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Metal-free cascade radical cyclization of 1,6-enynes with aldehydes†

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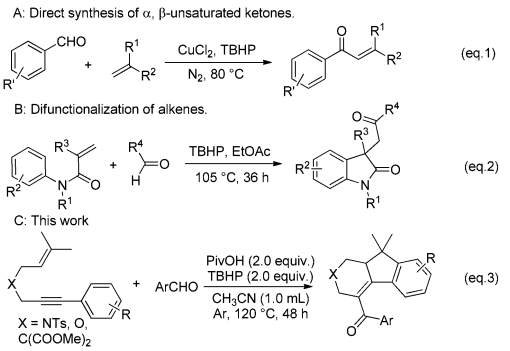
A new and efficient metal-free cascade cyclization of 1,6-enynes with aldehydes is developed for the synthesis of tricyclic fluorene derivatives. The reaction involves a radical process and one C(sp^2)–C(sp^2) and two C(sp^2)–C(sp^3) bonds are formed simultaneously in one pot by using PivOH and TBHP.

In the realm of polycyclic compounds synthesis, cascade cyclization of enynes has evolved as a highly efficient strategy to achieve the synthesis of natural products and pharmaceutical molecules.[1,2] In particular, transition-metal-catalyzed cyclization of 1,6-enynes offers unprecedented efficiency, higher atom-economy and more operational simplicity in the synthesis of versatile polycyclic compounds.[2] Despite these achievements, scalable synthesis has been hampered by using eco-unfriendly, noble metal catalysts or expensive reagents. Further, it is also problematic to separate the metal contaminants from products. As such, a more sustainable and practical approach is highly desirable towards the cyclization of 1,6-enynes.

Radical-mediated reactions have motivated tremendous interest due to their simple operation and high efficiency.[3] Among them, free-radical carbonylation involving an aldehyde C(sp^2)–H bond with other bonds to form a new carbon–carbon bond has also received extensive attention and some progress has been made.[4] Recently, Lei and co-workers have developed an efficient copper-catalyzed oxidative coupling of alkenes with aldehydes leading to the formation of α,β-unsaturated ketones (Scheme 1, eqn (1)).[4h] Later on, Li and his group reported a metal-free oxidative tandem coupling of activated alkenes with carbonyl C(sp^2)–H bonds and aryl C(sp^2)–H bonds (Scheme 1, eqn (2)).[4i] On the basis of our study towards radical and enyne cyclizations,[5] we wish that the addition of aldehyde C–H bonds to 1,6-enynes could be carried out to form tricyclic fluorene compounds, which have played important roles in a wide range of fields, including OFET (organic field-effect transistors), OPV (organic photovoltaic cells), organic synthesis, *etc.*[6] Herein, we disclose a metal-free TBHP–mediated cascade radical cyclization of 1,6-enynes with aldehydes for the construction of fluorene derivatives (Scheme 1, eqn (3)).



Scheme 1 Existing free-radical carbonylation methods and a summary of the present study.

We chose 1,6-enyne **1a** (0.2 mmol) and benzaldehyde **2a** (1.0 mmol) as our model substrates to investigate the reaction conditions, and the results are summarized in Table 1. At first, the reaction was carried out in the presence of 2.0 equivalents of *tert*-butylhydroperoxide (TBHP, 70% aqueous solution) at 120 °C under argon in CH_3CN for 48 h. To our delight, the desired product dimethyl 4-benzoyl-9,9-dimethyl-9,9*a*-dihydro-1*H*-fluorene-2,2(3*H*)-dicarboxylate **3a** was isolated in 42% yield (Table 1, entry 1). Some other oxidants proved to be less effective compared with TBHP (70% aqueous solution) (Table 1, entries 1–3). Several additives were also tested (Table 1, entries 4–7), and PivOH provided the highest yield in 67% (Table 1, entry 4), because it could promote the reaction to proceed smoothly and inhibit the side reactions.[3j] Other solvents, such as DCE, and EtOAc, were applied instead of CH_3CN, but no better results were obtained (Table 1, entries 8 and 9). The control experiment proved that the oxidant was essential in facilitating the reaction (Table 1, entry 10). The temperature, additive and oxidant loadings were key factors in terms of the reaction yield (Table 1,

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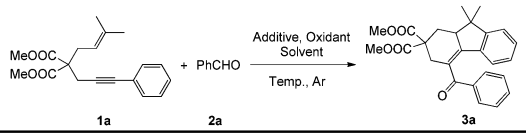
Table 1 Optimization of the reaction conditions[a]



Entry	[O]	[Add.][b]	Solvent	Yield[c]
1	TBHP	—	CH_3CN	42
2[d]	TBHP	—	CH_3CN	37
3	DTBP	—	CH_3CN	16
4	**TBHP**	**PivOH**	**CH_3CN**	**67**
5	TBHP	TFA	CH_3CN	35
6	TBHP	HOAc	CH_3CN	23
7	TBHP	Caproic acid	CH_3CN	40
8	TBHP	PivOH	DCE	43
9	TBHP	PivOH	EtOAc	45
10	—	PivOH	CH_3CN	N.R.[e]
11[f]	TBHP	PivOH	CH_3CN	48
12[g]	TBHP	PivOH	CH_3CN	38
13[h]	TBHP	PivOH	CH_3CN	51

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mmol, 5.0 equiv.), TBHP (0.4 mmol, 2.0 equiv., 70% aqueous solution), catalysts (5.0 mol%), 120 °C, 48 h, under argon, unless otherwise noted. [b] Additives (0.4 mml, 2.0 equiv.). [c] Isolated yield. [d] TBHP (5–6 M in decane). [e] N.R. = no reaction. [f] TBHP (0.3 mmol, 1.5 equiv.). [g] Under 100 °C. [h] PivOH (1.0 equiv.).

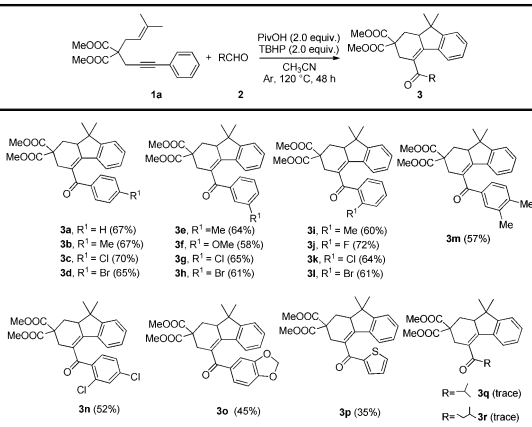
entries 11–13). Therefore, the optimized reaction conditions were affirmed as follows: PivOH (2.0 equiv.) and TBHP (2.0 equiv.) at 120 °C under argon in CH_3CN for 48 h (Table 1, entry 4).

Under the optimized reaction conditions (Table 1, entry 4), we examined the scope of aldehydes in the cascade oxidative cyclization reactions. As summarized in Table 2, various aromatic and heteroaromatic aldehydes were able to participate in this reaction to afford the desired fluorene derivatives (Table 2, **3a–p**), while only a trace amount of the product of aliphatic aldehydes (Table 2, **3q–r**) was obtained. Both electron-donating and electron-withdrawing groups on the aromatic ring were well suited (Table 2, **3a–n**). Specifically, the halogen substituents were tolerated under the PivOH-promoted reaction conditions (Table 2, **3c–3d**, **3g–3h**, **3j–3l**, and **3n**), which provided the possibility for further functionalization in the transition metal-catalyzed coupling reaction. Meanwhile, the structure of compound **3n** was confirmed by X-ray diffraction analysis (see ESI†). Interestingly, the benzo[*d*][1,3]dioxole-5-carbaldehyde (**2o**) could also undergo the reaction, giving product **3o** in 45% yield. Notably, the 2-thenaldehyde (**2p**) was a partner as well in this cascade reaction, although the final outcome is not ideal (Table 2, **3p**).

Encouraged by these promising results, we further applied the optimized reaction conditions to examine the substrate scope of 1,6-enynes. In most cases, 1,6-enynes proceeded smoothly to give the desired products **4a–n** in moderate to good yields (Table 3). However, only a trace amount of the desired product (9,9-dimethyl-1,3,9,9*a*-tetrahydroindeno[2,1-*c*]pyran-4-yl)(phenyl)methanone (**4o**) was detected because of the rapid decomposition of ether under the standard conditions. A variety of 1,6-enynes substituted at the *ortho, meta* or *para* position with electron-donating alkyl or alkoxy groups were viable in the reaction (Table 3, **4a–4b** and **4h–4i**). Upon using substrates with methyl-substituents at the *meta* position of the aryl ring of the 1,6-enynes, a mixture of two regioisomers was isolated (Table 3, **4h** and **4h′**). The presence of either halogen or electron-withdrawing groups also proved to be compatible with the reaction conditions (Table 3, **4c–4f** and **4j**). Moreover, it is noteworthy that some functional groups were also successfully applied in this transformation (Table 3, **4g** and **4k–n**). Interestingly, the tosylamide could react smoothly with **2a**, albeit in a somewhat low yield (Table 3, **4m–n**).

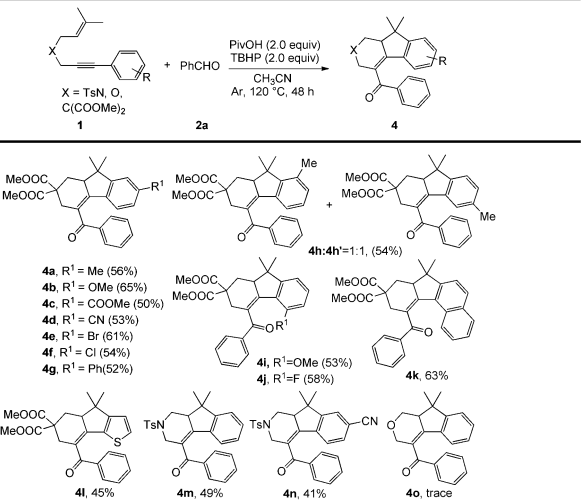
To gain a better understanding of the mechanism, some control experiments were carried out. Initially, the intramolecular and intermolecular kinetic isotope effect (KIE) experiments were performed under the standard reaction conditions. No kinetic isotope effect (k_H/k_D = 1.0, Scheme 2, eqn (1) and (2)) was observed, which suggests that the reaction proceeds *via* a free radical process or SEAR routing which was similar to the previous reports.[7] Furthermore, when 4.0 equivalents of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) was added into the reaction system, no reaction was observed (see ESI†),

Table 2 Synthesis of fluorenes from various aldehydes **2** with 1,6-enyne **1a**[a]



[a] All the reactions were carried out with **1** (0.2 mmol, 1.0 equiv.), **2a** (1.0 mmol, 5.0 equiv.), TBHP (0.4 mmol, 70% aqueous solution, 2.0 equiv.), PivOH (0.4 mmol, 2.0 equiv.), and CH_3CN (1 mL), at 120 °C, for 48 h, under argon, all the yields refer to isolated products after chromatography on silica gel.

Table 3 Synthesis of fluorenes from various 1,6-enynes **1** with benzaldehyde **2a**[a]



[a] All the reactions were carried out with **1** (0.2 mmol, 1.0 equiv.), **2a** (1.0 mmol, 5.0 equiv.), TBHP (0.4 mmol, 70% aqueous solution, 2.0 equiv.), PivOH (0.4 mmol, 2.0 equiv.), and CH_3CN (1 mL), at 120 °C, for 48 h, under argon, all the yields refer to isolated products after chromatography on silica gel.

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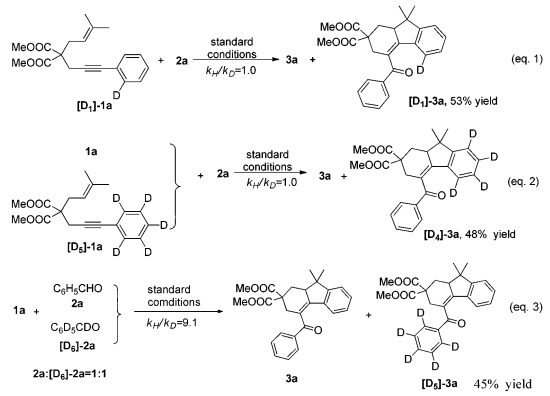
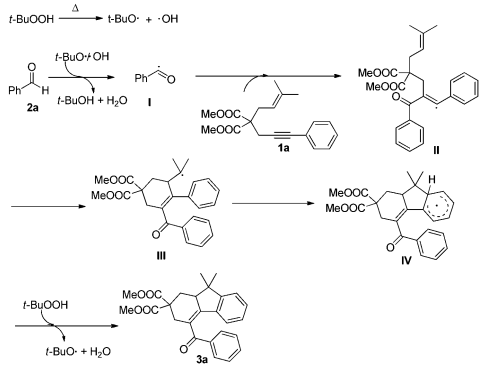


Scheme 2 Control experiments.



Scheme 3 Proposed mechanism.

which clearly indicated that the reaction was involved in a radical substitution process. A large KIE (k_H/k_D = 9.1) for the reaction involving a 1 : 1 mixture of aldehyde and [D_6]-aldehyde was obtained (Scheme 2, eqn (3)), implying that the cleavage of the carbonyl C–H bond is the rate-determining step.

A possible mechanism is proposed on the basis of the results described above and previous work in this field (Scheme 3).[4h,i,8] Firstly, alkyloxy and hydroxy radicals are generated from TBHP under heating conditions. Subsequently, the alkyloxy and/or hydroxy radicals capture a hydrogen atom from aldehyde **2a** to produce acyl radical **I**, and then acyl radical **I** attacks the carbon–carbon triple bond of enyne **1a** to afford radical intermediate **II**. Tertiary carbon radical **III** was generated successively through an intramolecular cyclization. Again, intramolecular cyclization of intermediate **III** with an aryl ring gives rise to radical intermediate **IV**. Finally, the direct oxidation by TBHP and deprotonation of radical intermediate **IV** takes place to furnish the product **3a.**

In summary, we have described a metal-free cascade radical cyclization of 1,6-enynes with aldehydes for the synthesis of functionalized fluorene derivatives in one pot. Another notable feature of the developed process is cascade-type formation of one C(sp^2)–C(sp^2) and two C(sp^2)–C(sp^3) bonds by using PivOH and TBHP, which is significant in organic synthesis. Further investigations on the detailed mechanisms and applications of this methodology are in progress in our laboratory.

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