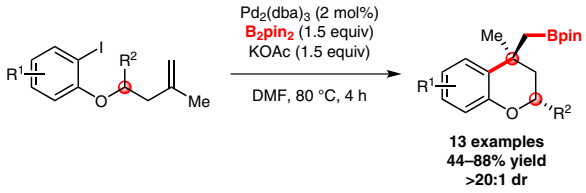
Synthesis H. Yoon et al. Paper

Diastereoselective Pd-Catalyzed Domino Heck/Arylborylation Sequence Forming Borylated Chromans

Hyung Yoon
Young Jin Jang
Mark Lautens*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, M5S 3H6, Canada
mlautens@chem.utoronto.ca



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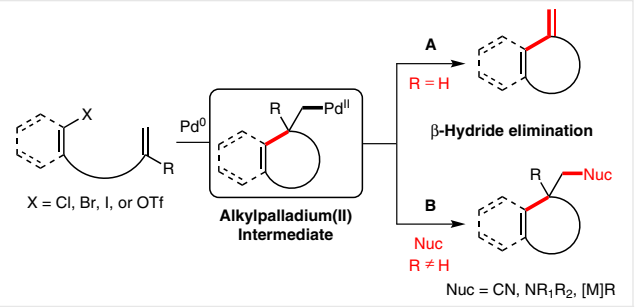
Abstract A diastereoselective palladium-catalyzed domino Heck/arylborylation of aryl iodides yielding an alkylboronate containing a chroman is reported. The generated alkylpalladium(II) intermediate is intercepted with bis(pinacolato)diboron (B_2pin_2) in good yield as a single diastereomer.

Key words palladium, Heck reaction, alkylboronate, diastereoselective, chroman, benzopyran

Organoboronates are valuable reagents due to their ease of preparation and high susceptibility toward functionalization. The increased use and demand of highly functionalized and/or stereochemically defined organoboronates prompts the development of novel and stereoselective methods to introduce carbon–boron bonds.[1] General methods to install organoboronates include Pd-catalyzed Miyaura borylation,[2] quenching trialkyl borates with organometallic reagents,[3] and C–H borylation reactions.[4] Despite numerous reports, methods to construct structurally complex and stereodefined alkylboronates still remain scarce. In this regard, we envisioned an intramolecular Pd-catalyzed domino Heck/arylborylation sequence to access a new class of sterically encumbered alkylboronates in a catalytic manner.

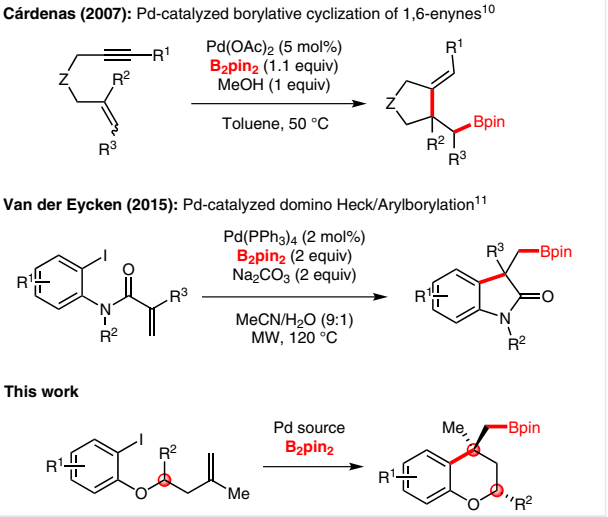
The Pd-catalyzed intramolecular Heck reaction has been intensely investigated and applied towards the synthesis of various natural products [Scheme 1,(A)].[5,6] Contrary to the Heck reaction, the resulting alkylpalladium(II) intermediate can be intercepted by various nucleophiles in the absence of β-hydrogens [Scheme 1 (B)]. Pioneered by the group of Grigg, nucleophiles including cyanides, amines, and organozinc and organotin reagents are applicable to this class of reactions.[7] Since the initial reports, novel nucleophiles and stereoselective methods were investigated by various groups. Additionally, this class of reaction was applied towards the synthesis of natural products.[8,9] However, the application of this type of reaction toward the synthesis of stereoselective and heterocyclic alkylboronates still remains scarce.



Scheme 1 General Pd-catalyzed intramolecular Heck reaction (A) and domino Heck/anion capture reaction (B)

In recent years, groups such as Cárdenas and Bäckvall have developed the Pd-catalyzed borylative cyclization sequences involving polyunsaturated substrates to produce various alkylboronates (Scheme 2).[10] Encouraged by these findings, we sought to develop a Pd-catalyzed domino Heck/arylborylation sequence.

During the preparation of this manuscript, Van der Eycken reported a useful microwave-assisted Pd-catalyzed domino Heck/arylborylation sequence of *o*-iodoanilides to form [(2-oxoindolin-3-yl)methyl]boronates (Scheme 2).[11] Complimentary to their recent findings, we report the first highly diastereoselective Pd-catalyzed domino Heck/arylborylation sequence of tethered aryl iodides to furnish borylated chromans (Scheme 2).



Scheme 2 Recent advances in Pd-catalyzed domino borylation reactions

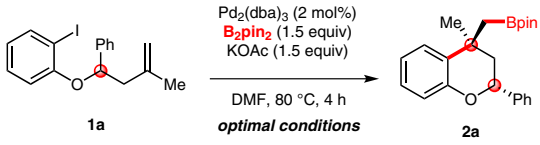
Subjecting the aryl iodide **1a** to $Pd_2(dba)_3$ (2 mol%), KOAc (1.5 equiv), and bis(pinacolato)diboron (B_2pin_2) (1.5 equiv) in DMF at 80 °C for 4 hours was found to be the optimal conditions. The tethered aryl iodide **1a** furnished the desired alkylboronate **2a** in 82% yield and >20:1 dr, and the relative stereochemistry was unambiguously confirmed by X-ray crystallography (see Supporting Information). A series of variation experiments were performed to examine the effects of changes to the optimal conditions (Table 1). It should be noted that in all cases, no direct borylation occurred forming the respective arylboronate.

Solvents less polar than DMF, like toluene and 1,4-dioxane, led to none of the desired product (entries 2 and 3). Other Pd sources including those reported by Cárdenas[10] and Buchwald,[12] produced the desired product with consistent dr but in lower yields (entries 4 and 5, respectively). The incorporation of bidentate ligands such as DPPF led to no reactivity (entry 6). Acetate bases were found to be the optimal bases as opposed to carbonates and alkylamines (entries 7–9). Attempts to lower the equivalents of KOAc and B_2pin_2 led to full conversion but a lower yield of the desired product (entries 10 and 11). Lastly, aryl bromides and aryl chlorides led to incomplete conversion into **2a** (entries 12 and 13).

With the optimized conditions in hand, we evaluated the scope of the reaction (Scheme 3). It should be noted that each of the examples listed **2a**–**m** produced exclusively the *trans*-diastereomer (>20:1 dr). Electron-rich aryl iodide **1c** cyclized in good yield with prolonged reaction time (**2c**, 62% yield, 12 h). Trifluoromethyl-bearing aryl iodide **1b** afforded **2b** in excellent yield (88% yield). Multisubstituted aryl iodides **1d** and **1e** produced the desired products **2d** and **2e** in 75% and 72% yield, respectively, with higher catalyst loading. Electron-rich, electron-poor, and *ortho*-substituted aryl groups were tolerated in good to excellent yields (**2f**–**h**, 74–88% yield). A thienyl group was also tolerated and afforded the final product **2i** in 73% yield. Aryl iodides bearing aliphatic groups, **1j** and **1k**, cyclized in moderate to good yield to produce the respective alkylboronates **2j** and **2k** (56% and 70% yield, respectively). Iodopyridyl group was tolerated in modest yields with prolonged reaction times while, iodoquinolinols were tolerated under the standard reaction conditions in good yield (**2l** and **2m**, 44% and 78% yield, respectively). Unfortunately, when *ortho*-substituted aryl iodide **1n** was used, no reactivity was observed even with higher catalyst loading or longer reaction times. Notably, under the optimal conditions, aryl iodides bearing an amine linker did not react to form the respective borylated isoquinolines.

We propose a plausible mechanism in line with those previously postulated for both the Pd-catalyzed domino Heck cascade reactions and Miyaura borylation (Scheme 4).[2,7] The aryl iodide **1a** undergoes oxidative addition and carbopalladation forming the alkylpalladium(II) intermediate **B**. The high diastereoselectivity of the carbopalladation forming **B** is consistent with previous literature.[13,14] The *trans*-adduct is thought to form exclusively from the minimized axial–axial interactions. Intermediate **B** then transmetalates with KOAc to form the acetoxypalladium(II) in-

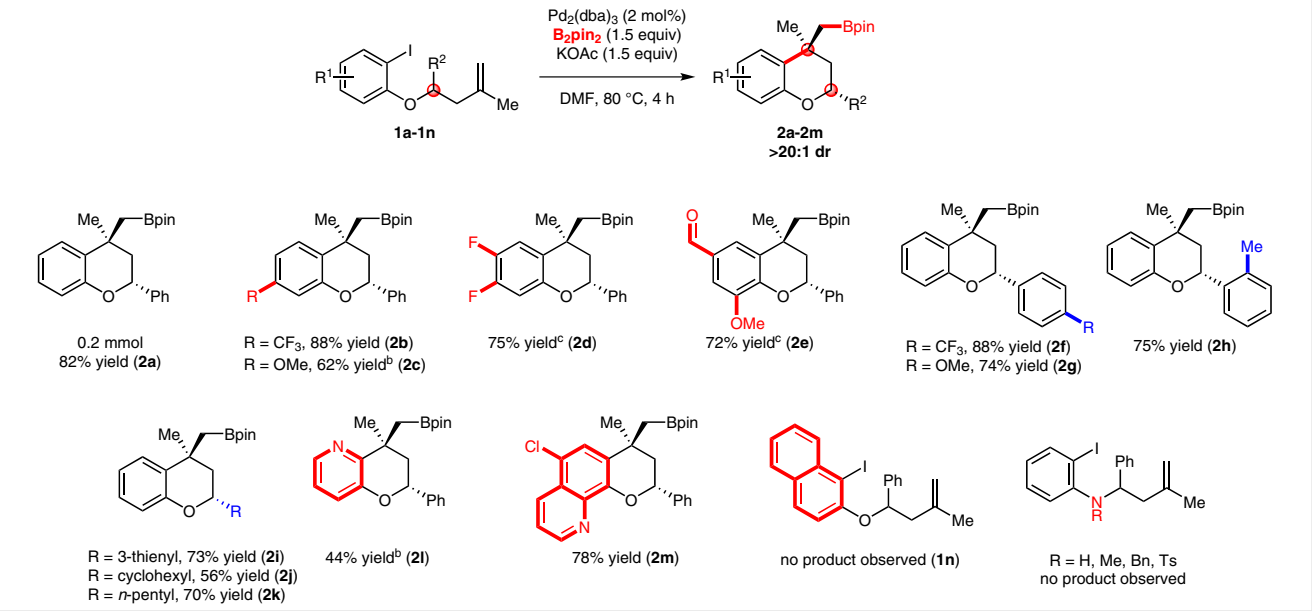
Table 1 Diastereoselective Pd-Catalyzed Domino Heck/Arylborylation: Effect on Reaction Parameters



1a 2a

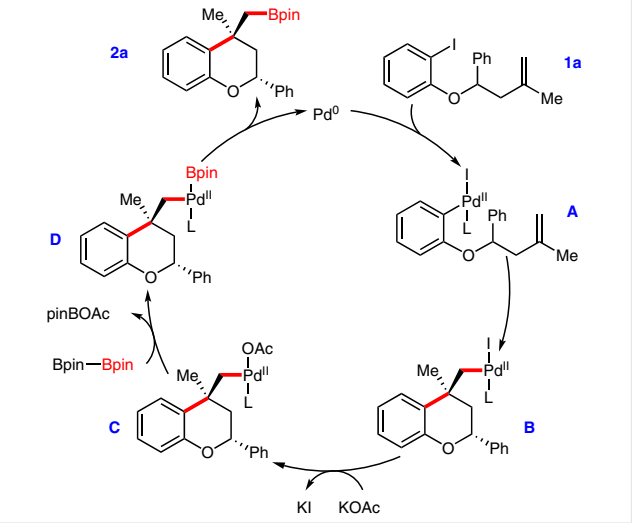
Entry	Variation from 'optimal' conditions	Yield (%)[a,b]
1	none	80 (82)
2	toluene instead of DMF	0
3	1,4-dioxane instead of DMF	0
4	$Pd(OAc)_2$ instead of Pd_2dba_3	73
5	Pd XPhos G1 instead of Pd_2dba_3	74
6[c]	DPPF added	0
7	NaOAc instead of KOAc	52
8	K_2CO_3 instead of KOAc	45
9	Et_3N instead of KOAc	9
10	1.1 equiv instead of 1.5 equiv of KOAc	62
11	1.1 equiv instead of 1.5 equiv of B_2pin_2	47
12	ArBr instead of ArI	43
13	ArCl instead of ArI	16

[a] Determined by ^1H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as internal standard.
[b] Yield in parentheses are isolated yields.
[c] Reaction was run with 4 mol% DPPF.



Scheme 3 Diastereoselective Pd-catalyzed domino Heck/arylborylation: reaction scope. Reactions performed on a 0.2-mmol scale unless otherwise stated; yields shown are isolated yields. [a] 2.75-mmol scale, 1 mol% catalyst loading, 0.2 M. [b] 12 h. [c] 4 mol% catalyst.

termediate **C**. The bound acetoxy group assists in the transmetalation with B_2pin_2 to generate intermediate **D**.[15] Finally, C–B reductive elimination regenerates Pd(0) and the desired alkylboronate **2a**.

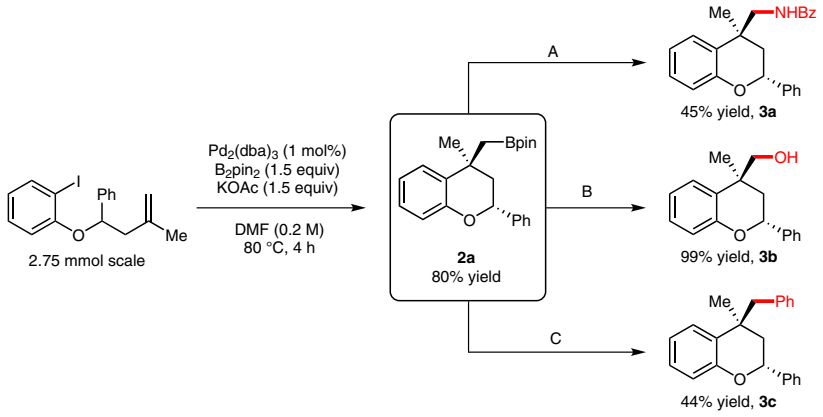


Scheme 4 Postulated mechanism of diastereoselective Pd-catalyzed domino Heck/arylborylation

The gram-scale reaction occurred smoothly with consistent yield and selectivity to give the model substrate **2a** with 1 mol% catalyst at 0.2 M (80% yield). Derivatization of the alkylboronate to various functional groups was performed (Scheme 5). A Cu(I)-catalyzed Chan–Lam coupling outlined by Watson[16] yielded the desired amide **3a** in moderate yield (45% yield). The oxidation of the alkylboronate to the alcohol **3b** proceeded in near quantitative yield (99% yield).[17] A Pd-catalyzed Suzuki reaction of **2a** was accomplished using a variation of a method outlined by Molander[18] and Capretta[19] producing the desired product **3c** in moderate yield (44% yield).

In conclusion, we have developed a highly diastereoselective Pd-catalyzed domino Heck/arylborylation of aryl iodides yielding alkylboronate-containing chromans in yields up to 88% as a single diastereomer. In addition, we were able to demonstrate the functional group convertibility of the alkylboronate to other synthetically useful moieties.

All non-aqueous reactions were performed in flame-dried round-bottom flasks sealed with a fitted rubber septum under an inert atmosphere of argon unless otherwise stated. All reactions were magnetically stirred and elevated temperatures were reported as the temperature of the surrounding oil bath. Reactions were monitored by TLC or by crude ^{1}H NMR analysis of a worked up aliquot. TLC visualization was performed under a UV lamp or $KMnO_4$/CAM stain developed with heat. Solvent evaporation was conducted by rotary evaporation at the appropriate temperature and pressure. Unless stated otherwise, all reagents were used as received and the following reaction solvents were distilled under anhydrous conditions over the appropriate drying agent and transferred under argon via a syringe. CH_2Cl_2 was distilled over CaH_2, THF was distilled over Na (1%) and benzophenone (1%), 1,4-dioxane was distilled over Na (1%), and benzophenone (1%), and Et_3N was distilled over KOH. DMF was distilled over 5-Å molecular sieves and stored over 5-Å molecular sieves (water content was kept lower than 50 ppm). 1,3,5-Trimethoxybenzene was crushed into a fine powder by a mortar and pestle, dried overnight in vacuo and stored in a desiccator. All reported yields reflect spectro-



Scheme 5 Gram-scale diastereoselective Pd-catalyzed domino Heck/arylborylation and derivatization. *Reaction conditions*: (A) benzamide, CuBr, di-*tert*-butyl peroxide, NaOTMS, *t*-BuOH, 75 °C. (B) 30% H_2O_2, 3 M NaOH, THF, 0 °C. (C) PhI, $Pd(OAc)_2$, 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphadamantane, *t*-BuOK, toluene, 100 °C.

scopically (^{1}H NMR) pure material unless otherwise stated. ^{1}H and ^{13}C NMR spectra of catalytic starting material and products were obtained on the Agilent DD2 500 equipped with a 5-mm Xsens Cold Probe. The starting material precursor ^{1}H and ^{13}C NMR spectra were obtained from one of the following spectrometers: Varian NMR system 400, Bruker Avance III 400, Varian Mercury 400, or Varian Mercury 300. All ^{19}F NMR spectra were obtained on the Varian Mercury 300 and Varian Mercury 400. Measurements were carried out at 23 °C. The solvent resonance was used as the internal standard for ^{1}H NMR ($CDCl_3$ δ = 7.26) and ^{13}C NMR ($CDCl_3$ δ = 77.0); *J* values are rounded off to the nearest 0.5 Hz. All accurate mass values were obtained from the following spectrometers: Agilent 6538 Q-TOF (ESI) and JEOL AccuTOF-DART. Melting points were obtained on a Fisher-Johns Melting Point Apparatus and uncorrected. IR spectra were obtained as a neat film or dissolved in $CHCl_3$ on a NaCl disk using a Shimadzu FTIR-8400S FT-IR spectrophotometer.

Pd-Catalyzed Domino Heck/Arylborylation: General Procedure

To a flame-dried or oven-dried 2-dram vial cooled under argon, the aryl iodide (1 equiv), $Pd_2(dba)_3$ (4 mol% Pd), B_2pin_2 (1.5 equiv), and KOAc (1.5 equiv) were added and allowed to purge for 10 min. DMF (0.1 M) was added. A Teflon-lined screw cap was fitted on the 2-dram vial, which was sealed with Teflon tape and place in a preheated oil bath at 80 °C for 4 h. Once TLC or ^{1}H NMR analysis confirmed full conversion of the starting material, the mixture was cooled to r.t. Once cooled, the reaction was extracted with EtOAc/H_2O (3 ×) and the combined extracts were dried (Na_2SO_4) and passed through a 2-cm plug of silica gel in a pipette using EtOAc. The pure chroman was obtained via flash column chromatography (silica gel) using the indicated mobile phase.

4,4,5,5-Tetramethyl-2-{[(2*R*,4*S*)-4-methyl-2-phenylchroman-4-yl]methyl}-1,3,2-dioxaborolane (2a)

Column chromatography (hexanes/EtOAc 10:1) gave **2a** (60 mg, 0.164 mmol, 82%) as a white solid; mp 74–75 °C.

IR (neat): 3065, 3032, 2976, 2930, 1607, 1578, 1485, 1447, 1356, 1327, 1220, 1145, 1066, 1011, 970 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51–7.47 (m, 2 H), 7.43–7.39 (m, 2 H), 7.39–7.35 (m, 1 H), 7.35–7.31 (m, 1 H), 7.11 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 6.93–6.89 (m, 2 H), 5.28 (dd, *J* = 12.0, 2.0 Hz, 1 H), 2.27 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.93 (ddd, *J* = 14.0, 12.0, 1.5 Hz, 1 H), 1.47 (s, 3 H), 1.44–1.40 (m, 2 H), 1.27 (d, *J* = 1.5 Hz, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.43, 142.35, 132.74, 128.40, 127.56, 127.06, 126.59, 125.88, 120.37, 117.05, 83.13, 74.42, 45.60, 33.43, 29.25, 24.96, 24.89.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 33.00.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{23}H_{29}BO_3$ + NH_4: 382.25535; found: 382.25588.

4,4,5,5-Tetramethyl-2-{[(2*R*,4*S*)-4-methyl-2-phenyl-7-(trifluoromethyl)chroman-4-yl]methyl}-1,3,2-dioxaborolane (2b)

Column chromatography (hexanes/EtOAc 5:1) gave **2b** (76 mg, 0.176 mmol, 88%) as a clear, colorless oil.

IR (neat): 3032, 2978, 2932, 1578, 1506, 1456, 1427, 1325, 1275, 1215, 1124, 1089, 1067, 1017, 970 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.47 (m, 3 H), 7.46–7.41 (m, 2 H), 7.38–7.33 (m, 1 H), 7.22–7.19 (m, 1 H), 7.19–7.15 (m, 1 H), 5.34 (dd, *J* = 12.0, 2.0 Hz, 1 H), 2.33 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.95 (ddd, *J* = 14.0, 12.0, 1.0 Hz, 1 H), 1.50 (s, 3 H), 1.47–1.38 (m, 2 H), 1.29 (s, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.60, 141.60, 136.47 (q, *J* = 1.0 Hz), 129.40 (q, *J* = 32.5 Hz), 128.47, 127.78, 127.24, 125.77, 124.01 (q, *J* = 272.0 Hz), 116.77 (q, *J* = 4.0 Hz), 114.31 (q, *J* = 4.0 Hz), 83.29, 74.79, 45.08, 33.56, 28.95, 24.90, 24.83.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 32.79.

^{19}F NMR (377 MHz, $CDCl_3$): δ = –62.56.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{24}H_{28}BF_3O_3$ + NH_4: 450.24273; found: 450.24332.

2-{[(2*R*,4*S*)-7-Methoxy-4-methyl-2-phenylchroman-4-yl]methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2c)

Column chromatography (hexanes/EtOAc 10:1) gave **2c** (49 mg, 0.124 mmol, 62%) as a clear, colorless oil.

IR (neat): 3030, 2976, 2932, 1620, 1504, 1418, 1354, 1321, 1248, 1198, 1161, 1144, 1119, 1082, 1041 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.50 (m, 2 H), 7.46–7.41 (m, 2 H), 7.38–7.32 (m, 1 H), 7.30 (d, *J* = 8.5 Hz, 1 H), 6.55 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.50 (d, *J* = 2.5 Hz, 1 H), 5.30 (dd, *J* = 12.0, 2.0 Hz, 1 H), 3.79 (s, 3 H), 2.26 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.94 (dd, *J* = 12.0, 1.5 Hz, 1 H), 1.47 (s, 3 H), 1.41 (s, 2 H), 1.29 (s, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.67, 154.24, 142.18, 128.37, 127.56, 127.26, 125.86, 124.98, 107.52, 101.31, 83.05, 74.71, 55.13, 45.79, 32.96, 29.38, 24.92, 24.84.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 33.11.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{24}H_{32}BO_4$: 395.23936; found: 395.23874.

2-{[(2*R*,4*S*)-6,7-Difluoro-4-methyl-2-phenylchroman-4-yl]methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2d)

Column chromatography (hexanes/EtOAc 10:1) gave **2d** (60 mg, 0.15 mmol, 75%) as a clear, colorless oil.

IR (neat): 3066, 2978, 2940, 1506, 1456, 1423, 1354, 1329, 1281, 1194, 1142, 1030, 970 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.40 (m, 4 H), 7.37–7.33 (m, 1 H), 7.20 (dd, *J* = 12.0, 9.0 Hz, 1 H), 6.71 (dd, *J* = 11.5, 7.0 Hz, 1 H), 5.26 (dd, *J* = 12.0, 2.0 Hz, 1 H), 2.23 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.91 (ddd, *J* = 14.0, 12.0, 1.0 Hz, 1 H), 1.45 (s, 3 H), 1.38 (d, *J* = 4.0 Hz, 2 H), 1.29 (d, *J* = 2.5 Hz, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.59 (dd, *J* = 9.5, 2.0 Hz) overlapping 148.39 (dd, *J* = 247.0, 13.0 Hz), 144.71 (dd, *J* = 239.0, 13.0 Hz), 141.60, 128.52, 128.42 (t, *J* = 4.0 Hz), 127.86, 125.86, 114.54 (dd, *J* = 18.5, 1.0 Hz), 105.63 (d, *J* = 19.5 Hz), 83.34, 74.89, 45.46, 33.45, 29.27, 24.96, 24.89.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 32.86.

^{19}F NMR (377 MHz, $CDCl_3$): δ = –139.57 to –139.78 (m), –148.28 to –148.48 (m).

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{23}H_{27}BF_2O_3$ + NH_4: 418.23650; found: 418.23632.

(2*R*,4*S*)-8-Methoxy-4-methyl-2-phenyl-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]chroman-6-carbaldehyde (2e)

Column chromatography (hexanes/EtOAc 5:1) gave **2e** (61 mg, 0.144 mmol, 72%) as a white solid; mp 103–104 °C.

IR (neat): 2976, 2933, 2837, 1684, 1582, 1480, 1452, 1391, 1354, 1278, 1261, 1236, 1215, 1144, 1078, 1009 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.83 (s, 1 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 7.48–7.44 (m, 2 H), 7.42–7.36 (m, 2 H), 7.34–7.29 (m, 1 H), 7.27–7.25 (m, 1 H), 5.36 (dd, *J* = 12.0, 2.0 Hz, 1 H), 3.90 (s, 3 H), 2.30 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.96–1.87 (m, 1 H), 1.49 (s, 3 H), 1.40 (q, *J* = 15.0 Hz, 2 H), 1.25 (d, *J* = 5.5 Hz, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 191.14, 149.42, 149.11, 141.22, 133.09, 128.93, 128.50, 127.83, 125.86, 124.47, 107.15, 83.30, 75.47, 56.08, 45.21, 33.50, 28.97, 24.94, 24.89.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 33.51.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{25}H_{32}BO_5$: 423.23428; found: 423.23405.

4,4,5,5-Tetramethyl-2-({(2*R*,4*S*)-4-methyl-2-[4-(trifluoromethyl)phenyl]chroman-4-yl}methyl)-1,3,2-dioxaborolane (2f)

Column chromatography (hexanes/EtOAc 10:1) gave **2f** (76 mg, 0.176 mmol, 88%) as a clear, colorless oil.

IR (neat): 3030, 2978, 2930, 2911, 1622, 1578, 1485, 1449, 1356, 1325, 1221, 1165, 1125, 1066, 1017 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75–7.61 (m, 4 H), 7.44–7.38 (m, 1 H), 7.18–7.12 (m, 1 H), 7.00–6.93 (m, 2 H), 5.39 (dd, *J* = 12.0, 1.0 Hz, 1 H), 2.35 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.92 (ddd, *J* = 14.0, 12.0, 1.0 Hz, 1 H), 1.51 (s, 3 H), 1.49–1.44 (m, 2 H), 1.32 (s, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.97, 146.48 (q, *J* = 1.0 Hz), 132.67, 129.63 (q, *J* = 32.5 Hz), 127.16, 126.53, 126.04, 125.30 (q, *J* = 3.5 Hz), 123.83 (q, *J* = 272.0 Hz), 120.71, 117.01, 83.19, 73.76, 45.49, 33.42, 29.16, 24.90, 24.86.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 32.78.

^{19}F NMR (377 MHz, $CDCl_3$): δ = –62.39.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{24}H_{28}BF_3O_3$ + NH_4: 450.24273; found: 450.24317.

2-{[(2*R*,4*S*)-2-(4-Methoxyphenyl)-4-methylchroman-4-yl]methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2g)

Column chromatography (hexanes/EtOAc 6:1) gave **2g** (58 mg, 0.148 mmol, 74%) as a white solid; mp 82–84 °C.

IR (neat): 2976, 2930, 1578, 1516, 1485, 1447, 1327, 1302, 1248, 1221, 1175, 1144, 1119, 1076, 1037 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 2 H), 7.36 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.10 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 6.98–6.92 (m, 2 H), 6.93–6.86 (m, 2 H), 5.22 (dd, *J* = 12.0, 2.0 Hz, 1 H), 3.84 (s, 3 H), 2.22 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.93 (ddd, *J* = 14.0, 12.0, 1.0 Hz, 1 H), 1.47 (s, 3 H), 1.40 (d, *J* = 5.5 Hz, 2 H), 1.26 (s, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.13, 153.54, 134.43, 132.70, 127.25, 127.01, 126.61, 120.29, 117.03, 113.83, 83.10, 74.09, 55.29, 45.42, 33.45, 29.30, 24.96, 24.87.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 33.16.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{24}H_{31}BNO_4$ + NH_4: 412.26591; found: 412.26627.

4,4,5,5-Tetramethyl-2-{[(2*R*,4*S*)-4-methyl-2-(*o*-tolyl)chroman-4-yl]methyl}-1,3,2-dioxaborolane (2h)

Column chromatography (hexanes/EtOAc 6:1) gave **2h** (57 mg, 0.15 mmol, 75%) as a white solid; mp 75–77 °C.

IR (neat): 2976, 29, 2928, 1598, 1485, 1449, 1356, 1325, 1227, 1165, 1144, 1119, 1011, 970 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.40 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.33–7.27 (m, 1 H), 7.27–7.22 (m, 1 H), 7.22–7.18 (m, 1 H), 7.13 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1 H), 6.97–6.89 (m, 2 H), 5.48 (dd, *J* = 12.0, 2.0 Hz, 1 H), 2.45 (s, 3 H), 2.33 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.86 (ddd, *J* = 14.0, 12.0, 1.0 Hz, 1 H), 1.49–1.43 (m, 5 H), 1.26 (s, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.70, 140.32, 134.42, 132.81, 130.22, 127.29, 127.03, 126.77, 126.27, 125.57, 120.38, 117.07, 83.12, 71.34, 44.11, 33.61, 29.32, 24.93, 24.82, 18.86.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 33.16.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{24}H_{31}BNO_3$ + NH_4: 396.27100; found: 396.27101.

4,4,5,5-Tetramethyl-2-{[(2*R*,4*S*)-4-methyl-2-(thiophen-3-yl)chroman-4-yl]methyl}-1,3,2-dioxaborolane (2i)

Column chromatography (hexanes/EtOAc 10:1) gave **2i** (54 mg, 0.146 mmol, 73%) as a white solid; mp 68–70 °C.

IR (neat): 2976, 2930, 1578, 1485, 1449, 1356, 1327, 1219, 1144, 1115, 1005, 847, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.31 (dd, *J* = 5.0, 1.0 Hz, 1 H), 7.13 (ddd, *J* = 3.5, 1.0, 1.0 Hz, 1 H), 7.09 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 7.03 (dd, *J* = 5.0, 3.5 Hz, 1 H), 6.91 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 6.88 (dd, *J* = 8.0, 1.5 Hz, 1 H), 5.54–5.50 (m, 1 H), 2.39 (dd, *J* = 14.0, 2.0 Hz, 1 H), 2.08 (dd, *J* = 14.0, 12.0 Hz, 1 H), 1.48 (s, 3 H), 1.38 (s, 2 H), 1.25 (d, *J* = 1.5 Hz, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.02, 145.38, 132.48, 127.07, 126.61, 126.54, 124.81, 124.15, 120.61, 117.07, 83.15, 70.58, 45.30, 33.41, 29.38, 24.96, 24.83.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 32.96.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{21}H_{27}BO_3S$ + NH_4: 388.21177; found: 388.21152.

2-{[(2*R*,4*S*)-2-Cyclohexyl-4-methylchroman-4-yl]methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2j)

Column chromatography (hexanes/EtOAc 10:1) gave **2j** (41 mg, 0.112 mmol, 56%) as a clear, colorless oil.

IR (neat): 2976, 2926, 2853, 1578, 1485, 1449, 1356, 1325, 1269, 1233, 1163, 1144, 1111, 1069, 1045 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.05 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 6.88–6.81 (m, 1 H), 6.79 (dd, *J* = 8.0, 1.0 Hz, 1 H), 3.96 (ddd, *J* = 12.0, 6.0, 1.5 Hz, 1 H), 2.11–2.00 (m, 2 H), 1.88–1.77 (m, 3 H), 1.78–1.70 (m, 1 H), 1.68–1.56 (m, 2 H), 1.45 (s, 3 H), 1.41–1.12 (m, 19 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.87, 133.21, 126.81, 126.58, 119.78, 116.78, 82.99, 76.29, 42.58, 39.27, 32.90, 29.54, 28.61, 28.36, 26.69, 26.28, 26.21, 24.96, 24.95.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 33.10.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{23}H_{36}BO_3$: 371.27525; found: 371.27648.

4,4,5,5-Tetramethyl-2-{[(2*S*,4*S*)-4-methyl-2-pentylchroman-4-yl]methyl}-1,3,2-dioxaborolane (2k)

Column chromatography (hexanes/EtOAc 9:1) gave **2k** (50 mg, 0.14 mmol, 70%) as a clear, colorless oil.

IR (neat): 2976, 2457, 2932, 2861, 1578, 1485, 1447, 1387, 1356. 1327, 1231, 1165, 1144, 1121 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.05 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 6.89–6.81 (m, 1 H), 6.79 (dd, *J* = 8.0, 1.5 Hz, 1 H), 4.20–4.13 (m, 1 H), 2.09 (dd, *J* = 13.5, 2.0 Hz, 1 H), 1.84–1.73 (m, 1 H), 1.68–1.52 (m, 3 H), 1.52–1.29 (m, 10 H), 1.27 (d, *J* = 2.5 Hz, 12 H), 0.99–0.91 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.57, 133.03, 126.74, 126.62, 119.86, 116.70, 82.91, 72.21, 42.50, 35.86, 32.86, 31.81, 29.51, 24.89, 24.81, 24.79, 22.63, 14.02.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 33.10.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{22}H_{36}BO_3$: 359.27575; found: 359.27579.

(2*R*,4*S*)-4-Methyl-2-phenyl-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,4-dihydro-2*H*-pyrano[3,2-*b*]pyridine (2l)

Column chromatography (hexanes/EtOAc 6:1) gave **2l** (32 mg, 0.088 mmol, 44%) as an off white solid; mp 75–77 °C.

IR (neat): 3063, 2978, 2930, 1570, 1441, 1356, 1329, 1285, 1267, 1231, 1144, 1113, 1094, 1067, 1007 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (dd, *J* = 4.5, 1.5 Hz, 1 H), 7.48–7.44 (m, 2 H), 7.43–7.38 (m, 2 H), 7.36–7.31 (m, 1 H), 7.15 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.03 (dd, *J* = 8.0, 4.5 Hz, 1 H), 5.25 (dd, *J* = 12.0, 2.0 Hz, 1 H), 2.34 (dd, *J* = 14.0, 2.0 Hz, 1 H), 2.06 (ddd, *J* = 14.0, 12.0, 1.0 Hz, 1 H), 1.54–1.49 (m, 4 H), 1.26 (m, 13 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.77, 149.73, 141.44, 141.31, 128.49, 127.84, 125.92, 124.04, 122.19, 83.07, 74.93, 45.83, 36.27, 27.87, 24.95, 24.88.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 33.07.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{22}H_{28}BO_3$ + NH_4: 366.22405; found: 366.22475.

(2*R*,4*S*)-6-Chloro-4-methyl-2-phenyl-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,4-dihydro-2*H*-pyrano[3,2-*h*]quinoline (2m)

Column chromatography (hexanes/EtOAc 6:1) gave **2m** (70 mg, 0.156 mmol, 78%) as a yellow solid; mp 96–98 °C.

IR (neat): 2976, 2930, 1578, 1516, 1485, 1447, 1327, 1302, 1248, 1221, 1175, 1144, 1119, 1076, 1037 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.95 (dd, *J* = 4.0, 1.5 Hz, 1 H), 8.46 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.69 (s, 1 H), 7.60–7.53 (m, 2 H), 7.47 (dd, *J* = 8.5, 4.0 Hz, 1 H), 7.44–7.36 (m, 2 H), 7.34–7.28 (m, 1 H), 5.44 (dd, *J* = 12.0, 2.0 Hz, 1 H), 2.34 (dd, *J* = 14.0, 2.0 Hz, 1 H), 2.06 (ddd, *J* = 14.0, 12.0, 1.0 Hz, 1 H), 1.55–1.37 (m, 5 H), 1.26 (d, *J* = 7.1 Hz, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.81, 147.93, 141.56, 140.79, 132.57, 130.36, 128.50, 127.74, 126.22, 125.47, 125.44, 121.56, 121.37, 83.34, 75.49, 45.84, 33.97, 28.94, 24.98, 24.88.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 33.50.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{26}H_{29}BClO_3$ + NH_4: 450.20073; found: 450.20092.

Chan–Lam Coupling: *N*-{[(2*R*,4*S*)-4-Methyl-2-phenylchroman-4-yl]methyl}benzamide (3a)

To a flame-dried or oven-dried 1-dram vial cooled under argon, benzamide (24.2 mg, 0.2 mmol, 1 equiv), **2a** (109.2 mg, 0.3 mmol, 1.5 equiv), CuBr (5.7 mg, 0.04 mmol, 20 mol%), NaOTMS (45 mg, 0.4 mmol, 2 equiv), and di-*tert*-butyl peroxide (110 µL, 0.6 mmol, 3 equiv) were added and allowed to purge for 10 min. *t*-BuOH (0.4 M) was added. A Teflon-lined screw cap was fitted on the 1-dram vial, which was sealed with Teflon tape and place in a preheated oil bath at 75 °C for 48 h. The mixture was cooled to r.t. Once cooled, the reaction was passed through a 2-cm plug of Celite in a pipette using EtOAc. The chroman was purified by flash column chromatography (hexanes/EtOAc 3:1) to give **3a** (35 mg, 0.146 mmol, 45%) as an off-white solid; mp 173–174 °C.

IR (neat): 3414, 3322, 3063, 3032, 2965, 2926, 1640, 1578, 1534, 1487, 1447, 1295, 1229, 1119, 1063 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80–7.72 (m, 2 H), 7.55–7.48 (m, 3 H), 7.48–7.42 (m, 2 H), 7.42–7.35 (m, 2 H), 7.35–7.28 (m, 2 H), 7.24–7.18 (m, 1 H), 7.03–6.95 (m, 2 H), 5.39 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.14 (dd, *J* = 14.0, 8.0 Hz, 1 H), 3.47 (ddd, *J* = 14.0, 5.5, 1.0 Hz, 1 H), 2.17 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.86 (ddd, *J* = 14.0, 12.0, 1.0 Hz, 1 H), 1.40 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.88, 154.77, 141.69, 134.55, 131.62, 128.70, 128.48, 128.16, 127.73, 127.19, 126.86, 126.83, 125.98, 120.74, 117.75, 74.47, 49.66, 41.63, 36.50, 26.08.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{24}H_{24}NO_2$: 358.18070; found: 358.18011.

Oxidation: [(2*R*,4*S*)-4-Methyl-2-phenylchroman-4-yl]methanol (3b)

To a 2-dram vial, **2a** (72.8 mg, 0.2 mmol, 1 equiv) was added. THF (0.133 M) was added and the vial was cooled to 0 °C. Aq NaOH (0.8 mL, 3 M) and 30% H_2O_2 (0.4 mL) were added dropwise. A Teflon-lined screw cap was fitted on the 2-dram vial, sealed with Teflon tape and stirred at r.t. for 30 min. Once TLC analysis confirmed full conversion, the reaction was extracted with EtOAc/H_2O (3 ×) and the combined extracts were dried (Na_2SO_4) and passed through a 2-cm plug of silica gel in a pipette using EtOAc. The chroman was purified by flash column chromatography (hexanes/EtOAc 3:1) to give **3b** (50.4 mg, 0.198 mmol, 99%) as an off-white solid; mp 82–84 °C.

IR (neat): 3521, 2966, 2929, 2874, 1578, 1487, 1455, 1372, 1291, 1214, 1120, 1088, 1001 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.51–7.45 (m, 2 H), 7.45–7.38 (m, 2 H), 7.36–7.32 (m, 1 H), 7.32–7.28 (m, 1 H), 7.19 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 1 H), 6.99–6.94 (m, 2 H), 5.25 (dd, *J* = 12.0, 2.0 Hz, 1 H), 3.85 (d, *J* = 11.0 Hz, 1 H), 3.71 (d, *J* = 11.0 Hz, 1 H), 2.27 (dd, *J* = 14.0, 2.5 Hz, 1 H), 1.91 (dd, *J* = 14.0, 12.0 Hz, 1 H), 1.66 (s, 1 H), 1.35 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.09, 141.62, 128.49, 127.95, 127.87, 127.16, 126.57, 126.05, 120.67, 117.43, 74.67, 71.75, 40.94, 36.84, 25.07.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{17}H_{19}O_2$: 255.13850; found: 255.13796.

Suzuki Coupling: (2*R*,4*S*)-4-Benzyl-4-methyl-2-phenylchroman (3c)

To a flame-dried or oven-dried 2-dram vial cooled under argon, **2a** (36.4 mg, 0.1 mmol, 1 equiv), $Pd(OAc)_2$ (2.26 mg, 0.01 mmol, 10 mol%), *t*-BuOK (33.7 mg, 0.3 mmol, 3 equiv), and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (4.7 mg, 0.01 mmol, 10 mol%) were added and allowed to purge for 10 min. Toluene (0.1 M) and iodobenzene (17 µL, 0.15 mmol, 1.5 equiv) were added. A Teflon-lined screw cap was fitted on the 2-dram vial, which was sealed with Teflon tape and place in a preheated oil bath at 100 °C for 12 h. The mixture was cooled to r.t. Once cooled, the reaction was passed through a 2-cm plug of silica gel in a pipette using EtOAc. The chroman was purified by flash column chromatography (hexanes/EtOAc 10:1) to give **3c** (13.2 mg, 0.042 mmol, 44%) as a clear colorless oil.

IR (neat): 3062, 3028, 2961, 2929, 1578, 1484, 1448, 1297, 1278, 1225, 1119, 1083, 1066, 1009 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.39 (m, 4 H), 7.38–7.22 (m, 4 H), 7.21–7.16 (m, 1 H), 7.12–7.07 (m, 2 H), 7.00–6.93 (m, 2 H), 4.94 (dd, *J* = 12.0, 2.0 Hz, 1 H), 3.20 (d, *J* = 13.5 Hz, 1 H), 2.99 (d, *J* = 13.5 Hz, 1 H), 2.12 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.88 (dd, *J* = 14.0, 12.0 Hz, 1 H), 1.37 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.27, 141.84, 138.09, 130.70, 129.86, 128.55, 128.06, 127.86, 127.49, 127.47, 126.56, 125.96, 120.52, 117.31, 74.26, 49.61, 42.81, 35.95, 28.65.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{23}H_{23}O$: 315.17489; found: 315.17435.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561567.

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