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Oxidative Arylation of Isochroman

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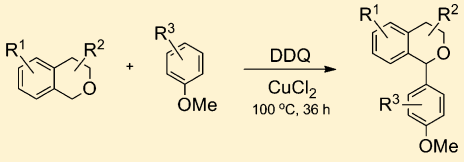
Supporting Information

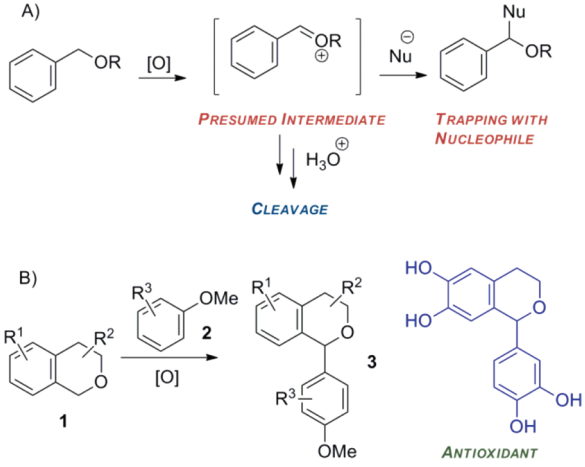
ABSTRACT: We report the use of a previously intractable nucleophile, anisole, in an oxidative "cross-dehydrogenative coupling" (CDC) reaction with the cyclic ether isochroman, as well as derivatives of both components. Metal catalysis was required for the reaction to proceed efficiently, and the reaction is highly sensitive to modification of either coupling partner but is able to produce a range of novel compounds via what is a synthetic alternative to the traditional oxa-Pictet–Spengler reaction.



INTRODUCTION

It has been long known that oxidation of a benzylic ether can lead to cleavage of that ether (Scheme 1A); this is the basis for the use of the *p*-methoxybenzyl (PMP) protecting group (and analogues).[1] Treatment of such ether-based protecting groups with the oxidant DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) in common solvents such as dichloromethane results in efficient cleavage, usually in a few minutes at room temperature.

Scheme 1. (A) Oxidative Cleavage of Benzylic Ethers, or Trapping of the Intermediate Oxonium Ion with a Nucleophile; (B) Method Reported Here



The chemistry can be controlled to give carbon–heteroatom[2] and carbon–carbon[3] bond formation in what Li has termed "cross-dehydrogenative coupling" (CDC),[4] often resulting in convenient one-pot reaction protocols.

The majority of such CDCs involve oxidative couplings next to nitrogen atoms, with few examples of coupling next to oxygen[5] or sulfur.[6] An attempt to perform a CDC reaction between the cyclic ether isochroman and anisole catalyzed by iron salts and using a hydroperoxide oxidant failed to give any product, and instead highly electron-rich aromatic groups were required.[7] Recent examples of aromatic rings acting as nucleophiles in a CDC reaction adjacent to a nitrogen atom required either the addition of a metal triflate[8] or the use of π-excessive heteroarenes.[9] Shi's recently reported oxidative arylation reaction employed diarylmethanes as the proelectrophile, activated to reaction by a combination of DDQ and iron catalysis; anisole only gave regiocontrol in the arylation with the use of an *ortho* blocking group.[10]

We undertook to find conditions for the still-unreported coupling between anisole and isochroman and to investigate the synthesis of various substituted derivatives (Scheme 1B). There are several reasons for investigating this chemistry. First, while many CDC methods are now known, there are very few studies of their mechanisms. We are interested in elucidating such mechanisms and so have a particular interest in any challenging or unsuccessful examples and what these tell us about the scope of CDC processes; the apparent refusal of anisole to participate was from this standpoint of some interest. Compared with our recent report of a CDC between a benzylic amine and nitromethane, which proceeds quantitatively at room temperature in a few minutes,[11] one cannot but ask why coupling between anisole and isochroman should be such a challenge.

1-Arylated isochromans are normally formed *via* the oxa-Pictet–Spengler reaction,[12] typically requiring electron-donating groups attached to the phenethylalcohol moiety. A CDC process would offer an attractive alternative disconnection for a one-step synthesis of such compounds that does not require the *de novo* synthesis of the oxygen-containing ring. Apart from the example mentioned above,[7] this is an approach that has only previously been achieved using attack of reactive nucleophiles (*e.g.*, Grignard or organozinc reagents, enolates) on isochromans that were previously oxidized at the 1-position.[13] The resulting structures (**3**), which are found in some natural foodstuffs such as olive oil,[14] have demonstrated anti-inflammatory activity *via* inhibition of cyclooxygenase-2[15] and have commercial significance as antioxidants (Scheme 1B inset).[16]

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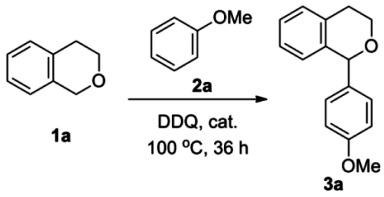
RESULTS AND DISCUSSION

A DDQ-mediated C−C bond formation between isochroman and anisole was successful without solvent, yielding the desired product **3a** in a low yield (Table 1, entry 1). Addition of catalytic iron(II) chloride gave a 50% yield (entry 2); various metal salts were screened, and some afforded the product in poor to fair yields (entries 3−7), but copper halides were found to be the best catalysts (entries 8 and 9). Interestingly, higher or lower catalyst loadings did not improve the yield (entries 10−13). Lowering the amount of anisole relative to other reagents decreased the product yield; it was found that at least 3 equiv of anisole was required to yield a reasonable amount of the product (entries 14−6), but larger amounts (6 equiv) were found to be preferable for the reaction to be well mixed and easier to handle. A slight increase in the amount of DDQ from 1 to 1.1 equiv improved the yield (entry 17), and the use of a sealed tube was found to be beneficial (entries 18 and 19). Further increases in the amount of DDQ did not give improved yields (entries 20−23). Use of atmospheric oxygen as oxidant did not afford the desired product (entry 24). Lower reaction temperatures gave reduced yields (entries 25 and 26). The product yield was decreased using a decreased reaction time (entries 27 and 28) but not increased with an extended reaction time (entry 29). Collectively the optimum conditions were found to be a reagent ratio of 1:6:1.1:0.1 (isochroman/anisole/DDQ/catalyst) without solvent in a sealed tube at 100 °C for 36 h, giving the product **3a** in 76% yield.

We next explored variation in anisole substitution (Table 2). The coupling reaction was insensitive to single methyl substitution of the anisole (entries 2 and 3). 2-Bromoanisole afforded the desired product in greatly reduced yield (entry 4), which was surprising given the similar electronic effect of bromine and methyl on an aromatic ring. Several other products (<10% isochroman and a mixture of ring-opened products) were formed with the main byproduct being the overoxidized product isochroman-1-one in 25% yield. Several naphthyl-based nucleophiles gave good yields of novel ring systems **3e−g**, with the structures of two of them being proven by X-ray crystallography (**3e** and **3g**, Supporting Information). The successful formation

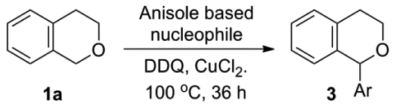
Table 1. Optimization of the Arylation

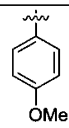
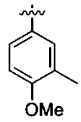
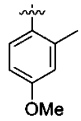
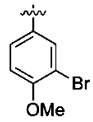
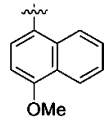
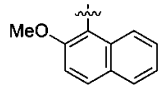
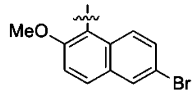
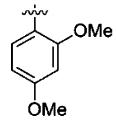


entry	catalyst	equiv **1a**/**2a**/DDQ/cat.	yield **3a** [%][a]
1		1/6/1/0	27
2	$FeCl_2$	1/6/1/0.1	50
3	$Fe(OAc)_2$	1/6/1/0.1	33
4	$PdCl_2$	1/6/1/0.1	56
5	$ZnCl_2$	1/6/1/0.1	49
6	$NiCl_2$	1/6/1/0.1	0
7	$Cu(OTf)_2$	1/6/1/0.1	18
8	$CuBr_2$	1/6/1/0.1	71
9	$CuCl_2$	1/6/1/0.1	71
10	$CuCl_2$	1/6/1/0.05	63
11	$CuCl_2$	1/6/1/0.02	55
12	$CuCl_2$	1/6/1/0.2	64
13	$CuCl_2$	1/6/1/0.4	60
14	$CuCl_2$	1/3/1/0.1	70
15	$CuCl_2$	1/2/1/0.1	59
16	$CuCl_2$	1/1/1/0.1	43
17	$CuCl_2$	1/6/1.1/0.1	75
18	$CuCl_2$	1/6/1/0.1[b]	72
19	**$CuCl_2$**	**1/6/1.1/0.1**[b]	**76**
20	$CuCl_2$	1/6/1.3/0.1	71
21	$CuCl_2$	1/6/1.3/0.1[b]	75
22	$CuCl_2$	1/6/1.5/0.1	65
23	$CuCl_2$	1/6/2/0.1	59
24	$CuCl_2$	1/6/0/0.1[c]	0
25	$CuCl_2$	1/6/1.1/0.1[d]	0
26	$CuCl_2$	1/6/1.1/0.1[e]	12
27	$CuCl_2$	1/6/1.1/0.1[f]	17
28	$CuCl_2$	1/6/1.1/0.1[g]	65
29	$CuCl_2$	1/6/1.1/0.1[h]	73

[a]Isolated yield. [b]Sealed tube. [c]Open to the air. [d]At rt. [e]At 50 °C. [f]12 h reaction time. [g]24 h reaction time. [h]48 h reaction time.

Table 2. Coupling between Isochroman and Anisole Derivatives



entry	series	Ar	yield (%)
1	a		76
2	b		75
3	c		68
4	d		6
5	e		73
6	f		74
7	g		83
8	h		0

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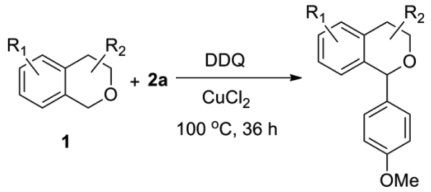
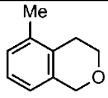
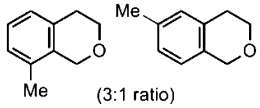
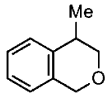
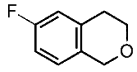
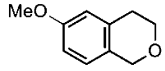
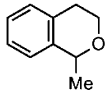
of product **3g** is in stark contrast to the failure of the reaction to give product **3d**, where the bromine atom is attached to the same ring that participates in the bond-forming reaction. When the more electron-rich 3-methoxyanisole is used as a nucleophile, none of the expected product is formed. Isochroman is consumed, but a mixture is generated that includes a nearly quantitative yield of isochroman-1-one (*ca.* 50% by mass, but production requires 2 equiv of DDQ).

We next turned to structural variation in the isochroman (Table 3). Reactions employing isochromans substituted with

Table 3. Coupling between Anisole and Various Isochromans



entry	series	1	yield **3** (%)
1	i		75
2	j	 (3:1 ratio)	45 (8-Me)
3	k		61
4	l		69
5	m		0
6	n		38
7	o		0

methyl groups in the 4-, 5-, and 6- and 8-positions gave considerable variation in product yields (entries 1−3). In the case of the inseparable mixture of 6- and 8-methylisochroman (1:3 ratio, entry 2) the minor isomer did not generate product, whereas the 8-methyl isomer did. The methyl group in the 6-isomer is distant from the site of reaction but presumably exerts a sufficiently strong electronic influence. Reaction of racemic 4-methylisochroman (entry 3) gave the product **3k** as a 1:1 mixture of diastereomers; this implies either that the addition of anisole to the intermediate oxonium ion is reversible or more likely that there is no facial selectivity in the addition. The latter possibility suggests there is no $\pi-\pi$ interaction between anisole and oxonium ion immediately prior to C−C bond formation, since such an association would likely result in a majority of *anti* product ((*R*,*R*) or (*S*,*S*)), where aromatic ring and methyl substituent would be on opposite faces of the final molecule. A strongly electron-withdrawing group in the 6-position (entry 4) led to a high yield of product, while a strongly electron-donating substituent (entry 5) gave no product. The latter reaction yielded ring-opened side products. The marginally electron-donating substituent (*m*-Br, entry 6) also gave a low yield of product, indicating a high level of sensitivity to the electronics of the isochroman ring, presumably because electron-donating substituents reduce the reactivity of the presumed intermediate oxonium ion. The effect of an extra substituent at the site of reaction was examined using 1-methylisochroman, providing only a small quantity of unidentified oxidation byproducts and 43% recovery of starting material (entry 7). This starting material has been found to be unreactive in a related reaction.[5c] To the best of our knowledge there are still no examples of the formation of carbon−carbon bonds at the 1-position of 1-alkyl substituted isochroman (with the exception of the use of stabilizing groups in the 1-position employed in the generation of anions through deprotonation, which then react with electrophiles).[17]

Experiments to elucidate the mechanism of this reaction are ongoing. It is likely that the reaction involves the rapid initial production of an oxonium ion; oxidative coupling between isochroman and *O*-based nucleophiles have been reported to proceed at room temperature.[2b] To test this, the parent reaction described above was performed in the absence of copper at room temperature and in the presence of 1 equiv of ethanol. Product arising from attachment of ethanol (1-ethoxyisochroman) was isolated in 63% yield. Repeating the reaction of entry 1 in Table 2 in the presence of 1 equiv of ethanol gave 1-ethoxyisochroman in 65% yield, with no formation of product **3a**. These results (coupled with those in Table 1) suggest not only that the formation of the oxonium ion is rapid under ambient conditions but also that heating and copper catalysis are required for the anisole to become an effective nucleophile. It is tempting to suggest simple nucleophilic attack by the arene on the oxonium ion. According to the Mayr nucleophilicity/electrophilicity tables[18] anisole and oxonium ions should spontaneously react. That the reactive partners in the present reaction do not react together unaided implies a more complex mechanism. Indeed, if the mechanism were a straightforward combination of nucleophile and electrophile, it would be expected that the reaction would be easier with methoxyanisole as nucleophile, yet when this reagent was used, no product was obtained. These observations suggest the copper salt employed is not merely engaged in counterion metathesis with the anion associated with the oxonium ion, though at present this possibility cannot be excluded. The copper may be involved in a redox process (as was recently suggested by Klussman in a related reaction[19]), a possibility supported by the lack of any reaction when Ni(II) was employed. Standard reduction potentials can explain the lack of reactivity of Ni(II) (−0.23 V) yet do not explain the formation of product in the case of Zn(II) (−0.76 V); Zn(I) complexes are, however, known, while Ni(I) complexes are not.[20] If this redox process is not the oxidation of isochroman, the copper may be participating in an unusual mechanistic cycle that couples the anisole with the oxonium ion *via* Minisci chemistry involving attachment of a radical to an activated heterocycle (Scheme 2);[21] this possibility was recently suggested by Shirakawa and Hayashi for a related coupling.[8] Such a mechanism would require the conversion of an aryl C−H bond into a C−Cu bond without adjacent directing groups; such transformations have been proposed in Cu-catalyzed cross-coupling reactions,[22] and related structures have been crystallographically proven as intermediates

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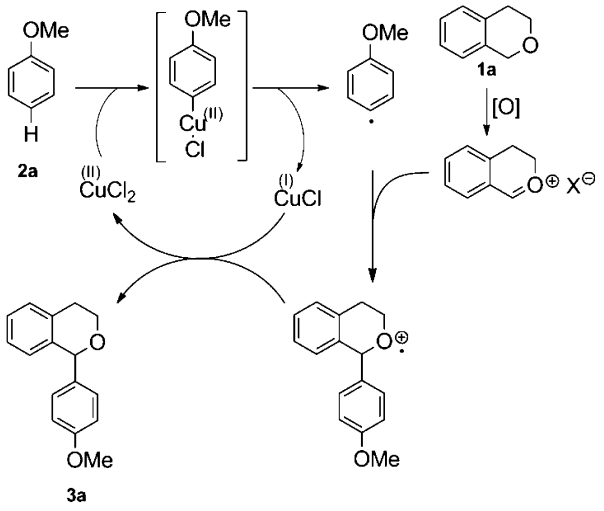
Scheme 2. Tentative Mechanism for the Cu-Catalyzed Oxidative Coupling of Isochroman with Anisole (X^- = Counterion Such as $DDQH^-$ or Cl^-)



in reactions involving aromatic rings contained within azamacrocycles.[23] Collapse of such an intermediate to an aryl radical would be the step facilitated by a redox-active metal ion. Coupling with the oxonium ion (the equivalent of Minisci's protonated heterocycle) would give an intermediate radical cation that would complete the catalytic cycle by oxidizing the copper center. Proof of this mechanism is our current focus; it should be noted that other copper oxidation states, including Cu(III), could be valid intermediates in such a cycle. An alternative possibility to this mechanism is initial electron transfer from anisole to Cu(II) to generate Cu(I) followed by a Cu(I) mediated coupling of the two cations, as suggested by a referee. We cannot at this stage rule out this mechanism; it should be noted that both mechanisms require redox cycling of the metal ion. We have isolated a solid from the reaction between isochroman and DDQ. It is likely that this solid contains the intermediate oxonium ion or a derivative. While full characterization of this solid is ongoing, we have shown it is capable of producing product **3a** when the solid is mixed with anisole and copper but no further oxidant, and this reaction fails to produce product when 1 equiv of TEMPO is included, strongly suggesting that the final carbon−carbon bond-forming event is radical-mediated, as shown in the proposed mechanism. One observation that remains unexplained is why no product was ever observed arising from *ortho*-attack of the anisole, nor any product from anisole's *meta*-position, which might be possible if the free radical coupling in Scheme 2 is correct. The mechanism of the reaction is in any case not straightforward because DDQ will oxidize anisole before isochroman, meaning oxidized anisole is probably the species responsible for the oxidation of isochroman. The outcome of this one-pot process probably arises from a delicate balance of kinetics and thermodynamics.

■ CONCLUSION

We have reported the first oxidative coupling between isochroman and anisole. This represents an alternative to the more traditional oxa-Pictet−Spengler reaction to such compounds. The chemistry has several methodological advantages: (i) copper(II) is an inexpensive metal ion exhibiting low toxicity, (ii) DDQ is an oxidant that is simple to handle under ambient conditions and may be recycled,[24] and (iii) the one-pot CDC protocol is operationally simple and requires no solvent, merely an excess of one reagent that may be recovered. The reaction exemplifies the advantage of CDC processes more generally, in that no resources need to be consumed in the generation of isolated nucleophiles and electrophiles.

■ EXPERIMENTAL SECTION

General Information. ^{1}H NMR chemical shifts are reported in parts per million (δ) referenced to an internal TMS signal (peak at 0.00 ppm), whereas ^{13}C NMR chemical shifts are reported with reference to TMS using the carbon signals of the deuterated solvent ($CDCl_3$: 77.16 ppm). *J* coupling constant values are reported in Hertz. Ionization of mass spectra samples was carried out using atmospheric pressure chemical ionization (APCI). Flash column chromatography was performed over silica gel 0.040−0.060 mm. Thin layer chromatography (TLC) was performed using silica gel precoated aluminum sheets (0.2 mm thickness) and visualized with ultraviolet light at 254 nm. All reagents were purchased from commercial vendors and used without further purification.

General Procedures for the Arylation of Isochromans. To a sealed tube were added **1** (1.00 mmol unless otherwise stated, 1 equiv), DDQ (1.1 equiv), copper(II) chloride (0.1 equiv), and **2** (6 equiv). The reaction mixture was stirred at 100 °C for 36 h. The mixture was allowed to cool to rt. Silica (0.80 g) was added to the reaction mixture, and the resulting powder was directly applied to the top of a flash column (typically eluting with hexane/ethyl acetate).

*1-(4-Methoxyphenyl)isochroman (**3a**).* Obtained on 1.0 mmol scale and purified by flash column chromatography (hexane/ethyl acetate = 20:1) and then recrystallized from hexane and ethyl acetate to give 1-(4-methoxyphenyl)isochroman **3a** as white needles (182 mg, 76% yield): mp 75−76 °C (lit.[13a] 75−77 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.80 (1 H, dt, *J* = 16.5, 3.7, H^4), 3.13 (1 H, ddd, *J* = 16.2, 9.3, 5.7, H^4), 3.80 (3 H, s, CH_3), 3.92 (1 H, ddd, *J* = 11.3, 9.3, 4.0, H^3), 4.17 (1 H, ddd, *J* = 11.4, 5.4, 4.1, H^3), 5.70 (1 H, s, H^1), 6.76 (1 H, d, *J* = 7.7, H^{ar}), 6.87 (2 H, d, *J* = 8.7, H^{ar}), 7.05−7.10 (1 H, m, H^{ar}), 7.16−7.17 (2 H, m, H^{ar}), 7.22 (2 H, d, *J* = 8.6, H^{ar}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.0, 55.4, 63.9, 79.3, 113.9, 126.0, 126.7, 127.1, 128.8, 130.3, 134.1, 134.7, 137.8, 159.6; IR ν_{max}/cm^{-1} 2839, 1611, 1512, 1456, 1247, 1175, 1090, 1034. 828, 747; LRMS *m*/*z* (%) (APCI) 239.0 $[M - H]^+$ (100). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.82; H, 6.93.

*1-(3-Methyl-4-methoxyphenyl)isochroman (**3b**).* Obtained on 1.0 mmol scale and purified by flash column chromatography to give 191 mg of 1-(3-methyl-4-methoxyphenyl)isochroman as a colorless oil (75% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (3 H, s, CCH_3), 2.78 (1 H, dt, *J* = 16.3, 3.6, H^4), 3.13 (1 H, ddd, *J* = 16.3, 9.2, 5.6, H^4), 3.80 (3 H, s, OCH_3), 3.90 (1 H, td, *J* = 11.3, 3.9, H^3), 4.18 (1 H, ddd, *J* = 11.3, 5.5, 3.9, H^3), 5.66 (1 H, s, H^1), 6.77 (2 H, d, *J* = 7.9, H^{ar}), 7.05−7.09 (3 H, m, H^{ar}), 7.15−7.16 (2H, m, H^{ar}); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.4, 29.0, 55.4, 63.9, 79.5, 109.6, 126.0, 126.6, 126.8, 127.1, 127.6, 128.7, 131.2, 134.0, 134.1, 137.9, 157.7; IR ν_{max}/cm^{-1} 2924, 1603, 1576, 1500, 1450, 1290, 1247, 812; LRMS *m*/*z* (%) (APCI) 254.1 $[M]^+$ (50), 223.1 $[M - OCH_3]^+$ (100); HRMS calcd for $C_{17}H_{18}O_2^+$ $(M)^+$: 254.13069, found 254.13062.

*1-(2-Methyl-4-methoxyphenyl)isochroman (**3c**).* Obtained on 1.0 mmol scale and purified by flash column chromatography to give 174 mg of 1-(2-methyl-4-methoxyphenyl)isochroman as a light yellow oil (68% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (3 H, s, CCH_3), 2.81 (1 H, dt, *J* = 16.4, 3.8, H^4), 3.12 (1 H, ddd, *J* =16.4, 9.3, 5.6, H^4), 3.78 (3 H, s, OCH_3), 3.91 (1 H, ddd, *J* = 11.3, 9.5, 4.0, H^3), 4.18 (1 H, ddd, *J* = 11.3, 5.3, 4.1, H^3), 5.87 (1 H, s, H^1), 6.66 (1 H, dd, *J* = 8.4, 2.7, H^{ar}), 6.71 (1 H, d, *J* = 7.7, H^{ar}), 6.74 (1 H, d, *J* = 2.6, H^{ar}), 7.00 (1 H, d, *J* = 8.4, H^{ar}), 7.03−7.09 (1 H, m, H^{ar}), 7.13−7.18 (2 H, m, H^{ar}); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.7, 28.9, 55.3, 64.0, 77.4, 110.7, 116.6, 126.1, 126.5, 126.5, 128.7, 131.3, 132.5, 134.1, 138.0, 139.0, 159.3; IR ν_{max}/cm^{-1} 2927, 1608, 1579, 1503, 1452, 1293, 1247, 812; LRMS *m*/*z* (%) (APCI) 254.8 $[M]^+$ (100); HRMS calcd for $C_{17}H_{18}O_2^+$ $(M)^+$: 254.13069, found 254.13066.

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*1-(3-Bromo-4-methoxyphenyl)isochroman (**3d**).* Obtained on 1.0 mmol scale and purified by flash column chromatography to give 19 mg of 1-(3-bromo-4-methoxyphenyl)isochroman as a light yellow liquid (6% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (1 H, dt, J = 16.4, 3.8, H^4), 3.13 (1 H, m, H^4), 3.89 (3 H, s, CH_3), 3.87−3.95 (1 H, m, H^3, overlapping with CH_3), 4.17 (1 H, ddd, J = 11.4, 5.5, 4.0, H^3), 5.66 (1 H, s, H^1), 6.75 (1 H, d, J = 7.6, H^{ar}), 6.86 (1 H, d, J = 8.4, H^{ar}), 7.09 (1 H, td, J = 8.3, 2.5, H^{ar}), 7.12−7.23 (3 H, m, H^{ar}), 7.49 (1 H, d, J = 2.1, H^{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 56.4, 64.0, 78.7, 111.7, 111.8, 126.2, 126.9, 127.0, 129.0, 129.2, 133.9, 134.0, 136.2, 137.1, 155.8; IR ν_{max}/cm^{-1} 2926, 1598, 1494, 1454, 1259, 1053, 746; LRMS m/z (%) (APCI) 317.1 $[M]^+$ (12), 239.1 (100); HRMS calcd for $C_{16}H_{14}BrO_2^+$ $(M - H)^+$: 317.01717 and 319.01512, found 317.01681 and 319.01465.

*1-(4-Methoxynaphthalen-1-yl)isochroman (**3e**).* Obtained on 1.0 mmol scale and purified by flash column chromatography to give 213 mg of 1-(4-methoxynaphthalen-1-yl)isochroman as white prisms (73% yield): mp 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94 (1 H, td, J = 16.3, 4.6, H^4), 3.10−3.25 (1 H, m, H^4), 3.93−4.07 (1 H, m, overlapping with CH_3, H^3), 4.00 (3 H, s, CH_3), 4.13−4.23 (1 H, m, H^3), 6.33 (1 H, s, H^1), 6.71 (1 H, d, J = 7.9, H^{ar}), 6.77 (1 H, d, J = 7.8, H^{ar}), 7.03 (1 H, t, J = 7.9, H^{ar}), 7.13−7.23 (3 H, m, H^{ar}), 7.40−7.50 (2 H, m, H^{ar}), 8.10−8.15 (1 H, m, H^{ar}), 8.26−8.32 (1 H, m, H^{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 55.7, 63.5, 77.4, 102.7, 122.5, 124.9, 125.2, 126.1, 126.5, 126.7, 126.8, 126.8, 128.7, 128.9, 129.5, 132.8, 134.1, 137.8, 156.0; IR ν_{max}/cm^{-1} 2962, 1584, 1459, 1391, 1241, 1087, 1056, 907, 724; LRMS m/z (%) (APCI) 132.6 (74), 272.8 (100), 290.6 $[M - H]^+$ (71); HRMS calcd for $C_{20}H_{19}O_2^+$ (MH^+): 291.13796, found 291.13791. Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73, H, 6.25. Found: C, 82.60, H, 6.42.

CCDC 834014 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

*1-(2-Methoxynaphthalen-1-yl)isochroman (**3f**).* Obtained on a 1.0 mmol scale and purified by flash column chromatography to give 226 mg of 1-(2-methoxynaphthalen-1-yl)isochroman as white prisms (78% yield): mp 131.5−132.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (1 H, dd, J = 16.4, 2.6, H^4), 3.42−3.56 (1 H, m, H^4), 3.96 (3 H, s, CH_3), 4.13 (1 H, td, J = 11.6, 3.2, H^3), 4.45 (1 H, dd, J = 11.3, 5.9, H^3), 6.56 (1 H, d, J = 7.7, H^{ar}), 6.80 (1 H, s, H^1), 6.91 (1 H, t, J = 7.5, H^{ar}), 7.10 (1 H, t, J = 7.5, H^{ar}), 7.18−7.25 (3 H, m, H^{ar}), 7.32 (1 H, d, J = 9.0, H^{ar}), 7.69−7.76 (1 H, m, H^{ar}), 7.84 (1 H, d, J = 9.1, H^{ar}), 7.87−7.91 (1 H, m, H^{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.1, 57.1, 66.6, 72.8, 113.4, 122.1, 123.5, 125.3, 126.0, 126.3, 126.3, 126.4, 128.4, 128.7, 130.2, 130.8, 132.4, 133.3, 139.2, 155.8; IR ν_{max}/cm^{-1} 2843, 1624, 1596, 1509, 1460, 1244, 1069, 994, 905, 727; LRMS m/z (%) (APCI) 132.6 (100), 272.8 (96), 290.5 $[M - H]^+$ (70); HRMS calcd for $C_{20}H_{19}O_2^+$ (MH^+): 291.13796, found 291.13791. Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73, H, 6.25. Found: C, 82.85, H, 6.39.

*1-(6-Bromo-2-methoxynaphthalen-1-yl)isochroman (**3g**).* Obtained on 1.0 mmol scale and purified by flash column chromatography to give 291 mg of 1-(6-bromo-2-methoxynaphthalen-1-yl)isochroman as white prisms (79% yield): mp 165−166 °C (no literature data available); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (1 H, dd, J = 16.5, 2.6, H^4), 3.40−3.55 (1 H, m, H^4), 3.97 (3 H, s, CH_3), 4.12 (1 H, td, J = 11.7, 3.3, H^3), 4.45 (1 H, dd, J = 11.3, 6.1, H^3), 6.51 (1 H, d, J = 7.7, H^{ar}), 6.77 (1 H, s, H^1), 6.92 (1 H, t, J = 7.4, H^{ar}), 7.12 (1 H, t, J = 7.4, H^{ar}), 7.19 (1 H, d, J = 7.5, H^{ar}), 7.23−7.30 (1 H, m, H^{ar}), 7.34 (1 H, d, J = 9.1, H^{ar}), 7.76 (2 H, t, J = 7.5, H^{ar}), 7.87 (1 H, d, J = 2.0, H^{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 57.0, 66.7, 72.6, 114.2, 117.3, 122.5, 125.3, 126.3, 126.5, 127.9, 128.9, 129.5, 129.8, 130.2, 130.9, 131.3, 133.2, 138.8, 156.0; IR ν_{max}/cm^{-1} 2932, 1588, 1496, 1459, 1251, 1072, 742; LRMS m/z (%) (APCI) 132.7 (100), 271.8 (46), 370.4 $[M + H]^+$ (6). Anal. Calcd for $C_{20}H_{17}BrO_2$: C, 65.05, H, 4.64. Found: C, 65.12, H, 4.62.

CCDC 834015 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

*1-(4-Methoxyphenyl)-5-methylisochroman (**3i**).* Obtained on 1.0 mmol scale and purified by flash column chromatography to give a clear oil, which was crystallized from hexane and ethyl acetate to give 190 mg of 1-(4-methoxyphenyl)-5-methylisochroman as white needles (75% yield): mp 98.5−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (3 H, s, CCH_3), 2.70 (1 H, td, J = 16.6, 4.1, H^4), 2.85−2.99 (1 H, m, H^4), 3.80 (3 H, s, OCH_3), 3.93 (1 H, ddd, J = 11.6, 9.0, 4.4, H^3), 4.19 (1 H, ddd, J = 11.5, 5.7, 4.3, H^3), 5.70 (1H, s, H^1), 6.61 (1 H, d, J = 7.5, H^{ar}), 6.86 (2 H, d, J = 8.6, H^{ar}), 6.94−7.08 (2 H, m, H^{ar}), 7.21 (2 H, d, J = 8.6, H^{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.7, 55.4, 63.5, 79.4, 113.9, 124.8, 125.5, 128.0, 130.3, 132.7, 134.9, 136.2, 137.6, 159.5; IR ν_{max}/cm^{-1} 2834, 1606, 1589, 1507, 1458, 1241, 1171, 1102,1026, 999, 825, 797, 744; LRMS m/z (%) (APCI) 252.8 $[M - H]^+$ (100); HRMS calcd for $C_{17}H_{17}O_2^+$ $(M - H)^+$: 253.12231, found 253.12238. Anal. Calcd for $C_{17}H_{18}O_2 \cdot 0.2H_2O$: C, 79.16, H, 7.19, found C, 79.35, H, 7.18.

*1-(4-Methoxyphenyl)-8-methylisochroman (**3j**).* Obtained single product on 0.2 mmol scale of 3:1 mixture of 8-methyl isochroman and 6-methylisochroman respectively and purified by flash column chromatography to give a clear oil, which was recrystallized from hexane and ethyl acetate to give 26 mg of 1-(4-methoxyphenyl)-6-methylisochroman as white needles (45% yield): mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (3 H, s, CCH_3), 2.76 (1 H, dt, J = 16.5, 3.6, H^4), 3.00−3.09 (1 H, m, H^4), 3.74−3.82 (2 H, m, overlapping with OCH_3, H^3), 3.79 (3 H, s, OCH_3), 5.81 (1 H, s, H^1), 6.83 (2 H, d, J = 8.6, H^{ar}), 6.98 (1 H, d, J = 7.4, H^{ar}), 7.05 (1 H, d, J = 7.5, H^{ar}), 7.08 (1 H, d, J = 8.7, H^{ar}), 7.16 (1 H, t, J = 7.5, H^{ar}) ; ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.2, 28.9, 55.3, 59.1, 75.4, 113.7, 126.8, 126.8, 128.2, 130.4, 133.2, 134.3, 134.5, 135.1, 159.3; IR ν_{max}/cm^{-1} 2924, 1601, 1507, 1462, 1247, 1168, 1096, 1029, 819, 773. LRMS m/z (%) (APCI) 252.8 $[M - H]^+$ (100); HRMS calcd for $C_{17}H_{17}O_2^+$ $(M - H)^+$: 253.12231, found 253.12247.

*1-(4-Methoxyphenyl)-4-methylisochroman (**3k**).* Obtained on 2.0 mmol scale and purified by flash column chromatography to give 331 mg of 1-(4-methoxyphenyl)-4-methylisochroman as a light yellow oil (65% yield): found 1:1 ratio of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3 H, d, J = 7.0, CCH_3), 1.46 (3 H, d, J = 7.1, CCH_3), 2.85−2.94 (1 H, m, H^4), 3.14 (1 H, apparent sextet, J = 6.9, H^4), 3.54 (1 H, dd, J = 11.3, 8.0 H^3), 3.79 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 3.90 (1 H, dd, J = 11.2, 2.9, H^3), 4.00 (1 H, dd, J = 11.3, 3.6, H^3), 4.09 (1 H, dd, J = 11.3, 5.1, H^3), 5.65 (1 H, s, H^1), 5.73 (1 H, s, H^1), 6.72 (1 H, d, J = 7.8, H^{ar}),6.75 (1 H, d, J = 7.8, H^{ar}), 6.82−6.89 (4 H, m, H^{ar}), 7.02−7.09 (2 H, m, H^{ar}), 7.16−7.33 (8 H, m, H^{ar}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.9, 21.7, 32.0, 32.9, 55.4, 55.4, 69.7, 70.0, 79.5, 79.8, 113.8, 113.9, 125.8, 126.0, 126.8, 126.9, 126.9, 126.9, 127.0, 128.3, 130.2, 130.3, 134.7, 134.8, 137.0, 137.2, 139.5, 139.6. 159.5, 159.6; IR ν_{max}/cm^{-1} 2959, 1609, 1511, 1452, 1243, 1174, 1107, 1030, 821, 753. LRMS m/z (%) (APCI) 252.8 $[M - H]^+$ (100); HRMS calcd for $C_{17}H_{17}O_2^+$ $(M - H)^+$: 253.12231, found 253.12248.

*6-Fluoro-1-(4-methoxyphenyl)isochroman (**3l**).* Obtained on 1.0 mmol scale and purified by flash column chromatography to give 178 mg of 6-fluoro-1-(4-methoxyphenyl)isochroman as white prisms (69% yield): mp 89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (1 H, dt, J = 16.5, 3.8, H^4), 3.11 (1 H, ddd, J = 16.5, 5.7, 3.6, H^4), 3.80 (3 H, s, CH_3), 3.89 (1 H, ddd, J = 11.4, 9.4, 4.0, H^3), 4.15 (1 H, ddd, J = 11.4, 5.4, 4.0, H^3), 5.65 (1H, s, H^1), 6.71 (1 H, dd, J = 8.6, J_{H-F} = 5.8, H^{ar}), 6.77 (1 H, td, J = 8.6, 2.6, H^{ar}), 6.84−6.89 (3 H, m, H^{ar}), 7.20 (2 H, d, J = 8.6, H^{ar}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 29.1, 55.4, 63.5, 79.0, 113.3 (d, J_{C-F} = 21.4), 114.0, 115.0 (d, J_{C-F} = 20.8), 128.8 (d, J_{C-F} = 8.3) 130.2, 133.5 (d, J_{C-F} = 3.0), 134.4, 136.3 (d, J_{C-F} = 7.5), 159.6, 161.5 (d, J_{C-F} =245.2); IR ν_{max}/cm^{-1} 2962, 1596, 1503, 1245, 1091, 1057, 827; LRMS m/z (%) (APCI) 257.0 $[M - H]^+$ (70), 226.8 (100). Anal. Calcd for $C_{16}H_{15}FO_2$; C, 74.40, H, 5.85. Found: C, 74.44, H, 5.85.

*5-Bromo-1-(4-methoxyphenyl)isochroman (**3n**).* Obtained on 1.0 mmol scale and purified by flash column chromatography to give 122 mg of 5-bromo-1-(4-methoxyphenyl)isochroman as white needles (38% yield); (a sample was recrystallized from hexane and ethyl acetate to remove traces of grease. The recrystallized sample was used for characterization): mp 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86

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(1 H, dt, J = 17.2, 4.2, H^4), 2.99 (1 H, ddd, J = 17.1, 9.0, 5.8, H^4), 3.80 (3 H, s, CH_3), 3.90 (1 H, ddd, J = 11.6, 9.0, 4.5, H^3), 4.19 (1 H, ddd, J = 11.6, 5.7, 4.1, H^3), 5.66 (1 H, s, H^1), 6.72 (1 H, d, J = 7.7, H^{ar}), 6.87 (2 H, d, J = 8.8, H^{ar}), 6.95 (1 H, t, J = 7.8, H^{ar}), 7.19 (2 H, d, J = 8.7, H^{ar}), 7.44 (1 H, d, J = 7.9, H^{ar}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 29.8, 55.4, 63.5, 79.0, 114.0, 125.2, 126.2, 127.1, 130.3, 130.7, 133.9, 134.0, 140.5, 159.7; IR ν_{max}/cm^{-1} 2835, 1611, 1511, 1244, 1049, 1033, 825, 763; LRMS: m/z (%) (APCI) 319.1 $[M]^+$ (42), 289.2 (74), 135.1 (100); HRMS calcd for $C_{16}H_{14}BrO_2^+$ ($M - H$)$^+$: 317.01717 and 319.01512, found 317.01644 and 319.01478. Anal. Calcd for $C_{16}H_{15}BrO_2 \cdot 1/12$(hexane) C, 60.72, H, 4.99. Found: C, 60.94, H, 4.63.

1-Ethoxyisochroman. Obtained on 1.0 mmol scale from the competition experiment between anisole and ethanol and purified by flash column chromatography (20:1 hexane/EtOAc) to give 116 mg of 1-ethoxyisochroman as a colorless oil (65%): ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.28 (3H, t, J = 7.1, $H^{2\prime}$), 2.60 (1H, ddd, J = 16.5, 3.2, 1.6, H^4), 3.00 (1H, ddd, J = 16.5, 11.9, 6.1, H^4), 3.63−3.75 (1H, m, H^3, or $H^{1\prime}$), 3.83−3.97 (2H, m, H^3 or $H^{1\prime}$), 4.14 (1H, td, J = 11.5, 3.6, H^3), 5.54 (1H, s, H^1), 7.08−7.23 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 15.5, 28.1, 57.9, 63.6, 96.7, 126.4, 127.5, 128.1, 128.6, 134.2, 124.5; IR, ν_{max}/cm^{-1} 2973, 1158, 1119, 1092, 1072, 1047; MS m/z (APCI) 133 $[M - OCH_2CH_3]^+$ 100%, 177 $[M - H]^+$ 10%. This compound is known. However, ^{1}H and ^{13}C NMR spectroscopic data are not available in the literature.

General Procedure for the Preparation of Substituted Isochromans. Substituted isochromans **1i**−**1l** and **1n** were prepared according to the procedure reported previously.[25]

*3,4-Dihydro-5-methyl-1H-isochromene (**1i**).* Obtained on 0.8 mmol scale (115 mg, 78% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (3 H, s, CH_3), 2.70 (2 H, t, J = 5.7, H^4), 4.00 (2 H, t, J = 5.8, H^3), 4.76 (2 H, s, H^1), 6.82 (1 H, d, J = 7.1, H^{ar}), 7.00−7.10 (2 H, m, H^{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 26.2, 65.6, 68.4, 122.1, 125.8, 127.8, 131.8, 134.9, 136.6; IR ν_{max}/cm^{-1} 2929, 1468, 1424, 1384, 1312, 1234, 1107, 1061, 997, 772. LRMS m/z (%) (APCI) 148.7 $[M + H]^+$ (100). Spectroscopic data match those in the literature.[13f]

*3,4-Dihydro-8-methyl-1H-isochromene and 3,4-dihydro-6-methyl-1H-isochromene (**1j**).* Obtained on 2.4 mmol scale (121 mg, 35% yield): ^{1}H NMR (300 MHz, $CDCl_3$ 3,4-dihydro-8-methyl-1*H*-isochromene is designated by * and 3,4-dihydro-6-methyl-1*H*-isochromene by #) δ 2.13 (3 H, s, CH_3*), 2.30 (3 H, s, $CH_3^{\#}$), 2.80 (2 H, t, J = 5.7, $H^{4\#}$), 2.84 (2 H, t, J = 5.6, H^{4}*), 3.93 (2 H, t, J = 5.7, H^{3}*), 3.95 (2 H, t, J = 5.6, $H^{3\#}$), 4.70 (2 H, s, H^{1}*), 4.73 (2 H, s, $H^{1\#}$), 6.87 (1 H, d, J = 7.7, $H^{ar\#}$), 6.94 (1 H, s, $H^{ar\#}$), 6.95−7.03 (2 H, m, H^{ar}*, 1 H, m, $H^{ar\#}$), 7.08 (1 H, t, J = 7.4, H^{ar}*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 21.2, 28.5, 28.9, 65.0, 65.5, 66.6, 68.0, 124.4, 126.2, 126.7, 126.9, 127.7, 129.5, 132.0, 133.2, 133.3, 133.3, 133.6, 136.0; IR ν_{max}/cm^{-1} 2938, 1469, 1383, 1103, 1058, 987, 778. The procedure used in this paper gave a 3:1 ratio of 8-methyl- to 6-methyl isochromans. A literature report selectively gives the 8-methyl derivative, which matched the major product from the above synthesis.[26] Another literature report,[13f] using an alternative procedure, gives a 1:2 product ratio (i.e., reversed product selectivity).

*4-Methylisochroman (**1k**).* Obtained on 4.5 mmol scale (566 mg, 86% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3 H, d, J = 7.0, CH_3), 2.88−2.98 (1 H, m, H^4), 3.67 (1 H, dd, J = 11.2, 5.4, H^3), 3.97 (1 H, dd, J = 11.2, 4.4, H^3), 4.78 (2 H, d, J = 5.7, H^1), 7.14 (1 H, dd, J = 7.0, 2.0, H^{ar}), 7.17−7.23 (2 H, m, H^{ar}), 7.31−7.35 (1 H, m, H^{ar}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.4, 32,0, 68.5, 71.6, 124.3, 126.1, 126.7, 127.9, 134.4, 138.8; IR ν_{max}/cm^{-1} 2959, 2831, 1490, 1452, 1114, 1059, 756, 730; LRMS m/z (%) (APCI) 148.2 $[M]^+$ (100). Spectroscopic data match those in the literature.[27]

*3,4-Dihydro-6-fluoro-1H-isochromene (**1l**).* Obtained on 1.3 mmol scale (110 mg, 55% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (2 H, t, J = 5.7, H^4), 3.95 (2 H, t, J = 5.7, H^3), 4.73 (2 H, s, H^1), 6.82 (1 H, d, J =8.7, H^{ar}), 6.86 (1 H, dd, J = 8.6, 2.6, H^{ar}), 6.93 (1 H, t, J = 8.4, H^{ar}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.5, 65.1, 67.7, 113.3 (d, J_{C-F} = 21.7), 115.4 (d, J_{C-F} = 20.8), 126.0 (d, J_{C-F} = 8.3), 130.6 (d, J_{C-F} =2.9), 135.4 (d, J_{C-F} = 7.6), 161.4 (d, J_{C-F} =244.2); (NB − peak at 130.6 (smallest J_{C-F} value) arises from carbon lacking attached H, indicating this compound is indeed 6-fluoro- and not 8-fluoro derivative); IR ν_{max}/cm^{-1} 2928, 1434, 1368, 1097, 1058, 1006, 956, 787. LRMS m/z (%) (APCI) 152.9 $[M + H]^+$ (100). Spectroscopic data match those in the literature.[13f]

*5-Bromo-3,4-dihydro-1H-isochromene (**1n**).* Obtained on 7.5 mmol scale (0.83 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (2 H, t, J = 5.6, H^4), 3.99 (2 H, t, J = 5.7, H^3), 4.78 (2 H, s, H^1), 7.05−7.25 (2 H, m, H^{ar}), 7.52 (1 H, d, J = 7.5, H^{ar}); IR ν_{max}/cm^{-1} 2941, 1445, 1387, 1099, 1064, 1008, 956, 780, 753. LRMS m/z (%) (APCI) 212.9 $[M]^+$ (100). Spectroscopic data match those in the literature.[25]

3,4-Dihydro-6-methoxy-1*H*-isochromene (**1m**) and 1-methyl isochroman (**1o**) were prepared according to the procedure reported previously.[28]

*3,4-Dihydro-6-methoxy-1H-isochromene (**1m**).* Obtained on 26 mmol scale (1.02 g, 24% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.83 (2 H, t, J = 5.5, H^4), 3.79 (3 H, s, CH_3), 3.97 (2 H, t, J = 5.6, H^3), 4.72 (2 H, s, H^1), 6.66 (1H, s, H^5), 6.73 (1H, dd, J = 8.4, 2.4, H^6), 6.89 (1H, d, J = 8.4, H^7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 55.2, 65.2, 67.6, 112.3, 113.5, 125.4, 127.0, 134.4, 158.0; IR ν_{max}/cm^{-1}, 2934, 1610, 1503, 1464, 1382, 1312, 1272, 1243, 1096, 1034, 851; LRMS m/z (%) (APCI) 162.9 $[M - H]^+$ (100). Spectroscopic data match those in the literature.[13f]

*Preparation of 1-Methyl Isochroman (**1o**).* Obtained on 16 mmol scale (0.61 g, 33% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (3 H, d, J = 6.5, CH_3), 2.69 (1 H, td, J = 16.3, 3.3, H^3), 3.03 (1 H, ddd, J = 16.2, 10.1, 5.7, H^3), 3.80 (1 H, ddd, J = 11.3, 10.1, 3.7, H^4), 4.15 (1 H, ddd, J = 11.3, 5.6, 3.3), 4.86 (1 H, q, J = 6.5, H^1), 7.06 − 7.19 (4 H, m, H^{arm}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 29.1, 63.6, 72.3, 124.7, 126.1, 126.2, 128.8, 133.4, 139.6.; IR ν_{max}/cm^{-1} 3031, 2927, 1451, 1372, 1292, 1264, 1170, 1114, 756; LRMS m/z (%) (APCI) 146.9 $[M - H]^+$ (100). Spectroscopic data match those in the literature.[29]

General Procedure for the Preparation of Substituted Anisoles. Substituted anisoles **2b**−**f** were prepared according to the procedure reported previously.[30]

*2-Methylanisole (**2b**).* Obtained on 20 mmol scale (1.41 g, 58% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (3 H, s, CCH_3), 3.83 (3 H, s, OCH_3), 6.81 − 6.88 (2 H, m, H^{arm}), 7.12 − 7.18 (2 H, m, H^{arm}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.2, 55.2, 109.9, 126.6, 126.6, 130.6, 157.7; IR ν_{max}/cm^{-1} 2950, 2835, 1602, 1591, 1494, 1465, 1239; LRMS m/z (%) (APCI) 122.9 $[M + H]^+$ (35), 107.9 $[M - CH_3]^+$. (100). Spectroscopic data match those in the literature.[31]

*3-Methylanisole (**2c**).* Obtained on 20 mmol scale (1.38 g, 56% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (3 H, s, CCH_3), 3.79 (3 H, s, OCH_3), 6.70 − 6.78 (3 H, m, H^{arm}), 7.14 − 7.17 (1 H, t, J = 7.7, H^{arm}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 55.1, 110.8, 114.7, 121.1, 129.1, 139.4, 159.6; IR ν_{max}/cm^{-1} 2952, 2920, 2835, 1602, 1585, 1489, 1463, 1289, 1151; LRMS m/z (%) (APCI) 122.9 $[M + H]^+$ (43), 107.9 $[M - CH_3]$ (100). Spectroscopic data match those in the literature.[32]

*2-Bromoanisole (**2d**).* Obtained on 5.0 mmol scale (0.87 g, 93%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.90 (3 H, s, CH_3), 6.81 (1 H, dt, J = 7.6, 1.3, H^{arm}), 6.90 (1 H, dd, J = 8.3, 1.3, H^{arm}), 7.27 (1 H, m, H^{arm}), 7.54 (1 H, dd, J = 7.8, 1.6, H^{arm}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.1 111.7, 112.0, 121.8, 128.5, 133.3, 155.9; IR ν_{max}/cm^{-1}, 2838, 1586, 1479, 1247, 1053, 1021. Spectroscopic data match those in the literature.[33]

*1-Methoxynaphthalene (**2e**).* Obtained on 50 mmol scale (7.2 g, 91% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (3 H, s, CH_3), 6.69 (1 H, d, J = 7.5, H^{ar}), 7.25−7.45 (4 H, m, H^{ar}), 7.72−7.75 (1 H, m, H^{ar}), 8.23−8.27 (1 H, m, H^{ar}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.4, 103.9, 120.3, 122.1, 125.3, 125.8, 126.0, 126.5, 127.6, 134.6, 155.6; IR ν_{max}/cm^{-1} 3053, 2955, 1580, 1462, 1393, 1266, 1237, 1101, 1068, 789, 765, 712. LRMS m/z (%) (APCI) 158.1 $[M]^+$ (65). Spectroscopic data match those in the literature.[34]

*2-Methoxynaphthalene (**2f**).* Obtained on 50 mmol scale (6.8 g, 86% yield): mp 72−74 °C (lit.[35] 73−74 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (3 H, s, CH_3), 7.11−7.17 (2 H, m, H^{ar}), 7.29−7.34 (1 H, m, H^{ar}), 7.39−7.45 (1H, m, H^{ar}), 7.70−7.77 (3 H, m, H^{ar}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.4, 105.9, 118.8, 123.7, 126.5, 126.8, 127.8, 129.1, 129.5, 134.7, 157.7; IR ν_{max}/cm^{-1} 3056, 2960, 1630, 15997, 1470, 1263, 1220, 1172, 1029, 839, 816, 745. LRMS m/z (%)

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(APCI) 158.1 $[M]^+$ (100). Spectroscopic data match those in the literature.[36]

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for all novel compounds and crystallographic information in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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