Synthesis H. J. Jin et al. Paper

Regioselective Domino Synthesis of 2-Alkylflavans via Hidden Brønsted Acid Catalysis

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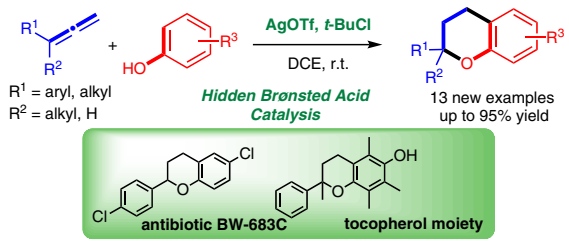

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Abstract A range of alkyl-substituted flavans, which are important structural elements in natural products and pharmaceutical molecules, were prepared by successive hidden Brønsted acid catalyzed domino reaction, intermolecular hydroarylation, and intramolecular hydroalkoxylation. 1,1-Disubstituted allenes were activated under mild acidic AgOTf/t-BuCl condition to initiate the regioselective Friedel–Crafts reaction with phenol derivatives, and the consecutive reaction triggered by the 6-*endo*cyclization led to the formation of a new type of 2-alkylflavan. Mechanistic study of the reaction intermediates and control experiments support the catalytic pathway and advantage of hidden Brønsted acid catalysis.

Key words 2-alkylflavan, hidden Brønsted acid catalyst, arylallene, domino cyclocoupling, regioselectivity

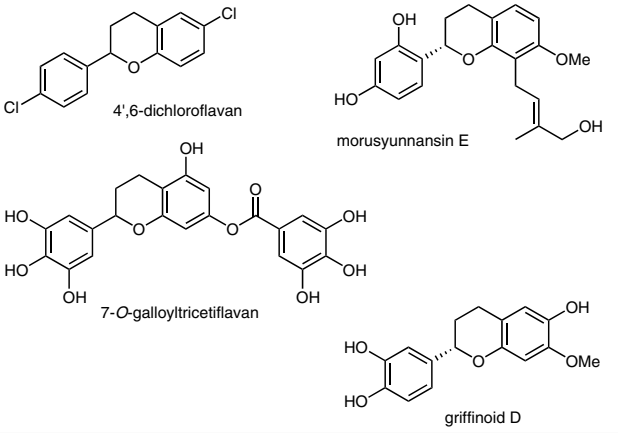
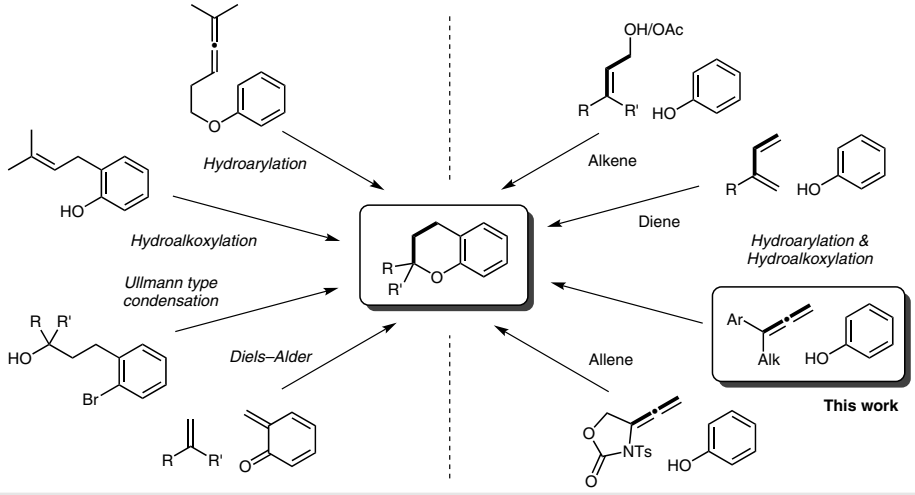


Figure 1 Representative structures of biologically active flavan compounds

Flavans with a 2-arylchroman structure are naturally occurring materials found extensively throughout the plant kingdom, with more than 17 000 compounds that show interesting biological and pharmacological activities.[1,2] For example, 4′,6-dichloroflavan inhibits rhinovirus replication in vitro,[1a] and the antiviral component, 7-*O*-galloyltricetiflavan, from *P. clypearia* exhibits activity against respiratory syncytial virus and Herpes simplex virus type I (Figure 1).[1b] Tyrosinase inhibitory agents, morusyunnansins, were isolated from the leaves of *M. yunnanensis*,[1c] and griffinoid D from the stems of *Combretum griffithii* shows antiplasmodial activity and cytotoxicity toward cancer cell lines.[1d] From these various bioactivities, flavans have attracted the attention of many synthetic chemists; therefore, general procedures for their synthesis have been developed, as shown in Scheme 1.

A variety of methods for flavan synthesis have been developed. An early approach utilized a hetero-Diels–Alder reaction between a substituted alkene and *o*-quinone methide. *o*-Acetoxymethylphenol, 4*H*-1,2-benzoxazine, and *o*-hydroxybenzyl alcohol were employed as *o*-quinone methide precursors under thermal and acidic conditions, which reacted with styrene to provide flavan derivatives.[3a–c] *o*-Quinone methides were also generated as methylene intermediates from phenol and formaldehyde in a three-component reaction.[3d–f] Intramolecular C–O bond formation of *o*-bromophenylpropanols using copper catalysis[4] and alkenyl phenols under acidic media were developed;[5] moreover, gold-catalyzed hydroarylation of allenyl ethers afforded chroman derivatives.[6] Tandem C–C and C–O coupling between various C3 units and phenol have been extensively investigated for construction of the chroman structure. Silver or copper triflate catalyzed the addition of phenols to 1,3-dienes, and Hintermann proposed this type of condition as 'hidden Brønsted acid catalysis' in which Brønsted acid (TfOH) was released from metal triflate in dichlo-

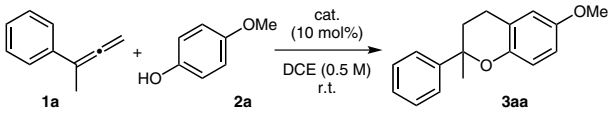


Scheme 1 Various approaches for the synthesis of flavans

roethane (DCE) or *t*-BuCl.[7] The 1,3-dienes tested in previous reports were limited to few commercial sources, and inappropriate to construct the flavan (2-arylchroman) skeleton. Molybdenum or indium complexes catalyzed the reaction of allylic alcohols/acetates with phenols.[8] Allene as a C3 component also underwent a tandem reaction under Brønsted acid catalysis (2.5 mol% Tf_2NH). However, allenes possessing an electron-withdrawing group, allene sulfonamides, were solely examined to provide functionalized chromans.[9] As part of our ongoing interest in economical domino reactions with allenes, interesting substrates to control stereo- and regioselectivities, we report a short and efficient procedure for the first synthesis of 2-alkylflavans from aryl- and alkyl-substituted allenes, employing hidden Brønsted acid catalyzed intermolecular hydroarylation and intramolecular hydroalkoxylation reactions. This one-pot synthesis exhibited high regioselectivity for both hydroarylation at the terminal allene position and hydroalkoxylation forming six-membered pyran derivatives.

To examine the feasibility of a domino reaction of allene and phenol, 1,1-disubstituted allene **1a** and 4-methoxyphenol (**2a**) were selected as representative substrates in the investigation of various Lewis acid catalysts. In a preliminary investigation, reaction of a monosubstituted allene and phenol provided the product mixture of the desired flavan and two hydroarylated regioisomers (Table S1 in Supporting Information). It was thought that the additional methyl substituent on **1a** might promote the C–O bond formation reaction and the use of 4-methoxyphenol (**2a**) might control the regioselectivity and increase the reactivity in the hydroarylation step. As shown in Table 1, the catalytic activities of iron salts were tested first, and exhibited efficiency in the hydrofunctionalization reaction of allenes.[10] Various iron catalysts led to formation of flavan **3aa** in moderate yield after long reaction times (Table 1, entries 1–4). Other metal triflate salts, such as Ga(III), Sc(II), Cu(II), Sn(II), and Ag(I), resulted in low to good yields (entries 5–9). Bearing in mind some ambiguity that the counteranion of the metal salt could generate Brønsted acid by proton transfer,[11] the hidden Brønsted acid system was also intro-

Table 1 Optimization of Conditions for Flavan Synthesis[a]



Entry	Catalyst	Time (h)	Yield (%)[b]
1	$FeCl_3$	24	15
2	$Fe(acac)_3$	24	0
3	$Fe(OTs)_3$	72	45
4	$Fe(OTf)_3$	72	15
5	$Ga(OTf)_3$	15	78
6	$Sc(OTf)_2$	72	0
7	$Cu(OTf)_2$	72	71
8	$Sn(OTf)_2$	15	80
9	AgOTf	40	60
10[c]	AgOTf, *t*-BuCl	2	82
11[d]	AgOTf, *t*-BuCl	2	90
12	TfOH	72	37
13	TsOH	72	64
14	CF_3CO_2H	72	16
15	AcOH	72	0

[a] Reaction conditions: allene **1a** (1.5 mmol), 4-methoxyphenol (**2a**; 1.0 mmol), catalyst (10 mol%), DCE (0.5 M) under N_2, unless otherwise specified.
[b] Isolated yield.
[c] Reaction with 10 mol% AgOTf and 40 mol% *t*-BuCl.
[d] Reaction with 3 mol% AgOTf and 12 mol% *t*-BuCl.

duced to these substrates.[12] Mildly generated TfOH from AgOTf and *t*-BuCl was found to efficiently perform the sequential transformation of allene **1a** with 3 mol% AgOTf in shorter time (entry 11). It is of interest to note that *t*-BuCl was found to be a better co-agent for the hidden acid formation than dichloroethane, in terms of the reaction efficiency (entries 9 and 10). Direct treatment with TfOH led to decomposition of the starting allene, the corresponding intermediate, and the product, presumably due to the strong acidity of TfOH; moreover, low conversion was observed under these conditions with other types of Brønsted acid catalysts (entries 12–15).

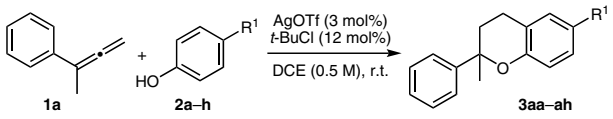
With AgOTf (3 mol%) and *t*-BuCl (12 mol%) as the selected catalyst system, the scope of the tandem reaction was examined with a variety of phenol derivatives (Table 2). For substituted phenols **2a–d**, with electron-donating groups such as MeO, BnO, Me, or *t*-Bu at the *para*-position, the corresponding flavan derivatives **3aa–ad** were isolated in 66–95% yield; however, an electron-withdrawing chloro-substituent significantly retarded the rate of reaction. Phenol **2g** bearing a methoxy substituent at the *meta*-position is presumably not sufficiently electron-rich to undergo the first hydroarylation reaction. 2,3,5-Trimethylbenzene-1,4-diol (**2h**) also participated in the reaction to afford flavan **3ah**, which has the α-tocopherol core structure.

The allene substrate scope was next explored (Table 3). With 4-methoxyphenol (**2a**), a broad range of allenes with methyl- or bromo-substituted benzene, naphthalene, and thiophene substituents (**1b**, **1d–f**) proved to be suitable substrates for the current catalytic system, giving the corresponding products in good yields. However, the presence of a methoxy group, electron-donating through conjugation, seemed to significantly decrease the efficiency of the reaction, presumably due to formation of a quite stable and delocalized carbocation intermediate (Table 3, entry 2). Ethyl-, isopropyl-, and dialkyl-substituted allenes were also compatible with the reaction, delivering the corresponding flavans in up to 80% yield (entries 6–8). Additionally, compound **3ja** with two chroman units was also prepared, albeit in low yield, due to the chemical lability of diallene **1j**. According to two identical methyl (CH_3) peaks in ^1H NMR, a mixture of meso compound and diastereomer of **3ja** seemed to be produced in a similar amount.

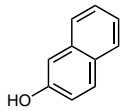
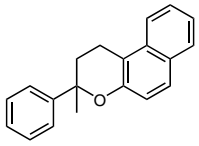
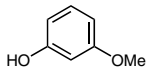
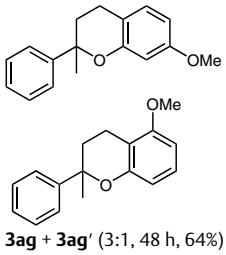
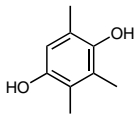
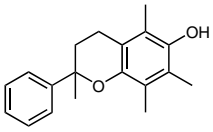
Remarkably, the one-pot construction of **3ke** was achieved by reacting mono-substituted allene **1k** with *p*-chlorophenol (**2e**) (Scheme 2). Although the yield was moderate, the formation of antibiotic 4′,6-dichloroflavan **3ke** (BW-683C) showcases this highly attractive method for flavan synthesis from readily accessible starting materials.

The increased reactivity of electron-rich phenols and more highly substituted allene derivatives suggests that the reaction mechanism involves carbocation intermediates in the presence of hidden Brønsted acid. Flavan **3aa** can be obtained from **1a** and **2a** by two different reaction pathways:

Table 2 Domino Synthesis of Flavan Derivatives from Various Phenols

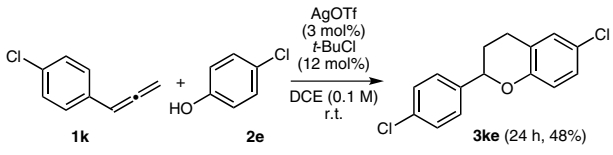


1a 2a–h 3aa–ah

Entry	Phenol	Product (time, yield)[a]
1	**2a** (R^1 = OMe)	**3aa** (1 h, 90%)
2	**2b** (R^1 = OBn)	**3ab** (12 h, 95%)
3	**2c** (R^1 = Me)	**3ac** (1 h, 66%)
4	**2d** (R^1 = *t*-Bu)	**3ad** (2 h, 68%)
5	**2e** (R^1 = Cl)	**3ae** (12 h, 36%)
6	 **2f**	 **3af** (2 h, 90%)
7	 **2g**	 **3ag** + **3ag′** (3:1, 48 h, 64%)
8	 **2h**	 **3ah** (2 h, 80%)

[a] Isolated yield.

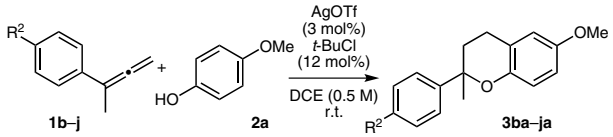
the first route involves intermolecular hydroarylation to **4aa**, followed by intramolecular hydroalkoxylation;[7] an alternative route involves the same reactions but in the opposite order (Scheme 3; eq. 1). However, the preliminary results of phenyl allene (**1l**, see Table S1 in Supporting Information) with phenol, forming two hydroarylated regioisomers (**4li** and **4li′**) indicated a more favorable intermolecular hydroarylation, while no intermediate resulting from intermolecular hydroalkoxylation was observed un-



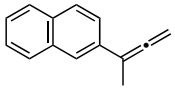
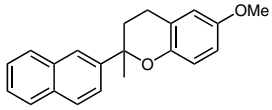
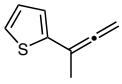
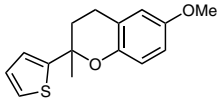
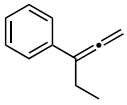
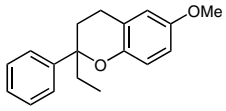
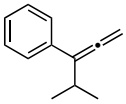
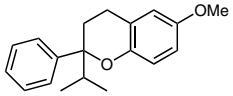
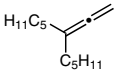
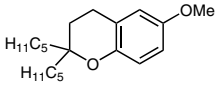
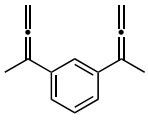
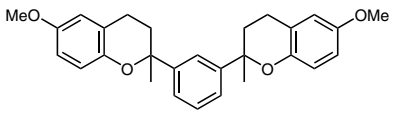
1k 2e **3ke** (24 h, 48%)

Scheme 2 Synthesis of the antibiotic 4′,6-dichloroflavan

Table 3 Domino Synthesis of Flavan Derivatives from Various Allenes



1b–j 2a 3ba–ja

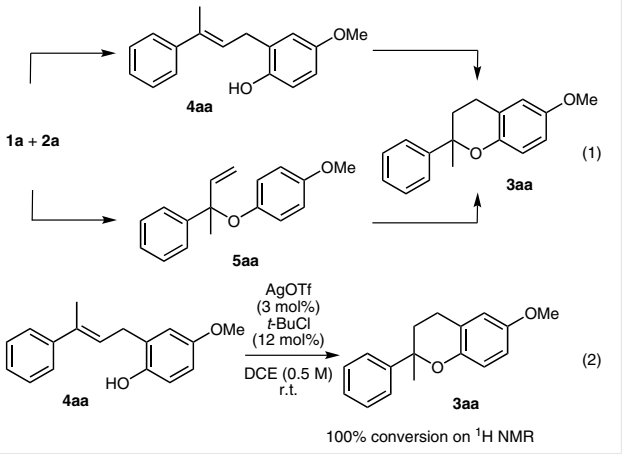
Entry	Allene	Product (time, yield)[a]
1	**1b** (R^2 = Me)	**3ba** (17 h, 58%)
2	**1c** (R^2 = OMe)	**3ca** (20 h, 5%)
3	**1d** (R^2 = Br)	**3da** (48 h, 49%)
4	 **1e**	 **3ea** (5 h, 60%)
5	 **1f**	 **3fa** (48 h, 49%)
6	 **1g**	 **3ga** (12 h, 80%)
7	 **1h**	 **3ha** (12 h, 37%)
8	 **1i**	 **3ia** (48 h, 72%)
9	 **1j**	 **3ja** (1 h, 13%)

[a] Isolated yield.

der various conditions. This mechanism is further supported by the reaction of **4aa**, which was quantitatively converted to **3aa** in the presence of hidden Brønsted acid catalyst (Scheme 3; eq. 2). Additionally, the reactions did not proceed in the presence of the non-coordinating base 2,6-di-*tert*-butylpyridine, which only binds to protons.

A catalytic cycle involving Brønsted acid catalysis has been proposed to explain the observed pattern of reactivity (Scheme 4). The addition of *t*-BuCl to a stirred solution of AgOTf at ambient temperature in DCE immediately produced a white precipitate of AgCl, and TfOH was generated in situ by E1 elimination.[7c] The hidden Brønsted acid catalyst reacted with allene to form the carbocation intermediate **I**, which was resonance-stabilized as a tertiary benzylic carbocation. Hydroarylation and subsequent intermolecular hydroalkoxylation afforded the alkyl-substituted flavan derivative.

In conclusion, a highly efficient catalytic system is presented for the construction of the flavan skeleton via intermolecular hydroarylation and intramolecular hydroalkoxylation reactions of allenes and phenols. AgOTf and *t*-BuCl



Scheme 3 Mechanistic investigation

as hidden Brønsted acid precursors catalyzed regioselective domino reactions from readily accessible aryl allenes and phenols under mild conditions to prepare a variety of unknown flavans, in expectation of wide industrial applicability. Further studies on consecutive functionalization reactions using various accumulated multiple bond systems and chiral flavan synthesis is underway.

Unless otherwise specified, all reactions were conducted under a slight positive pressure of dry nitrogen. All solvents were reagent grade and other commercially available reagents were used as received. Flash chromatography was carried out using silica gel (70–230 mesh ASTM). NMR spectra were recorded in $CDCl_3$ using one of several JEOL 300 MHz spectrometers. Mass spectra were recorded using electron impact (EI) method.

Flavan Derivatives 3; General Procedure

The hidden Brønsted acid catalyst was prepared first as follows: AgOTf (3 mol%) and *t*-BuCl (12 mol%) were stirred for 10 min at r.t. and any volatiles were removed under reduced pressure. The resulting concentrated mixture was diluted in DCE (0.5 M) and treated with allene **1** (1.5 mmol) and phenol **2** (1.0 mmol) at r.t. The reaction progress was monitored by TLC analysis, and quenched by the addition of sat. aq NH_4Cl (3 mL). The organic layer was separated, extracted with CH_2Cl_2 (3 × 3 mL), dried ($MgSO_4$), and concentrated. Silica gel column chromatography provided the desired flavan **3**. All the products were fully characterized by ^1H and ^{13}C NMR spectroscopy and HRMS analysis.

6-Methoxy-2-methyl-2-phenylchroman (3aa)

According to the general procedure, a yellow oil (0.23 g, 90%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

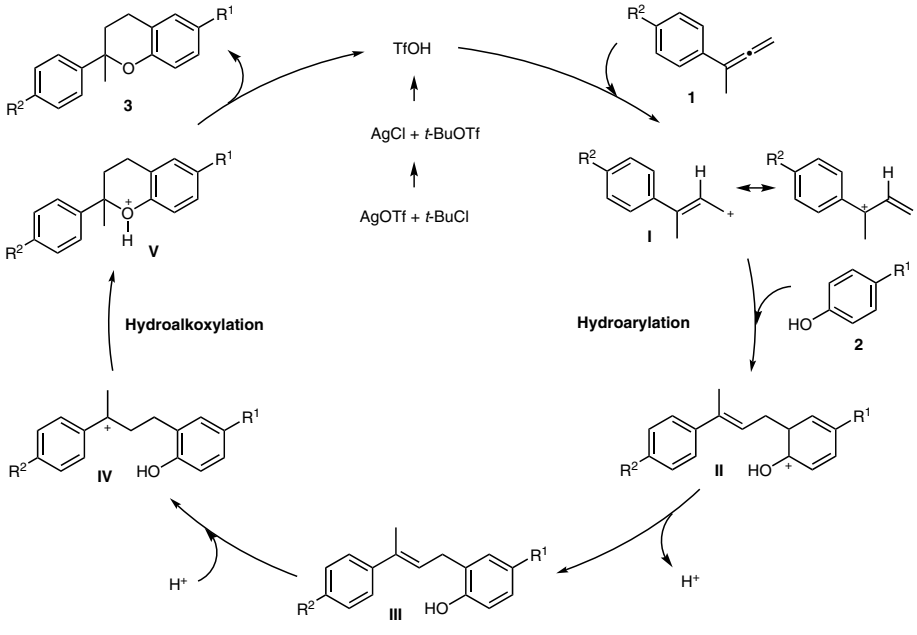
^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.15 (m, 5 H), 6.90 (d, *J* = 8.8 Hz, 1 H), 6.70 (dd, *J* = 9.0, 3.1 Hz, 1 H), 6.48 (d, *J* = 3.1 Hz, 1 H), 3.69 (s, 3 H), 2.61 (dt, *J* = 15.9, 4.3 Hz, 1 H), 2.47–2.31 (m, 2 H), 2.10–1.99 (m, 1 H), 1.61 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.1, 148.2, 145.7, 128.4, 126.7, 125.0, 122.1, 117.5, 113.8, 113.5, 78.0, 55.5 32.7, 30.1, 22.9.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{18}O_2$: 254.1307; found: 254.1304.

(*E*)-4-Methoxy-2-(3-phenylbut-2-enyl)phenol (4aa)

During the preparation of **3aa** under the hidden Brønsted acid catalysis, the formation of the intermediate **4aa** was observed, which could be isolated as a mixture with *p*-methoxyphenol.



Scheme 4 Plausible mechanism

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.29 (m, 4 H), 7.26–7.22 (m, 1 H), 6.82–6.78 (m, 1 H), 6.74–6.71 (m, 1 H), 6.68–6.65 (m, 1 H), 5.93 (t, *J* = 7.3 Hz, 1 H), 3.75 (s, 3 H), 3.53 (d, *J* = 7.3 Hz, 2 H), 2.16 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9, 143.4, 137.0, 128.3, 128.0, 127.9, 127.0, 125.8, 125.3, 116.2, 115.8, 112.1, 55.7, 29.9, 15.9.

6-(Benzyloxy)-2-methyl-2-phenylchroman (3ab)

According to the general procedure, a yellow solid (0.31 g, 95%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1); mp 122–123 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.17 (m, 10 H), 6.90 (d, *J* = 8.8 Hz, 1 H), 6.78 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.58 (d, *J* = 2.9 Hz, 1 H), 4.95 (s, 2 H), 2.62 (dt, *J* = 17.2, 5.3 Hz, 1 H), 2.49–2.33 (m, 2 H), 2.16–2.01 (m, 1 H), 1.62 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 148.6, 145.9, 137.7, 128.7, 128.5, 128.0, 127.7, 126.9, 125.2, 122.4, 117.6, 115.2, 114.6, 78.2, 70.7, 32.9, 30.3, 23.0.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{23}H_{22}O_2$: 330.1620; found: 330.1621.

2,6-Dimethyl-2-phenylchroman (3ac)[8a]

According to the general procedure, a yellow oil (0.16 g, 66%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.15 (m, 5 H), 6.93 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 8.1 Hz, 1 H), 6.75 (s, 1 H), 2.59 (dt, *J* = 16.7, 5.0 Hz, 1 H), 2.45–2.31 (m, 2 H), 2.21 (s, 3 H), 2.04 (ddd, *J* = 15.2, 9.9, 4.0 Hz, 1 H), 1.62 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.0, 145.9, 129.9, 129.5, 128.5, 128.2, 126.8, 125.1, 121.4, 116.8, 78.3, 33.0, 30.3, 22.6, 20.5.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{18}O$: 238.1358; found: 254.1355.

6-(*tert*-Butyl)-2-methyl-2-phenylchroman (3ad)

According to the general procedure, a yellow solid (0.19 g, 68%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1); mp 68–71 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10–7.20 (m, 5 H), 7.16 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.94 (d, *J* = 2.5 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 2.65 (dt, *J* = 15.9, 4.7 Hz, 1 H), 2.50–2.32 (m, 2 H), 2.07 (ddd, *J* = 14.1, 8.8, 4.2 Hz, 1 H), 1.63 (s, 3 H), 1.26 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.0, 146.1, 142.7, 128.5, 126.8, 126.2, 125.2, 124.6, 120.8, 116.4, 78.3, 34.0, 33.2, 31.6, 30.1, 22.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{24}O$: 280.1827; found: 280.1828.

6-Chloro-2-methyl-2-phenylchroman (3ae)

According to the general procedure in DCE (0.1 M), a yellow oil (94 mg, 36%) was obtained after column chromatography on silica gel (hexane/EtOAc 70:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.16 (m, 5 H), 7.08 (dd, *J* = 8.6, 2.4 Hz, 1 H), 6.92 (d, *J* = 2.2 Hz, 1 H), 6.90, (d, *J* = 8.8 Hz, 1 H), 2.62 (dt, *J* = 17.0, 5.0 Hz, 1 H), 2.47–2.34 (m, 2 H), 2.05 (ddd, *J* = 15.2, 9.9, 4.0 Hz, 1 H), 1.63 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.0, 145.3, 129.1, 128.6, 127.5, 127.1, 125.0, 124.8, 123.4, 118.4, 78.8, 32.5, 30.3, 22.6.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{15}ClO$: 258.0811; found: 258.0813.

3-Methyl-3-phenyl-2,3-dihydro-1*H*-benzo[*f*]chromene (3af)[3d]

According to the general procedure, a white solid (0.25 g, 90%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1); mp 94–97 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76–7.65 (m, 3 H), 7.44–7.38 (m, 3 H), 7.32–7.15 (m, 5 H), 3.04 (dt, *J* = 16.2, 4.3 Hz, 1 H), 2.67–2.52 (m, 2 H), 2.23 (ddd, *J* = 15.4, 9.7, 4.4 Hz, 1 H), 1.70 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.5, 145.3, 132.9, 128.8, 128.4, 127.9, 126.8, 126.2, 124.9, 123.1, 122.0, 119.4, 113.5, 78.1, 32.5, 29.9, 19.2.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{18}O$: 274.1358; found: 274.1355.

7-Methoxy-2-methyl-2-phenylchroman (3ag)

According to the general procedure, a yellow oil (0.17 g, 64%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1) as a 3:1 mixture of **3ag** and its regioisomer **3ag′** (5-methoxy-2-methyl-2-phenylchroman).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 5 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.56 (d, *J* = 2.2 Hz, 1 H), 6.41, (dd, *J* = 8.4, 2.6 Hz, 1 H), 3.80 (s, 3 H), 2.62–2.55 (m, 1 H), 2.41–2.30 (m, 2 H), 2.10–2.00 (m, 1 H), 1.64 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 155.0, 145.8, 130.0, 128.5, 126.8, 125.1, 113.9, 107.1, 101.7, 78.6, 55.4, 33.2, 30.1, 21.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{18}O_2$: 254.1307: found: 254.1311.

2,5,7,8-Tetramethyl-2-phenylchroman-6-ol (3ah)[13]

According to the general procedure, a yellow oil (0.23 g, 80%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.16 (m, 5 H), 4.17 (s, 1 H), 2.64–2.56 (m, 1 H), 2.43–2.24 (m, 2 H), 2.29 (s, 3 H), 2.19 (s, 3 H), 2.07 (ddd, *J* = 12.5, 6.6, 3.1 Hz, 1 H), 2.00 (s, 3 H), 1.59 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.3, 145.8, 145.0, 128.5, 126.7, 125.0, 122.4, 121.2, 118.6, 117.7, 76.7, 32.8, 30.2, 21.1, 12.3, 12.0, 11.3.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{19}H_{22}O_2$: 282.1620; found: 282.1622.

6-Methoxy-2-methyl-2-(*p*-tolyl)chroman (3ba)

According to the general procedure, a yellow oil (0.16 g, 58%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 9.0 Hz, 1 H), 6.70 (dd, *J* = 8.6, 2.7 Hz, 1 H), 6.48 (d, *J* = 3.1 Hz, 1 H), 3.71 (s, 3 H), 2.65–2.58 (m, 1 H), 2.53–2.31 (m, 2 H), 2.30 (s, 3 H), 2.04 (ddd, *J* = 14.6, 9.1, 4.3 Hz, 1 H), 1.67 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2, 148.4, 142.9, 136.4, 129.2, 125.1, 122.3, 117.6, 114.0, 113.7, 78.1, 55.7, 32.8, 30.4, 23.0, 21.0.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{20}O_2$: 268.1463; found: 268.1461.

6-Methoxy-2-(4-methoxyphenyl)-2-methylchroman (3ca)

According to the general procedure in DCE (0.1 M), a yellow oil (22 mg, 5%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.1 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 1 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 6.71 (dd, *J* = 8.1, 2.9 Hz, 1 H), 6.49 (d, *J* = 2.6 Hz, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 2.70–2.53 (m, 1 H), 2.53–2.41 (m, 1 H), 2.41–2.29 (m, 1 H), 2.12–1.97 (m, 1 H), 1.60 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5, 153.3, 148.4, 138.0, 126.4, 122.3, 117.6, 114.0, 113.9, 113.7, 77.9, 55.7, 55.3, 32.9, 30.4, 23.0.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{20}O_3$: 284.1412; found: 284.1407.

2-(4-Bromophenyl)-6-methoxy-2-methylchroman (3da)

According to the general procedure, a yellow oil (0.17 g, 49%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.38 (m, 2 H), 7.26–7.21 (m, 2 H), 6.88 (d, *J* = 8.8 Hz, 1 H), 6.71 (dd, *J* = 9.1, 2.9 Hz, 1 H), 6.48 (d, *J* = 2.9 Hz, 1 H), 3.72 (s, 3 H), 2.64 (dt, *J* = 16.7, 4.6 Hz, 1 H), 2.47–2.29 (m, 2 H). 2.05 (ddd, *J* = 14.6, 9.3, 4.0 Hz, 1 H), 1.59 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4, 148.0, 145.0, 131.7, 127.1, 122.1, 120.8, 117.7, 114.0, 113.8, 77.8, 55.7, 32.6, 30.3, 22.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{17}BrO_2$: 332.0412; found: 332.0412.

6-Methoxy-2-methyl-2-(naphthalen-2-yl)chroman (3ea)

According to the general procedure, a yellow oil (0.18 g, 60%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.75 (m, 4 H), 7.50 (dd, *J* = 2.0, 8.6 Hz, 1 H), 7.45–7.41 (m, 2 H), 6.97 (d, *J* = 8.8 Hz, 1 H), 6.74 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.47 (d, *J* = 2.4 Hz, 1 H), 3.70 (s, 3 H), 2.66 (dt, *J* = 17.0, 5.2 Hz, 1 H), 2.54–2.42 (m, 2 H), 2.14 (ddd, *J* = 15.5, 10.0, 4.1 Hz, 1 H), 1.70 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 148.4, 143.2, 133.4, 132.5, 128.3, 128.7, 126.2, 125.9, 124.1, 123.5, 122.3, 117.7, 114.0, 113.8, 18.3, 55.7, 32.8, 30.3, 23.1.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{21}H_{20}O_2$: 304.1463; found: 304.1460.

6-Methoxy-2-methyl-2-(thiophen-2-yl)chroman (3fa)

According to the general procedure, a yellow oil (0.13 g, 49%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.14 (m, 1 H), 6.91–6.83 (m, 3 H), 6.70 (dd, *J* = 9.0, 3.1 Hz, 1 H), 6.53 (d, *J* = 3.3 Hz, 1 H), 3.73 (s, 3 H), 3.73–2.66 (m, 1 H), 2.37–2.29 (m, 1 H), 2.18–2.08 (m, 1 H), 1.71 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 130.0, 127.3, 126.8, 124.1, 123.0, 121.8, 117.8, 114.0, 113.7, 77.3, 55.7, 34.1, 30.7, 23.0.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{16}O_2S$: 260.0871; found: 260.0874.

2-Ethyl-6-methoxy-2-phenylchroman (3ga)

According to the general procedure, a yellow oil (0.22 g, 80%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.17 (m, 5 H), 6.91 (d, *J* = 8.8 Hz, 1 H), 6.71 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.47, (d, *J* = 2.9 Hz, 1 H), 3.71 (s, 3 H), 2.60 (dt, *J* = 16.5, 4.2 Hz, 1 H), 2.47–2.29 (m, 2 H), 2.08 (ddd, *J* = 14.7, 9.2, 3.8 Hz, 1 H), 1.91 (dq, *J* = 23.3, 7.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.1, 148.3, 144.1, 128.3, 126.7, 125.9, 122.6, 117.6, 113.9, 113.6, 80.6, 55.7, 35.7, 30.9, 22.8, 7.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{20}O_2$: 268.1463; found: 268.1466.

2-Isopropyl-6-methoxy-2-phenylchroman (3ha)

According to the general procedure, a yellow oil (0.11 g, 37%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.14 (m, 5 H), 6.89 (d, *J* = 8.8 Hz, 1 H), 6.68 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.41, (d, *J* = 3.3 Hz, 1 H), 3.69 (s, 3 H), 2.57–2.42 (m, 1 H), 2.40–2.30 (m, 2 H), 2.16–2.01 (m, 2 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 0.87 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.1, 148.6, 142.8, 128.0, 126.8, 126.6, 122.8, 117.6, 113.9, 113.6, 28.6, 55.7, 38.7, 27.8, 22.9, 17.3, 16.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{19}H_{22}O_2$: 282.1620; found: 282.1622.

6-Methoxy-2,2-dipentylchroman (3ia)

According to the general procedure, a yellow oil (0.22 g, 72%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.68–6.58 (m, 3 H), 3.74 (s, 3 H), 2.69 (t, *J* = 7.0 Hz, 2 H), 1.78, (t, *J* = 6.8 Hz, 2 H), 1.38–1.20 (m, 16 H), 0.88, (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.9, 134.7, 122.1, 117.9, 114.1, 113.4, 77.9, 55.8, 36.3, 32.4, 28.9, 23.0, 22.7, 22.3, 14.1.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{33}O_2$: 305.2481; found: 305.2484.

1,3-Bis(6-methoxy-2-methylchroman-2-yl)benzene (3ja)

According to the general procedure using *p*-methoxyphenol (96 mg, 0.77 mmol, 2.0 equiv) and 1,3-di(buta-2,3-dien-2-yl)benzene (**1j**; 69 mg, 0.38 mmol, 1.0 equiv), a yellow oil (21 mg, 13%) was obtained after column chromatography on silica gel (hexane/EtOAc 50:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 12.1 Hz, 1 H), 7.20–7.19 (m, 3 H), 6.88 (d, *J* = 8.8 Hz, 1 H), 6.83 (d, *J* = 8.8 Hz, 1 H), 6.72–6.66 (m, 2 H), 6.45 (d, *J* = 2.9 Hz, 1 H), 6.41 (d, *J* = 2.9 Hz, 1 H), 3.71 (s, 6 H), 2.63–1.96 (m, 8 H), 1.60 (s, 3 H), 1.53 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 148.2, 148.1, 145.7, 145.3, 128.5, 128.3, 123.5, 123.4, 122.4, 122.1, 121.9, 117.5, 113.8, 113.5, 113.4, 78.1, 55.6, 32.8, 32.5, 30.3, 30.0, 22.8, 22.6.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{28}H_{30}O_4$: 430.2144; found: 430.2140.

6-Chloro-2-(4-chlorophenyl)chroman (3ke)[14]

According to the general procedure in DCE (0.1 M), a white solid (0.11 g, 48%) was obtained after column chromatography on silica gel (hexane/EtOAc 80:1); mp 94–97 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.31 (m, 4 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 6.82 (d, *J* = 9.2 Hz, 1 H), 5.02 (dd, *J* = 10.0, 2.5 Hz, 1 H), 2.95 (ddd, *J* = 16.8, 11.0, 6.0 Hz, 1 H), 2.81–2.70 (m, 1 H), 2.24–2.13 (m, 1 H), 2.09–1.94 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 140.0, 133.9, 129.3, 128.9, 127.6, 127.5, 125.4, 123.4, 118.4, 77.2, 29.5, 24.8.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{15}ClO$: 258.0811; found: 258.0813.

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Supporting Information

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