Boronic acid/Brønsted acid co-catalyst systems for the synthesis of 2H-chromenes from phenols and α,β-unsaturated carbonyls†

Victoria Dimakos, Tishaan Singh and Mark S. Taylor*

Protocols for the synthesis of substituted 2H-chromenes from α,β-unsaturated carbonyls and phenols are described. Optimal combinations of arylboronic acids and Brønsted acids have been identified, such that both can be employed in catalytic quantities to accelerate these condensations. The method has been used to synthesize a variety of substituted 2H-chromenes, as well as photochromic naphthopyrans. The use of pentafluorophenylboronic acid and diphenylphosphinic acid enabled an expansion of the electrophilic scope to include α,β-unsaturated ketones. Hall’s ‘phase-switching’ of boronic acids has been exploited to achieve the separation of the two co-catalysts from unpurified reaction mixtures by a simple liquid–liquid extraction.

Introduction

The 2H-chromene ring system is a core structure of numerous biologically active natural products, and its annelated congeners (naphthopyrans and related structures) display useful photochromic properties. Several methods exist for the synthesis of 2H-chromenes, enabling access to a variety of substitution patterns. Transition metal-catalyzed transformations have been exploited for 2H-chromene synthesis include alkyne hydroarylation, allylic substitution and olefin metathesis. Approaches based on Brønsted or Lewis acid-catalyzed condensations or cyclizations have also been reported.

Boronic acid-promoted condensations of phenols with α,β-unsaturated carbonyl compounds provide access to 2H-chromenes from readily available starting materials (Scheme 1). This mode of reactivity was initially reported by scientists at Merck, and was further developed into a general method for 2H-chromene synthesis by Snieckus and co-workers. The likely reaction pathway involves formation of a benzodioxaborinine intermediate by Nagata alkylation, followed by fragmentation to an ortho-quinone methide and electrocyclic ring closure. Over the years, boronic acid-mediated condensations of this type have been applied to the synthesis of several classes of benzopyran-based natural products.

The protocol for boronic acid-promoted 2H-chromene synthesis has changed relatively little since Dufresne’s initial report more than two decades ago. This described the use of 1.6 equivalents of phenylboronic acid (PhB(OH)2) and 30 mol% of propionic acid relative to phenol, with removal of water by azotropic reflux in toluene using a Dean–Stark trap. Snieckus and co-workers reported similar conditions, employing 1 equivalent of PhB(OH)2 and an excess (>85 equiv.) of acetic acid, also in toluene with a Dean–Stark apparatus. A survey of Brønsted acids (including carboxylic acids, sulfonic acids and H2SO4) was carried out in 2007, revealing that propionic acid (1 equiv.) and acetic acid (1 equiv. of PhB(OH)2 in toluene at reflux) provided best results for the coupling of umbelliferone and 3-methyl-2-butenal (1 equiv. of PhB(OH)2 in toluene at reflux). Each of these studies points towards the combination of stoichiometric phenylboronic acid and a carboxylic acid promoter.

Although the thermolysis of the benzodioxaborinine intermediate provides a pathway for catalyst turnover, examples of...
protocols that employ substoichiometric quantities of arylboronic acid are scarce. Wilson and co-workers showed that 25 mol% of PhB(OH)2 was able to promote the condensation of phloroglucinol with 3-methyl-2-butenal, yielding a mixture of bis- and tris-annulated products (39% and 55% yields, respectively, for a total of >9 turnovers).17 As part of the synthesis of a series of pyranocarbazole alkaloids, Knölker’s group found that condensations of citral with a hydroxycarbazole could be achieved in 75% yield using 20 mol% of PhB(OH)2 in toluene at reflux.15 Another relevant study by McCubbin showed that pentafluorophenylboronic acid (10 mol%) was able to catalyse condensations of 2-naphthol with propargylic alcohols, generating substituted naphthopyran products.18

These same conditions were used to effect Friedel–Crafts propargylations of other electron-rich aromatics, and it is not clear whether there is a direct mechanistic connection to the above-mentioned phenol–enal annihilations. In any case, it appeared to us that evaluating a range of organoboron acid and Brønsted acid catalysts might be an opportunity to improve the efficiency or expand the scope of such condensations, especially given the impressive progress that has been achieved in the development of ‘designer’ boronic acids for use in catalysis in recent years.14,19

Here, we describe a systematic evaluation of organoboron acid/Brønsted acid combinations for the synthesis of 2H-chromenes from phenols and α,β-unsaturated carbonyl compounds. By variation of the two promoters, we have developed efficient and operationally simple protocols in which both are employed in catalytic quantities. These conditions have been applied to a range of reaction partners, including α,β-unsaturated ketones as well as aldehydes.

Results and discussion

3-Methoxyphenol (2a) and enone 3a were chosen as the substrates for evaluation of organoboron acid and Brønsted acid co-catalysts (Table 1). Previous reports of boronic acid-promoted 2H-chromenes from phenols and α,β-unsaturated carbonyl compounds. By variation of the two promoters, we have developed efficient and operationally simple protocols in which both are employed in catalytic quantities. These conditions have been applied to a range of reaction partners, including α,β-unsaturated ketones as well as aldehydes.

### Table 1 Catalyst optimization for the synthesis of 2H-chromene 4a

| Entry | Organoboron acid | Brønsted acid HX | Yielda |
|-------|------------------|------------------|-------|
| 1     | Ph2BOH           | —                | <5%   |
| 2     | 1a               | —                | 5%    |
| 3     | Ph2BOH           | PhCO2H           | 15%   |
| 4     | 1a               | PhCO2H           | 30%   |
| 5     | PhB(OH)2         | PhCO2H           | 20%   |
| 6     | 1b               | PhCO2H           | 30%   |
| 7     | 1c               | PhCO2H           | 40%   |
| 8     | 1d               | PhCO2H           | 45%   |
| 9     | 1e               | PhCO2H           | 45%   |
| 10    | PhB(OH)2         | CH2=CHCO2H       | 10%   |
| 11    | PhB(OH)2         | Ph2POH           | 60%   |
| 12    | PhB(OH)2         | CH2=CHCO2H       | 60%   |
| 13    | 1c               | Ph2POH           | 70%   |
| 14    | 1c               | CSA              | <5%   |
| 15    | 1e               | CH2=CHCO2H       | 15%   |
| 16    | 1e               | Ph2POH           | 70%   |

a Determined by 1H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. Reactions were carried out under inert atmosphere.

We began by testing diarylborinic acids R2BOH: these are more Lewis acidic than the corresponding boronic acids RB (OH)2, and are useful catalysts for several types of transformations, including carbon–carbon21 and carbon–heteroatom bond-forming reactions,22 dehydrations23 and oxidations.24 However, both Ph2BOH and oxaboraanthracene-derived borinic acid 1a showed only modest activity: yields of 4a were low (≤5%) in the absence of a Brønsted acid (entries 1 and 2), and were not significantly different from that obtained with PhB(OH)2 when benzoic acid was employed as a co-catalyst (entries 3–5). On the other hand, an improvement in yield was achieved using more Lewis acidic arylboronic acids 1c–1e (entries 7–9). Several Brønsted acids, including carboxylic, phosphinic and sulfonic acids, were then surveyed (entries 10–16). Diphenylphosphinic acid provided superior results to propionic and benzoic acid, whereas the use of the stronger acid camphorsulfonic acid (CSA) resulted in decomposition. Although further mechanistic study is needed to make a definitive conclusion on this point, we speculate that increasing the acidity of both the boronic acid and Brønsted acid components (relative to the original PhB(OH)2/carbonic acid system) accelerates the addition of the phenol to the rather poorly electrophilic enone. It should be noted that the yields reported in Table 1 are for reactions carried out under an inert argon atmosphere. Inferior results were obtained when air was not excluded. However, azeotropic removal of water using a Dean–Stark apparatus was not required under this protocol.

Having identified the combination of pentafluorophenylboronic acid and diphenylphosphinic acid (20 mol%) each as being optimal, we investigated the scope of this process (Scheme 2). Enones 3a–3e were successfully coupled with 3-methoxyphenol and 1-naphthol, yielding 2,4-disubstituted and 2,2,4-trisubstituted 2H-chromene products. These were obtained in high levels of purity after column chromatography on silica gel, with the exception of products 4f and 4g, which were isolated along with small amounts (<10%) of the corresponding 4-methylenecromene regioisomers.

Condensations of α,β-unsaturated aldehydes with phenols were also investigated under boronic acid/Brønsted acid co-catalysis (Scheme 3). Unlike the aforementioned reactions with enones, syntheses of 2H-chromenes from α,β-unsaturated alde-
Hydes did not require an argon atmosphere, and benzoic acid (rather than Ph$_2$PO$_2$H) was found to be the most suitable Brønsted acid catalyst. Variation in the identity of the optimal boronic acid was also observed. The parent PhB(OH)$_2$ was able to promote condensations of activated phenols, and provided superior results in cases where electron-deficient (1c) promoted decomposition of the phenol (2a) or aldehyde (5b) component. On the other hand, 1c displayed higher activity than Ph$_2$BOH for condensations of less nucleophilic phenols (2b and 2g–2i).

When unsubstituted phenol was subjected to these conditions, little to no product was observed.

To establish the preparative utility of this method, we undertook the synthesis of naphthopyran 6g on gram scale (5 mmol). For this larger-scale experiment, we took advantage of the ‘phase-switching’ protocol developed by Hall and co-workers. This technique uses simple liquid–liquid extractions to separate boronic acids from other organic compounds, based on the pH-switchable solubility of boronic acids in aqueous sorbitol solution (increased solubility at high pH due to formation of a tetracoordinate boronate ester). In the present case, working up the reaction mixture by extraction with basic aqueous sorbitol solution resulted in a straightforward separation of the product (organic phase) from the arylboronic acid and carboxylic acid components (aqueous phase). The product was purified by elution through a short plug of silica gel, while the catalyst mixture was recovered after acidification and extraction of the aqueous sorbitol solution (Scheme 4). The recovered catalyst mixture was re-used without further purification in a second gram scale synthesis, affording 6g in 70% yield.

Scheme 2 Condensations of α,β-unsaturated ketones with phenol derivatives. Reaction conditions: phenol (0.2 mmol), enone (0.4 mmol), 1e (20 mol%), Ph$_2$PO$_2$H (20 mol%) in heptane (1 mL) at 100 °C for 3 h under argon. Isolated yields after purification by chromatography on silica gel are listed. Products 4f and 4g were obtained as mixtures of endocyclic and exocyclic olefin isomers.

Scheme 3 Condensations of α,β-unsaturated aldehydes with phenol derivatives. Reaction conditions: phenol (0.5 mmol), aldehyde (1.0 mmol), ArB(OH)$_2$ (5–20 mol%), PhCO$_2$H (20 mol%), in heptane (2.5 mL) at 60–100 °C for 17 h. For details, see the Experimental section. Isolated yields after purification by chromatography on silica gel are listed. PhB(OH)$_2$ was used as the catalyst. 1c was used as the catalyst. The reaction was carried out using 6.0 equiv. of 5a. Ph$_2$PO$_2$H (10 mol%) was used as the Bronsted acid co-catalyst.

Scheme 4 Separation of co-catalysts from naphthopyran product by phase-switching.
Hall and co-workers have shown that electron-deficient boronic acids catalyze the Meyer–Schuster rearrangement of propargylic alcohols to α,β-unsaturated compounds. We envisioned that an in situ rearrangement of this type could enable the synthesis of 2H-chromene derivatives from propargylic alcohols under our optimized reaction conditions. To test this idea, we investigated condensations of 2-naphthol with readily available 1,1-diarylp propane-1-ol derivatives as a way to access gem-diaryl substituted naphthopyran products (Scheme 5). The latter have been studied extensively for applications in ophthalmic lenses due to their useful photochromic properties. Using 20 mol% each of 1H and benzoic acid, naphthopyran 6l was generated from 2-naphthol and propargylic alcohol 7a. The yield of this process was comparable to that obtained from enal 5d (Scheme 3), and the isomerization of 7a to 5d was evident upon monitoring the condensation reaction by thin layer chromatography. In a similar way, the photochromic and solvatochromic naphthopyran 6m was synthesized from 7b. As mentioned in the introduction, McCubbin and co-workers have also developed condensations of 2-naphthol with propargylic alcohols, using pentafluorophenylboronic acid and 4 A molecular sieves in dichloromethane at room temperature. Propargylic alcohols having a (trimethylsilyl) alkynyl or phenylalkynyl group, rather than a terminal alkynyl group, were employed. The proposed mechanism involved Friedel–Crafts allenylation followed by cyclization through addition of the phenol group across the terminal carbon–carbon double bond. Subjecting compound 7a and 2-naphthol to these conditions resulted in appreciable consumption of 7a (approximately 55% conversion), but only a 10% yield of naphthopyran 6l (conversion and yield were determined by 1H NMR with an internal standard). Thus, these superficially similar protocols appear to differ in scope, and may proceed by different mechanisms.

Conclusions

Through variation of the arylboronic acid and Brønsted acid components, we have identified combinations that show optimal catalytic activity for 2H-chromene synthesis via condensations of phenols and α,β-unsaturated carbonyls. The use of an electron-deficient boronic acid (C6F5B(OH)2 or 3,5-(CF3)2C6H4B(OH)2), in concert with diphenylphosphinic acid, is particularly effective for condensations of less reactive substrates such as α,β-unsaturated ketones or non-activated phenols. Hall’s ‘phase-switching’ protocol has been used to achieve a convenient separation of both catalyst components from unpurified reaction mixtures by a simple liquid–liquid extraction.

Experimental

General methods

Reactions were carried out without effort to exclude air or moisture, unless otherwise indicated. Stainless steel needles and syringes were used to transfer air- and moisture-sensitive liquids. Flash chromatography was carried out using neutral silica gel (60 Å, 230–400 mesh, Silicycle). Analytical thin layer chromatography was carried out using aluminum-backed silica gel 60 F254 plates (EMD), and compounds were visualized through the use of UV light or basic KMnO4 stain. HPLC grade THF was dried and purified using a solvent purification system equipped with columns of activated alumina, under nitrogen (Innovative Technology, Inc.). Anhydrous heptane was purchased from Sigma Aldrich. Distilled water was obtained from an in-house supply. All other solvents and reagents were purchased from Sigma Aldrich or Alfa Aesar and used without further purification. Screw cap test tubes were purchased from Pyrex® (13 mm × 100 mm, mfr. no. = Corning, 9825-13).

Nuclear magnetic resonance (NMR) solvents were purchased from Sigma Aldrich or Alfa Aesar and used without correction for the mass of the electron. Infrared (IR) spectra were recorded on a JASCO FTIR T6000 spectrometer equipped with a DART (direct analysis in real time) ion source, and are not corrected for the mass of the electron. Infrared (IR) spectra were obtained on a Perkin-Elmer Spectrum 100 instrument equipped with a single-bounce diamond/ZnSe ATR accessory as solids or thin films, as indicated. Spectral features are tabulated as follows: wavenumber (cm–1); intensity (s-strong, m-medium, w-weak).

General procedure A: condensations of phenols and naphthols with α,β-unsaturated ketones. An oven-dried 25 mL Schlenk tube equipped with a teflon-coated magnetic stir bar was evacuated and purged with argon. The phenol (0.2 mmol), pentafluorophenylboronic acid (8.5 mg, 0.04 mmol, 20 mol%), diphenylphosphinic acid (8.7 mg, 0.04 mmol, 20 mol%), α,β-unsaturated ketone (0.4 mmol) and heptane (1 mL) were added to the tube under argon. The tube was evacuated and back-filled three times with argon after addition of the solid reagents and prior to the addition of the liquid reagents. The tube was capped, sealed and stirred at 100 °C for three hours. The tube was then cooled to room temperature and the...
mixture was concentrated in vacuo. The resulting crude material was purified by flash chromatography on silica gel.

**General procedure B: condensations of phenols and naphthols with α,β-unsaturated aldehydes.** To a screw cap test tube equipped with a teflon-coated magnetic stir bar were added phenol (0.5 mmol), arylboronic acid (5-20 mol%), Bronsted acid (20 mol%), α,β-unsaturated aldehyde (1.0 mmol) and heptane (2.5 mL). The tube was capped in ambient atmosphere and stirred at 60–100 °C. The catalyst loading and reaction temperature for each substrate combination are provided below. After 17 hours, the mixture was concentrated in vacuo and the resulting crude material was purified by flash chromatography on silica gel.

7-Methoxy-4-methyl-2-propyl-2H-chromene (4a). Synthesized according to general procedure A, from 3-methoxyphenol (24.7 mg, 0.20 mmol) and 3-heptene-2-one (47.6 mg, 0.42 mmol). Isolated as a pale yellow oil after flash chromatography on silica gel, eluting with 2% diethyl ether/hexanes (47.6 mg, 70%). **1H NMR (500 MHz, C$_6$D$_6$)$_2$: $\delta$ 6.95 (d, $J = 8.4$ Hz, 1H), 6.65 (d, $J = 2.6$ Hz, 1H), 6.49 (dd, $J = 8.4$, 2.6 Hz, 1H), 5.10 (dq, $J = 3.0$, 1.4 Hz, 1H), 4.72 (dddq, $J = 7.9$, 4.9, 3.3, 1.7 Hz, 1H), 3.28 (s, 3H), 1.80 (dd, $J = 1.6$, 1.6 Hz, 3H), 1.77–1.69 (m, 1H), 1.59–1.32 (m, 4H), 0.84 (dd, $J = 7.3$, 7.2 Hz, 3H). **13C NMR (126 MHz, C$_6$D$_6$)$_2$: $\delta$ 161.4, 155.9, 129.7, 124.6, 120.1, 117.5, 107.1, 102.2, 75.4, 54.8, 38.1, 18.6, 18.6, 18.1, 14.2, 14.2.** IR (neat, cm$^{-1}$): 3031 (w), 2999 (w), 2917 (w), 2835 (w), 1652 (w), 1612 (w), 1570 (s), 1504 (s), 1443 (m), 1379 (m), 1311 (m), 1275 (m), 1194 (m), 1159 (s), 1145 (s), 1132 (s), 1067 (m), 1031 (s), 809 (m). HRMS (DART-TOF, $m/z$): Calculated for C$_{12}$H$_{14}$O$_2$ [M + H$^+$$]$: 219.1385. Found: 219.1383.

4-Methyl-2,2-diphenyl-2H-naphtho[1,2-b]pyran (4c). Synthesized according to general procedure A, from 1-naphthol (29.1 mg, 0.20 mmol) and trans-chalcone (83.6 mg, 0.40 mmol). Isolated as a pale yellow solid after flash chromatography on silica gel, eluting with 2% diethyl ether/hexanes (50.6 mg, 75%). **1H NMR (500 MHz, C$_6$D$_6$)$_2$: $\delta$ 8.49–8.43 (m, 1H), 7.56–7.53 (m, 1H), 7.47–7.44 (m, 2H), 7.33–7.29 (m, 3H), 7.27–7.17 (m, 5H), 7.14–7.10 (m, 2H), 7.08–7.04 (m, 1H), 5.88 (d, $J = 3.7$ Hz, 1H), 5.65 (d, $J = 3.7$ Hz, 1H). **13C NMR (126 MHz, C$_6$D$_6$)$_2$: $\delta$ 150.2, 141.4, 138.9, 137.8, 135.2, 129.2, 128.9, 128.7, 128.5, 128.1, 128.0, 127.3, 127.0, 126.0, 125.5, 123.8, 122.9, 122.3, 120.7, 117.6, 77.6. IR (neat, cm$^{-1}$): 3057 (w), 2922 (w), 2851 (w), 1638 (w), 1615 (w), 1599 (w), 1562 (w), 1494 (w), 1454 (w), 1385 (m), 1345 (m), 1298 (m), 1257 (m), 1209 (m) 1096 (m), 953 (m), 808 (s), 748 (s), 695 (s). HRMS (DART-TOF, $m/z$): Calculated for C$_{21}$H$_{19}$O$_3$ [M + H$^+$$]$: 335.1436. Found: 335.1438.
(w), 1389 (m), 1377 (m), 1259 (m), 1205 (m), 1092 (m), 1074 (m), 947 (m), 811 (s), 739 (s), 695 (s), 678 (m). HRMS (DART-TOF, m/z): δ 273.1279. Found: 273.1279. 

**2,2,4-Trimethyl-2H-naphtho[1,2-b]pyran (4g).** Synthesized according to general procedure A, from 1-naphthol (28.8 mg, 0.20 mmol) and mesityl oxide (39.3 mg, 0.40 mmol). Isolated as a pale yellow oil after flash chromatography on silica gel, eluting with 2% diethyl ether/hexanes. The title compound was isolated as an inseparable mixture of regioisomers (14:1, 1H NMR) (21.4 mg, 48%).

**1H NMR (500 MHz, CDCl$_3$):** δ 8.51–8.49 (m, 1H), 7.66–7.63 (m, 1H), 7.34–7.29 (m, 2H), 7.26 (dd, δ = 8.1, 6.8, 1.4 Hz, 1H), 7.23 (d, δ = 8.5 Hz, 1H), 5.12 (q, δ = 1.5 Hz, 1H), 1.84 (d, δ = 1.5 Hz, 3H), 1.35 (s, 6H). **13C NMR (125 MHz, CDCl$_3$):** δ 148.9, 135.0, 128.6, 127.9, 126.0, 125.8, 125.6, 122.9, 121.8, 120.0, 117.4, 76.6, 28.0, 18.3. IR (neat, cm$^{-1}$): 3056 (w), 2973 (w), 2923 (w), 2855 (w), 1657 (w), 1619 (w), 1565 (w), 1508 (w), 1499 (w), 1377 (s), 1358 (m), 1279 (m), 1208 (m), 1158 (m), 1146 (m), 1077 (s), 951 (m), 924 (m), 815 (s), 799 (s), 744 (s), 685 (m). HRMS (DART-TOF, m/z): Calculated for C$_{16}$H$_{17}$O$_{1}$ [(M + H)$^+$]: 225.1279. Found: 225.1279.

**5,7-Dimethoxy-2,2-dimethyl-2H-chromene (6d).** Synthesized according to general procedure B, from 3,5-dimethoxyphenol (78.6 mg, 0.51 mmol) and 3-methyl-2-butenal (100 µl, 1.0 mmol) using phenylboronic acid (5 mol%) and benzoic acid (20 mol%) at 100 °C. Isolated as a pale yellow oil after flash chromatography on silica gel, eluting with 1-2% EtOAc/pentane (109.4 mg, 97%). Spectral data were in agreement with previous reports. **1H NMR (500 MHz, CDCl$_3$):** δ 6.59 (dd, δ = 9.9, 0.7 Hz, 1H), 6.03 (dd, δ = 2.3, 0.7 Hz, 1H), 6.01 (d, δ = 2.3 Hz, 1H), 5.42 (d, δ = 9.9 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 1.41 (s, 6H). **13C NMR (125 MHz, CDCl$_3$):** δ 161.1, 156.3, 154.8, 126.0, 116.8, 104.3, 94.1, 91.6, 76.4, 55.7, 55.5, 27.9.

**2,2,6,10,10-Hexamethylyl-2H-1H-dipyrano[6,5-f,6′,5′-h]chromene (6e).** Synthesized according to general procedure B, from 1,3,5-trihydroxybenzene (60.8 mg, 0.48 mmol) and 3-methyl-2-butenal (300 µl, 3.0 mmol) using phenylboronic acid (20 mol%) and benzoic acid (20 mol%) at 100 °C. Isolated as a pale yellow solid after flash chromatography on silica gel, eluting with 0.5–1% EtOAc/pentane (133.3 mg, 85%). Spectral data were in agreement with previous reports.

**6-Methoxy-2,2-dimethyl-2H-chromene (6f).** Synthesized according to general procedure B, from 4-methoxyphenol (60.2 mg, 0.5 mmol) and 3-methyl-2-butenal (100 µl, 1.0 mmol) using 3,5-bis(trifluoromethyl)phenylboronic acid (20 mol%) and diphenyolphosphinic acid (10 mol%) at 100 °C. Isolated as a pale yellow oil after flash chromatography on silica gel, eluting with 0.5–1% EtOAc/pentane (70.5 mg, 76%). Spectral data were in agreement with previous reports. **1H NMR (400 MHz, CDCl$_3$):** δ 6.71 (d, δ = 8.7 Hz, 1H), 6.66 (dd, δ = 8.7, 2.9 Hz, 1H), 6.55 (d, δ = 2.8 Hz, 1H), 6.28 (d, δ = 9.8 Hz, 1H), 5.64 (d, δ = 9.8 Hz, 1H), 3.75 (s, 3H), 1.41 (s, 6H). **13C NMR (100 MHz, CDCl$_3$):** δ 153.9, 146.9, 131.9, 122.5, 122.0, 116.9, 114.3, 111.6, 75.9, 55.9, 27.8.

**2,2-Dimethyl-2H-naphtho[1,2-b]pyran (6g).** Synthesized according to general procedure B, from 1-naphthol (72.9 mg, 0.5 mmol) and 3-methyl-2-butenal (100 µl, 1.0 mmol) using 3,5-bis(trifluoromethyl)phenylboronic acid (20 mol%) and benzoic acid (20 mol%) at 60 °C. Isolated as a pale yellow oil after flash chromatography on silica gel, eluting with 0.5–1% EtOAc/pentane (98.6 mg, 93%). Spectral data were in agreement with previous reports. **1H NMR (400 MHz, CDCl$_3$):** δ 8.24–8.18 (m, 1H), 7.76–7.70 (m, 1H), 7.47–7.39 (m, 2H), 7.34
(d, J = 8.3 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.45 (d, J = 9.7 Hz, 1H), 5.64 (d, J = 9.7 Hz, 1H), 1.53 (s, 6H). 13C NMR (100 MHz, CDCl3): δ 148.4, 134.6, 129.4, 127.7, 126.2, 125.3, 125.2, 124.6, 122.9, 122.1, 119.9, 115.5, 76.9, 28.1.

**Gram scale synthesis of 2,2-dimethyl-2H-naphtho[1,2-b]pyran (6g).** An oven-dried 100 mL round bottomed flask equipped with a teflon-coated magnetic stir bar was charged with 1-naphthol (720.1 mg, 5 mmol), 3-methyl-2-butanol (0.97 mL, 10 mmol), bis[trifluoromethyl]phenylboronic acid (257.9 mg, 20 mol%), benzoic acid (121.8 mg, 20 mol%) and heptane (25 mL). The reaction mixture was stirred at 60 °C for 17 hours. The mixture was then cooled to room temperature, diluted with ethyl acetate (50 mL) and then transferred to a separatory funnel to which a 75 mL of a sorbitol : Na2CO3 (1 M : 1 M) solution. The organic phase was then dried with MgSO4, filtered and concentrated in vacuo to give the title compound as a pale yellow oil (947.5 mg, 90%).

5,7-Dimethoxy-flav-3-ene (6j). Synthesized according to general procedure B, from 3,5-dimethoxyphenol (76.5 mg, 0.5 mmol) and trans-cinnamaldehyde (130 µL, 1.0 mmol) using phenylboronic acid (5 mol%) and benzoic acid (20 mol%) at 100 °C. Isolated as a viscous yellow oil after flash chromatography on silica gel, eluting with 1–2% EtOAc/pentane (108.6 mg, 81%). Spectral data were in agreement with previous reports.9 1H NMR (400 MHz, CDCl3): δ 7.79–7.44 (m, 2H), 7.40–7.29 (m, 3H), 6.81 (ddd, J = 10.0, 1.9, 0.6 Hz, 1H), 6.06 (d, J = 2.2 Hz, 1H), 6.03 (d, J = 2.3 Hz, 1H), 5.83 (ddd, J = 3.4, 1.9 Hz, 1H), 5.62 (dd, J = 9.9, 3.5 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H). HRMS (DART-TOF+, m/z): Calculated for C17H17O3 [(M + H)+]: 269.1174. Found: 269.1178.

7-Methoxy-2-propyl-2H-chromene (6k). Synthesized according to general procedure B, from 3-methoxyphenol (62.2 mg, 0.5 mmol) and trans-2-hexen-1-ol (120 µL, 1.0 mmol) using phenylboronic acid (20 mol%) and benzoic acid (20 mol%) at 100 °C. Isolated as a pale yellow oil after flash chromatography on silica gel, eluting with 0.5–1% EtOAc/pentane (83.5 mg, 82%). Spectral data were in agreement with previous reports.10 1H NMR (400 MHz, CDCl3): δ 6.86 (d, J = 8.2 Hz, 1H), 6.40 (dd, J = 8.2, 2.5 Hz, 1H), 6.37 (d, J = 2.5 Hz, 1H), 6.34 (dd, J = 9.9, 1.4 Hz, 1H), 5.54 (ddd, J = 9.8, 3.3 Hz, 1H), 4.83 (ddd, J = 6.8, 5.0, 3.4, 1.7 Hz, 1H), 3.77 (s, 3H), 1.83–1.74 (m, 1H), 1.68–1.40 (m, 3H), 0.96 (t, J = 7.3 Hz, 3H). 13C NMR (100 MHz, CDCl3): δ 160.7, 155.0, 127.2, 123.6, 123.2, 115.5, 106.8, 102.0, 75.2, 55.4, 37.7, 18.2, 14.1. HRMS (DART-TOF+, m/z): Calculated for C19H20O [(M + H)+]: 205.1234. Found: 205.1228.

3,3-Diphenyl-[3H]-naphtho-[2,1-b]pyran (6l). To a 2-dram vial equipped with a teflon-coated magnetic stir bar was added 2-naphthol (28.8 mg, 0.2 mmol), β-phenylcinnamaldehyde (83.3 mg, 0.4 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (20 mol%) and benzoic acid (20 mol%) and heptane (1 mL). The reaction mixture was stirred at 80 °C for 17 hours, after which the mixture was cooled to room temperature and then concentrated in vacuo. The resulting crude material was purified by silica gel chromatography (1–2% EtOAc/hexanes) to afford the title compound in as a white solid (75%, 50 mg). Spectral data were in agreement with previous reports.11 1H NMR (500 MHz, CDCl3): δ 7.96 (d, J = 8.5 Hz, 1H), 7.73–7.69 (m, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.52–7.42 (m, 5H), 7.35–7.28 (m, 6H), 7.27–7.23 (m, 2H), 7.20 (dd, J = 8.8, 0.7 Hz, 1H), 6.27 (d, J = 10.0 Hz, 1H). 13C NMR (126 MHz, CDCl3): δ 150.7, 145.0, 130.0, 130.0, 129.5, 128.2, 127.7, 127.2, 126.7, 123.7, 121.5, 119.7, 118.5, 114.1, 82.7.

3,3-Bis[4-(N,N-dimethylamino)phenyl]-3-naphtho[2,1-b]pyran (6m). To a 2-dram vial equipped with a teflon-coated magnetic stir bar was added 2-naphthol (21.0 mg, 0.146 mmol), 1,1-bis[4-(dimethylamino)phenyl]prop-2-yn-1-ol (83.8 mg, 0.29 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (20 mol%) and benzoic acid (20 mol%) and heptane (0.73 mL). The reaction mixture was stirred at 80 °C for 17 hours, after which the mixture was cooled to room tempera-
tured and then concentrated in vacuo. The resulting crude material was purified by silica gel chromatography (20% EtOAc/hexanes) to afford the title compound in as an off white solid (53%, 61.4 mg, Rf = 0.4 (30% EtOAc/hexanes). Spectral data were in agreement with previous reports.37 1H NMR (500 MHz, CDCl3): δ 7.97–7.92 (m, 1H), 7.71–7.67 (m, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.46–7.40 (m, 1H), 7.34 (d, J = 8.5 Hz, 4H), 7.30–7.26 (m, 1H), 7.25 (d, J = 10.0 Hz, 1H), 7.16 (dd, J = 8.8, 0.7 Hz, 1H), 6.67 (s, 4H), 6.21 (d, J = 9.9 Hz, 1H), 2.92 (s, 12H).

4,4-Diphenylbut-3-en-2-one (3d). Prepared according to a modified literature procedure.33 Zinc dust (<10 μm, 600 mg, 6.5, 1.3 eq.) was added to a flask containing 4 mL of 2 M HCl (30 minutes) and stirred vigorously until the surface of the zinc became lustrous. The aqueous solution was decanted and the zinc powder was washed by successive decantation with H2O (4× 10 mL). The powder was then washed successively with MeOH (2 mL), acetone (4 mL) and dry THF (2 mL) and quickly transferred to an oven dried round bottomed flask. The powder was dried under vacuum for 20 minutes, after which the flask was filled with argon. A solution of benzophenone (908 mg, 5 mmol, 1 eq.) and propargyl bromide (80 wt% in toluene, 2 mL), acetone (4 mL) and dry THF (2 mL) and quickly transferred to an oven dried round bottomed flask. The powder was dried under vacuum for 20 minutes, after which the flask was filled with argon. A solution of benzophenone (908 mg, 5 mmol, 1 eq.) and propargyl bromide (80 wt% in toluene, 0.9 mL, 7.8 mmol, 1.6 eq.) in dry THF was prepared in an oven dried round bottomed flask that was evacuated and backfilled with argon. The solution was then added to the activated zinc powder at 0 °C with vigorous stirring at room temperature. After three hours, the reaction mixture was poured into ice water and a 20 w/v% solution of acetic acid was added to the reaction mixture until acidic to pH paper. The mixture was extracted twice with diethyl ether and the combined organic layers washed successively with water, and saturated aq. NaHCO3, and then dried over Na2SO4. Filtration and evaporation of the solvent afforded crude 1,1-diphenyl-but-3-yn-1-ol, which was subjected to a Rupe rearrangement without further purification. To a solution of the crude alcohol in concentrated acetic acid (4 mL) was added concentrated H2SO4 (50 μL). The reaction mixture was stirred vigorously at 70 °C for 40 minutes, and then poured into ice water and extracted twice with CH2Cl2. The combined organic layers were washed with H2O, saturated aq. NaHCO3, and then dried over Na2SO4. The crude mixture was concentrated in vacuo and then purified by silica gel chromatography (10% EtOAc/hexanes) to afford the title compound as an orange oil (422 mg, 38%). Spectral data were in agreement with previous reports.27 1H NMR (400 MHz, CDCl3): δ 7.65–7.58 (m, 4H), 7.36–7.27 (m, 6H), 2.88 (s, 1H), 2.76 (s, 1H).

1,1-Bis[(N,N-dimethylamino)phenyl]prop-2-yn-1-ol (7b). Prepared according to a modified literature procedure.33 To a solution of trimethylsilylacetylene (0.7 mL, 5 mmol, 2 eq.) in THF (8 mL) at −10 °C was added a solution of nBuLi (2.5 M in hexanes, 2 mL, 5 mmol, 2.0 eq.) dropwise under an atmosphere of argon. The resulting solution was stirred at −10 °C for 30 minutes after which time benzophenone (677.5 mg, 2.5 mmol, 1 eq.) was added. The solution was then warmed to room temperature and stirred for 4 hours, after which time KOH (1.4 g, 25 mmol, 5 eq.) in methanol was added at 0 °C and stirred for 20 minutes. The mixture was then poured into a solution of saturated aq. NH4Cl and extracted three times with EtOAc. The combined organic layers were washed sequentially with H2O and saturated aq. NaCl, and then dried over Na2SO4. The drying agent was then removed by filtration and the solution was concentrated in vacuo. The title compound was obtained by silica gel chromatography (10% EtOAc/hexanes, Rf = 0.3) as a white solid (90 mg, 87%). Spectral data were in agreement with previous reports.34 1H NMR (400 MHz, CDCl3): δ 7.65–7.58 (m, 4H), 7.36–7.27 (m, 6H), 2.88 (s, 1H), 2.76 (s, 1H).

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