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Intermolecular oxidative decarbonylative [2 + 2 + 2] carbocyclization of *N*-(2-ethynylaryl)acrylamides with tertiary and secondary alkyl aldehydes involving C(sp³)–H functionalization[†]

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A new metal-free oxidative decarbonylative [2 + 2 + 2] carbocyclization of *N*-(2-ethynylaryl)acrylamides with tertiary and secondary alkyl aldehydes is described. This reaction enables the formation of three new C-C bonds in a single reaction by a sequence of oxidative decarbonylation, radical addition across C-C unsaturated bonds, C-H functionalization and annulation, and represents the first oxidative decarbonylative [2 + 2 + 2] carbocyclization approach using tertiary and secondary alkyl aldehydes as a two carbon unit for assembling six-membered carbocycle-fused polycycles.

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Introduction

High-order carbocyclization reactions represent one of the most powerful methods for building complex carbocyclic frameworks. In this field, one particularly fascinating area is the intermolecular [2 + 2 + m] carbocyclization of 1,*n*-enynes, which continues to gain much attention due to its straightforward and highly atom-economic features.¹⁻⁴ Significant achievements include the [2 + 2 + 2] carbocyclization strategy which can allow the formation of a six-membered carbocycle within a complex polycyclic system by introducing a two-carbon unit across 1.nenynes.^{2,3} Despite these advances, there are still limitations with the available transformations, such as the requirement for noble metal catalysts and narrow two-carbon unit scope (e.g., alkynes,^{3*a-e*} alkenes^{3*h-m*} and arylsulfonyl chlorides^{3*n*}). Therefore, it would be welcomed to develop more efficient methods, especially metal-free use of new two-carbon unit strategies, to achieve the [2 + 2 + 2] carbocyclization of 1,*n*-enynes, which unfortunately remains a great challenge.

The decarbonylation reaction has proven among the most important methods for the formation of diverse chemical bonds in synthesis, the majority of which focus on the cleavage of C-CHO bonds by extrusion of carbon monoxide (CO) gas and

^bKey Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China then transformation through radical⁵ and anionic intermediates.6,7 Such successful transformations include transition metal-catalyzed Pauson-Khand-type reactions of 1,n-enynes using aldehydes as the carbon monoxide (CO) source (Scheme 1a).⁷ To our knowledge, however, approaches for carbocyclization of 1,n-enynes with aldehydes as the "R" source have never been reported.5g Intrigued by these results, we envisioned that extension of the decarbonylation concept to the combination of N-(2-ethynylaryl)acrylamides and alkyl aldehydes would offer a novel method to assemble six-membered carbocycle-fused polycyclic architectures. Herein, we report a novel oxidative radical decarbonylative [2 + 2 + 2] carbocyclization of N-(2ethynylaryl)acrylamides with tertiary and secondary alkyl aldehydes that can be achieved under metal-free conditions through a sequence of oxidative decarbonylation, radical addition across C-C unsaturated bonds, C-H functionalization and annulation (Scheme 1b).10 To the best of our knowledge, this method is the first metal-free radical-mediated decarbonylative $\begin{bmatrix} 2 + 2 + 2 \end{bmatrix}$ carbocyclization reaction of N-(2-ethynylaryl)acrylamides with

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Scheme 1 [2 + 2 + m] carbocyclization of 1,*n*-enynes with aldehydes.

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tertiary alkyl aldehydes as a two carbon unit, which provides selective and straightforward access to important six-membered carbocycle-fused polycyclic skeletons, including tetrahydrophenanthridin-6(5*H*)-ones, 6*H*-indeno[1,2-*c*]quinolin-6-one, 6*H*-benzo[*c*]chromen-6-one and 1*H*-fluorene.⁹ Moreover, this reaction is applicable to secondary alkyl aldehydes and the selectivity is shifted towards the decarbonylative [2 + 2 + 1] carbocyclization with *N*-(2-ethynylaryl)acrylamides.

Results and discussion

Our initial investigations focused on optimization of the decarbonylative [2 + 2 + 2] carbocyclization between N-methyl-N-(2-(phenylethynyl)phenyl)methacrylamide (1a) and pivalaldehyde (2a) (Table 1).11 When amide 1a and aldehyde 2a were subjected to tert-butyl perbenzoate (TBPB) oxidation in PhCF₃ at 100 °C for 24 h, the desired decarbonylative [2 + 2 + 2]carbocyclization product 3aa was obtained in 81% yield (entry 1). Inspired by this result, a series of other oxidants, including tert-butyl hydroperoxide (TBHP), di-tert-butyl peroxide (DTBP) and $K_2S_2O_8$, were examined (entries 2-4): they showed lower activity for the reaction than TBPB in terms of yields. A screening of the amount of TBPB revealed that 3 equiv. of TBPB was the best choice for further optimization (entries 5 and 6). We found that while a higher reaction temperature (110 °C) slightly affected the reaction (entry 7), a lower reaction temperature (90 °C) had an obviously negative effect (entry 8). Other solvents, including MeCN (entry 9), MeCONMe₂ (entry 10) and PhCl (entry 11), were found to be less effective than PhCF₃, thus giving diminished yields. Gratifyingly, the reaction could

Table 1	Screening of optimal reaction conditions ^a		
	Ph H	TBPB (3 equiv)	

		Isolated yield
Entry	Variation from the standard conditions	(%)
1	None	81
2	TBHP instead of TBPB	10
3	DTBP instead of TBPB	22
4	K ₂ S ₂ O ₈ instead of TBPB	Trace
5	TBPB (3.5 equiv.)	80
6	TBPB (2.5 equiv.)	71
7	At 110 °C	80
8	At 90 °C	62
9	MeCN instead of PhCF ₃	67
10	MeCONMe ₂ instead of PhCF ₃	20
11	PhCl instead of PhCF ₃	40
12^b	None	73

Ar. 24 h

^{*a*} Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv.), TBPB (3 equiv.), PhCF₃ (2 mL), argon, 100 °C for 24 h. TBHP (5 M in decane). Some by-products, including vinyl C–N bond-decomposition products, were observed. ^{*b*} **1a** (1 g, 3.64 mmol) and PhCF₃ (5 mL) for 48 h.

be satisfactorily performed at a 1 gram scale of amide **1a**, providing **3aa** in moderate yield (entry 12).

The scope of this decarbonylative [2 + 2 + 2] carbocyclization protocol was probed with regard to both the N-(2-ethynylaryl)acrylamide 1 and aldehyde 2 (Table 2). Gratifyingly, a variety of N-(2-ethynylaryl)acrylamides 1b-s underwent the reaction with pivalaldehyde (2a) and TBPB to afford phenanthridin-6(5H)ones 3 in moderate to good yields. We found that amides 1b-e bearing a wide range of N-substituents, such as N-Bn, N-allyl, N-Ts and even free N-H, were viable substrates to assemble 3baea in moderate yields. With respect to the alkyne moiety in N-(2ethynylaryl)acrylamides, the reaction was perfectly tolerant of various aryl substituents, namely 4-MeC₆H₄, 4-MeOC₆H₄, 4-BrC₆H₄, 4-ClC₆H₄, 4-FC₆H₄, 4-CNC₆H₄, 3-MeC₆H₄, 3-BrC₆H₄ and pyridin-3-yl groups, at the terminal alkyne, and the nature of the aryl group had no detrimental effect on the reaction (3fa-na).11 It was noted that in the case of the alkyl-substituted alkyne 10 a moderate yield of the product (30a) was still achieved. It is important to emphasize that amides 1p-r with substituents, such as Me and Cl, on the 4- or 5-position of the N-aryl moiety were smoothly converted to 3pa-ra in 70-75% yields. To our surprise, amide 1s with a phenyl group on the 2-position of the acrylamide moiety shifted the selectivity towards

Table 2 Carbocyclization of N-(2-ethynylaryl)acrylamides (1) with tertiary alkyl aldehydes (2)^{*a*}



 a Reaction conditions: 1 (0.2 mmol), 2a (2 equiv.), TBPB (3 equiv.), PhCF3 (2 mL), argon, 100 $^\circ \rm C$ for 24 h.

functionalization of the phenyl $C(sp^2)$ -H bond, not the *tert*butyl $C(sp^3)$ -H bond, thus furnishing 6*H*-indeno[1,2-*c*]quinolin-6-one **3sa** rather than the phenanthridin-6(5*H*)-one.

In the presence of amide **1a** and TBPB, tertiary alkyl aldehydes, namely 3-ethyl-3-formylpentanenitrile (**2b**) and 2,2-dimethylpent-4-enal (**2c**), were also found to be viable substrates to produce the decarbonylative [2 + 2 + 2] carbocyclization products **3ab** and **3ac**. Notably, in the case of 2,2-dimethylpent-4-enal (**2c**) the functionalization of the more active allyl C(sp³)-H bond takes precedence over the methyl C(sp³)-H bond: 2,2-dimethylpent-4-enal (**2c**) successfully underwent the reaction with *N*-(2-ethynylaryl)acrylamides **1f**, **1k** and **1t**, affording **3fc**, **3kc** and **3tc** in moderate to good yields with high diastereoselectivity.

As shown in Scheme 2, the decarbonylative [2 + 2 + 2] carbocyclization protocol also allowed the formation of useful 6*H*-benzo[*c*]chromen-6-one **3ua** (eqn (1)) and 1*H*-fluorenes **3va** and **3vc** (eqn (2)) from the corresponding 2-(phenylethynyl)phenyl methacrylate (**1u**) and methyl 2-(2-(phenylethynyl)benzyl)acrylate (**1v**), but a linear enyne, 4-methyl-*N*-(2-methylallyl)-*N*-(3-phenylprop-2-yn-1-yl)-benzenesulfonamide (**1w**), was not a suitable substrate.

We found that secondary alkyl aldehydes **2d–f** were viable substrates to perform the decarbonylative carbocyclization reaction, but the selectivity was shifted towards the functionalization of the $C(sp^3)$ –H bond adjacent to the aldehyde group, resulting in the construction of five-membered carbocycle-fused polycyclic skeletons (eqn (3)). For example, isobutyraldehyde (**2d**) underwent the decarbonylative [2 + 2 + 1] carbocyclization reaction to afford 4*H*-cyclopenta[*c*]quinolin-4-one **4ad** in 60% yield. Using cyclopentanecarbaldehyde (**2e**) or cyclohexanecarbaldehyde (**2f**)



Scheme 2 Variation of other 1,*n*-enynes and secondary alkyl aldehydes.



Scheme 3 Control experiments and possible reaction mechanism.

also delivered the decarbonylative [2 + 2 + 1] carbocyclization products **4ae** and **4af** with a spirocyclic scaffold. Unfortunately, cyclopropane aldehyde (**2g**) was not a suitable aldehyde. Attempts to carbocyclize primary alkyl aldehydes, such as butyraldehyde (**2h**) and caprylic aldehyde (**2i**), failed to give the desired products. but instead provided the CO-inserted Pauson–Khand-type product, 3*a*,5-dimethyl-1-phenyl-3,3*a*-dihydro-2*H*-cyclopenta[*c*] quinoline-2,4(5*H*)-dione (**5**), in 57% and 8% yields, respectively (eqn (4)).⁷

To understand the mechanism, the control reaction of amide 1a with aldehyde 2a and TBPB was completely suppressed by a stoichiometric amount of radical inhibitors, including TEMPO, hydroquinone and BHT. Moreover, aldehyde 2a was converted into 1-(tert-butoxy)-2,2,6,6-tetramethylpiperidine (6) by reacting with TEMPO (eqn (5) in Scheme 3). These results implied that the decarbonylative [2 +2 + 2] carbocyclization protocol involves a radical process. Therefore, the mechanism of this reaction is presented in Scheme 3.4,5,8,10 Aldehyde 2a is converted into alkyl radical A via oxidative decarbonylation with the aid of TBPB.5 Addition of the alkyl radical A across the C-C double bond in amide 1a affords new alkyl radical intermediate B, followed by cyclization to produce unstable vinyl radical intermediate C.4,10 The intermediate C readily undergoes a 1,6-H shift followed by annulation to form intermediate E.8 Oxidation of intermediate E by TBPB affords the cationic intermediate F.^{4,5,8} Finally, deprotonation of intermediate F results in the formation of the product 3aa.

Conclusions

In summary, we have developed the first oxidative decarbonylative [2 + 2 + m] annulation reaction of 1,*n*-enynes with tertiary and secondary alkyl aldehydes as a two-carbon unit source for the synthesis of diverse six-membered carbocycle-fused polycycles under metal-free conditions. This method proceeds through a sequence of oxidative decarbonylation, 1,6-H shift and annulation, and allows the one-step formation of three new C–C bonds with broad substrate scope and excellent functional group tolerance. Moreover, this method is applicable to secondary alkyl aldehydes leading to five-membered carbocyclic-ring-fused polycycles. Further studies will focus on the development of enantioselective aspects and other 1,*n*-enyne oxidative radical annulation reactions.

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