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Aromatic Cations from Oxidative Carbon−Hydrogen Bond Cleavage in Bimolecular Carbon−Carbon Bond Forming Reactions

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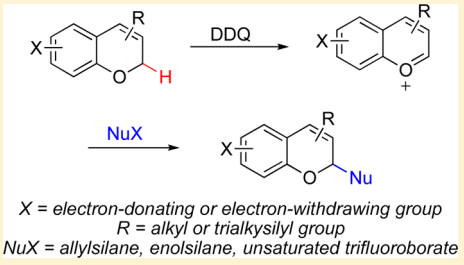
Supporting Information

ABSTRACT: Chromenes and isochromenes react quickly with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to form persistent aromatic oxocarbenium ions through oxidative carbon−hydrogen cleavage. This process is tolerant of electron-donating and electron-withdrawing groups on the benzene ring and additional substitution on the pyran ring. A variety of nucleophiles can be added to these cations to generate a diverse set of structures.



INTRODUCTION

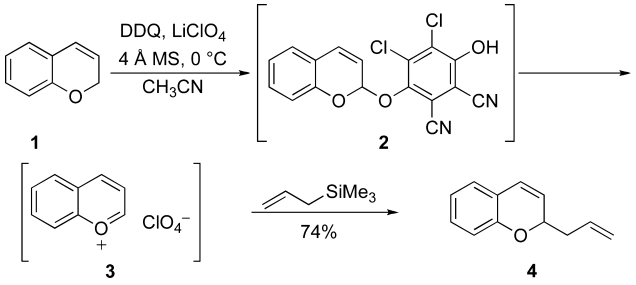
Carbon−hydrogen bond functionalization reactions are becoming increasingly common in chemical synthesis because of their capacity to deliver increases in molecular complexity and functional group content from readily available precursors with minimal waste generation.[1] While these processes are most frequently achieved through transition metal-mediated catalysis, a growing number of transformations proceed through cation formation via carbon−hydrogen bond oxidation. We[2] and others[3] have developed a number of stereoselective cyclization reactions based on ether, amide, and sulfide oxidation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). These processes proceed through the formation of stabilized carbocations followed by intramolecular additions of π-nucleophiles. Extending this approach to the development of oxidative bimolecular reactions offers the enticing prospect of using carbon−hydrogen functionalization as an entry to fragment coupling in complex molecule synthesis. Indeed numerous examples of bimolecular reactions that proceed through oxidative carbon−hydrogen bond cleavage have been reported. The challenges of preparing cations that have a sufficient lifetime to engage in bimolecular reactions dictates that these transformations employ readily oxidized substrates such as electron-rich alkenes,[4] isochromans and related alkoxybenzyl ethers,[5] xanthenes,[6] and amines, with tetrahydroisoquinolines being particularly common.[7]

The significant benefits of developing fragment coupling reactions based on oxidative carbon−hydrogen bond cleavage for devising convergent syntheses and for preparing structurally diverse low molecular weight libraries for fragment-based screening[8] led us to consider new substrate designs for these processes. Our objective was to develop substrates that undergo facile oxidation to form cations that can react with a range of nucleophiles while retaining a functional handle for additional manipulations. In this manuscript we report that chromenes and isochromenes react with DDQ to form aromatic cations. These processes proceed effectively even when the substrates contain electron-withdrawing groups. The intermediate cations react with several nucleophiles including weakly nucleophilic potassium trifluoroborates and prochiral allylsilanes. Suitable substitution on the substrates creates the potential for facile product diversification.

RESULTS AND DISCUSSION

Mechanistic studies in our group[9] showed that cation stability is an important determinant in the rate of oxidative carbon−hydrogen bond cleavage. This led us to consider aromaticity as a stabilizing element in carbocation formation. Our initial studies (Scheme 1) focused on the use of 2*H*-chromene (**1**) as

Scheme 1. Nucleophilic Addition to Chromene through Oxidative Carbon−Hydrogen Bond Cleavage



a substrate. This structure and the majority of the chromenes in this were efficiently accessed by treating aryl propargyl ethers with $Ph_3PAuNTf_2$ through the Stratakis protocol.[10] These compounds are useful entries for this endeavor because their substitution products can be converted to core subunits of numerous biologically active benzopyran-containing natural

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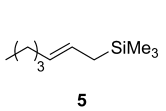
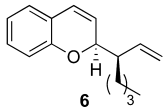
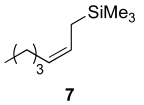
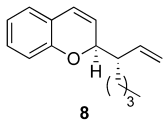
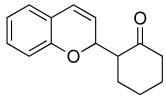
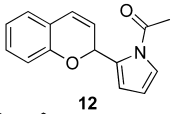
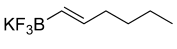
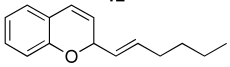
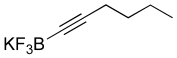
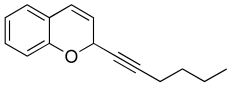
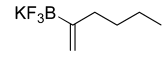
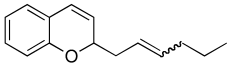
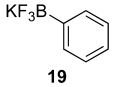
products.[11] Exposing **1** to DDQ in CH_3CN at 0 °C resulted in starting material disappearance within 30 min to form putative intermediate **2**. This transformation proceeded most smoothly in the presence of 4 Å MS to prevent the formation of ether dimers that result from reactions with water. $LiClO_4$ was incorporated in this step to promote the conversion of **2** to ion pair **3**. The addition of allyl trimethylsilane led to the rapid formation of **4** in 74% yield. This reaction proceeded most efficiently when conducted by generating a "cation pool"[12] prior to nucleophilic addition rather than by adding the nucleophile prior to oxidation. The process can also be conducted in other solvents, such as CH_2Cl_2 or toluene with minimal impact on efficiency.

The scope of the reaction was probed by perturbing the structure of the chromene and by changing the nucleophile. The results of varying the nucleophile are shown in Table 1. Prochiral substituted allylic silanes are useful nucleophiles and provide good to excellent levels of diastereocontrol (entries 1 and 2). Notably, changing the geometry of the alkene results in a change of the major diastereomer. Enolsilanes are also excellent nucleophiles (entry 3), although diastereocontrol is low for the cyclohexanone-derived species. Interestingly, the enolsilane of *N*-acetyl pyrrole provided the electrophilic aromatic substitution product rather than the product of direct enolate addition (entry 4). This result cannot be attributed to cleavage of the enolsilane prior to addition since *N*-acetyl pyrrole itself reacted far slower than its enolsilane. This outcome could be attributed to a rapid enolsilane addition followed by ionization and rearrangement steps. Potassium alkynyl- and alkenyltrifluoroborates[13] provide an effective source of sp- and sp^2-hybridized carbon nucleophiles (entries 5–7). While boron *ate*-complexes have been shown to be effective nucleophiles for additions into oxocarbenium ions,[14] to the best of our knowledge this is the first report of adding these species to oxidatively generated electrophiles. Note that the 1,1-disubstituted reagent proceeds through an unexpected mode of addition to provide an allylated product (entry 7). Potassium phenyl trifluoroborate was unreactive in this system (entry 8).

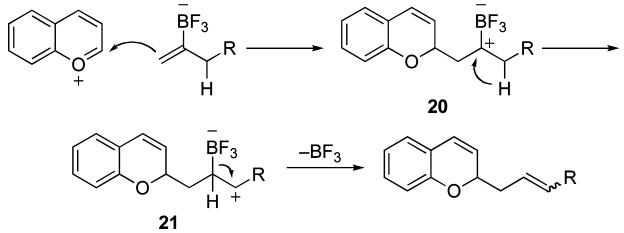
These processes are sensitive to the steric demands of the nucleophile, with the reactions of silanes **5** and **7** requiring 12 h to reach completion, while the reaction with allyl trimethylsilane only required 30 min. This accounts for the low reactivity of potassium phenyl trifluoroborate and the unexpected reaction of trifluoroborate **17**. The proposed mechanism for isomerization of **17** (Scheme 2) proceeds through a sterically

Table 1. Nucleophile Scope[a]

entry	nucleophile	product	yield[b]
1	 **5**	 **6**	63% dr = 1:0[c]
2	 **7**	 **8**	51% dr = 6:1[c]
3	 **9**	 **10**	71% dr = 1.6:1[d]
4	 **11**	 **12**	47%
5	 **13**	 **14**	65%
6	 **15**	 **16**	66%
7	 **17**	 **18**	66% *E*:*Z* = 5:1
8	 **19**		–

[a]Representative protocol: DDQ (1.3 equiv) was added to a mixture of 2*H*-chromene (1 equiv, 0.1 M), $LiClO_4$ (1 equiv), and 4 Å MS in CH_3CN at 0 °C. The mixture was stirred at 0 °C for 30 min, and then the nucleophile was added. See the Supporting Information for details on reaction times and purification protocols. [b]Isolated yields of purified materials. [c]Stereochemical assignment based on a crystal structure of a derivative. See subsequent discussion for details. [d]The stereochemistry was not assigned for this product mixture.

Scheme 2. Rearrangement of 1,1-Disubstituted Vinyl Trifluoroborate



dictated nucleophilic addition to form cation **20**. Hydride migration to form cation **21** and BF_3 loss leads to **18** as a mixture of geometrical isomers. Overman has reported a similar reactivity pattern for intramolecular vinylsilane additions into oxocarbenium ions.[15]

The stereochemical outcomes of the allylsilane additions also merit discussion. Allylsilanes can react with oxocarbenium ions through antiperiplanar or synclinal transition states.[16] We hypothesize that the preferred nucleophilic approach will place the hydrogen underneath the ring, as shown in Figure 1. A comparison of the synclinal (**22**) and antiperiplanar (**23**) transition states for the addition of *E*-silane **5** into the

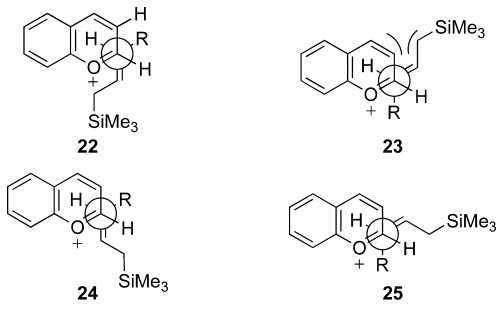


Figure 1. Approach trajectories for prochiral allylic silanes.

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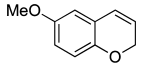
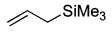
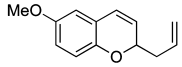
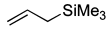
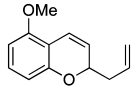
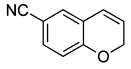
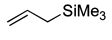
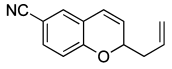
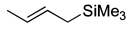
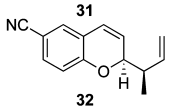
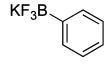
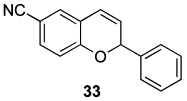
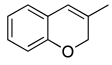
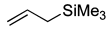
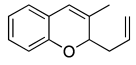
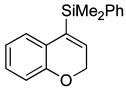
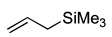
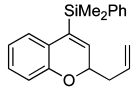
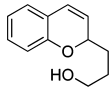
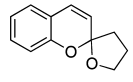
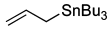
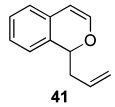
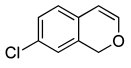
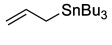
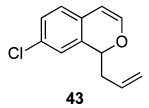
intermediate oxocarbenium ion shows a steric clash for **23** that is not present in **22**, thereby accounting for the high observed stereocontrol. No major steric clash is apparent in **24** and **25**, the synclinal and antiperiplanar transition states for the addition of *Z*-silane **7** into the oxocarbenium ion. The selectivity for the observed product suggests a slight inherent preference for the antiperiplanar transition state that results from the oxygen being less sterically demanding than the methine group. A similar analysis of the nucleophilic approach of enolsilanes (not shown) does not reveal an obvious preference, consistent with the observation of little stereocontrol.

Variations in the substrate were also studied, and the results are shown in Table 2. The methoxy group was incorporated as

Table 2. Substrate Scope[a]

entry	substrate	nucleophile	product	yield (%)
1	 **26**		 **27**	64
2	 **28**		 **29**	46
3	 **30**		 **31**	92
4	**30**		 **32**	74
5	**30**		 **33**	46
6	 **34**		 **35**	60
7	 **36**		 **37**	72
8	 **38**	–	 **39**	93
9	 **40**		 **41**	79
10	 **42**		 **43**	91

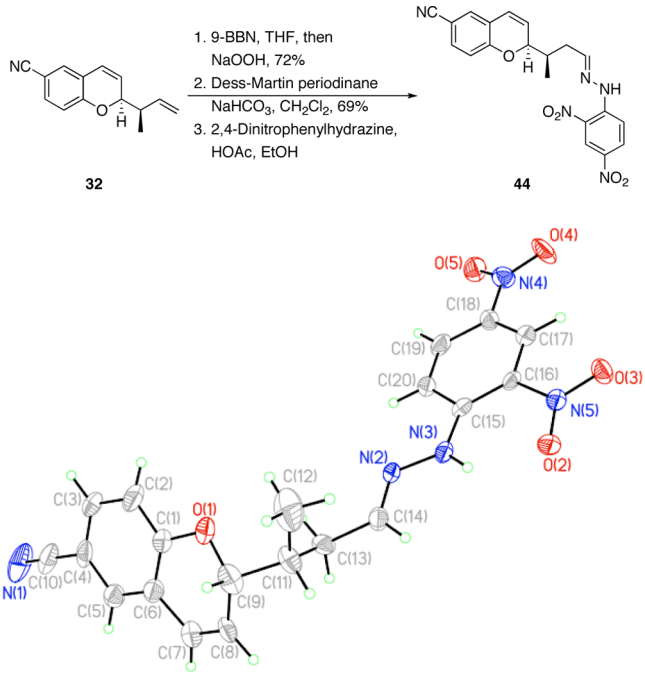
[a]Please see the Supporting Information for experimental details.

a representative electron-donating group (entries 1 and 2), while a cyano group was incorporated as a representative electron-withdrawing group (entries 3–5). Substitution is also tolerated on the pyran section of the compounds, with methyl-substituted substrate **34** and silyl-substituted substrate **36** reacting under standard conditions to yield **35** and **37**, respectively. Spirocycles can be prepared through intramolecular additions, as demonstrated by the conversion of **38** to **39** (entry 8) and in accord with recent results from the Brimble group.[17] Isochromenes are also suitable substrates for these reactions (entries 9 and 10).

As expected, the oxidation of electron-rich chromenes proceeds more readily than the oxidation of electron-deficient chromenes, which require heating for efficient cation formation. The capacity to prepare a cyano-substituted cation, however, highlights the utility of employing aromatic intermediates to promote reactivity. Nucleophilic additions proceed more efficiently into the cyano-substituted cations. Yields are higher for these reactions, and nucleophiles that were unreactive toward the parent 2*H*-chromene, such as potassium phenyltrifluoroborate (entry 5), proved to be reactive toward the less-stable ions. These trends are also observed for the isochromenes, where the oxidation of **40** proceeds instantaneously at −30 °C, while the oxidation of **42** proceeds over 25 min at −5 °C, but the yield of **43** is higher than the yield of **41**. The compatibility of a chloro-substituent with this protocol will prove to be useful for further diversification reactions.

Crotylation product **32** (entry 4) was used to determine the stereochemical outcome of the addition (Scheme 3). Attempts

Scheme 3. Structural Proof for the Crotylation Reaction



to crystallize this compound for X-ray diffraction analysis were unsuccessful, so we prepared derivatives. Selective hydroboration of the terminal alkene with 9-BBN followed by a basic peroxide workup provided the expected primary alcohol. Acylation to form the common crystallization promoting *p*-bromobenzoate and *p*-phenylbenzoate esters did not yield suitable crystals. Therefore the alcohol was oxidized with the Dess–Martin periodinane,[18] and the resulting aldehyde was converted to 2,4-dinitrophenylhydrazone **44** under standard conditions. This product provided suitable crystals for the diffraction study that led to unambiguous stereochemical assignment and the transition state analysis in Figure 1.

The tolerance toward substitution in the pyran subunit is critical for expanding the scope of this protocol. The silyl substituent in **36** was selected because of its exceptional capacity for conversion to other functional groups. Vinyl silanes

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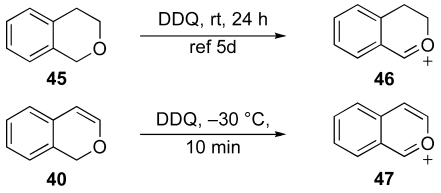
can be converted to carbonyl groups through peroxide-mediated oxidation[19] and can be employed in cross-coupling reactions,[20] suggesting that compounds such as **37** can serve as versatile progenitors to libraries for biological screening studies.

The kinetic impact of proceeding through aromatic cationic intermediates is quite dramatic in the oxidation of isochromene **40**. Previously reported DDQ-mediated oxidations of isochroman (**45**) to form oxocarbenium ion **46**[5] required 24 h at rt for complete starting material consumption, whereas the oxidation of **40** proceeds to completion within minutes at −30 °C to form **47** (Scheme 4).

Scheme 4. Impact of Aromaticity on Oxidation Rate



CONCLUSIONS

We have shown that DDQ-mediated oxidative carbon−hydrogen bond cleavage reactions proceed quite efficiently to provide aromatic carbocations. These intermediates possess a sufficient lifetime to engage in bimolecular reactions with a number of stable nucleophiles, leading to useful fragment-coupling protocols. Transition state models for the addition of prochiral nucleophiles have been developed, which will be useful in predicting the capacity for absolute stereochemical induction with chiral reagents. The procedure is tolerant of electron-withdrawing groups on the substrate, leading to a useful substrate scope expansion for oxidative cation generation. Defining new substrates for this process will be essential for the impact of this increasingly common protocol to progress.

EXPERIMENTAL SECTION

General Procedures. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 300, 400, or 500 MHz and 75, 100, or 125 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Tetramethylsilane (TMS) or the solvent peak was used as a reference value, for ^{1}H NMR: TMS (in $CDCl_3$) = 0.00 ppm, for ^{13}C NMR: TMS (in $CDCl_3$) = 0.00. Data are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Analytical TLC was performed on precoated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using 32−63 60 Å silica gel. Methylene chloride was distilled under N_2 from CaH_2. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were used as purchased for chromatography. Benzene was dried with 4 Å molecular sieves. THF was distilled from sodium. Other reagents were obtained from commercial sources without further purification. Substrates **1**, **26**, **28**, and **30** were prepared following the Stratakis protocol.[10] Substrate **40** was prepared following Descotes protocol.[21] Substrate **42** was prepared through the Saá route.[22] Nucleophile **11** was prepared according to the Simchen protocol.[23] Nucleophile **15** was prepared according to Molander's protocol.[24] All reactions were performed in oven or flame-dried glassware with magnetic stirring unless otherwise noted.

General Procedure for the Oxidative Coupling. To a solution of the benzopyran (1.0 equiv) in freshly distilled acetonitrile (0.1 M) at 0 °C was added $LiClO_4$ (1.5 equiv) and 4 Å MS (250 mg/mmol). After 5 min, DDQ (1.3 equiv) was added to the reaction mixture, and it was stirred until TLC analysis showed complete starting material consumption. The nucleophile (2.0 equiv) was added, and the reaction was stirred until completion (monitored via TLC analysis). The reaction was quenched with 10% aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with diethyl ether (3 × 10 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude mixture was purified by flash chromatography.

2-Allyl-2*H*-chromene (4). The general procedure for the oxidative coupling was followed using benzopyran **1** (264 mg, 2.00 mmol), $LiClO_4$ (319 mg, 3.00 mmol), 4 Å MS (500 mg), DDQ (590 mg, 2.60 mmol), and acetonitrile (20 mL). After 30 min the oxidation was complete, and allyl trimethylsilane (457 mg, 4.00 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1−5% ethyl acetate in hexanes) to yield the substituted benzopyran (254 mg, 74%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (td, J = 7.6, 1.6 Hz, 1H), 6.88 (dd, J = 7.6, 1.6 Hz, 1H), 6.76 (t, J = 7.6 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.33 (d, J = 9.6 Hz, 1H), 5.82 (ddt, J = 17.2, 10.4, 7.2 Hz, 1H), 5.61 (dd, J = 9.6, 3.2 Hz, 1H), 5.07 (d, J = 9.6 Hz, 1H), 5.04 (s, 1H), 4.82−4.85 (m, 1H), 2.46−2.53 (m, 1H), 2.34−2.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.3, 133.3, 129.1, 126.4,125.0,124.2, 121.8, 121.0, 117.8, 115.9, 74.7, 39.7; IR (neat) 3075, 2934, 1640, 1605, 1486, 1271, 1206, 1041, 754 cm^{-1}, HRMS (ESI) m/z calcd for $C_{12}H_{11}O$ $[M - H]^+$ 171.0810, found 171.0813.

(±)-(*S*)-2-((*R*)-Hept-1-en-3-yl)-2*H*-chromene (6). The general procedure for the oxidative coupling was followed using benzopyran **1** (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete, and silane **5** (341 mg, 2.00 mmol) was added. The reaction was complete after 16 h and was purified using flash chromatography (1−5% ethyl acetate in hexanes) to yield the substituted benzopyran (144 mg, 63%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (td, J = 7.6, 1.6 Hz, 1H), 6.94 (dd, J = 7.2, 1.2 Hz, 1H), 6.83 (td, J = 7.2, 0.8 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.42 (dd, J = 10.0, 1.2 Hz, 1H), 5.68−5.76 (m, 1H), 5.66 (dd, J = 10.0, 3.2 Hz, 1H), 5.11 (dd, J = 10.0, 1.6 Hz, 1H), 5.06 (dd, J = 16.8, 1.2 Hz, 1H), 4.85−4.87 (m, 1H), 2.37 (sep, J = 4.8 Hz, 1H), 1.59−1.68 (m, 1H), 1.41−1.51 (m, 1H), 1.19−1.37 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.9, 138.0, 129.0, 126.4, 124.4, 124.3, 121.9, 120.8, 116.9, 115.7, 77.8, 49.6, 29.5, 29.4, 22.7, 14.0; IR (neat) 3073, 2928, 2857, 1639, 1486, 1230, 1206, 1040, 915, 753; HRMS (ESI) m/z calcd for $C_{16}H_{21}O$ $[M + H]^+$ 229.1592, found 229.1594.

(±)-(*S*)-2-((*S*)-Hept-1-en-3-yl)-2*H*-chromene (8). The general procedure for the oxidative coupling was followed using benzopyran **1** (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete, and silane **7** (341 mg, 2.00 mmol) was added. The reaction was complete after 16 h and was purified using flash chromatography (1−5% ethyl acetate in hexanes) to yield the substituted benzopyran (6:1 *anti*:*syn*) (117 mg, 51%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09 (td, J = 8.0, 1.5 Hz, 1H), 6.95 (dd, J = 7.0, 1.5 Hz, 1H), 6.83 (td, J = 7.5, 1.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.41 (dd, J = 10.0, 1.0 Hz, 1H), 5.65−5.72 (m, 2H), 5.11 (dd, J = 10.5, 2.0 Hz, 1H), 5.07 (dd, J = 17.0, 1.0 Hz, 1H), 4.74−4.76 (m, 1H), 2.37−2.43 (m, 1H), 1.72−1.78 (m, 1H), 1.16−1.38 (m, 5H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 138.1, 129.1, 126.4, 124.5, 124.2, 122.0, 120.8, 117.4, 115.8, 77.7, 49.6, 29.3, 29.1, 22.7, 14.0; IR (neat) 3073, 2919, 2852, 1638, 1485, 1229, 1038, 750; HRMS (ESI) m/z calcd for $C_{16}H_{21}O$ $[M + H]^+$ 229.1592, found 229.1586.

2-(2*H*-Chromen-2-yl)cyclohexanone (10). The general procedure for the oxidative coupling was followed using benzopyran **1** (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete, and enol silane **9** (341 mg, 2.00 mmol)

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was added. The reaction was complete after 30 min and was purified using flash chromatography (5−15% ethyl acetate in hexanes) to yield the substituted benzopyran (dr 1:1.6) (162 mg, 71%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03−7.12 (m, 1H), 6.92−6.97 (m, 1H), 6.83−6.86 (m, 1H), 6.78 (d, J = 8.4 Hz, 0.38H), 6.72 (d, J = 8.0 Hz, 0.62H), 6.39−6.45 (m, 1H), 5.86 (dd, J = 10.0, 3.6 Hz, 0.38H), 5.69 (dd, J = 10.0, 3.2 Hz, 0.62H), 5.47−5.50 (m, 0.62H), 5.17 (ddd, J = 7.6, 4.0, 1.2 Hz, 0.38H), 2.87−2.93 (m, 0.62H), 2.67−2.74 (m, 0.38H), 2.22−2.47 (m, 2.62H), 2.04−2.12 (m, 1H), 1.86−1.94 (m, 1.38H), 1.55−1.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.8, 210.6, 153.8, 152.9, 129.1, 126.4, 126.4, 125.4, 124.7, 123.8, 123.0, 121.8, 121.3, 121.1, 120.9, 115.9, 115.4, 73.8, 73.2, 55.7, 55.3, 42.6, 42.2, 29.6, 27.9, 27.6, 27.4, 24.5, 24.4; IR (neat) 3044, 2938, 2862, 1707, 1605, 1485, 1454, 1271, 1230, 1037, 778; HRMS (EI) m/z calcd for $C_{15}H_{16}O_2$ $[M]^+$ 228.1150, found 228.1173.

1-(2-(2*H*-Chromen-2-yl)-1*H*-pyrrol-1-yl)ethanone (12). The general procedure for the oxidative coupling was followed using benzopyran **1** (26 mg, 0.20 mmol), $LiClO_4$ (32 mg, 0.30 mmol), 4 Å MS (50 mg), DDQ (59 mg, 0.26 mmol), and acetonitrile (2.0 mL). After 30 min the oxidation was complete, and enol silane **11** (72 mg, 0.400 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (5−15% ethyl acetate in hexanes) to yield the substituted benzopyran (22 mg, 47%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (dd, J = 3.0, 1.5 Hz, 1H), 7.10 (td, J = 7.5, 1.5 Hz, 1H), 7.00 (dd, J = 7.5, 1.5 Hz, 1H), 6.85 (td, J = 7.5, 1.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 4.0 Hz, 1H), 6.52 (d, J = 10.0 Hz, 1H), 6.37−6.38 (m, 1H), 6.16 (t, J = 3.0 Hz, 1H), 5.93 (dd, J = 10.0, 4.0 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.0, 153.0, 134.4, 129.2, 126.5, 124.1, 123.3, 122.1, 121.5, 121.1, 116.2, 115.0, 111.8, 69.8, 24.1; IR (neat) 3043, 2921, 1721, 1484, 1226, 1126, 1037, 939, 756; HRMS (ESI) m/z calcd for $C_{15}H_{13}NO_2Na$ $[M + Na]^+$ 262.0844, found 262.0851.

(*E*)-2-(Dec-1-enyl)-2*H*-chromene (14). The general procedure for the oxidative coupling was followed using benzopyran **1** (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete, and trifluoroborate **13** (492 mg, 2.00 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1−5% ethyl acetate in hexanes) to yield the substituted benzopyran (176 mg, 65%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (td, J = 7.2, 1.2 Hz, 1H), 6.98 (dd, J = 7.2, 0.8 Hz, 1H), 6.86 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.43 (d, J = 9.6 Hz, 1H), 5.81 (dt, J = 15.2, 6.8 Hz, 1H), 5.65−5.71 (m, 2H), 5.27−5.29 (m, 1H), 2.07 (q, J = 6.8 Hz, 2H), 1.28−1.40 (m, 12H), 0.91 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.2, 134.5, 129.1, 127.8, 126.4, 124.7, 123.7, 121.6, 120.9, 116.0, 75.8, 32.1, 31.8, 29.4, 29.2, 29.1, 28.9, 22.7, 14.1; IR (neat) 3042, 2924, 2853, 1638, 1485, 1456, 1227, 1036, 768; HRMS (ESI) m/z calcd for $C_{19}H_{25}O$ $[M - H]^+$ 269.1905, found 269.1899.

2-(Dec-1-ynyl)-2*H*-chromene (16). The general procedure for the oxidative coupling was followed using benzopyran **1** (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete, and trifluoroborate **15** (488 mg, 2.00 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1−5% ethyl acetate in hexanes) to yield the substituted benzopyran (176 mg, 66%) as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (td, J = 7.8, 1.5 Hz, 1H), 7.02 (dd, J = 7.2, 1.2 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H) 6.88 (d, J = 8.1 Hz, 1H), 6.46 (d, J = 9.6 Hz, 1H), 5.76 (dd, J = 9.6, 3.9 Hz, 1H), 5.56 (q, J = 1.8 Hz, 1H), 2.21 (td, J = 6.9, 1.8 Hz, 2H), 1.49 (quin, J = 7.2 Hz, 2H), 1.26−1.34 (m, 10H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.6, 129.3, 126.6, 124.2, 123.0, 121.6, 121.5, 116.4, 87.1, 77.2, 64.9, 31.8, 29.1, 29.0, 28.8, 28.4, 22.6, 18.8, 14.1; IR (neat) 3045, 2925, 2854, 2277, 2219, 1606, 1485, 1293, 1198, 1111, 754; HRMS (EI) m/z calcd for $C_{19}H_{24}O$ $[M]^+$ 268.1827, found 268.1864.

2-(Dec-2-enyl)-2*H*-chromene (18). The general procedure for the oxidative coupling was followed using benzopyran **1** (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete, and trifluoroborate **17** (492 mg, 2.00 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1−5% ethyl acetate in hexanes) to yield the substituted benzopyran (5:1 olefin mixture) (179 mg, 66%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (td, J = 7.0, 0.8 Hz, 1H), 6.95−6.97 (m, 1H), 6.83−6.86 (m, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.40−6.42 (m, 1H), 5.70 (dd, J = 9.5, 3.0 Hz, 1H), 5.53−5.58 (m, 1H), 5.45−5.51 (m, 1H), 4.86−4.91 (m, 1H), 2.46−2.54 (m, 1.67H), 2.37−2.42 (m, 0.33H), 1.93−2.05 (m, 2H), 1.22−1.34 (m, 10H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.4, 153.4, 134.3, 133.2, 129.1, 129.0, 126.4, 126.3, 125.4, 125.3, 124.3, 124.1, 124.0, 123.5, 122.0, 121.8, 120.9, 120.9, 115.9, 74.9, 74.9, 38.7, 33.4, 32.6, 31.8, 29.5, 29.4, 29.2, 29.2, 29.2, 29.1, 27.4, 22.7, 14.1; IR (neat) 3011, 2925, 2853, 1638, 1468, 1457, 1230, 1112, 753; HRMS (ESI) m/z calcd for $C_{19}H_{27}O$ $[M + H]^+$ 271.2062, found 271. 2050.

2-Allyl-6-methoxy-2*H*-chromene (27). The general procedure for the oxidative coupling was followed using benzopyran **26** (162 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete, and allyl trimethylsilane (229 mg, 2.00 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1−10% ethyl acetate in hexanes) to yield the substituted benzopyran (129 mg, 64%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.73 (d, J = 8.8 Hz, 1H), 6.67 (dd, J = 8.4, 2.8 Hz, 1H), 6.55 (d, J = 2.8 Hz, 1H), 6.39 (d, J = 10.0 Hz, 1H), 5.90 (ddt, J = 17.2, 10.4, 7.2, 1H), 5.75 (dd, J = 9.6, 3.2 Hz, 1H), 5.15 (d, J = 8.8 Hz, 1H), 5.12 (s, 1H), 4.85 (m, 1H), 3.76 (s, 3H), 2.54−2.61 (m, 1H), 2.41−2.48 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.9, 147.1, 133.4, 126.1, 124.3, 122.5, 117.8, 116.5, 114.2, 111.6, 74.3, 55.6, 39.4; IR (neat) 3075, 2936, 2832, 1577, 1491, 1432, 1268, 1045, 920, 708; HRMS (ESI) m/z calcd for $C_{13}H_{15}O_2$ $[M + H]^+$ 203.1072, found 203.1069.

2-Allyl-5-methoxy-2*H*-chromene (29). The general procedure for the oxidative coupling was followed using benzopyran **28** (140 mg, 0.863 mmol), $LiClO_4$ (138 mg, 1.29 mmol), 4 Å MS (200 mg), DDQ (252 mg, 1.11 mmol), and acetonitrile (8.6 mL). After 30 min the oxidation was complete, and allyl trimethylsilane (197 mg, 1.72 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1−10% ethyl acetate in hexanes) to yield the substituted benzopyran (80 mg, 46%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.06 (t, J = 8.5 Hz, 1H), 6.76 (d, J = 10.0 Hz, 1H), 6.46 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 8.0 Hz, 1H), 5.91 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H), 5.66 (dd, J = 10.0, 3.0 Hz, 1H), 5.15 (d, J = 17.0 Hz, 1H), 5.13 (d, J = 9.5 Hz, 1H), 4.85−4.87 (m, 1H), 3.83 (s, 3H), 2.56−2.61 (m, 1H), 2.43−2.48 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2, 154.1, 133.4, 129.0, 123.2, 118.9, 117.8, 111.3, 109.1, 103.3, 74.1, 55.6, 39.5; IR (neat) 3074, 2934, 1634, 1580, 1310, 1101, 917, 749; HRMS (ESI) m/z calcd $C_{13}H_{13}O_2$ $[M - H]^+$ 201.0916, found 201. 0918.

2-Allyl-2*H*-chromene-6-carbonitrile (31). To a solution of benzopyran **30** (31 mg, 0.20 mmol) in freshly distilled acetonitrile (2.0 mL) at rt was added $LiClO_4$ (32 mg, 0.30 mmol) and 4 Å MS (50.0 mg). After 5 min, DDQ (59 mg, 0.260 mmol) was added, and the reaction was warmed to 75 °C for 2 h. The reaction was cooled to rt, allyl trimethylsilane (46 mg, 0.40 mmol) was added, and the reaction was stirred for 15 min. The solution was quenched with 10% aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with diethyl ether (3 × 5 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude residue was purified using flash chromatography (3−12% ethyl acetate in hexanes) to yield the substituted benzopyran (36 mg, 92%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (dd, J = 8.4, 1.6 Hz, 1H), 7.23 (d, J = 1.2 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.38 (d, J = 10.0 Hz, 1H), 5.87 (ddt, J = 17.6, 10.8, 7.2 Hz, 1H), 5.78 (dd, J = 10.0, 3.2 Hz, 1H), 5.17 (d, J = 6.4 Hz, 1H), 5.14 (s, 1H), 5.06 (m, 1H), 2.47−2.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.1, 133.4, 132.3, 130.2, 126.6, 122.5, 122.2, 119.1, 118.7, 116.8, 104.1, 75.4, 40.1; IR (neat) 3078, 2926, 2225, 1640, 1488, 1251, 1130, 1021, 830, 715; HRMS (ESI) m/z calcd for $C_{13}H_{12}NO$ $[M + H]^+$ 198.0919, found 198.0917.

(±)-(*S*)-2-((*R*)-But-3-en-2-yl)-2*H*-chromene-6-carbonitrile (33). To a solution of benzopyran **30** (314 mg, 2.00 mmol) in freshly

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distilled acetonitrile (20 mL) at rt was added $LiClO_4$ (319 mg, 3.00 mmol) and 4 Å MS (500 mg). After 5 min, DDQ (590 mg, 2.60 mmol) was added, and the reaction was warmed to 80 °C for 2 h. The reaction was cooled to rt, (*E*)-crotyl trimethylsilane (513 mg, 4.00 mmol) was added, and the reaction was stirred for 16 h. The solution was quenched with 10% aqueous $NaHCO_3$ solution (20 mL). The reaction mixture was extracted with diethyl ether (3 × 20 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude residue was purified using flash chromatography (2−15% ethyl acetate in hexanes) to yield the substituted benzopyran (312 mg, 74%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (dd, J = 8.4, 1.6 Hz, 1H), 7.21 (d, J = 1.6 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.40 (d, J = 10.0 Hz, 1H), 5.78−5.87 (m, 1H), 5.73 (dd, J = 10.4, 3.2 Hz, 1H), 5.13 (d, J = 0.8 Hz, 1H), 5.09 (d, J = 7.2 Hz, 1H), 4.95−4.98 (m, 1H), 2.62 (sex, J = 6.8 Hz, 1H), 1.14 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.4, 137.8, 133.3, 129.9, 125.0, 122.9, 122.0, 118.9, 116.3, 116.1, 103.7, 79.3, 43.0, 14.2; IR (neat) 2971, 2868, 2224, 1640, 1573, 1488, 1251, 1232, 1012, 920; HRMS (ESI) m/z calcd for $C_{14}H_{14}NO$ $[M + H]^+$ 212.1075, found 212.1077.

2-Phenyl-2*H*-chromene-6-carbonitrile (33). To a solution of benzopyran **30** (157 mg, 1.00 mmol) in freshly distilled acetonitrile (10 mL) at rt was added $LiClO_4$ (160 mg, 1.50 mmol) and 4 Å MS (250 mg). After 5 min, DDQ (295 mg, 1.30 mmol) was added, and the reaction was warmed to 70 °C for 2 h. The reaction was cooled to rt, trifluoroborate **19** (368 mg, 2.00 mmol) was added, and the reaction was warmed to 70 °C for 16 h. The solution was cooled to rt and quenched with 10% aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with diethyl ether (3 × 10 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude residue was purified using flash chromatography (2−10% ethyl acetate in hexanes) to yield the substituted benzopyran (104 mg, 45%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.41 (m, 6H), 7.30 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 10.0 Hz, 1H), 6.03 (m, 1H), 5.90 (dd, J = 10.0, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.6, 139.6, 133.6, 130.2, 128.8, 128.8, 126.9, 126.2, 122.1, 121.6, 119.0, 116.8, 104.2, 77.9; IR (neat) 3061, 3032, 2221, 1649, 1602, 1488, 1251, 1128, 1026, 849, 718; HRMS (ESI) m/z calcd for $C_{16}H_{12}NO$ $[M + H]^+$ 234.0919, found 234.0927.

2-Allyl-3-methyl-2*H*-chromene (35). The general procedure for the oxidative coupling was followed using benzopyran **34** (175 mg, 1.20 mmol), $LiClO_4$ (191 mg, 1.80 mmol), 4 Å MS (300 mg), DDQ (354 mg, 1.56 mmol), and acetonitrile (12 mL). After 30 min the oxidation was complete, and allyl trimethylsilane (274 mg, 2.40 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1−5% ethyl acetate in hexanes) to yield the substituted benzopyran (134 mg, 60%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06 (td, J = 7.6, 1.6 Hz, 1H), 6.91 (dd, J = 7.2, 1.6 Hz, 1H), 6.84 (td, J = 7.2, 1.2 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.18 (s, 1H), 5.88−5.98 (m, 1H), 5.11−5.13 (m, 1H), 5.08 (t, J = 1.2 Hz, 1H), 4.71 (dd, J = 8.4, 3.6 Hz, 1H), 2.46−2.54 (m, 1H), 2.33−2.41 (m, 1H), 1.85 (d, J = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.3, 134.0, 133.6, 128.2, 125.5, 122.6, 121.0, 119.6, 117.5, 115.9, 78.2, 37.2, 19.7; IR (neat) 3074, 2913, 1640, 1578, 1442, 1240, 1104, 916, 752; HRMS (ESI) m/z calcd for $C_{13}H_{13}O$ $[M - H]^+$ 185.0966, found 185.0962.

2-Allyl-4-(dimethylphenylsilyl)-2*H*-chromene (36). The general procedure for the oxidative coupling was followed using benzopyran **37** (266 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 2 h the oxidation was complete, and allyl trimethylsilane (229 mg, 2.00 mmol) was added. The reaction was complete after 1 h and was purified using flash chromatography (1−5% ethyl acetate in hexanes) to yield the substituted benzopyran (216 mg, 71%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55−7.58 (m, 2H), 7.34−7.41 (m, 3H), 7.06 (td, J = 8.0, 1.6 Hz, 1H), 7.00 (dd, J = 7.6, 1.6 Hz, 1H), 6.82 (dd, J = 8.0, 1.2 Hz, 1H), 6.74 (td, J = 7.2, 1.2 Hz, 1H), 6.05 (d, J = 3.6 Hz, 1H), 5.86−5.96 (m, 1H), 5.15−5.17 (m, 1H), 5.12 (t, J = 1.2 Hz, 1H), 4.80 (ddd, J = 6.8, 5.6, 3.2 Hz, 1H), 2.56−2.63 (m, 1H), 2.43−2.50 (m, 1H), 0.50 (s, 3H), 0.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.7, 137.8, 137.1, 134.0, 133.5, 133.0, 129.2, 128.6, 127.8, 127.4, 124.3, 120.9, 117.9, 116.6, 73.8, 39.0, −2.1, −2.1; IR (neat) 3068, 2956, 1641, 1595, 1482, 1450,1227, 1114, 814; HRMS (ESI) m/z calcd for $C_{20}H_{21}OSi$ $[M - H]^+$ 305.1362, found 305.1364.

4′,5′-Dihydro-3′*H*-spiro[chromene-2,2′-furan] (39). To a solution of benzopyran **38** (85 mg, 0.45 mmol) in freshly distilled acetonitrile (4.4 mL) at 0 °C was added $LiClO_4$ (71 mg, 0.67 mmol) and 4 Å MS (100 mg). After 5 min, DDQ (130 mg, 0.581 mmol) was added to the reaction mixture, and it was stirred for 15 min before being quenched with 10% aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with diethyl ether (3 × 5 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude residue was purified using flash chromatography (5−10% ethyl acetate in hexanes) to yield the substituted benzopyran (77 mg, 93%) as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (td, J = 7.5, 1.5 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.72 (d, J = 9.6 Hz, 1H), 5.76 (d, J = 9.6 Hz, 1H), 4.12−4.19 (m, 1H), 3.98 (q, J = 7.5 Hz, 1H), 2.32−2.44 (m, 2H), 1.96−2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.7, 129.1, 126.8, 126.8, 122.5, 121.1, 120.3, 116.4, 105.2, 68.2, 39.1, 24.5; IR (neat) 3047, 2955, 1624, 1571, 1254, 1065, 1016, 988, 756; HRMS (EI) m/z calcd for $C_{12}H_{12}O_2$ $[M]^+$ 188.0837, found 188.0874.

1-Allyl-1*H*-isochromene (40). To a solution of benzopyran **41** (132 mg, 1.00 mmol) in freshly distilled CH_2Cl_2 (10 mL) at −35 °C was added $LiClO_4$ (160 mg, 1.50 mmol) and 4 Å MS (250 mg). After 5 min, DDQ (295 mg, 1.30 mmol) was added, and the reaction was warmed to −30 °C over 10 min. Allyl tributyltin (662 mg, 2.00 mmol) was added, and the reaction was warmed to rt over 30 min. The solution was quenched with 10% aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude residue was purified using flash chromatography (1% ethyl acetate in hexanes) to yield the substituted benzopyran (135 mg, 79%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (td, J = 7.6, 1.2 Hz, 1H), 7.17 (td, J = 7.6, 1.2 Hz, 1H), 7.00 (d, J = 4.0 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 6.52 (d, J = 5.6 Hz, 1H), 5.93 (ddt, J = 17.2, 10.4, 6.8 Hz, 1H), 5.78 (d, J = 6.0 Hz, 1H), 5.16−5.21 (m, 2H), 5.14 (s, 1H), 2.79−2.86 (m, 1H), 2.51−2.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.1, 134.1, 130.7, 129.5, 127.9, 126.4, 124.2, 123.3, 117.6, 104.5, 76.9, 38.5; IR (neat) 3069, 2937, 2829, 1626, 1488, 1452, 1226, 1051, 917, 769; HRMS (EI) m/z calcd for $C_{12}H_{12}O$ $[M]^+$ 172.0888, found 172.0920.

1-Allyl-7-chloro-1*H*-isochromene (43). To a solution of benzopyran **42** (33.3 mg, 0.200 mmol) in freshly distilled CH_2Cl_2 (2.0 mL) at −20 °C was added $LiClO_4$ (31.9 mg, 0.300 mmol) and 4 Å MS (50 mg). After 5 min, DDQ (59.0 mg, 0.260 mmol) was added, and the reaction was warmed to −5 °C over 25 min. Allyl tributyltin (132 mg, 0.400 mmol) was added, and the reaction was warmed to rt over 30 min. The solution was quenched with 10% aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude residue was purified using flash chromatography (1% ethyl acetate in hexanes) to yield the substituted benzopyran (37.4 mg, 91%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (dd, J = 8.0, 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 6.0 Hz, 1H), 5.83−5.93 (m, 1H), 5.73 (d, J = 5.6 Hz, 1H), 5.10−5.17 (m, 3H), 2.74−2.82 (m, 1H) 2.48−2.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.4, 133.6, 132.3, 131.6, 128.2, 127.9, 124.5, 118.0, 103.8, 76.5, 38.4; IR (neat) 3073, 2929, 2849, 1626, 1484, 1226, 1086, 919, 827; HRMS (ESI) m/z calcd for $C_{12}H_{12}OCl$ $[M + H]^+$ 207.0577, found 207.0611.

1-(2-Methylallyloxy)-2-(prop-1-enyl)benzene. To a solution of 2-(prop-1-enyl)phenol (6:1 *E*:*Z* mixture) (1.40 g, 10.4 mmol) and K_2CO_3 (1.73 g, 12.5 mmol) in DMF (20 mL) at 0 °C was added 3-bromo-2-methylprop-1-ene (1.70 g, 12.5 mmol). The reaction was warmed to rt and was stirred for 16 h. The reaction was quenched with H_2O (20 mL), extracted with diethyl ether (3 × 20 mL), dried over $MgSO_4$, and was concentrated under a vacuum. The crude residue was purified using flash chromatography (5% ethyl acetate in hexanes) to yield the diene (6:1 *E*:*Z* mixture) (1.74 g, 89%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (dd, J = 7.6, 1.2 Hz, 0.83H), 7.29 (d, J = 7.2 Hz, 0.17H), 7.21 (t, J = 8.0 Hz, 0.17H), 7.16 (td, J = 8.4, 1.6 Hz,

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0.83H), 6.83−6.96 (m, 2H), 6.78 (dd, J = 15.6, 1.2 Hz, 0.83H), 6.61 (d, J = 11.6 Hz, 0.17H), 6.25 (dq, J = 16.0, 6.8 Hz, 0.83H), 5.84 (dq, J = 11.6, 6.8 Hz, 0.17H), 5.12 (s, 1H), 5.01 (s, 0.83H), 4.99 (s, 0.17H), 4.47 (s, 2H), 1.91 (dd, J = 6.4, 1.6 Hz, 3H), 1.86 (s, 2.49H), 1.81 (s, 0.51H). These data are consistent with literature values.[25]

3-Methyl-2*H*-chromene (34). To a solution of the diene from the previous protocol (3.12 g, 16.5 mmol) in CH_2Cl_2 (150 mL) was added Hoveyda−Grubbs second generation catalyst (50 mg, 0.080 mmmol). The reaction mixture was heated to 50 °C and stirred for 2 d. More Hoveyda−Grubbs second generation catalyst (50 mg, 0.080 mmmol) was added and stirred for an additional 2 d. The reaction mixture was cooled to rt and concentrated under a vacuum. The crude residue was purified using flash chromatography (1% ethyl acetate in hexanes) to yield the benzopryran (1.97 g, 82%) as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (td, J = 7.8, 1.8 Hz, 1H), 6.91 (dd, J = 7.2, 1.5 Hz, 1H), 6.84 (t, J = 7.2 Hz, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.16 (s, 1H), 4.69 (s, 2H), 1.80 (s, 3H). These data are consistent with literature values.[25]

1-(Allyloxy)-2-(1-dimethylphenylsilylvinyl)benzene. To a solution of (1-bromovinyl)dimethyl(phenyl)silane[26] (3.98 g, 18.6 mmol) in dry, degassed THF (35 mL) at 0 °C was added magnesium ribbon (0.809 g, 33.3 mmol) and LiCl (0.926 g, 21.8 mmol). After stirring for 3 h, the Grignard reagent was cannulated off the excess magnesium ribbon into a different flask. $FeCl_3$ (0.084 g, 0.520 mmol) was added to a vial under an inert atmosphere in a glovebox. The vial was removed from the glovebox, and THF (2.0 mL) and TMEDA (0.242 g, 2.08 mmol) were added prior to cannulating the solution into the flask containing the Grignard reagent. 1-(Allyloxy)-2-bromobenzene (2.50 g, 10.4 mmol) was added, and the flask was stirred for 3 h. Another 1.00 equiv of Grignard reagent was prepared in the same manner as described above and added to the solution via cannulation. After stirring for 16 h, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (50 mL). The solution was extracted with diethyl ether (3 × 50 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude residue was purified using MPLC (2−10% toluene in hexanes) to yield the diene (1.00 g, 33%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52−7.55 (m, 2H), 7.30−7.35 (m, 3H), 7.16 (td, J = 8.0, 2.0 Hz, 1H), 7.00 (dd, J = 7.5, 1.5 Hz, 1H), 6.89 (td, J = 7.5, 1.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.89 (d, J = 3.0 Hz, 1H), 5.86 (ddt, J = 17.0, 10.5, 5.0 Hz, 1H), 5.67 (d, J = 3.0 Hz, 1H), 5.28 (dq, J = 17.0, 1.5 Hz, 1H), 5.20 (dq, J = 10.5, 1.5 Hz, 1H), 4.34 (dt, J = 5.0, 1.5 Hz, 2H), 0.36 (s, 6H).

4-(Dimethylphenylsilyl)-2*H*-chromene (36). To a solution of 1-(allyloxy)-2-(1-dimethylphenylsilylvinyl)benzene (107 mg, 0.363 mmol) in CH_2Cl_2 (5.0 mL) was added Hoveyda−Grubbs second generation catalyst (2.3 mg, 0.004 mmmol). The reaction mixture was heated to 50 °C and stirred for 6 h. The reaction mixture was cooled to rt and concentrated under a vacuum. The crude residue was purified using flash chromatography (2−5% ethyl acetate in hexanes) to yield the benzopryran (69 mg, 72%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56−7.59 (m, 2H), 7.35−7.38 (m, 3H), 7.07 (td, J = 7.6, 1.2 Hz, 1H), 7.01 (dd, J = 7.6, 1.2 Hz, 1H), 6.82 (dd, J = 8.0, 0.8 Hz, 1H), 6.76 (td, J = 7.6, 0.8 Hz, 1H), 6.15 (t, J = 4.0 Hz, 1H), 4.73 (d, J = 3.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 137.8, 134.0, 134.0, 133.7, 129.2, 128.6, 127.9, 127.5, 124.8, 121.1, 116.2, 65.2, −2.1; IR (neat) 3067, 2957, 2919, 1704, 1602, 1484, 1427, 1252, 1220, 1115, 1013, 912, 815, 777, 702; HRMS (ESI) m/z calcd for $C_{17}H_{17}OSi$ [M − H]$^+$ 265.1049, found 265.1049.

3-(2*H*-Chromen-2-yl)propan-1-ol (40). To a solution of terminal alkene **4** (130 mg, 0.75 mg) in THF (2.0 mL) was added 9-BBN dimer (124 mg, 0.52 mmol). After stirring for 1 h, the reaction was cooled to 0 °C. A solution of 2.0 M aqueous NaOH (0.75 mL) and 30% aqueous H_2O_2 (0.75 mL) was added, and the reaction was warmed to rt. After 30 min, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over MgSO4, and concentrated under a vacuum. The crude residue was purified using flash chromatography (2−25% ethyl acetate in hexanes) to yield the primary alcohol (92 mg, 65%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.11 (td, J = 7.6, 1.6 Hz, 1H), 6.97 (dd, J = 7.6, 1.6 Hz, 1H), 6.85 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.41 (d, J = 10.0 Hz, 1H), 5.68 (dd, J = 9.6 3.2 Hz, 1H), 4.91−4.93 (m, 1H), 3.72 (t, J = 6.0 Hz, 2H), 1.76−2.06 (m, 4H); ^{3}C NMR ($CDCl_3$, 100 MHz) δ 153.1, 129.1, 126.4, 125.6, 124.0, 121.8, 121.0, 115.8, 74.9, 62.4, 31.6, 28.1; IR (neat) 3375, 3042, 2919, 1637, 1604, 1485, 1271, 1205, 1038, 932, 753; HRMS (ESI) m/z calcd for $C_{12}H_{14}O_2$ [M]$^+$ 190.0994, found 190.0975.

(*E*)-1-(Trimethylsilyl)-hept-2-ene (5). To a flask containing *E*-1-iodo-1-hexene (7.50 g, 35.7 mmol) in dry, degassed THF (100 mL) at 0 °C was added $Pd(PPh_3)_4$ (1.03 g, 0.893 mmol) and a 1.0 M solution of (trimethylsilyl)methylmagnesium chloride in diethyl ether (46.4 mL, 46.4 mmol). After 2 h, the reaction was quenched with H_2O (50 mL) and a saturated solution of NH_4Cl (50 mL). The aqueous layer was extracted with hexanes (3 × 50 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude residue was purified using flash chromatography (100% hexanes) to yield the silane (5.28 g, 87%) as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.33−5.43 (m, 1H), 5.19−5.29 (m, 1H),1.98 (q, J = 8.8 Hz, 2H), 1.39 (d, J = 10.4 Hz, 2H), 1.28−1.32 (m, 4H), 0.89 (t, J = 8.8 Hz, 3H), −0.01 (s, 9H). These data are consistent with literature values.[27]

(*Z*)-1-(Trimethylsilyl)-hept-2-ene (7). To a flask containing sodium borohydride (0.149 g, 3.93 mmol) in ethanol (4.75 mL) was added a 1.0 M aqueous solution of NaOH (0.25 mL). This solution was sonicated for 5 min, and the remaining solids were filtered away. This $NaBH_4$ solution was then added to a flask containing $Ni(OAc)_2{\cdot}4H_2O$ (1.03 g, 4.15 mmol) in ethanol (300 mL). After stirring for 5 min, ethylenediamine (0.55 mL, 8.28 mmol) was added. After stirring for an additional 5 min, 1-(trimethylsilyl)-hept-2-yne[28] (3.50 g, 20.7 mmol) was added, and the N_2 atmosphere was replaced with an H_2 atmosphere using a balloon. The reaction mixture stirred vigorously for 3 h and was then quenched with H_2O (300 mL). The solution was extracted with hexanes (3 × 200 mL), dried over $MgSO_4$, and was concentrated under a vacuum. The crude residue was purified using flash chromatography (2% diethyl ether in pentanes) to yield the silane (3.31 g, 94%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.36−5.42 (m, 1H), 5.24−5.30 (m, 1H), 1.97−2.01 (2H, m), 1.47 (dt, J = 8.5, 0.5 Hz, 2H), 1.27−1.36 (m, 2H), 0.89 (t, J = 7.0 Hz, 3H), 0.01 (s, 9H). These data are consistent with literature values.[27]

Potassium (*E*)-Dec-1-enyltrifluoroborate (13). To a solution of (*E*)-2-(dec-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[29] (1.50 g, 5.63 mmol) in acetonitrile (14 mL) was added KHF_2 (1.55 g, 19.9 mmol) and H_2O (4.6 mL). The solution was stirred for 2 h and was concentrated. The resulting solid was dissolved in hot acetone and filtered to remove undesired salts. The filtrate was concentrated and dissolved in a minimal volume of hot acetone to dissolve the solid completely. Adding diethyl ether to the solution solidified the desired product. The solid was collected by vacuum filtration to yield the trifluoroborate salt (0.831 g, 60%) as a white solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.44 (dt, J = 17.2, 6.0 Hz, 1H), 5.15−5.22 (m, 1H), 1.85 (q, J = 6.0 Hz, 2H), 1.21−1.29 (m, 12H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 112.2, 112.2, 36.3, 31.5, 29.6, 29.3, 28.9, 28.5, 22.2,14.0; ^{11}B NMR (DMSO-d_6, 125 MHz) δ 2.62; ^{19}F NMR (DMSO-d_6, 376 MHz) δ −140.9; IR (neat) 2917, 2849, 1577, 1540, 1466, 1422, 1155, 1107; HRMS (ESI) m/z calcd for $C_{10}H_{19}BF_3K$ [M]$^+$ 246.1169, found 246.1148; mp >245 °C. These data are consistent with literature values.[30]

(*E*)-Crotyl Trimethylsilane. To a suspension of LAH (6.51 g, 171 mmol) in dimethoxyethane (100 mL) at 0 °C was added 2-butyn-1-ol (10.0 g, 142 mmol) via dimethoxyethane (25 mL) over 20 min. The reaction was warmed to rt and stirred for 48 h before cooling to 0 °C and quenching carefully with H_2O (6.5 mL), 15% aqueous NaOH (6.5 mL), and H_2O (19.5 mL). The remaining solids were filtered off using diethyl ether to wash the solid, and the solution was concentrated at 0 °C under minimal pressure to avoid loss of desired product. The resulting oil was used in the next step without further purification.

To a solution of the crude *E*-crotyl alcohol (10.1 g, 140 mmol) in diethyl ether (150 mL) at 0 °C was added PBr_3 (7.98 mL, 84.0 mmol) dropwise. After 1 h, the reaction was quenched by pouring the solution into a beaker of iced H_2O. The resulting biphasic mixture was extracted with diethyl ether (3 × 150 mL) and dried over $MgSO_4$. The solution was concentrated at 0 °C under minimal pressure to avoid loss of the desired product. The resulting oil was used in the next step without further purification.

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CuCl (0.354 g, 3.56 mmol) was placed into a flask under an inert atmosphere in a glovebox. The flask was sealed and removed from the glovebox, where dry, degassed diethyl ether (75 mL) and triethylamine (26.3 mL, 190 mmol) were added at 0 °C. The crude *E*-crotyl bromide (16.0 g, 119 mmol) was added over 20 min before the reaction was stirred for 1 h at 0 °C and 1 h at rt. The resulting solids were removed by passing the solution through a pad of Celite via diethyl ether. The solution was concentrated at 0 °C under minimal pressure to avoid loss desired product. The resulting oil was used in the next step without further purification.

To a flask containing diethyl ether (100 mL) at 0 °C was added a 3.0 M solution methylmagnesium iodide in diethyl ether (130 mL, 389 mmol). The crude *E*-crotyl trichlorosilane (16.4 g, 86.5 mmol) was added dropwise over 30 min. The resulting solution was refluxed at 40 °C for 16 h. The reaction was cooled to 0 °C and quenched carefully with a saturated solution of NH_4Cl (100 mL). The biphasic mixture was extracted with diethyl ether (3 × 50 mL) and dried over $MgSO_4$. The solution was concentrated at 0 °C under minimal pressure to avoid loss of desired product. The resulting oil was distilled (114 °C) to obtain pure *E*-crotyl silane (6.62 g, 36% over 4 steps) as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.35−5.46 (m, 1H), 5.20−5.32 (m, 1H), 1.65 (dd, J = 6.0, 1.2 Hz, 3H), 1.39 (dt, J = 7.5, 1.2 Hz, 2H), −0.01 (s, 9H). These data are consistent with literature values.[31]

(±)-(*R*)-2-((*R*)-4-Hydroxybutan-2-yl)-2*H*-chromene-6-carbonitrile. To a solution of terminal alkene **32** (312 mg, 1.48 mg) in THF (2.0 mL) was added 9-BBN dimer (285 mg, 1.03 mmol). After stirring for 1 h the reaction was cooled to 0 °C. A solution of 3.0 M aqueous NaOH (1.5 mL) and 30% aqueous H_2O_2 (1.5 mL) was added, and the reaction was warmed to rt. After 30 min, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude residue was purified using flash chromatography (2−25% ethyl acetate in hexanes) to yield the primary alcohol (242 mg, 72%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (dd, J = 8.5, 2.0 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 6.42 (dd, J = 10.0, 2.0 Hz, 1H), 5.76 (dd, J = 10.0, 3.0 Hz, 1H), 4.94−4.96 (m, 1H), 3.75−3.79 (m, 1H), 3.68−3.73 (m, 1H), 2.04−2.09 (m, 1H), 1.88−1.92 (m, 1H), 1.45−1.51 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H).

(±)-(*R*)-2-((*R*)-4-Oxobutan-2-yl)-2*H*-chromene-6-carbonitrile. To a mixture of the hydroboration product (125 mg, 0.550 mmol) and $NaHCO_3$ (92 mg, 1.1 mmol) in CH_2Cl_2 (5.5 mL) was added Dess−Martin periodinane (350 mg, 0.825 mmol). After 1 h, the reaction was quenched with H_2O (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, and concentrated under a vacuum. The crude residue was purified using flash chromatography (10−20% ethyl acetate in hexanes) to yield the aldehyde (86 mg, 69%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.79 (s, 1H), 7.39 (dd, J = 8.0, 1.6 Hz, 1H), 7.24 (d, J = 1.6 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 10.4 Hz, 1H), 5.76 (dd, J = 10.0, 3.2 Hz, 1H), 4.88−4.89 (m, 1H), 2.74 (dd, J = 16.8, 3.6 Hz, 1H), 2.52 (quin, J = 6.4 Hz, 1H), 2.38 (ddd, J = 16.8, 8.0, 1.6 Hz, 1H), 1.11 (d, J = 6.8 Hz, 1H).

(±)-(*R*)-2-((*R,E*)-4-(2-(2,4-dinitrophenyl)hydrazono)butan-2-yl)-2*H*-chromene-6-carbonitrile (44). To a solution of the aldehyde (86 mg, 0.38 mmol) and 2,4-dinitrophenylhydrazine (107 mg, 0.377 mmol) in ethanol (3.0 mL) was added one drop of acetic acid. The resulting mixture was refluxed for 2 h and cooled back to rt. The resulting solid was collected via vacuum filtration. The crude solid was purified using flash chromatography (0.5% triethylamine, 10−40% ethyl acetate in hexanes) to yield the hydrazone as an 8:1 mixture of geometrical isomers (90 mg, 59%). The solid was recrystallized using the 2-layer method with diethyl ether and hexanes: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.19 (s, 0.11H), 11.06 (s, 0.89H), 9.16 (m, 0.11H), 9.15 (d, J = 2.4 Hz, 0.89H), 8.36 (dd, J = 9.6, 2.0 Hz, 0.11H), 8.32 (dd, J = 9.6, 2.4 Hz, 0.89H), 7.96 (d, J = 9.6 Hz, 0.11H), 7.89 (d, J = 9.6 Hz), 7.56 (t, J = 5.6 Hz, 1H), 7.42 (dd, J = 8.8, 1.6 Hz, 1H), 7.23 (d, J = 1.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 0.11H), 6.81 (d, J = 8.8 Hz, 0.89H), 6.52 (m, 0.11H) 6.49 (d, J = 10.0 Hz, 0.89H), 5.84 (m, 0.11H), 5.75 (dd, J = 9.6, 2.4 Hz, 0.89H), 4.95 (m, 0.89H), 4.92 (m, 0.11H), 2.67−2.79 (m, 1H), 2.36−2.44 (m, 1H), 2.26−2.32 (m, 1H), 1.18 (d, J = 6.8 Hz, 2.67H), 1.14 (d, J = 7.2 Hz, 0.33H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.1, 156.8, 150.6, 148.8, 145.1, 144.9, 138.3, 137.8, 133.7, 133.6, 130.3, 130.0, 129.9, 129.5, 128.7, 128.2, 125.0, 124.7, 123.7, 123.4, 123.3, 123.2, 121.9, 121.8, 118.8, 116.7, 116.5, 116.4, 104.4, 104.2, 79.6, 79.4, 37.2, 34.6, 15.9, 15.5; mp 138−141 °C.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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