Synthesis R. K. Orr et al. Paper

A Modular Synthesis of 2-Alkyl- and 2-Arylchromans via a Three-Step Sequence

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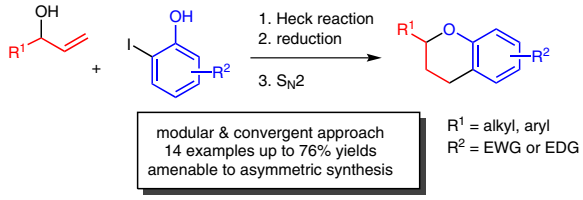

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Abstract A convergent three-step method for the synthesis of 2-substituted chromans is described. These results have been accomplished via the Heck coupling of readily accessible allylic alcohols and 2-iodophenols, followed by reduction and Mitsunobu cyclization. The utility and generality of this method is demonstrated through the synthesis of a series of 2-aryl-, 2-heteroaryl- and 2-alkylchromans, as well as an azachroman derivative. The asymmetric version of this approach via a Noyori-catalyzed ketone reduction and subsequent cyclization is likewise highlighted.

Key words asymmetric synthesis, chromans, catalysis, Heck reaction, Mitsunobu reaction, heterocycles

Functionalized chroman derivatives represent an important class of pharmacologically active compounds exhibiting a broad range of biological activity.[1] The most well-known examples include active natural products such as the antioxidant, vitamin E (**1**), and the psychoactive, tetrahydrocannabinol (THC, **2**).[2] Medicinal chemists have also reported a variety of active pharmaceutical ingredients containing the chroman core, such as the marketed antihypertensive, nebivolol (**3**),[3] along with the antidiabetic, troglitazone (Figure 1).[4]

We became interested in the synthesis of chromans as part of a medicinal chemistry effort in which the chroman moiety represented a key pharmacophore. As part of that effort, a highly convergent and modular racemic synthesis of 2-aryl- and 2-alkyl-substituted chromans was sought to expedite the SAR efforts. Initially, we investigated the classical synthesis of chromans via the inverse-electron-demand Diels–Alder reaction between in situ generated *ortho*-quinone methides **4** and styrenes (Scheme 1).[5] While convergent, this approach suffered from limited reaction scope and low yields, possibly due to the harsh reaction conditions and competitive decomposition of the *ortho*-quinone methide **4**, which were unable to be further optimized according to literature protocols. While a number of other conventional methods of chroman synthesis were investigated, all failed to meet the objectives to fully prosecute the SAR of the target.[6] Faced with this challenge, we set out to develop a convergent, general and robust racemic chroman

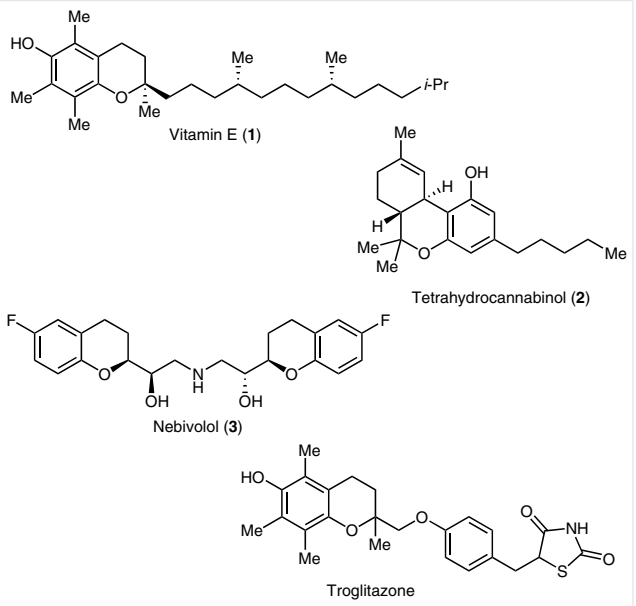
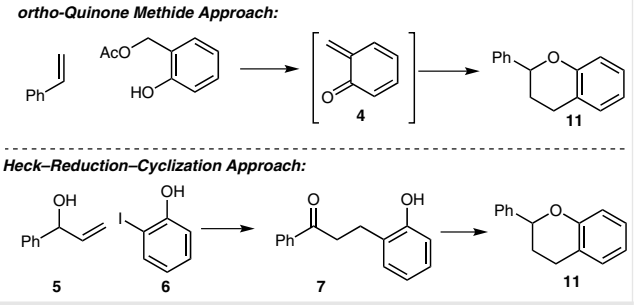


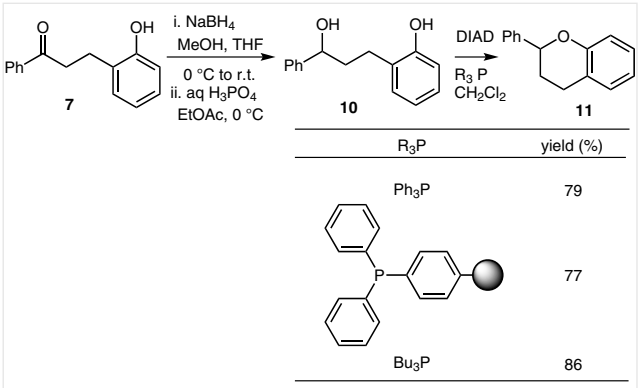
Figure 1 Biologically active chroman natural products and pharmaceuticals

synthesis to best enable thorough evaluation of the diverse chemical matter. Targeting the use of readily available starting materials, an approach was designed involving an initial Heck coupling reaction between an allylic alcohol **5** and 2-halophenol **6** to form the desired carbon framework. A reduction of the newly formed ketone **7**, followed by cyclization, would then afford the desired chroman ring **11** (Scheme 1). In this paper, we disclose our findings on this novel method for chroman synthesis.



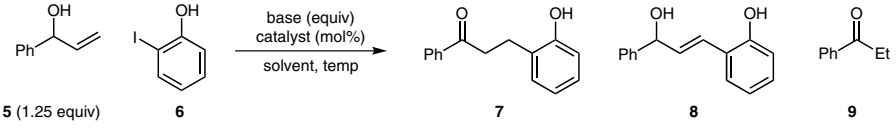
Scheme 1

Previous work at Merck has demonstrated the utility of Heck reactions between allylic alcohols and aryl halides towards a robust, large-scale synthesis of montelukast.[7] The corresponding transformation with 2-halophenols, however, has limited application due to the formation of complex reaction mixtures and poor reaction scope.[8,9] We started our foray into an improved 2-substituted chroman synthesis by investigation of literature conditions [$Pd(OAc)_2$, Cs_2CO_3 or Et_3N] which revealed that 2-iodophenol (**6**) underwent a coupling with 1-phenylprop-2-en-1-ol (**5**) in modest yield.[7] Upon careful analysis of the reaction mixture, it was established that formation of undesired allylic alcohol byproduct **8** and ketone **9** was responsible for the mass balance.[10] Unsatisfied with this result, we set out to optimize this Heck reaction in order to develop a robust and efficient reaction to support our chroman synthesis strategy.[11] Bulky electron-rich phosphine ligand palladium precursors were screened, with modified Fu conditions affording excellent conversion into product and a 73% assay yield along with a significant amount of propiophenone (**9**) (Table 1, entry 1).[12,13] Further investigation of Buchwald-type phosphines revealed a preference for very bulky derivatives bearing di-*tert*-butyl groups on phosphorus (Table 1, entries 2–5).[14] In particular, tBuXPhos generation 2 palladium precatalyst (tBuXPhos Pd G2) afforded an improved yield of ketone **7** due to reduced formation of the two major byproducts **8** and **9** (<10% combined; Table 1, entry 6). With



Scheme 2

Table 1 Optimization of the Heck Reaction



5 (1.25 equiv) **6** **7** **8** **9**

Entry	Catalyst (mol%)	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	tBu_3P Pd G2 (3)	Cy_2NMe (1.25)	toluene	100	3	73 (89[b])
2	BrettPhos Pd G3 (3)	Cy_2NMe (1.25)	toluene	100	3	72 (88[b])
3	tBuBrettPhos Pd G3 (3)	Cy_2NMe (1.25)	toluene	100	3	77 (86[b])
4	RockPhos Pd G3 (3)	Cy_2NMe (1.25)	toluene	100	3	84 (93[b])
5	tBuXPhos Pd G3 (3)	Cy_2NMe (1.25)	toluene	100	3	84 (93[b])
6	tBuXPhos Pd G2 (3)	Cs_2CO_3 (1.25)	toluene	100	3	86 (97[b])
7	tBuXPhos Pd G2 (3)	Cy_2NMe (1.25)	toluene	100	3	65 (78[b])
8[c]	tBuXPhos Pd G2 (5)	Cy_2NMe (2.5)	toluene	100	1	93, 88[d] (99[b])

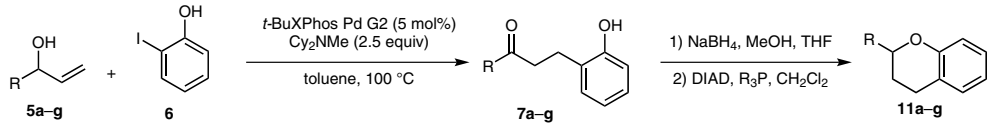
[a] Yield of reaction by HPLC assay, determined by comparison to the product standard.
[b] Conversion of 2-iodophenol into product, determined by HPLC at 210 nm.
[c] Allylic alcohol **5** (2 equiv) was used.
[d] Isolated yield after silica gel chromatography.

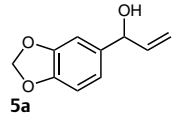
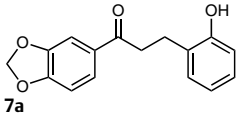
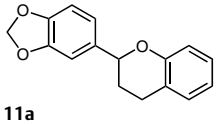
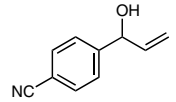
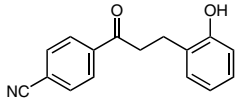
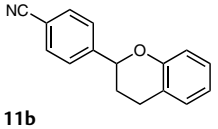
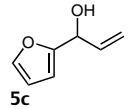
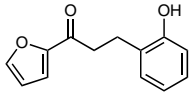
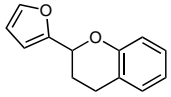
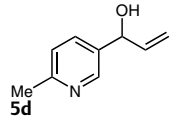
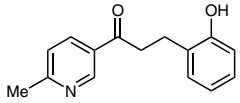
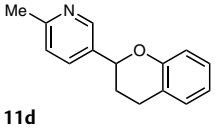
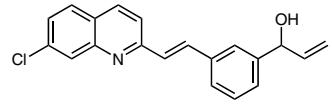
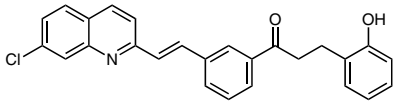
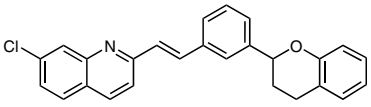
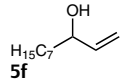
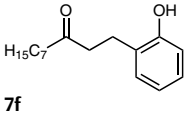
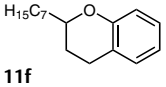
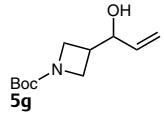
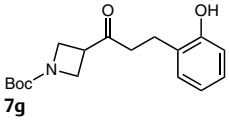
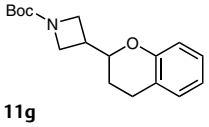
the optimal ligand in hand, bases and reagent stoichiometry were explored in the Heck reaction (Table 1, entries 6 and 7). Utilizing a combination of tBuXPhos Pd G2 precatalyst, 2.0 equivalents of allylic alcohol **5** and 2.5 equivalents of *N*,*N*-dicyclohexylmethylamine in toluene at 100 °C for 1 hour, a 93% assay yield was achieved. Gram-scale demonstration of these conditions afforded the desired product **7** in 88% isolated yield (Table 1, entry 8).[15]

With improved conditions for the Heck reaction in hand, the conversion of ketone **7** into the desired 2-phenylchroman product **11** was then investigated. Ketone **7** was reduced with sodium borohydride, and mild acidic workup afforded the diol intermediate **10**.[16] Crude intermediate **10** was then subjected to Mitsunobu conditions to provide chroman **11** in good yield (Scheme 2). A slight increase in yield was observed with the use of tributylphosphine compared to triphenylphosphine and the polymer-bound version of triphenylphosphine.[17]

To test the scope and robustness of the newly developed conditions, a series of allylic alcohols **5a–g** was investigated in the Heck reaction with 2-iodophenol (**6**) (Table 2). Similar to the optimization substrate, a significant increase in

Table 2 Scope of the Allylic Alcohol Component



Entry	Allylic alcohol	Heck product	Yield (%)	Chroman product	Yield (%)
1	 **5a**	 **7a**	88	 **11a**	79[a]
2	 **5b**	 **7b**	71	 **11b**	87[b]
3	 **5c**	 **7c**	75	 **11c**	62[b]
4	 **5d**	 **7d**	56	 **11d**	62[b]
5	 **5e**	 **7e**	74	 **11e**	65[b]
6	 **5f**	 **7f**	75	 **11f**	71[b]
7	 **5g**	 **7g**	70	 **11g**	74[a]

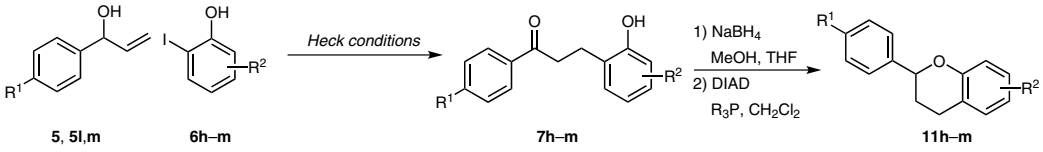
[a] With *n*-Bu_3P.
[b] With Ph_3P.

yield was observed with electron-rich allylic alcohol **5a**, while the Heck yield using electron-deficient benzonitrile **5b** was only slightly improved due to what is tentatively assigned as the allylic alcohol byproduct **8b** (15%; Table 2, entries 1 and 2).[18] On the contrary, a slight increase in yield was observed for the electron-deficient substrate **7b** during the reduction and cyclization sequence, thus providing a comparable overall yield for the sequence.

The synthesis of 2-heteroaryl- and 2-alkylchromans **11c–g** has proven challenging by existing literature methods.[19] For instance, utilizing conditions specified in Table 1, entries 1–3, complex mixtures were observed with considerable amounts of unreacted starting material (>30%). Using our methodology, heteroaryl-substituted allylic alcohols **5c–e** proved competent in the Heck, reduction and cyclization reactions, affording the corresponding products **11c–e** in good yields (Table 2, entries 3–5). Notably, the standard Heck conditions demonstrated the selectivity for the monosubstituted olefin and iodide of the highly functionalized allylic alcohol **5e** en route to montelukast (Table 2, entry 5). Finally, both linear and branched aliphatic allylic alcohols **5f**,**g** performed well as starting materials in this sequence, vastly increasing the scope of this transformation and allowing for a high degree of chemical diversity of chromans produced by this method (Table 2, entries 6 and 7).[20,21]

Next, the impact of substituents on the 2-iodophenol component, **6h–m**, was investigated for the formation of 2-phenylchromans **11h–m** (Table 3).[20] Electron-deficient 2-iodophenols **6h–j** were suitable substrates under standard reaction conditions with 1-phenylprop-2-en-1-ol (**5**) as the reaction partner in the Heck reaction (Table 3, entries 1–3). However, the use of 2-hydroxy-3-iodopyridine **6k** led to significant amounts of protodehalogenation byproduct under the standard reaction conditions, and <10% of product **7k** was obtained. Investigation of additional bases revealed that phosphazene superbases, notably P2-Et, significantly suppressed this byproduct formation, and afforded Heck product **7k** in 67% yield (Table 3, entry 4).[22]

Table 3 Scope of the Iodophenol Component



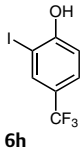
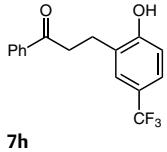
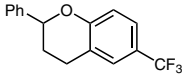
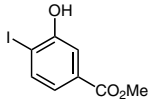
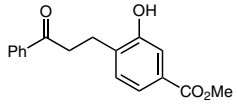
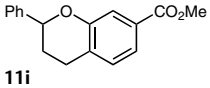
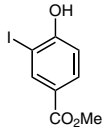
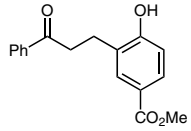
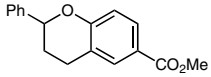
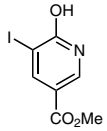
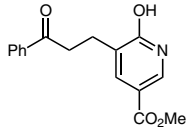
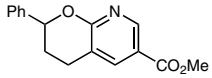
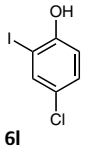
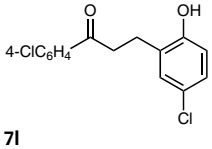
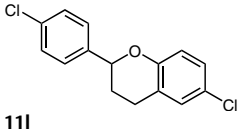
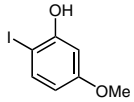
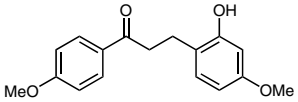
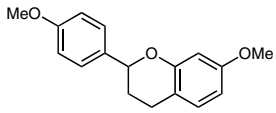
Entry	Allylic alcohol R^1	Iodophenol	Heck product	Yield (%)	Chroman product	Yield (%)
1	H (**5**)	 **6h**	 **7h**	76[a]	 **11h**	66[d]
2	H (**5**)	 **6i**	 **7i**	70[a]	 **11i**	75[d]
3	H (**5**)	 **6j**	 **7j**	63[a]	 **11j**	72[d]
4	H (**5**)	 **6k**	 **7k**	67[b]	 **11k**	85[e]

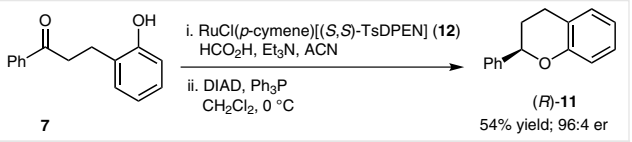
Table 3 (continued)

Entry	Allylic alcohol R^1	Iodophenol	Heck product	Yield (%)	Chroman product	Yield (%)
5	Cl (**5l**)	 **6l**	 **7l**	60[a]	 **11l**	50[e]
6	MeO (**5m**)	 **6m**	 **7m**	46[c]	 **11m**	60[f]

[a] tBuXPhos Pd G2 (5 mol%), Cy_2NMe (2.0 equiv), toluene, 100 °C.
[b] tBuXPhos Pd G2 (5 mol%), P2-Et (1.1 equiv), allylic alcohol **5** (1.1 equiv), toluene, 80 °C.
[c] tBuXPhos Pd G2 (7 mol%), slow addition of P2-Et (1.1 equiv), DMA, 80 °C.
[d] R_3P = polymer-bound Ph_3P.
[e] Ph_3P.
[f] Cyclization occurred during H_3PO_4 workup.

To further establish the modular nature of this approach, substrates substituted on both the allylic alcohol and iodophenol were utilized in this chemistry. For example, application to the synthesis of the antibiotic 4′,6-dichloroflavan (BW-683C, **11l**; Table 3, entry 5) was accomplished in high yield utilizing chlorinated starting materials **5l** and **6l**.[23] The core of the natural product tupichinol C (**11m**; Table 3, entry 6) was also prepared in modest yield via allylic alcohol **5m** and iodophenol **6m**.[24] With this highly electron-rich substrate, similar to the aza substrate **6k**, the Heck reaction required the use of P2-Et as base, along with slow addition of the base and DMA as solvent. Upon reduction of the ketone and acidic workup, the corresponding diol underwent spontaneous cyclization to form the chroman **11m**.[25]

While a racemic synthesis was desirable for initial biological evaluation of both enantiomers of the chroman product, an asymmetric approach was required to prepare multigram quantities of individual enantiomers of these compounds for in vivo studies. The asymmetric reduction of aryl alkyl ketones is well-documented utilizing the Noyori conditions; however, erosion of enantioselectivity is a known issue with the Mitsunobu reaction of chiral benzylic substrates.[26,27] The use of the readily available RuCl(*p*-cymene)[(*S*,*S*)-TsDPEN] catalyst (**12**) and in situ hydrogen generation from transfer hydrogenation conditions with substrate **7** afforded the corresponding chiral alcohol (*S*)-**10** in good enantioselectivity (95:5 er).[28] To our delight, no loss in enantiomeric excess was observed upon cyclization, when utilizing slow addition of the DIAD and temperature control at 0 °C, to form (*R*)-chroman **11** (Scheme 3).



Scheme 3 Asymmetric synthesis of chroman **11**

In summary, we have discovered a novel synthesis of 2-substituted chromans from allylic alcohols and 2-iodophenols via a three-step sequence. Significant optimization of the Heck reaction between allylic alcohols and iodophenols allowed for the use of a variety of substrates previously inaccessible by other methods. This modular chemistry functions on a broad range of substrates, including pharmaceutically relevant and natural product examples. Our chemistry has been readily applied to the gram-scale synthesis of chromans. In addition, application of the asymmetric version of this sequence has been demonstrated, with efforts underway to apply this asymmetric method to prepare more advanced chroman derivatives.

Commercial grade reagents and solvents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were measured with 400, 500 or 600 MHz Bruker Avance spectrometers. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from TMS (with the $CHCl_3$ peak at 7.27 used as a reference). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from TMS (with the central peak of $CDCl_3$ at 77.0 ppm used as a reference). High-resolution mass spectrometry was performed on a Waters Acquity UPLC for the LC and Waters Xevo G2 for MS, except for samples **11a**, **11b** and **11h** which were analyzed by GC-MS on an Agilent 6890 GC and a Waters GCT Premier mass detector. Purifications were carried out by flash column chromatography on a Teledyne Isco CombiFlash R_f system using a gradient elution of 0–40% EtOAc/hexanes.

3-(2-Hydroxyphenyl)-1-phenylpropan-1-one (7); Typical Procedure for Heck Products 7, 7a–m

To a flask were added 1-phenylprop-2-en-1-ol (**5**) (1.196 mL, 9.09 mmol), 2-iodophenol (**6**) (1 g, 4.55 mmol) and tBuXPhos Pd G2 precatalyst (0.156 g, 0.227 mmol). Then toluene (18 mL) was added to the flask and the solvent was degassed by bubbling N_2 through the solution for 15 min. Cy_2NMe (2.420 mL, 11.36 mmol) was then added to the flask and the solvent was degassed by bubbling N_2 through the solution for an additional 5 min. The reaction mixture was heated to 100 °C for 1 h, cooled to r.t. and concentrated to 1/3 volume. The residue was purified by silica gel chromatography to give 0.91 g (88%) of compound **7** as a colorless oil. The spectroscopic data obtained for this compound are in accordance with the previously prepared material.[7]

1-(Benzo[*d*][1,3]dioxol-5-yl)-3-(2-hydroxyphenyl)propan-1-one (7a)

Yield: 1.341 g (88%).

The spectroscopic data obtained for this compound are in accordance with the previously prepared material.[7]

4-(3-(2-Hydroxyphenyl)propanoyl)benzonitrile (7b)

Yield: 1.02 g (71%).

The spectroscopic data obtained for this compound are in accordance with the previously prepared material.[7]

1-(Furan-2-yl)-3-(2-hydroxyphenyl)propan-1-one (7c)

Yield: 0.229 g (75%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.02 (t, *J* = 6.12 Hz, 2 H), 3.32 (t, *J* = 6.12 Hz, 2 H), 6.54 (s, 1 H), 6.86 (t, *J* = 7.37 Hz, 1 H), 6.91 (d, *J* = 8.34 Hz, 1 H), 7.12 (t, *J* = 6.83 Hz, 2 H), 7.61 (d, *J* = 7.07 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.5, 39.8, 112.6, 117.2, 118.3, 120.7, 127.6, 128.0, 130.6, 147.0, 152.3, 154.4, 190.8.

HRMS (TOF-MS): *m*/*z* [M – H]$^+$ calcd for $C_{13}H_{11}O_3$: 215.0714; found: 215.0715.

3-(2-Hydroxyphenyl)-1-(6-methylpyridin-3-yl)propan-1-one (7d)

According to the general procedure, treatment of 1-(6-methylpyridin-3-yl)prop-2-en-1-ol (**5d**) (0.814 g, 5.45 mmol) with 2-iodophenol (**6**) (0.800 g, 3.64 mmol) in the presence of tBuXPhos Pd G2 precatalyst (0.125 g, 0.182 mmol) and Cy_2NMe (1.94 mL, 9.09 mmol) afforded 0.491 g (56%) of **7d** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (s, 3 H), 3.08 (t, *J* = 6.13 Hz, 2 H), 3.45 (t, *J* = 6.13 Hz, 2 H), 6.93–6.87 (m, 2 H), 7.14 (dd, *J* = 11.14, 7.43 Hz, 2 H), 7.70 (br s, 1 H), 8.17 (dd, *J* = 8.16, 2.29 Hz, 1 H), 9.10 (d, *J* = 2.25 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.6, 24.8, 40.4, 117.3, 120.8, 123.4, 127.4, 128.1, 129.2, 130.6, 136.0, 149.5, 154.4, 163.9, 200.5.

HRMS (TOF-MS): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}NO_2$: 242.1176; found: 241.1169.

(*E*)-1-(3-(2-(7-Chloroquinolin-2-yl)vinyl)phenyl)-3-(2-hydroxyphenyl)propan-1-one (7e)

Yield: 1.4 g (74%); white solid; mp 145–147 °C. This material was purified for analytical purposes by crystallization from MTBE (45% yield, without optimization of the crystallization).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.03 (s, 1 H), 3.10 (t, *J* = 6.14 Hz, 2 H), 3.50 (t, *J* = 6.15 Hz, 2 H), 6.89 (td, *J* = 7.41, 1.22 Hz, 1 H), 6.96 (d, *J* = 8.04 Hz, 1 H), 7.19–7.13 (m, 2 H), 7.52–7.44 (m, 3 H), 7.67 (d, *J* = 8.54 Hz, 1 H), 7.76–7.73 (m, 2 H), 7.81 (d, *J* = 7.73 Hz, 1 H), 7.95 (d, *J* = 7.89 Hz, 1 H), 8.16–8.11 (m, 2 H), 8.29 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.9, 40.5, 117.3, 119.7, 119.7, 120.7, 125.8, 127.0, 127.1, 127.5, 127.7, 128.0, 128.1, 128.5, 128.8, 129.3, 130.6, 132.4, 136.7, 154.6, 201.7.

HRMS (TOF-MS): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{21}ClNO_2$: 414.1255; found: 414.1249.

1-(2-Hydroxyphenyl)decan-3-one (7f)

Yield: 1.02 g (75%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ (~10% ketal form) = 0.88 (m, 3 H), 1.26 (m, 8 H), 1.55 (m, 2 H), 2.41 (m, 2 H), 2.86 (m, 4 H), 6.84 (m, 1 H), 6.90 (m, 1 H), 7.05 (d, *J* = 7.34 Hz, 1 H), 7.12 (m, 1 H), 7.77 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (~10% ketal form) = 14.0, 22.6, 23.2, 23.8, 28.9, 29.0, 31.6, 42.6, 44.3, 117.4, 120.6, 127.7, 128.0, 130.5, 154.4, 214.3.

HRMS (TOF-MS): *m*/*z* [M – H]$^-$ calcd for $C_{16}H_{23}O_2$: 247.1704; found: 247.1707.

tert-Butyl 3-(3-(2-Hydroxyphenyl)propanoyl)azetidine-1-carboxylate (7g)

According to the general procedure, treatment of *tert*-butyl 3-(1-hydroxyallyl)azetidine-1-carboxylate (**5g**) (1.236 g, 5.80 mmol) with 2-iodophenol (**6**) (0.85 g, 3.86 mmol) in the presence of tBuXPhos Pd G2 precatalyst (0.133 g, 0.193 mmol) and Cy_2NMe (2.06 mL, 9.6 mmol) afforded 0.828 g (70%) of **7g** as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ (~70% ketal form) = 0.88 (m, 3 H), 1.26 (m, 8 H), 1.55 (m, 2 H), 2.41 (m, 2 H), 2.86 (m, 4 H), 6.84 (m, 1 H), 6.90 (m, 1 H), 7.05 (d, *J* = 7.34 Hz, 1 H), 7.12 (m, 1 H), 7.77 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (~70% ketal form) = 14.0, 22.6, 23.2, 23.8, 28.9, 29.0, 31.6, 42.6, 44.3, 117.4, 120.6, 127.7, 128.0, 130.5, 154.4, 214.3.

HRMS (TOF-MS): *m*/*z* [M – H]$^+$ calcd for $C_{17}H_{22}NO_4$: 304.1554; found: 304.1540.

3-(2-Hydroxy-5-(trifluoromethyl)phenyl)-1-phenylpropan-1-one (7h)

Yield: 0.272 g (76%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.10 (t, *J* = 5.83 Hz, 2 H), 3.52 (t, *J* = 5.84 Hz, 2 H), 7.01 (d, *J* = 8.31 Hz, 1 H), 7.40 (d, *J* = 11.43 Hz, 2 H), 7.49 (t, *J* = 7.69 Hz, 2 H), 7.62 (t, *J* = 7.42 Hz, 1 H), 8.02–8.00 (m, 2 H), 8.76 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.2, 40.3, 117.9, 122.8 (q, *J* = 32.4 Hz), 124.5 (q, *J* = 271.4 Hz), 125.4 (q, *J* = 3.7 Hz), 127.9 (q, *J* = 3.8 Hz), 128.0, 128.4, 128.8, 134.2, 135.7, 157.6, 202.2.

HRMS (TOF-MS): *m*/*z* [M – H]$^-$ calcd for $C_{16}H_{12}F_3O_2$: 293.0795; found: 293.0801.

Methyl 3-Hydroxy-4-(3-oxo-3-phenylpropyl)benzoate (7i)

Yield: 0.308 g (70%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.10 (t, *J* = 6.20 Hz, 2 H), 3.47 (t, *J* = 6.21 Hz, 2 H), 3.90 (s, 3 H), 7.21 (d, *J* = 7.89 Hz, 1 H), 7.47 (t, *J* = 7.70 Hz, 2 H), 7.62–7.53 (m, 3 H), 8.00–7.98 (m, 2 H), 8.14 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.9, 39.8, 52.1, 118.3, 121.9, 128.4, 128.7, 129.8, 130.6, 133.4, 133.9, 136.0, 154.6, 167.1, 201.6.

HRMS (TOF-MS): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{15}O_4$: 283.0976; found: 283.0976.

Methyl 4-Hydroxy-3-(3-oxo-3-phenylpropyl)benzoate (7j)

Yield: 0.277 g (63%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.08 (t, *J* = 5.95 Hz, 2 H), 3.49 (t, *J* = 5.95 Hz, 2 H), 3.89 (s, 3 H), 6.94 (d, *J* = 8.46 Hz, 1 H), 7.47 (t, *J* = 7.73 Hz, 2 H), 7.59–7.56 (m, 1 H), 7.82 (dd, *J* = 8.45, 2.20 Hz, 1 H), 7.89 (d, *J* = 2.20 Hz, 1 H), 8.00–7.98 (m, 2 H), 8.88 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.9, 39.8, 52.1, 118.3, 121.9, 128.4, 128.5, 128.7, 129.8, 130.6, 133.4, 133.9, 136.0, 154.6, 167.1, 201.6.

HRMS (TOF-MS): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{15}O_4$: 283.0976; found: 283.0964.

Methyl 6-Hydroxy-5-(3-oxo-3-phenylpropyl)nicotinate (7k)

Yield: 0.293 g (67%); colorless liquid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.56 (t, *J* = 7.31 Hz, 2 H), 4.11 (t, *J* = 7.34 Hz, 2 H), 4.57 (s, 3 H), 8.32 (t, *J* = 7.63 Hz, 2 H), 8.44 (t, *J* = 7.38 Hz, 1 H), 8.54 (d, *J* = 2.44 Hz, 1 H), 8.79–8.74 (m, 3 H), 12.93 (s, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 26.2, 37.5, 53.0, 109.2, 129.2, 130.0, 132.3, 134.4, 137.0, 137.8, 139.4, 163.8, 165.8, 200.5.

HRMS (TOF-MS): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}NO_4$: 286.1074; found: 286.1064.

3-(5-Chloro-2-hydroxyphenyl)-1-(4-chlorophenyl)propan-1-one (7l)

Yield: 0.348 g (60%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.00 (t, *J* = 5.95 Hz, 2 H), 3.42 (t, *J* = 5.96 Hz, 2 H), 6.86 (d, *J* = 8.54 Hz, 1 H), 7.11–7.07 (m, 2 H), 7.45 (d, *J* = 8.31 Hz, 2 H), 7.92 (d, *J* = 8.31 Hz, 2 H), 7.99 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.3, 40.2, 118.9, 125.3, 127.9, 129.1, 129.3, 129.8, 130.2, 134.2, 140.6, 153.2, 200.7.

HRMS (TOF-MS): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{11}Cl_2O_2$: 293.0142; found: 293.0144.

3-(2-Hydroxy-4-methoxyphenyl)-1-(4-methoxyphenyl)propan-1-one (7m)

Yield: 0.289 g (46%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.97 (t, *J* = 5.83 Hz, 2 H), 3.37 (t, *J* = 5.85 Hz, 2 H), 3.76 (s, 3 H), 3.87 (s, 3 H), 6.46 (dd, *J* = 8.26, 2.70 Hz, 1 H), 6.53 (d, *J* = 2.60 Hz, 1 H), 6.93–6.91 (m, 2 H), 7.02 (d, *J* = 8.37 Hz, 1 H), 7.98–7.96 (m, 2 H), 8.60 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.0, 40.3, 55.3, 55.5, 102.8, 106.8, 113.8, 120.3, 129.1, 130.8, 131.1, 155.7, 159.6, 164.1, 200.9.

HRMS (TOF-MS): *m*/*z* [M – H]$^+$ calcd for $C_{17}H_{17}O_4$: 285.1132; found: 285.1127.

2-Phenylchromane (11); Typical Reduction/Cyclization Procedure for Products 11, 11a–m

To 3-(2-hydroxyphenyl)-1-phenylpropan-1-one (**7**) (225 mg, 0.994 mmol) in THF (4 mL) and MeOH (4 mL) at 0 °C was added $NaBH_4$ (37.6 mg, 0.994 mmol). The reaction mixture was warmed to r.t. and stirred for 1 h. After cooling to 0 °C, EtOAc (5 mL) was added and then the reaction was quenched with 1 N aqueous H_3PO_4 (5 mL). The organic layer was removed and the aqueous layer was extracted with EtOAc (5 mL). The organic layers were combined and washed with sat. aqueous NaCl. The organic solution was dried with Na_2SO_4, filtered and concentrated in vacuo. This material was used in the following step without further purification.

The crude material was then dissolved in CH_2Cl_2 (4 mL) and *n*-Bu_3P (0.368 mL, 1.492 mmol) was added. To this mixture was added DIAD (0.212 mL, 1.094 mmol) in CH_2Cl_2 (1 mL) slowly over 1 h at r.t. The reaction mixture was then stirred at r.t. overnight, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography to give 0.180 g (86%) of compound **11** as a colorless oil. The spectroscopic data obtained for this compound are in accordance with the previously prepared material.[29]

2-(Benzo[*d*][1,3]dioxol-5-yl)chromane (11a)

According to the general procedure, treatment of 1-(benzo[*d*][1,3]dioxol-5-yl)-3-(2-hydroxyphenyl)propan-1-one (**7a**) (1.4 g, 5.18 mmol) with $NaBH_4$ (0.295 g, 7.8 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded the crude diol intermediate. Treatment of this crude material with *n*-Bu_3P (1.1 mL, 4.6 mmol) followed by slow addition of DIAD (1.02 mL, 5.2 mmol) afforded 0.91 g (79%) of **11a** as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.10–2.02 (m, 1 H), 2.27 (ddt, *J* = 13.70, 5.89, 3.02 Hz, 1 H), 2.82 (dt, *J* = 16.51, 4.36 Hz, 1 H), 3.04 (ddd, *J* = 16.48, 11.18, 5.93 Hz, 1 H), 5.16 (dd, *J* = 10.06, 2.45 Hz, 1 H), 6.97–6.93 (m, 2 H), 7.21–7.13 (m, 2 H), 7.58 (d, *J* = 8.10 Hz, 2 H), 7.71 (d, *J* = 8.14 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.8, 30.0, 77.4, 111.6, 116.9, 118.8, 120.9, 121.6, 126.6, 127.6, 129.7, 132.4, 147.1, 154.5.

HRMS (ESI-MS): *m*/*z* [M]$^+$ calcd for $C_{16}H_{14}O_3$: 254.0937; found: 254.0941.

4-(Chroman-2-yl)benzonitrile (11b)

According to the general procedure, treatment of 4-(1-hydroxyallyl)benzonitrile (**7b**) (1.1 g, 4.38 mmol) with $NaBH_4$ (0.25 g, 6.57 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded the crude diol intermediate. Treatment of this crude material with Ph_3P (1.25 g, 4.78 mmol) followed by slow addition of DIAD (1.1 mL, 5.4 mmol) afforded 0.896 g (87%) of **11b** as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.13–2.06 (m, 1 H), 2.20 (ddt, *J* = 13.66, 5.93, 2.83 Hz, 1 H), 2.84 (ddd, *J* = 16.47, 5.19, 3.11 Hz, 1 H), 3.05–2.98 (m, 1 H), 5.00 (dd, *J* = 10.30, 2.38 Hz, 1 H), 6.94–6.85 (m, 4 H), 6.98 (d, *J* = 1.68 Hz, 2 H), 7.17–7.11 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.2, 30.0, 77.7, 101.1, 106.8, 108.2, 117.0, 119.6, 120.4, 121.8, 127.4, 129.6, 135.7, 147.3, 147.9, 155.1.

HRMS (GC-MS): *m*/*z* [M]$^+$ calcd for $C_{16}H_{13}NO$: 235.0992; found: 235.1002.

2-(Furan-2-yl)chromane (11c)

According to the general procedure, treatment of 1-(furan-2-yl)-3-(2-hydroxyphenyl)propan-1-one (**7c**) (0.140 g, 0.647 mmol) with $NaBH_4$ (0.0245 g, 0.647 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded the crude diol intermediate. Treatment of this crude material with Ph_3P (0.255 g, 0.971 mmol) followed by slow addition of DIAD (0.138 mL, 0.712 mmol) afforded 0.080 g (62%) of **11c** as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34–2.27 (m, 2 H), 2.86 (dt, *J* = 16.49, 4.62 Hz, 1 H), 2.98 (ddd, *J* = 16.53, 10.29, 6.63 Hz, 1 H), 5.14 (dd, *J* = 9.28, 3.10 Hz, 1 H), 6.40 (s, 2 H), 6.92–6.88 (m, 2 H), 7.15–7.09 (m, 2 H), 7.46 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.6, 26.0, 71.2, 107.3, 110.3, 117.0, 120.6, 121.6, 127.4, 129.6, 142.5, 153.8, 154.5.

HRMS (GC-MS, EI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{12}O_2$: 200.0837; found: 200.0841.

5-(Chroman-2-yl)-2-methylpyridine (11d)

According to the general procedure, treatment of 3-(2-hydroxyphenyl)-1-(6-methylpyridin-3-yl)propan-1-one (**7d**) (0.305 g, 1.264 mmol) with $NaBH_4$ (0.048 g, 1.264 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 and washing with sat. aq $NaHCO_3$ afforded the crude diol intermediate. Treatment of this crude material with triphenylphosphine (0.497 g, 1.896 mmol) followed by slow addition of DIAD (0.270 mL, 1.390 mmol) afforded 0.177 g (62%) of **11d** as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.10 (m, 1 H), 2.21 (m, 1 H), 2.58 (s, 3 H), 2.81 (m, 1 H), 3.02 (m, 1 H), 5.08 (dd, *J* = 1.96, 10.76 Hz, 1 H), 6.89 (m, 2 H), 7.10 (d, *J* = 7.34 Hz, 1 H), 7.14 (m, 1 H), 7.19 (d, *J* = 8.31 Hz, 1 H), 7.67 (dd, *J* = 1.96, 7.83 Hz, 1 H), 8.55 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.1, 24.9, 29.7, 75.5, 116.9, 120.6, 121.5, 123.1, 127.4, 129.5, 134.1, 134.1, 147.1, 154.7, 158.0.

HRMS (TOF-MS): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}NO$: 226.1226; found: 226.1218.

(*E*)-7-Chloro-2-(3-(chroman-2-yl)styryl)quinoline (11e)

According to the general procedure, treatment of (*E*)-1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-hydroxyphenyl)propan-1-one (**7e**) (0.100 g, 0.242 mmol) with $NaBH_4$ (0.0091 g, 0.242 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 and washing of the organic layer with sat. aqueous $NaHCO_3$ afforded the crude diol intermediate. Treatment of this crude material with Ph_3P (0.089 g, 0.338 mmol) followed by slow addition of DIAD (0.052 mL, 0.266 mmol) afforded 0.065 g (65%) of **11e** as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (dtd, *J* = 13.73, 10.89, 5.19 Hz, 1 H), 2.29 (ddt, *J* = 13.71, 5.84, 2.87 Hz, 1 H), 2.86 (dt, *J* = 16.46, 4.03 Hz, 1 H), 3.09–3.02 (m, 1 H), 5.13 (dd, *J* = 10.26, 2.37 Hz, 1 H), 6.97–6.90 (m, 2 H), 7.20–7.13 (m, 2 H), 7.48–7.41 (m, 4 H), 7.68–7.62 (m, 2 H), 7.75 (t, *J* = 8.82 Hz, 3 H), 8.13–8.10 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.2, 29.8, 30.1, 77.6, 117.0, 119.6, 120.5, 121.8, 125.0, 125.7, 126.6, 126.9, 127.3, 127.5, 128.0, 128.6, 128.7, 129.1, 129.6, 135.3, 136.4, 136.6, 142.5, 155.0, 156.8.

HRMS (TOF-MS): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{21}ClNO$: 398.1306; found: 398.1299.

2-Heptylchromane (11f)

According to the general procedure, treatment of 1-(2-hydroxyphenyl)decan-3-one (**7f**) (1.03 g, 4.15 mmol) with $NaBH_4$ (0.235 g, 6.22 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded the crude diol intermediate. Treatment of this crude material with Ph_3P (1.63 g, 6.22 mmol) followed by slow addition of DIAD (0.887 mL, 4.56 mmol) afforded 0.684 g (71%) of **11f** as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (m, 3 H), 1.35 (m, 8 H), 1.47 (s, 1 H), 1.61 (m, 4 H), 2.02 (m, 1 H), 2.89 (m, 2 H), 4.00 (m, 1 H), 6.84 (m, 2 H), 7.27 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.7, 25.2, 27.3, 29.2, 29.6, 31.8, 35.4, 75.8, 116.6, 119.8, 121.9, 127.0, 129.4, 155.0.

HRMS (GC-MS, EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{24}O$: 232.1827; found: 232.1816.

tert-Butyl 3-(Chroman-2-yl)azetidine-1-carboxylate (11g)

According to the general procedure, treatment of *tert*-butyl 3-(3-(2-hydroxyphenyl)propanoyl)azetidine-1-carboxylate (**7g**) (0.150 g, 0.491 mmol) with $NaBH_4$ (0.0288 g, 0.762 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded the crude diol intermediate. Treatment of this crude material with *n*-Bu_3P (0.188 mL, 0.737 mmol) followed by slow addition of DIAD (0.105 mL, 0.540 mmol) afforded 0.105 g (74%) of **11g** as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 1.60 (m, 1 H), 1.96 (m, 1 H), 2.75 (m, 2 H), 2.80 (m, 1 H), 3.86 (m, 1 H), 3.99 (m, 1 H), 4.08 (m, 3 H), 6.87 (m, 2 H), 7.12 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 24.5, 24.6, 28.1, 28.3, 32.9, 79.2, 116.6, 120.2, 121.5, 127.2, 129.3, 154.5, 156.2.

HRMS (TOF-MS): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}NO_3$: 290.1751; found: 290.1760.

2-Phenyl-6-(trifluoromethyl)chromane (11h)

According to the general procedure, treatment of 3-(2-hydroxy-5-(trifluoromethyl)phenyl)-1-phenylpropan-1-one (**7h**) (0.225 g, 0.765 mmol) with $NaBH_4$ (0.0289 g, 0.765 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded the crude diol intermediate. Treatment of this crude material with resin-bound Ph_3P (0.384 g, 1.147 mmol) followed by slow addition of DIAD (0.149 mL, 0.765 mmol) afforded 0.140 g (66%) of **11h** as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.19–2.11 (m, 1 H), 2.31 (ddt, *J* = 13.84, 5.85, 3.00 Hz, 1 H), 2.88 (dt, *J* = 16.58, 4.29 Hz, 1 H), 3.06 (ddd, *J* = 16.55, 11.27, 5.87 Hz, 1 H), 5.17 (dd, *J* = 10.08, 2.50 Hz, 1 H), 7.03 (d, *J* = 8.34 Hz, 1 H), 7.46–7.37 (m, 7 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.9, 29.4, 78.2, 117.3, 122.2, 122.5 (q, *J* = 32 Hz), 124.6 (q, *J* = 271 Hz), 124.6 (q, *J* = 3.9 Hz), 126.0, 126.9 (q, *J* = 3.9 Hz), 128.1, 128.7, 141.0, 157.7.

HRMS (ESI-MS): *m*/*z* [M]$^+$ calcd for $C_{16}H_{13}F_3O$: 278.0913; found: 278.0924.

Methyl 2-Phenylchromane-7-carboxylate (11i)

According to the general procedure, treatment of methyl 3-hydroxy-4-(3-oxo-3-phenylpropyl)benzoate (**7i**) (0.207 g, 0.728 mmol) with $NaBH_4$ (0.0275 g, 0.728 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded the crude diol intermediate. Treatment of this crude material with resin-bound Ph_3P (0.366 g, 1.092 mmol) followed by slow addition of DIAD (0.142 mL, 0.728 mmol) afforded 0.147 g (75%) of **11i** as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.16–2.08 (m, 1 H), 2.28 (ddt, *J* = 13.79, 5.87, 3.01 Hz, 1 H), 2.89–2.84 (m, 1 H), 3.04 (ddd, *J* = 17.02, 11.10, 5.95 Hz, 1 H), 3.92 (s, 3 H), 5.13 (dd, *J* = 10.02, 2.38 Hz, 1 H), 7.17 (d, *J* = 7.91 Hz, 1 H), 7.45–7.34 (m, 5 H), 7.58 (dd, *J* = 7.90, 1.65 Hz, 1 H), 7.63 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.2, 29.5, 52.1, 77.8, 118.3, 121.4, 125.9, 127.3, 128.0, 128.6, 129.5, 129.6, 141.3, 155.0, 167.0.

HRMS (TOF-MS): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}O_3$: 269.1172; found: 269.1168.

Methyl 2-Phenylchromane-6-carboxylate (11j)

According to the general procedure, treatment of methyl 4-hydroxy-3-(3-oxo-3-phenylpropyl)benzoate (**7j**) (0.100 g, 0.352 mmol) with $NaBH_4$ (0.0133 g, 0.352 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded the crude diol intermediate. Treatment of

this crude material with resin-bound Ph_3P (0.177 g, 0.528 mmol) followed by slow addition of DIAD (0.0684 mL, 0.352 mmol) afforded 0.0679 g (72%) of **11j** as a colorless liquid.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.12 (dddd, *J* = 13.81, 11.26, 10.09, 5.16 Hz, 1 H), 2.28 (ddt, *J* = 13.82, 5.81, 3.00 Hz, 1 H), 2.86 (dt, *J* = 16.48, 4.31 Hz, 1 H), 3.03 (ddd, *J* = 16.46, 11.29, 5.83 Hz, 1 H), 3.91 (s, 3 H), 5.16 (dd, *J* = 10.08, 2.51 Hz, 1 H), 6.97–6.95 (m, 1 H), 7.45–7.35 (m, 5 H), 7.86–7.84 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.9, 29.6, 51.9, 78.3, 116.9, 121.7, 122.2, 126.0, 128.1, 128.6, 129.3, 131.7, 141.0, 159.2, 167.1.

HRMS (TOF-MS): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}O_3$: 269.1172; found: 269.1161.

Methyl 2-Phenyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine-6-carboxylate (11k)

According to the general procedure, treatment of methyl 6-hydroxy-5-(3-oxo-3-phenylpropyl)nicotinate (**7k**) (0.055 g, 0.193 mmol) with $NaBH_4$ (0.0073 g, 0.193 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded the crude diol intermediate. Treatment of this crude material with Ph_3P (0.076 g, 0.289 mmol) followed by slow addition of DIAD (0.0375 mL, 0.193 mmol) afforded 0.044 g (85%) of **11k** as a colorless liquid.

^1H NMR (500 MHz, CD_3OD): δ = 3.56 (t, *J* = 7.31 Hz, 2 H), 4.11 (t, *J* = 7.34 Hz, 2 H), 4.57 (s, 3 H), 8.32 (t, *J* = 7.63 Hz, 2 H), 8.44 (t, *J* = 7.38 Hz, 1 H), 8.54 (d, *J* = 2.44 Hz, 1 H), 8.79–8.74 (m, 3 H), 12.93 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): 24.3, 28.9, 52.1, 79.3, 116.6, 120.1, 125.8, 128.1, 128.6, 139.7, 140.0, 164.5, 165.8.

HRMS (TOF-MS): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{16}NO_3$: 270.1125; found: 270.1125.

6-Chloro-2-(4-chlorophenyl)chromane (11l)

According to the general procedure, treatment of 3-(5-chloro-2-hydroxyphenyl)-1-(4-chlorophenyl)propan-1-one (**7l**) (0.248 g, 0.840 mmol) with $NaBH_4$ (0.0318 g, 0.840 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded the crude diol intermediate. Treatment of this crude material with Ph_3P (0.308 g, 1.176 mmol) followed by slow addition of DIAD (0.163 mL, 0.840 mmol) afforded 0.117 g (50%) of **11l** as a colorless liquid. The spectroscopic data obtained for this compound are in accordance with the previously prepared material.[6a]

7-Methoxy-2-(4-methoxyphenyl)chromane (11m)

According to the general procedure, treatment of 3-(2-hydroxy-4-methoxyphenyl)-1-(4-methoxyphenyl)propan-1-one (**7m**) (0.150 g, 0.524 mmol) with $NaBH_4$ (0.0198 g, 0.524 mmol) followed by quenching with 1.0 M aqueous H_3PO_4 afforded 0.090 g (60%) of **11m** as a colorless liquid.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.20–2.07 (m, 2 H), 2.77 (ddd, *J* = 16.08, 5.19, 3.14 Hz, 1 H), 2.98–2.92 (m, 1 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 5.02 (dd, *J* = 10.23, 2.43 Hz, 1 H), 6.52–6.50 (m, 2 H), 7.01–6.93 (m, 3 H), 7.38 (d, *J* = 8.48 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.6, 30.0, 55.3, 55.4, 77.7, 101.6, 107.4, 113.9, 114.0, 127.4, 130.0, 133.8, 156.0, 159.1, 159.4.

HRMS (TOF-MS): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}O_3$: 271.1329; found: 271.1326.

(*R*)-2-Phenylchromane [(*R*)-11]

To 3-(2-hydroxyphenyl)-1-phenylpropan-1-one (**7**) (50 mg, 0.221 mmol) and RuCl(*p*-cymene)[(*S*,*S*)-TsDPEN] (**12**) (7.04 mg, 0.011 mmol) in MeCN (2210 µL) at 0 °C were added Et_3N (55.4 µL, 0.398 mmol) and formic acid (46.6 µL, 1.215 mmol). The reaction mixture was warmed to r.t. and stirred for 3 d. Then, the reaction was quenched with EtOAc and aqueous pH 7 phosphate buffer. The organic layer was washed with brine, dried with Na_2SO_4, filtered and concentrated. The material was analyzed by chiral HPLC (Waters ACQUITY UPC2; sCO_2/MeOH 5–50% gradient over 10 min, AD-3 column) and then used crude in the following step.

To (*S*)-2-(3-hydroxy-3-phenylpropyl)phenol [(*S*)-**10**] (50.4 mg, 0.221 mmol) in CH_2Cl_2 (2 mL) was added Ph_3P (81 mg, 0.309 mmol) at 0 °C. Then, a solution of DIAD (60.1 µL, 0.309 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 30 min. The reaction mixture slowly warmed to r.t. and was stirred overnight. The crude material was chromatographed to afford (*R*)-2-phenylchromane [(*R*)-**11**] (25.07 mg, 0.119 mmol, 54%). A sample was analyzed by chiral HPLC (Waters ACQUITY UPC2; sCO_2/MeOH 5–50% gradient over 10 min, OD-3 column).

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588075.

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(19) For more information, see ref. 6c (Boronic acid and Grignard addition to chromene acetals).

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(22) P2-Et = Tetramethyl(tris(dimethylamino)phosphoranylidene) phosphorictriamid-Et-imin (Aldrich). On the contrary, utilization of P2-Et for Heck coupling with allylic alcohol **5** and 2-iodophenol (**6**) afforded a diminished yield of ketone **7**. For more on the use of P2-Et, see: Buitrago Santanilla, A.; Christensen, M.; Campeau, L.-C.; Davies, I. W.; Dreher, S. D. *Org. Lett.* **2015**, *17*, 3370.

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(25) See ref. 16. No attempts were made to investigate alternative conditions for the workup.

(26) For a review on the Noyori asymmetric reduction of ketones, see: (a) Noyori, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 79. (b) Kitamura, M.; Nakatsuka, H. *Chem. Commun.* **2011**, *47*, 842. (c) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40.

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