JOC The Journal of Organic Chemistry

Article

Synthesis of Functionalized Chromene and Chroman Derivatives via Cesium Carbonate Promoted Formal [4 + 2] Annulation of 2'-Hydroxychalcones with Allenoates

Hossein Rouh, Yangxue Liu, Nandakumar Katakam, Lilian Pham, Yi-Long Zhu, and Guigen Li

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02627 • Publication Date (Web): 27 Nov 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of Functionalized Chromene and Chroman Derivatives *via* Cesium Carbonate Promoted Formal [4 + 2] Annulation of 2'-Hydroxychalcones with Allenoates†

Hossein Rouh[#], Yangxue Liu[#], Nandakumar Katakam[#], Lilian Pham[#], Yi-Long Zhu[#,$] and Guigen Li[*#,‡]

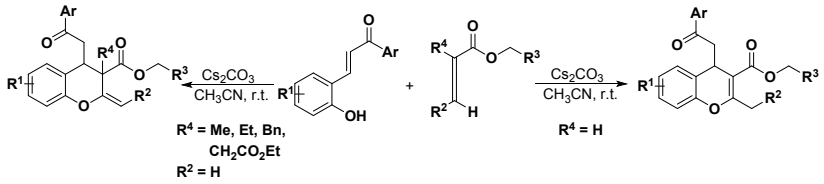
[#]Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, USA

[‡]Institute of Chemistry and BioMedical Sciences, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210093, China

[$]College of Pharmacy, Nanjing Tech University, Nanjing 211816, P. R. China

*E-mail: guigen.li@ttu.edu.

† We would like to dedicate this work to Professor Victor J. Hruby on occasion of his 80th birthday.

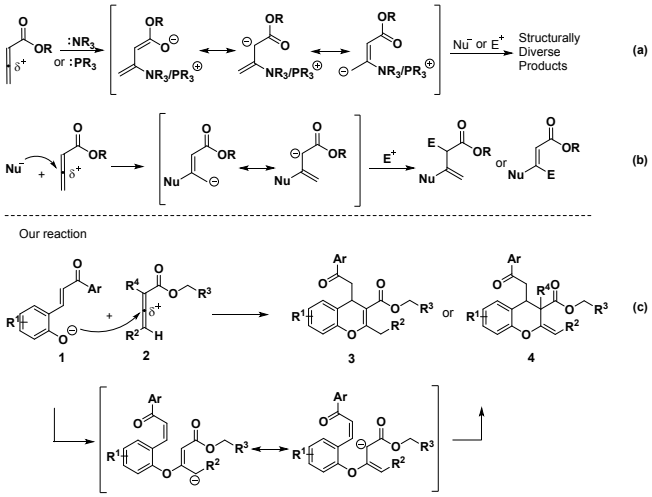


ABSTRACT: A new strategy has been established for the synthesis of functionalized chromene and chroman derivatives via a Cs_2CO_3-catalyzed domino addition of 2'-hydroxychalcone derivatives with allenoates, which can serve as a general avenue for the construction of multi-replaced chromene derivatives. Chemoselectivity of this synthesis was found to depend on substituents on substrates. Good to excellent yields were achieved under simple and mild conditions at the room temperature.

INTRODUCTION

Chromene and chroman rings are important classes of oxygenated heterocycles and present in a variety of biologically active natural products.[1] Many molecules containing these frameworks gracefully exhibit superior biological activities, such as antirhinovirus[2], anticancer[3], antifungal[4] and so on. Therefore, the development of efficient synthetic methods to access these motifs has received a tremendous amount of attention, and many strategies have been reported in literature.[5] Over the past decades, a significant progress in allenes chemistry has been made by many research labs.[6] In particular, the transformations of allenoate under nucleophilic Lewis base catalysis and phosphine catalysis have received considerable interest due to their modifying flexibility of molecular complexity.[7] What they have in common is that they heavily rely on the key zwitterionic intermediate (Scheme 1a). Allenes can react as either nucleophiles or electrophiles, depending on the substituents on the parent framework for altering the reactivity preferences. For example, the allenoates can behave as electrophiles when electron-withdrawing groups are present.[8] It also has been reported that allenoate can react with nucleophiles in the presence of carbonate catalysts.[9,10-12] Shi and co-workers first reported carbonate-catalyzed reactions of ethyl

Scheme 1. Strategies for the reactions of allenoates with nucleophiles or electrophiles.

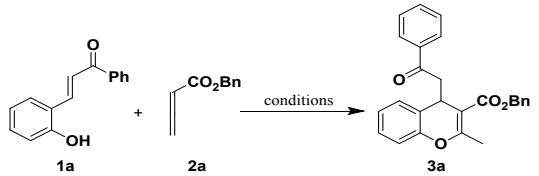


allenoate with salicylic aldehydes to access the functionalized chromenes in good yields.[10] Selig and co-workers reported a method for the synthesis of 2,3-disubstituted quinolines *via* carbonate-catalyzed reaction of allenoates with N-protected o-aminobenzaldehydes.[11] Recently, Zhou and co-workers reported a carbonate-catalyzed reaction of allenoates and 2-(2-hydroxyphenyl) isoindoline-1,3-dione for the construction of functionalized benzooxazepino-[5,4-a] isoindolone derivatives.[12] However, a cesium carbonate promoted reaction of allenoates with 2'-hydroxychalcone derivatives has not been reported yet. Herein, we report the cyclization reactions of 2'-hydroxychalcone derivatives with allenoate to chemoselectively give new types of highly functionalized chromene and chroman derivatives in good to excellent yields in the presence of cesium carbonate at room temperature. On the basis of this facile synthetic protocol, a variety of interesting chromene and chroman derivatives can be obtained in a simple way.

RESULTS AND DISCUSSION

At the outset of our study, 3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one 1a and benzyl buta-2,3-dienoate **2a** were selected for the initial reaction in the presence of 40 mol % cesium carbonate in DMSO at 60 °C gave the desired product **3a** in 43% isolated yield (Table 1, entry 1). When we use the combination of Cs_2CO_3 with DMSO at room temperature, we can also get a good result in 48% yield (entry 2). So, we chose to let the reaction proceed at room temperature. An increased

Table 1. Condition optimization for the [4 + 2] Annulation

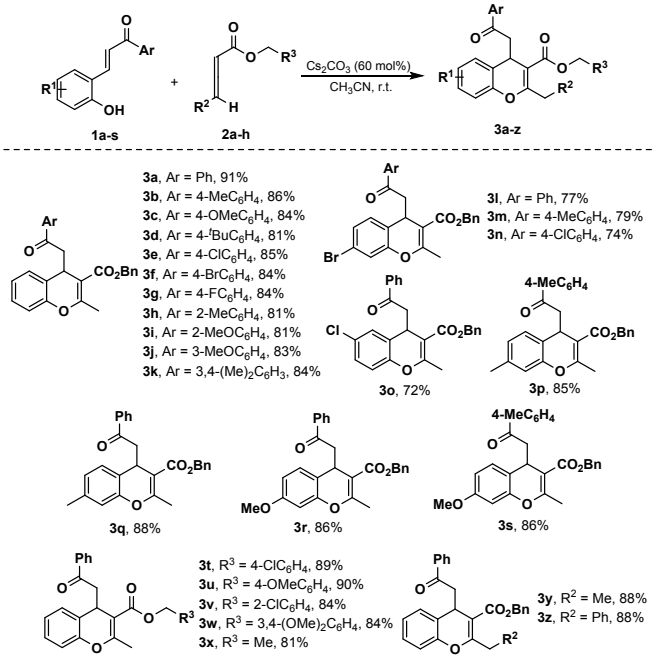


entry	2a (equiv.)	Cat. (mol%.)	Solvent	Temp.	Yield[b]
1	1.0	Cs_2CO_3 (40%)	DMSO	60 ^{0}C	43%
2	1.0	Cs_2CO_3 (40%)	DMSO	r.t.	48%
3	1.0	Cs_2CO_3 (40%)	CH_3CN	r.t.	55%
4	1.2	Cs_2CO_3 (40%)	CH_3CN	r.t.	61%
5	1.5	Cs_2CO_3 (40%)	CH_3CN	r.t.	62%
6	2.0	Cs_2CO_3 (40%)	CH_3CN	r.t.	73%
7	2.0	Cs_2CO_3 (60%)	CH_3CN	r.t.	92%
8	2.0	Cs_2CO_3 (100%)	CH_3CN	r.t.	78%
9	2.0	DBU (60%)	CH_3CN	r.t.	15%
10	2.0	DABCO (60%)	CH_3CN	r.t.	17%
11	2.0	K_2CO_3 (60%)	CH_3CN	r.t.	45%
12	2.0	Na_2CO_3 (60%)	CH_3CN	r.t.	43%
13	2.0	Cs_2CO_3 (60%)	ethanol	r.t.	8%
14	2.0	Cs_2CO_3 (60%)	H_2O	r.t.	N.R.
15	2.0	Cs_2CO_3 (60%)	DCM	r.t.	23%
16	2.0	Cs_2CO_3 (60%)	THF	r.t.	39%
17	2.0	Cs_2CO_3 (60%)	toluene	r.t.	27%

[a]To a mixture of **1a** (1.0 equiv., 0.5 mmol) and **2a** (*n* equiv.) in anhydrous solvent, catalyst (*n* mol%) was added. The resulting solution was stirred at room temperature. [b]Isolated yield based on **1a**.

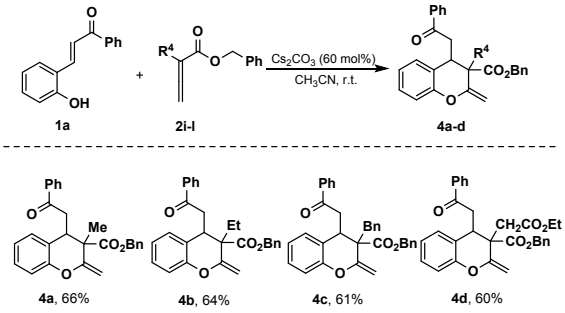
load of **2a** could significantly improve the yield (entry 6 vs entries 3-5). With the increase of the amount of cesium carbonate, the yield of the reaction has been significantly improved, and up to 92% yield was obtained (entry 7 vs entry 6). As the amount of catalyst continues to increase, it is not conducive to the progress of the reaction. (entry 7 vs entry 8). Next, several bases commonly used in the annulate reactions were investigated, like DBU, DABCO, K_2CO_3, and Na_2CO_3, all showed poor catalytic activities. Afterward, we adjusted other solvents, such as ethanol, H_2O, dichloromethane (DCM), tetrahydrofuran (THF) and toluene, which were inferior to acetonitrile in terms of reaction yields (entry 7 vs entry 13-17).With the optimized reaction conditions in hand, a wide range of intramolecular cyclization reactions, using different substituted 2'-hydroxychalcone derivatives and allenoates were examined for this transformation (Scheme 2). Both aromatic moieties in 2'-hydroxychalcone structures could be varied, regardless of the electronic nature and substitution patterns of the aryl structures, and annulation products were obtained in good to excellent yields (Scheme 2, **3a-s**).

Scheme 2. Substrate Scope for the Synthesis of 3[a]



[a]Reaction conditions: 2'-hydroxychalcone **1** (0.5 mmol), allenoate **2** (1.0 mmol), CS_2CO_3 (0.3 mmol, 60 mol%), acetonitrile (4.0 mL), Ar conditions. [b]Isolated yield based on substrates **1**.

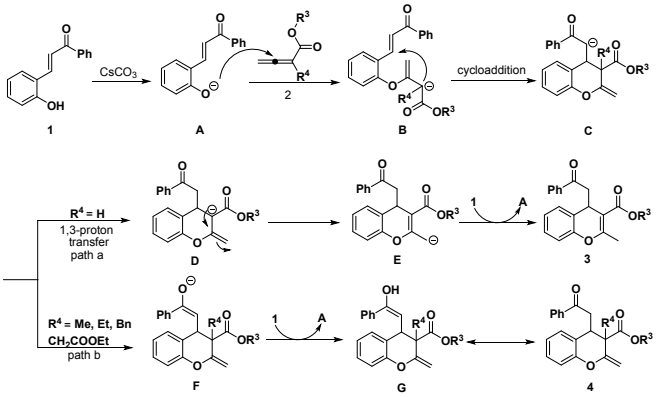
Scheme 3. Regioselective synthesis of products 4[a].



[a]Reaction conditions: 2'-hydroxychalcone **1** (0.5 mmol), allenoate **2** (1.0 mmol), CS_2CO_3 (0.3 mmol, 60 mol%), acetonitrile (4.0 mL), Ar conditions. [b]Isolated yield based on substrates **1**.

Additionally, the multiple substitution of the aromatic groups was an adaptable substrate in this transformation, allowing its [4+2] annulation to the corresponding γ-chromene in 84% yield. With a phenyl group on the 2'-hydroxychalcone (Ar) motif, the variant of substituents on the phenolic hydroxyl moiety(R^1), including MeO, Me, Cl, and Br, were successful engaged in these transformations under the above conditions. The presence of electron donating groups at the para-position of the phenyl ring (R^1) seemed to improve the reaction efficiency, as the corresponding products **3p**, **3q**, **3r** and **3s** could be obtained in higher yields than those with electron withdrawing groups (Scheme 2, **3l** vs. **3q**, **3m** vs. **3s**). In general, the nature of the substituent on the benzene ring of the 2'-hydroxychalcone had a slight impact on the yields. Next, we decided to change the ester group of allenoates and use the non-terminal allenoates to expand its synthetic utility. As we had expected, a large variety of different substituents, including 4-ClC_6H_4, 4-$OMeC_6H_4$, 2-ClC_6H_4, 3,4-$(MeO)_2C_6H_4$ and Me would be accommodated, confirming the efficiency of the reaction, as the corresponding products **3t**-**3x** were generated in 81–90% yields. Similarly, non-terminal allenoates also show good tolerance (Scheme 2, **3y** and **3z**). To our delight, α-substituted allenoate also reacted smoothly with 1a, but we didn't get the same product as previous. A new class of chroman derivates can be successfully synthesized by this method in moderate yields (Scheme 3, **4a-d**). Therefore, a multi-substituted chromene and chroman derivates can be achieved, by controlling the α-substituents of the allenoate. The resultant functionalized **3** and **4** were fully characterized by their NMR spectroscopy and HRMS. The structure of the product was undeniably confirmed by X-ray crystallographic analysis of compound **3a** (see the Supporting Information).

Scheme 4. Proposed Mechanism for Forming 3 and 4



On the basis of our investigations[6-12] and the earlier reports[13], a plausible mechanism for the reaction is shown in scheme 4. Initially the non-nucleophilic base cesium carbonate deprotonates **1** to generate oxy-anionic intermediate **A**. The intermediate **A** then undergoes conjugate addition with allenoate **2** to form the intermediate **B**. The following intramolecular cycloaddition reaction produces the intermediate **C**. When the substituents of α-position of allenoate (R^4) are different, two proton transfer modes of intermediate C could occur to formed intermediate **D** (path a) and **F** (path b), respectively. Subsequent resonate of intermediate **D** leads to the formation of intermediate **E**, which abstracts a proton from **1** to afford compound **3** and regenerates intermediate **A** to accomplish the catalytic cycle. Because of the group of α-position (R^4 = Me, Et, Bn, and CH_2COOEt), intermediate **F** through the abstract proton and tautomerization processes form chroman derivates **4**.

CONCLUSION

In summary, we have discovered a new a strategy for the construction of densely functionalized 4*H*-chromene and chroman derivatives *via* a highly efficient [4+2] annulation of 2'-Hydroxychalcone with allenoates. By adjusting the substituent of α-substituents of allenoate, we can selectively synthesize chromene or chroman derivates in a good to excellent yield. This method complements with any other ways for the access to functional chromene or chroman derivatives for potential applications in biological activity screening.

EXPERIMENTAL SECTION

General Information. All melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a 400 MHz instrument with TMS as internal standard. Chemical shifts (δ) are reported in ppm with respect to TMS. Data are represented as follows: chemical shift, mutiplicity (s = singlet, d = doublet, t = triplet, and m = multiplet), coupling constant (*J*, Hz), and integration. HRMS analyses were carried out using a TOF-MS instrument with an ESI source. X-ray crystallographic analysis was performed with a SMART CCD and a P4 diffractometer.

General Procedure for the Preparation of 2'-hydroxychalcone.[14] To a solution of various acetophenones (1.00 eq) and salicylaldehyde (1.25 eq) in Ethanol (2.5mL/mmol), potassium hydroxide 40% (3 eq) is added

drop-wise at room temperature. After 24 hours, the mixture is cooled with ice and neutralized carefully using 2N hydrochloric acid. The crude mixture was extracted with ethyl acetate, washed with water and brine afforded the chalcones which were purified by column chromatography using hexane: ethyl acetate (30%) as eluent to give pure chalcones (50%-92%).

General Procedure for the Preparation of γ -substituted allenoates.[15] A flask was charged with stabilized ylide and CH_2Cl_2, and Et_3N. After 10 minutes the appropriate acid chloride was added as a solution (5 mL) in CH_2Cl_2 slowly such that the temperature of the reaction remained constant. After 30 minutes, the color of the reaction mixture changes to clear yellow. After completion of the reaction (TLC), the solution was concentrated to afford a gummy residue. This was treated with hexane (25 mL), stirred well, and allowed to sit undisturbed for 2 hours. The mixture was filtered, and the filtrate was evaporated, and product was separated with column chromatography (Ethyl acetate/ Petroleum Ether 5%).

General Procedure for the Preparation of α-substituted allenoates.[15] Alkyl halide (1.00 eq.) was added to a stirred solution of the ylide (1.00 eq) in $CHCl_3$ at room temperature. The mixture was reflux overnight. The solvent was evaporated under reduced pressure and CH_2Cl_2 follow by triethylamine (2.00 eq). were added to the resulting phosphonium salt. After stirring for 1 h, acetyl chloride (1.1 equiv.) dissolved in CH_2Cl_2 (5 mL) was added dropwise over 30 min. After completion of the reaction (TLC), the solution was concentrated to afford a gummy residue. This was treated with hexane/Ethyl acetate (10:1), stirred well, and allowed to sit undisturbed for 2 hours. The mixture was filtered, and the filtrate was evaporated, and product was separated with column chromatography (Ethyl acetate/ Petroleum Ether 5%).

General procedure for the synthesis Products 3 and 4. In an oven dried and argon flushed round bottom flask, 2'-hydroxychalcone (**1**, 1.0 eq, 0.5 mmol) is dissolved in 2 ml acetonitrile. After 5 minutes, 60% cesium carbonate is added, and the reaction continued for 5 more minutes. Then allenoate (**2**, 2.0 eq, 1.0 mmol) dissolved in 2 ml acetonitrile is added drop-wise and over 5 minutes. The reaction is continued for 4 hours and after completion of reaction (confirmed by TLC), the solvent is concentrated, and the product is separated directly by column chromatography (EA/PE 5%) to afford pure products **3** and **4**.

*Benzyl 2-methyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3a**)*. Yellow solid, 182 mg, 91% yield; mp 91-93 ºC; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.81 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.49-7.50 (m, 1H), 7.39-7.26 (m, 7H), 7.18-7.10 (m, 2H), 7.00-6.92 (m, 2H), 5.27-5.12 (m, 2H), 4.60 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.28-3.13 (m, 2H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 198.2, 166.9, 163.4, 150.6, 137.1, 136.2, 133, 128.8, 128.7, 128.6, 128.3, 128.2, 127.8, 124.9, 124.5, 116.1, 105.3, 66.2, 48.3, 31.7, 19.9. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1708, 1685, 1265, 738, 704. IR (film, ν, cm−1) 3054, 2986, 2305, 1708, 1685, 1265, 738, 704; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{26}H_{22}O_4Na$ 421.1415; found 421.1398.

*Benzyl 2-methyl-4-(2-oxo-2-(p-tolyl)ethyl)-4H-chromene-3-carboxylate (**3b**)*. White solid, 178 mg, 86% yield, Mp 85-87 ºC. ^{1}H NMR (400 MHz, CDCl3; δ, ppm) 7.72 (d, *J* = 8.2 Hz, 2H), 7.37-7.27 (m, 5H), 7.18-7.11 (m, 4H), 7.00-6.93 (m, 2H), 5.19 (s, 2H), 4.59 (dd, *J* = 8.0, 4.1 Hz, 1H), 3.23-3.11 (m, 2H), 2.42 (s, 3H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 197.8, 166.9, 163.3, 150.6, 143.8, 136.3, 134.7, 129.3, 128.9, 128.7, 128.4, 128.3, 128.2, 127.8, 124, 124.6, 116.1, 105.4, 66.3, 48.2, 31.8, 21.7, 19.9. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1708, 1685, 1420, 1265, 738, 705; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{27}H_{24}O_4Na$ 435.1572; found 435.1560.

*Benzyl 4-(2-(4-methoxyphenyl)-2-oxoethyl)-2-methyl-4H-chromene-3-carboxylate (**3c**)*. White solid, 180 mg, 84% yield; mp 92-94 ºC; 1H NMR (400 MHz, CDCl3; δ, ppm) 7.80 (d, *J* = 8.6 Hz, 2H), 7.38-7.25 (m, 5H), 7.12 (t, *J* = 7.2 Hz, 2H), 6.96 (t, *J* = 7.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.20 (s, 2H), 4.57 (dd, *J* = 8.8, 3.6 Hz, 1H), 3.82 (s, 3H), 3.22-3.04 (m, 2H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 196.7, 166.9, 163.4, 163.3, 150.6, 136.3, 130.6, 130.2, 128.81, 128.7, 128.3, 128.2, 127.8, 124.9, 124.5, 116.1, 113.7, 105.4, 66.3, 55.5, 48.0, 31.0, 19.9. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1684, 1508, 1265, 738, 705; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{27}H_{24}O_5Na$ 451.1521; found 451.1504.

*Benzyl 4-(2-(4-(tert-butyl) phenyl)-2-oxoethyl)-2-methyl-4H-chromene-3-carboxylate (**3d**)*. White solid, 184 mg, 81% yield, mp 60-62 ºC. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.79 (d, *J* = 8.4 Hz, 2H), 7.40-7.29 (m, 7H), 7.15 (dd, *J* = 15.4, 6.4 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 2H), 5.22 (s, 2H), 4.62 (dd, *J* = 8.4, 3.5 Hz, 1H), 3.29-3.11 (m, 2H), 2.45 (s, 3H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 197.8, 166.9, 163.4, 156.7, 150.6, 136.3, 134.5, 128.9, 128.7, 128.4, 128.3, 128.2, 127.8, 125.6, 124.9, 124.5, 116.1, 105.3, 66.3, 48.4, 35.2, 31.8, 31.2, 20.0. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1707, 1684, 1265, 738, 705; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{30}H_{30}O_4Na$ 477.2041; found 477.2028.

*Benzyl 4-(2-(4-chlorophenyl)-2-oxoethyl)-2-methyl-4H-chromene-3-carboxylate (**3e**)*. White solid, 184 mg, 85% yield, mp 89-91 ºC. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.73 (d, *J* = 8.6 Hz, 2H), 7.40-7.25 (m, 7H), 7.14 (t, *J* = 7.2 Hz, 2H), 7.02-6.92 (m, 2H), 5.26-5.14 (m, 2H), 4.56 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.23-3.08 (m, 2H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 196.8, 166.6, 163.1, 151.2, 139.7, 136.0, 135.2, 130.1, 129.7, 129.0, 128.8, 128.45, 128.4, 127.7, 123.8, 120.8, 119.5, 105.4, 66.5, 47.9, 31.3, 19.9. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1685, 1420, 1265, 738, 705; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{26}H_{21}ClO_4Na$ 455.1026; found 455.1009.

*Benzyl 4-(2-(4-bromophenyl)-2-oxoethyl)-2-methyl-4H-chromene-3-carboxylate (**3f**)*. Yellow solid, 200 mg, 84% yield, mp 104-107 ºC. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.65 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.37-7.27 (m, 5H), 7.17 -7.09 (m, 2H), 7.01-6.93 (m, 2H), 5.26-5.13 (m, 2H), 4.55 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.23-3.06 (m, 2H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl3; δ, ppm) 196.8, 166.6, 163.13, 151.2, 139.7, 136.0, 135.2, 130.1, 129.7, 129.0, 128.8, 128.4, 128.4, 127.7, 123.8, 120.8, 119.5, 105.4, 66.5, 47.9, 31.3, 19.8. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1708, 1685, 1420, 1265, 738, 704; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{26}H_{21}BrO_4Na$ 499.0520; found 499.0506.

*Benzyl 4-(2-(4-fluorophenyl)-2-oxoethyl)-2-methyl-4H-chromene-3-carboxylate (**3g**)*. White solid, 175mg, 84% yield, mp 55-57 ºC. 1H NMR (400 MHz, CDCl3; δ, ppm) 7.85-7.79 (m, 2H), 7.37-7.27 (m, 5H), 7.13 (t, *J* = 7.2 Hz, 2H), 7.02-6.93 (m, 4H), 5.24-5.15 (m, 2H), 4.56 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.23-3.07 (m, 2H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 196.6, 167.0, 166.9, 164.4, 163.5, 150.6,

136.2, 133.5, 133.5, 131.0, 130.9, 128.7, 128.3, 128.3, 127.9, 124.6, 124.6, 116.2, 115.8, 115.6, 105.1, 66.4, 48.2, 31.9, 20.0. IR (film, *v*, cm^{-1}) 3053, 2984, 2305, 1708, 1685, 1598, 1420, 1265, 738, 704; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{26}H_{21}FO_4Na$ 439.1321; found 439.1310.

*Benzyl 2-methyl-4-(2-oxo-2-(o-tolyl)ethyl)-4H-chromene-3-carboxylate (**3h**)*. Yellow oil, 167 mg, 81% yield. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.41-7.24 (m, 7H), 7.21-7.11 (m, 3H), 7.05 (t, *J* = 7.6 Hz, 1H), 7.02-6.96 (m, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.29-5.15 (m, 2H), 4.60 (t, *J* = 6.0 Hz, 1H), 3.13 (d, *J* = 5.6 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$; δ, ppm) 202.1, 166.9, 163.3, 150.6, 138.2, 137.9, 136.3, 132.0, 131.3, 128.8, 128.7, 128.4, 129.0, 127.8, 127.6, 125.6, 125.0, 124.55, 116.2, 105.2, 66.3, 50.9, 31.6, 21.2, 19.9. IR (film, *v*, cm^{-1}) 3053, 2986, 2305, 1708, 1685, 1421, 1265, 895, 738, 704; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{27}H_{24}O_4Na$ 435.1572; found 435.1562.

*Benzyl 4-(2-(2-methoxyphenyl)-2-oxoethyl)-2-methyl-4H-chromene-3-carboxylate (**3i**)*. Yellow oil, 174 mg, 81% yield. ^1H NMR (400 MHz, CDCl3; δ, ppm) 7.51 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.40-7.26 (m, 7H), 7.11 (t, *J* = 7.0 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 2H), 4.64 (dd, *J* = 7.9, 3.6 Hz, 1H), 3.70 (s, 3H), 3.36 (dd, *J* = 16.6, 8.0 Hz, 1H), 3.14 (dd, *J* = 16.6, 3.6 Hz, 1H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 200.5, 167.0, 162.8, 158.4, 150.5, 136.4, 133.4, 130.3, 128.9, 128.7, 128.6, 128.040, 127.5, 125.5, 124.4, 120.6, 115.9, 111.4, 105.4, 66.0, 55.4, 53.5, 52.9, 31.3, 19.8. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1707, 1685, 1437, 1265, 737, 704; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{27}H_{24}O_5Na$ 451.1521; found 451.1511.

*Benzyl 4-(2-(3-methoxyphenyl)-2-oxoethyl)-2-methyl-4H-chromene-3-carboxylate (**3j**)***.** Yellow oil, 178 mg, 83% yield. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.42-7.37 (m, 2H), 7.36-7.27 (m, 5H), 7.25-7.09 (m, 3H), 7.07-7.02 (m, 1H), 7.02-6.94 (m, 2H), 5.20 (d, *J* = 1.6 Hz, 2H), 4.60 (dd, *J* = 7.8, 4.0 Hz, 1H), 3.81 (s, 3H), 3.25-3.12 (m, 2H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 198.0, 166.9, 163.3, 159.9, 150.6, 138.4, 136.2, 129.6, 128.8, 128.7, 128.2, 128.2, 127.8, 124.8, 124.6, 121.0, 119.7, 116.1, 112.2, 105.2, 66.2, 55.5, 48.3, 31.7, 20.0. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1707, 1685, 1458, 1421, 1265, 738, 705; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{27}H_{24}O_5Na$ 451.1521; found 451.1504.

*Benzyl 4-(2-(3,4-dimethylphenyl)-2-oxoethyl)-2-methyl-4H-chromene-3-carboxylate (**3k**)***.** Colorless oil, 180 mg, 84% yield. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.62 (s, 1H), 7.56 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.37-7.26 (m, 5H), 7.21 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.13 (td, *J* = 7.6, 1.6 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.01-6.94 (m, 2H), 5.20 (s, 2H), 4.62 (dd, *J* = 6.8, 5.2 Hz, 1H), 3.23-3.13 (m, 2H), 2.44 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 198.0, 166.9, 163.2, 150.6, 142.5, 136.9, 136.3, 135.1, 129.8, 129.4, 128.9, 128.7, 128.2, 128.2, 127.7, 126.1, 125.1, 124.5, 116.1, 105.4, 66.2, 48.2, 31.6, 20.1, 19.9, 19.9. IR (film, *v*, cm^{-1}) 3054, 2983, 2305, 1709, 1682, 1488, 1265, 738, 703; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{28}H_{26}O_4Na$ 449.1728; found 449.1712.

*Benzyl 7-bromo-2-methyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3l**)***.** Yellow oil, 184 mg, 77% yield. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.81 (d, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.40-7.24 (m, 7H), 7.14 (d, *J* = 1.6 Hz, 1H), 7.12-7.06 (m, 2H), 5.25-5.15 (m, 2H), 4.56 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.25-3.12 (m, 2H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 197.9, 166.6, 163.0, 151.2, 136.9, 136.1, 133.2, 130.2, 128.7, 128.7, 128.3, 128.2, 127.6, 124.5, 124.0, 120.6, 119.4, 105.5, 66.4, 47.9, 31.1, 19.8. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1710, 1685, 1420, 1265, 738, 705; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{26}H_{21}BrO_4Na$ 499.0520; found 499.0507.

*Benzyl 7-bromo-2-methyl-4-(2-oxo-2-(p-tolyl)ethyl)-4H-chromene-3-carboxylate (**3m**)***.** White solid, 194 mg, 79% yield, mp 100-102 ºC. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.77-7.66 (m, 2H), 7.36-7.27 (m, 5H), 7.18-7.11 (m, 3H), 7.10-7.05 (m, 2H), 5.25-5.15 (m, 2H), 4.55 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.24-3.08 (m, 2H), 2.41 (s, 3H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 197.5, 166.6, 162.9, 151.1, 144.0, 136.1, 134.4, 130.2, 129.3, 128.7, 128.3, 128.3, 127.6, 124.4, 124.1, 120.6, 119.4, 105.6, 66.4, 47.9, 31.2, 21.7, 19.8. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1709, 1684, 1420, 1265, 738, 705; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{27}H_{23}BrO_4Na$ 513.0677; found 513.0672.

*Benzyl 7-bromo-4-(2-(4-chlorophenyl)-2-oxoethyl)-2-methyl-4H-chromene-3-carboxylate (**3n**)*. White solid, 190 mg, 74% yield, mp 98-100 ºC. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.73 (d, *J* = 8.6 Hz, 2H), 7.35-7.27 (m, 7H), 7.13 (d, *J* = 2.0 Hz, 1H), 7.10 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 5.25-5.13 (m, 2H), 4.51 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.21-3.05 (m, 2H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 196.7, 166.6, 163.1, 151.1, 139.7, 136.0, 135.1, 130.1, 129.63, 129.0, 128.7, 128.4, 128.4, 127.6, 123.8, 120.7, 119.5, 105.3, 66.5, 47.9, 31.3, 19.8. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1708, 1421, 1265, 895, 738, 705; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{26}H_{20}BrClO_4Na$ 533.013; found 533.0130.

*Benzyl 6-chloro-2-methyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3o**)*. White solid, 156 mg, 72% yield, mp 114-116 ºC. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.81 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.39-7.26 (m, 7H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 5.23-5.14 (m, 2H), 4.56 (t, *J* = 5.6 Hz, 1H), 3.21 (d, *J* = 6.0 Hz, 2H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 197.7, 166.6, 163.1, 149.2, 136.9, 136.1, 133.2, 129.3, 128.7, 128.7, 128.6, 128.4, 128.3, 128.2, 127.9, 126.7, 117.5, 105.0, 66.4, 48.0, 31.3, 19.8. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1708, 1420, 1265, 738, 705; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{26}H_{21}ClO_4Na$ 455.1026; found 455.1041.

*Benzyl 2,7-dimethyl-4-(2-oxo-2-(p-tolyl)ethyl)-4H-chromene-3-carboxylate (**3p**)*. Yellow solid, 181 mg, 85% yield, mp 79-82 ºC. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.75 (d, *J* = 8.4 Hz, 2H), 7.39-7.27 (m, 5H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.83-6.77 (m, 2H), 5.21 (s, 2H), 4.57 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.25-3.08 (m, 2H), 2.43 (s, 3H), 2.37 (s, 3H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 198.0, 167.0, 163.4, 150.4, 143.8, 137.8, 136.3, 134.7, 129.3, 128.7, 128.5, 128.4, 128.3, 128.2, 125.4, 121.8 116.5, 105.4, 66.2, 48.4, 31.5, 21.7, 21.1, 20.0. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1708, 1684, 1421, 1265, 738, 705; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{28}H_{26}O_4Na$ 449.1728; found 449.1717.

*Benzyl 2,7-dimethyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3q**)*. Yellow oil, 182 mg, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.83 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.39-7.27 (m, 7H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 6.6 Hz, 2H), 5.25-5.16 (m, 2H), 4.57 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.28-3.10 (m, 2H), 2.42 (s, 3H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 198.3, 167.0, 163.4, 150.4, 138.0, 137.1, 136.3, 133.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 125.4, 121.8, 116.5, 105.3, 66.2, 48.4, 31.5, 21.1, 20.0. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1707, 1685, 1421, 1265, 738, 705; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{27}H_{24}O_4Na$ 435.1572; found 435.1550.

*Benzyl 7-methoxy-2-methyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3r**)*. Yellow solid, 187 mg, 87% yield, mp 73-76 ºC. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.81 (d, *J* = 8.2 Hz, 2H), 7.48 (t, *J* = 6.8 Hz, 1H), 7.39 -7.25 (m, 7H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.54 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.50 (d, *J* = 2.2 Hz, 1H), 5.24-5.14 (m, 2H), 4.53 (dd, *J* = 8.4, 3.7 Hz, 1H), 3.72 (s, 3H), 3.25-3.07 (m, 2H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 198.4, 167.0, 163.2, 159.3, 151.2, 137.1, 136.2, 133.0, 129.3, 128.7, 128.6, 128.4, 128.3, 128.2, 116.9, 111.0, 105.6, 101.4, 66.3, 55.5, 48.4, 31.2, 19.9. IR (film, *v*, cm^{-1}) 3054, 2985, 2305, 1708, 1686, 1506, 1265, 739, 704; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{27}H_{24}O_5Na$ 451.1521, found 451.1504.

*Benzyl 7-methoxy-2-methyl-4-(2-oxo-2-(p-tolyl)ethyl)-4H-chromene-3-carboxylate (**3s**)*. Yellow oil, 190 mg, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.73 (d, *J* = 8.2 Hz, 2H), 7.37-7.27 (m, 5H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 1H), 5.19 (s, 2H), 4.53 (dd, *J* = 8.6, 3.6 Hz, 1H), 3.72 (s, 3H), 3.22-3.06 (m, 2H), 2.41 (s, 3H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 198.1, 167.0, 163.1, 159.3, 151.2, 143.8, 136.3, 134.7, 129.4, 129.3, 128.7, 128.4, 128.3, 128.2, 116.9, 111.0, 105.7, 101.3, 66.3, 55.5, 48.4, 31.2, 21.7, 19.9. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1707, 1684, 1637, 1421,1265, 738, 705; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{28}H_{26}O_5Na$ 465.1677; found 465.1668.

*4-Chlorobenzyl 2-methyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3t**)*. Yellow solid, 193 mg, 89% yield, mp 96-98 ºC. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.83-7.78 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.29-7.19 (m, 5H), 7.14 (td, *J* = 7.8, 1.6 Hz, 1H), 7.02-6.94 (m, 2H), 5.18-5.09 (m, 2H), 4.61 (dd, *J* = 6.8, 5.0 Hz, 1H), 3.25-3.14 (m, 2H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 198.1, 166.7, 163.5, 150.5, 137.0, 134.7, 134.1, 133.1, 129.7, 128.9, 128.8, 128.6, 128.2, 127.9, 124.9, 124.7, 116.1, 105.1, 65.4, 48.4, 31.4, 19.93. IR (film, *v*, cm^{-1}) 3053, 2986, 2305, 1687, 1421, 1265, 738, 705; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{26}H_{21}ClO_4Na$ 455.1026; found 455.1012.

*4-Methoxybenzyl 2-methyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3u**)*. Yellow solid, 193 mg, 90% yield, mp 78-81 ºC. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.81 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.20-7.09 (m, 2H), 7.01-6.92 (m, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.19-5.06 (m, 2H), 4.59 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.76 (s, 3H), 3.24-3.12 (m, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 198.2, 166.9, 163.1, 159.6, 150.6, 137.1, 133.0, 130.1, 128.8, 128.6, 128.4, 128.3, 127.8, 124.9, 124.5, 116.1, 114.0, 105.3, 66.0, 55.3, 48.3, 31.6, 19.8. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1707, 1685, 1488, 1265, 738, 704; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{27}H_{24}O_5Na$ 451.1521; found 451.1511.

*2-Chlorobenzyl 2-methyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3v**)*. Yellow Oil, 182 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.82 (d, *J* = 7.0 Hz, 2H), 7.51-7.41 (m, 2H), 7.34 (t, *J* = 8.0 Hz, 3H), 7.25-7.17 (m, 3H), 7.13 (td, *J* = 7.8, 1.6 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 2H), 5.36-5.24 (m, 2H), 4.62 (dd, *J* = 8.0, 3.8 Hz, 1H), 3.31-3.17 (m, 2H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 198.1, 166.7, 163.7, 150.6, 137.1, 133.9, 133.0, 130.3, 129.7, 129.6, 128.9, 128.6, 128.3, 127.8, 127.1, 124.9, 124.6, 124.5, 116.1, 105.1, 63.8, 48.3, 31.6, 20.0. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1708, 1685, 1420, 1265, 739, 705; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{26}H_{21}ClO_4Na$ 455.1026; found 455.1010.

*3,4-Dimethoxybenzyl 2-methyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3w**)*. Yellow Oil, 193 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.79 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.20-7.08 (m, 2H), 6.96 (td, *J* = 8.4, 2.0 Hz, 2H), 6.89 (d, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.18-5.05 (m, 2H), 4.60 (t, *J* = 6.0 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.18 (s, 1H), 3.17 (d, *J* = 2.0 Hz, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 198.1, 166.9, 163.2, 150.5, 149.0, 137.00, 133.1, 128.8, 128.7, 128.7, 128.6, 128.2, 127.8, 124.9, 124.7, 121.2, 116.1, 111.7, 111.0, 105.3, 66.3, 55.9, 55.9, 48.4, 31.5, 19.9. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1706, 1685, 1518, 1420, 1265, 738, 704; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{28}H_{26}O_6Na$ 481.1627; found 481.1612.

*Ethyl 2-methyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3x**)*. Yellow oil, 136 mg, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.88 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44-7.37 (m, 2H), 7.18 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.13 (td, *J* = 7.8, 1.6 Hz, 1H), 7.02-6.92 (m, 2H), 4.56 (dd, *J* = 8.2, 4.0 Hz, 1H), 4.24-4.13 (m, 2H), 3.28-3.13 (m, 2H), 2.42 (s, 3H), 1.25 (t, *J* = 7.2, 0.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 198.2, 167.1, 162.8, 150.7, 137.1, 133.1, 128.8, 128.6, 128.3, 127.8, 125.0, 124.5, 116.08, 105.6, 60.4, 48.3, 31.7, 19.8, 14.4. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1701, 1685, 1448, 1265, 739, 705; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{21}H_{20}O_4Na$ 359.1259; found 359.1240.

*Benzyl 2-ethyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3y**)*. Yellow solid, 182 mg, 88% yield, mp 100-103 ºC. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.81 (d, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.39-7.24 (m, 7H), 7.20-7.10 (m, 2H), 6.98 (dd, *J* = 7.4, 4.0 Hz, 2H), 5.25-5.15 (m, 2H), 4.59 (dd, *J* = 8.4, 3.8 Hz, 1H), 3.28-3.12 (m, 2H), 2.96 (dq, *J* = 14.8, 7.4 Hz, 1H), 2.76-2.65 (m, 1H), 1.18 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$; δ, ppm) 198.2, 168.0, 166.6, 150.9, 137.1, 136.2, 133.0, 128.8, 128.7, 128.6, 128.3, 128.2, 127.8, 125.0, 124.5, 116.0, 104.7, 66.3, 48.2, 31.9, 26.3, 11.8. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1708, 1685, 1265,1420, 738, 705; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for $C_{27}H_{24}O_4Na$ 435.1572; found 435.1562.

*Benzyl 2-benzyl-4-(2-oxo-2-phenylethyl)-4H-chromene-3-carboxylate (**3z**)*. White solid, 209 mg, 88% yield, mp 71-74 ºC. ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.81 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.54-7.46 (m, 1H), 7.38-7.08 (m, 14H), 7.00-6.91 (m, 2H), 5.27-5.17 (m, 2H), 4.66 (dd, *J* = 8.4, 3.8 Hz, 1H), 4.37 (d,

J = 14.2 Hz, 1H), 4.06 (d, *J* = 14.4 Hz, 1H), 3.31-3.15 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 198.1, 166.6, 164.2, 150.7, 137.4, 137.0, 136.0, 133.1, 129.0, 128.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 127.9, 126.6, 124.9, 124.6, 116.2, 106.4, 66.5, 48.2, 38.1, 32.0. IR (film, *v*, cm^{-1}) 3053, 2986, 2305, 1687, 1421,1265, 738, 704; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{32}H_{26}O_4Na$ 497.1728; found 497.1717.

Benzyl 3-methyl-2-methylene-4-(2-oxo-2-phenylethyl) chromane-3-carboxylate ***(4a)***. Yellow oil, 136 mg, 66% yield. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.86 (d, *J* = 7.8 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 4.8 Hz, 3H), 7.20-7.11 (m, 3H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.85 (dd, *J* = 17.2, 8.2 Hz, 2H), 5.11-5.00 (m, 2H), 4.87 (d, *J* = 1.6 Hz, 1H), 4.70 (d, *J* = 1.6 Hz, 1H), 3.89 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.42 (dd, *J* = 18.2, 3.8 Hz, 1H), 3.17 (dd, *J* = 18.2, 7.6 Hz, 1H), 1.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 197.8, 172.3, 156.0, 151.5, 136.7, 135.5, 133.3, 128.7, 128.6, 128.3, 128.3, 128.2, 128.2, 128.2, 124.8, 121.9, 115.7, 92.6, 67.1, 47.9, 42.1, 38.8, 22.8. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1729, 1685, 1490, 1456, 1265, 746, 704; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{27}H_{24}O_4Na$ 435.1572; found 435.1561.

Benzyl 3-ethyl-2-methylene-4-(2-oxo-2-phenylethyl) chromane-3-carboxylate ***(4b)***. Yellow oil, 137 mg, 137 mg, 64% yield. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.78 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.41-7.29 (m, 4H), 7.28-7.21 (m, 3H), 7.18-7.09 (m, 2H), 6.83 (td, *J* = 8.4, 2.2 Hz, 2H), 5.19-5.00 (m, 4H), 4.01 (dd, *J* = 8.2, 3.8 Hz, 1H), 3.19 (dd, *J* = 17.6, 3.6 Hz, 1H), 3.02 (dd, *J* = 17.6, 8.4 Hz, 1H), 1.80 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.67 (dq, *J* = 14.6, 7.4 Hz, 1H), 0.81 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 197.5, 171.5, 152.5, 151.2, 136.9, 135.5, 133.1, 129.5, 128.7, 128.6, 128.6, 128.6, 128.4, 128.1, 124.8, 121.7, 115.5, 95.2, 77.5, 77.1, 76.8, 67.0, 53.1, 43.8, 37.7, 28.3, 9.0. IR (film, *v*, cm^{-1}) 3054, 2986, 2305, 1734, 1685, 1458, 1117, 1265, 738, 704; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{28}H_{26}O_4Na$ 449.1728; found 449.1710.

Benzyl 3-benzyl-2-methylene-4-(2-oxo-2-phenylethyl) chromane-3-carboxylate ***(4c)***. Yellow solid, 147 mg, 60% yield. mp 92-94 ºC. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.79-7.69 (m, 2H), 7.52-7.45 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.30-7.21 (m, 6H), 7.21-7.15 (m, 4H), 7.00-6.88 (m, 4H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.06-4.99 (m, 3H), 4.12 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.18-2.97 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 197.2, 170.6, 151.9, 151.2, 136.9, 135.8, 135.1, 133.2, 133.1, 130.2, 130.1, 128.9, 128.7, 128.6, 128.6, 128.1, 128.1, 127.1, 124.7, 121.9, 115.6, 96.3, 67.1, 54.2, 44.5, 41.5, 37.8. IR (film, *v*, cm^{-1}) 3054, 2985, 2305, 1734, 1708, 1685, 1488, 1265,1186, 738, 704; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{33}H_{28}O_4Na$ 511.1885; found 511.1867.

Benzyl 3-(2-ethoxy-2-oxoethyl)-2-methylene-4-(2-oxo-2-phenylethyl)chromane-3-carboxylate ***(4d)***. colorless oil, 148 mg, 61% yield. ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.80 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.40-7.35 (m, 2H), 7.34-7.23 (m, 5H), 7.17-7.11 (m, 2H), 6.90-6.83 (m, 2H), 5.14-5.06 (m, 2H), 5.05 (s, 2H), 4.05-3.94 (m, 3H), 3.50 (dd, *J* = 17.6, 4.8 Hz, 1H), 2.94 (dd, *J* = 17.6, 7.2 Hz, 1H), 2.87 (d, *J* = 16.8 Hz, 1H), 2.68 (d, *J* = 16.8 Hz, 1H), 1.12 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 197.1, 170.6, 170.0, 151.8, 150.9, 136.8, 135.3, 133.2, 129.3, 128.8, 128.8, 128.7, 128.6, 128.6, 128.4, 128.1, 122.1, 115.8, 96.2, 67.5, 60.8, 49.4, 43.3, 40.2, 38.4, 14.1. IR (film, *v*, cm^{-1}) 3054, 2986, 2305,1739, 1708, 1685, 1488, 1457, 1265, 739, 704; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{30}H_{28}O_6Na$ 507.1783; found 507.1768.

ASSOCIATED CONTENT

Supporting Information

Spectroscopic data for all new compounds **3a-3z, 4a-4d,** and X-ray crystal data (CIF) for **3a.** This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*(G.L.) E-mail: Guigen.Li@ttu.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We would like to acknowledge the financial support from the National Natural Science Foundation of China (No. 21332005, 21672100) and Robert A. Welch Foundation (D-1361, USA).

REFERENCES

1. (a) Pratap, R.; Ram, V. J. Natural and synthetic chromenes, fused chromenes, and versatility of dihydrobenzo[h]chromenes in organic synthesis. *Chem. Rev.* **2014**, 114, 10476-10526. (b) Bowers, W. S.; Ohta, T.; Cleere, J. S.; Marsella, P. A. Discovery of insect anti-juvenile hormones in plants. *Science* **1976**, 193, 542-547. (c) Gómez-Garibay, F.; Calderón, J. S.; De La O Arciniega, M.; Céspedes, C. L.; Téllez-Valdés, O.; Taboada, J. An unusual isopropenyldihydrofuran biflavanol from Tephrosia crassifolia. *Phytochemistry* **1999**, 52, 1159-1163.

2. Bauer, D. J.; Selway, J. W. T.; Batchelor, J. F.; Tisdale, M.; Caldwell Ian C.; Young, D. A. B. 4′,6-Dichloroflavan (BW683C), a new anti-rhinovirus compound. *Nature* **1981**, 292, 369-370.

3. (a) Kemnitzer, W.; Jiang, S.; Zhang, H.; Kasibhatla, S.; CroganGrundy, C.; Blais, C.; Attardo, G.; Denis, R.; Barriault, N.; Vaillancourt, L.; Charron, S.; Dodd, J.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. Discovery of 4-aryl-2-oxo-2H-chromenes as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. *Bioorg. Med. Chem. Lett.* **2008**, 18, 5571-5575.

4. Pérez-Pérez, M. J.; Balzarini, J.; Rozenski, J.; De Clercq, E.; Herdewijn, P. Synthesis and antiviral activity of phosphonate derivatives of enantiomeric dihydro-2H-pyranyl nucleosides. *Bioorg. Med. Chem. Lett.* **1995**, 5, 1115-1118.

5. For selected examples, sees: (a) Jiang, Z.-Z.; Gao, A.; Li, H.; Chen, D.; Ding, C.-H.; Xu, B.; Hou, X.-L. Enantioselective Synthesis of Chromenes via a PalladiumCatalyzed Asymmetric Redox-Relay Heck Reaction. *Chem. Asian J.* **2017**, 12, 3119-3122. (b) Yao, W.; Dou, X.; Lu, Y. Highly Enantioselective Synthesis of 3,4-Dihydropyrans through a Phosphine-Catalyzed [4+2] Annulation of Allenones and β, γ-Unsaturated α-Keto Esters. *J. Am. Chem. Soc.* **2015**, 137, 54−57. (c) Ashtekar, K. D.; Staples, R. J.; Borhan, B. Development of a Formal Catalytic Asymmetric [4+2] Addition of Ethyl-2,3- butadienoate with Acyclic Enones. *Org. Lett.* **2011**, 13, 5732-5735. (d) Pei, C.-K.; Jiang, Y.; Shi, M. Synthesis of optically active dihydropyrans from asymmetric [4+2] cycloaddition of β, γ-unsaturated α-ketoesters with allenic esters. *Org. Biomol. Chem.* **2012**, 10, 4355–4361. (e) Zhao, G.-L.; Shi, Y.-L.; Shi, M. Synthesis of Functionalized 2H-1-Benzopyrans by DBU-Catalyzed Reactions of Salicylic Aldehydes with Allenic Ketones and Esters. *Org. Lett.* **2005**, 7, 4527-4530. (f) Huang, M.-H.; Hao, W.-J.; Jiang, B. Recent Advances in Radical-Enabled Bicyclization and Annulation/1,n-Bifunctionalization Reactions. *Chem. Asian J.* **2018**, 13,2958-2977. (g) Huang, M.-H.; Hao,

W.-J.; Li, G.; Tu, S.-J.; Jiang, B. Recent advances in radical transformations of internal alkynes. *Chem. Commun.* **2018**, 54, 10791-10811.

6. (a) Ma, S. Electrophilic Addition and Cyclization Reactions of Allenes. *Acc. Chem. Res.* **2009**, 42, 1679-1688. (b) Cui, C.-X.; Shan, C.; Zhang, Y.-P.; Chen, X.-L.; Qu, L.-B.; Lan, Y. Mechanism of Phosphine-Catalyzed Allene Coupling Reactions: Advances in Theoretical Investigations. *Chem. Asian J.* **2018**, 13, 1076-1088. (c) Wang, Z.; Xu, X.; Kwon, O. Phosphine catalysis of allenes with electrophiles. *Chem. Soc. Rev.* **2014**, 43, 2927-2940. (d) López, F.; Mascareñas, J. [4+2] and [4+3] catalytic cycloadditions of allenes. *Chem. Soc. Rev.* **2014**, 43, 2904-2915. (e) Santhoshkumar, R.; ChengFickle, C.-H. Reactivity of Allenes in Transition-Metal-Catalyzed C-H Functionalizations. *Asian J. Org. Chem.* **2018**, 7, 1151-1163. (f) Yang, B.; Qiu, Y.; Bäckvall, Jan-E. Control of Selectivity in Palladium(II)-Catalyzed Oxidative Transformations of Allenes. *Acc. Chem. Res.* **2018**, 51, 1520-1531.

7. (a) Li, H.; Lu, Y. Enantioselective Construction of All-Carbon Quaternary Stereogenic Centers by Using Phosphine Catalysis. *Asian J. Org. Chem.* **2017**, 6, 1130-1145. (b) Wang, T.; Han, X.; Zhong, F.; Yao, W.; Lu, Y. Amino Acid-Derived Bifunctional Phosphines for Enantioselective Transformations. *Acc. Chem. Res.* **2016**, 49, 1369-1378. (c) Zhou, R.; He, Z. Advances in Annulation Reactions Initiated by Phosphorus Ylides Generated in situ. *Eur. J. Org. Chem.* **2016**, 1937–1954. (d) Lu, X.; Zhang, C.; Xu, Z. Reactions of Electron-Deficient Alkynes and Allenes under Phosphine Catalysis. *Acc. Chem. Res.* **2001**, 34, 535-544. (e) Meng, X.; Huang, Y.; Zhao, H.; Xie, P.; Ma, J.; Chen, R. PPh_3-Catalyzed Domino Reaction: A Facile Method for the Synthesis of Chroman Derivatives. *Org. Lett.* **2009**, 11, 991-994.

8. (a) Cowen, B. J.; Miller, S. J.; Enantioselective catalysis and complexity generation from allenoates. *Chem. Soc. Rev.* **2009**, 38, 3102-3116. (b) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X. Mechanism, Regioselectivity, and the Kinetics of Phosphine-Catalyzed [3 + 2] Cycloaddition Reactions of Allenoates and Electron-Deficient Alkenes. *Chem. Eur. J.* **2008**, 14, 4361-4373. (c) Creech, G. S.; Zhu, X.-F.; Fonovic, B.; Dudding, T.; Kwon, O. Theory-guided design of Brønsted acid-assisted phosphine catalysis: synthesis of dihydropyrones from aldehydes and allenoates. *Tetrahedron* **2008**, 64, 6935-6942.

9. (a) Gu, Y.; Li, F.; Hu, P.; Liao, D.; Tong, X. Tertiary Amine-Catalyzed (4 + 2) Annulations of δ-Acetoxy Allenoates: Synthesis of Multisubstituted 4*H*-Pyran and 4*H*-Chromene. *Org. Lett.* **2015**, 17, 1106-1109. (b) Ni, C.; Yuan, Y.; Zhang, Y.; Chen, J.; Wang, D.; Tong, X. Construction of polycyclic frameworks via a DMAP-catalysed tandem addition-(4 + 2) annulation sequence of δ-acetoxy allenoate. *Org. Biomol. Chem.* **2017**, 15, 4807-4810. (c) Lorton, C.; Voituriez, A. Phosphine-Promoted Synthesis of 9*H*-Pyrrolo[1,2-a]indole Derivatives via an γ-Umpolung Addition/Intramolecular Wittig Reaction. *J. Org. Chem.* **2018**, 83, 5801−5806. (d) Wang, D.; Tong, X. Phosphine-Catalyzed Asymmetric (3+2) Annulations of δ-Acetoxy Allenoates with 2-Naphthols. *Org. Lett.* **2017**, 19, 6392−6395. (e) Zielke, K.; Waser, M. Formal (4 + 1)-Addition of Allenoates to o-Quinone Methides. *Org. Lett.* **2018**, 20, 768–771.

10. (a) Shi, M.; Dai, L.-Z.; Shi, Y.-L.; Zhao, G.-L. Potassium Carbonate-Catalyzed Reactions of Salicylic Aldehydes with Allenic Ketones and Esters: an Effective Way to Synthesize Functionalized 2H-Chromenes. *Adv. Synth. Catal.* **2006**, 348, 967-972. (b) Zhao, G.-L.; Shi, Y.-L.; Shi, M. Synthesis of Functionalized 2H-1-Benzopyrans by DBU-Catalyzed Reactions of Salicylic Aldehydes with Allenic Ketones and Esters. *Org. Lett.* **2005**, 7, 4527-4530.

11. Selig, P.; Raven, W. A Convenient Allenoate-Based Synthesis of 2-Quinolin-2-yl Malonates and β-Ketoesters. *Org. Lett.* **2014**, 16, 5192-5195.

12. Yao, C.; Bao, Y.; Lu, T.; Zhou, Q. Stereoselective Synthesis of Functionalized Benzooxazepino[5,4-α]isoindolone Derivatives via Cesium Carbonate Catalyzed Formal [5+2] Annulation of 2-(2-Hydroxyphenyl)isoindoline-1,3-dione with Allenoates. *Org. Lett.* **2018**, 20, 2152-2155.

13. (a) Shen, Y.; Cui, S..; Wang, J.; Chen, X.; Lu, P.; Wang, Y. Copper-Catalyzed Three-Component Synthesis of 2-Iminodihydrocoumarins and 2-Iminocoumarins. *Adv. Synth. Catal.* **2010**, 352, 1139-1144. (b) Liu, F.; Wang, J.-Y.; Zhou, P.; Li, G.; Hao, W.-J.; Tu, S.-J.; Jiang, B. Merging [2+2] Cycloaddition with Radical 1,4-Addition: Metal-Free Access to Functionalized Cyclobuta[a]naphthalen-4-ols. *Angew. Chem. Int. Ed.* **2017**, 56, 15570-15574. (C) Sha, H.-K.; Liu, F.; Lu, J.; Liu, Z.-Q.; Hao, W.-J.; Tang, J.-L.; Tu, S.-J.; Jiang, B. Metal-free benzannulation of yne-allenone esters for atom economical synthesis of functionalized 1-naphthols. *Green Chem.* **2018**, 20, 3476-3485. (d) Sha, H.-K.; Xu, T.; Liu, F.; Tang, B.-Z.; Hao, W.-J.; Tu, S.-J.; Jiang, B. Metal-free naphthannulation reactions of yne-allenone esters for accessing polycyclic aromatic hydrocarbons. *Chem. Commun.* **2018**,54, 10415-10418. (e) Kuppusamy, R.; Muralirajan, K.; Cheng C.-H. Cobalt (III)-Catalyzed [5 + 1] Annulation for 2*H*-Chromenes Synthesis via Vinylic C-H Activation and Intramolecular Nucleophilic Addition. *ACS Catal.* **2016**, 6, 3909-3913.

14. Xu, W.; Li, Q.; Cao, C.; Zhang, F.; Zheng, H. Intramolecular oxidative coupling: I_2/TBHP/NaN_3 mediated synthesis of benzofuran derivatives. *Org. Biomol. Chem.* **2015**,13, 6158-6161.

15. Pashikanti, S.; Calderone, J. A.; Nguyen, M. K.; Sibley, C. D.; Santos, W. L. Regio- and Stereoselective Copper(II)-Catalyzed Hydrosilylation of Activated Allenes in Water: Access to Vinylsilanes. *Org. Lett.* **2016**, 18, 2443–2446.