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A NOVEL SOLID-PHASE SYNTHESIS OF 2*H*-CHROMENES

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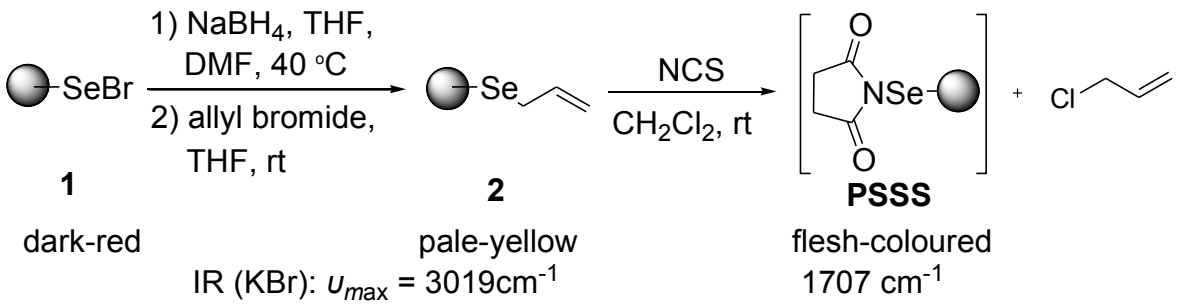
Abstract – A method for synthesizing substituted 2*H*-chromenes using TMSOTf-catalyzed polystyrene-supported succinimidyl selenide-induced intramolecular seleno-arylation of tethered alkenes as a key step has been developed. The catalytic process provides an efficient method for the stereoselective and regioselective synthesis of 3,4-dihydro-2*H*-chromenes possessing a seleno-functionality, followed by *syn*-elimination of selenoxides to provide 2*H*-chromenes in good yields and with high purities.

The regioselective and stereoselective solid-phase synthesis of heterocycles and its application to the generation of drug-like molecules has attracted widespread attention.[1] 2*H*-Chromenes display a broad spectrum of biological activities[2] such as anticancer, antioxidant, anti-inflammatory, antitubercular, antiviral, antitumor, antibacterial/antimicrobial, antidiabetic, anticoagulant, antianaphylatic, diuretic, fungicidal, and anti-HIV activity; additionally, the 2*H*-chromene substructure is an important structural motif present in a variety of medicines, natural products,[3] and materials showing unique photophysical properties.[4] Hence, the structural importance of the benzopyran moiety has elicited a great deal of interest in the field of organic synthesis and chemical biology to develop new and improved synthesis of these molecular skeletons. The synthesis of 2*H*-chromenes is structured around the three main approaches applied in catalytic 2*H*-chromene synthesis: (i) catalysis with (transition) metals,[5] (ii) metal-free Brønsted and Lewis acid/base catalysis, which includes examples of nonenantioselective organocatalysis,[6] and (iii) enantioselective organo-catalysis.[7] Despite such synthetic advances, the original method of Iwai and Ide[8] remains as a very useful method as it can provide the simplest 2*H*-chromene ring from an easily

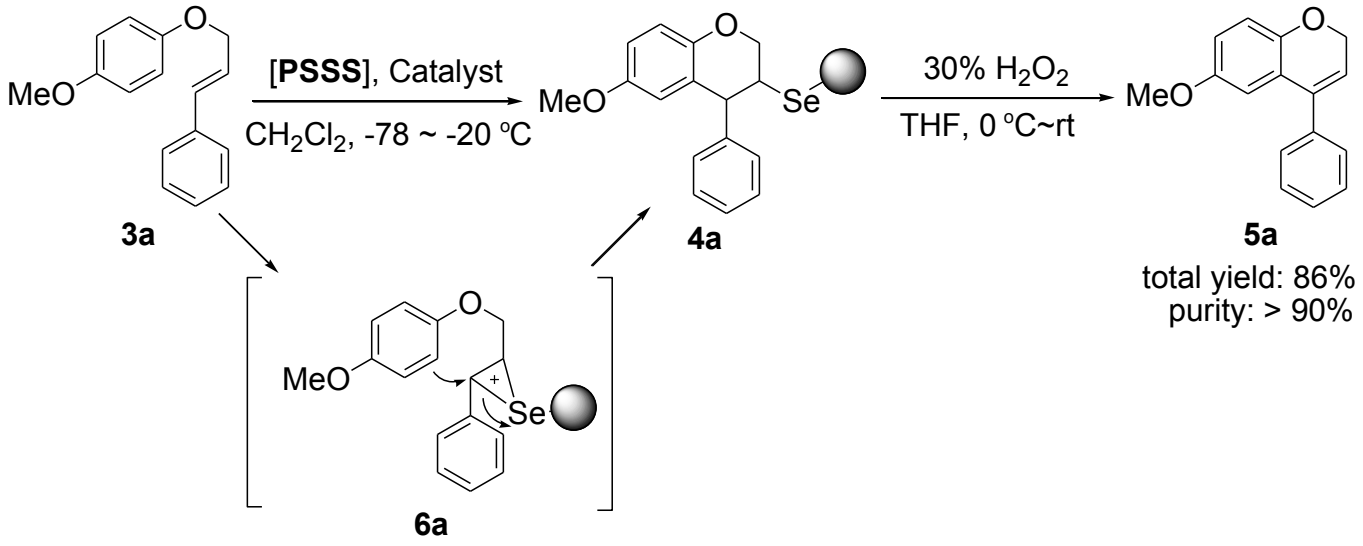
accessible phenol in just two steps. However, the post reaction workup is quite tedious, and it produces significant amount of environmentally unfriendly waste besides the poor yield. A method for the solid-phase synthesis of 2*H*-chromenes in good yields has been developed by Nicolaou et al.[9] This approach was based on an electrophilic cyclization reaction via forming a carbon-heteroatom bond and using the resin-bounded selenenyl bromide.[9] However, to the best of our knowledge, the solid-phase synthesis of 2*H*-chromenes via the selenium-induced and a carbon-carbon bond forming cyclization reaction has not been reported. In recent years, we have been keen to study the solid-phase synthesis of heterocyclic compounds,[10] using organoselenium as a linker and the reagent since organoselenium compounds can be utilized as synthetic intermediates[11] and selenium-carbon bond can be easily broken by various methods.[12] Herein, we report an efficient solid-phase synthesis of 2*H*-chromenes via Lewis acid-catalyzed, polymer-supported selenium-mediated, and intramolecular carbon-carbon bond forming reaction, as well as the subsequent oxidative cleavage of selenium resins. Advantages of this method are easy post reaction workup operations, odorlessness, easy preparation of the substrates, and good yield of the product.

Firstly, the solid-phase cyclization of 1-methoxy-4-[[(2*E*)-3-phenyl-2-propen-1-yl]oxy]benzene (**3a**)[13] with polystyrene-supported selenenyl bromide (**1**)[14] (Br: 0.99 mmol/g) was explored at -78 °C to 40 °C in dry CH_2Cl_2 for 48 h. But the selenium resin-bound annular intermediate **4a** was not produced, since no product **5a** was obtained by treatment of the selenium resin-bound intermediate with 30% H_2O_2 at 0 °C to room temperature. Inspired by Hajra's work of Lewis acid-catalyzed intramolecular halo-arylation of tethered alkenes,[15] we had successfully developed convenient solid-phase syntheses of quinolines[10f] and coumarins[10e] via TMSOTf-catalyzed intramolecular seleno-arylation of alkenes, using polystyrene-supported succinimidyl selenide (**PSSS**) as a selenium source. **PSSS** resin was prepared from dark-red polystyrene-supported selenenyl bromide (**1**)[14] (Br: 0.99 mmol/g) sequentially via reduction reaction with $NaBH_4$, alkylation reaction with allyl bromide, and amidation reaction with *N*-chlorosuccinimide (NCS). The reactions were monitored by FTIR (Scheme 1). With the help of Lewis acid, **PSSS** could react with



Scheme 1. Synthesis of polystyrene-supported succinimidyl selenide (PSSS)

3a to form seleniranium ion intermediate **6a** which was subsequently attacked by the intramolecular aromatic carbon-centered nucleophile from the *anti*-side to form a new carbon-carbon bond, and offer the annular product **4a** (Scheme 2). Considering **PSSS** is sensitive to moisture, a one-pot synthesis of polymer-supported annular product **4** was employed. After completion of the reaction of the resin **2** with NCS, **PSSS** was directly washed by dry CH_2Cl_2 under nitrogen atmosphere without being removed from the reaction flask. **PSSS** was then treated with 10 mol% TMSOTf and **3a** in dry CH_2Cl_2 at -78 °C for 2 h. And then the reaction mixture was kept at -20 °C for 4 h to afford 3-polystyrene-supported seleno-6-methoxy-4-phenyl-3,4-dihydro-2*H*-chromene (**4a**). The treatment of **4a** with H_2O_2 in THF at 0 °C to room temperature gave 6-methoxy-4-phenyl-2*H*-chromene (**5a**) in 86% isolated yield and with more than 90 % purity (Scheme 2).



Scheme 2. Solid-phase synthesis of 2*H*-chromene **5a**

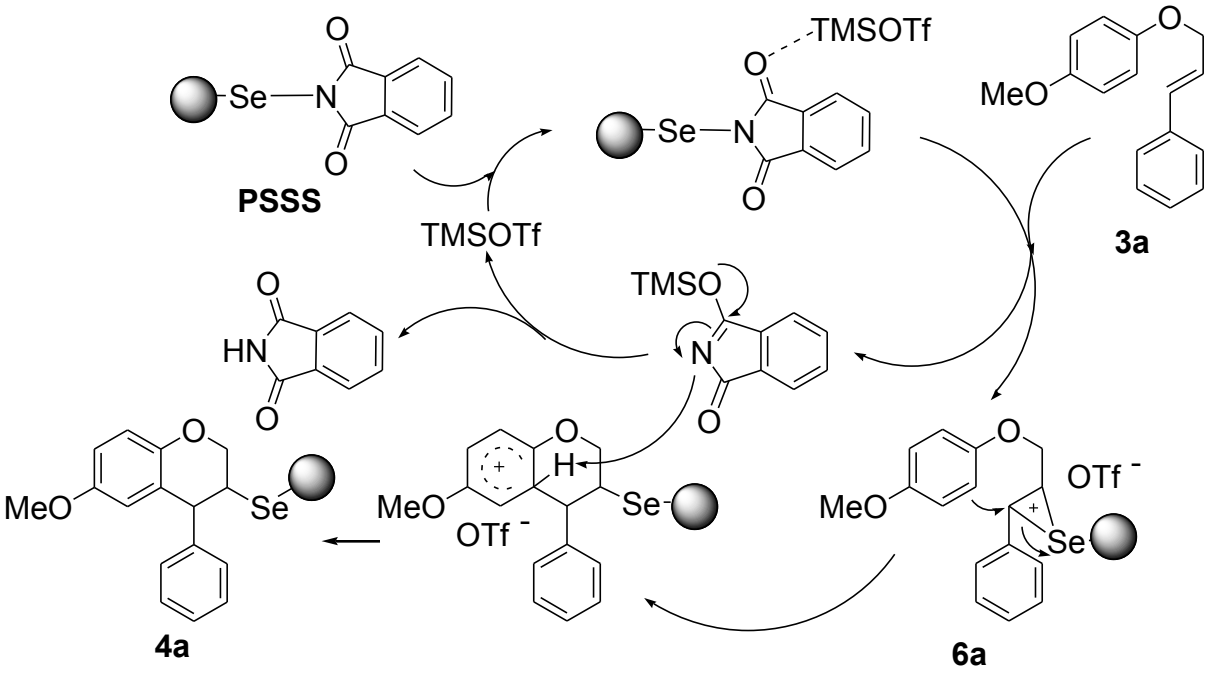
Furthermore, a range of cyclization reaction conditions involving **3a** and **PSSS** were explored. The results are depicted in Table 1. This reaction was rather sluggish in the absence of catalyst, even under reflux conditions (Table 1, entry 1). An investigation using a series of Lewis and Brønsted acids identified TMSOTf as an active catalyst. Addition of double dose of TMSOTf and a prolonged reaction time did not improve the yield of **5a** (Table 1, entries 11 and 12); the yield and the purity of **5a** decreased when 5 mol% of TMSOTf was employed (Table 1, entry 10); the employment of 10 mol% $BF_3{\cdot}Et_2O$, $AlCl_3$, $FeCl_3$, $ZnCl_2$, TsOH, TFA, and HOAc afforded the product in very low yield when the cyclization reaction was performed at -78 °C for 2 h and then -20 °C for 4 h in dry CH_2Cl_2 (Table 1, entries 5-8, 15-17); less than 5% yield of the annular product was obtained when the reaction was performed only at -78 °C or at -20 °C (Table 1, entries 13 and 14); no product was obtained when other Lewis acids such as $TiCl_4$, $Sm(OTf)_3$, and AgOTf were used (Table 1, entries 2-4).

Table 1. Optimization of solid-phase conditions of cyclization

Entry	Lewis acid	Amount of catalyst (mol%)	Reaction time[c] (h)	Total yield of **5a**[a] (%)[a]	Purity of **5a**[b] (%)[b]
1	none	-	6	nr	-
2	$TiCl_4$	10	6	nr	-
3	$Sm(OTf)_3$	10	6	nr	-
4	AgOTf	10	6	nr	-
5	$BF_3{\cdot}Et_2O$	10	6	<5	-
6	$AlCl_3$	10	6	<5	-
7	$FeCl_3$	10	6	<5	-
8	$ZnCl_2$	10	6	<5	-
9	TMSOTf	10	6	86	> 90
10	TMSOTf	5	6	70	> 80
11	TMSOTf	20	6	85	> 90
12	TMSOTf	10	8[d]	82	> 90
13	TMSOTf	10	6[e]	31	-
14	TMSOTf	10	4[f]	<5	-
15	TsOH	10	6	<5	-
16	TFA	10	6	<5	-
17	HOAc	10	6	<5	-

[a] Yields of the crude products based on the loading of polystyrene-supported selenenyl bromide (Br, 0.99 mmol/g); nr = no reaction.
[b] Determined by HPLC analysis.
[c] The cyclization reaction was performed at -78 °C for 2 h and then -20 °C for 4 h.
[d] The cyclization reaction was performed at -78 °C for 2 h and then -20 °C for 6 h.
[e] The cyclization reaction was performed at -78 °C for 6 h.
[f] The cyclization reaction was performed at -20 °C for 4 h.

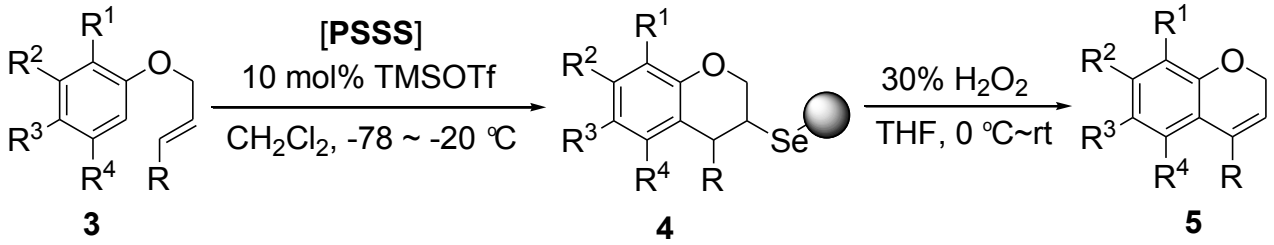
Mechanistically, it appears that TMSOTf activates **PSSS** by chelating to the amide carbonyl group to facilitate the formation of the seleniranium ion intermediate **6a** from alkenes; the subsequent reaction with arene led to the formation of annular products **4a** and the regeneration of the TMSOTf catalyst (Scheme 3).



Scheme 3. Mechanistic hypothesis for the intramolecular **PSSS**-promoted carboannulation reaction of compound **3a**

Then the polystyrene-supported selenium-mediated cyclization reactions of a series of olefins **3** in the one-pot procedure were studied. The products **5** were obtained in good yields and with high purities via intramolecular cyclization reaction and *syn*-elimination of selenoxides. The results are summarized in Table 2. It is quite obvious that when R^1, R^2, R^3, and R^4 were H, bromo, electron-donating substituents such as alkoxyl and alkyl, the carbon-based annulation reaction proceeded smoothly to give annular compounds (Table 2, entries 1-15); good results were also obtained when R was alkyl, phenyl, electron-donating group-substituted phenyl, and electron-withdrawing group-substituted phenyl (Table 2, entries 1-9, 11-15); no annular products were obtained when R^1, R^2, R^3, and R^4 were electron-withdrawing substituents such as formyl (Table 2, entry 16); besides the annular product **5k** was obtained in the yield of 60%, an unidentified by-product was found when R was H (Table 2, entry 10); both 7-methoxy-4-phenyl-2*H*-chromene (**5d**) and 5-methoxy-4-phenyl-2*H*-chromene (**5e**) were obtained from (*E*)-1-(cinnamyloxy)-3-methoxybenzene (**3d**) in the yields of 46% and 41% respectively (Table 2, entry 4). It is interesting that the TMSOTf-catalyzed **PSSS**-mediated cyclization reaction of compounds **3** gave rise to the six-membered cyclic compounds **4** as a result of *6-endo-trig* cyclization of compounds **3**. The five-membered cyclic compounds were not obtained.

Table 2. Solid-phase synthesis of 2*H*-chromenes **5** via **PSSS**-mediated cyclization reaction



3 **4** **5**

Entry	R	R^1	R^2	R^3	R^4	Product	Total yield (%)[a]	Purity (%)[b]
1	Ph	H	H	MeO	H	**5a**	86	> 90
2	Ph	MeO	H	H	H	**5b**	82	> 95
3	Ph	H	MeO	MeO	H	**5c**	85	> 90
4	Ph	H	MeO	H	H	**5d**	87[c]	-
	Ph	H	H	H	MeO	**5e**		
5	Ph	Me	Me	H	Me	**5f**	83	> 95
6	Ph	H	H	*t*-Bu	H	**5g**	82	> 95
7	Ph	*t*-Bu	H	*t*-Bu	H	**5h**	78	> 90
8	Ph	*t*-Bu	H	Me	H	**5i**	80	> 90
9	Ph	*i*-Pr	H	H	Me	**5j**	85	> 95
10	H	H	H	MeO	H	**5k**	60[d]	-
11	3',5'-$(MeO)_2C_6H_3$	H	H	Me	H	**5l**	82	> 90
12	4'-MeO-2'-$NO_2C_6H_3$	H	H	Me	H	**5m**	75	> 90
13	4'-FC_6H_4	H	H	Me	H	**5n**	79	> 90
14	4'- MeC_6H_4	Br	MeO	H	H	**5o**	80	> 90
15	Me	H	H	MeO	H	**5p**	83	> 95
16	Ph	CHO	H	H	H	**5q**	0	-

[a] Yields of the crude products based on the loading of polystyrene-supported selenenyl bromide (Br, 0.99 mmol/g);
[b] Determined by HPLC analysis; the products **5** with high purities were obtained because of water is the only by-product in the oxidative cleavage of selenium resins with 30% H_2O_2 aqueous solution.
[c] Combined yield of 46% yield of **5d** and 41% yield of **5e**.
[d] An unidentified by-product was observed.

In conclusion, we have developed a highly regioselective selenium-mediated intramolecular Friedel-Crafts alkylation of substituted 1-(allyloxy)benzene **3** using polymer-supported organoselenium reagent as a selenium source. Among the catalysts investigated, TMSOTf was found to be the best one. The target products were obtained in good yields and with good purities by the cleavage of the selenium

linker. Furthermore, the easy workup procedure and easily prepared the substrates provide an approach that is well-suited for building the parallel libraries upon the basis of further transformation of polymer-supported seleno-3,4-dihydro-2*H*-chromene **4**. The further modifications of resin **4** are currently ongoing.

EXPERIMENTAL

Melting points were measured with an X-6 micro-melting apparatus and were uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance 300 spectrometer in $CDCl_3$ with TMS as the internal standard; chemical shifts were quoted in ppm and J values were given in Hz. IR spectra were recorded on a Thermo Nicolet Avatar 360 spectrometer. HRMS were performed on an Agllent LC/Msd TOF instrument. HPLC were run on an Agilernt 1100 High performance liquid chromatograph with a tunable UV detector. Dry CH_2Cl_2 and DMF were distilled from CaH_2. Dry THF was distilled from Na. Purities and yields of the products were determined by the crude products and NMR, HRMS, and FTIR were determined by the purified products (the crude products were subjected to TLC on silica gel with AcOEt and light petroleum as eluent to give the purified products. Allyl polystyrene-supported selenide **2**[10f] and the substrates **3**[13] were prepared according the literatures.

General procedure for the preparation of 3-polystyrene-supported seleno-3,4-dihydro-2*H*-chromene (4): To a suspension of the swollen resin **2** (1.0 g) in dry CH_2Cl_2 (15 mL) was added NCS (0.668 g, 5.0 mmol) at 0 °C. The mixture was stirred for 0.5 h at 0 °C and 2 h at room temperature. After filtrating and washing with dry CH_2Cl_2 (15 mL×3), **PSSS** resin was suspended with dry CH_2Cl_2 (15 mL) and cooled to -78 °C. Trimethylsilyl trifluoromethanesulfonate (0.022 g, 0.10 mmol) was added into the reaction mixture. After stirring for 0.5 h at -78 °C, substituted 1-(allyloxy)benzene **3** (5.0 mmol) was added into the reaction mixture under nitrogen atmosphere. The suspension was stirred for another 2 h at -78 °C and then stored in a freezer at -20 °C for 4 h. Saturated $NaHCO_3$ aqueous solution (5 mL) was poured into the flask to quench the reaction. The resin **4** was collected by filtration, washed with THF (20 mL×2), Et_2O (20 mL×2), THF/H_2O (V/V = 3:1, 20 mL×2), H_2O (20 mL×2), THF (20 mL×2), MeOH (20 mL×2), and CH_2Cl_2 (20 mL×2), and dried under vacuum.

General procedure for the preparation of 2*H*-chromenes 5: To a suspension of the swollen resin **4** in THF (15 mL) was added 30% aqueous H_2O_2 (1.2 mL). After stirring for 1 h at 0 °C and for another 20 min at room temperature, the mixture was filtered and the resin was washed with CH_2Cl_2 (15 mL×2). The filtrate was washed with H_2O (30 mL×2), dried over $MgSO_4$ and filtered. After removal of the solvents under reduced pressure, the crude products **5** were obtained and then subjected to column chromatography on silica gel (*n*-hexane/AcOEt (V/V) =10:1) to give the purified products **5.**

6-Methoxy-4-phenyl-2*H*-chromene (5a)[16]: Light yellow solid, mp 66.3-68.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.34 (m, 5H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.72 (dd, *J* = 8.7 Hz, 3.0 Hz, 1H), 6.58 (d, *J* = 3.0 Hz, 1H), 5.85 (t, *J* = 3.9 Hz, 1H), 4.79 (d, *J* = 4.2 Hz, 2H), 3.67 (s, 3H); IR (KBr): υ_{max} = 1655, 1618, 1507, 1484, 1254, 1202 cm^{-1}; HRMS *m/z*: calcd for $C_{16}H_{14}O_2$ $[M]^+$ 238.0994; found 238.0999.

8-Methoxy-4-phenyl-2*H*-chromene (5b)[17]: Light yellow solid, mp 70.4-72.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.30 (m, 5H), 6.84-6.76 (m, 2H), 6.65-6.61 (m, 1H), 5.79 (t, *J* = 3.9 Hz, 1H), 4.89 (d, *J* = 3.9 Hz, 2H), 3.88 (s, 3H); IR (KBr): υ_{max} = 1646, 1614, 1454, 1401, 1263, 1168 cm^{-1}; HRMS *m/z*: calcd for $C_{16}H_{14}O_2$ $[M]^+$ 238.0994; found 238.0983.

6,7-Dimethoxy-4-phenyl-2*H*-chromene (5c): Brown-orange oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42-7.31 (m, 5H), 6.58 (s, 1H), 6.54 (s, 1H), 5.68 (t, *J* = 3.9Hz, 1H), 4.76 (d, *J* = 3.9 Hz, 2H), 3.86 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 149.5, 143.3, 138.4, 137.2, 128.5, 128.4, 127.8, 117.3, 115.6, 109.6, 100.8, 65.3, 56.6, 56.0; IR (KBr): υ_{max} = 1654, 1612, 1505, 1454, 1401, 1169 cm^{-1}; HRMS *m/z*: calcd for $C_{17}H_{16}O_3$ $[M]^+$ 268.1099; found 268.10990.

7-Methoxy-4-phenyl-2*H*-chromene (5d)[18]: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36-7.18 (m, 6H), 6.93 (s, 1H), 6.46 (s, 1H), 5.61 (t, *J* = 3.9Hz, 1H), 4.78 (d, *J* = 3.9 Hz, 2H), 3.81 (s, 3H); IR (KBr): υ_{max} = 1655, 1613, 1596, 1479, 1444, 1381, 1319, 1266, 1140, 1032 cm^{-1}; HRMS *m/z*: calcd for $C_{16}H_{14}O_2$ $[M]^+$ 238.0994; found 238.0993.

5-Methoxy-4-phenyl-2*H*-chromene (5e): Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27-7.24 (m, 5H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.32 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 5.56 (t, *J* = 3.9Hz, 1H), 4.74 (d, *J* = 3.9 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 156.1, 138.5, 137.0, 128.6, 128.4, 127.7, 126.7, 117.0, 106.9, 102.0, 65.6, 55.4; IR (KBr): υ_{max} = 1655, 1614, 1498, 1446, 1270, 1198, 1160, 1116, 1032 cm^{-1}; HRMS *m/z*: calcd for $C_{16}H_{14}O_2$ $[M]^+$ 238.0994; found 238.0982.

5,7,8-Trimethyl-4-phenyl-2*H*-chromene (5f): Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.19 (m, 5H), 6.57 (s, 1H), 5.88 (t, *J* = 4.8 Hz, 1H), 4.55 (d, *J* = 4.8 Hz, 2H), 2.24 (s, 3H), 2.17 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3, 141.6, 139.1, 137.7, 132.3, 128.3, 127.6, 127.1, 125.9, 121.6, 121.5, 121.1, 64.4, 22.3, 20.0, 11.8; IR (KBr): υ_{max} = 1664, 1601, 1449, 1112, 1061 cm^{-1}; HRMS *m/z*: calcd for $C_{18}H_{18}O$ $[M]^+$ 250.1358; found 250.1368.

6-(*tert*-Butyl)-4-phenyl-2*H*-chromene (5g): Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38-7.34 (m, 5H), 7.18 (d, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 5.78 (t, *J* = 3.9Hz, 1H), 4.79 (d, *J* = 3.9 Hz, 2H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.7, 143.9, 138.5, 137.6, 128.7, 128.5, 127.9, 127.1, 126.1, 123.0, 120.0, 115.7, 65.3, 34.3, 31.5; IR (KBr): υ_{max} =1656, 1612, 1504, 1451, 1399 cm^{-1}; HRMS *m/z*: calcd for $C_{19}H_{20}O$ $[M]^+$ 264.1514; found 264.1510.

6,8-Di(*tert*-butyl)-4-phenyl-2*H*-chromene (5h): Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 5H), 7.23 (s, 1H), 6.92 (s, 1H), 5.87 (t, *J* = 3.9 Hz, 1H), 4.73 (d, *J* = 3.9 Hz, 2H), 1.42 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.0, 142.7, 139.1, 138.3, 137.1, 128.7, 128.2, 127.6, 124.0, 123.7, 121.1, 119.6, 64.0, 34.8, 34.4, 31.5, 30.0; IR (KBr): υ_{max} = 1654, 1611, 1503, 1449, 1400 cm^{-1}; HRMS *m/z*: calcd for $C_{23}H_{28}O$ $[M]^+$ 320.2140; found 320.2146.

8-(*tert*-Butyl)-6-methyl-4-phenyl-2*H*-chromene (5i): Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.31 (m, 5H), 6.99(d, *J* = 1.8 Hz, 1H), 6.69(d, *J* = 1.5 Hz, 1H), 5.81 (t, *J* = 3.9Hz, 1H), 4.67 (d, *J* = 3.9 Hz, 2H), 2.17 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.2, 139.1. 138.1, 137.9, 129.6, 128.8, 128.6, 128.4, 127.7, 127.5, 124.9, 124.5, 120.1, 64.1, 34.6, 30.0, 21.2; IR (KBr): υ_{max} = 1653, 1612, 1452, 1401 cm^{-1}; HRMS *m/z*: calcd for $C_{20}H_{22}O$ $[M]^+$ 278.1671; found 278.1679.

8-Isopropyl-5-methyl-4-phenyl-2*H*-chromene (5j): Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30-7.20 (m, 5H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 5.93 (t, *J* = 4.5 Hz, 1H), 4.53 (d, *J* = 4.8 Hz, 2H), 3.36-3.23 (m, 1H), 1.71 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =153.6, 141.6, 139.1, 133.9, 133.1, 128.4, 127.6, 127.2, 125.8, 124.5, 123.6, 122.6, 64.2, 27.2, 22.9, 22.5; IR (KBr): υ_{max} = 1654, 1613, 1453, 1401, 1168, 1083 cm^{-1}; HRMS *m/z*: calcd for $C_{19}H_{20}O$ $[M]^+$ 264.1514; found 264.1505.

6-Methoxy-2*H*-chromene (5k)[19]: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76-6.61 (m, 2H), 6.54 (d, *J* = 2.4 Hz, 1H), 6.40 (d, *J* = 9.3 Hz, 1H), 5.81 (dt, *J* = 9.3, 4.2 Hz, 1H), 4.76 (dd, *J* = 4.2, 2.4 Hz, 2H), 3.75 (s, 3H). IR (NaCl): υ_{max} = 2981, 2826, 1474, 1265, 1210, 1150 cm^{-1}; HRMS *m/z*: calcd for $C_{10}H_{10}O_2$ $[M]^+$ 162.0681; found 162.0670.

4-(3',5'-Dimethoxyphenyl)-6-methyl-2*H*-chromene (5l)[20]: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.85 (d, *J* = 8.2 Hz, 1H), 6.80 (s, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.41 (s, 3H), 5.71 (t, *J* = 3.9 Hz, 1H), 4.70 (d, *J* = 4.0 Hz, 2H), 3.71 (s, 6H), 2.11 (s, 3H); IR (neat): υ_{max} = 1606, 1490, 1454, 1420, 1351, 1220, 1204, 1152 cm^{-1}; HRMS (APCI) *m/z*: calcd for $C_{18}H_{19}O_3$ $[M+H]^+$ 283.1334; found 283.1325.

4-(4'-Methoxy-2'-nitrophenyl)-6-methyl-2*H*-chromene (5m)[20]: Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 2.7 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.16 (dd, *J* = 8.6 Hz, 2.7 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.37 (s, 1H), 5.66 (t, *J* = 3.9 Hz, 1H), 4.81 (m, 2H), 3.90 (s, 3H), 2.11 (s, 3H); IR (neat): υ_{max} = 1622, 1530, 1490, 1341, 1269, 1224, 1125 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{17}H_{15}NNaO_4$ $[M+Na]^+$ 320.0899; found 320.0889.

4-(4-Fluorophenyl)-6-methyl-2*H*-chromene (5n)[20]: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.28 (m, 2H), 7.15-7.11 (t, *J* = 8.7 Hz, 2H), 7.03-6.70 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.86-6.81 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 1.8 Hz, 1H), 5.77 (t, *J* = 4.2 Hz, 1H), 4.80 (d, *J* = 4.2 Hz, 2H), 2.20 (s, 3H); IR (neat): υ_{max} = 2836, 1731, 1509, 1481, 1346, 1297, 1173 cm^{-1}; HRMS (APCI) *m/z*: calcd for $C_{16}H_{14}FO$

$[M+H]^+$ 241.1029; found 241.1021.

8-Bromo-7-methoxy-4-(*p*-tolyl)-2*H*-chromene (5o)[20]: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 4H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.40 (d, *J* = 8.6 Hz, 1H), 5.64 (t, *J* = 3.9 Hz, 1H), 4.96 (d, *J* = 3.9 Hz, 2H), 3.86 (s, 3H), 2.37 (s, 3H); IR (neat): υ_{max} = 2960, 2843, 1601, 1480, 1456, 1348, 1272 cm^{-1}; HRMS (APCI) *m/z*: calcd for $C_{17}H_{16}BrO_2$ $[M+H]^+$ 331.0334; found 331.0322.

6-Methoxy-4-methyl-2*H*-chromene (5p)[20]: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.79–6.67 (m, 3H), 5.61 (dd, *J* = 3.6, 1.8 Hz, 1H), 4.68 (dd, *J* = 3.6, 1.8 Hz, 2H), 3.76 (s, 3H), 2.00 (dd, *J* = 3.3, 1.8 Hz, 3H); IR (neat): υ_{max} = 2830, 1581, 1493 cm^{-1}; HRMS *m/z*: calcd for $C_{11}H_{12}O_2$ $[M]^+$ 176.0837; found 176.0828.

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REFERENCES

1. For selected examples, see: (a) J. Campbell and H. E. Blackwell, *J. Comb. Chem*., 2009, **11**, 1094; (b) S. T. L. Quement, T. E. Nielsen, and M. Meldal, *J. Comb. Chem.*, 2007, **9**, 1060; (c) C. Macleod, B. I. Martinez-Teipel, W. M. Barker, and R. E. Dolle, *J. Comb. Chem.*, 2006, **8**, 132.
2. For selected examples, see: (a) M. K. Hussain, M. I. Ansari, N. Yadav, P. K. Gupta, A. K. Gupta, R. Saxena, I. Fatima, M. Manohar, P. Kushwaha, V. Khedgikar, J. Gautam, R. Kant, P. R. Maulik, R. Trivedi, A. Dwivedi, K. R. Kumar, A. K. Saxena, and K. Hajela, *RSC Adv*., 2014, **4**, 8828; (b) S. R. Trenor, A. R. Shultz, B. J. Love, and T. E. Long, *Chem. Rev*., 2004, **104**, 3059; (c) D. Z. Qiang, J. B. Shi, B. A. Song, and X. H. Liu, *RSC Adv*., 2014, **4**, 5607; (d) M. Azizmohammadi, M. Khoobi, A. Ramazani, S. Emami, A. Zarrin, O. Firuzi, R. Miri, and A. Shafiee, *Eur. J. Med. Chem*., 2013, **59**, 15; (e) Y. L. N. Murthy, K. P. Suhasini, A. S. Pathania, S. Bhushan, and Y. Nagendra Sastry, *Eur. J. Med. Chem*., 2013, **62**, 545; (f) J. Jankun, S. H. Selman, and R. S wiercz, *Nature*, 1997, **387**, 561; (h) J. A. Kumar, G. Saidachary, G. Mallesham, B. Sridhar, N. Jain, S. V. Kalivendi, V. J. Rao, and B. C. Raju, *Eur. J. Med. Chem*., 2013, **65**, 389; (i) J. Mun, A. A. Jabbar, N. S. Devi, S. Yin, Y. Wang, C. Tan, D. Culver, J. P. Snyder, E. G. V. Meir, and M. M. Goodman, *J. Med. Chem*., 2012, **55**, 6738.
3. (a) E. E. Schweizer and O. Meeder-Nycz, In 'Chromenes, Chromanes, Chromones', Vol. 31, ed. by G. P. Ellis, Wiley-Interscience, New York, 1977, pp. 11-139; (b) G. P. Ellis and I. M. Lockhart, 'The Chemistry of Heterocyclic Compounds: Chromenes, Chromanones, and Chromones', Vol. 31, ed. by G. P. Ellis, Wiley-VCH, New York, 2009, pp. 1-1196; (c) W. B. Fravel and N. A. Nedolya, 'In Comprehensive Heterocyclic Chemistry III', Vol. 7, ed. by A. R. Katritzky, C. A. Ramsden, E. F. V.

Scriven, and R. J. K. Taylor, Elsevier Ltd, Oxford, 2008, pp. 701-726.

4. (a) P. Bamfield and M. G. Hutchings, 'Chromic Phenomena: The Technological Applications of Colour Chemistry, 2nd ed.' The Royal Society of Chemistry, Cambridge, 2010, 15; (b) J. N. Moorthy, S. Mandal, A. Mukhopadhyay, and S. Samanta, *J. Am. Chem. Soc.*, 2013, **135**, 6872; (c) C. Ranjith, K. K. Vijayan, V. K. Praveen, and N. S. S. Kumar, *Spectrochim. Acta, Part A*, 2010, **75**, 1610; (d) J. Sun, J. Zhao, H. Guo, and W. Wu, *Chem. Commun.*, 2012, **48**, 4169; (e) X. Yi, P. Yang, D. Huang, and J. Zhao, *Dyes Pigm.*, 2013, **96**, 104; (f) A. Kobayashi, K. Takehira, T. Yoshihara, S. Uchiyama, and S. Tobita, *Photochem. Photobiol. Sci.*, 2012, **11**, 1368; (g) C. M. Sousa, J. Pina, J. Seixas de Melo, J. Berthet, S. Delbaere, and P. J. Coelho, *Eur. J. Org. Chem.*, 2012, 1768.
5. For selected examples, see: (a) H. X. Siyang, X. R. Wu, X. Y. Ji, X. Y. Wu, and P. N. Liu, *Chem. Commun.*, 2014, **50**, 8514; (b) Z.-Q. Wang, Y. Lei, M.-B. Zhou, G.-X. Chen, R.-J. Song, Y.-X. Xie, and J.-H. Li, *Org. Lett.*, 2011, **13**, 14; (c) X. Xu, J. Liu, L. Liang, H. Li, and Y. Li, *Adv. Synth. Catal.*, 2009, **351**, 2599; (d) N. Majumdar, K. A. Korthals, and W. D. Wulff, *J. Am. Chem. Soc.*, 2012, **134**, 1357; (e) N. D. Paul, S. Mandal, M. Otte, X. Cui, X. P. Zhang, and B. de Bruin, *J. Am. Chem. Soc.*, 2014, **136**, 1090; (f) A. Aponick, B. Biannic, and M. R. Jong, *Chem. Commun.*, 2010, **46**, 6849; (g) V. Hornillos, A. W. van Zijl, and B. L. Feringa, *Chem. Commun.*, 2012, **48**, 3712; (h) X. Pan, M. Chen, L. Yao, and J. Wu, *Chem. Commun.*, 2014, **50**, 5891; (i) T. J. A. Graham and A. G. Doyle, *Org. Lett.*, 2012, **14**, 1616.
6. For selected examples, see: (a) M. Shi, L.-Z. Dai, Y.-L. Shi, and G.-L. Zhao, *Adv. Synth. Catal.*, 2006, **348**, 967; (b) L.-W. Ye, X.-L. Sun, C.-Y. Zhu, and Y. Tang, *Org. Lett.*, 2006, **8**, 3853; (c) E. Yoshioka, S. Kohtani, and H. Miyabe, *Angew. Chem. Int. Ed.*, 2011, **50**, 6638; (d) T. E. Reynolds and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2007, **46**, 7806.
7. (a) P. N. Moquist, T. Kodama, and S. E. Schaus, *Angew. Chem. Int. Ed.*, 2010, **49**, 7096; (b) H. Li, J. Wang, T. E-Nunu, L. Zu, W. Jiang, S. Wei, and W. Wang, *Chem. Commun.*, 2007, 507; (c) M. Rueping, U. Uria, M.-Y. Lin, and I. Atodiresei, *J. Am. Chem. Soc.*, 2011, **133**, 3732.
8. (a) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, 1963, **11**, 1042; (b) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, 1962, **10**, 926.
9. (a) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G.-Q. Cao, S. Barluenga, and H. J. Mitchell, *J. Am. Chem. Soc.*, 2000, **122**, 9939; (b) K. C. Nicolaou, J. A. Pfefferkorn, H. J. Mitchell, A. J. Roecker, S. Barluenga, G.-Q. Cao, R. L. Affleck, and J. E. Lillig, *J. Am. Chem. Soc.*, 2000, **122**, 9954.
10. (a) X. Huang, E. Tang, and W. M. Xu, *J. Comb. Chem.*, 2005, **7**, 802; (b) E. Tang, X. Huang, and W. M. Xu, *Tetrahedron*, 2004, **60**, 9963; (c) W. M. Xu, X. Huang, and E. Tang, *J. Comb. Chem.*, 2005, **7**, 726; (d) E. Tang, B. Z. Chen, L. P. Zhang, W. Li, and J. Lin, *Synlett*, 2011, 707. (e) E. Tang and W. Li, *Synlett*, 2012, **23**, 907; (f) E. Tang, D. S. Mao, W. Li, Z. Y. Gao, and P. F. Yao, *Heterocycles*,

2012, **85**, 667; (g) E. Tang, W. Li, Z. Y. Gao, and X. Gu, *Chin. Chem. Lett*., 2012, **23**, 631.

11. N. Petragnani, H. A. Stefani, and C. J. Valdug, *Tetrahedron*, 2001, **57**, 1411.
12. K. C. Nicolaou, J. A. Pfefferkorn, G. Q. Cao, S. Kim, and J. Kessabi, *Org. Lett*., 1999, **1**, 807.
13. I. C. Manley-King and J. Jacobus, *Bioorg. Chem*., 2012, **40**, 114.
14. K. C. Nicolaou, J. Pastor, S. Barluenga, and N. Winssinger, *Chem. Commun*., 1998, 1947.
15. S. Hajra, B. Maji, and A. Karmakar, *Tetrahedron Lett*., 2005, **46**, 8599.
16. L. Alonso-Marañón, M. M. Martínez, L. A. Sarandeses, and J. P. Sestelo, *Org. Biomol. Chem*., 2015, **13**, 379.
17. S.-R. Li, H.-M. Chen, and P.-Y. Chen, *J. Chin. Chem. Soc*., 2008, **55**, 923.
18. L. Calmus, A. Corbu, and J. Cossy, *Adv. Synth. Catal*., 2015, **357**, 1381.
19. R. S. Menon, A. D. Findlay, A. C. Bissember, and M. G. Banwell, *J. Org. Chem*., 2009, **74**, 8901.
20. D. Renko, O. Provot, E. Rasolofonjatovo, E. Rasolofonjatovo, J. Bignon, J. Rodrigo, J. Dubois, J. D. Brion, A. Hamze, and M. Alami, *Eur. J. Med. Chem*., 2015, **90**, 834.