JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00461 • Publication Date (Web): 13 May 2019

ACS Publications

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Palladium-Catalyzed Cascade Intramolecular Cyclization and Allylation of Enynoates with Allylic Alcohols

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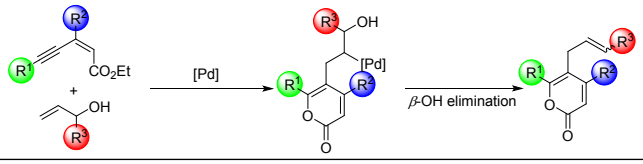
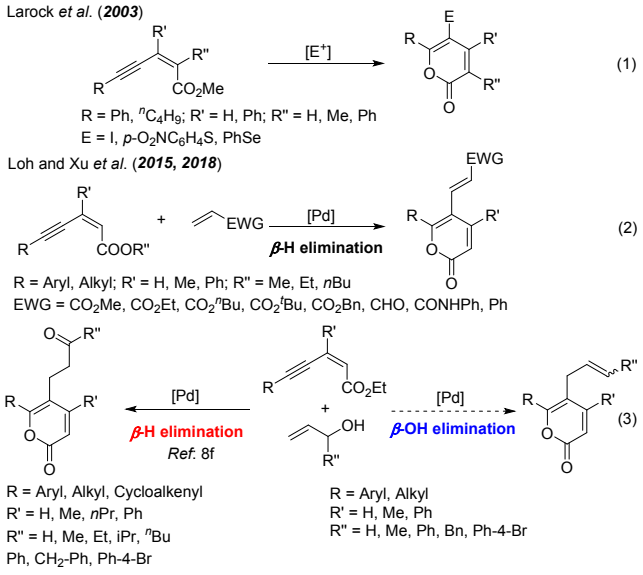
Supporting Information

ABSTRACT: A Pd(II)-catalyzed mild and highly regioselective 6-*endo* cyclization/allylation reactions of enynoates with simple allylic alcohols has been developed. Under mild reaction conditions, the vinyl palladium species generated in situ after cyclization could insert C-C double bond of allylic alcohol through cross-coupling reaction and lead to the formation of allyl pyrone via *β*-OH elimination. This cascade cross coupling reaction represents a direct and atom economic methodology for the construction of novel allyl pyrones in moderate to good yields.



INTRODUCTION

Pyrone is one of the significant structural subunit in numerous bioactive natural products and pharmaceutically relevant compounds.[1] They are also prevalent building blocks in some total synthetic routes.[2] Consequently, forerunners have made a lot of attempts to prepare compounds containing pyrone as a core moiety.[3] However, regardless of prior approaches, more efficient and convenient synthesis was still desirable for functionalized pyrones.[4] Therefore, for the cyclization reactions of enynoates, several strategies have been developed by Burton[5], Larock[6], Rossi[7] et al. by using different electrophiles during the past few decades. There are still some unresolved problems such as chemoselectivity between 6-*endo* and 5-*exo* products and limited scope of substrates have remained challenging. At the same time, transition-metal-catalyzed cyclization reactions of enynoates to achieve pyrones have been studied, as an effective route to prepare the multi-substituted pyrones.[8] Owing to the limitation of conventional approaches and organometallic methods, very recently our group and other researchers reported the palladium-catalyzed intramolecular alkyne addition reactions through an oxygen atom of an enynoate or enynoic acid.[9] Although remarkable progress in this field has been made, but still, it is challenging to develop highly efficient catalytic system for the synthesis of diversely functionalized pyrones.[10] Moreover, in the aforementioned examples, the coupling partners in cascade reactions were limited to electron-deficient olefins and styrene analogous. In last few decades, allylic alcohol was reported as an allyl provider to attach directly with interval dienes.[11] Allylic alcohols have many advantages like abundant in nature, easy to prepare and environmentally friendly. Fortunately, there are already some methods to control the allylic alcohol as an allyl provider or an alkyl reagent with the *β*-elimination step.[12]



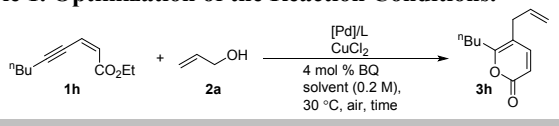
Scheme 1. Palladium-catalyzed cyclization reactions to synthesize pyrones.

RESULTS AND DISCUSSION

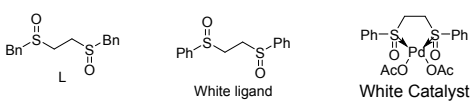
In this work, we achieved our goal by using palladium catalyzed tandem cyclization and cross-coupling reaction of enynoates with allylic alcohols (Scheme 1). A model substrate (*Z*)-enynoate **1h** and allylic alcohol **2a** was used for reaction parameters optimization (Table 1). From the earlier work in our group, we found that such type of tandem reaction was efficiently catalyzed by Pd(II) salts. The anion species also plays an important role in elimination step. Moreover, carbon-carbon triple bond could be well activated with Lewis acid. Thus, we first tried palladium chloride along with 1,2-bis(benzylsulfinyl)ethane as a ligand.[13] Only trace desire

product observed after stirring for 24 hours with 59 % starting material recovered (Table 1, entry 1). Anhydrous copper chloride was tested as a Lewis acid, which could access to easy hydroxyl elimination and increased the yield of product up to 41 % (Table 1, entry 2). After employing these reaction conditions, a side reaction of polymerization happened during the reaction which was speculated by the disappearance of enynoate in crude ^{1}H NMR. Therefore, 4 % addition of benzoquinone as polymerization inhibitor helps to increase the yield to 49 % (Table 1, entry 3). A higher $CuCl_2$ concentration increased the yield up to 61 % (Table 1, entry 5). When the reaction was performed under oxygen atmosphere, the yield of the product was decreased (Table 1, entry 6). The suitable ratio of ligand and palladium chloride was 1.4:1 with a 73 % isolated yield of the desired product (Table 1, entry 7). A higher ratio of ligand reduced the yield to 65 % (Table 1, entry 8). After screening various solvents, toluene is the best one for reaction (Table 1, entry 7). When the loading of palladium chloride was increased to 5 mol %, only little effect on yield was observed. With the ligand being changed to White ligand, the yield was decreased to 50 %. Only trace amount of product was obtained without copper chloride (Table 1, entry 13), and a 35 % yield of the desired product without ligand (Table 1, entry 14). These results prove that an optimized ratio of copper chloride and ligand is required for a good product yield. Attempt for many kinds of palladium salts confirms that the use of different anion in the catalyst was also important (Table 1, entry 15-18). There was no product observed and the starting material was recovered in the absence of palladium catalyst (Table 1, entry 19).

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



Entry	[Pd] (mol %)	L (mol %)	$CuCl_2$ (mol %)	solvent	time (h)	yield (%)[b]
1[d]	$PdCl_2$ (4)	4	0	toluene	24 h	trace
2[d]	$PdCl_2$ (4)	4	10	toluene	24 h	41
3	$PdCl_2$ (4)	4	10	toluene	24 h	49
4[e]	$PdCl_2$ (4)	4	10	toluene	24 h	40
5	$PdCl_2$ (4)	4	20	toluene	24 h	61
6[f]	$PdCl_2$ (4)	4	20	toluene	24 h	47
7	**$PdCl_2$ (4)**	**5.6**	**20**	**toluene**	**12 h**	**74 (73[c])**
8	$PdCl_2$ (4)	6.4	20	toluene	24 h	65
9	$PdCl_2$ (4)	5.6	20	cyclohexane	24 h	68
10	$PdCl_2$ (4)	5.6	20	DMF	12 h	0
11	**$PdCl_2$ (5)**	**7**	**20**	**toluene**	**12 h**	**73 (72[c])**
12[g]	$PdCl_2$ (5)	7	20	toluene	24 h	50
13	$PdCl_2$ (4)	4	0	toluene	24 h	trace
14	$PdCl_2$ (4)	0	10	toluene	24 h	35
15	$Pd(OAc)_2$ (10)	12	20	toluene	24 h	0
16	$Pd(MeCN)_4(BF_4)_2$ (10)	12	20	toluene	24 h	0
17	$Pd(dba)_2$ (10)	12	20	toluene	24 h	0
18	White Catalyst (5)	0	20	toluene	14 h	36
19	No [Pd]	6.4	30	toluene	24 h	N.R.

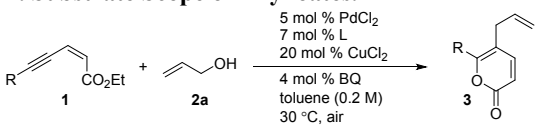


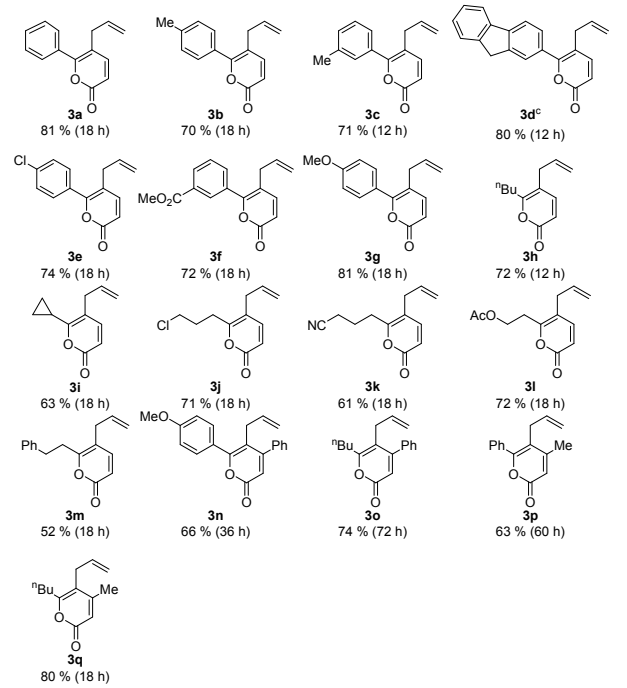
[a] Unless noted otherwise, reactions were carried out on a 0.3 mmol scale of **1h** with 3 equiv of **2a** in 1.5 mL of solvent. [b] NMR yield with 1,3,5-trimethylbenzene as internal standard. [c] Isolated yield. [d] No BQ added. [e] Nitrogen atmosphere. [f] Oxygen atmosphere. [g] White ligand used as ligand.

When we started to expand the scope of different enynoates, it was found that the standard condition was not compatible to aryl-substituted enynoates. Ethyl (*Z*)-5-phenylpent-2-en-4-ynoate gave a 60 % isolated yield only. So, the catalyst loading was adjusted to 5 % and the ligand loading was raised to 7 %. This adjustment improved the reaction universality a lot with getting an 81 % yield for ethyl (*Z*)-5-phenylpent-2-en-4-ynoate (**3a**). Therefore, this condition was then used to expand enynoate substrates scope.

Here is a generality of the cascade reaction between enynoates and allylic alcohol (Table 2). All of the substrates with a weak electron-withdrawing group or electron-donating group on the phenyl ring could give a good yield (Table 2, entries **3b**-**3g**). Also, aliphatic enynoates afford a moderate to good yield at all (Table 2, entries **3h**-**3l**). Substrates with a methyl or a phenyl group at the *β*-position of enynoates all afford the corresponding products in good to high yields (Table 2, entries **3n**-**3q**).

Table 2. Substrate Scope of Enynoates.[a,b]



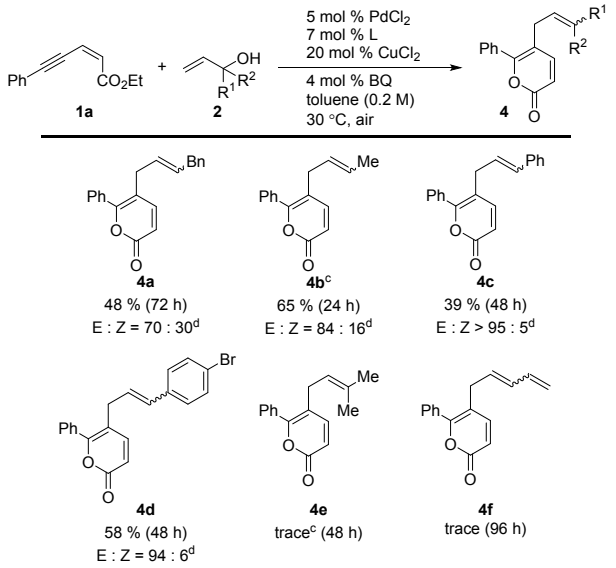


[a] Reaction conditions: The reactions were carried out under the standard conditions: **1** (0.3 mmol), **2a** (0.9 mmol, 3 equiv), palladium chloride (0.015 mmol, 0.05 equiv), 1,2-bis(benzylsulfinyl)ethane (0.021 mmol, 0.07 equiv), copper chloride (0.06 mmol, 0.2 equiv), BQ (0.012 mmol, 0.04 equiv) in 1.5mL toluene were stirred at 30 °C for corresponding hours shown in parentheses. [b] Isolated yield. [c] 5 eq. allylic alcohol was added.

Different allylic alcohols were next examined as coupling partners, which showed the steric effect was very significant (Table 3). Only 1-methylallyl alcohol could give a moderate yield of 65 %. When the methyl group was replaced by phenyl rings, the yield was decreased to 39 % (**4c**) and 58 % (**4d**) isolated yields or a benzyl group with 48 % (**4a**) isolated yield.

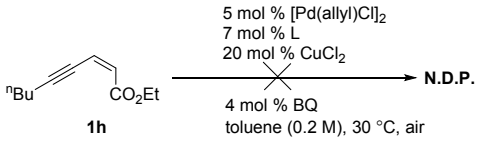
Judging from a 1D NOESY spectra of **4b**, the (*E*)-isomer was confirmed as the major composition of the isolated mixture. It was shown that the geometric selectivity was excellent for 1-aryl alcohols, but a little worse for 1-aliphatic alcohols.

Table 3. Substrate Scope of Different Allylic Alcohols.[a,b]



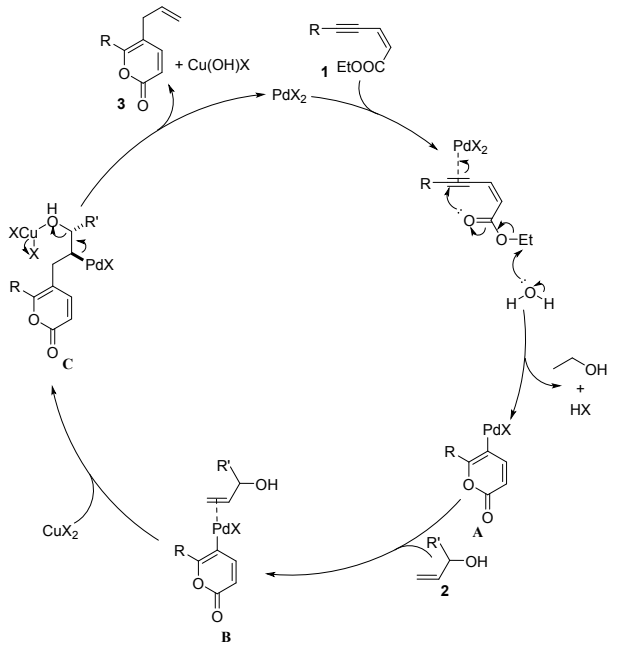
[a] Reaction conditions: The reactions were carried out under the standard conditions: **1a** (0.3 mmol), **2** (0.9 mmol, 3 equiv), palladium chloride (0.015 mmol, 0.05 equiv), 1,2-bis(benzylsulfinyl)ethane (0.021 mmol, 0.07 equiv), copper chloride (0.06 mmol, 0.2 equiv), BQ (0.012 mmol, 0.04 equiv) in 1.5 mL toluene were stirred at 30 °C for corresponding hours shown in parentheses. [b] Isolated yield. [c] 5 eq. allylic alcohol was added. [d] Isomer ratio was determined from crude NMR.

To preclude the possibility that a pi-allyl complex might be formed to start the catalytic cycle, equivalent bis(pi-allyl)dichlorodipalladium was tried as the catalyst without allylic alcohol adjunction (Scheme 2). No desire product was observed and 80 % of enynoate was recovered after 24 hours.



Scheme 2. Controlled Experiment with Bis(pi-allyl)dichlorodipalladium as Catalyst.

The proposed mechanism for the Pd(II)-catalyzed 6-*endo* cyclization and allylation of enynoates was shown in Scheme 3. First, a 6-*endo* cyclization reaction of enynoates was occurred catalyzed by Pd(II) and an active vinylpalladium species (**A**) was formed. This species easily attracts an allylic alcohol to construct species **B**. The ethyl was also removed and converted to ethanol, which was detected by crude NMR. This may prove that the ethyl departs the substrate with a substitution reaction rather than a fragmentation from one side. After an olefin insertion from the less hindered side, an alkylpalladium species(**C**) was formed followed by an *anti*-palladium *β*-hydroxyl elimination assisted with copper(II) to release the final product as a 5-allyl pyrone structure and release the palladium salt. The Pd(II) catalyst was then regenerate to attempt next catalytic cycle.



Scheme 3. Proposed Mechanism.

CONCLUSION

In summary, we have developed a palladium catalyzed tandem regioselective 6-*endo* cyclization and allylation reaction. Under mild reaction conditions, a series of multifunctionalized pyrones were synthesized with one-pot reactions of enynoate and allylic alcohol. This cascade reaction provides a simple, easy cost-effective route for the regioselective synthesis of allyl pyrones. The applications of these reactions with synthesis point of view are continuing in our group.

EXPERIMENTAL SECTION

General Information

$PdCl_2$, $CuCl_2$ and allylic alcohols were purchased from commercial suppliers and used as received unless otherwise noted. All reactions were performed in air unless otherwise specified. All commercial solvents and reagents were employed without further purification. Reactions were monitored through analytical thin layer chromatography (SiO_2 60 F-254 plates). The spots visualization were performed under UV radiation (254 nm), further visualization was possible using basic solution of potassium permanganate. Flash chromatography was carried out using 200-300 mesh silica gel (SiO_2 60) with distilled solvents. Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance ($^{13}C\{^1H\}$ NMR) spectra were recorded on Bruker Advance 400M NMR spectrometers. Chloroform-*d* was used as the solvent and $SiMe_4$ (TMS) as internal standard. Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from TMS (δ 0.00 ppm) and relative to the signal of chloroform-*d* (δ 7.260 ppm, singlet). Multiplicities are recorded as: *s* (singlet); *d* (doublet); *t*

(triplet); *q* (quartet); *dd* (doublets of doublet); *m* (multiplets). Coupling constants are expressed as a *J* value in Hz. $^{13}C\{^1H\}$ NMR are reported as δ in units of parts per million (ppm) downfield from TMS (δ 0.00 ppm) and relative to the signal of chloroform-*d* (δ 77.03 ppm, triplet). Notable, splitting signals of ^{13}C nucleus was difficult to differentiate and $^{13}C\{^1H\}$ NMR signals were reported as singlet. HRMS spectra were recorded on Water XEVO-G2 Q-TOF (Waters Corporation).

Preparation of Terminal alkynes and (*Z*)-Enynoates

Synthesis of terminal alkynes according to the following procedures.[14]

In a dry round bottle flask, a solution of CuI (380.9 mg, 2.0 mmol, 5.0 mol%), $Pd(PPh_3)_2Cl_2$ (701.9 mg, 1.0 mmol, 2.5 mol%) and alkyl iodide (40.0 mmol, 1.0 equiv.) in 300 mL of Et_3N was added trimethylsilylacetylene (40.0 mmol, 1.0 equiv.) dropwise under argon atmosphere. The mixture was stirred at room temperature until the starting materials were completely consumed. The reaction mixture was then filtered with a short diatomite column and removed the solvent in *vacuum*. The resulting crude product was dissolved in 150 mL of methanol and added K_2CO_3 (11.06 g, 80.0 mmol, 2.0 equiv.). The reaction mixture was diluted with Et_2O (200 mL) after stirred at room temperature for 2 hours. After washing with water (150 mL) and drying over anhydrous Na_2SO_4, the residue was concentrated under reduced pressure and purified by flash column chromatography (petroleum ether/ethyl acetate = 50/1 as eluting solvent) to afford the corresponding alkyne.[15] 2-Ethynylnaphthalene and 2-Ethynyl-1-methyl-1*H*-indole were synthesized according to the reported conditions.[16, 17]

All (*Z*)-configuration enynoates were prepared according to the reported literatures. [18, 9, 7a]

The (*Z*)-ethyl-3-iodoacryate[18], enynoates except *β*-substituted (*Z*)-enynoates (**1a-1m**)[9], and the *β*-substituted (*Z*)-enynoates (**1n-1q**)[7a] were prepared according to the reported literatures, respectively. The crude product of *β*-substituted (*Z*)-enynoates were purified by flash column chromatography (petroleum ether/ethyl acetate = 20/1 as eluting solvent).

Allylic alcohols (**2b** and **2d-2g**) were prepared according to the reported literatures.[19, 20]

Procedure for the Synthesis of Products (3a-3q), (4a-4d). In an oven dried 15 mL glass tube charged with a stir bar, toluene (1.5 mL) was added to a mixture of $PdCl_2$ (2.7 mg, 0.015 mmol, 5 mol%), 1,2-bis(benzylsulfinyl)ethane (6.4 mg, 0.021 mmol, 7 mol%), $CuCl_2$ (8.1 mg, 0.06 mmol, 20 mol%) and benzoquinone (1.3 mg, 0.012 mmol, 4 mol%) under air. The mixture was stirred for 5 minute and then the enynoate (0.3 mmol, 1.0 equiv.) with corresponding allylic alcohol (0.9 mmol, 3.0 equiv.) were subsequently added to the mixture. The reaction mixture was stirred at 30 °C until the starting material enynoate was completely consumed (Monitored by TLC). The reaction mixture was diluted with ethyl acetate and then washed with water twice (10 mL x 2) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 20/1 as eluting solvent) to afford the product.

5-allyl-6-phenyl-2*H*-pyran-2-one (**3a**). Colorless solid; 51.6 mg, 0.243 mmol, yield: 81 %;. ^1H NMR (400 MHz, CDCl3) δ 7.60-7.53 (m, 2H), 7.48-7.42 (m, 3H), 7.31 (d, *J* = 9.5 Hz, 1H), 6.32 (d, *J* = 9.5 Hz, 1H), 5.93 (ddt, *J* = 17.1, 10.3, 5.7 Hz, 1H), 5.21 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.11 (dd, *J* = 17.1, 1.5 Hz, 1H), 3.20 (dt, *J* = 5.6, 1.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.1, 158.7, 147.4, 135.4, 132.1, 130.1, 128.5, 128.4, 117.4, 114.7, 113.1, 33.9; HRMS (EI): m/z Calcd. for $C_{14}H_{13}O_2$ $[M+H]^+$: 213.0911, found: 213.0910.

5-allyl-6-(p-tolyl)-2*H*-pyran-2-one (**3b**). Colorless solid; 47.4 mg, 0.210 mmol, yield: 70 %; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 9.4 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 2H), 6.29 (d, *J* = 9.4 Hz, 1H), 5.93 (ddt, *J* = 17.2, 10.2, 5.6 Hz, 1H), 5.21 (d, *J* = 10.2 Hz, 1H), 5.10 (d, *J* = 17.2 Hz, 1H), 3.20 (d, *J* = 5.6 Hz, 2H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.3, 158.9, 147.5, 140.4, 135.5, 129.3, 129.1, 128.4, 117.4, 114.3, 112.8, 34.0, 21.4; HRMS (EI): m/z Calcd. for $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1067, found: 227.1071.

5-allyl-6-(m-tolyl)-2*H*-pyran-2-one (**3c**). Yellow oil; 47.9 mg, 0.213 mmol, yield: 71 %; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.36-7.23 (m, 4H), 6.30 (d, *J* = 9.4 Hz, 1H), 5.92 (ddt, *J* = 17.0, 10.4, 4.7 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 5.10 (d, *J* = 17.1 Hz, 1H), 3.19 (d, *J* = 4.7 Hz, 2H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.2, 158.8, 147.4, 138.3, 135.4, 132.0, 130.9, 129.1, 128.2, 125.5, 117.4, 114.4, 113.1, 33.9, 21.4; HRMS (EI): m/z Calcd. for $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1067, found: 227.1069.

5-allyl-6-(9*H*-fluoren-2-yl)-2*H*-pyran-2-one (**3d**). Colorless solid; 72.4 mg, 0.240 mmol, yield: 80 %; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.73 (m, 3H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.42-7.29 (m, 3H), 6.31 (d, *J* = 9.4 Hz, 1H), 5.96 (ddt, *J* = 17.2, 10.8, 5.6 Hz, 1H), 5.23 (d, *J* = 10.2 Hz, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 3.92 (s, 2H), 3.25 (d, *J* = 5.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.3, 159.2, 147.6, 143.8, 143.6, 143.3, 140.7, 135.5, 130.3, 127.6, 127.4, 127.0, 125.2, 125.2, 120.5, 119.6, 117.5, 114.3, 113.0, 36.9, 34.1; HRMS (EI): m/z Calcd. for $C_{21}H_{17}O_2$ $[M+H]^+$: 301.1224, found: 301.1220.

5-allyl-6-(4-chlorophenyl)-2*H*-pyran-2-one (**3e**). Yellow solid; 54.6 mg, 0.222 mmol, yield: 74 %; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 9.5 Hz, 1H), 6.33 (d, *J* = 9.5 Hz, 1H), 5.94 (ddt, *J* = 17.2, 10.7, 5.6 Hz, 1H), 5.23 (d, *J* = 10.2 Hz, 1H), 5.10 (d, *J* = 17.2 Hz, 1H), 3.18 (d, *J* = 5.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.8, 157.4, 147.3, 136.3, 135.1, 130.4, 129.8, 128.8, 117.6, 115.0, 113.4, 33.9; HRMS (EI): m/z Calcd. for $C_{14}H_{12}ClO_2$ $[M+H]^+$: 247.0521, found: 247.0522.

Methyl 3-(5-allyl-2-oxo-2*H*-pyran-6-yl)benzoate (**3f**). Yellow oil; 58.2 mg, 0.216 mmol, yield: 72 %; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.54 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.33 (d, *J* = 9.5 Hz, 1H), 6.35 (d, *J* = 9.5 Hz, 1H), 5.94 (ddt, *J* = 17.1, 9.9, 5.6 Hz, 1H), 5.25 (d, *J* = 9.9 Hz, 1H), 5.13 (d, *J* = 17.1 Hz, 1H), 3.94 (s, 3H), 3.20 (d, *J* = 5.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3, 161.8, 157.4, 147.2, 135.0, 132.7, 132.4, 131.1, 130.6, 129.7, 128.7, 117.7, 115.2, 113.7, 52.4, 33.9; HRMS (EI): m/z Calcd. for $C_{16}H_{15}O_4$ $[M+H]^+$: 271.0965, found: 271.0969.

5-allyl-6-(4-methoxyphenyl)-2*H*-pyran-2-one (**3g**). Colorless oil; 58.8 mg, 0.243 mmol, yield: 81 %; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.50 (m, 2H), 7.29 (d, *J* = 9.4 Hz, 1H), 6.98-6.92 (m, 2H), 6.27 (d, *J* = 9.4 Hz, 1H), 5.95 (ddt, *J* = 17.0, 10.2, 5.6 Hz, 1H), 5.21 (dq, *J* = 10.2, 1.4 Hz, 1H), 5.10 (dq, *J* = 17.1, 1.6 Hz, 1H), 3.85 (s, 3H), 3.20 (dt, *J* = 5.7, 1.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.3, 161.0,

158.7, 147.7, 135.5, 130.0, 124.5, 117.3, 113.8, 113.8, 112.3, 55.4, 34.0; HRMS (EI): m/z Calcd. for $C_{15}H_{15}O_3$ $[M+H]^+$: 243.1016, found: 243.1014.

5-allyl-6-butyl-2*H*-pyran-2-one (**3h**). Colorless oil; 41.6 mg, 0.216 mmol, yield: 72 %; 140.4 mg, 0.730 mmol, yield: 73 % for 1 mmol scale reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 9.4 Hz, 1H), 6.16 (d, *J* = 9.4 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.2, 6.1 Hz, 1H), 5.12 (dd, *J* = 10.1, 1.1 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.2 Hz, 1H), 3.07 (d, *J* = 6.0 Hz, 2H), 2.49 (t, *J* = 7.7 Hz, 2H), 1.64 (tt, *J* = 7.7, 7.6 Hz, 2H), 1.36 (tq, *J* = 7.6, 7.3 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.8, 162.7, 147.1, 135.0, 116.8, 113.4, 112.4, 33.3, 30.6, 29.6, 22.4, 13.8; HRMS (EI): m/z Calcd. for $C_{12}H_{17}O_2$ $[M+H]^+$: 193.1294, found: 193.1290.

5-allyl-6-cyclopropyl-2*H*-pyran-2-one (**3i**). Yellow oil; 33.5 mg, 0.189 mmol, yield: 63 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 9.4 Hz, 1H), 6.07 (d, *J* = 9.4 Hz, 1H), 5.87 (ddt, *J* = 17.1, 10.4, 6.0 Hz, 1H), 5.13 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.07 (dd, *J* = 17.1, 1.7 Hz, 1H), 3.19 (d, *J* = 6.0 Hz, 2H), 1.91-1.82 (m, 1H), 1.22-1.15 (m, 2H), 1.00-0.93 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.6, 162.3, 147.3, 135.0, 116.6, 112.0, 111.7, 33.2, 11.3, 8.3; HRMS (EI): m/z Calcd. for $C_{11}H_{13}O_2$ $[M+H]^+$: 177.0911, found: 177.0905.

5-allyl-6-(3-chloropropyl)-2*H*-pyran-2-one (**3j**). Colorless oil; 45.1 mg, 0.213 mmol, yield: 71 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 9.5 Hz, 1H), 6.19 (d, *J* = 9.5 Hz, 1H), 5.83 (ddt, *J* = 17.0, 10.1, 6.1 Hz, 1H), 5.13 (dq, *J* = 10.1, 1.5 Hz, 1H), 5.06 (dq, *J* = 17.1, 1.7 Hz, 1H), 3.60-3.55 (m, 2H), 3.11 (dt, *J* = 6.1, 1.6 Hz, 2H), 2.70 (dd, *J* = 7.1 Hz, 2H), 2.20-2.10 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.4, 160.5, 147.0, 134.8, 117.0, 114.0, 113.4, 44.0, 33.2, 29.8, 27.8; HRMS (EI): m/z Calcd. for $C_{11}H_{14}ClO_2$ $[M+H]^+$: 213.0677, found: 213.0674.

4-(5-allyl-2-oxo-2*H*-pyran-6-yl)butanenitrile (**3k**). Colorless oil; 37.0 mg, 0.183 mmol, yield: 61 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 9.5 Hz, 1H), 6.22 (d, *J* = 9.5 Hz, 1H), 5.83 (ddt, *J* = 17.0, 10.1, 6.0 Hz, 1H), 5.15 (dq, *J* = 10.1, 1.5 Hz, 1H), 5.06 (dq, *J* = 17.1, 1.7 Hz, 1H), 3.11 (dt, *J* = 6.0, 1.6 Hz, 2H), 2.72-2.66 (m, 2H), 2.42 (t, *J* = 6.9 Hz, 2H), 2.06 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.1, 159.3, 147.0, 134.6, 118.8, 117.2, 114.4, 113.6, 33.2, 29.2, 22.9, 16.7; HRMS (EI): m/z Calcd. for $C_{12}H_{14}NO_2$ $[M+H]^+$: 204.1020, found: 204.1023.

2-(5-allyl-2-oxo-2*H*-pyran-6-yl)ethyl acetate (**3l**). Yellow oil; 47.9 mg, 0.216 mmol, yield: 72 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 9.5 Hz, 1H), 6.22 (d, *J* = 9.5 Hz, 1H), 5.82 (ddt, *J* = 17.0, 10.3, 6.0 Hz, 1H), 5.14 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.35 (t, *J* = 6.5 Hz, 2H), 3.09 (d, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 6.5 Hz, 2H), 2.04 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 162.1, 157.9, 146.7, 134.6, 117.2, 114.5, 114.1, 61.2, 33.1, 30.4, 20.9; HRMS (EI): m/z Calcd. for $C_{12}H_{15}O_4$ $[M+H]^+$: 223.0965, found: 223.0968.

5-allyl-6-phenethyl-2*H*-pyran-2-one (**3m**). Colorless oil; 37.4 mg, 0.156 mmol, yield: 52 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.13 (m, 5H), 7.11 (d, *J* = 9.4 Hz, 1H), 6.17 (d, *J* = 9.4 Hz, 1H), 5.59 (ddt, *J* = 17.0, 10.3, 6.1 Hz, 1H), 5.05 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.95 (dt, *J* = 17.0, 1.6 Hz, 1H), 2.97 (t, *J* = 7.7 Hz, 2H), 2.87 (d, *J* = 6.0 Hz, 2H), 2.78 (t, *J* = 7.7 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.7, 161.0, 147.0, 140.1, 134.8, 128.6, 128.4, 126.4, 116.9, 113.7, 113.2, 33.6, 33.1, 32.9; HRMS (EI): m/z Calcd. for $C_{16}H_{17}O_2$ $[M+H]^+$: 241.1224, found: 241.1230.

5-allyl-6-(4-methoxyphenyl)-4-phenyl-2*H*-pyran-2-one (**3n**). Colorless oil; 62.6 mg, 0.198 mmol, yield: 66 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.57 (m, 2H), 7.44-7.39 (m, 3H), 7.32-7.28 (m, 2H), 6.97-6.92 (m, 2H), 6.19 (s, 1H), 5.63 (ddt, *J* = 17.3, 10.3, 5.1 Hz, 1H), 5.00 (dq, *J* = 10.3, 1.7 Hz, 1H), 4.79 (dq, *J* = 17.2, 1.8 Hz, 1H), 3.86 (s, 3H), 3.13 (dt, *J* = 5.2, 1.9 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.1, 160.9, 160.8, 159.4, 137.4, 136.1, 130.3, 128.8, 128.2, 127.7, 125.2, 116.7, 113.8, 113.7, 112.6, 55.4, 31.6; HRMS (EI): m/z Calcd. for $C_{21}H_{19}O_3$ $[M+H]^+$: 319.1329, found: 319.1328.

5-allyl-6-butyl-4-phenyl-2*H*-pyran-2-one (**3o**). Light yellow oil; 59.2 mg, 0.222 mmol, yield: 74 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7,36 (m, 3H), 7.28-7.22 (m, 2H), 6.08 (s, 1H), 5.71 (ddt, *J* = 17.1, 10.3, 5.2 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.85 (d, *J* = 17.2 Hz, 1H), 3.00 (d, *J* = 5.0 Hz, 2H), 2.54 (t, *J* = 7.4 Hz, 2H), 1.76-1.67 (m, 2H), 1.46-1.34 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.7, 162.6, 160.4, 137.3, 135.4, 128.9, 128.4, 127.5, 116.1, 112.7, 111.7, 31.2, 30.7, 29.6, 22.6, 13.8; HRMS (EI): m/z Calcd. for $C_{18}H_{21}O_2$ $[M+H]^+$: 269.1537, found: 269.1541.

5-allyl-4-methyl-6-phenyl-2*H*-pyran-2-one (**3p**). Colorless solid; 42.7 mg, 0.189 mmol, yield: 63 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.50 (m, 2H), 7.47-7.38 (m, 3H), 6.19 (s, 1H), 6.01 (ddt, *J* = 17.1, 9.8, 3.4 Hz, 1H), 5.23 (d, *J* = 10.1 Hz, 1H), 5.04 (d, *J* = 17.3 Hz, 1H), 3.18 (d, *J* = 3.4 Hz, 2H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.1, 158.6, 157.7, 135.8, 132.6, 130.0, 128.4, 128.3, 116.6, 113.7, 113.4, 31.4, 19.9; HRMS (EI): m/z Calcd. for $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1067, found: 227.1072.

5-allyl-6-butyl-4-methyl-2*H*-pyran-2-one (**3q**). Colorless oil; 49.6 mg, 0.240 mmol, yield: 80 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.86 (ddt, *J* = 17.1, 10.3, 5.2 Hz, 1H), 5.09 (d, *J* = 10.2 Hz, 1H), 4.94 (d, *J* = 17.2 Hz, 1H), 3.11 (d, *J* = 4.9 Hz, 2H), 2.54-2.44 (m, 2H), 2.12 (s, 3H), 1.69-1.58 (m, 2H), 1.42-1.31 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.7, 162.2, 157.4, 134.8, 116.0, 112.8, 112.0, 30.7, 30.1, 29.7, 22.4, 20.0, 13.8; HRMS (EI): m/z Calcd. for $C_{13}H_{19}O_2$ $[M+H]^+$: 207.1380, found: 207.1377.

6-phenyl-5-(4-phenylbut-2-en-1-yl)-2*H*-pyran-2-one (**4a**). Colorless solid; 44.1 mg, 0.144 mmol, yield: 48 %. The *E* : *Z* ratio was determined after purification by flash chromatography to be approximately 82 : 18 by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.52 (m, 2H), 7.47-7.39 (m, 3H), 7.33-7.27 (m, 3H), 7.24-7.13 (m, 3H), 6.30 (d, *J* = 9.5 Hz, 1H), 5.80 (*Z* isomer) (dt, *J* = 9.0, 8.4 Hz, 1H × 0.18H), 5.73-5.49 (m, 1H × 0.18 + 2H × 0.82), 3.40 (d, *J* = 6.5 Hz, 2H), 3.32 (*Z* isomer) (d, *J* = 6.9 Hz, 2H × 0.18), 3.18 (*E* isomer) (dq, *J* = 5.5, 1.5 Hz, 2H × 0.82); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.2, 158.4, 147.4, 146.9, 140.05, 140.02, 132.3, 132.2, 132.1, 131.0, 130.1, 128.8, 128.62, 128.57, 128.53, 128.50, 128.45, 128.43, 128.25, 128.21, 127.2, 126.2, 114.9, 114.7, 113.9, 77.4, 77.0, 76.7, 38.9, 33.5, 32.8, 27.81; HRMS (EI): m/z Calcd. for $C_{21}H_{19}O_2$ $[M+H]^+$: 303.1380, found: 303.1384.

5-(but-2-en-1-yl)-6-phenyl-2*H*-pyran-2-one (**4b**). Colorless solid; 41.7 mg, 0.195 mmol, yield: 65 %. The *E* : *Z* ratio was determined after purification by flash chromatography to be approximately 82 : 18 by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.52 (m, 2H), 7.49-7.41 (m, 3H), 7.32 (d, *J* =

9.5 Hz, 1H), 6.31 (d, *J* = 9.5 Hz, 1H), 5.71-5.36 (m, 2H), 3.20 (*Z* isomer) (d, *J* = 7.0 Hz, 2H × 0.18), 3.12 (*E* isomer) (s, 2H × 0.82), 1.73 (*E* isomer) (s, 3H × 0.82), 1.64 (*Z* isomer) (d, *J* = 6.6 Hz, 3H × 0.18); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.2, 162.1, 158.2, 158.1, 147.6, 147.1, 132.25, 132.17, 130.02, 129.99, 128.8, 128.6, 128.43, 128.40, 128.2, 127.9, 127.0, 126.8, 114.9, 114.8, 114.6, 114.1, 32.8, 27.4, 18.0, 13.0; HRMS (EI): m/z Calcd. for $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1067, found: 227.1073.

6-phenyl-5-(3-phenylallyl)-2*H*-pyran-2-one (**4c**). Colorless solid; 33.8 mg, 0.117 mmol, yield: 39 %, *E* : *Z* > 95 : 5; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.58 (m, 2H), 7.48-7.44 (m, 3H), 7.39-7.31 (m, 5H), 7.28-7.22 (m, 1H), 6.46-6.40 (m, 1H), 6.36-6.25 (m, 2H), 3.37 (dd, *J* = 5.9, 1.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.1, 158.7, 147.4, 136.7, 132.4, 132.1, 130.2, 128.7, 128.6, 128.5, 127.7, 126.9, 126.2, 114.8, 113.4, 33.2; HRMS (EI): m/z Calcd. for $C_{20}H_{17}O_2$ $[M+H]^+$: 289.1223, found: 289.1221.

5-(3-(4-bromophenyl)allyl)-6-phenyl-2*H*-pyran-2-one (**4d**). Yellow solid; 63.4 mg, 0.174 mmol, yield: 58 %. The *E* : *Z* ratio was determined after purification by flash chromatography to be approximately 95 : 5 by ^1H NMR. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.54 (*E* isomer) (m, 2H × 0.95), 7.49-7.41 (m, 5H), 7.35 (*E* isomer) (d, *J* = 9.4 Hz, 1H × 0.95), 7.30 (*Z* isomer) (d, *J* = 9.7 Hz, 1H × 0.05), 7.25-7.21 (*E* isomer) (m, 2H × 0.95), 7.06 (*Z* isomer) (d, *J* = 8.3 Hz, 2H × 0.05), 6.56 (*Z* isomer) (d, J = 10.8 Hz, 1H × 0.05), 6.40-6.23 (m, 3H), 5.71 (*Z* isomer) (dt, *J* = 11.5, 7.2 Hz, 2H × 0.05),3.45 (*Z* isomer) (dd, *J* = 7.2, 2.0 Hz, 2H × 0.05), 3.35 (*E* isomer) (dd, *J* = 5.5, 1.1 Hz, 2H × 0.95); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.0, 158.8, 147.2, 135.6, 132.0, 131.8, 131.5, 131.3, 130.3, 129.3, 128.65, 128.56, 128.54, 128.4, 127.8, 121.5, 115.0, 114.9, 113.1, 33.2, 29.7; HRMS (EI): m/z Calcd. for $C_{20}H_{16}BrO_2$ $[M+H]^+$: 367.0328, found: 367.0331.

SUPPORTING INFORMATION

Spectral data for all novel compounds (^1H NMR, ^{13}C NMR).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully acknowledge the funding support of Anhui Provincial Natural Science Foundation (1708085MB29), the National Natural Science Foundation of China (21672198) and the State Key Program of National Natural Science Foundation of China (21432009).

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