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Base-Mediated Cyclocondensation of Salicylaldehydes and 2-Bromoallyl Sulfones for the Synthesis of 3-Sulfonylchromene Derivatives and Their Regioselective Friedel–Crafts Heteroarylation Reactions

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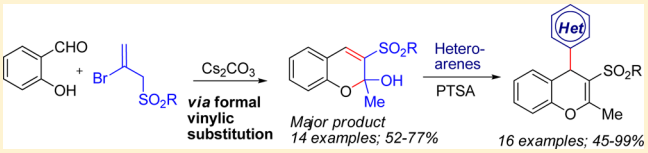
Supporting Information

ABSTRACT: Cesium carbonate-mediated reaction of 2-hydroxybenzaldehydes and 2-bromoallyl sulfones afforded 2*H*- and 4*H*-chromenol derivatives endowed with a 3-arylsulfonyl group. 2-Bromoallyl sulfones functioned as synthetic equivalents of allenyl sulfones under these conditions. The 2*H*- and 4*H*-chromenol derivatives underwent regioselective Friedel–Crafts reactions with heteroarenes in the presence of *p*-toluenesulfonic acid to afford 4-heteroaryl-4*H*-chromene derivatives in excellent yields.



INTRODUCTION

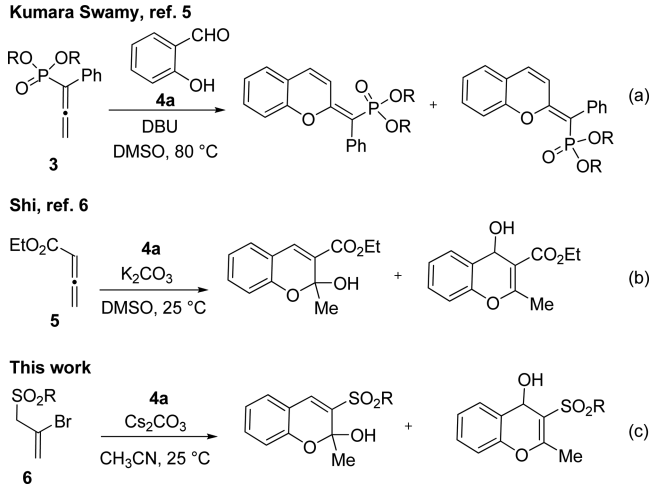
Unsaturated 1-benzopyran derivatives, commonly known as chromenes, form the central unit of many biologically active natural products as well as synthetic therapeutic agents.[1] The chromene nucleus is, therefore, generally regarded as a privileged scaffold in medicinal chemistry. It exists in two isomeric forms, 2*H*-chromene **1** and 4*H*-chromene **2**, that can be distinguished by the site of unsaturation (Figure 1).

Figure 1. Isomeric forms of chromene.

Consequently, method development for chromene synthesis has become an important and fertile area of investigation.[2,3] Although a number of methods are available for their construction, there is considerable demand for general approaches that deliver substituted chromenes from readily available precursors.

Salicyclic aldehydes constitute a group of useful building blocks for the synthesis of 1-benzopyran derivatives. Recent investigations by Shi, Bräse, and others have established that the base-mediated cyclocondensation of salicylic aldehydes and α,β-unsaturated carbonyl compounds is a versatile method for accessing dihydrobenzopyran derivatives.[4] More pertinent to the work reported here is the use of *o*-hydroxybenzaldehydes and electron deficient allenes as building blocks for chromene derivatives. DBU-catalyzed cyclocondensation of allenyl phophonates **3** and salicylaldehyde **4a** was developed by Kumara Swamy (Scheme 1a).[5] Shi reported that allenyl esters **5** react with **4a** in the presence of catalytic quantities of base to afford 2*H*- and 4*H*-chromenes (Scheme 1b).[6] Our interest in the cyclocondensation reactions of unsaturated sulfones[7] prompted us to explore their utility in the synthesis of sulfone-bearing chromenes. In the process, it was revealed that 3-sulfonylchromenes can be readily synthesized from salicyclic aldehydes and bromoallyl sulfones **6** via a base-mediated annulation (Scheme 1c). Importantly, the direct use of sensitive allenyl sulfones[8] was avoided by devising and exploiting a base-mediated vinylic bromide displacement on bromoallyl sulfone **6**.

Scheme 1. Base-Mediated Cyclocondensations of Salicyclic Aldehydes and Electron Deficient Allenes for the Synthesis of Chromene Derivatives



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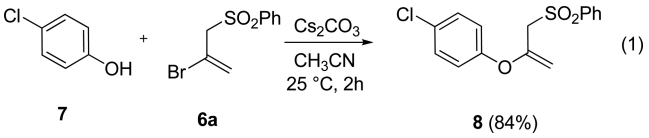
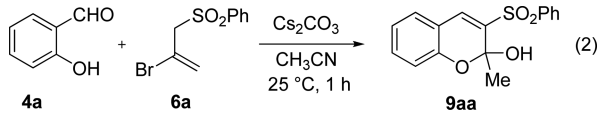
RESULTS AND DISCUSSION

The results described in this article originated from our observation that bromoallyl sulfone **6a**[9] readily undergoes base-mediated vinylic substitution reactions with nucleophiles. For example, the treatment of **6a** with 4-chlorophenol **7** in the presence of 2 equiv of cesium carbonate afforded enol ether **8** in 84% yield (eq 1). Evidently, **8** is formed via a formal vinylic



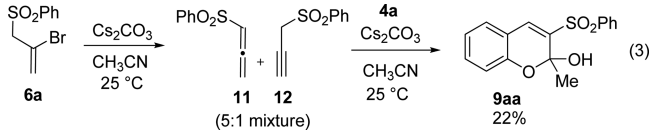
substitution that usually requires the use of transition metal catalysts. Analogous vinylic displacement reactions of sulfonamide nucleophiles and subsequent gold-catalyzed cycloisomerization reactions were recently developed in our laboratory.[10]

We surmised that under the basic conditions of vinylic substitution, the sulfonylmethylene moiety of the enol ether product (such as **8**) may be deprotonated and engaged in an annulation reaction with a tethered electrophile. Although deprotonation adjacent to sulfonyl group typically requires a strong base such as butyl lithium, our recent investigations revealed that milder bases like cesium carbonate and DBU are effective in promoting intramolecular condensations of sulfones and aldehydes.[7] Thus, salicylaldehyde **4a** was employed as the phenol component in the vinylic substitution, and in the event, 2*H*-chromene derivative **9aa** was obtained as the product in 69% yield (eq 2).



Further experiments to explore the scope and generality of this annulation reaction revealed an interesting pattern of reactivity. Salicylaldehyde as well as *o*-hydroxybenzaldehydes carrying electron-donating substituents generally afforded 2*H*-chromene derivatives **9** preferentially (Table 1, entries 1−6). On the other hand, *o*-hydroxybenzaldehydes endowed with one or more electron-withdrawing substituents furnished isomeric 4*H*-chromene derivatives **10** as the sole or major product (Table 1, entries 8 and 10−14). Halogen-bearing salicylaldehydes deviated from this general trend to some extent (entries 7 and 9). It may be noted that formation of 2*H*- and 4*H*-chromenes was observed in the base-catalyzed reactions of salicylaldehydes and allenoates by Shi; however, no clear trend in reactivity was discernible.[6a]

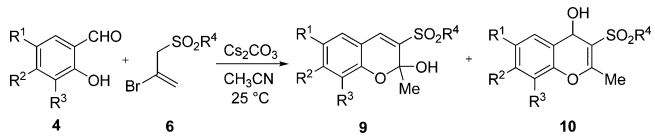
To gain insights into the mechanistic underpinnings of this transformation, the reaction of bromoallyl sulfones with cesium carbonate was conducted. An inseparable mixture of allenyl sulfone **11**[11] and propargyl sulfone **12**[12] was obtained after workup and column chromatography. Further treatment of the mixture of **11** and **12** with salicylaldehyde **4a** and base afforded 2*H*-chromene **9aa** in 22% yield (eq 3). The use of bromoallyl



sulfone **6** in this transformation is, therefore, advantageous in view of the improved pot-economy as well as overall efficiency. Moreover, allenyl sulfones (such as **11**) are base-sensitive and tend to undergo nucleophile-triggered oligomerization reactions.[8] The relative scarcity of studies involving allenyl sulfones vis-à-vis analogous allenoates may be attributed to these factors. Here, the utility of 2-bromoallyl sufones **6a** and **6b** as stable and readily available surrogates of allenyl sulfones is demonstrated.

Additionally, it was observed that 4*H*-chromene **10eb** readily isomerized to furnish the corresponding 2*H*-isomer **9eb** in near quantitative yield upon exposure to catalytic PTSA in DMSO (eq 4).

Table 1. Scope of the Cyclocondensation of Salicylic Aldehydes and 2-Bromoallyl Sulfones[a]



entry	aldehyde	bromoallyl sulfone	time (h)	product(s)	yield[b] (%)
1	**4a**, $R^1 = R^2 = R^3 = H$	**6a**, R^4 = Ph	1	**9aa**	69
2	**4a**, $R^1 = R^2 = R^3 = H$	**6b**, R^4 = *p*-tolyl	2	**9ab**	65
3	**4b**, R^1 = OMe, $R^2 = R^3 = H$	**6a**, R^4 = Ph	3	**9ba**	61
4	**4b**, R^1 = OMe, $R^2 = R^3 = H$	**6b**, R^4 = *p*-tolyl	4	**9bb**	75
5	**4c**, R^1 = H, R^2 = OMe, R^3 = H	**6a**, R^4 = Ph	2	**9ca**	55
6	**4c**, R^1 = H, R^2 = OMe, R^3 = H	**6b**, R^4 = *p*-tolyl	2	**9cb**	60
7	**4d**, R^1 = Cl, $R^2 = R^3 = H$	**6a**, R^4 = Ph	2	**9da**	52
8	**4d**, R^1 = Cl, $R^2 = R^3 = H$	**6b**, R^4 = *p*-tolyl	2	**10db**	67
9	**4e**, R^1 = Br, $R^2 = R^3 = H$	**6a**, R^4 = Ph	4	**9ea** and **10ea**[c]	53
10	**4e**, R^1 = Br, $R^2 = R^3 = H$	**6b**, R^4 = *p*-tolyl	4	**10eb**	62
11	**4f**, R^1 = Cl, R^2 = H, R^3 = Br	**6a**, R^4 = Ph	4	**10fa**	66
12	**4f**, R^1 = Cl, R^2 = H, R^3 = Br	**6b**, R^4 = *p*-tolyl	4	**9fb** and **10fb**[d]	77
13	**4g**, $R^1 = NO_2$, R^2 = H, R^3 = Br	**6a**, R^4 = Ph	4	**10ga**	55
14	**4g**, $R^1 = NO_2$, R^2 = H, R^3 = Br	**6b**, R^4 = *p*-tolyl	4	**10gb**	54

[a]Reaction conditions: **4a−g** (1.0 mmol), **6a** or **6b** (1.5 mmol), Cs_2CO_3 (2.5 mmol), and CH_3CN (8 mL). [b]Isolated yield. [c]A 10:3 inseparable mixture. [d]A 4:10 inseparable mixture.

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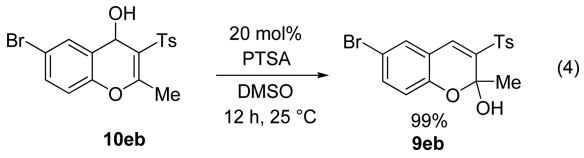
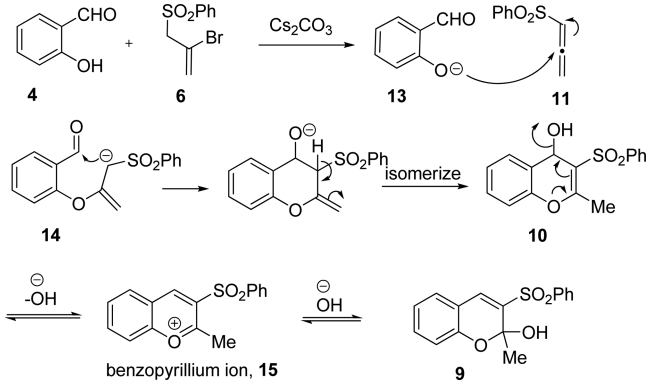


In view of these observations (eq 3), allenyl sulfone **11** is deemed to be a very likely intermediate in the reaction of salicylaldehyde with bromoallyl sulfones **6**. A mechanistic rationale for the formation of chromene derivatives is presented in Scheme 2. Conjugate addition of the phenoxide ion **13** to the

Scheme 2. Plausible Mechanistic Rationalization for the Formation of Chromene Derivatives

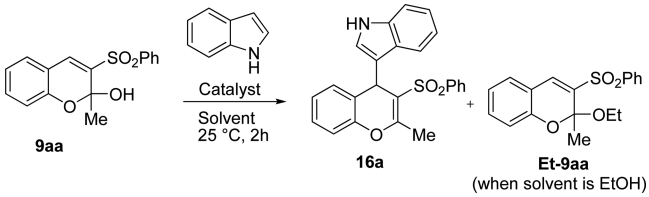


sulfonyl allene **11** generates an α-sulfonyl carbanion **14**. Intramolecular nucleophilic addition of the α-sulfonyl carbanion to the aldehyde and subsequent double-bond isomerization affords the 4*H*-chromene derivative **10**. Isomerization of the latter to the 2*H*-chromene derivative **9** may proceed via the benzopyrilium ion **15**. A similar isomerization was observed by Shi in the base-catalyzed reaction of salicylaldehydes with allenyl carboxylates.[6a] The preferential formation of the 2*H*-chromene derivatives **9** from *o*-hydroxybenzaldehydes carrying electron-releasing groups on the ring may be explained by the enhanced stability of the corresponding benzopyrilium ions **15**.

The apparent involvement of benzopyrilium ions **15** in the formation of **9** prompted us to explore the possibility of its reactions with electron rich aromatic compounds such as indole with an eye on generating heteroaryl chromene derivatives.[13] The reaction of **9aa** with indole was attempted in the presence of various acid catalysts in ethanol and dichloromethane, and the results are summarized in Table 2. In almost all cases, facile conversion of **9aa** to 4*H*-chromene **16a** was observed. The 4-(3-indolyl)-4*H*-chromene derivative **16a** was characterized by spectroscopic analysis. The benzylic proton of **16a** appeared as a singlet at δ 5.53, and the corresponding carbon resonated at δ 33.5 in the ^{1}H and ^{13}C NMR spectra. All other signals were in agreement with the assigned structure. The reactions in ethanol consistently afforded higher yields of **16a**, albeit with varying amounts of ethyl ketal **Et-9aa**. The use of *p*-toluenesulfonic acid as the mediator (50 mol %), however, produced only the 4*H*-chromene derivative **16a** in 72% yield (entry 8). The quantitative yield of **16a** was obtained when the loading of *p*-TSA was increased to 70 mol % (entry 10).

It is conceivable that the corresponding benzopyrilium ion **15** underwent a regioselective Friedel–Crafts reaction with indole at the more accessible secondary benzylic carbon. The scope of this reaction was examined subsequently, and it was

Table 2. Optimization of Conditions for the Acid-Mediated Reaction of 9aa and Indole[a]

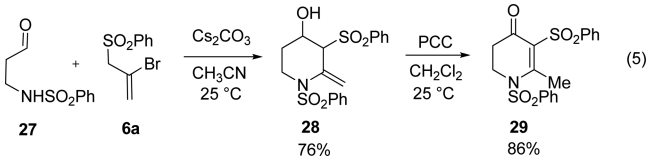


entry	catalyst (mol %)	solvent	products	yields[b] (%)
1	BF_3-OEt_2 (50)	CH_2Cl_2	**16a**	42
		EtOH	**16a** and **Et-9aa**	51 and 23
2	$Bi(OTf)_3$ (50)	CH_2Cl_2	**16a**	48
		EtOH	**16a** and **Et-9aa**	57 and 13
3	$Yb(OTf)_3$ (50)	CH_2Cl_2	**16a**	44
		EtOH	**16a** and **Et-9aa**	52 and 27
4	$AlCl_3$ (50)	EtOH	**16a** and **Et-9aa**	40 and 15
5	$FeCl_3$ (50)	EtOH	**16a** and **Et-9aa**	49 and 24
6	$SnCl_4$ (50)	EtOH	**16a** and **Et-9aa**	51 and 28
7	$ZnCl_2$ (50)	EtOH	**16a** and **Et-9aa**	44 and 41
8	*p*-TSA (50)	EtOH	**16a**	72
9	*p*-TSA (60)	EtOH	**16a**	84
10	***p*-TSA (70)**	**EtOH**	**16a**	**99**

[a]Reaction conditions: indole (0.15 mmol), **9aa** (0.2 mmol), acid mediator (50–70 mol %), solvent (2 mL), 25 °C, 2 h. [b]Isolated yields.

found that a variety of indoles react in an analogous fashion to afford the corresponding 4-(3-indolyl)-4*H*-chromenes **16–22** in excellent yields (Table 3). Other heterocyclic aromatics such as pyrrole and furan also furnished the corresponding 4-hetroaryl-4*H*-chromenes **23–26**. It is important to note that 4-heteroaryl-4*H*-chromenes were formed from isomeric chromenol **9** or **10**. This is illustrated by the formation of products **22** and **24** from 4*H*-chromenol **10eb** as well as the formation of **25** from **10fa**. This observation is consistent with the intermediacy of the purported benzopyrilium ion. Additionally, attempted reactions of aromatic compounds such as thiophene, toluene, and benzene led to the formation of ethanol-derived ketal **Et-9aa**. The latter was isolated in 71% yield when the reaction was run without any heteroarene. A variety of 4-aryl-4*H*-chromenes have been shown to possess excellent anticancer activities,[14] and this protocol allows for the facile construction of hitherto unknown sulfonyl derivatives of 4-heteroaryl-4*H*-chromenes. It may be mentioned here that our efforts to reductively remove or substitute the sulfonyl groups of 4-heteroaryl-4*H*-chromenes were not successful.

The base-mediated cyclocondensation reaction initiated by the vinylic displacement of the bromoallyl sulfone **6a** can also be adapted for the construction of other related heterocycles (eq 5). In light of our recent findings about the addition of



sulfonamide nucleophiles to bromoallyl sulfones,[10] we surmised that the β-(aminosulfonyl)aldehyde **27**[15] could partake in a vinylic displacement–cyclization reaction with bromoallyl sulfone **6a** to afford a six-membered nitrogen heterocycle. The widespread occurrence of piperidines and piperidones in

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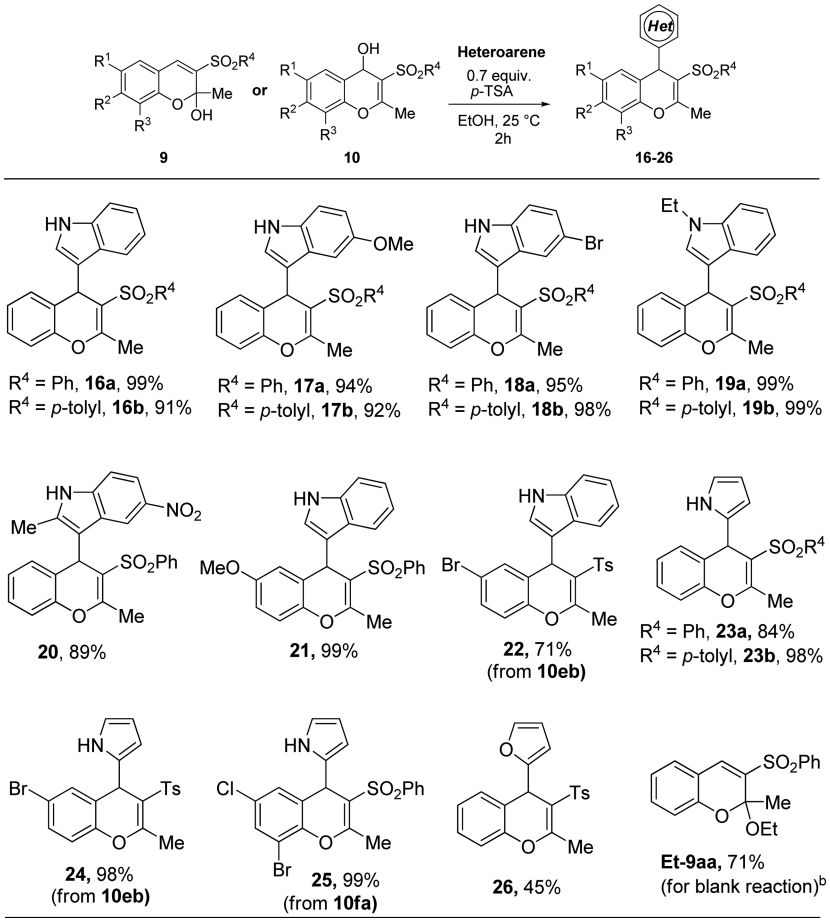
Table 3. Scope of the *p*-TSA-Mediated Reaction of Heteroaromatic Compounds with 9 and 10[a]



[a]Reaction conditions: heteroarene (0.30 mmol), 2*H*-chromene (0.40 mmol), *p*-TSA (0.21 mmol), EtOH (2 mL), 25 °C, 2 h. Isolated yields given. [b]Reaction conducted under the conditions described in footnote *a* but in the absence of heteroarene.

natural alkaloids and synthetic compounds of medicinal importance provided an additional impetus for this preliminary study.[16] Gratifyingly, the reaction of **27** with **6a** under the conditions of vinylic displacement afforded the substituted piperidine **28** in 76% yield. Oxidation of the latter by pyridinium chlorochromate (PCC) furnished the 4-piperidone derivative **29** in 86% yield. It may be noted that the oxidation was accompanied by the migration of the exocyclic double bond of **28** to an endocyclic position in conjugation with the carbonyl group (eq 5).

CONCLUSION

The following important developments have emerged from this study. (i) A transition metal-free, vinylic bromide displacement reaction of bromoallyl sulfones **6** with phenolate nucleophiles was discovered. (ii) Under these conditions, **6** functioned as a synthetic equivalent of allenyl sulfones and underwent a smooth cyclocondensation with salicylic aldehydes. (iii) The sulfonyl chromenols thus formed underwent acid-mediated regioselective Friedel–Crafts reactions to afford 4-heteroaryl-4*H*-chromenes. Additionally, in view of the biological activities displayed by chromenes in general and 4-aryl-4*H*-chromenes in particular, the synthetic methods described here have potential for applications in medicinal chemistry programs. The success of *p*-TSA-mediated addition of heteroaromatics to the chromenols bodes well for the development of asymmetric versions of the reaction by using chiral Brønsted acids.[17] Preliminary results suggest that the vinylic bromide displacement method can also be applied for the construction of six-membered nitrogen heterocycles.

EXPERIMENTAL SECTION

All reactions were performed in flame-dried round-bottom flasks, fitted with rubber septa under a positive pressure of nitrogen. Analytical thin-layer chromatography (TLC) was performed using aluminum-backed UVF254 precoated silica gel flexible plates. Removal of solvent under reduced pressure refers to distillation with a rotary evaporator attached to a vacuum pump (~3 mmHg). Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was conducted using silica gel (60–120 mesh and 100–200 mesh) packed in glass columns. Melting points were obtained in open capillary tubes using a micromelting point apparatus and are uncorrected. NMR spectra were recorded on a 300, 400, or 500 MHz nuclear magnetic resonance spectrometer. The proton resonances are annotated as chemical shifts (δ) relative to tetramethylsilane (δ 0.0) using the residual solvent signal as an internal standard or tetramethylsilane itself: chloroform-*d* (δ 7.26, singlet), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant (*J*, in hertz), and the number of protons for a given resonance indicated by *n*H. The chemical shifts of ^{13}C NMR are reported in parts per million relative to the central line of the triplet at 77.0 ppm for $CDCl_3$. IR spectra were recorded on an FT-IR spectrometer, and wavenumbers of maximal absorption peaks are presented in inverse centimeters. High-resolution mass analyses (HRMS) were performed on a mass spectrometer using ESI-TOF techniques. Acetonitrile (LR grade), dimethyl sulfoxide (LR

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grade), ethanol (95%), cesium carbonate (AR), and *p*-toluenesulfonic acid were purchased from local suppliers and used as received. 2-Hydroxybenzaldehydes **4a−g**, 2,3-dibromopropene, sodium benzenesulfinate, sodium *p*-toluenesulfinate, 3-amino-1-propanol, pyridinium chlorochromate (PCC), and the heteroarenes used for the Friedel−Crafts reactions were used as received from suppliers. 2-(Bromoallylsulfonyl)benzene **6a**,[9] allenyl sulfone **11**,[11] and propargyl sulfone **12**[12] are known compounds and were identified by comparison of their spectroscopic data with the reported values. *N*-(3-Oxopropyl)benzenesulfonamide **27** was prepared from 3-amino-1-propanol as reported previously.[15]

General Procedure for the Preparation of 1-(2-Bromoallyl)-sulfonylbenzene 6a or 1-(2-Bromoallyl)sulfonyl-4-methylbenzene 6b. Sodium benzenesulfinate or sodium *p*-toluenesulfinate (10 mmol) was added to DMF (10 mL) in a round-bottom flask and left to stir for 20 min. To this suspension was added 2,3-dibromopropene (technical grade 80%, 1.22 mL, 10 mmol), and the mixture was stirred at room temperature under nitrogen for 12 h. After the completion of the reaction, ice and ethyl acetate (20 mL) were added and the mixture was stirred for 15 min. Water (20 mL) was added, and the organic layer was separated in a separatory funnel. The aqueous layer was extracted with ethyl acetate (2 × 15 mL); the organic layers were combined, and the solvent was removed on a rotavapor. The residue obtained was purified by column chromatography on silica gel using ethyl acetate/hexane mixtures as the eluent to obtain pure samples of **6a** or **6b**.

*(2-Bromoallylsulfonyl)benzene (**6a**).*[9] White solid (1.51 g, 58%): R_f = 0.6 (30% ethyl acetate in hexanes); mp 77−79 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 8.5 Hz, 2H), 7.71−7.68 (m, 1H), 7.60−7.57 (m, 2H), 5.84 (d, J = 2.1 Hz, 1H), 5.77 (d, J = 2.1 Hz, 1H), 4.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 134.1, 129.1, 128.7, 126.5, 117.1, 66.2; IR (KBr) ν_{max} 3423, 2981, 2919, 1622, 1584, 1447, 1393, 1307, 1256, 1141, 907 cm^{-1}.

*1-(2-Bromoallylsulfonyl)-4-methylbenzene (**6b**).* White solid (1.56 g, 57%): R_f = 0.6 (30% ethyl acetate in hexanes); mp 89−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 5.83 (d, J = 2.1 Hz, 1H), 5.77 (d, J = 2.1 Hz, 1H), 4.14 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 134.8, 129.7, 128.7, 126.3, 117.3, 66.3, 21.6; IR (KBr) ν_{max} 2920, 1623, 1467, 1393, 1308, 1256, 1141, 1084, 908 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{11}BrO_2SNa$ (M + Na) 296.9561, found 296.9568.

General Procedure for the Cesium Carbonate-Mediated Reaction of Phenolic Substrates (4a−g and 7) with 2-Bomoallyl Sulfones 6a and 6b. 2-Bromoallyl sulfonylbenzene **6a** or 2-bromoallyl sulfonyl-4-methylbenzene **6b** (1.5 mmol) and the phenolic substrate (1.0 mmol) were dissolved in acetonitrile (8 mL) at room temperature in a 25 mL round-bottom flask. Cesium carbonate (815 mg, 2.5 mmol) was added, and the reaction mixture was stirred under nitrogen for the required amount of time. Upon completion, the solvent was evaporated on a rotavapor, water (20 mL) was added, and the resulting solution was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated on a rotavapor, and the residue obtained was subjected to column chromatography on silica gel using an ethyl acetate/hexane mixture as the eluent.

*1-Chloro-4-[3-(phenylsulfonyl)prop-1-en-2-yloxy]benzene (**8**).* White solid (259 mg, 84%): R_f = 0.6 (30% ethyl acetate in hexanes); mp 78−80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 7.5 Hz, 2H), 7.69−7.66 (m, 1H), 7.59−7.56 (m, 2H), 7.28−7.26 (m, 2H), 6.79 (d, J = 8.5 Hz, 2H), 4.42 (d, J = 2.1 Hz, 1H), 4.20 (d, J = 2.1 Hz, 1H), 4.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 151.6, 138.8, 133.9, 130.2, 129.8, 129.08, 128.6, 122.3, 96.1, 61.3; IR (KBr) ν_{max} 2926, 2358, 1643, 1485, 1318, 1290, 1218, 1149, 1083, 968 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}ClO_3SNa$ (M + Na) 331.0172, found 331.0166.

*2-Methyl-3-(phenylsulfonyl)-2H-chromen-2-ol (**9aa**).* Yellow solid (208 mg, 69%): R_f = 0.5 (30% ethyl acetate in hexanes); mp 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 2H), 7.83 (s, 1H), 7.66−7.62 (m, 1H), 7.57−7.54 (m, 2H), 7.38−7.35 (m, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 3.52 (s, 1H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 140.4, 135.2, 134.1, 133.5, 133.2, 129.5, 129.1, 128.1, 122.2, 118.3, 117.0, 97.4, 26.6; IR (KBr) ν_{max} 3438, 3062, 2924, 1688, 1613, 1481, 1303, 1149, 1113, 941, 862, 751, 727, 682, 641 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{14}O_4SNa$ (M + Na) 325.0510, found 325.0508.

*2-Methyl-3-tosyl-2H-chromen-2-ol (**9ab**).* Yellow solid (205 mg, 65%): R_f = 0.4 (30% ethyl acetate in hexanes); mp 161−163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 2H), 7.79 (s, 1H), 7.38−7.33 (m, 4H), 7.07−7.02 (m, 1H), 6.97 (d, J = 8.1 Hz, 1H), 3.51 (s, 1H), 2.44 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 144.6, 137.4, 134.7, 134.4, 133.1, 129.8, 129.4, 128.2, 122.2, 118.4, 117.0, 97.5, 26.5, 21.6; IR (KBr) ν_{max} 3447, 3063, 2952, 1618, 1304, 1146, 943, 754, 676 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}O_4SNa$ (M + Na) 339.0667, found 339.0670.

*6-Methoxy-2-methyl-3-(phenylsulfonyl)-2H-chromen-2-ol (**9ba**).* Yellow solid (202 mg, 61%): R_f = 0.5 (30% ethyl acetate in hexanes); mp 155−157 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97−7.95 (m, 2H), 7.78 (s, 1H), 7.65−7.62 (m, 1H), 7.57−7.53 (m, 2H), 6.94 (dd, J = 2.8, 8.9 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 3.80 (s, 3H), 3.47 (s, 1H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 146.8, 140.4, 135.2, 134.7, 133.5, 129.1, 128.2, 119.9, 118.6, 117.9, 112.7, 97.3, 55.8, 26.3; IR (KBr) ν_{max} 3457, 3105, 3009, 2945, 1572, 1491, 1301, 1148, 1083, 940, 725, 690 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}O_5SNa$ (M + Na) 355.0616, found 355.0620.

*6-Methoxy-2-methyl-3-tosyl-2H-chromen-2-ol (**9bb**).* Pale yellow solid (260 mg, 75%): R_f = 0.3 (30% ethyl acetate in hexanes); mp 148−150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 7.8 Hz, 2H), 7.74 (s, 1H), 7.34 (d, J = 7.8 Hz, 2H), 6.94−6.89 (m, 2H), 6.85 (s, 1H), 3.80 (s, 3H), 3.47 (s, 1H), 2.44 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 146.8, 144.6, 137.3, 135.0, 134.7, 129.8, 128.2, 119.8, 118.7, 117.9, 112.6, 97.3, 55.8, 26.2, 21.6; IR (KBr) ν_{max} 3407, 3083, 2951, 1569, 1488, 1305, 1267, 1149, 1095, 1027, 822, 687 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}O_5SNa$ (M + Na) 369.0773, found 369.0778.

*7-Methoxy-2-methyl-3-(phenylsulfonyl)-2H-chromen-2-ol (**9ca**).* Pale yellow solid (183 mg, 55%): R_f = 0.4 (30% ethyl acetate in hexanes); mp 124−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 7.2 Hz, 2H), 7.79 (s, 1H), 7.65−7.60 (m, 1H), 7.56−7.52 (m, 2H), 7.26 (d, J = 8.5 Hz, 1H), 6.61 (dd, J = 2.2, 8.5 Hz, 1H), 6.50 (d, J = 2.2 Hz, 1H), 3.81 (s, 3H), 3.57 (s, 1H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 154.6, 140.8, 135.4, 133.4, 130.7, 130.4, 129.1, 128.0, 111.6, 109.6, 101.7, 97.8, 55.6, 26.4; IR (KBr) ν_{max} 3447, 3064, 2930, 1616, 1297, 1147, 1093, 730, 622 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}O_5SNa$ (M + Na) 355.0616, found 355.0619.

*7-Methoxy-2-methyl-3-tosyl-2H-chromen-2-ol (**9cb**).* Pale yellow solid (208 mg, 60%): R_f = 0.4 (30% ethyl acetate in hexanes); mp 136−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 2H), 7.77 (s, 1H), 7.35−7.25 (m, 3H), 6.61 (d, J = 8.3 Hz, 1H), 6.51 (s, 1H), 3.82 (s, 3H), 3.67 (s, 1H), 2.45 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 154.5, 144.3, 137.8, 134.9, 130.8, 130.6, 129.7, 128.1, 111.7, 109.5, 101.7, 97.8, 55.5, 26.4, 21.6; IR (KBr) ν_{max} 3447, 3000, 2944, 1609, 1285, 1141, 1091, 673 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}O_5SNa$ (M + Na) 369.0773, found 369.0770.

*6-Chloro-2-methyl-3-(phenylsulfonyl)-2H-chromen-2-ol (**9da**).* Pale yellow solid (175 mg, 52%): R_f = 0.6 (30% ethyl acetate in hexanes); mp 145−147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 7.5 Hz, 2H), 7.73 (s, 1H), 7.67−7.64 (m, 1H), 7.58−7.55 (m, 2H), 7.33−7.29 (m, 2H), 6.91 (d, J = 8.5 Hz, 1H), 3.51 (s, 1H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 140.0, 135.6, 133.9, 133.8, 132.8, 129.2, 128.6, 128.3, 127.2, 119.5, 118.5, 97.8, 26.6; IR (KBr) ν_{max} 3436, 3061, 3006, 2950, 1619, 1476, 1308, 1156, 1087, 950, 866, 730, 685 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}ClO_4SNa$ (M + Na) 359.0121, found 359.0127.

*6-Chloro-2-methyl-3-tosyl-4H-chromen-4-ol (**10db**).* Pale yellow solid (235 mg, 67%): R_f = 0.6 (30% ethyl acetate in hexanes); mp 181−183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 2.3 Hz, 1H), 7.37−7.28 (m, 3H), 7.02 (d, J = 8.3 Hz, 1H), 5.70 (d, J = 3.8 Hz, 1H), 3.70 (d, J = 3.8 Hz, 1H), 2.45 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 147.9, 144.4, 138.7, 130.1, 129.9, 129.8, 129.5, 127.2, 122.6, 117.9, 116.1, 60.8, 21.6, 18.5; IR (KBr) ν_{max}

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3486, 2914, 1635, 1480, 1303, 1248, 1146, 1088, 983, 819, 677, 604 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}ClO_4SNa$ (M + Na) 373.0277, found 373.0278.

*6-Bromo-2-methyl-3-(phenylsulfonyl)-2H-chromen-2-ol (**9ea**) and 6-Bromo-2-methyl-3-(phenylsulfonyl)-4H-chromen-4-ol (**10ea**) (1:0.3 inseparable mixture).* Pale yellow solid (201 mg, 53%): R_f = 0.5 (30% ethyl acetate in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.00−7.94 (m, 2.6H), 7.72 (s, 1H), 7.65−7.43 (m, 6.8H), 6.96 (d, J = 8.9 Hz, 0.3H), 6.86 (d, J = 8.5 Hz, 1H), 5.71 (d, J = 2.6 Hz, 0.3H), 3.67 (d, J = 2.6 Hz, 0.3H), 3.55 (s, 1H), 2.43 (s, 1H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 140.0, 135.7, 133.8, 133.7, 133.4, 132.7, 132.5, 131.6, 129.3, 129.2, 128.3, 127.9, 127.1, 120.0, 118.9, 118.2, 114.3, 97.7, 60.7, 26.6, 18.6; IR (KBr) ν_{max} 3486, 3441, 3058, 1477, 1306, 1247, 1150, 1105, 1084, 881, 719, 648 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}BrO_4SNa$ (M + Na) 402.9616, found 402.9608.

*6-Bromo-2-methyl-3-tosyl-4H-chromen-4-ol (**10eb**).* Yellow solid (244 mg, 62%): R_f = 0.6 (30% ethyl acetate in hexanes); mp 206−208 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 2.3 Hz, 1H), 7.42 (dd, J = 2.3, 8.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.9 Hz, 1H), 5.68 (d, J = 3.2 Hz, 1H), 3.70 (d, J = 3.2 Hz, 1H), 2.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 148.4, 144.5, 138.7, 132.7, 132.5, 129.9, 127.2, 123.0, 118.2, 117.5, 116.2, 60.7, 21.6, 18.5; IR (KBr) ν_{max} 3486, 3065, 2910, 1635, 1477, 1299, 1247, 1145, 1088, 980, 817, 674 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}BrO_4SNa$ (M + Na) 416.9772, found 416.9777.

*8-Bromo-6-chloro-2-methyl-3-(phenylsulfonyl)-4H-chromen-4-ol (**10fa**).* Pale yellow solid (273 mg, 66%): R_f = 0.7 (30% ethyl acetate in hexanes); mp 176−178 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.5 Hz, 2H), 7.65−7.62 (m, 1H), 7.58−7.55 (m, 3H), 7.43 (s, 1H), 5.70 (d, J = 3.8 Hz, 1H), 3.66 (s, 1H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 145.2, 141.4, 133.6, 133.0, 130.3, 129.4, 128.8, 127.2, 123.6, 116.5, 111.0, 61.1, 18.5; IR (KBr) ν_{max} 3460, 3070, 2922, 1639, 1455, 1326, 1253, 1149, 1089, 1020, 726, 628 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{12}BrClO_4SNa$ (M + Na) 436.9226, found 436.9231.

*8-Bromo-6-chloro-2-methyl-3-tosyl-2H-chromen-2-ol (**9fb**) and 8-Bromo-6-chloro-2-methyl-3-tosyl-4H-chromen-4-ol (**10fb**) (0.4:1 inseparable mixture).* Pale yellow solid (330 mg, 77%): R_f = 0.6 (30% ethyl acetate in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.4 Hz, 0.8H), 7.66 (s, 0.4H), 7.56 (d, J = 2.4 Hz, 0.4H), 7.54 (d, J = 2.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2.8H), 7.28 (d, J = 2.4 Hz, 0.4H), 5.67 (d, J = 3.5 Hz, 1H), 3.72 (d, J = 3.5 Hz, 1H), 3.69 (s, 0.4H), 2.50 (s, 3H), 2.45 (s, 1.2H), 2.44 (s, 3H), 1.69 (s, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 148.5, 145.2, 145.1, 145.0, 144.6, 138.4, 137.0, 136.8, 135.2, 132.9, 130.2, 129.9, 128.7, 128.4, 127.8, 127.2, 123.7, 120.4, 116.8, 111.5, 111.0, 98.9, 61.0, 26.6, 21.7, 21.6, 18.4; IR (KBr) ν_{max} 3447, 2927, 1639, 1454, 1325, 1293, 1251, 1143, 1089, 1042, 680 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{14}BrClO_4SNa$ (M + Na) 450.9382, found 450.9386.

*2-Methyl-6-nitro-3-(phenylsulfonyl)-4H-chromen-4-ol (**10ga**).* Pale yellow solid (191 mg, 55%): R_f = 0.5 (30% ethyl acetate in hexanes); mp 212−214 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.21 (d, J = 8.9 Hz, 1H), 8.01 (d, J = 7.6 Hz, 2H), 7.65−7.58 (m, 3H), 7.20 (d, J = 8.9 Hz, 1H), 5.80 (s, 1H), 3.87 (s, 1H), 2.49 (s, 3H). Because of the poor solubility of **10ga** in $CDCl_3$, ^{13}C NMR was measured in DMSO-d_6. During measurement, **10ga** isomerized to generate a mixture of 2*H*-chromenes **9ga** and **10ga**: ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.4, 157.6, 153.1, 144.0, 142.3, 141.5, 140.6, 136.5, 133.8, 133.6, 133.4, 129.4, 129.3, 127.8, 127.4, 126.0, 125.7, 125.1, 124.6, 118.7, 117.7, 117.5, 98.6, 79.2, 58.7, 26.8, 18.3; IR (KBr) ν_{max} 3509, 3086, 2925, 1642, 1526, 1342, 1294, 1242, 1139, 1086, 985, 756, 640 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}NO_6SNa$ (M + Na) 370.0361, found 370.0365.

*2-Methyl-6-nitro-3-tosyl-4H-chromen-4-ol (**10gb**).* Pale yellow solid (195 mg, 54%): R_f = 0.6 (30% ethyl acetate in hexanes); mp 185−187 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.20 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 7.0 Hz, 2H), 7.36 (d, J = 7.0 Hz, 2H), 7.19 (d, J = 8.7 Hz, 1H), 5.76 (s, 1H), 3.85 (s, 1H), 2.49 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 153.3, 144.8, 144.6, 138.2, 130.0, 127.3, 126.4, 125.1, 122.1, 117.6, 117.2, 60.5, 21.6, 18.4; IR (KBr) ν_{max} 3477, 3097, 2924, 2854, 1642, 1535, 1343, 1298, 1247, 1146, 1091, 681 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}NO_6SNa$ (M + Na) 384.0518, found 384.0526.

CS_2CO_3-Mediated Conversion of 2-Bromoallyl Sulfones 6a to Allenyl Sulfone 11 and Propargyl Sulfone 12. Cesium carbonate (391 mg, 1.2 mmol) was added to a solution of bromoallyl sulfone **6a** (260 mg, 1.0 mmol) in acetonitrile (2 mL) at room temperature and stirred for 2h. The solvent was removed on a rotavapor; deionized water (10 mL) was added, and the aqueous solution was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts was washed with brine, dried over anhydrous sodium sulfate, and concentrated on a rotavapor. The residue on column chromatography on silica gel using a petroleum ether/ethyl acetate eluent afforded 130 mg of an oil that was identified as a 5:1 mixture of allenyl sulfone **11**[11] and propargyl sulfone **12**.[12] The reaction of the isolated mixture of **11** and **12** with salicylaldehyde was conducted according to the general procedure to obtain **9aa** in 22% isolated yield.

*NMR Data for the Mixture of **11** and **12**.* ^1H NMR (500 MHz, $CDCl_3$) δ 8.00−7.98 (m, 0.4H), 7.93−7.91 (m, 2H), 7.72−7.69 (m, 0.2H), 7.66−7.62 (m, 1H), 7.61−7.59 (m, 0.4H), 7.58−7.54 (m, 2H), 6.26 (t, J = 6.4 Hz, 1H), 5.45 (d, J = 6.4 Hz, 2H), 3.97 (d, J = 2.7 Hz, 0.4H), 2.39 (t, J = 0.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 141.1, 134.3, 133.5, 129.2, 129.1, 128.8 (2), 127.5, 127.3, 100.9, 84.1, 76.2, 71.5, 48.3.

PTSA-Catalyzed Isomerization of 4*H*-Chromene 10eb to 2*H*-Chromene 9eb. To a solution of 4*H*-chromene **10eb** (39 mg, 0.1 mmol) in dimethyl sulfoxide (0.5 mL) was added PTSA (0.4 mg, 20 mol %), and the reaction mixture was allowed to sir at 25 °C overnight. Water (5 mL) was added, and the solution was extracted with ethyl acetate (3 × 5 mL). The organic extracts were combined and washed with a saturated sodium bicarbonate solution (10 mL) and brine. After evaporation of the solvent on a rotavapor, the residue was chromatographed on a silica column using hexane/ethyl acetate mixtures as the eluent to obtain 6-bromo-2-methyl-3-tosyl-2*H*-chromen-2-ol **9eb** as a white solid (39 mg, 99%): R_f = 0.5 (30% ethyl acetate in hexanes); mp 160−162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2H), 7.67 (s, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.43 (dd, J = 2.3, 8.6 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.6 Hz, 1H), 3.53 (s, 1H), 2.45 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 144.9, 137.2, 136.2, 135.6, 133.1, 131.6, 129.9, 128.5, 120.2, 118.9, 114.3, 97.9, 26.6, 21.6; IR (KBr) ν_{max} 3450, 2920, 1618, 1475, 1397, 1312, 1267, 1247, 1170, 1151, 1095, 945 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}BrO_4SNa$ (M + Na) 416.9772, found 416.9780.

Optimized General Procedure for the PTSA-Mediated Reaction of Chromenes (9 and 10) with Heteroarenes. Chromene derivative **9** or **10** (0.40 mmol) and the (hetero)arene (0.30 mmol) were dissolved in ethanol (2 mL) at room temperature. PTSA (36 mg, 0.21 mmol) was added, and the reaction mixture was stirred for 2 h. Water (10 mL) was added, and the solution was extracted with ethyl acetate (3 × 10 mL). The organic extracts were combined and washed with a saturated sodium bicarbonate solution (10 mL) and brine. After evaporation of the solvent on a rotavapor, the residue was chromatographed on a silica column using hexane/ethyl acetate mixtures as the eluent to obtain analytically pure samples of products **16**−**27**.

*3-[2-Methyl-3-(phenylsulfonyl)-4H-chromen-4-yl]-1H-indole (**16a**).* Pale yellow solid (119 mg, 99%): R_f = 0.5 (40% ethyl acetate in hexanes); mp 187−189 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.26−7.23 (m, 3H), 7.19−7.09 (m, 5H), 7.06−6.95 (m, 5H), 6.90 (t, J = 7.2 Hz, 1H), 5.53 (s, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 148.9, 142.1, 136.3, 131.8, 129.1, 127.9, 127.6, 126.3, 125.3, 124.9, 124.2, 122.7, 121.9, 119.7, 119.0, 118.6, 116.0, 115.5, 111.1, 33.5, 19.0; IR (KBr) ν_{max} 3389, 3060, 2886, 1638, 1487, 1452, 1318, 1286, 1237, 1141, 1089, 757, 727, 630 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{19}NO_3SNa$ (M + Na) 424.0983, found 424.0972.

*3-(2-Methyl-3-tosyl-4H-chromen-4-yl)-1H-indole (**16b**).* Colorless solid (114 mg, 91%): R_f = 0.6 (40% ethyl acetate in hexanes); mp

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173−175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.14−7.09 (m, 5H), 7.06−6.99 (m, 2H), 6.96 (dt, J = 1.1, 7.5 Hz, 1H), 6.91−6.88 (m, 1H), 6.77 (d, J = 8.1 Hz, 2H), 5.51 (s, 1H), 2.51 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 148.9, 142.7, 139.2, 136.4, 129.1, 128.5, 127.6, 126.6, 126.4, 125.3, 124.9, 124.3, 122.7, 121.8, 119.6, 119.0, 118.6, 115.9, 111.1, 33.6, 21.3, 18.9; IR (KBr) ν_{max} 3370, 3052, 2920, 1636, 1489, 1316, 1287, 1238, 1143, 1088, 742, 671, 608 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}NO_3SNa$ (M + Na) 438.1140, found 438.1123.

*5-Methoxy-3-[2-methyl-3-(phenylsulfonyl)-4H-chromen-4-yl]-1H-indole (**17a**).* Colorless solid (122 mg, 94%): R_f = 0.5 (40% ethyl acetate in hexanes); mp 110−112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.27−7.25 (m, 2H), 7.22−7.19 (m, 1H), 7.15−7.11 (m, 2H), 7.08−7.06 (m, 2H), 7.03−6.97 (m, 4H), 6.72−6.70 (m, 2H), 5.50 (s, 1H), 3.70 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 153.9, 149.0, 142.1, 131.9, 131.4, 129.2, 127.9, 127.7, 126.3, 125.7, 125.0, 124.1, 123.4, 118.7, 115.8, 115.5, 112.1, 111.8, 100.4, 55.6, 33.5, 18.9; IR (KBr) ν_{max} 3388, 3061, 2927, 1636, 1583, 1485, 1452, 1299, 1230, 1146, 1088, 755, 629 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}NO_4SNa$ (M + Na) 454.1089, found 454.1084.

*5-Methoxy-3-(2-methyl-3-tosyl-4H-chromen-4-yl)-1H-indole (**17b**).* Pale yellow solid (123 mg, 92%): R_f = 0.5 (40% ethyl acetate in hexanes); mp 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.14−7.07 (m, 6H), 7.02−6.96 (m, 2H), 6.80 (d, J = 7.7 Hz, 2H), 6.71−6.68 (m, 2H), 5.48 (s, 1H), 3.70 (s, 3H), 2.49 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 153.9, 149.1, 142.7, 139.2, 131.5, 129.2, 128.6, 127.7, 126.4, 125.8, 125.0, 124.2, 123.4, 118.8, 115.8, 112.0, 111.7, 100.6, 55.6, 33.5, 21.3, 18.9; IR (KBr) ν_{max} 3340, 2922, 1639, 1485, 1453, 1297, 1234, 1144, 1087, 1039, 751, 667 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{23}NO_4SNa$ (M + Na) 468.1245, found 468.1240.

*5-Bromo-3-[2-methyl-3-(phenylsulfonyl)-4H-chromen-4-yl]-1H-indole (**18a**).* Yellow solid (137 mg, 95%): R_f = 0.4 (40% ethyl acetate in hexanes); mp 188−190 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.33−7.31 (m, 3H), 7.21 (t, J = 7.3 Hz, 1H), 7.16−7.09 (m, 3H), 7.07−7.02 (m, 5H), 6.98 (dt, J = 1.2, 7.6 Hz, 1H), 5.46 (s, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 148.7, 141.9, 134.9, 132.1, 128.9, 128.1, 127.9, 126.9, 126.3, 125.0, 124.7, 124.0, 123.8, 121.1, 118.7, 116.2, 115.2, 112.9, 112.7, 33.4, 19.0; IR (KBr) ν_{max} 3331, 3661, 2922, 1638, 1451, 1322, 1289, 1231, 1140, 1087, 764, 721, 628 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{18}BrNO_3SNa$ (M + Na) 502.0088, found 502.0010.

*5-Bromo-3-(2-methyl-3-tosyl-4H-chromen-4-yl)-1H-indole (**18b**).* Yellow solid (145 mg, 98%): R_f = 0.4 (40% ethyl acetate in hexanes); mp 178−180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.29 (s, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.14−7.08 (m, 3H), 7.04−6.95 (m, 4H), 6.84 (d, J = 8.2 Hz, 2H), 5.42 (s, 1H), 2.55 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 148.6, 143.0, 138.8, 134.9, 128.85, 128.7, 127.8, 126.9, 126.35, 124.9, 124.5, 124.0, 123.8, 121.1, 118.6, 116.1, 115.5, 112.8, 112.6, 33.4, 21.3, 18.9; IR (KBr) ν_{max} 3400, 2922, 1635, 1456, 1289, 1233, 1145, 1090, 752, 674 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{20}BrNO_3SNa$ (M + Na) 518.0224, found 518.0218.

*1-Ethyl-3-[2-methyl-3-(phenylsulfonyl)-4H-chromen-4-yl]-1H-indole (**19a**).* Pale yellow solid (127 mg, 99%): R_f = 0.7 (40% ethyl acetate in hexanes); mp 170−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 8.1 Hz, 1H), 7.21 (dd, J = 1.1, 8.4 Hz, 2H), 7.17−7.09 (m, 4H), 7.07−7.04 (m, 1H), 7.02 (dd, J = 0.9, 8.1 Hz, 1H), 6.98−6.93 (m, 4H), 6.90−6.87 (m, 1H), 5.51 (s, 1H), 3.97 (q, J = 7.3 Hz, 2H), 2.54 (s, 3H), 1.37 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 148.8, 142.2, 136.0, 131.6, 129.1, 127.7, 127.5, 126.1, 126.0, 125.6, 124.9, 124.4, 121.3, 119.1, 118.8, 117.4, 115.9, 115.6, 109.1, 40.6, 33.4, 19.0, 15.3; IR (KBr) ν_{max} 3448, 3123, 3054, 2962, 2927, 1637, 1321, 1297, 1235, 1149, 745, 719, 628 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{23}NO_3SNa$ (M + Na) 452.1296, found 452.1291.

*1-Ethyl-3-(2-methyl-3-tosyl-4H-chromen-4-yl)-1H-indole (**19b**).* Colorless solid (132 mg, 99%): R_f = 0.7 (40% ethyl acetate in hexanes); mp 144−146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 7.9 Hz, 1H), 7.14−7.04 (m, 6H), 7.01 (dd, J = 1.1, 8.2 Hz, 1H), 6.97−6.93 (m, 2H), 6.89 (dt, J = 0.9, 7.9 Hz, 1H), 6.73 (d, J = 8.1 Hz, 2H), 5.49 (s, 1H), 3.99 (q, J = 7.3 Hz, 2H), 2.53 (s, 3H), 2.16 (s, 3H), 1.38 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 148.8, 142.5, 139.3, 136.0, 129.0, 128.4, 127.5, 126.3, 126.0, 125.6, 124.8, 124.5, 121.2, 119.1, 118.9, 117.4, 115.9, 109.1, 40.6, 33.4, 21.2, 19.0, 15.4; IR (KBr) ν_{max} 3431, 3048, 2972, 2927, 1636, 1590, 1463, 1321, 1292, 1234, 1146, 765, 736, 696, 661 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{25}NO_3SNa$ (M + Na) 466.1453, found 466.1449.

*2-Methyl-3-[2-methyl-3-(phenylsulfonyl)-4H-chromen-4-yl]-6-nitro-1H-indole (**20**).* Yellow solid (123 mg, 89%): R_f = 0.2 (40% ethyl acetate in hexanes); mp 254−256 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.03 (s, 1H), 7.86 (dd, J = 2.1, 8.9 Hz, 1H), 7.23 (d, J = 7.4 Hz, 2H), 7.15−7.12 (m, 2H), 7.08 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 8.9 Hz, 1H), 6.98−6.95 (m, 4H), 5.56 (s, 1H), 2.65 (s, 3H), 2.56 (s, 3H); ^{13}C NMR [75 MHz, $(CD_3)_2SO$ + $CDCl_3$] δ 158.6, 147.7, 141.0, 140.0, 137.9, 135.6, 131.2, 128.2, 127.2, 127.1, 125.1, 124.9, 124.3, 122.8, 115.4, 115.2, 113.5, 109.7, 31.1, 18.1, 11.0; IR (KBr) ν_{max} 3376, 3051, 2924, 2362, 1643, 1479, 1326, 1231, 1151, 756, 719, 626 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{20}N_2O_5SNa$ (M + Na) 483.0991, found 483.0998.

*3-[6-Methoxy-2-methyl-3-(phenylsulfonyl)-4H-chromen-4-yl]-1H-indole (**21**).* Orange solid (128 mg, 99%): R_f = 0.4 (40% ethyl acetate in hexanes); mp 172−174 °C (CH_2Cl_2/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.26−7.22 (m, 3H), 7.19−7.15 (m, 2H), 7.10 (d, J = 2.3 Hz, 1H), 7.05 (t, J = 7.1 Hz, 1H), 7.00−6.95 (m, 3H), 6.92−6.88 (m, 1H), 6.66 (dd, J = 2.9, 8.9 Hz, 1H), 6.61 (d, J = 2.9 Hz, 1H), 5.50 (s, 1H), 3.64 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 156.5, 143.1, 142.2, 136.4, 131.8, 127.9, 126.2, 125.4, 124.9, 122.7, 121.9, 119.7, 118.8, 118.6, 116.9, 114.4, 113.8, 113.1, 111.1, 55.5, 34.0, 19.0; IR (KBr) ν_{max} 3350, 3055, 2919, 2845, 1625, 1497, 1285, 1227, 1143, 1089, 744, 622 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}NO_4SNa$ (M + Na) 454.1089, found 454.1080.

*3-(6-Bromo-2-methyl-3-tosyl-4H-chromen-4-yl)-1H-indole (**22**).* Pale yellow solid (105 mg, 71%): R_f = 0.6 (40% ethyl acetate in hexanes); mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.22−7.19 (m, 3H), 7.16 (d, J = 8.0 Hz, 1H), 7.12−7.04 (m, 4H), 6.91−6.88 (m, 2H), 6.76 (d, J = 8.1 Hz, 2H), 5.45 (s, 1H), 2.51 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 148.0, 142.8, 138.9, 136.4, 131.8, 130.7, 128.6, 126.4, 126.3, 125.2, 122.9, 122.0, 119.8, 118.4, 118.3, 117.8, 117.1, 115.8, 111.2, 33.5, 21.3, 18.9; IR (KBr) ν_{max} 3442, 3125, 3060, 2922, 1638, 1477, 1318, 1292, 1230, 1146, 1089, 814, 741, 672 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{20}BrNO_3SNa$ (M + Na) 518.0224, found 518.0229.

*2-[2-Methyl-3-(phenylsulfonyl)-4H-chromen-4-yl]-1H-pyrrole (**23a**).* Colorless solid (88 mg, 84%): R_f = 0.7 (40% ethyl acetate in hexanes); mp 193−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.55−7.50 (m, 3H), 7.43−7.39 (m, 2H), 7.26−7.22 (m, 1H), 7.18 (dd, J = 1.2, 7.6 Hz, 1H), 7.13−7.09 (m, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.67−6.65 (m, 1H), 6.03−6.01 (m, 1H), 5.47−5.45 (m, 1H), 5.26 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 150.0, 142.4, 134.0, 132.8, 129.3, 129.0, 128.2, 126.6, 125.1, 122.6, 117.5, 116.1, 115.9, 108.2, 106.9, 34.9, 18.8; IR (KBr) ν_{max} 3370, 2924, 1642, 1289, 1242, 1146, 1089, 760, 724, 629 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}NO_3SNa$ (M + Na) 374.0827, found 374.0834.

*2-(2-Methyl-3-tosyl-4H-chromen-4-yl)-1H-pyrrole (**23b**).* Colorless solid (107 mg, 98%): R_f = 0.7 (40% ethyl acetate in hexanes); mp 186−188 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.26−7.17 (m, 4H), 7.12−7.09 (m, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.68−6.66 (m, 1H), 6.02 (dd, J = 2.8, 5.8 Hz, 1H), 5.44 (s, 1H), 5.23 (s, 1H), 2.38 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 150.1, 143.8, 139.5, 134.1, 129.6, 129.3, 128.2, 126.7, 125.0, 122.7, 117.5, 116.2, 116.0, 108.1, 106.8, 34.9, 21.5, 18.7; IR (KBr) ν_{max} 3366, 2927, 1637, 1322, 1297, 1236, 1145, 753, 730, 667 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{19}NO_3SNa$ (M + Na) 388.0983, found 388.0984.

*2-(6-Bromo-2-methyl-3-tosyl-4H-chromen-4-yl)-1H-pyrrole (**24**).* Colorless solid (130 mg, 98%): R_f = 0.7 (40% ethyl acetate in hexanes); mp 191−193 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.35−7.31 (m, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 8.5 Hz, 1H), 6.69 (s, 1H), 6.05−6.04 (m, 1H), 5.47 (s, 1H), 5.18 (s, 1H), 2.39 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz,

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$CDCl_3$) δ 160.0, 149.2, 144.0, 139.2, 133.3, 131.8, 131.3, 129.7, 126.7, 124.8, 117.9, 117.8, 117.3, 116.3, 108.3, 107.1, 34.7, 21.5, 18.7; IR (KBr) ν_{max} 3376, 2925, 1635, 1478, 1317, 1291, 1235, 1145, 1123, 1086, 814, 727, 674 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{18}BrNO_3SNa$ (M + Na) 466.0088, found 466.0083.

*2-[8-Bromo-6-chloro-2-methyl-3-(phenylsulfonyl)-4H-chromen-4-yl]-1H-pyrrole (**25**).* Pale yellow solid (138 mg, 99%): R_f = 0.7 (40% ethyl acetate in hexanes); mp 213-215 °C (CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.56−7.50 (m, 3H), 7.46−7.41 (m, 3H), 7.11 (d, J = 2.0 Hz, 1H), 6.67 (s, 1H), 6.05 (d, J = 2.6 Hz, 1H), 5.55 (s, 1H), 5.22 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 145.8, 141.8, 133.2, 132.6, 131.7, 130.1, 129.1, 128.1, 126.7, 125.5, 118.0, 116.8, 110.9, 108.6, 107.4, 35.4, 18.6; IR (KBr) ν_{max} 3393, 3071, 2932, 1644, 1452, 1284, 1245, 1136, 1089, 726, 687 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{15}BrClNO_3SNa$ (M + Na) 485.9542, found 485.9530.

*4-(Furan-2-yl)-2-methyl-3-tosyl-4H-chromene (**26**).* White solid (49 mg, 45%): R_f = 0.7 (40% ethyl acetate in hexanes); mp 163−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.1 Hz, 2H), 7.21−7.16 (m, 4H), 7.12 (s, 1H), 7.09−7.06 (m, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.19−6.18 (m, 2H), 5.36 (s, 1H), 2.43 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 155.3, 149.4, 143.4, 141.9, 139.4, 129.4, 128.7, 128.2, 127.0, 125.0, 121.8, 116.3, 114.2, 110.3, 106.6, 35.6, 21.5, 19.0; IR (KBr) ν_{max} 3308, 3064, 2963, 2926, 2854, 1716, 1623, 1557, 1278, 1229, 1183, 1127, 879, 768, 727 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{18}O_4SNa$ (M + Na) 389.0823, found 389.0832.

*2-Ethoxy-2-methyl-3-(phenylsulfonyl)-2H-chromene (**Et-9aa**).* Pale yellow solid (70 mg, 71%): R_f = 0.7 (40% ethyl acetate in hexanes); mp 118−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96−7.93 (m, 3H), 7.62−7.59 (m, 1H), 7.54−7.51 (m, 2H), 7.36−7.33 (m, 2H), 7.03−7.00 (m, 1H), 6.92 (d, J = 8.5 Hz, 1H), 3.27−3.21 (m, 1H), 3.14−3.08 (m, 1H), 1.87 (s, 3H), 0.69 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 141.2, 136.3, 133.2, 133.1, 132.8, 129.5, 128.9, 128.2, 121.8, 117.8, 115.9, 99.9, 58.0, 25.8, 14.6; IR (KBr) ν_{max} 3425, 3061, 3016, 2972, 2928, 2886, 2363, 1623, 1447, 1307, 1154, 1114, 1084, 1047, 765, 725, 691, 630 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}O_4SNa$ (M + Na) 353.0823, found 353.0809.

Synthesis of 2-Methylene-1,3-bis(phenylsulfonyl)piperidin-4-ol (28). Cesium carbonate (408 mg, 1.25 mmol) was added to a solution of *N*-(3-oxopropyl)benzenesulfonamide[15] **27** (107 mg, 0.50 mmol) and 2-bromoallyl sulfonylbenzene **6a** (195 mg, 0.75 mmol) in acetonitrile (5 mL) kept at room temperature. The reaction mixture was stirred for 3 h, and the solvent was evaporated on a rotavapor. Water (20 mL) was added, and the resulting solution was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated on a rotavapor, and the residue obtained was subjected to column chromatography on silica gel using an ethyl acetate/hexane mixture as the eluent to afford 2-methylene-1,3-bis(phenylsulfonyl)piperidin-4-ol **28** (149 mg, 76%) as a pale yellow viscous liquid: R_f = 0.4 (50% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 7.3 Hz, 2H), 7.74 (d, J = 7.2 Hz, 2H), 7.65 (td, J = 1.2, 7.5 Hz, 2H), 7.58−7.55 (m, 2H), 7.51 (t, J = 7.85 Hz, 2H), 5.25 (d, J = 1.2 Hz, 1H), 4.76−4.74 (m, 1H), 4.20 (d, J = 1.2 Hz, 1H), 3.69−3.64 (m, 2H), 3.57−3.52 (m, 1H), 2.66 (d, J = 3.1 Hz, 1H), 2.38−2.32 (m, 1H), 1.87−1.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.1, 134.1, 133.1, 132.0, 129.5, 129.0, 128.8, 128.3, 113.7, 73.4, 63.6, 42.0, 29.3; IR (KBr) ν_{max}: 3452, 2926, 2855, 1714, 1630, 1446, 1310, 1153, 1084, 762, 570 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{20}NO_5S_2$ (M + H) 394.0783, found 394.0780.

PCC Oxidation of 28. Pyridinium chlorochromate (66 mg, 0.30 mmol) was added to a solution of alcohol **28** (100 mg, 0.25 mmol) in dichloromethane (5 mL) at room temperature and stirred for 5 h. The reaction mixture was then poured into a separating funnel containing water (20 mL). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated on a rotavapor, and the residue obtained was subjected to column chromatography on silica gel using an ethyl acetate/hexane mixture as the eluent to afford 6-methyl-1,5-bis(phenylsulfonyl)-2,3-dihydropyridin-4(1*H*)-one **29** as a brown solid (86 mg, 86%): R_f = 0.6 (50% ethyl acetate in hexanes); mp 196−198 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 7.4 Hz, 2H), 7.75−7.73 (m, 1H), 7.65−7.50 (m, 5H), 4.23−4.21 (m, 2H), 2.89 (s, 3H), 2.57−2.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.7, 164.5, 142.4, 139.3, 134.7, 133.1, 130.1, 128.7, 127.8, 126.9, 124.4, 47.1, 37.9, 19.0; IR (KBr) ν_{max} 3424, 3063, 2922, 1666, 1508, 1368, 1327, 1300, 1152, 1078, 919, 735, 686, 533 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}NO_5S_2$ (M + H) 392.0626, found 392.0619.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02324.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

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