Hexafluoroisopropanol and Acetyl Chloride Promoted Catalytic Hydroarylation with Phenols

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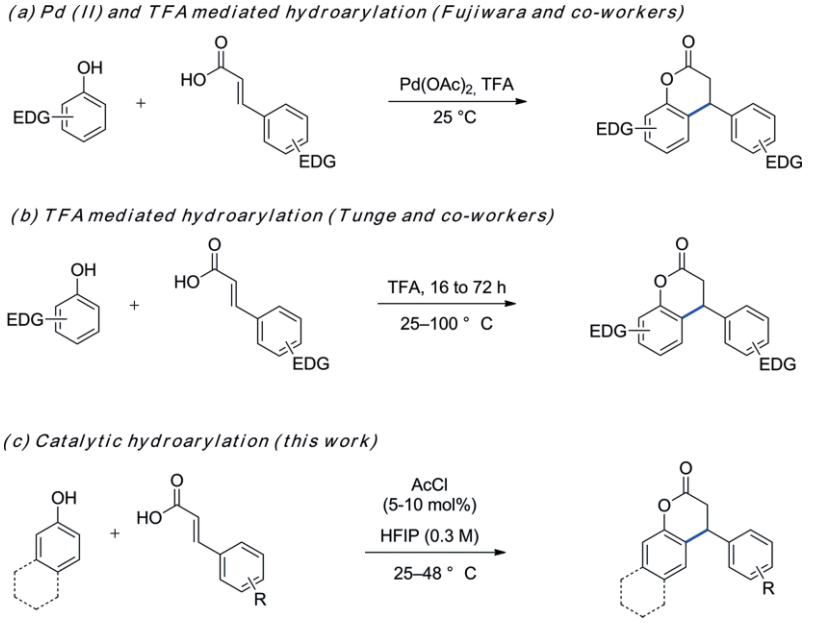
Dedicated to Al Padwa on the occasion of his 80th birthday

Abstract: We report a catalytic hydroarylation method to convert phenols to dihydrocoumarins in hexafluoroisopropanol (HFIP) using acid generated from sub-stoichiometric amounts of acetyl chloride as catalyst. Attractive elements include easy set-up and isolation, and applicability to a range of phenols including natural product substrates.

Introduction

The hydroarylation of α,β-unsaturated acids with substituted phenols is a variation of Friedel–Crafts alkylation reaction that leads to dihydrocoumarin derivatives. A seminal report on hydroarylation of alkynes and alkenes with arenes in trifluoroacetic acid (TFA) by Fujiwara and co-workers invoked electrophilic Pd^{II} and Pt^{II} cationic species as key intermediates



Scheme 1. Methods for hydroarylation of α,β-unsaturated acids.

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(Scheme 1a).[1,2] Although hydroarylation of alkynes requires activation by Pd^{II} or Pt^{II} compounds in conjunction with TFA, analogous hydroarylation of alkenes requires only TFA. This was demonstrated by Tunge and co-workers, who showed that the TFA-mediated hydroarylation of cinnamic acids did not require palladium and afforded a range of dihydrocoumarin products at ambient temperature in 16 to 72 h (Scheme 1b).[3] As expected for electrophilic substitutions, electron-rich arenes as well as cinnamic acids were preferred, while electron-neutral and -poor cinnamic acids required elevated reaction

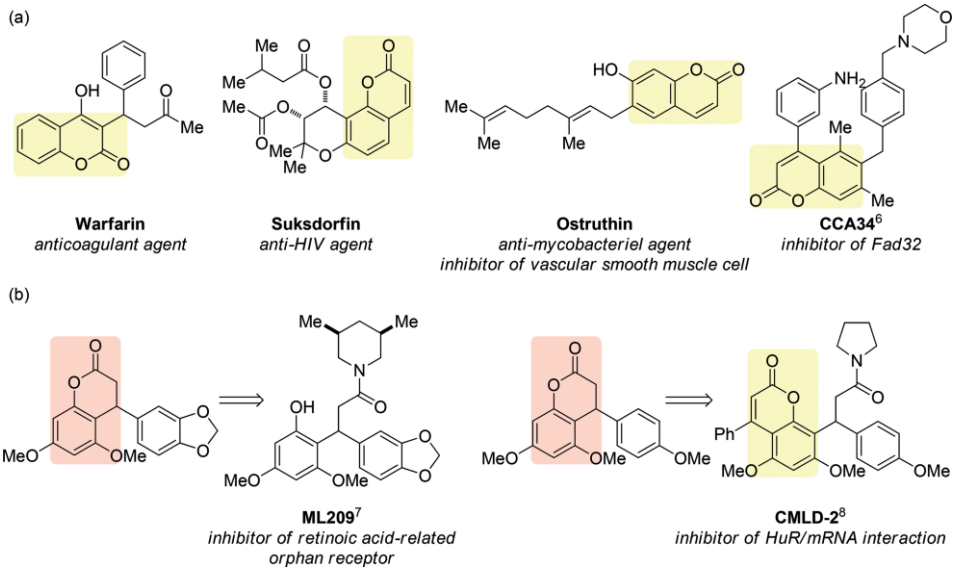


Figure 1. (a) Coumarin-containing (highlighted in yellow) natural products and (b) other bioactive compounds obtained from dihydrocoumarins (highlighted in red).

temperatures (ca. 100 °C) and prolonged reaction times (up to 72 h).

Coumarins and dihydrocoumarins are common in natural products and other bioactive agents,[4,5] such as the anticoagulant warfarin, suksdorfin (an anti-infective agent), and ostruthin (an anti-mycobacterial agent) (Figure 1). Furthermore, coumarin derivatives prepared via hydroarylation have found biological application as inhibitors of Fad32 as anti-tuberculosis agents,[6] RORγ inhibitors for treatment of T_H17-related autoimmune diseases,[7] and disruptors of HuR/RNA interactions relevant to many types of cancer.[8] As part of our laboratory's investigations toward the last class, we sought a convenient variation of this hydroarylation chemistry. In this paper, we report a hydroarylation reaction that can be carried out in the strong hydrogen-bond donating solvent hexafluoroisopropanol (HFIP) using in situ generated HCl from acetyl chloride (AcCl) (Scheme 1c).

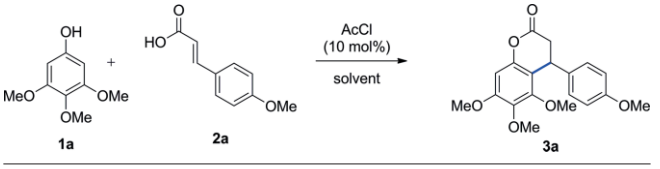
Results and Discussion

Reaction Conditions Development and Examination of Scope

The present project arose from our observations that HFIP represented a particularly attractive solvent for promoting polar reactions involving in situ generated HCl, such as the intramolecular Schmidt reaction[9] and related chemistry,[10] as well as the Friedel–Crafts acylation of electron-rich aromatics.[11,12] In those contexts, using HFIP allowed us to avoid relatively harsh Lewis acids that often led to product inhibition. The utility of HFIP in these contexts led us to investigate its use in promoting the hydroarylation reactions.

We first examined the known[3] hydroarylation reaction between 3,4,5-trimethoxyphenol **1a** and *p*-methoxycinnamic acid **2a**. Carrying out the reaction in HFIP (p*K*a 9.3) with 10 mol-% of AcCl provided the dihydrocoumarin product **3a** in 97 % yield in 1 h at room temperature (Table 1, entry 1). In contrast, repeating the same reaction in TFA in our laboratory gave a 31 % yield of **3a** after 1 h.[3] We next compared the efficiency of this reaction to those carried out in other fluorinated solvents. Using trifluoroethanol (TFE, p*K*a 12.4) as a solvent resulted in only 18 % conversion to the product (the starting materials were poorly soluble, even with heating). Perfluoro-*tert*-butyl alcohol (PFTB, p*K*a 5.4) resulted in 81 % conversion, but required initial heating for about 10 to 20 seconds with a heat gun to dissolve the starting materials (entry 4). Control experiments, such as running the reaction solely in acetyl chloride (AcCl) (entry 5) or leaving out AcCl (entry 6), resulted in no conversion. The screening results suggested that HFIP would be the solvent of choice for promoting these hydroarylation reactions.

Table 1. Optimization results.[a]

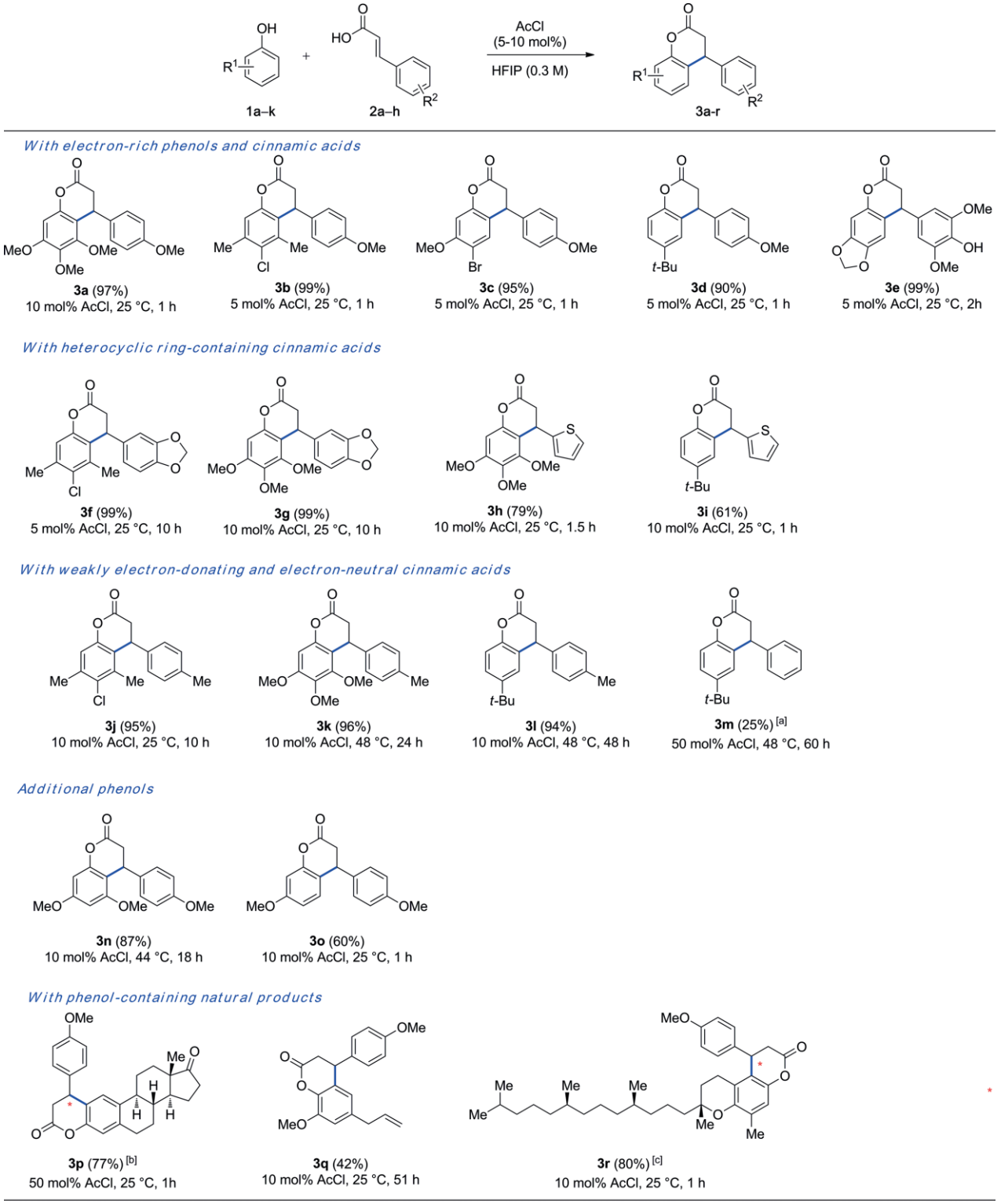


Entry	Solvent	Pre-catalyst	Yield[b]
1	HFIP	AcCl	97 %
2	TFA	none	31 %
3	TFE	AcCl	18 %[c]
4	PFTB	AcCl	81 %[d]
5	AcCl	none	0 %
6	HFIP	none	0 %

[a] Reaction details: 0.3 mmol of **1a** and 0.3 mmol of **2a** in 1 mL of solvent stirred at room temp. for 1 h. [b] NMR yield using benzoyl benzoate (δ = 5.4 ppm in $CDCl_3$) as an internal standard. [c] Starting materials are sparingly soluble in TFE, even with heating. [d] Initial heating was required to dissolve the reactants. Boiling point of PFTB = 45 °C.

Having demonstrated the utility of AcCl/HFIP for the reaction, its scope was evaluated by surveying the reactions of selected phenols and cinnamic acids under these conditions

(Scheme 2). With electron-rich partners, the reaction went to completion in 1 h at ambient temperature furnishing the dihydrocoumarins in > 95 % yields requiring 5–10 mol-% of AcCl. Moreover, the products containing an aryl chloride (**3b**, **3f**, **3j**) or aryl bromide (**3c**) provide a handle for additional functionalization.



All are isolated yields.
[a] Unreacted starting materials were recovered.
[b] Product is a 1.3:1 mixture of isomers as determined by NMR.
[c] Product is a 2.8:1 mixture of isomers as determined by NMR.

Scheme 2. Substrate scope for hydroarylation reactions between phenols and cinnamic acids.

Tunge and co-workers had previously noted that elevated reaction temperature (100 °C) with prolonged reaction time (16 h to 72 h) were required for cinnamic acid reaction partners that are less electron rich than *p*-methoxycinnamic acid (σ_p = –0.268).[13] Accordingly, we assessed the efficiency of our catalytic system for less electron rich substrates. Thus, *p*-methylcinnamic acid (σ_p = –0.170), resulted in the corresponding dihydrocoumarin products **3j**, **3k**, and **3l** in high yields (> 90 %) with 10 mol-% of AcCl (Scheme 2). Using the present reaction conditions, these reactions went to completion in 24–48 h at 25–48 °C. Unsubstituted *trans*-cinnamic acid (electron-neutral) was more sluggish and required 50 mol-% of AcCl at 48 °C to furnish the corresponding dihydrocoumarin product **3m** in 25 % yield after 60 h along with starting materials that were recovered (12 %, isolated yield).

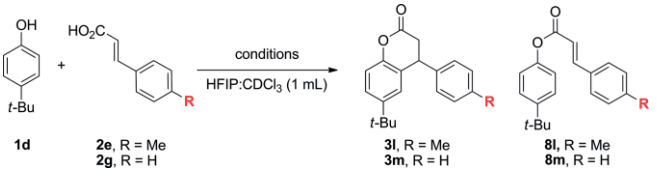
Diversification of drug molecules or natural products to create analogs for screening or repurposing is now an established and vital strategy for medicinal chemists.[14] Toward that end, we hydroarylated phenol-containing natural products estrone, eugenol, and δ-tocopherol using the current conditions, affording derivatives **3p**, **3q**, and **3r**. The estrone derivative **3p** was obtained as a single constitutional isomer but as a 1.3:1 mixture of epimers as confirmed by NMR analysis. Stereochemistry of the major epimer was not assigned. On the other hand, the reaction with δ-tocopherol furnished two isomeric products in a 2.8:1 mixture (determined by NMR) with a 0.19 ppm difference between the tolyl CH_3 peaks in the ^1H NMR spectroscopy. The constitutional structure of the major isomer **3r** was confirmed by 1D and 2D NOESY studies, but the configuration of the newly formed stereogenic center was not established. The minor isomer is most likely an epimer at the newly-formed benzylic stereocenter in **3r**, although we cannot rule out the possibility of it being a constitutional isomer.

We also examined the scope of the hydroarylation reactions with a derivative of cinnamic acid and analogues of phenols (Scheme 3). Thus, the hydroarylation of cinnamide **4** gave the 1,4-addition product **5** in 43 % yield after 56 h, requiring 50 mol-% of AcCl (Scheme 3a). Previous analogous conversions were reported to require excess of harsh Lewis acids[15] or multiple steps.[16] In addition, Jagdale and Sudalai reported a solvent-free variation using *p*-TSA at 125 °C.[17] Minor quantities of the dihydrocoumarin product (5 %) corresponding to the structure **3d** as well as unreacted starting materials (29 %) were also isolated in this reaction. Finally, the chemistry of a thiophenol derivatives were briefly examined. When 4-(*tert*-butyl)thiophenol was treated with *p*-methoxycinnamic acid **2a** using 20 mol-% of AcCl in HFIP, 58 % of the 1,4-addition product **7** and 15 % thiochromanone product **6** were observed after 18 h (Scheme 3b). Reaction of thiophenol with **2a** gave similar results (see supporting information Table S1 for details on reactivity of thiophenols and anilines in the hydroarylation reaction).

Structure and Mechanism

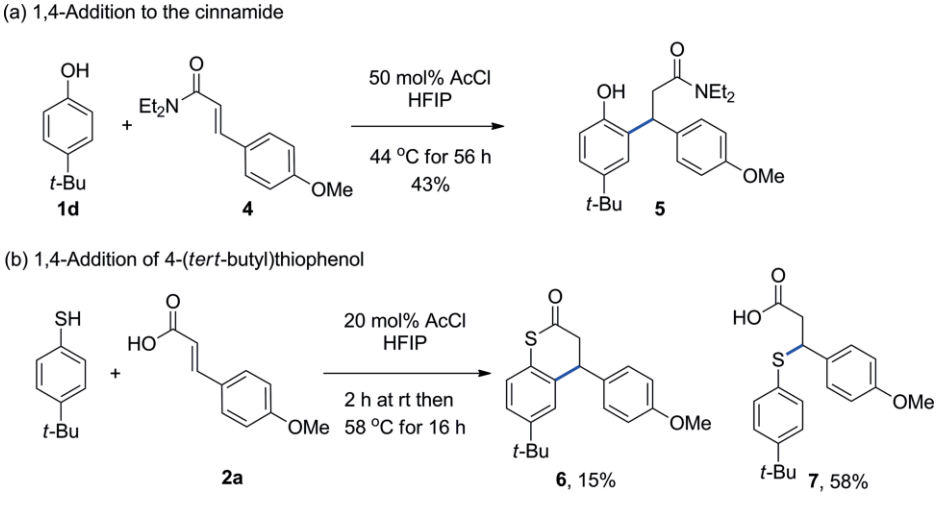
The utility of HFIP in promoting reactions involving ionic intermediates is generally attributed to its high hydrogen-bonding ability and ionizing power coupled with low nucleophilicity. We carried out a concise set of studies to examine the disposition

Table 2. Optimization results replicating the NMR conditions.[a]



Entry	R	HFIP (equiv.)	$CDCl_3$ (mL)	AcCl (equiv.)	Yield[b] (**3l** or **3m**)	Yield[b] (**8l** or **8m**)
1	Me	0.31 mL (10)	0.70	0.1	42 %[c]	8 %[c]
2	Me	0.63 mL (20)	0.37	0.1	91 %	–[b]
3	Me	0.63 mL (20)	0.37	0.5	100 %	–
4	H	0.31 mL (10)	0.70	0.1	0 %	20 %[b]
5	H	0.63 mL (20)	0.37	0.5	48 %	–

[a] All the reactions were carried out at 48 °C for 48 h using 0.3 mmol of **1d** and **2e** or **2g**, respectively. [a] NMR yield using benzyl benzoate (δ =5.4 ppm in $CDCl_3$) as an internal standard. [b] Starting materials observed by NMR spectroscopy. [c] Isolated yield.



Scheme 3. Examination of reactivity of (a) cinnamide and (b) thiophenol derivatives.

of HFIP as a solvent in these reactions using *p*-methylcinnamic acid as a representative substrate, chosen because it was easy to monitor its H-bond interactions with HFIP using NMR spectroscopy. Presence of an additional H-bond acceptor/donor substituents, such as the methoxy group in *p*-methoxycinnamic acid, which reacts faster, complicated these observations. These

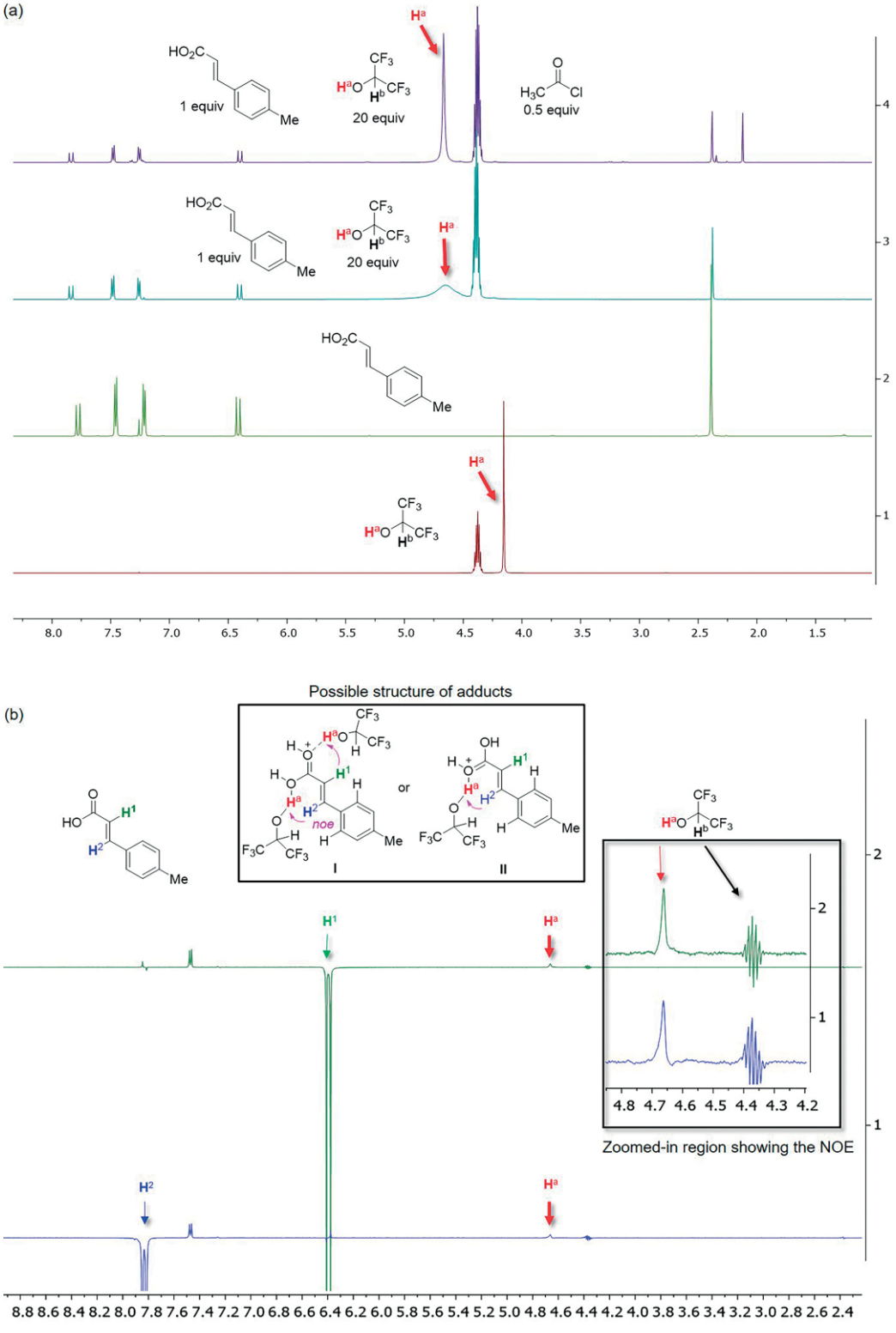


Figure 2. (a) Stacked ^{1}H NMR spectra showing the shift of the OH peak of HFIP: (1), in a mixture of 1 equiv. of *p*-methylcinnamic acid (2), 20 equiv. of HFIP (3), and upon addition of 0.5 equiv. of AcCl (4), in $CDCl_3$. (b) 1D gradient NOE with T_{mix} = 500 ms for the mixture of 1 equiv. of *p*-methylcinnamic acid, 20 equiv. of HFIP, and 0.5 equiv. of AcCl when irradiating H-2 (1) and H-1 (2) of *p*-methylcinnamic acid; insets contain zoomed-in region of 1D gradient NOE spectra showing plausible structure of adducts (I and II), and observed NOE interactions with arrows.

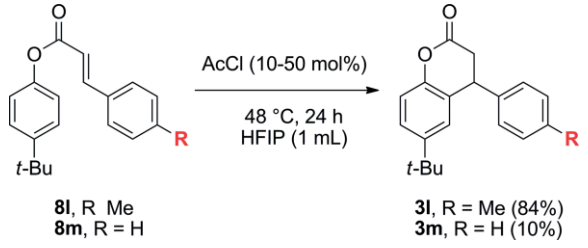
studies generally used 20 equiv. of HFIP because these conditions approximated the rates and yields of the reactions carried out in pure HFIP (cf. entries 1 and 2 in Table 2).

A clear shift of the OH signal of pure HFIP in de-acidified $CDCl_3$ from 4.15 ppm to a broad singlet at δ = 4.65 ppm for a mixture containing 1 equiv. of *p*-methylcinnamic acid and 20 equiv. HFIP was observed in ^{1}H NMR (Figure 2a). HFIP exists in aggregates,[18] so the chemical shift and broadness of its OH peak is expected to be concentration dependent. Upon addition of 0.5 equiv. of AcCl to this mixture, the broad singlet at δ = 4.65 ppm sharpened and moved slightly to 4.67 ppm. These results are consistent with H-bonding interactions with the cinnamic acid, with a greater rate of exchange when HCl is present pursuant to the addition of AcCl.

To characterize the putative H-bonded adduct, nuclear Overhauser effect (NOE) studies were carried out. Irradiation of the alkene protons at δ = 6.40 and 7.84 ppm resulted in an NOE with the HFIP OH signal at δ = 4.67 ppm (Figure 2b). These results are consistent with H-bonded interactions between the unsaturated acid and solvent; some possible structures are depicted. Related NOEs representing H-bonded adduct between the HFIP and phenyliodine(III) diacetate have been reported by Compton and co-workers.[19]

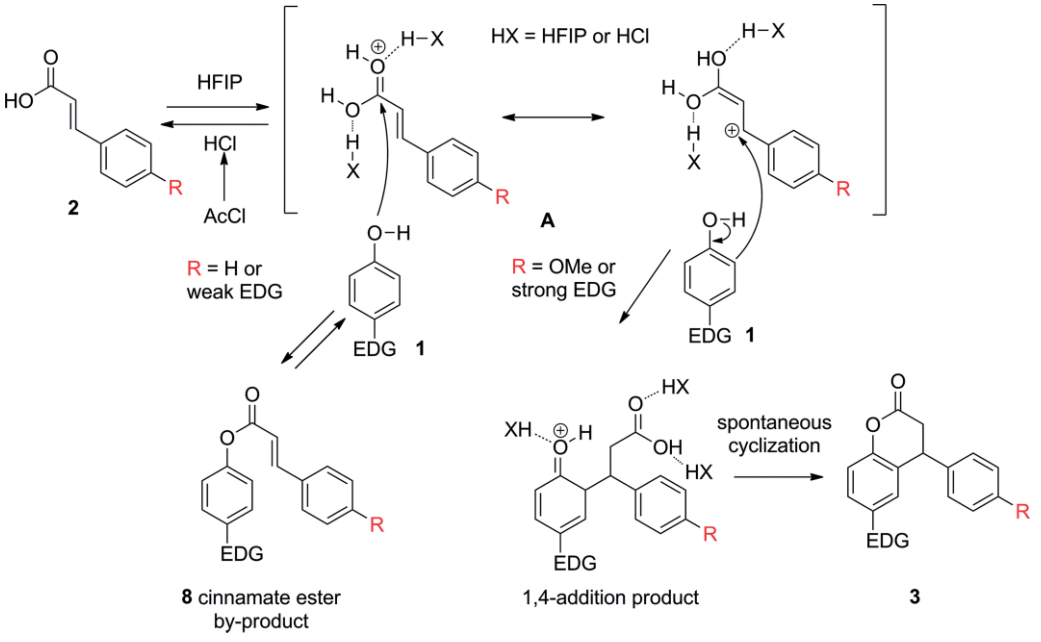
In an effort to understand the effect of cinnamic acid substituents on this reaction, conversions and product formations were examined by comparing the reactions of *p*-methylcinnamic acid **2e** and cinnamic acid **2g**, respectively, with 4-(*tert*-butyl)phenol **1d** (Table 2, entries 1 vs. 4 and 3 vs. 5). Similar concentrations of $CDCl_3$ were added to each reaction in an effort to replicate the NMR conditions. The results indicate a clearly slower reaction for the less electron-rich **2g**. In addition, esters resulting from simple acylation but not cyclization were observed in lieu of or in addition to fully cyclized products when the reactions were run in the presence of 10 equiv. of HFIP (entries 1 and 4), but not in the presence of 20 equiv. of HFIP (entries 2, 3, and 5).

We next reacted the cinnamate esters **8l** and **8m** in HFIP-conditions to see the effect of the aryl group substituents on the cyclization (Scheme 4). As anticipated, cinnamate ester with a *p*-methyl substituent **8l** afforded the cyclized dihydrocoumarin product **3l** in 84 % yield after 24 h (cf. Table 2, entry 2 with Scheme 4), whereas the reaction of **8m** was relatively sluggish. In the case of **8m**, 44 % of hydrolysis products of the ester were also isolated along with 14 % of unreacted starting material; this suggests that cyclized product formation in this case may result from an intermolecular pathway, as also suggested by Tunge and co-workers.[3]



Scheme 4. Effect of aryl substituents on cyclization of cinnamate esters.

Based on our observations and NMR studies, we propose the mechanism shown in Scheme 5. Dissolution of *para*-substituted cinnamic acid **2** in HFIP and AcCl generates an oxocarbenium intermediate **A** stabilized by HFIP, HCl, or both. With electron-donating groups such as *p*-OMe, this carbocation furnishes dihydrocoumarin **3** via 1,4-addition of the *ortho* carbon of the phenol followed by cyclization. However, with poorer electron-donating groups such as *p*-Me or the electronically neutral *trans*-cinnamic acid (R = H), the desired reaction is slower and ordinary Fischer esterification competes, generating cinnamate



Scheme 5. Possible mechanism for hydroarylation.

ester **8**. This material can be converted into the desired dihydrocoumarin product **3** by addition of AcCl in HFIP, but the observation of a significant amount of hydrolysis product under these conditions suggests that the reaction may occur by first ester hydrolysis followed by C–C bond formation as in the standard intermolecular version (Scheme 2).

Conclusions

We have demonstrated a catalytic hydroarylation process as an efficient route to dihydrocoumarins with broad utility. These reaction conditions in HFIP using AcCl leading to in situ generation of HCl represents an experimentally attractive means of accomplishing this useful transformation. Additionally, fast reaction time (within 1 h for most substrates) under ambient temperatures along with the operationally simple chemistry set up and isolation techniques without the need of any aqueous work up make this method particularly appealing.

Experimental Section

General Procedure for the Hydroarylation Reaction: To a suspension of phenol (0.30 mmol, 1.0 equiv.) and cinnamic or acrylic acid (0.30 mmol, 1.0 equiv.) in HFIP (1.0 mL) in a N_2-flushed 1-dram vial at room temp. was added acetyl chloride (0.015 or 0.030 mmol, 0.050 or 0.10 equiv.) and the resulting mixture was continued to stir at room temp. for 1–24 h. The reaction mixture was concentrated under N_2 and the resulting residue was dissolved in a minimum quantity of ether, DCM, or hexanes and loaded onto silica gel in a sample cartridge. Purification on an automated purification system using a 4 g or 12 g of silica flash column afforded the corresponding product after concentration and drying under vacuum.

5,6,7-Trimethoxy-4-(4-methoxyphenyl)chroman-2-one (3a): Following the general procedure, **3a** was obtained as an off-white solid (98 mg, 95 %). The ^{1}H NMR spectrum of **3a** matched reported material. The ^{1}H NMR of **3a** is in agreement with the literature report.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06–6.95 (m, 2 H), 6.84–6.74 (m, 2 H), 6.51 (s, 1 H), 4.57–4.48 (m, 1 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 3.75 (s, 3 H), 3.66 (s, 3 H), 3.01–2.94 (m, 2 H) ppm.

6-Chloro-4-(4-methoxyphenyl)-5,7-dimethylchroman-2-one (3b): Following the general procedure, **3b** was obtained as a colorless oily solid (94 mg, 99 %). The ^{1}H NMR of **3b** is in agreement with the literature report.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99–6.89 (m, 3 H), 6.83–6.68 (m, 2 H), 4.42–4.36 (m, 1 H), 3.74 (s, 3 H), 3.03–2.86 (m, 2 H), 2.40 (s, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = ppm. ^{13}C NMR (101 MHz, CDCl3): δ = 167.1, 159.1, 150.2, 137.2, 134.9, 131.9, 131.0, 128.1, 122.7, 117.1, 114.7, 55.4, 38.5, 37.9, 21.2, 16.5 ppm.

6-Bromo-7-methoxy-4-(4-methoxyphenyl)chroman-2-one (3c): Following the general procedure, a solution of 4-bromo-3-methoxyphenol (61 mg, 0.300 mmol, 1.0 equiv.) and 4-methoxycinnamic acid (53 mg, 0.300 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (2.1 µL, 0.030 mmol, 0.10 equiv.) for 1 h at room temp. Reaction mixture was concentrated and a solution of the resulting residue in ether was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–100 % EtOAc/hexanes over 15 min) afforded **3c** as off-white solid (103 mg, 95 %). Mp: 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 0.8 Hz, 1 H), 7.08–7.01 (m, 2 H), 6.92–6.84 (m, 2 H), 6.68 (s, 1 H), 4.22 (X of ABX, *J* = 8.2, 5.9 Hz, 1 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 3.02 (A part of ABX system, J_{AB} = 15.8, J_{AX} = 5.7 Hz, 1 H), 2.95 (B part of ABX system, J_{AB} = 15.8, J_{BX} = 8.3 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.2, 159.3, 156.1, 151.7, 132.2, 132.0, 128.6, 119.4, 114.8, 106.7, 101.5, 56.7, 55.5, 39.3, 37.4 ppm. IR (solution): $\tilde{\nu}$ = 3006, 1773 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{17}H_{15}BrO_4$ $[M + H]^+$ 363.0226; found 363.0220.

6-(*tert*-Butyl)-4-(4-methoxyphenyl)chroman-2-one (3d): Following the general procedure, **3d** was obtained as a colorless viscous oil (84 mg, 90 %). The ^{1}H NMR of **3d** is in agreement with the literature report.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 8.5, 2.4 Hz, 1 H), 7.10–7.06 (m, 3 H), 7.02 (dd, *J* = 2.5, 0.8 Hz, 1 H), 6.90–6.84 (m, 2 H), 4.29 (X part of ABX system, m, 1 H), 3.80 (s, 3 H), 3.04 (A part of ABX system, J_{AB} = 15.8, J_{AX} = 5.8 Hz, 1 H), 2.89 (B part of ABX system, J_{AB} = 15.8, J_{BX} = 7.2 Hz, 1 H), 1.25 (s, 9 H) ppm.

8-(4-Hydroxy-3,5-dimethoxyphenyl)-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromen-6-one (3e): Following the general procedure, a solution of benzo[*d*][1,3]dioxol-5-ol (41.5 mg, 0.300 mmol, 1.0 equiv.) and 4-hydroxy-3,5-dimethoxycinnamic acid (67.3 mg, 0.300 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (1.07 µL, 0.015 mmol, 0.05 equiv.) for 2 h at room temp. Reaction mixture was concentrated and a solution of the resulting residue in DCM was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–50 % EtOAc/hexanes over 50 min) afforded **3e** as an orange-yellow solid (99 mg, 96 %). Mp: 158.5–160.0 °C. TLC (30 % EtOAc/hexanes): R_f = 0.13. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (s, 1 H), 6.38 (m, 1 H), 6.33 (s, 2 H), 5.91 (q, *J* = 1.3 Hz, 2 H), 5.59 (s, 1 H), 4.10 (X part of ABX system, J_{AX} = 5.9, J_{BX} = 8.0 Hz, 1 H), 3.79 (s, 6 H), 2.97 (A part of ABX system, J_{AB} = 15.8, J_{AX} = 5.7 Hz, 1 H), 2.90 (B part of ABX system, J_{AB} = 15.8, J_{BX} = 8.2 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.7, 147.55, 147.52 (2 C), 146.1, 144.5, 134.3, 131.6, 118.3, 107.3, 104.3 (2 C), 101.8, 99.1, 56.4 (2 C), 40.8, 37.2 ppm. IR (neat): $\tilde{\nu}$ = 3482, 1758 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{18}H_{17}O_7$ $[M + H]^+$ 345.0974; found 345.0940.

4-(Benzo[*d*][1,3]dioxol-5-yl)-6-chloro-5,7-dimethylchroman-2-one (3f): Following the general procedure, **3f** was obtained as an off-white oily solid (98 mg, 99 %). The ^{1}H NMR of **3f** is in agreement with the literature report.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (s, 1 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 6.50 (d, *J* = 1.9 Hz, 1 H), 6.49–6.44 (m, 1 H), 5.90 (AB q, *J* = 1.4 Hz, $\Delta\nu_{AB}$ = 2.0 Hz, 2 H), 4.36 (m, 1 H), 3.02–2.92 (complex, 2 H), 2.40 (s, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.9, 150.2, 148.5, 147.2, 137.4, 134.9, 133.7, 131.1, 122.4, 120.3, 117.1, 108.9, 107.5, 101.4, 39.0, 37.9, 21.2, 16.5 ppm.

4-(Benzo[*d*][1,3]dioxol-5-yl)-5,6,7-trimethoxychroman-2-one (3g): Following the general procedure, a suspension of 3,4,5-trimethoxyphenol (55.3 mg, 0.300 mmol, 1.0 equiv.) and 3,4-(methylenedioxy)cinnamic acid (57.7 mg, 0.300 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (2.1 µL, 0.030 mmol, 0.10 equiv.) for 10 h at room temp. Reaction mixture was concentrated and a solution of the resulting residue in ether was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–30 % EtOAc/hexanes over 30 min) afforded **3g** as a pale yellow oily solid (107 mg, 99 %). Mp: 105–110 °C. TLC (30 % EtOAc/hexanes): R_f = 0.38. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (d, *J* = 8.0 Hz, 1 H), 6.57 (d, *J* = 1.8 Hz, 1 H), 6.52 (dd, *J* = 8.0, 1.8 Hz, 1 H), 6.48 (s, 1 H), 5.88 (s, 2 H), 4.48 (X part of ABX system, J_{AX} = 2.9, J_{BX} = 5.8 Hz, 1 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.68 (s, 3 H), 2.98–2.88 (AB part of ABX system, complex, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.4, 153.9, 150.6, 148.2, 147.8, 146.9, 139.1, 135.7, 119.9, 111.1, 108.6,

107.4, 101.2, 97.0, 61.3, 61.1, 56.3, 37.6, 35.3 ppm. IR (neat): $\tilde{\nu}$ = 1755, 1613 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{19}H_{19}O_7$ $[M + H]^+$ 359.1131; found 359.1108.

5,6,7-Trimethoxy-4-(thiophen-2-yl)chroman-2-one (3h): Following the general procedure, a suspension of 3,4,5-trimethoxyphenol (55.2 mg, 0.300 mmol, 1.0 equiv.) and 2-thiopheneacrylic acid (46.2 mg, 0.300 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (2.1 µL, 0.030 mmol, 0.10 equiv.) for 1.5 h at room temp. Reaction mixture was concentrated and a solution of the resulting residue in DCM was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–30 % EtOAc/hexanes over 30 min) afforded **3h** as a pale yellow solid (76.0 mg, 79 %). Mp: 132–134.5 °C. TLC (30 % EtOAc/hexanes) R_f = 0.50. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (dd, *J* = 5.1, 1.2 Hz, 1 H), 6.87 (dd, *J* = 5.1, 3.5 Hz, 1 H), 6.73 (dt, *J* = 3.5, 1.1 Hz, 1 H), 6.46 (s, 1 H), 4.80 (X part of ABX system, m, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.13 (A part of ABX system, J_{AB} = 15.9, J_{AX} = 1.8 Hz, 1 H), 2.98 (B part of ABX system, J_{AB} = 15.9, J_{BX} = 6.7 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.2, 154.1, 150.4, 147.5, 145.1, 138.9, 127.2, 124.7, 124.4, 111.2, 97.0, 61.5, 61.2, 56.3, 37.5, 30.9 ppm. IR (neat): $\tilde{\nu}$ = 1759 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{16}H_{17}O_5S$ $[M + H]^+$ 321.0797; found 321.0769.

6-(*tert*-Butyl)-4-(thiophen-2-yl)chroman-2-one (3i): Following the general procedure, a solution of 4-(*tert*-butyl)phenol (45 mg, 0.30 mmol, 1.0 equiv.) and 2-thiopheneacrylic acid (46 mg, 0.30 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (2.1 µL, 0.03 mmol, 0.10 equiv.) for 1 h at room temp. Reaction mixture was concentrated and a solution of the resulting residue in DCM was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–100 % EtOAc/hexanes over 15 min) afforded **3i** as oily compound (52 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 8.5, 2.4 Hz, 1 H), 7.23 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.20 (d, *J* = 2.2 Hz, 1 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1 H), 6.80 (dt, *J* = 3.6, 1.1 Hz, 1 H), 4.58 (X part of ABX system, t, *J* = 5.8 Hz, 1 H), 3.14 (A part of ABX system, J_{AB} = 15.9, J_{AX} = 5.7 Hz, 1 H), 3.11 (B part of ABX system, J_{AB} = 15.9, J_{BX} = 5.9 Hz, 1 H), 1.29 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.5, 149.1, 148.0, 144.1, 127.2, 126.1, 125.2, 125.2, 125.1, 124.7, 116.8, 37.7, 36.6, 34.6, 31.5 ppm. IR (solution): $\tilde{\nu}$ = 1768 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{17}H_{18}O_2S$ $[M + H]^+$ 287.1100; found 287.1096.

6-Chloro-5,7-dimethyl-4-(*p*-tolyl)chroman-2-one (3j): Following the general procedure, **3h** was obtained as a colorless solid (86 mg, 95 %). The ^{1}H NMR of **3j** is in agreement with the literature report.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 7.9 Hz, 2 H), 6.97–6.90 (m, 3 H), 4.42 (t, *J* = 4.4 Hz, 1 H), 3.05–2.97 (complex, 2 H), 2.41 (s, 3 H), 2.29 (s, 3 H), 2.25 (s, 3 H) ppm.

5,6,7-Trimethoxy-4-(*p*-tolyl)chroman-2-one (3k): Following the general procedure, a solution of 3,4,5-trimethoxyphenol (55 mg, 0.30 mmol, 1.0 equiv.) and 4-methylcinnamic acid (49 mg, 0.30 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (2.1 µL, 0.03 mmol, 0.10 equiv.) for 24 h at 48 °C. Reaction mixture was concentrated and a solution of the resulting residue in ether was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–100 % EtOAc/hexanes over 15 min) afforded **3k** as an oily solid (95 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09–7.04 (m, 2 H), 7.01–6.96 (m, 2 H), 6.51 (s, 1 H), 4.53 (m, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.66 (s, 3 H), 3.02–2.93 (complex, 2 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.6, 153.7, 150.6, 147.8, 139.1, 138.8, 137.0, 129.7, 126.7, 111.3, 96.9, 61.2, 61.1, 56.2, 37.4, 35.2, 21.1 ppm. IR (solution): $\tilde{\nu}$ = 2937, 1767 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{19}H_{20}O_5$ $[M + H]^+$ 329.1384; found 329.1376.

6-(*tert*-Butyl)-4-(*p*-tolyl)chroman-2-one (3l): Following the general procedure, a solution of 4-(*tert*-butyl)phenol (45 mg, 0.30 mmol, 1.0 equiv.) and 4-methylcinnamic acid (49 mg, 0.30 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (2.1 µL, 0.03 mmol, 0.10 equiv.) for 48 h at 48 °C. Reaction mixture was concentrated and a solution of the resulting residue in ether was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–100 % EtOAc/hexanes over 15 min) afforded **3l** as a white solid (83 mg, 94 %). Mp: 75–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 8.6, 2.4 Hz, 1 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 7.09–7.00 (m, 4 H), 4.30 (X part of ABX system, m, 1 H), 3.05 (A part of ABX system, J_{AB} = 15.8, J_{AX} = 5.9 Hz, 1 H), 2.99 (B part of ABX system, J_{AB} = 15.8, J_{BX} = 7.0 Hz, 1 H), 2.34 (s, 3 H), 1.26 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1, 149.7, 147.8, 137.8, 137.3, 129.8, 127.4, 125.7, 125.3, 125.1, 116.6, 40.8, 37.6, 34.6, 31.5, 21.2 ppm. IR (solution): $\tilde{\nu}$ = 2967, 1763 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{20}H_{22}O_2$ $[M + H]^+$ 295.1693; found 295.1689.

6-(*tert*-Butyl)-4-phenylchroman-2-one (3m): Following the general procedure, **3m** was obtained as an off-white solid (21 mg, 25 %). The ^{1}H NMR of **3m** is in agreement with the literature report.[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 3 H), 7.19–7.11 (m, 2 H), 7.07 (d, *J* = 8.5 Hz, 1 H), 7.01 (dd, *J* = 2.4, 0.8 Hz, 1 H), 4.33 (X part of ABX system, t, *J* = 6.5 Hz, 1 H), 3.07 (A part of ABX system, J_{AB} = 15.8, J_{AX} = 6.0 Hz, 1 H), 3.01 (B part of ABX system, J_{AB} = 15.8, J_{BX} = 7.0 Hz, 1 H), 1.24 (s, 9 H) ppm.

5,7-Dimethoxy-4-(4-methoxyphenyl)chroman-2-one (3n): Following the general procedure, **3n** was obtained as an off-white solid (81 mg, 85 %). The ^{1}H NMR of **3n** is in agreement with the literature report.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06–6.97 (m, 2 H), 6.82–6.73 (m, 2 H), 6.31 (d, *J* = 2.3 Hz, 1 H), 6.28 (d, *J* = 2.3 Hz, 1 H), 4.51 (t, *J* = 4.4 Hz, 1 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 2.97 (d, *J* = 4.4 Hz, 2 H) ppm.

7-Methoxy-4-(4-methoxyphenyl)chroman-2-one (3o): Following the general procedure, a solution of 3-methoxyphenol (33 µL, 0.30 mmol, 1.0 equiv.) and 4-methoxycinnamic acid (53 mg, 0.30 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (2.1 µL, 0.03 mmol, 0.10 equiv.) for 1 h at room temp. Reaction mixture was concentrated and a solution of the resulting residue in ether was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–100 % EtOAc/hexanes over 15 min) afforded **3o** as off-white solid (51 mg, 60 %). Mp: 137–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.02 (m, 2 H), 6.91–6.83 (m, 2 H), 6.67 (d, *J* = 2.5 Hz, 1 H), 6.63 (dd, *J* = 8.4, 2.6 Hz, 1 H), 4.23 (X part of ABX system, J_{AX} = 5.9, J_{BX} = 8.0 Hz, 1 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.02 (A part of ABX system, J_{AB} = 15.8, J_{AX} = 5.8 Hz, 1 H), 3.11 (B part of ABX system, J_{AB} = 15.8, J_{BX} = 8.1 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.0, 160.0, 159.0, 152.5, 132.7, 128.9, 128.6, 118.1, 114.5, 110.8, 102.6, 55.7, 55.4, 39.4, 37.6 ppm. IR (solution): $\tilde{\nu}$ = 1768 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}O_4$ $[M + H]^+$ 285.1121; found 285.1122.

(3a*S*,3b*R*,11b*S*,13a*S*)-10-(4-Methoxyphenyl)-13a-methyl-2,3,3a,3b,4,5,9,10,11b,12,13,13a-dodecahydrocyclopenta-[5,6]naphtho[1,2-*g*]chromene-1,8-dione (3p): Following the general procedure, a solution of estrone (45 mg, 0.30 mmol, 1.0 equiv.) and 4-methoxycinnamic acid (53.4 mg, 0.300 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (10.7 µL, 0.15 mmol, 0.50 equiv.) for 1 h at room temp. Reaction mixture was concentrated and a solution of the resulting residue in DCM was loaded

on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–100 % EtOAc/hexanes over 15 min) afforded **3p** as an oily compound (90 mg, 70 %) as a 1.3:1 mixture of epimers (determined by integration in ^{1}H NMR) that could not be separated using column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) of major epimer (full spectrum with all peaks): δ = 7.05 (m, 2 H), 6.91 (s, 1 H), 6.89–6.78 (complex, 3 H), 4.23 (m, 1 H), 3.77 (s, 3 H), 3.02–2.89 (complex, 4 H), 2.48 (m, 1 H), 2.52–2.00 (complex, 5 H), 1.88 (m, 1 H), 1.64–1.38 (complex, 6 H), 0.88 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) of major epimer (full spectrum with all peaks): δ = 220.7, 168.0, 158.9, 149.71, 137.5, 136.4, 132.8, 128.4, 125.22, 123.2, 116.94, 114.51, 55.3, 50.43, 47.92, 44.0, 33.99, 38.13, 37.6, 35.9, 31.5, 29.2, 26.4, 25.9, 21.62, 13.87 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) of minor epimer (diagnostic peaks only): δ = 3.78 (s, 3 H), 0.87 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) of minor epimer (diagnostic peaks only): δ = 220.7, 168.1, 149.70, 137.4, 136.2, 132.7, 128.5, 125.27, 123.3, 116.89, 114.49, 50.44, 47.95, 44.2, 40.01, 38.11, 37.7, 29.3, 26.3, 25.8, 21.61, 13.89 ppm. IR (solution): $\tilde{\nu}$ = 1763, 1735 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{28}H_{30}O_4$ [M + H]$^+$ 431.2217; found 431.2205.

6-Allyl-8-methoxy-4-(4-methoxyphenyl)chroman-2-one (3q): Following the general procedure, a solution of 4-allyl-2-methoxyphenol (49 mg, 0.30 mmol, 1.0 equiv.) and 4-methoxycinnamic acid (53 mg, 0.300 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (2.1 µL, 0.03 mmol, 0.10 equiv.) for 1 h at room temp. Reaction mixture was concentrated and a solution of the resulting residue in DCM was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–100 % EtOAc/hexanes over 15 min) afforded **3q** as yellowish liquid (41 mg, 42 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.00 (m, 2 H), 6.83–6.76 (m, 3 H), 6.63 (s, 1 H), 5.88 (ddt, *J* = 16.6, 10.2, 6.3 Hz, 1 H), 5.08–4.84 (m, 2 H), 4.65 (X part of ABX system, m, 1 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.44–3.20 (m, 2 H), 2.96 (A part of ABX system, J_{AB} = 16.0, J_{AX} = 8.5 Hz, 1 H), 2.92 (B part of ABX system, J_{AB} = 16.0, J_{BX} = 7.2 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.8, 158.1, 145.1, 144.0, 137.5, 135.5, 134.4, 129.3, 128.8, 115.9, 114.0, 113.4, 112.7, 56.0, 55.3, 41.3, 40.8, 36.8 ppm. IR (solution): $\tilde{\nu}$ = 1710 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{20}H_{20}O_4$ [M + H]$^+$ 325.1434; ion corresponding to [M + H]$^+$ was not observed under ESI conditions.

(8*R*)-1-(4-Methoxyphenyl)-6,8-dimethyl-8-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-1,8,9,10-tetrahydropyrano[3,2-*f*]chromen-3(2*H*)-one (3r): Following the general procedure, a solution of (*R*)-2,8-dimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]chroman-6-ol (100 mg, 0.248 mmol, 1.0 equiv.) and 4-methoxycinnamic acid (44 mg, 0.248 mmol, 1.0 equiv.) in HFIP (0.83 mL) was treated with acetyl chloride (1.8 µL, 0.025 mmol, 0.10 equiv.) for 1 h at room temp. Reaction mixture was concentrated and a solution of the resulting residue in DCM was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–100 % EtOAc/hexanes over 15 min) afforded a 2.8:1 mixture of constitutional isomers containing **3r** as yellowish liquid (83 mg) and **3s** as yellowish liquid (29 mg), total yield of 112 mg (80 %). Ratio of the constitutional isomers were determined by integration in ^{1}H NMR spectroscopy. The constitutional structure of the major isomer **3r** was confirmed by 1D and 2D NOESY studies, but the configuration of the newly formed stereogenic center was not established. The minor isomer is most likely an epimer at the newly-formed benzylic stereocenter in **3r**, although we cannot rule out the possibility of it being a constitutional isomer. Small quantities of the major isomer **3r** was isolated for characterization purposes, otherwise the mixture of the isomers co-eluted under the conditions of normal phase column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) of major constitutional isomer **3r** (full spectrum with all peaks): δ = 6.96 (m, 2 H), 6.83 (s, 1 H), 6.79 (m, 2 H), 4.26 (m, 1 H), 3.75 (s, 3 H), 3.04–2.91 (complex, 2 H), 2.67 (m, 1 H), 2.30 (m, 1 H), 2.20 (s, 3 H), 1.69 (m, 2 H), 1.59–1.01 (complex, 24 H), 0.94–0.68 (complex, 12 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) of major constitutional isomer **3r** (full spectrum with all peaks): δ = 168.0, 158.9, 149.1, 144.6, 132.4, 128.2, 127.3, 120.4, 118.4, 117.0, 114.6, 75.6, 55.4, 40.7, 39.5, 38.2, 37.6, 37.5, 37.5, 37.4, 37.1, 32.9, 32.7, 30.8, 28.1, 24.9, 24.5, 23.4, 22.9, 22.8, 20.9, 19.9, 19.7, 19.6, 16.3 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) of minor isomer **3s** (diagnostic peaks only): δ = 6.74 (s, 1 H), 4.35 (m, 1 H), 2.01 (s, 3 H) ppm. IR (solution): $\tilde{\nu}$ = 3005, 1762 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{37}H_{54}O_4$ [M + H]$^+$ 563.4095; found 563.4094.

3-[5-(*tert*-Butyl)-2-hydroxyphenyl]-*N*,*N*-diethyl-3-(4-methoxyphenyl)propanamide (5): Following the general procedure, a solution of 4-(*tert*-butyl)phenol (45 mg, 0.30 mmol, 1.0 equiv.) and (*E*)-*N*,*N*-diethyl-3-(4-methoxyphenyl)acrylamide **4** (70 mg, 0.30 mmol, 1.0 equiv.) in HFIP (1.0 mL) was treated with acetyl chloride (10.7 µL, 0.15 mmol, 0.50 equiv.) for 56 h at 44 °C. Reaction mixture was concentrated and a solution of the resulting residue in DCM was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g of silica flash column (0–100 % EtOAc/hexanes over 15 min) afforded **5** as yellowish liquid (49 mg, 43 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (br. s, 1 H), 7.23–7.18 (m, 2 H), 7.05 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.89 (d, *J* = 2.5 Hz, 1 H), 6.87–6.81 (m, 3 H), 4.96 (t, *J* = 6.9 Hz, 1 H), 3.79 (s, 3 H), 3.48–3.20 (m, 4 H), 3.10 (d, *J* = 6.9 Hz, 2 H), 1.15 (s, 9 H), 1.12–0.97 (m, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.2, 158.0, 152.1, 143.0, 136.6, 131.6, 129.1, 125.6, 124.3, 117.7, 113.8, 55.3, 42.3, 41.1, 39.8, 38.2, 34.1, 31.6, 14.1, 13.0 ppm. IR (solution): $\tilde{\nu}$ = 3005, 1622 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{24}H_{33}NO_3$ [M + H]$^+$ 384.2533; found 384.2526.

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