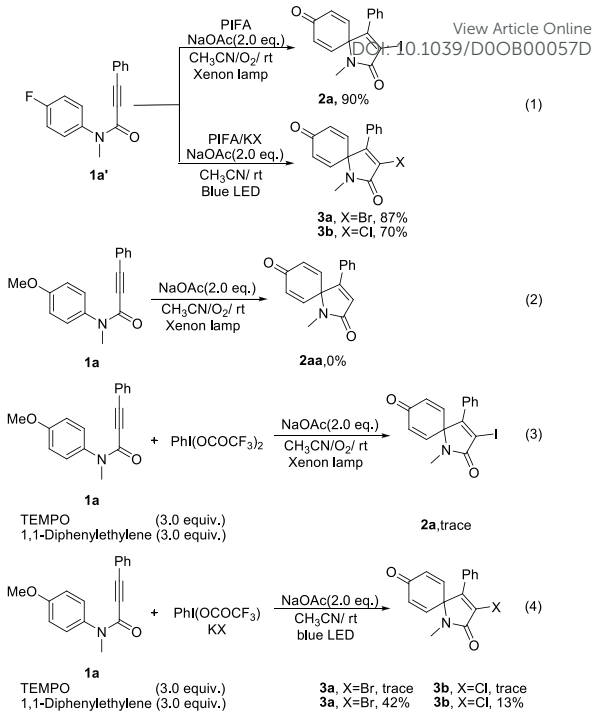
Table 4. Substrate Scope of Brominated Spiro[4,5]trienones and Chlorinated Spiro[4,5]trienones[a]



[a]All reactions were performed in a Schlenk tube with **1** (1.0 equiv, 0.2 mmol), PIFA (1.5 equiv), KX (2.0 equiv), NaOAc (2 equiv) in CH_3CN (2 mL) at room temperature with the irradiation of a 15W blue LED for 2 h.

In order to understand the possible reaction mechanism, the following control experiments were carried out (Scheme 2). The reactions of *N*-(*p*-fluoroaryl)propiolamide provided the corresponding halogenated spiro[4,5]trienones **2a/3a/3b** in good yields by delivering fluorine group, suggesting that the carbonyl oxygen atom is not derived from the methoxy group (Scheme 2, eq 1). When the reaction of **1a** was performed without PIFA, the spirocyclization product **2aa** was not detected, indicating that the free radical species formed by PIFA attacked triple bond before forming the spirocyclization intermediate **2aa** (Scheme 2, eq 2). Furthermore, a radical trapping experiment was conducted. When 3.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into reaction system, only trace amounts of the products **2a/3a/3b** were detected. However, mixing PIFA and TEMPO could lead to the total reduction of PIFA to iodobenzene. [15a, 21] The 1,1-diphenylacetylene as the free radical scavenger suppressed the spirocyclization, and the yields of **3a** and **3b** were only 42% and 13%, respectively, indicated that the reaction of halogenated spirocyclization mainly proceeds via a radical pathway (Scheme 2, eqs 3 and 4).

According to the previous reports[22] and our experimental results, a plausible mechanism for iodinated spirocyclization reaction is outlined in Scheme 3 path A. PIFA is photoexcited



Scheme 2. Control Experiments

to form iodanyl radical **A** and trifluoroacetoxy radical **B** under the irradiation of a Xenon lamp.[22c] Subsequently, the addition of iodanyl radical **A** to the triple bond of arylpropiolamide **1a** gave vinyl radical **C**. Next, the intermediate **D** was produced by spirocyclization and dearomatization of intermediate **C**. Then, the trifluoroacetoxy radical **B**, released in the previous step, attacked sp^2 carbon to form **E**. Meanwhile, under the oxygen atmosphere, the intermediate **D** could also converted to intermediate **F**. **E** and **F** were converted to **G** with leaving of the methoxy group[23]. An S_NAr reaction occurred to form **H**, which further afforded final product **2a**.[24] The oxygen atom of the newly formed carbonyl group is mainly from PIFA.

The mechanism for brominated spirocyclization and chlorinated spirocyclization reactions are illustrated in Scheme 3 path B and C. Initially, upon reaction with KX, intermediate species $PhI(OCOCF_3)X$ was formed in situ from PIFA.[15] Subsequently, two possible pathways could explain the formation of product **3a/3b**. As the major path, in path B, halogen radical was produced from $PhI(OCOCF_3)X$[25] under the irradiation of a blue LED. Next, the addition of halogen radical to the triple bond of arylpropiolamide **1a** gave vinyl radical **I**.[15e] The intermediate **I** underwent spirocyclization and oxidation to form intermediate **L**. Then, the trifluoroacetate anion attacked the electron-positive aromatic C(sp^2) to form **M**. Finally, the intermediate **M** was converted to the target products **3a/3b**. Additionally, in path C, a halide cation is generated by oxidation of halide ions with PIFA.[19,26] Electrophilic spirocyclization could be attributed to the synthesis of **3a**/**3b**.

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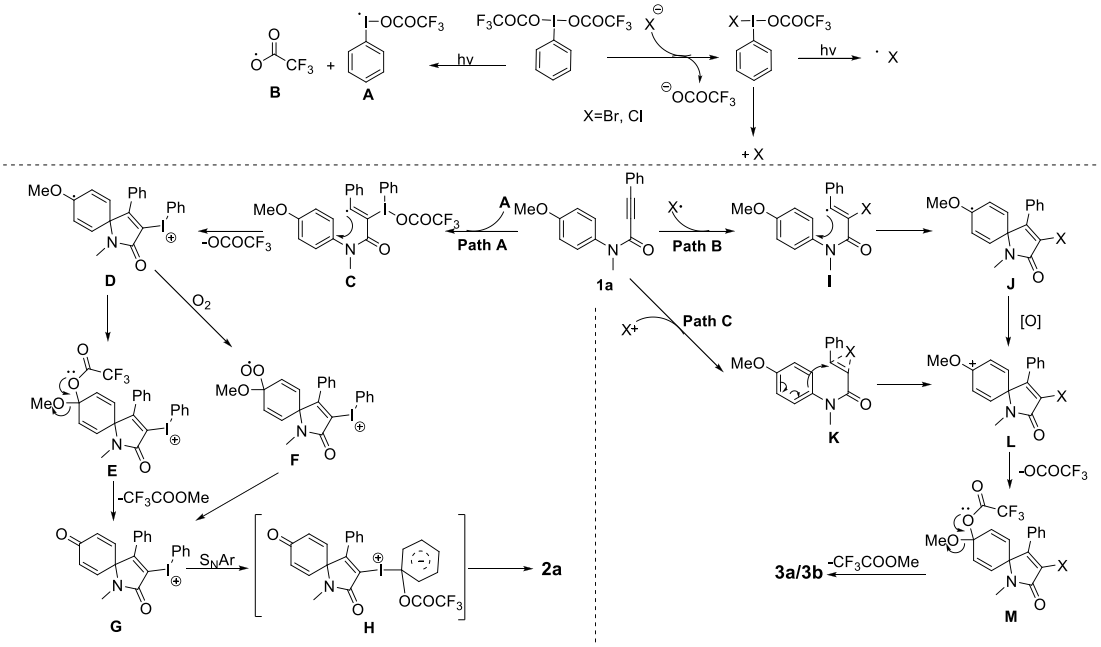
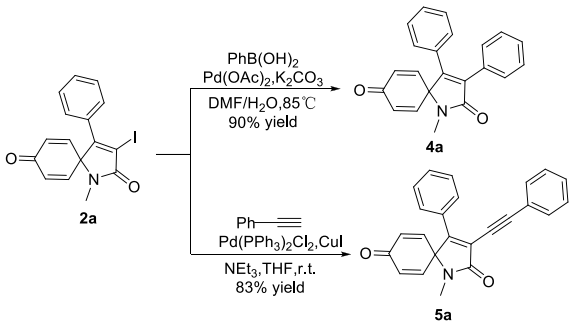


Scheme 3. Proposed Mechanistic



Scheme 4. The Utilization of Product 2a

Finally, the functionalization of the iodinated spirocyclization has been performed to explore the utility of this iodocyclization product. As shown in Scheme 4, the substrate **2a** underwent the Suzuki coupling and the Sonogashira coupling to afford products **4a** and **5a** in 90% and 83% yields, respectively (Scheme 4).

Conclusions

In conclusion, we have developed a metal photocatalyst-free photo-mediated halogenated spirocyclization of *N*-(*p*-methoxyaryl)propiolamides for the synthesis of halogenated spiro[4,5]trienones skeletons at room temperature. This process feature is a radical reaction, PIFA as iodination reagent in iodination spirocyclization reaction or a reagent for initiating bromine or chlorine radicals with KBr/KCl in brominated spirocyclization and chlorinated spirocyclization. With advantages such as mild conditions, environmental-friendly and non-toxic photocatalysts, this new synthetic method is expected to further applications of synthetic biologically active compounds.

Conflicts of interest

There are no conflicts to declare.

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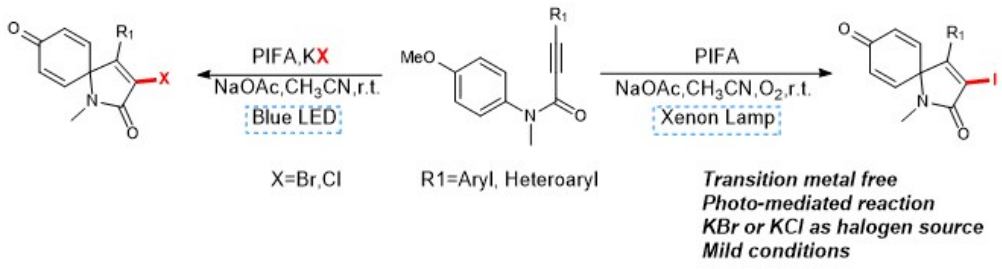

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