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Diastereoselective Tin-Free Tandem Radical Additions to 3-Formylchromones

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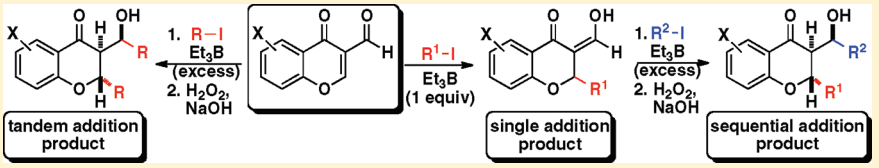
Supporting Information

ABSTRACT:



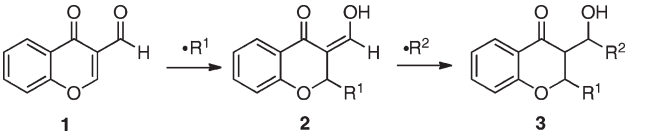
A tin-free tandem radical addition methodology onto 3-formylchromones is presented. This radical process yields functionalized chromone structures via two carbon−carbon bond-forming steps. These products contain up to three contiguous stereocenters with good to excellent dr's and yields.

Arguably, one of the most intensely studied areas within synthetic organic chemistry is the development of new stereoselective methods for the synthesis of biologically significant molecules.[1] Stereoselective free-radical reactions have been studied over the past several decades; however, there are still several obstacles to be overcome.[2] One major problem that plagues free-radical processes is the use of organotin reagents.[3] These reagents are toxic, and the byproducts can be very difficult to remove from reaction mixtures. A variety of alternatives for organotin reagents have been presented in the literature,[3] yet this is still a developing field of research. Some research groups have also reported tin-free radical additions using Et_3B[4] and Et_2Zn[5] as initiators and chain-transfer reagents.

Another drawback to stereoselective free-radical reactions is the lack of functional group complexity in the products synthesized via these methods.[2] Therefore, we set out to identify substrates that would produce useful, small molecule scaffolds utilizing tin-free radical processes. We ultimately focused on 3-formylchromone (**1**) as our radical acceptor (Scheme 1). This compound (and a variety of related structures) is commercially available[6] or easily prepared from simple procedures.[7] This substrate has been studied extensively in conjugate addition reactions with cuprates wherein products similar to enol **2** can be prepared,[8] and more recently, they have been studied in annulation reactions.[9] A variety of natural products contain modified chromone frameworks that are related to the structures produced in this new method (Figure 1).[10] Herein we demonstrate a highly diastereoselective tin-free tandem radical addition to 3-formylchromones yielding functionalized products with up to three contiguous stereocenters.

Our experiments began with the evaluation of *tert*-butyl radical additions onto 3-formylchromone. Simple silanes such as triethylsilane and PMHS (polymethylhydrosiloxane) were initially screened as possible alternatives to toxic alkyltin hydride as

Scheme 1. Radical Addition to 3-Formylchromone



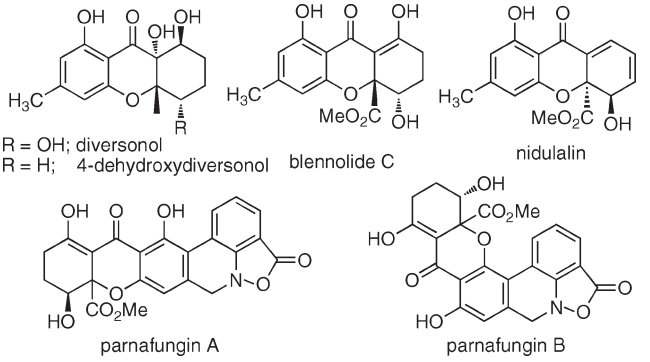


Figure 1. Natural products containing substituted chromone frameworks.

hydrogen atom sources for this free radical process. Although the desired products were produced under silane conditions, the crude reaction mixtures were difficult to purify, and as a result, product yields were low (data not shown). We ultimately discovered that a hydrogen atom source was not required in this process as triethylborane was acting as both an initiator and chain-transfer agent. Interestingly, a mixture of the single (**4**) and tandem

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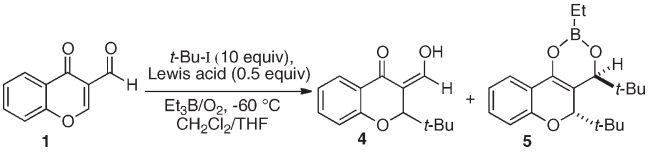
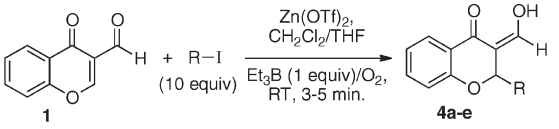
Table 1. Optimization of Radical Additions onto 3-Formylchromone



entry	Lewis acid	time (min)	Et_3B equiv	product	yield[a] (%)
1	$Yb(OTf)_3$	15	2	**4**:**5**[b]	76
2	$Yb(OTf)_3$	5	2	**4**:**5**[c]	87
3	$Yb(OTf)_3$	5	1	**4**	77
4	$Zn(OTf)_2$	5	2	**4**:**5**[d]	83
5	$Zn(OTf)_2$	5	1	**4**[e]	92
6	$Zn(OTf)_2$	5	1	**NR**[e,f]	0
7		5	1	**4**[e]	77
8	$Yb(OTf)_3$	180	5	**5**	85
9		180	5	**5**	93

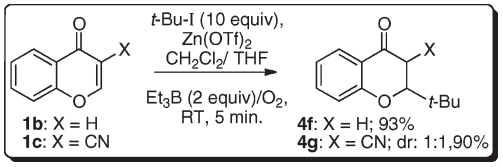
[a] Isolated yields. [b] A 3:1 mixture of **4**:**5** was observed. [c] A 15:1 mixture of **4**:**5** was observed. [d] A 17:1 mixture of **4**:**5** for entry 4. [e] Reaction carried out at room temperature. [f] One equiv of TEMPO was added to the reaction.

Table 2. Radical Precusor Scope for Single Additions to 3-Formylchromone



entry	product	R	yield[a] (%)
1	**4a**	*tert*-butyl	92
2	**4b**	isopropyl	85
3	**4c**	c-hexyl	88
4	**4d**	c-pentyl	81
5	**4e**	ethyl	83

[a] Isolated yields.



(**5**) addition adducts was isolated in the presence excess of triethylborane (Table 1).

Intrigued by this result, we set out to develop reaction conditions that would give either pure single or tandem addition products. After extensive experimentation, it was discovered that product distribution was dependent on reaction time and equivalents of radical initiator (Et_3B). Using 1.0−2.0 equiv of triethylborane and short reaction times (5 min or less), excellent yields of **4** were observed (Table 1, entries 1−5). With excess triethylborane and long reaction times (3 h), the tandem addition adduct **5** was produced as a single diastereomer in excellent yields (entries 8 and 9). A variety of Lewis acids were screened including $Yb(OTf)_3$, $Cu(OTf)_2$, $Sc(OTf)_3$, $PdCl_2$, and $Zn(OTf)_2$ (not all data shown). Ultimately, we found that $Zn(OTf)_2$ afforded the most reproducible and highest yielding reactions. Lewis acid additives seemed to give higher yields for the single addition products but were found to have little impact under the double addition reaction conditions. Addition of 1 equiv of radical inhibitor TEMPO resulted in no observed product, thereby suggesting a radical pathway (entry 6). Attempts to use diethylzinc as an initiator and chain-transfer agent were unsuccessful in this methodology.[11]

Next, we investigated the scope of our single radical addition method (Table 2). Using 0.5 equiv of $Zn(OTf)_2$, 1 equiv of Et_3B, with a reaction time of 3−5 min at room temperature,[12] compounds **4a**−**e** were prepared in excellent yields. Primary, secondary, and tertiary radicals all added very efficiently. We also studied chromones **1b** and **1c** under these reaction conditions. Chromone (**1b**) gave the radical adduct **4f** in nearly quantitative yields. 3-Cyanochromone also proved to be an excellent substrate for this tin-free radical method.[13] Again, the single addition product **4g** was isolated with excellent yields as a 1:1 mixture of diastereomers.

While conditions for the single addition reaction using 3-formylchromone were being optimized, it was discovered that triethylborane was incorporated into the tandem addition product **5**.[14] This boron enolate compound is remarkably stable and, in the case of R = *t*-Bu (**5**), can even be chromatographed. We made several attempts to trap boron enolate **5** with benzaldehyde (aldol reaction); however, only recovered starting material was observed.[15] Therefore, in order to access the desired aldol-like products (**6**), oxidative conditions were required to remove boron and give products **6a**−**i**. These results were very exciting as two carbon−carbon bonds and three contiguous stereocenters are formed in a single transformation with good stereoselectivity. Again, primary, secondary, and tertiary radicals all added efficiently to give compounds **6a**−**i** in good yields and dr's. Ethyl radical adds significantly slower to the enol intermediate so longer reaction times were necessary (6 h for ethyl and 3 h for the others). This tandem radical addition method is also tolerant of substituents on the aromatic ring. Of particular interest are the bromo and chloro derivatives (Table 3, entries 6 and 7) which contain synthetic handles for further transformations.

We were able to determine the relative stereochemistry for the major diastereomer in this reaction by obtaining an X-ray structure for compound **6i** (see Figure 2). This structure clearly shows the *trans* relationship between the two substituents on the pyrone ring. The stereochemistry suggests that the two radicals add from opposite faces of the substrate (see **6j**) followed by protonation to yield the thermodynamically favored *trans* compound.

Next, we wanted to investigate the sequential addition of two different radical precursors in order to increase the complexity of the products formed in this method (see Table 4). Initially, a single-pot procedure was envisioned for this process; however, we found that it was best to quench the single addition reaction on silica and then, to the crude product, add the second radical followed by oxidative (30% H_2O_2, 1 M NaOH) workup conditions to remove the boron. A variety of alkyl radicals were successfully added with good dr's and yields to give the desired compounds **7a**−**d**. This method allows for rapid substitution of the chromone core giving functionalized building blocks for more complex benzopyran targets.

A proposed mechanism is shown in Scheme 2.[16] The first step in this reaction is generation of an ethyl radical via the reaction of O_2 with triethylborane. Atom abstraction from the excess alkyl

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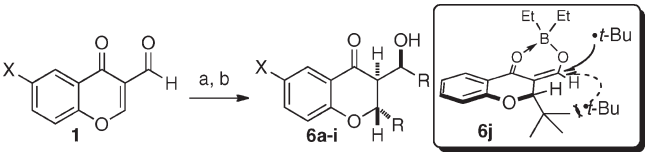
Table 3. Tandem Radical Additions to 3-Formylchromones[a]



entry	product	R	X	dr[b]	yield[c] (%)
1	**6a**	*tert*-butyl	H	10:1	82
2	**6b**	isopropyl	H	7:1	86
3	**6c**	c-hexyl	H	4:1	84
4	**6d**	c-pentyl	H	7:1	71
5	**6e**	ethyl	H	8:1	70[d]
6	**6f**	*tert*-butyl	chloro	10:1	83
7	**6g**	*tert*-butyl	bromo	10:1	81
8	**6h**	*tert*-butyl	fluoro	7:1	77
9	**6i**	*tert*-butyl	ethyl	10:1	86

[a] Reaction conditions: (a) R-I (10 equiv), Et_3B, CH_2Cl_2, −60 °C, 3−6 h; (b) 30% H_2O_2, 1 M NaOH, 0 °C, 2 h. [b] Determined by 200 MHz NMR. [c] Isolated yields. [d] Reaction without Et-I gave 10−15% of unreacted starting material. Under identical reaction conditions, no unreacted starting material was observed when 10 equiv of Et-I was used.

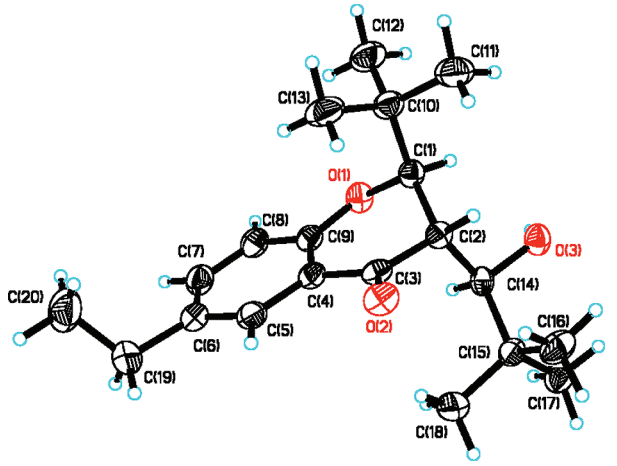
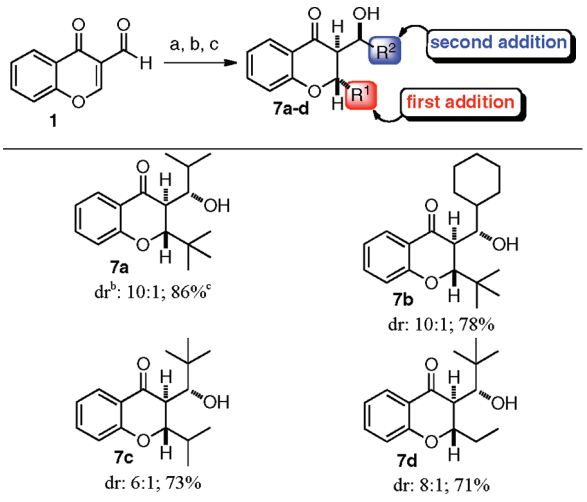


Figure 2. Crystal structure of **6i**.

iodide reagent produces the desired alkyl radical. Next, addition to the alkene acceptor gives a resonance-stabilized radical **8**, which undergoes a reaction with triethylborane to yield intermediate **9**. A second alkyl radical addition to conjugated enolate **9** yields free radical **10** that ultimately cyclizes to give boron enolate **11**. Due to the stability of **11**, oxidative conditions are required in order to isolate the final alcohol product **12**. The enolate formed after the single addition is more labile as the free enol is isolated after workup and purification via chromatography, whereas the cyclic enolate (**11**) is quite stable and can be chromatographed with little hydrolysis observed.[17]

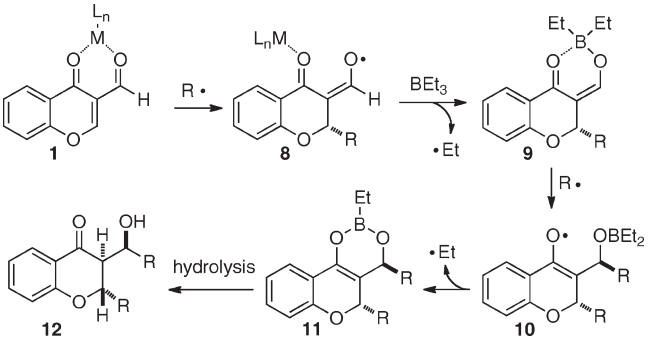
In conclusion, we have developed an efficient tin-free radical methodology for single, tandem, and sequential additions to 3-formylchromones. In this process, up to two carbon−carbon bonds and three contiguous stereocenters can be formed in a single step. These functionalized chromone products contain structural features of natural products and derivatives that have significant biological acitivities. Experiments focusing on the enantioselective variant of this method are currently underway.

Table 4. Sequential Radical Additions to 3-Formylchromone[a]



[a] Reaction conditions: (a) R^1-I (10 equiv), $Zn(OTf)_2$, Et_3B, CH_2Cl_2/THF, RT, 3−5 min b) R^2-I (10 equiv), Et_3B, CH_2Cl_2, −60 °C, 3 h. c) 30% H_2O_2, 1 M NaOH, 0 °C, 2 h. [b] Diastereomeric ratios determined by 200 MHz NMR. [c] Isolated yields.

Scheme 2. Proposed Mechanism



EXPERIMENTAL SECTION

General Experimental Methods. Spectroscopic data were recorded as follows: ^1H NMR and ^{13}C NMR spectra were run at 200 and 50 MHz, respectively. Infrared spectra were recorded using NaCl pellets. Absorptions are given in wavenumbers (cm^{-1}).

*General Procedure for Single Addition (**4a**−**g**).* To chromone (0.2 mmol) and $Zn(OTf)_2$ (0.1 mmol) in a 15 mL vial were added CH_2Cl_2 (1.5 mL) and THF (0.5 mL), and the mixture was stirred at room temperature. Alkyl iodide (2 mmol) was added, and the reaction was initiated using 1.0 M Et_3B in hexanes (0.2 mmol). The reaction mixture turned yellow immediately after the addition of Et_3B. The reaction was stirred for 3 min for tertiary and secondary radicals. For primary radicals the reaction was stirred for 5 min to get complete conversion of the single addition product. Immediate quenching on silica after 3−5 min for 3-formylchromone is crucial to get pure single addition product. Extended reaction times lead to a mixture of single and double addition products. The reaction mixture was quenched on a bed

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of silica gel and filtered using CH_2Cl_2. The solvent was concentrated under reduced pressure, adsorbed on silica, and purified using column chromatography (5−30% EtOAc in hexanes) to give pure products **4a**−**g**.

*(Z)-2-tert-Butyl-3-(hydroxymethylene)chroman-4-one (**4a**):* 94% yield; IR (cm^{-1}) 3201, 2961, 2870, 1607, 1465; ^1H NMR ($CDCl_3$, 200 MHz) δ 14.38 (bs, 1H), 8.05 (s, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.47−7.36 (m, 1H), 7.00−6.85 (m, 2H), 4.68 (s, 1H), 0.88 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 178.6, 176.7, 159.7, 136.0, 126.0, 121.1, 119.1, 116.9, 104.8, 83.7, 39.2, 25.5; (CI/MS) m/z calcd for $C_{14}H_{17}O_3$ [M + H] 233.2, found 233.2.

*(Z)-3-(Hydroxymethylene)-2-isopropylchroman-4-one (**4b**):* 85% yield; IR (cm^{-1}) 3084, 2966, 2934, 1686, 1607, 1465; ^1H NMR ($CDCl_3$, 200 MHz) δ 14.36 (bs, 1H), 7.92 (s, 1H), 7.82 (dd, J = 1.5, 7.8 Hz, 1H), 7.47−7.34 (m, 1H), 7.06−6.88 (m, 2H), 4.53 (d, J = 8.2 Hz, 1H), 1.87 (m, 1H), 1.12 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 180.1, 173.2, 158.5, 135.9, 126.4, 126.7, 120.1, 117.9, 107.9, 81.7, 32.9, 18.5; (CI/MS) m/z calcd for $C_{13}H_{13}O_3$ [M − H] 217.1, found 217.1.

*(Z)-2-Cyclohexyl-3-(hydroxymethylene)chroman-4-one (**4c**):* 88% yield; IR (cm^{-1}) 2969, 2783, 1640, 1604, 1485; ^1H NMR ($CDCl_3$, 200 MHz) δ 14.36 (bs, 1H), 7.82 (s, 1H), 7.76 (dd, J = 1.6, 7.8 Hz, 1H), 7.43−7.39 (m, 1H), 7.00−6.78 (m, 2H), 4.50 (d, J = 8.2 Hz, 1H), 2.30−2.11 (m, 5H), 1.76−0.98 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 179.6, 172.9, 158.2, 135.7, 126.2, 121.4, 119.8, 117.8, 107.2, 80.5, 41.8, 28.7, 28.3, 26.1, 25.7, 25.5; (CI/MS) m/z calcd for $C_{17}H_{21}O_2$ [M + H] 257.1, found 257.2.

*(Z)-2-Cyclopentyl-3-(hydroxymethylene)chroman-4-one (**4d**):* 81% yield; IR (cm^{-1}) 2968, 2862, 1642, 1603, 1487 ; ^1H NMR ($CDCl_3$, 200 MHz) δ 14.37 (bs, 1H), 7.82 (s, 1H), 7.76 (dd, J = 1.5, 7.8 Hz, 1H), 7.43−7.31 (m, 1H), 6.99−6.80 (m, 2H), 4.54 (d, J = 9.0 Hz, 1H), 2.30−2.11 (m, 1H), 1.76−0.98 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 180.9, 171.6, 158.6, 135.9, 126.4, 121.7, 120.3, 118.1, 109.2, 80.6, 44.3, 29.4, 29.0, 25.6, 25.4; (CI/MS) m/z calcd for $C_{15}H_{15}O_3$ [M − H] 243.1, found 243.2.

*(Z)-2-Ethyl-3-(hydroxymethylene)chroman-4-one (**4e**):* 83% yield; IR (cm^{-1}) 2967, 2933, 2876, 2360, 1645, 1608, 1465; ^1H NMR ($CDCl_3$, 200 MHz) δ 14.38 (bs, 1H), 7.85 (m, 2H), 7.49−7.39 (m, 1H), 7.06−6.88 (m, 2H), 4.87 (dd, J = 5.6, 7.9 Hz, 1H), 2.01−1.79 (m, 1H), 1.77−1.58 (m, 1H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 181.4, 170.9, 158.8, 135.9, 126.6, 121.8, 120.2, 118.2, 109.3, 77.6, 28.5, 9.8; (CI/MS) m/z calcd for $C_{12}H_{13}O_3$ [M + H] 205.1, found 205.2.

*2-tert-Butylchroman-4-one (**4f**).* This compound is reported in the literature, and the corresponding ^1H NMR, ^{13}C NMR, and HRMS are consistent with literature data.[18]

*2-tert-Butyl-4-oxochroman-3-carbonitrile (**4g**):* 87% yield; 1:1 inseparable mixture of diastereomers; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.29 (d, J = 7.4 Hz, 2H), 7.63−7.49 (m, 2H), 7.12−6.95 (m, 4H), 4.26 (dd, J = 1.0, 10.5 Hz, 1H), 3.97 (dd, J = 1.0, 2.0 Hz, 1H), 3.87 (dd, J = 1.0, 10.5 Hz, 1H), 3.63 (dd, J = 1.0, 2.0 Hz, 1H), 1.23 (s, 9H), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 183.7, 183.3, 162.0, 161.3, 137.6, 137.5, 128.6, 127.9, 122.7, 118.8, 118.5, 118.4, 118.2, 114.9, 114.2, 85.7, 85.1, 45.8, 39.1, 36.1, 35.4, 26.4, 26.3, 25.6; HRMS exact mass calcd for $C_{14}H_{15}NO_2Na$ $[M + Na]^+$ 252.1000, found 252.0993.

*General Procedure for Tandem Double Addition **6a**−**i**.* Chromone (0.2 mmol), CH_2Cl_2 (1.5 mL), and THF (0.5 mL) were added to a 15 mL vial, and the mixture was cooled to −60 °C while stirring. Alkyl iodide (2 mmol) was added, and the reaction was initiated using 1.0 M Et_3B in hexanes (1 mmol). The reaction mixture as stirred at −60 °C for 3 h. The reaction was quenched on a bed of silica, washed with ether, and concentrated to afford the boron enolate. The boron compound was then dissolved in 5 mL of THF and cooled to 0 °C. A mixture of 1 M NaOH (5 mL) and 30% H_2O_2 (5 mL) was added to the reaction flask and stirred for 2 h at 0 °C, during which time the reaction was usually completed. The reaction was ultimately deemed complete by monitoring via TLC (30% EtOAc in hexanes). The reaction mixture was transferred to a separatory funnel, extracted with EtOAc (2 × 15 mL), washed with brine, dried, and concentrated under reduced pressure. All dr's were determined on crude reaction mixtures. The compound was further adsorbed on silica gel and purified using column chromatography (5−30% EtOAc in hexanes) to give products **6a**−**i**.

*4,5-Di-tert-butyl-2-ethyl-4,5-dihydro-1,3,2-dioxaborinino[5,4-c]-chromene (**5**):* 93% yield; IR (cm^{-1}) 2957, 2872, 1666, 1607, 1489, 1396, 1363; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.71 (dd, J = 1.7, 7.6 Hz, 1H), 7.08 (td, J = 1.7, 7.6 Hz, 1H), 6.83−6.63 (m, 2H), 4.47 (s, 1H), 4.12 (s, 1H), 1.15−0.95 (m, 5H, B-CH_2CH_3), 0.93 (s, 9H), 0.86 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ155.9, 141.9, 130.2, 121.7, 120.5, 119.4, 115.1, 104.6, 83.9, 80.2, 40.9, 39.8, 26.6, 25.9, 7.8; ^{11}B NMR was recorded on a 400 MHz instrument using BF_3 as the external standard; ^{11}B signal was observed at 32.1 ppm; (CI/MS) m/z calcd for $C_{20}H_{30}BO_3$ [M + H] 329.2, found 329.2.

*2-tert-Butyl-3-(1-hydroxy-2,2-dimethylpropyl)chroman-4-one (**6a**):* 82% yield; IR (cm^{-1}) 3483, 2958, 2872, 1674, 1607, 1464; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.74 (dd, J = 1.9, 8.2 Hz, 1H), 7.52−7.38 (m, 1H), 6.97−6.85 (m, 2H), 4.70 (s, 1H), 3.49 (t. J = 4.8 Hz, 1H), 3.01 (d, J = 4.6 Hz, 1H), 2.11 (d, J = 5.2 Hz, 1H), 0.97 (s, 9H), 0.95 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.3, 160.9, 136.5, 126.8, 120.8, 120.6, 117.4, 85.4, 80.0, 48, 37.5, 37.2, 27.2, 26.4; HRMS exact mass calcd for $C_{18}H_{26}O_3Na$ $[M + Na]^+$ 313.1780, found 313.1765.

*3-(1-Hydroxy-2-methylpropyl)-2-isopropylchroman-4-one (**6b**):* 86% yield; IR (cm^{-1}) 3466, 2963, 2875, 1678, 1606, 1463, 1323; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.76−7.69 (m, 1H), 7.45−7.35 (m, 1H), 6.94−6.84 (m, 2H), 4.38 (dd, J = 2.3, 9.6 Hz, 1H), 3.76 (d, J = 7.9 Hz, 1H), 2.75 (dd, J = 2.4, 8.6 Hz, 1H), 2.07 (bs, 1H), 2.00−1.83 (m, 1H), 1.68−1.52 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.2, 159.5, 136.5, 126.9, 121.5, 121.1, 118.3, 83.9, 74.0, 52.4, 31.0, 28.7, 20.5, 19.5, 18.8, 15.2; HRMS exact mass calcd for $C_{16}H_{22}O_3Na$ $[M + Na]^+$ 285.1467, found 285.1463.

*2-Cyclohexyl-3-(cyclohexyl(hydroxy)methyl)chroman-4-one (**6c**):* 84% yield; IR (cm^{-1}) 3467, 2925, 2852, 1682, 1606, 1463, 1319; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.79 (dd, J = 1.8, 7.8 Hz, 1H), 7.51−7.41 (m, 1H), 7.01−6.88 (m, 2H), 4.51 (dd, J = 2.2, 9.1 Hz, 1H), 3.78 (d, J = 8.1 Hz, 1H), 2.87 (dd, J = 2.3, 9.3 Hz, 1H), 2.00−1.48 (m, 11H), 1.38−0.97 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.4, 159.6, 136.5, 126.9, 121.5, 121.1, 118.3, 82.9, 74.1, 51.1, 40.9, 38.0, 30.7, 29.5, 28.9, 26.5, 26.3, 26.1, 25.9, 25.7; HRMS exact mass calcd for $C_{22}H_{30}O_3Na$ $[M + Na]^+$ 365.2093, found 365.2094.

*2-Cyclopentyl-3-(cyclopentyl(hydroxy)methyl)chroman-4-one (**6d**):* 71% yield; IR (cm^{-1}) 3452, 2953, 2867, 1675, 1606, 1462, 1322; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.86 (dd, J = 1.7, 7.7 Hz, 1H), 7.49−7.40 (m, 1H), 6.99−6.88 (m, 2H), 4.57 (dd, J = 1.9, 10.3 Hz, 1H), 3.93 (dd, J = 5.2, 7.5 Hz, 1H), 2.62 (dd, J = 1.9, 7.5 Hz, 1H), 2.07−1.06 (m, 18H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.4, 159.5, 136.5, 126.8, 121.7, 121.1, 118.3, 82.8, 73.2, 55.2, 43.6, 40.7, 30.2, 29.6, 28.9, 26.9, 26.0, 25.9, 25.5, 25.4; HRMS exact mass calcd for $C_{20}H_{26}O_3Na$ $[M + Na]^+$ 337.1780, found 337.1764.

*2-Ethyl-3-(1-hydroxypropyl)chroman-4-one (**6e**):* 70% yield; IR (cm^{-1}) 3410, 2967, 2936, 1681, 1606, 1463, 1325; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.87−7.79 (m, 1H), 7.52−7.42 (m, 1H), 7.03−6.92 (m, 2H), 4.64−4.52 (m, 1H), 3.92−3.74 (m, 1H), 2.75 (t, J = 6.1 Hz, 1H), 1.97−1.69 (m, 2H), 1.51 (m, 2H), 1.05 (t, J = 7.5 Hz, 3H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.5, 160.4, 136.7, 127.1, 121.3, 121.1, 118.3, 79.9, 71.8, 55.5, 26.9, 25.1, 10.4, 9.8; HRMS exact mass calcd for $C_{14}H_{18}O_3Na$ $[M + Na]^+$ 257.1154, found 257.1146.

*2-tert-Butyl-6-chloro-3-(1-hydroxy-2,2-dimethylpropyl)chroman-4-one (**6f**):* 70% yield; IR (cm^{-1}) 3447, 2961, 2873, 1676, 1604, 1471, 1426, 1367; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.70 (d, J = 2.7 Hz, 1H), 7.37 (dd, J = 2.7, 8.9 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 4.71 (s, 1H), 3.47 (d, J = 4.3 Hz, 1H), 3.01 (d, J = 4.6 Hz, 1H), 2.05 (bs, 1H), 0.97 (s, 9H), 0.93 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.3, 159.5, 136.3, 126.1, 125.9, 121.5, 119.2, 85.7, 79.9, 47.8, 37.5, 37.2, 27.1, 26.4; HRMS exact mass calcd for $C_{18}H_{25}ClO_3Na$ $[M + Na]^+$ 347.1390, found 347.1375.

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*6-Bromo-2-tert-butyl-3-(1-hydroxy-2,2-dimethylpropyl)chroman-4-one (**6g**):* 81% yield; IR (cm^{-1}) 3494, 2960, 2872, 1677, 1600, 1469, 1421, 1277; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.84 (d, J = 2.6 Hz, 1H), 7.53−7.46 (m, 1H), 6.83 (d, J = 8.8 Hz, 1H), 4.71 (s, 1H), 3.46 (d, J = 4.5 Hz, 1H), 2.99 (d, J = 4.6 Hz, 1H), 0.95 (s, 9H), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.2, 160.0, 139.1, 129.2, 121.9, 119.5, 113.0, 85.7, 79.9, 47.8, 37.5, 37.2, 27.1, 26.3; HRMS exact mass calcd for $C_{18}H_{25}BrO_3Na$ $[M + Na]^+$ 391.0885, found 391.0872.

*2-tert-Butyl-6-fluoro-3-(1-hydroxy-2,2-dimethylpropyl)chroman-4-one (**6h**):* 77% yield; IR (cm^{-1}) 3494, 2961, 2871, 1676, 1486, 1439, 1278; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.40 (dd, J = 3.2, 8.2 Hz, 1H), 7.23−7.11 (m, 1H), 6.90 (dd, J = 4.3, 9.1 Hz, 1H), 4.70 (s, 1H), 3.49 (d, J = 4.6 Hz, 1H), 3.00 (d, J = 4.6 Hz, 1H), 2.07 (bs, 1H), 0.97 (s, 9H), 0.93 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.8, 157.2, 156.5 (d, J = 241.0 Hz), 124.1 (d, J = 24.4 Hz), 120.9 (d, J = 6.2 Hz), 119.0 (d, J = 7.2 Hz), 111.7 (d, J = 23.1 Hz), 85.6, 79.9, 47.8, 37.5, 37.2, 27.1, 26.3; HRMS exact mass calcd for $C_{18}H_{25}FO_3Na$ $[M + Na]^+$ 331.1685, found 331.1680.

*2-tert-Butyl-6-ethyl-3-(1-hydroxy-2,2-dimethylpropyl)chroman-4-one (**6i**):* 86% yield; IR (cm^{-1}) 3483, 2962, 2873, 1675, 1618, 1491; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.55 (d, J = 2.4 Hz, 1H), 7.28 (dd, J = 1.8, 8.5 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 4.65 (s, 1H), 3.48 (d, J = 4.3 Hz, 1H), 2.98 (d, J = 4.3 Hz, 1H), 2.56 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.5 Hz, 3H), 0.96 (s, 9H), 0.93 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.6, 159.2, 136.6, 136.4, 125.2, 120.4, 117.3, 85.2, 80.1, 47.9, 37.5, 37.2, 27.2, 26.4, 15.6; HRMS exact mass calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.2093, found 341.2096.

*General Procedure for Sequential Double Addition (**7a**−**d**).* The first radical addition to give the single addition product was done following the general procedure for single addition (see above). The crude compound was quenched on silica, concentrated, and used for the second radical addition without further purification. The crude material was dissolved in CH_2Cl_2 (1.5 mL) and THF (0.5 mL) and cooled to −60 °C. Alkyl iodide (2 mmol) was added, and the reaction was initiated using 1.0 M Et_3B in hexanes (1 mmol). The reaction mixture as stirred at −60 °C for 3 h. The reaction was quenched on a bed of silica, washed with ether, and concentrated to afford the boron enolate. The boron compound was then dissolved in THF (5 mL) and cooled to 0 °C. A mixture of 1 M NaOH (5 mL) and 30% H_2O_2 (5 mL) was added to the reaction flask and stirred for 2 h at 0 °C during which time the reaction was usually completed. The reaction was ultimately deemed complete by monitoring via TLC (30% EtOAc in hexanes). The reaction mixture was transferred to a separatory funnel, extracted with EtOAc (2 × 15 mL), washed with brine, dried, and concentrated under reduced pressure. The compound was further adsorbed on silica gel and purified using column chromatography (5−30% EtOAc in hexanes) to give products **7a**−**d**.

*2-tert-Butyl-3-(1-hydroxy-2-methylpropyl)chroman-4-one (**7a**):* 86% yield; IR (cm^{-1}) 3461, 2962, 2873, 1673, 1607, 1464, 1322; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.74 (dd, J = 2.0, 8.3 Hz, 1H), 7.45 (m, 1H), 6.97−6.88 (m, 2H), 4.62 (s, 1H), 3.71 (dd, J = 3.8, 7.8 Hz, 1H), 2.85 (d, J = 7.9 Hz, 1H), 1.78 (s, 1H), 1.72−1.63 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.93 (s, 9H), 0.92 (d, J = 6.7 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.2, 161.1, 136.6, 126.4, 121.0, 120.5, 117.5, 85.5, 75.9, 50.4, 37.0, 30.7, 27.0, 20.5, 15.2; HRMS exact mass calcd for $C_{17}H_{24}O_3Na$ $[M + Na]^+$ 299.1623, found 299.1621.

*2-tert-Butyl-3-(cyclohexyl(hydroxy)methyl)chroman-4-one (**7b**):* 78% yield; IR (cm^{-1}) 3461, 2962, 2873, 1673, 1607, 1464, 1322; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.81−7.73 (m, 1H), 7.49−7.35 (m, 1H), 6.85−6.75 (m, 2H), 4.59 (s, 1H), 3.74−3.65 (m, 1H), 2.89 (d, J = 7.5 Hz, 1H), 1.27−1.15 (m, 6H), 1.17−1.05 (m, 5H), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.4, 161.1, 136.6, 126.5, 121.1, 120.5, 117.5, 85.3, 75.9, 49.5, 40.5, 37.1, 30.7, 27.0, 26.5, 26.4, 26.0, 25.9; HRMS exact mass calcd for $C_{20}H_{28}O_3Na$ $[M + Na]^+$ 339.1936, found 339.1923.

*3-(1-Hydroxy-2,2-dimethylpropyl)-2-isopropylchroman-4-one (**7c**):* 73% yield; IR (cm^{-1}) 3447, 2962, 2873, 1680, 1607, 1463, 1322; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.82−7.73 (m, 1H), 7.53−7.42 (m, 1H), 6.99−6.82 (m, 2H), 4.56 (d, J = 10.5 Hz, 1H), 3.71−3.59 (m, 1H), 2.85 (d, J = 7.1 Hz, 1H), 2.19 (d, J = 5.3 Hz, 1H), 2.02−1.94 (m, 1H), 0.99 (d, J = 6.5 Hz, 3H), 0.93 (s, 9H), 0.99−0.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.5, 159.2, 136.7, 127.1, 121.8, 118.1, 85.7, 84.8, 77.8, 50.4, 36.3, 28.2, 26.4, 19.7, 18.2; HRMS exact mass calcd for $C_{17}H_{24}O_3Na$ $[M + Na]^+$ 299.1623, found 299.1625.

*2-Ethyl-3-(1-hydroxy-2,2-dimethylpropyl)chroman-4-one (**7d**):* 71% yield; 3477, 2963, 2875, 1680, 1606, 1463, 1320; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.68 (dd, J = 1.7, 7.7 Hz, 1H), 7.45−7.36 (m, 1H), 6.95−6.85 (m, 2H), 4.86 (dd, J = 5.1, 9.7 Hz, 1H), 3.67−3.55 (m, 1H), 2.57 (d, J = 7.1 Hz, 1H), 2.09 (d, J = 4.9 Hz, 1H), 1.79−1.70 (m, 1H), 1.54−1.44 (m, 1H), 0.92 (t, J = 7.2 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.5, 158.6, 136.3, 127.2, 121.4, 121.2, 118.2, 80.6, 53.2, 36.6, 30.9, 26.2, 24.7, 10.6; HRMS exact mass calcd for $C_{16}H_{22}O_3Na$ $[M + Na]^+$ 285.1467, found 285.1458.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra for new compounds **4a**−**e**,**g**, **6a**−**i**, and **7a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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