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Visible-light-induced novel cyclization of 2-(2-(arylethynyl)benzylidene)-malononitrile derivatives with 2,6-di(*tert*-butyl)-4-methylphenol to bridged spirocyclic compounds

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ABSTRACT

A green and highly efficient strategy for the preparation of bridged spirocyclic compounds *via* visible-light-induced cyclization of 2-(2-(arylethynyl)benzylidene)malononitrile derivatives with 2,6-di(*tert*-butyl)-4-methylphenol (BHT) at room temperature was developed. The photoinduced radical reactions generated the corresponding products in good yields under simple and mild reaction conditions.

Spirocycles are a class of privileged structural motifs, which occur in biologically active molecules, natural products, and chiral ligands, and have attracted a great deal of attention [1–3], especially for the bridged spirocyclic compounds, such as (−)-cylindricine C, FR901483 and TAN1251C as novel tricyclic azaspirane cores, spiroaspertrione A, andiconin B and grayanotoxin VII as shown in Fig. 1 [4–6]. Therefore, the high value of these compounds and the growing interest in chemistry call for efficient synthetic methods [7–9]. Generally, the synthesis of spirocyclics mainly depends on *ipso*-annulation through dearomatization, including transition-metal-mediated dearomatization, nucleophilic or electrophilic dearomatization, and oxidative dearomatization [10–12], as well as cascade *ipso*-cyclization reactions of alkynes *via* radical process [13–15].

Quinones, quinonemethides, and their phenolic precursors are widely distributed in natural products. A variety of phenolic and quinonoid compounds as biologically active secondary metabolites [16], are present in plants [17] and insects [18,19]. The quinone derivatives have aroused great interest for chemists due to their unique structures and high reactivity, and they widely used in the synthesis of organic compounds, electron chemistry [20] and materials chemistry [21–23]. In order to realize the quinones, Kita [24–26] and Ciufolini [27,28] reported the pioneering works to construct spirocyclic compounds by the oxidiation of phenol and subsequently transformations (Schemes 1a and b). Very recently, Zhang and Yang reported the electrooxidative dearomatization of biaryls for the synthesis of tri- and difluoromethylated (CF_3 and CHF_2) spiro[5.5]trienones (Scheme 1c) through a cascade radical *ipso*-cyclization reactions of alkynes, respectively [29,30].

As we all known, photoredox catalysis emerging as a powerful tool in synthetic chemistry have met to the demands of reaction economy, operational simplicity and environmental friendliness, and it received great attention and a number of important achievements have been made [31–37]. On the basis of our exploration in photocatalysis and related works [38–46], we herein reported a highly efficient strategy for the preparation of bridged spirocyclic compounds *via* a visible-light-induced cyclization of 2-(2-(arylethynyl)benzylidene)malononitrile derivatives with 2,6-di(*tert*-butyl)-4-methylphenol (BHT) at room temperature. The photoinduced radical reactions generated the corresponding products in good yields under simple and mild reaction conditions (Scheme 1d).

According to the strategy outlined in Scheme 1d, the model substrates 2-(2-(phenylethynyl)benzylidene)malononitrile (**1a**) and 2,6-di(*tert*-butyl)-4-methylphenol (**2**) were chosen to explore the optimal reaction conditions through the variations of photocatalyst, solvent, light source, molar ratio of **1a**/**2** and reaction

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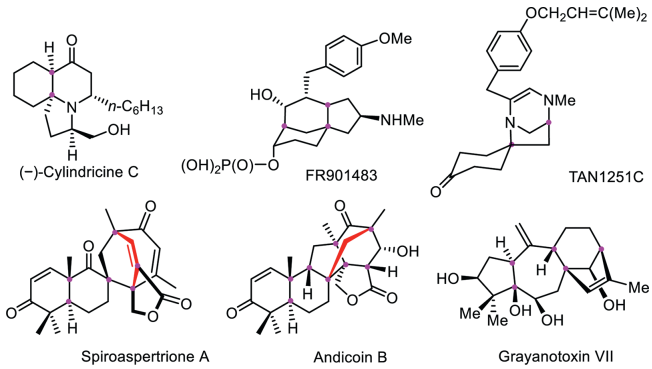
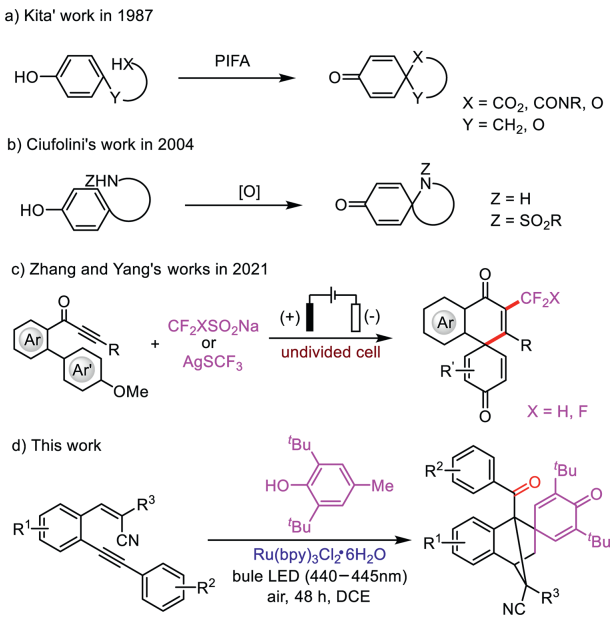


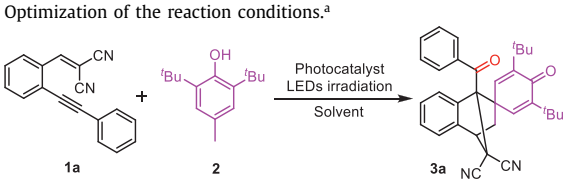
Fig. 1. Bridged spirocyclic compounds with biological activity.



Scheme 1. Representative synthesis of spirocyclic quinones.

time. To our delight, the reaction underwent smoothly under the irradiation of light emitting diode (LED, 380–385 nm) in air with $Ir(ppy)_3$ (2 mol%) as a photocatalyst and 1,2-dichloroethane (DCE) as a solvent for 12 h, the desired product **3a** was obtained in 22% yield (Table 1, entry 1). As shown in Table 1, an investigation of photocatalysts (PCs), including $Ir(ppy)_3$, Mes-Acr$^+$ClO$_4^-$, 4CzIPN, TPPT (2,4,6-triphenylpyrylium tetrafluoroborate), $Ru(bpy)_3(PF_6)_2$, $Ru(bpy)_3Cl_2$, rose bengal, eosin Y, $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$, and the selected LED source matching them in their maximum absorption ranges, respectively. For example, blue LEDs used for $Ru(bpy)_3(PF_6)_2$, $Ru(phen)_3Cl_2$, TPPT, Mes-Acr-Me$^+$ClO$_4^-$ and $Ru(bpy)_3Cl_2$; while green LED used for eosin Y and UV LED used for $Ir(ppy)_3$ [12], demonstrated that $Ru(bpy)_3Cl_2$ and blue LED irradiation was the most effective ones (entries 1–10). Meanwhile, blue LED (440–445 nm) was selected for the irradiation source for its highest yield of the desired product among the selected blue LEDs (450–455 nm, 435–440 nm, and 440–445 nm) (entry 7 *vs.* 11 *vs.* 12). Thereafter, the different solvents such as acetone, MeCN, hexane, EtOAc and dichloromethane (DCM) were examined, indicating that DCE as a solvent is the best of choice (entries 13–17). Moreover, increasing the molar ratio of **2**/**1a** could improve the yield of cyclization product **3a** (entry 18 *vs.* 12). Further investigation of the reaction time indicated that moderate to good yields of the product **3a** were obtained as the reactions were prolonged to 24–48 h, respectively (entries 19–21). In the absence

Table 1
Optimization of the reaction conditions.[a]

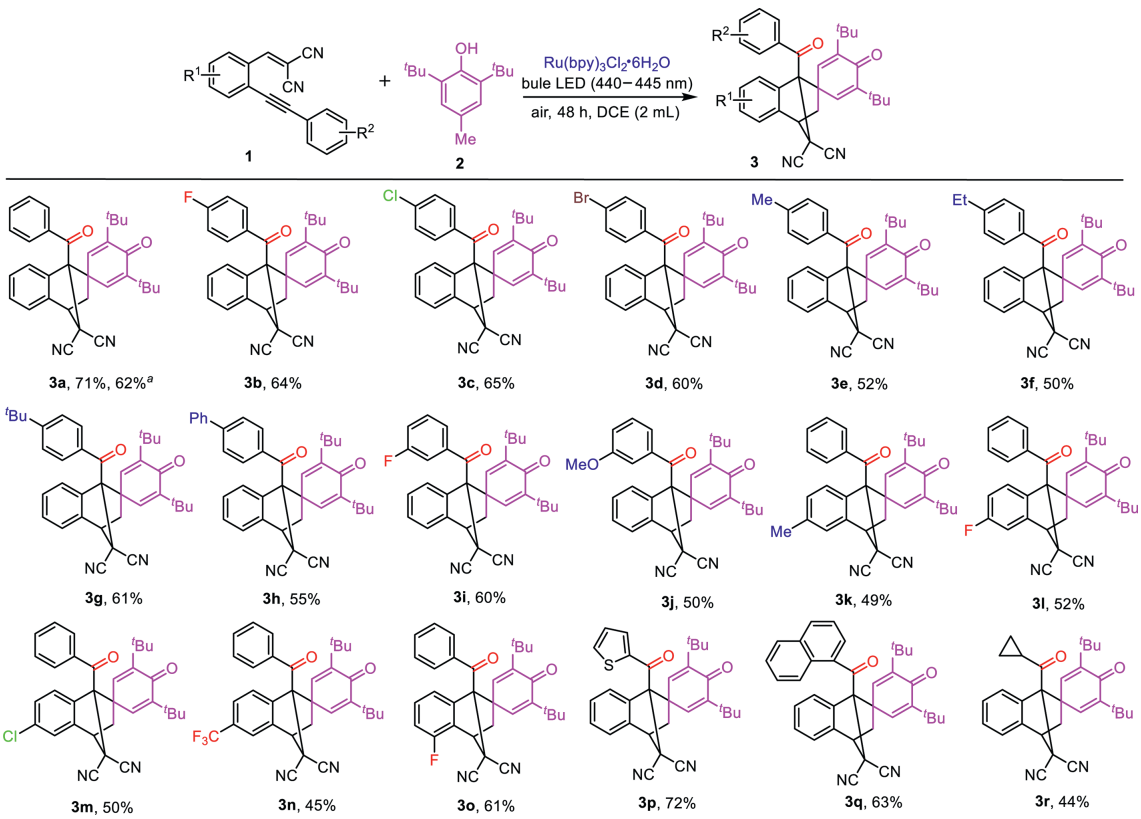


Entry	**2** (equiv.)	Photocatalyst	LEDs (nm)	Solvent	Yield (%)[b]
1	2.0	$Ir(ppy)_3$	380–385	DCE	20
2	2.0	Mes-Acr$^+$ClO$_4^-$	420–425	DCE	19
3	2.0	TPPT	410–415	DCE	<10
4	2.0	$Ru(bpy)_3(PF_6)_2$	450–455	DCE	23
5	2.0	$Ru(phen)_3Cl_2$	415–420	DCE	28
6	2.0	$Ru(bpy)_3Cl_2$	450–455	DCE	33
7	2.0	Rose Bengal	530–535	DCE	0
8	2.0	Eosin Y	530–535	DCE	0
9	2.0	4CzIPN	450–455	DCE	29
10	2.0	$Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$	450–455	DCE	22
11	2.0	$Ru(bpy)_3Cl_2$	435–440	DCE	36
12	2.0	$Ru(bpy)_3Cl_2$	440–445	DCE	39
13	2.0	$Ru(bpy)_3Cl_2$	440–445	Acetone	30
14	2.0	$Ru(bpy)_3Cl_2$	440–445	MeCN	28
15	2.0	$Ru(bpy)_3Cl_2$	440–445	DCM	25
16	2.0	$Ru(bpy)_3Cl_2$	440–445	EtOAc	<10
17	2.0	$Ru(bpy)_3Cl_2$	440–445	Hexane	0
18	3.0	$Ru(bpy)_3Cl_2$	440–445	DCE	46
19	3.0	$Ru(bpy)_3Cl_2$	440–445	DCE	51[c]
20	3.0	$Ru(bpy)_3Cl_2$	440–445	DCE	63[d]
21	3.0	$Ru(bpy)_3Cl_2$	440–445	DCE	71[e]
22	3.0	$Ru(bpy)_3Cl_2$	–	DCE	0
23	3.0	–	440–445	DCE	0
24	3.0	$Ru(bpy)_3Cl_2$	440–445	DCE	Trace[f]

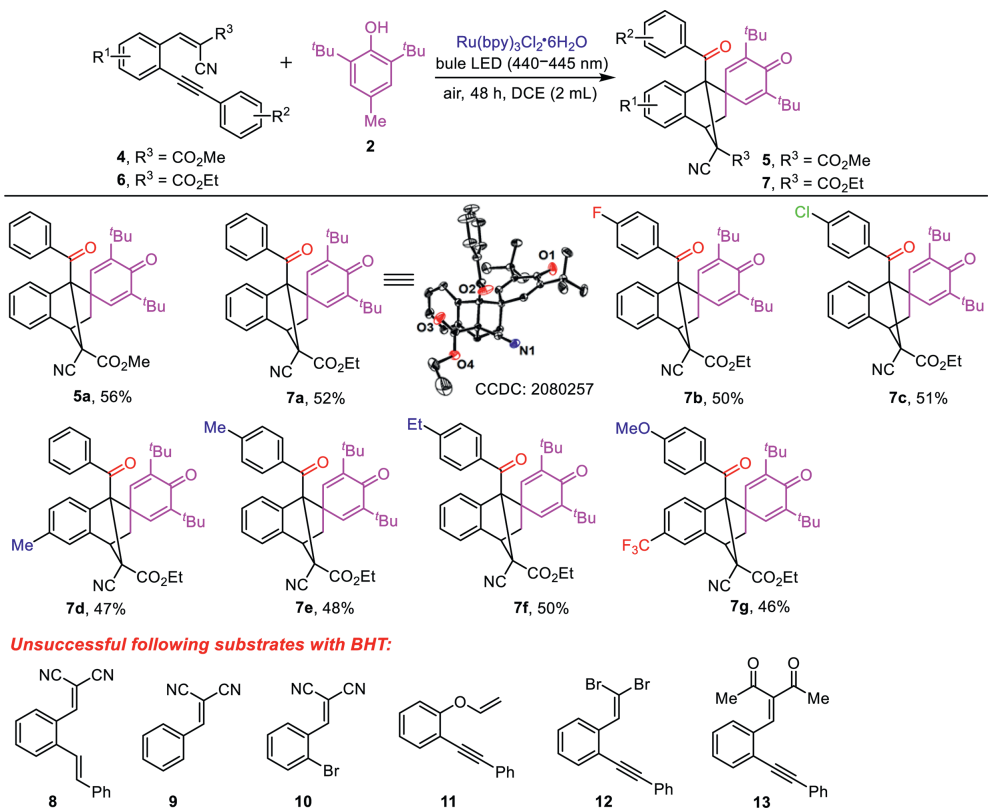
[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.40~0.60 mmol), photocatalyst (5.0 mol%), solvent (2.0 mL), room temperature, air atmosphere, under LED irradiation for 12 h.
[b] Isolated yield.
[c] For 24 h.
[d] For 36 h.
[e] For 48 h.
[f] Under nitrogen atmosphere.

of light irradiation or photocatalyst, no any product was observed (entries 22 and 23). It is worth noting that only trace amount of the desired product **3a** was detected observed when the reaction was performed in nitrogen atmosphere, (entry 24). Finally, the optimal reaction conditions are consist of 1.0 equiv. of **1a**, 3.0 equivalents of **2**, and 5 mol% of $Ru(bpy)_3Cl_2$ dissolved in DCE and irradiated with a blue LED (450–455 nm) for 48 h.

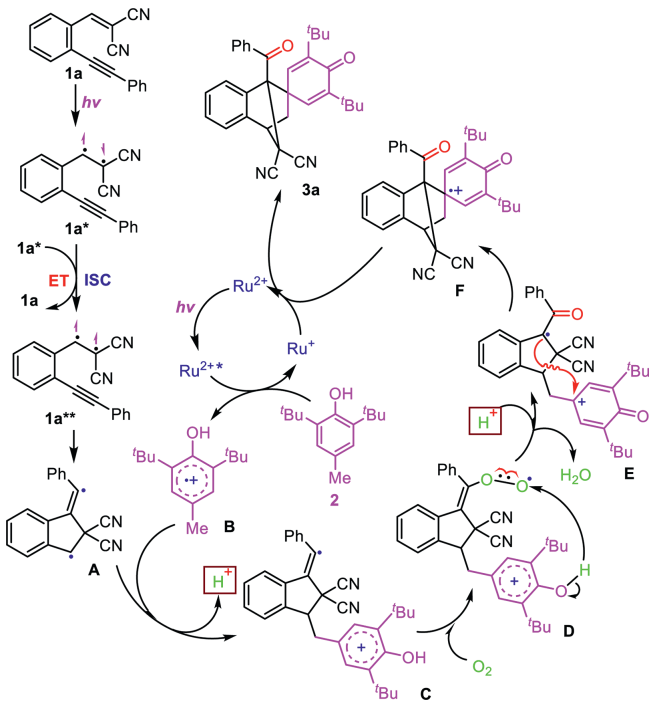
After learning the optimal conditions of the reaction, we investigated the universality of this transformation. First, a variety of 2-(2-(arylethynyl)benzylidene)malononitriles (**1**), derived from *ortho*-arylethynyl arylaldehydes and malononitrile, reacted with BHT (**2**) smoothly to generate the corresponding products **3a**–**3r** in moderate to good yields, as shown in Scheme 2. 2-(2-(Arylethynyl)benzylidene)malononitriles (**1**) with an electron-withdrawing group (R^2 = F, Cl, Br) or an electron-donating group (R^2 = Me, Et, ^{t}Bu) at the *para*-position of the benzene rings provided the desired products (**3b**–**3g**) in 50%–65% yields. It should be noted that 2-(2-(phenylethynyl)benzylidene)malononitrile (**1a**) and 2-(2-((*p*-phenyl)phenylethynyl)benzylidene)malononitrile (**1h**) produced the corresponding products **3a** and **3h** in 71% and 55% yields, respectively. When a substituent (R^2 = F, or MeO) was placed at the *meta*-position of the phenyl rings, the reaction produced 60% yield of **3i**, and 50% yield of **3j**. Subsequently, the scope of the substituted group (R^1) on substrates **1** was also examined (Scheme 2). The electron-rich group (R^1 = Me) or electron-poor group (R^1 = F, Cl, F_3C) on the aromatic rings delivered the corresponding products (**3k**–**3o**) in 45%–61% yields, neglecting the steric hindrance effect (**3o**). In addition, substrates



Scheme 2. The scope of substrates **1.** Reaction conditions: **1** (0.20 mmol), **2** (0.60 mmol), $Ru(bpy)_3Cl_2$ (5.0 mol%), DCE (2.0 mL), room temperature, air atmosphere, under blue LED (440–445 nm) irradiation for 48 h; isolated yield of the product; [a]isolated yield of **3a** in 2.0 mmol scale.



Scheme 3. The scope of substrates **4** and **6**. Reaction conditions: **4** or **6** (0.20 mmol), **2** (0.60 mmol), $Ru(bpy)_3Cl_2$ (5.0 mol%), DCE (2.0 mL), room temperature, air atmosphere, under blue LED (440–445 nm) irradiation for 48 h; isolated yield of the product.



Scheme 4. The proposed mechanism.

containing naphthyl (**1p**) or thiophenyl group (**1q**) reacted with **2** to produce the anticipated products **3p** and **3q** in 72%, and 63% yields, respectively. Remarkably, substrate derived from *ortho*-(cyclopropyl)ethynylbenzaldehyde (**1r**) was also well tolerated in this transformation, and the desired product (**3r**) was obtained in 44% yield. Furthermore, this visible-light-induced intermolecular cyclization of **1a** with **2** was scaled up to 2.0 mmol for practical applications, generating **3a** in 62% yield.

Eventually, the scope of substrates (**4** and **6**), which derived from *ortho*-(arylethynyl)arylaldehydes with methyl 2-cyanoacetate and ethyl 2-cyanoacetate was investigated, the results are illustrated in Scheme 3. Substrate **4a** and a variety of substrates **6**, including **6a–6g** reacted with BHT (**2**) to provide the corresponding products **5a** and **7a–7g** in 46%–56% yields. It is important to note that the structure of obtained product **7a** was confirmed by X-ray crystal diffraction analysis (see Supporting information for detail). The influence of the substituents (R^1 = Me, F_3C) from the arylaldehydes, and the substituents (R^2 = F, Cl, Me, Et, MeO) in the aromatic alkyne units, on the reaction indicated that they are well tolerated.

However, the following substrates (*E*)-2-(2-styrylbenzylidene)malononitrile (**8**), 2-benzylidenemalononitrile (**9**), 2-(2-bromobenzylidene)malononitrile (**10**), 1-(phenylethynyl)-2-(vinyloxy)benzene (**11**), 1-(2,2-dibromovinyl)-2-(phenylethynyl) benzene (**12**) and 3-(2-(phenylethynyl)benzylidene)pentane-2,4-dione (**13**) reacted with **2** (Scheme 3), and the substrates including phenol, *p*-cresol, *p*-benzenediol, 2,6-dimethyl-*p*-benzenediol, 2,4-dimethylphenol, 2,4,6-trimethylphenol, 2,6-di-*tert*-butyl-4-ethylphenol, 6-*tert*-butyl-2,4-xylenol and naphthalen-1-ol reacted with **1a** under the standard conditions, but failed.

On the basis of the above results and related reports [47,48], a plausible mechanism is proposed in Scheme 4. First, **1a** is excited by blue LED irradiation to generate its excited singlet species **1a***, which decays to its triplet exciplex **1a**** through an intersystem crossing (ISC) process with formed another **1a*** along with the formation of **1a** *via* an energy transfer (ET). The formed **1a**** undergoes an intramolecular radical addition to afford a five-membered ring diradical intermediate **A**, which is trapped by BHT and confirmed by HRMS analysis (see Supporting information for detail). On the other hand, $[Ru(bpy)_3]^{2+}$ is excited by the blue LED irradiation to its excited state $[Ru(bpy)_3]^{2+*}$, which then undergoes a single-electron transfer (SET) process with BHT (**2**) to afford a radical cation intermediate **B** and a $[Ru(bpy)_3]^{+}$. Then, a reaction of intermediates **A** and **B** generates intermediate **C**, which is oxidized by oxygen in the air to give intermediate **E** *via* an intermediate **D**. Finally, the obtained **E** undergoes an intermolecular cyclization to afford intermediate **F**, which is followed by an SET reduction with $[Ru(bpy)_3]^{+}$ to provide the desired product **3a** along with the formation of $[Ru(bpy)_3]^{2+}$ for the catalytic cycle. To support the reaction mechanism, the ultraviolet-visible spectra of **1a** indicated that it has stronger absorption around 430 nm and acts as a photosensitizer (Fig. S1 in Supporting information). In addition, the key intermediate **A** was captured BHT and its corresponding adduct was detected by high-resolution mass spectrum (HRMS) analysis (Fig. S2 in Supporting information).

In conclusion, we have developed a novel radical cyclization strategy to access bridged spirocyclic compounds from 2-(2-(arylethynyl)benzylidene)malononitriles and their derivatives with 2,6-di(*tert*-butyl)-4-methylphenol (BHT) under the irradiation of visible light (blue LED with 440–445 nm). The reactions generated the corresponding products in good yields under mild conditions. Further investigations on the detailed mechanism and the applications of this transformation are currently underway in our laboratory.

Declaration of competing interest

The authors declare that they have no financial and personal relationships with other people or organizations that can inappropriately influence their work. There is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.03.084.

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