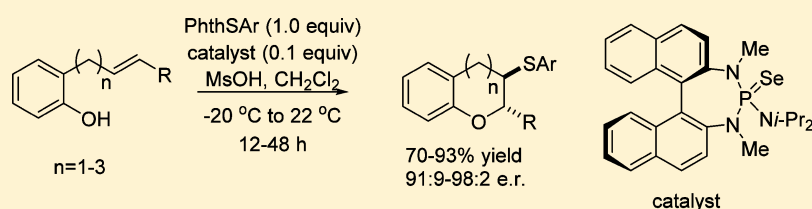# Catalytic, Enantioselective, Intramolecular Sulfenofunctionalization of Alkenes with Phenols

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[S] *Supporting Information*

ABSTRACT: The catalytic, enantioselective, cyclization of phenols with electrophilic sulfenophthalimides onto isolated or conjugated alkenes affords 2,3-disubstituted benzopyrans and benzoxepins. The reaction is catalyzed by a BINAM-based phosphoramide Lewis base catalyst which assists in the highly enantioselective formation of a thiiranium ion intermediate. The influence of nucleophile electron density, alkene substitution pattern, tether length and Lewis base functional groups on the rate, enantio- and site-selectivity for the cyclization is investigated. The reaction is not affected by the presence of substituents on the phenol ring. In contrast, substitutions around the alkene strongly affect the reaction outcome. Sequential lengthening of the tether results in decreased reactivity, which necessitated increased temperatures for reaction to occur. Sterically bulky aryl groups on the sulfenyl moiety prevented erosion of enantiomeric composition at these elevated temperatures. Alcohols and carboxylic acids preferentially captured thiiranium ions in competition with phenolic hydroxyl groups. An improved method for the selective C(2) allylation of phenols is also described.

■ INTRODUCTION

One of the simplest benzofused heterocycles, the chroman core, is a privileged scaffold for bioactive compounds, with representatives displaying antioxidant, antitumor, antibacterial, and other therapeutic properties (Chart 1).[1] Its presence in pharmaceutically relevant targets has led to a variety of methods for its enantioselective construction.

The importance of the chroman motif in organic molecules is reflected in the myriad protocols that have been developed for its synthesis. Five major disconnections have been identified, each of which leads to a different starting material (Scheme 1). These are (a) cyclization of a 2-allylphenol, (b) C−H functionalization of an *O*-alkyl phenol, (c) intermolecular double Michael reaction of a phenol with an unsaturated carbonyl derivative, (d) intramolecular Friedel−Crafts-type cyclization of an *O*-allylphenol, and (e) direct functionalization of the 2-position of the parent chroman.
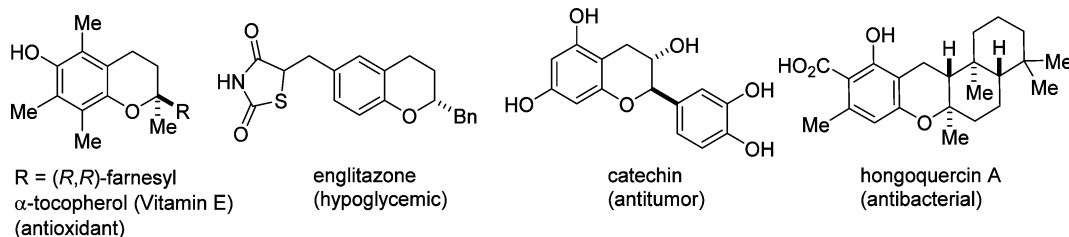
To date, for each of the pathways (a)−(c), enantioselective versions have been developed, whereas pathway (d) is diastereoselective due to the presence of a stereogenic center. The enantioselective variant of pathway (b) has been accomplished under Rh(II) catalysis,[2] pathway (c) is amenable to enantioselective catalysis by secondary amines,[3] whereas pathway (d) can be accessed either as a two-step epoxidation−ring-opening process or in a single step using transition-metal catalysis.[4] Each of these pathways have distinct substitution requirements that are reflected in the products they afford. Notably, none of these approaches directly lead to the 2- or 2,3-

difunctionalized chromans that are accessible through pathway (a).[5] Selected examples of enantioselective reactions that set the stereocenter at C(2) through pathway (a) include: (1) asymmetric allylic substitution, which proceeds through capture of an allylpalladium intermediate by the phenol oxygen (Scheme 2a);[6] (2) tandem oxidative functionalization/Heck coupling, wherein a similar allylpalladium intermediate is generated from an isolated alkene (Scheme 2b);[7] (3) oxidative functionalization of a skipped diene precursor to form an allylpalladium complex (Scheme 2c);[8] and (4) Lewis base catalyzed cyclofunctionalization of the γ-position of an ynoate with a phenolic hydroxyl group (Scheme 2d).[9]
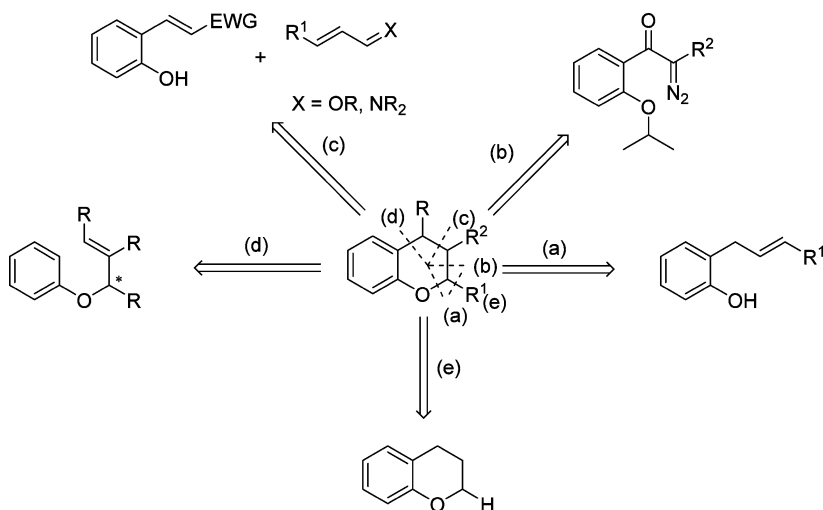
Despite the impressive selectivities and obvious utility of these methods, they are not applicable to the synthesis of chromans bearing an additional substituent at the 3-position. Hence, direct synthesis of enantioenriched, *anti*-2,3-difunctionalized chromans is usually accomplished diastereoselectively from an acyclic epoxide or diol precursor (Scheme 3a).[10] The difunctionalization of γ-substituted 2-allylphenol to afford chromans with stereocenters at both the 2- and 3-positions remains rare.[11] A recent example involves the stereocontrolled generation and intramolecular opening of a seleniranium ion by a phenolic hydroxyl group to form a 2-seleno-3-arylchroman (Scheme 3b).[12] The reaction proceeds via a DYKAT mechanism, since the seleniranium ion in question is not

Chart 1. Chroman-Containing Therapeutic Agents

R = (R,R)-farnesyl
α-tocopherol (Vitamin E)
(antioxidant)

englitazone
(hypoglycemic)

catechin
(antitumor)

hongoquercin A
(antibacterial)

Scheme 1. Retrosynthetic Disconnections for Construction of Chromans

stable under the reaction conditions. Only aryl substituents have been incorporated at the 2-position. The product could be functionalized further by formation of a C–C bond through the intermediacy of a C-centered radical with poor diastereoselectivity. The stereocenter adjacent to the oxygen atom remained unaffected.

As part of our ongoing program on enantioselective sulfenofunctionalization of alkenes, we were interested in extending the scope of this transformation to the synthesis of chromans. Sulfenofunctionalization of alkenes is a longstanding strategy for the efficient introduction of sulfur moieties into organic molecules.[13] The introduction of diverse, electrophilic sulfenylating reagents allows for tuning of both reactivity and selectivity in the desired application. Furthermore, the intermediate thiiranium ion is a strong electrophile that which undergoes facile reaction with nucleophiles resulting in a net *anti*-sulfenofunctionalization of alkenes (eq 1).[14]
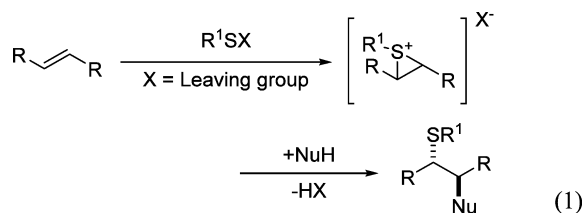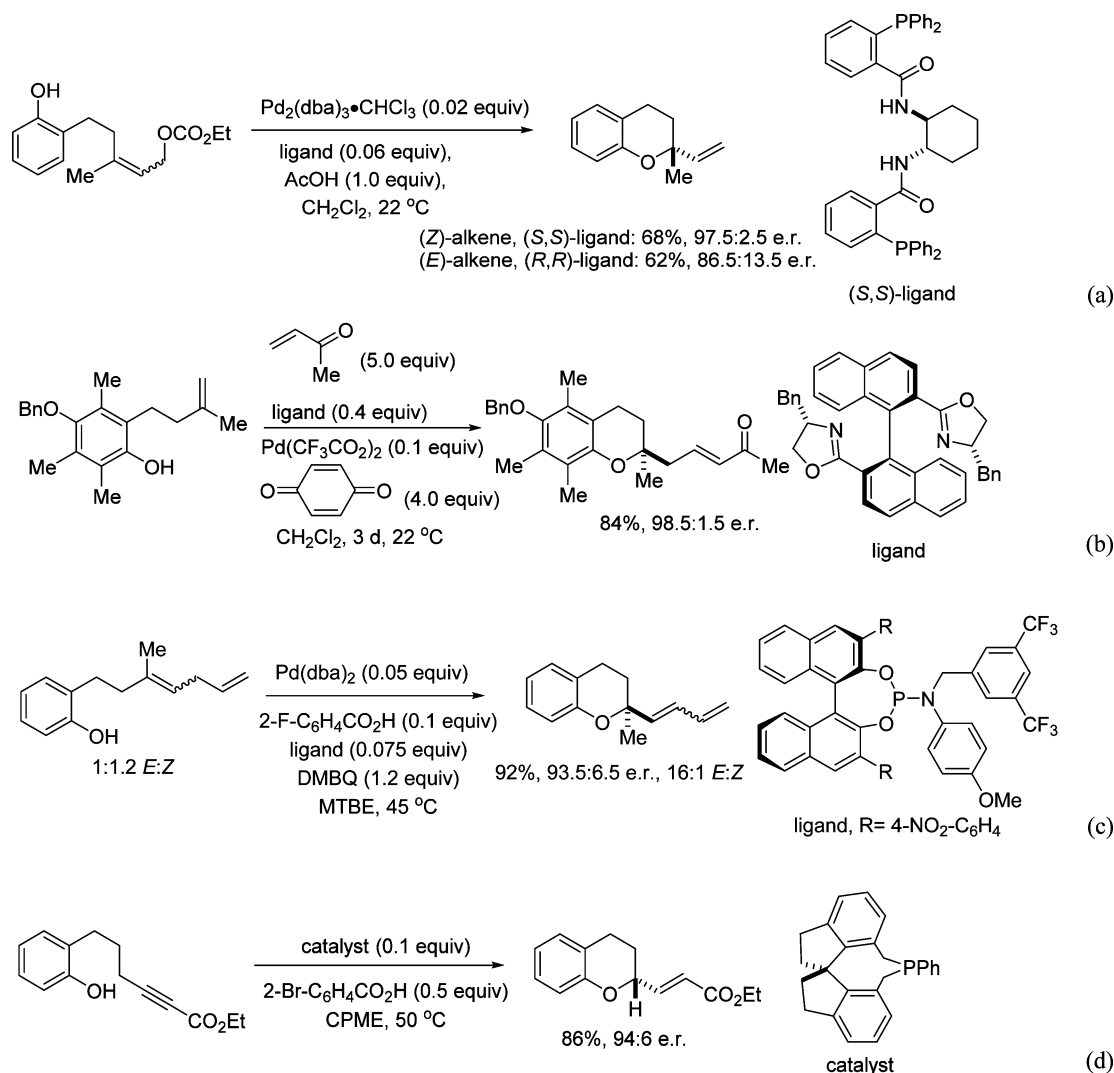

In recent years, the extension of the concept of Lewis base activation of Lewis acids developed in these laboratories has enabled the enantioselective sulfenofunctionalization of alkenes and enol ethers.[13a] Early studies identified three key racemization processes that could lead to the erosion of enantioenriched thiiranium ions: (1) C–S bond scission to

afford a configurationally unstable carbocation, (2) reversible transfer of the sulfenium ion to the nucleophile, thereby creating an achiral sulfenylating agent, and (3) olefin-to-olefin transfer of the thiiranium ion.[14,15] Subsequent investigations identified that both carbocation formation and olefin-to-olefin transfer could be suppressed by lowering the reaction temperature to −20 °C. The configurational stability of the thiiranium ions is maintained in the presence of hard nucleophiles, but not in the presence of weak Lewis bases, demonstrating that Lewis bases intimately interact with thiiranium ions. Intramolecular capture of thiiranium ions by C-, N-, and O-nucleophiles have all been successful. The reactions of tethered alcohols led to the formation of 2,3-difunctionalized pyrans in high yields and with good enantioselectivities (Scheme 4a).[16] Lactones were accessible from the intramolecular cyclization of carboxylic acids.[16] Tosyl-protected amines efficiently captured thiiranium ions to afford pyrrolidine and piperidine derivatives (Scheme 4b).[17] Friedel–Crafts-type capture by electron-rich arenes allowed access to substituted tetralins (Scheme 4c).[18] Finally, silyl enol ethers produce enantioenriched α-sulfenylated ketones in high selectivity without the intermediacy of thiiranium ions (Scheme 4d).[19] The catalyst exhibited complete control over the absolute configuration of the product irrespective of nucleophile. Comparable enantioselectivities with the same absolute configuration were observed for products from all nucleophiles tested so far. The broad nucleophile scope and high stereochemical control observed in both the formation and capture of thiiranium ions are hallmarks of this Lewis base catalyzed sulfenofunctionalization reaction.

The enantioselective olefin sulfenylation reaction relies on the principle of Lewis base activation of Lewis acids extensively

Scheme 2. Enantioselective Construction of Chromans

(Z)-alkene, (S,S)-ligand: 68%, 97.5:2.5 e.r.
(E)-alkene, (R,R)-ligand: 62%, 86.5:13.5 e.r.

(S,S)-ligand (a)

84%, 98.5:1.5 e.r.

ligand (b)

1:1.2 E:Z

92%, 93.5:6.5 e.r., 16:1 E:Z

ligand, R= 4-NO$_2$-C$_6$H$_4$ (c)

86%, 94:6 e.r.

catalyst (d)

developed for main group chemistry in these laboratories.[20] Comprehensive kinetic and spectroscopic studies have led to the formulation of a detailed catalytic cycle (Figure 1).[21] The cycle begins with protonation of N-phenylthiophthalimide (**1a**) by methanesulfonic acid acting as a cocatalyst. Displacement of the S-aryl group by chiral Lewis base catalyst **2** leads to the formation of active complex **i**. The rate of formation of **i** is not turnover-limiting, and **i** serves as the resting state of the catalyst. The subsequent reaction of complex **i** with an alkene leads to enantioenriched thiiranium ion **ii**. The formation of **ii** is both the turnover-limiting and the stereodetermining step. Inter- or intramolecular nucleophilic capture of the thiiranium ion and subsequent deprotonation affords the final product **iv** as well as regenerates **2** to continue the catalytic cycle.

The intermediates involved in the catalytic cycle have been investigated both spectroscopically and crystallographically. Active complex **i**, a competent intermediate in stoichiometric reactions, has been independently synthesized and extensively characterized.[21] Investigation of the reaction mixture by ^{31}P NMR spectroscopy revealed that **2** is rapidly and completely converted to **i** under the reaction conditions. Interestingly, the equimolar amounts of phthalimide and methanesulfonate formed as a byproduct of the initial reaction of **2** with **1** play important roles in the reaction by acting as buffers for the

remaining methanesulfonic acid and suppressing the background reaction.[22]

Initial-rate kinetic experiments determined that the reaction is first-order in catalyst and substrate but zero-order in electrophile **1a**. These results are consistent with turnover-limiting thiiranium ion formation.[21] Two further pieces of evidence corroborate the formation of **ii** as the slow step: (1) complex **i** is the resting state of the catalyst, and (2) the rate of the reaction is sensitive to changes in alkene electron density. Electron-poor alkenes react slower than electron-rich alkenes.

Formation of the thiiranium ion **ii** is also stereodetermining. Product enantioselectivity was insensitive to identity (C-, N-, O-nucleophiles), electron density, or steric bulk of the nucleophile but was very sensitive to alkene substitution pattern. Studies investigating the configurational stability of thiiranium ions in sulfenoetherification reactions also confirmed that no racemization occurs at the reaction temperature.

The transition state from **i** to **ii** was investigated computationally to formulate a stereochemical model that explains the observed enantioselectivity. Distortion/interaction analysis[23] identified the degree of distortion experienced by complex **i** to achieve optimal bond overlap with the alkene substrate to be the primary contributor to the energy difference between the competing diastereomeric transition states.[21] Computational

Scheme 3. Synthesis of 2,3-Disubstituted Chromans

82%, >99:1 e.r.　　　　　(a)

(b)
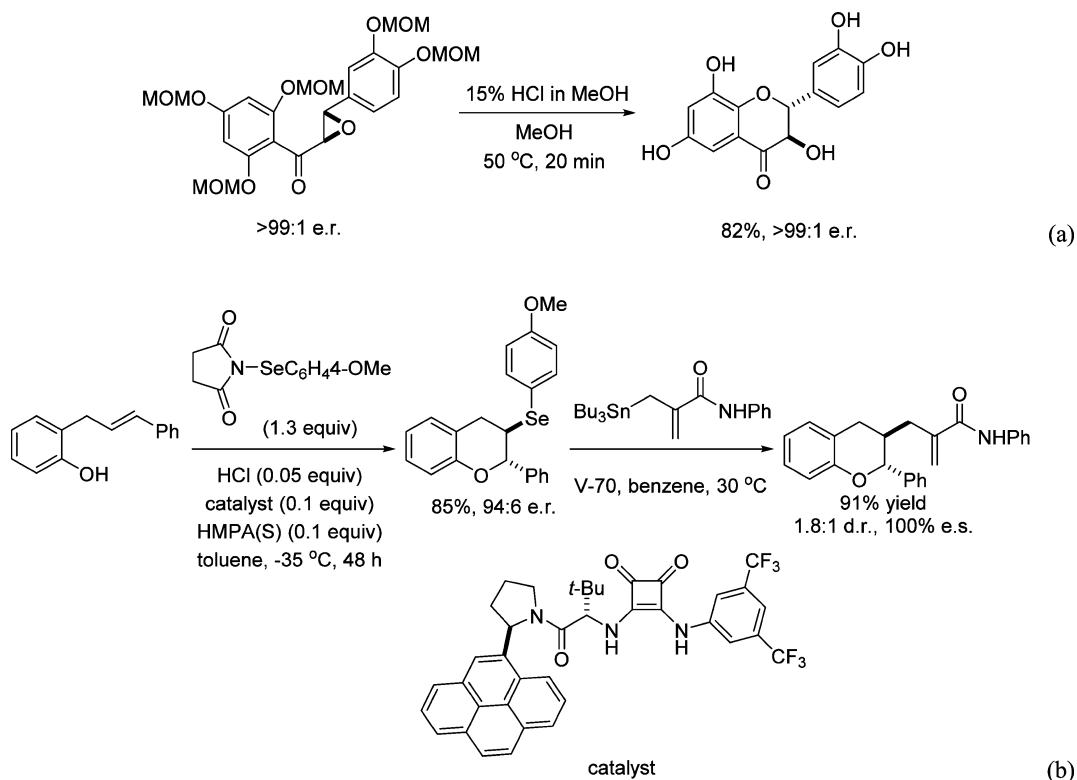
Scheme 4. Lewis Base Catalyzed Sulfenofunctionalization of Alkenes

1a X = CO, R = H
1b X = SO$_2$, R = H
1c X = CO, R = i-Pr

2a, R = -(CH$_2$)$_6$-
2b, R= i-Pr
2c, R= i-Bu
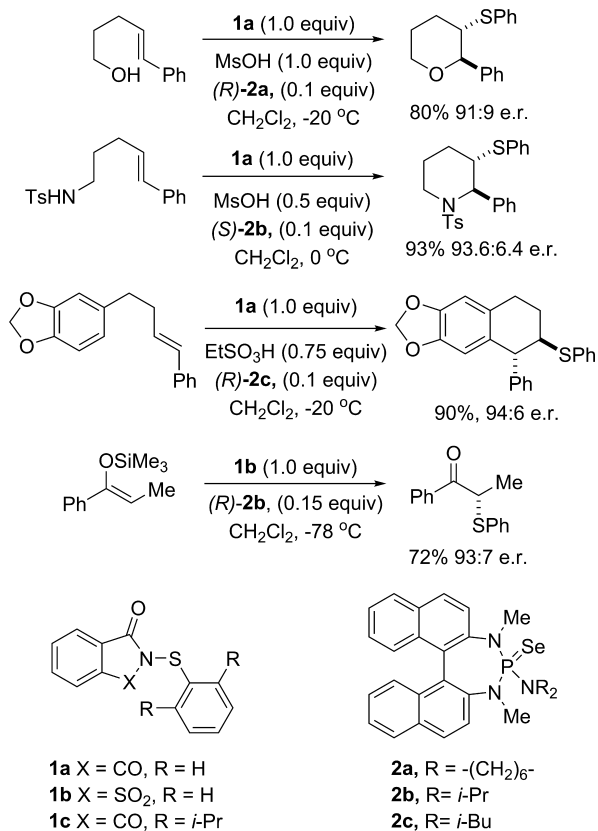
and experimental determination of the activation energy revealed that both the enthalpy ($\Delta H^{\ddagger}$ = 11.9 kcal/mol, calculated; 8.9 kcal/mol, experimental) and the entropy term ($\Delta S^{\ddagger}$ = 12 kcal/mol, calculated; 13.3 kcal/mol, experimental) contribute substantially to the overall reaction barrier ($\Delta G^{\ddagger}$ = 23.9 kcal/mol, calculated; 22.3 kcal/mol, experimental at −20 °C). The stereochemical model identified a van der Waals interaction between the arylsulfenyl moiety and the binaphthyl backbone. Gratifyingly, increased steric bulk at this position in the electrophile leads to improved selectivity overall, which substantiated predictions made by the current model. The absolute configurations of the sulfenofunctionalized products wholly depend on the absolute configuration of the catalyst and are in agreement with predictions made by the calculated model, which supported thiiranium formation as the enantiodetermining step.

Nucleophilic attack at either carbon of thiiranium ion **ii** is possible, raising the issue of site-selectivity.[24] In electronically biased thiiranium ions, capture follows Markovnikov selectivity.[16,25] If the thiiranium ion is sterically and electronically unbiased, mixtures of constitutional isomers are obtained.[26] Thiiranium ions whose constituent carbon atoms are sterically differentiated also afford mixtures of isomers.[16] Site-selectivity is further influenced by the nature of the nucleophile, as alcohols, carboxylic acids and protected amines display dissimilar levels of Markovnikov selectivity. It is worth noting that reversibility of capture has been demonstrated under the reaction conditions for electronically activated thiiranium ions, such as those derived from isolated *trans*-alkenes. Products of thiiranium ion capture by both tethered alcohols and tethered tosylamides are capable of undergoing *exo/endo* isomerization. The product distribution of sulfenofunctionalization therefore represents a composite of intrinsic kinetic selectivity and a substrate-dependent thermodynamic equilibration process.

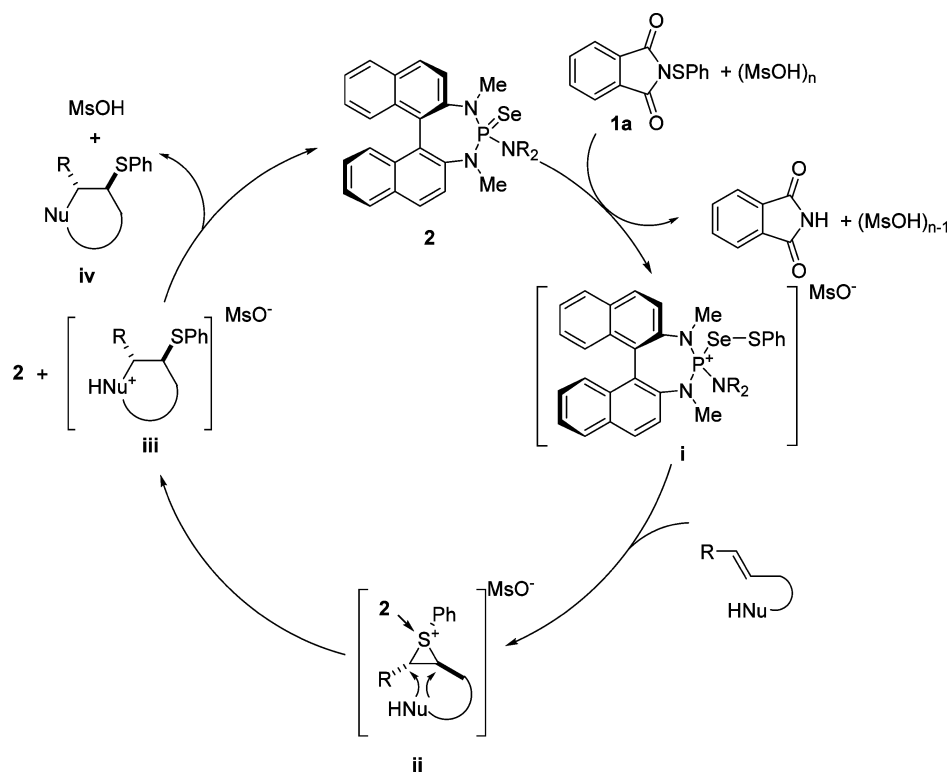In extension of these findings, we sought to apply the expertise gained in the study of enantioselective oxysulfenyla-

Figure 1. Catalytic cycle for the enantioselective, intramolecular sulfenylation.

Table 1. Optimization of the C-Cinnamylation of Phenol

entry	solvent	base	temp (°C)	ratio[a] 3/3'/3"	yield of 3 + 3"[b] (%)
1	Et$_2$O	Na	rt	4.5:0.3:1	65
2	THF	Na	rt	1:2.5:trace	12
3	CH$_2$Cl$_2$	Na	rt	4:0:1	37
4	CH$_2$Cl$_2$	Li	rt	c	0
5	CH$_2$Cl$_2$	K	rt	2:0.4:1	29
6	CH$_2$Cl$_2$	NaH	40	7:trace:1	66
7	CCl$_4$	NaH	80	9.5:0.4:1	68
8	benzene	NaH	80	9:1.5:1	74

[a]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. [b]Yield of isolated product. [c]Complex mixture.

tion of alkenes to the synthesis of difunctionalized chroman derivatives. If both the 2- and the 3-positions of the newly formed ring system are functionalized, the final products can be transformed into a variety of useful compounds, thus constituting a general and selective method for the synthesis of chroman derivatives.

■ RESULTS

1. Synthesis of C(2) Allylic Phenols. A prerequisite for this investigation was the availability of the C(2)-functionalized phenols. A number of different routes were employed that varied according to the number of intervening methylene groups and the substituents on the terminus of the alkene. Most of those routes are derived from literature precedent and are detailed in the Supporting Information without need for additional comment. However, one important class of

substrates, C(2) allylic phenols, presented a number of special challenges, the solutions to which merit a brief prelude.

Although many methods exist for the site-selective O-allylation of phenols, a corresponding general method for the C-selective allylation of phenols has not been described.[27] Because phenols are ambident nucleophiles (at O, C(2), and C(4)) and allylating agents are ambident electrophiles (leading to products of S$_N$2 or S$_N$2′ displacement), the formation of a single product represents challenges of site-selectivity and chemoselectivity. Moreover, the products of C-allylation are also competent nucleophiles that can lead to over-allylation. In a single study on the cinnamylation of phenols using sodium as the base, the C- vs O-selectivity was shown to be highly solvent dependent; C-selectivity dominated in diethyl ether, whereas O-selectivity dominated in dioxane.[28] Unfortunately, the site-selectivity at the cinnamyl moiety was not reported.

Table 2. Allylation of Substituted Phenols with Cinnamyl Chloride

entry	phenol	R^1	R^2	R^3	R^4	time (h)	product	yield (%)[a]
1	2a	H	H	Ph	H	16	3a	71%
2	2b	Me	H	Ph	H	16	3b	47%
3	2c	H	Me	Ph	H	16	3c	62%
4	2e	OMe	H	Ph	H	16	3e	49%
5	2f	Br	H	Ph	H	24	3f	56%
6	2g	Cl	H	Ph	H	24	3g	60%
7	2h	F	H	Ph	H	24	3h	76%
8[b]	2i	CF_3	H	Ph	H	24	3i	64%
9	2d			Ph	H	16	3d	79%
10	2l	H	H	CH_2CH_2Ph	H	16	3l	51%
11	2m	H	H	Me	Me	20	3m	65%

[a]Yield of isolated, purified product. [b]Toluene was used as the reaction solvent.

Following from this precedent, the selectivity of cinnamylation of phenol was examined with respect to the counterion and the solvent (Table 1). Repeating the previously reported conditions did in fact afford a predominance (15:1) of C- vs O-alkylation products **3** and **3′** in reasonable yield, but unfortunately, the product of $S_N2′$ reaction at C(2) (**3″**) was formed in significant quantities as well (entry 1). Changing the solvent to THF afforded a lower yield and a predominance of isomer **3′**, whereas dichloromethane gave results similar to those of diethyl ether (entries 2 and 3). Changing the counterion by using lithium or potassium metal in dichloromethane solvent provided no improvement (entries 4 and 5). In all of these cases, the formation of the phenolate was observed to be slow in dichloromethane, prompting a change to sodium hydride as the base. Under these conditions, the phenolate formed almost instantaneously (as judged by vigorous evolution of hydrogen). Warming the mixture to 40 °C led to a favorable increase in the formation of **3** with respect to the other isomers as did a switch to carbon tetrachloride or benzene and heating at 80 °C (entries 6−8).

The generality of this process was then evaluated by cinnamylation of a number of 2- and 4-substituted phenols under the optimized conditions. Thus, phenol itself afforded **3a** in 71% yield (Table 2, entry 1). Both o- and p-cresol could be alkylated under the same conditions in 47 and 62% yield, respectively (entries 2 and 3). Cinnamylation of 4-hydroxyanisole afforded **3e** in 49% yield (entry 4). Modestly electron-poor phenols such as **2f−h** were also reactive under these conditions, albeit with extended reaction times (entries 5−7). The highly electron poor 4-CF_3-substituted phenol **2i** required refluxing toluene to effect complete conversion (entry 8). 2-Naphthol was alkylated at the 1-position selectively in 79% yield (entry 9). The reaction was not limited to cinnamyl chlorides: (E)-5-phenyl-1-pent-3-enyl chloride also reacted with phenol to afford **3l** in 51% yield (entry 9). Finally, isoprenyl chloride could also be used in a similar fashion to afford the desired trisubstituted alkene **3m** in 65% yield (entry 11).[29]

2. Sulfenoetherification Reactions. In the course of previous investigations from these laboratories, the dependence of rate-, enantio-, and site-selectivity of sulfenoetherification on the substitution pattern and electron density of the alkene component was studied.[16] However, changes in the reaction outcome as a function of structural variations at the nucleophile were not determined. Furthermore, the tether length was kept constant across the different substrates. The primary goals of this study were to evaluate the influence of (1) the steric and electronic properties of the nucleophile, in isolation and in competition, (2) the tether length, and (3) the presence of

other Lewis basic functional groups for the sulfenoetherification of alkenes with phenolic hydroxyl groups as nucleophiles

2.1. Optimization of the Sulfenoetherification Reaction.

The use of a phenolic hydroxyl group as the nucleophile afforded a unique opportunity to systematically vary both the steric and the electronic properties of the nucleophile. (E)-Cinnamylphenol (3a)[12] was selected as a representative substrate for initial reaction optimization. The reaction temperature was chosen as −20 °C to avoid any potential enantiomeric erosion of the thiiranium ion.[14b] Previous studies showed that only 1.0 equiv of 1a was necessary for the reaction.[16] The initial rate experiments revealed that excess acid was detrimental to the reaction rate; thus, 0.75 equiv was chosen as the starting point for optimization. Solvent and concentration were unchanged from the previous conditions for sulfenoetherification reactions. For catalyst 2, the exocyclic amine substituent strongly affects the enantioselectivity of the sulfenofunctionalization process. Thus, catalyst 2a (used in the first study) afforded the desired product with poor selectivity (Table 3, entry 1). Catalyst 2b formed product 4a in 46% yield and with an er of 95.1:4.9 (entry 2). Changing to catalyst 2c resulted in slightly lower enantioselectivity of 93.1:6.9 (entry 3). Reducing the concentration of the reaction using catalyst 2b allowed the product to be obtained in 95% yield (entry 4).

Table 3. Optimization of the Sulfenocyclization Reaction[a]
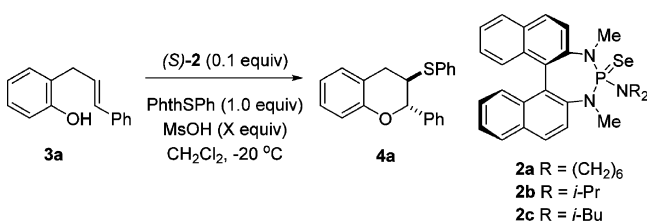
entry	[3] (M)	acid (equiv)	catalyst	yield[b] (%)	er[c]
1	0.4	0.75	2a	35[d]	65.6:34.4
2	0.4	0.75	2b	46[e]	95.1:4.9
3	0.4	0.75	2c	27[f]	93.1:6.9
4	0.15	0.75	2b	95	[g]
5	0.15	0.5	2b	93	95.3:4.7
6	0.15	0.25	2b	93	95.7:4.3
7	0.15	0.1	2b	32[h]	94.9:5.1
8	0.15	0.5[i]	2b	96	94.3:5.7

[a]Reactions run on 0.1 mmol scale. [b]Yield of isolated, purified product. [c]Determined by CSP-SFC. [d]Isolated product contaminated with 2a. [e]Isolated product contaminated with 2b. [f]Isolated product contaminated with 2c. [g]Not determined. [h]Incomplete conversion was observed. [i]EtSO$_3$H was used.

In all preceding sulfenofunctionalization studies, the loading of the Brønsted acid greatly affected the rate and selectivity of the reaction.[21] In the sulfenoetherification with alcohols, maximum reactivity was reached at 0.6 equiv of methanesulfonic acid. Cyclization of substrate 3a using 0.75 equiv of acid was complete within 24 h. Decreasing the amount of acid to 0.5 equiv or even 0.25 equiv did not decrease the yield in the same time frame (entries 5 and 6). In all cases, high selectivity (>30:1) for endo capture to form the chroman was observed. Further decrease in the acid loading resulted in incomplete conversion and reduced yield (entry 7). The use of ethanesulfonic acid did not affect the enantioselectivity and was not pursued further (entry 8).

2.2. Sulfenocyclizations of Substituted (E)-2-Cinnamylphenols: Influence of Phenol Ring Substituents.

The nucleophilicity of phenolic hydroxyl groups is influenced by both steric and electronic properties of ring substituents.[30] Accordingly, a series of substituted (E)-2-cinnamylphenols was prepared and evaluated (Table 4). The parent substrate, 3a, which afforded 4a in 84% yield, 94.9:5.1 er, and >30:1 endo-selectivity was used as a benchmark (Table 4, entry 1). Methyl substituents at the 4- and 6-positions on the ring did not alter the reaction outcome meaningfully (entries 2 and 3). The presence of an extended π-system resulted in no change in yield and a very small decrease in er (entry 4). In all cases, high (>30:1) constitutional selectivity was observed.

Next, the influence of heteroatom substituents on reaction outcome was evaluated. Electron-donating groups had little influence; for example, 3e bearing a 4-methoxy group cyclized to form 4e in 84% yield and 94.4:5.6 selectivity (entry 5). Bromophenol 3f cyclized to afford 4f in 81% yield and 93.8:6.2 er (entry 6), albeit with slightly extended reaction time. The more electronegative chloro- and fluoro-substituted substrates reacted in the same time frame, with 4g and 4h being produced in 70 and 82% yields, respectively (entries 7 and 8). The enantioselectivity of the reactions remained high with these substrates.

Phenol 3i, bearing a highly electron-withdrawing 4-CF$_3$ group, was insufficiently reactive at −20 °C. Increasing the reaction temperature to 22 °C caused significant erosion of enantioselectivity (er 70.7:29.3, SI). Sterically bulky electrophile N-2,6-diisopropylphenylthiophthalimide (1c) prevents erosion at elevated reaction temperatures by shielding the intermediate thiiranium ion.[21] Cyclization of 3i at room temperature using 1c proceeded smoothly, and 4i was isolated with 89% yield and 95.2:4.8 er (entry 9).

2.3. Sulfenocyclization of 2-Substituted Phenols: Influence of Alkene Substituent and Tether Length.

Changes in the alkene substitution pattern have been documented to dramatically alter selectivity for the sulfenofunctionalization process.[16] (E)-Disubstituted alkenes are the most selective substrates for sulfenoetherification, whereas terminal alkenes are only slightly less so. Trisubstituted, (Z)-, and 1,1-disubstituted alkenes reacted with poor selectivity. Thus, primarily (E)- and terminal alkenes were employed in this study. Initially, the (E)-phenyl substituent was varied. 2-Furyl-substituted benzopyran 4j was produced in 88% yield and 92.5:7.5 er, whereas 2-thienyl-substituted substrate 3k produced the desired product in 86% yield and 93.9:6.1 er (Table 5, entries 1 and 2). Changing the alkene substituent to an aliphatic group as in substrate 3l led to a 74% combined yield of a 1.5:1.0 mixture of isomers 4l and 5l with 96.6:3.4 er for 4l (entry 3). Trisubstituted alkenes generally led to less selective cyclizations with 1a.[16] To increase selectivity, electrophile 1c, which has an improved selectivity profile, was tested with substrate 3m.[21] In this case, use of 1c led to the formation of gem-disubstituted benzopyran 4m in 93% yield and 95.4:4.6 er (entry 4).

The site-selectivity of thiiranium capture during intramolecular sulfenocyclization is strongly influenced by the relative rates of formation of different size rings. The preparation of substrates with varying tether lengths enabled a systematic study of ring size effects (Table 5). Substrate 3n, which contains an (E)-2-styryl group at the end of a two-carbon tether, afforded the 7-endo cyclization product benzoxepane 4n in 92% yield and 94.4:5.6 er (entry 5). Further extending the

Table 4. Sulfenocyclizations of Substituted (E)-2-Cinnamylphenols[a]

entry	phenol		time (h)	product		yield (%)[b]	e.r.[c]
1		3a	24		4a	84	94.9:5.1
2		3b	24		4b	82	95.0:5.0
3		3c	24		4c	78	96.0:4.0
4		3d	24		4d	79	93.2:6.8
5		3e	24		4e	84	94.4:5.6
6		3f	36		4f	81	93.8:6.2
7		3g	36		4g	70	93.8:6.2
8		3h	36		4h	86	93.2:6.8
9		3i	12[d,e]		4i	89	95.2:4.8[f]

[a]Reactions run on 1.0 mmol scale. [b]Yield of isolated, purified product. [c]Determined by CSP-SFC. [d]Electrophile 1c was used, Ar^{iPr} = 2,6-(i-Pr)-C_6H_3. [e]Reaction run at 22 °C. [f]Determined after oxidation to the sulfone.

tether to three methylene groups in substrate 3o proved problematic: under the optimized conditions using electrophile 1a, no desired product was observed. Gratifyingly, use of electrophile 1c led to the surprising formation of *exo* cyclization product 5o in 76% yield and 92.6:7.4 er (entry 6). Next, the electronic bias imparted by the phenyl group was removed to evaluate the site-selectivity of closure with a terminal alkene in the reaction with electrophile 1c. Substrate 3p reacted via a 6-*exo*-mode cyclization to afford 5p with high site-selectivity, 91% yield, and 97.2:2.8 er (entry 7). Extension of the tether length by one more methylene group, as in substrate 3q, was gratifyingly successful, as the cyclization proceeded in a 7-*exo* mode to afford product 5q, with 84% yield and 97.7:2.3 er (entry 8).

The Lewis basic nature of the selenophosphoramide moiety prompted an investigation into the compatibility of the reaction conditions with other Lewis basic functional groups in the substrate. Substrate 3r, containing a carboxylic ester group three carbons removed from the reacting olefin, afforded 5r in good yield albeit with somewhat diminished enantioselectivity compared to 3l (cf. entry 9 and Table 5, entry 3). Replacement of the ester by the corresponding ether in 3s restored the enantioselectivity in comparable yield (entry 10). The relative reactivity of other oxygen nucleophiles with respect to phenolic hydroxyl groups was also tested. Both carboxylic acids and alcohols outcompeted phenols for thiiranium capture. Substrate 3t, bearing a carboxylic acid moiety, preferentially afforded lactone 8t in 92% yield and 92.2:7.8 er (entry 11). In the presence of a remote hydroxyl group, such as in substrate 3u,

Table 5. Sulfenocyclizations of 2-Substituted Phenols[a]

entry	substrate		PhthSAryl	time (h)	temp (°C)	product[c]		yield (%)[b]	endo:exo[a]	e.r.[e]
1[f]	3j		1a	24	-20	4j	4j	88	>30:1	92.5:7.5
2[f]	3k		1a	24	-20	4k	4k	86	>30:1	93.9:6.1
3[f]	3l		1a	24	-20	4l / 5l	4l, 5l	74	1.5:1.0	96.6:3.4 (4l) 96.3:3.7 (5l)
4[f]	3m		1c	24	0	4m	4m	93	>30:1	95.4:4.6[g]
5	3n		1a	18	-20	4n	4n	92	>30:1	94.4:5.6
6	3o		1c	24	0	5o	5o	76	<1:30	92.6:7.4[g]
7	3p		1c	12	0	5p	5p	91	<1:30	97.2:2.8[g]
8	3q		1c	48	0	5q	5q	84	<1:30	97.7:2.3[g]
9	3r		1a	24	-20	5r	5r	80	1:12	93.2:6.8
10	3s		1a	24	-20	5s	5s	85	<1:30	96.7:3.3
11	3t		1a	24	-20	8t	8t	92	<1:30	92.2:7.8
12	3u		1a	24	-20	6u / 7u	8u, 9u	88	1.1:1.0[h]	96.9:3.1 (8u) 97.1:2.9 (9u)

[a]Reactions run on 1.0 mmol scale. [b]Yield of isolated, purified product. [c]Ar^{iPr} = 2,6-(i-Pr)-C$_6$H$_3$. [d]Determined by ^{1}H NMR analysis of crude reaction mixtures. [e]Determined by CSP-SFC. [f]0.25 equiv MsOH was used. [g]Determined after oxidation to the sulfone. [h]endo/exo ratio for alcohol capture.

Scheme 5. Manipulations of 3-Phenylthiochroman
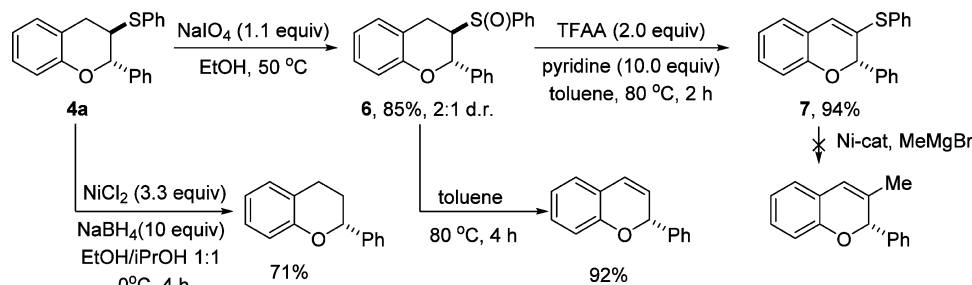
saturated oxacycles **8u** and **9u** were formed as a 1.1:1 mixture of constitutional isomers in 88% combined yield and with 96.9:3.1 er and 97.1:2.9 er respectively (entry 12).

2.4. Transformations of Sulfenofunctionalization Products. The sulfenyl moiety in the product thioether can act as a locus for further transformations. Thus, a series of manipulations to explore the reactivity of the thioether group were carried out (Scheme 5). Reductive cleavage of **4a** with nickel boride formed 2-phenylchroman in 71% yield. Oxidation of **4a** with sodium metaperiodate led to sulfoxide **6** in 85% yield and in a 2:1 diastereomer ratio. Both diastereomers underwent thermal elimination in toluene, leading to the formation of 2-phenylchromene in 92% yield. Attempts to engage the sulfoxide in a Pummerer rearrangement were not successful. Instead, vinyl thioether **7**, which results from loss of a proton from the thiocarbenium intermediate, was formed. In the presence of trifluoroacetic anhydride and pyridine, **7** was obtained in 94% yield. Unfortunately, **7** proved resistant to Ni-catalyzed cross coupling with Grignard reagents.

DISCUSSION

The systematic variation of reaction conditions, phenol substituents, tether length, and functional groups enabled a more thorough understanding of the factors governing the sulfenofunctionalization process. In this section, the influences of each of these components on observable reaction outcomes such as rate, enantioselectivity, and site-selectivity will be discussed in turn.
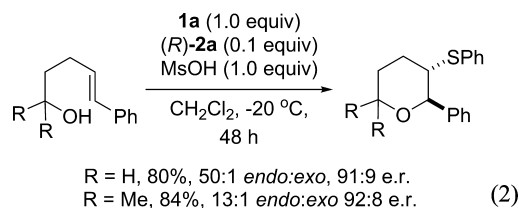
1. Optimization of the Sulfenofunctionalization Reaction. *1.1. Catalyst.* The optimization of the sulfenofunctionalization reaction focused on two main variables, the catalyst and the loading of the Brønsted acid. Exhaustive catalyst optimization for the sulfenofunctionalization process has been detailed elsewhere and was not repeated for this reaction.[16] Of the three best catalysts for sulfenofunctionalization, optimum selectivity was achieved with **2b** for reasons previously noted.[21] Conversion across all catalysts was comparable.

1.2. Brønsted Acid. Previous kinetic studies established that for an alcohol nucleophile the v_{max} was reached with 0.6 equiv of methanesulfonic acid (MsOH).[21] Further increases in the Brønsted acid loading led to decreases in reaction rate. Two major factors need to be considered for optimal MsOH loading: (1) the amount of acid necessary to fully transform the catalyst into active complex **i** and (2) the effective acidity of the reaction mixture as a result of solvation effects in nonpolar reaction media. In the proposed mechanistic cycle, the acid is present only in cocatalytic amounts; therefore, only 1.0 equiv of acid *with respect to catalyst* should be necessary. However, titration studies with ethanesulfonic acid together with **1a** and

2c established that up to 4 equiv of acid is needed before full conversion to the sulfenylated species is observed.[22] In the case of cyclizations of phenolic hydroxyl groups, high conversion could be achieved with as little as 2.5 equiv of MsOH with respect to catalyst. In contrast to alcohols, the phenolic hydroxyl group does not appear to act as a proton buffer.

The cyclization of **3a** was complete within 24 h at −20 °C, compared to 93% after 24 h at the same temperature for the corresponding alcohol substrate.[21] Thus, the rate of phenol cyclization is comparable to that of the alcohols. In the prior set of experiments, a large excess (10 equiv with respect to catalyst) of MsOH was employed, which led to rates slower than v_{max}. The decrease in rate at high MsOH concentrations was ascribed to protonation of the substrate by excess acid.[21] In the case of phenols, no substantial changes in rate were observed as a result of increased acid concentration in the range of 2.5−7.5 equiv of MsOH *with respect to catalyst*. The substantially lower Brønsted basicity of phenols (pK_a of $PhOH_2^+$, −6.5; pK_a $EtOH_2^+$, −2.2)[31] implies that a much smaller fraction of substrate is protonated even in the presence of an excess of acid. Thus, similar reaction rates are observed over a much broader range of acid stoichiometry.

2. Structural Effects on Rate and Selectivity. *2.1. Influence of the Nucleophile.* The rate, enantio-, and site-selectivity of sulfenofunctionalization of any alkene with a pendant nucleophile is dependent on a multitude of structural factors. Preceding studies showed a substantial impact of alkene environment on all three of these observables.[13a] However, no such systematic investigation for the nucleophile was undertaken. In an isolated example, the cyclization of a tertiary alcohol was comparable with that of a primary alcohol (eq 2).[16] A previous study regarding the rate of sulfenocyclization of a number of protected amines did not identify specific reactivity trends.[17] Thus, the cyclization of (*E*)-2-cinnamylphenols provided an opportunity to understand how the aforementioned observables are impacted by the steric and electronic properties of the nucleophile.
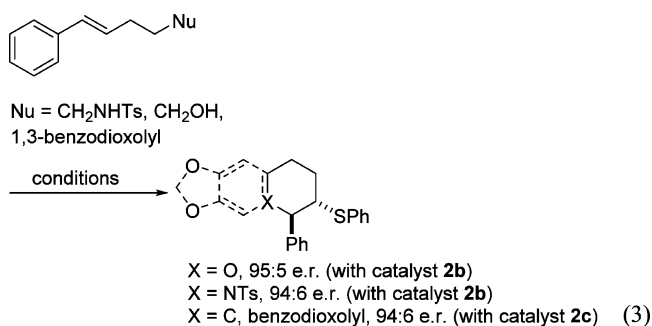

R = H, 80%, 50:1 *endo:exo*, 91:9 e.r.
R = Me, 84%, 13:1 *endo:exo* 92:8 e.r.   (2)

2.1.1. Reaction Rate. The turnover-limiting step of the sulfenofunctionalization reaction for alcohols is thiiranium ion formation; hence, for these substrates thiiranium ion capture is fast.[21] As mentioned previously, phenols are substantially weaker nucleophiles than alcohols.[31] However, the rates of

cyclization of **3a**, **3b**, **3c**, and **3e** were comparable. Thus, the turnover-limiting step does not change for electron-neutral or -rich phenol nucleophiles. Naphthols are slightly stronger nucleophiles than phenols, and in agreement with the aforementioned turnover-limiting thiiranium ion formation, the rate of cyclization of **3d** was not affected.[31]

Introduction of weakly electron-withdrawing substituents led to slightly slower overall rates. The electron-withdrawing property of the substituents on phenols is a composite effect of the inductive (σ_I) and resonance (σ_R) contributions of the substituent to the electron density on the phenol.[32] Chlorine and bromine both strongly withdraw electron density inductively (σ_I Br, 0.49; Cl, 0.43) but also donate electron density through π-resonance (σ_R Br, −0.16; Cl, −0.16).[32] Fluorine is a strongly withdrawing substituent inductively, but also a much better π-donor (σ_I F, 0.57; σ_R F, −0.33) such that its overall effect is comparable. In contrast, a trifluoromethyl group is both inductively and mesomerically electron withdrawing (σ_I CF$_3$, 0.46; σ_R CF$_3$, 0.09). The reaction of Br-, Cl-, and F-substituted phenols (**3f**, **3g**, and **3h**, respectively) were all only slightly slower at −20 °C compared to parent substrate **3a**. The reaction does not appear to be sensitive to either of these parameters. However, for CF$_3$-bearing substrate **3i** the reaction needed to be performed at room temperature.
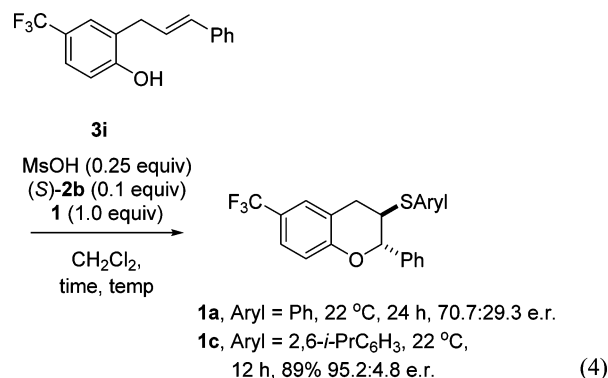
The substantial difference in rate between **3a** and **3i** (cf. Table 4, entries 1 and 9) suggests that the turnover-limiting step has changed from formation of the thiiranium ion to capture for electronically deactivated nucleophiles. Although the lifetime of the thiiranium ion intermediate derived from **3i** likely increases as a result of slow capture, the high chemical yield implies that the thiiranium ion is stable when **1c** is used as the electrophile.

2.1.2. Enantioselectivity. Because thiiranium ions are configurationally stable in dichloromethane at −20 °C,[14b] their enantiomeric composition should be retained throughout the remaining reaction steps.[21] Notably, capture of thiiranium ions derived from styrenes by C-, N-, and O-nucleophiles results in the same absolute configuration and comparable levels of product enantioenrichment (eq 3).[16,17]

Nu = CH$_2$NHTs, CH$_2$OH, 1,3-benzodioxolyl

X = O, 95:5 e.r. (with catalyst **2b**)
X = NTs, 94:6 e.r. (with catalyst **2b**)
X = C, benzodioxolyl, 94:6 e.r. (with catalyst **2c**) (3)
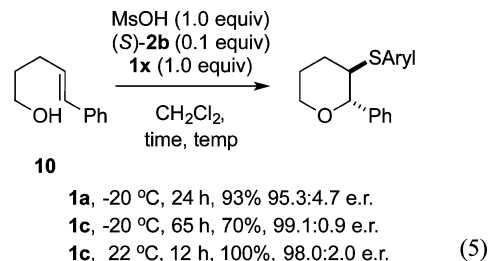
For the participation of phenolic hydroxyl groups, the enantioselectivity of sulfenocyclization remained uniformly high for electron-rich phenols. However, the change in mechanism from turnover-limiting formation to turnover-limiting capture raises the possibility of erosion of enantioselectivity as a consequence of increased thiiranium ion lifetime and attendant racemization. No decrease in enantioselectivity is observed for substrates bearing halogen substituents, confirming the overall stereochemical stability of the thiiranium ion for slightly extended lifetimes at −20 °C For the trifluoromethyl-substituted phenol, the lack of reactivity required that the

reaction be run at 23 °C, leading to decreased product enantioselectivity with electrophile **1a** (eq 4).

3i

MsOH (0.25 equiv)
(S)-**2b** (0.1 equiv)
1 (1.0 equiv)
CH$_2$Cl$_2$,
time, temp

1a, Aryl = Ph, 22 °C, 24 h, 70.7:29.3 e.r.
1c, Aryl = 2,6-i-PrC$_6$H$_3$, 22 °C,
 12 h, 89% 95.2:4.8 e.r.   (4)

To attenuate the racemization, electrophile **1c**, bearing a bulky 2,6-diisopropylphenyl group, was used. The 2,6-substituents impart both slightly higher intrinsic selectivity to **1c** as well as increased stability to the resulting thiiranium ions as was seen with alcohol **10** (eq 5).[21] The use of **1c** in the reaction of **3i** resulted in a dramatic increase in selectivity (eq 4). Thus, configurational erosions of thiiranium ions can be ameliorated through increased steric shielding of the sulfur atom.

MsOH (1.0 equiv)
(S)-**2b** (0.1 equiv)
1x (1.0 equiv)
CH$_2$Cl$_2$,
time, temp

10

1a, -20 °C, 24 h, 93% 95.3:4.7 e.r.
1c, -20 °C, 65 h, 70% 99.1:0.9 e.r.
1c, 22 °C, 12 h, 100%, 98.0:2.0 e.r.   (5)

2.1.3. Site-Selectivity. The site-selectivity for the sulfenoetherification follows the established Markovnikov rule.[25] Reaction of (E)-2-cinnamylphenols can proceed through either a 5-*exo* cyclization to afford a benzofuran or a 6-*endo* cyclization to afford a chroman. Only chromans were observed as reaction products in the cyclization of (E)-2-cinnamylphenols. Changes in the electron density or steric bulk of the nucleophile had no effect on site-selectivity. Opening of the thiiranium ion through a Friedel−Crafts-type process (i.e., C-aryl cyclization) was not observed, demonstrating that the chemoselectivity of capture is high, irrespective of arene electron density.[4c,18]

2.2. Influence of Alkene Environment. The alkene environment represents the most important variable that can influence both the rate and the selectivity of the sulfenocyclization process.[21] This sensitivity has been evident in numerous sulfenofunctionalizations.[16−19] In general, higher alkene electron density leads to increased reactivity. Enantioselectivity is most sensitive to the alkene substitution pattern, whereas site-selectivity is governed by the aforementioned Markovnikov selectivity, albeit complicated by the potential for isomerization of certain sets of constitutional isomers under the reaction conditions.

2.2.1. Rate. The rate of cyclization was expected to follow a well-defined trend of alkene electron density. The reaction times for substrates with disubstituted alkenes demonstrated that the reactivity difference between heteroaryl, aryl and alkyl substituents was not substantial for disubstituted alkenes

(**3a,k,l,s**; 24 h at −20 °C). However, because both mono- and trisubstituted alkenes required electrophile **1c** for high selectivity, direct comparison of the rate of cyclization for terminal alkene **3p** and trisubstituted alkene **3m** with their respective analogs **3s** and **3l** is not possible.

The strongly acidic nature of the reaction conditions raised the possibility of cationic alkene cyclization or polymerization as a competitive side reaction, especially for substrates with electron-rich alkenes.[33] For example, in the cyclization of a 4-tolyl-substituted alkene in the Friedel−Crafts alkylation process, a proton-initiated cyclization was observed (eq 6).[22] No evidence of acid-catalyzed polymerization or cyclization was observed for the current set of styrenes.

(6)
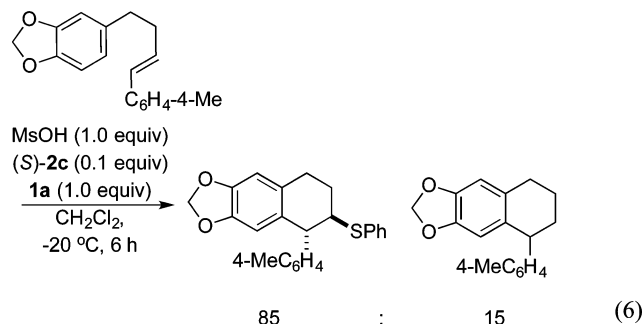
Conjugated electron-rich heteroarenes are significantly more susceptible to polymerization. Thus, when MsOH was added to a mixture of 2-furylalkene **3j**, **2b**, and **1a** in dichloromethane at −20 °C, rapid polymerization was observed and no identifiable product was obtained. If the order of addition was changed to introduce **3j** last, the desired reaction pathway was restored. The effective acid concentration in solution clearly has a substantial impact on the rate of polymerization for sensitive alkenes.[22]

2.2.2. Enantioselectivity. The enantiomeric composition of the final products in sulfenofunctionalizations is determined by the enantioenrichment of their precursor thiiranium ions.[16,17] The enantioselectivity of thiiranium ion formation is, in turn, determined by the transition-state complex consisting of alkene and intermediate **i**. Computation of the energies of the diastereomeric transition states revealed that catalyst distortion is the most important contributor to the difference in transition-state free energies.[21] Thus, changes in alkene substitution pattern and consequently the degree of distortion that the catalyst experiences to accommodate the substituents are expected to substantially impact the stereoselectivity of the process. Indeed, foregoing studies have demonstrated that the enantiotopic faces of (Z)- and 1,1-disubstituted alkenes are poorly differentiated by the active sulfenylating agent derived from **2b**.[16,21]

The enantioselectivity of the sulfenoetherifications herein was consistent among aryl-, heteroaryl-, and alkyl-substituted (E)-alkenes (**4a**, 94.9:5.1; **4k**, 93.9:6.1; **4l**, 96.6:3 **4k**). The nature of the oxygen nucleophile played only a minor role as phenols, alcohols, and carboxylic acids cyclized with comparable enantioselectivities (**4a**, 94.9:5.1; **8u**, 96.9:3.1; **8t**, 92.2:7.8). The high enantioselectivities observed independent of nucleophile parameters are in good agreement with the current hypothesis of stereodetermining thiiranium formation.

Terminal alkenes are usually difficult substrates for enantioselective alkene functionalizations due to the absence of steric differentiation at the terminus.[34] Lower enantiose-

lectivities have been observed previously for sulfenofunctionalization with this class of substrates (eq 7).[16] Therefore, more selective electrophile **1c** was employed for the cyclization of terminal alkenes **3p** and **3q**. Thus, the use of **1c** in the cyclization of **3p** afforded an enantioselectivity of 97.2:2.8. (cf. Table 5, entries 5 and 7). Similarly, cyclization of **3q** proceeded with high enantioselectivity even at elevated temperature (97.7:2.3).


1a, Aryl = Ph, 83%, 88.9:11.1 e.r.
1c, Aryl = 2,6-*i*-PrC$_6$H$_3$, 94%, 98.6:1.4 e.r.   (7)
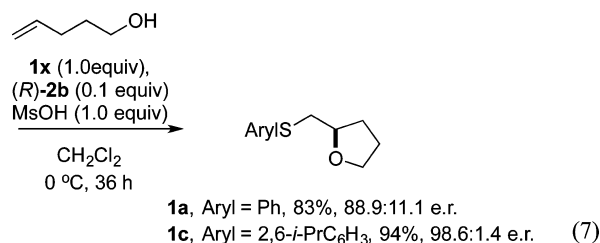
Trisubstituted alkenes are challenging substrates for selective sulfenofunctionalization. In the cyclization of pendant alcohols, both (E)- and (Z)-trisubstituted alkenes afford the corresponding products with poor enantioselectivities (60:40 and 70:30 respectively, eq 8).[16] The higher intrinsic selectivity of sulfenylating agent **1c** was beneficial to this class of substrates as well, as benzopyran **4m** was produced with 95.4:4.6 er.

R^1 = H, R^2 = Me, 22 °C, 24%, 60:40 e.r
R^1 = Me, R^2 = H, -20 °C, 82%, 70:30 e.r.   (8)
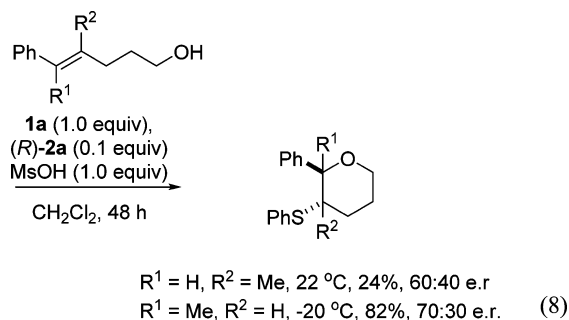
2.2.3. Site-Selectivity. The Markovnikov rule for site-selectivity holds well for the cyclization of alkenes wherein the nucleophile is three atoms removed (cf. 2.1.3). The investigation of constitutional site-selectivity of the reaction alcohols to thiiranium ions derived from biased alkenes demonstrated that cyclization preferentially occurs at the stabilized position. For unbiased alkenes, a mixture of isomers is obtained, although an in situ isomerization process from the 5-*exo* isomer to the 6-*endo* isomer precluded analysis of kinetically controlled selectivity.[16] In contrast, high 5-*exo* selectivity is observed for carboxylic acid cyclizations. The cyclization of phenolic hydroxyl groups proceeds similarly to the alcohols, with high Markovnikov site-selectivity. The influence of resonance stabilization (presence of a Ph substituent, cf. Table 5, entry 5) or inductive stabilization (disubstituted carbon atom of the thiiranium ion, Table 5, entry 4) is sufficient for high selectivity. Moreover, a mixture of isomers is observed in the absence of electronic bias (Table 5, entry 3). The presence of a phenolic hydroxyl group did not otherwise impact selectivity, as the cyclization of **3u** proceeded to give a mixture of isomers, whereas carboxylic acid **3t** displayed very high 5-*exo* selectivity, confirming previous trends (Table 5, entries 11 and 12).[16]

For capture of an electronically unbiased thiiranium ion by a phenolic hydroxyl group three atoms away, the Markovnikov rule predicts poor selectivity. Instead, the controlling factor is

the relative rate of *5-exo* to *6-endo* cyclization. Indeed, in the case of substrate **3l**, a 1.5:1.0 ratio of **4l/5l** from *endo* vs *exo* cyclization, respectively, was obtained (Table 5, entry 3). Direct comparison to the corresponding aliphatic alcohol, which afforded a 5:1 ratio of *endo:exo* isomers, is not warranted due to the presence of C_{sp2} atoms in the tether.[16] Instead, comparisons can be drawn to intramolecular phenolic opening of other tethered three-membered electrophiles. The opening of a disubstituted alkyl epoxide by a phenolic hydroxyl group proceeds exclusively *exo*, whereas the iodine-mediated cyclization of 2-crotylphenol,[35a] which proceeds through an iodonium intermediate, affords solely the *endo* product[35b] (eqs 9 and 10).

74%, 85:15 *anti:syn*
0% *endo* capture   (9)

90%, only *anti*
0% *exo* capture   (10)
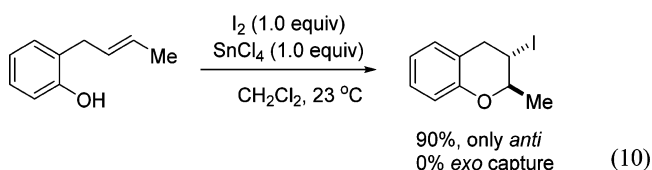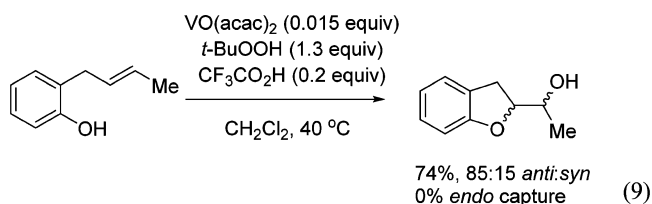
The intrinsic selectivity of phenol capture is therefore highly dependent on the nature of the electrophilic moiety, wherein increased charge and larger atoms in the three-membered ring result in higher formation of the *endo* product. Thiiranium ions are between these two extremes, and consequently, low selectivity is observed.

The ratio **4l/5l** is independent of conversion. In this particular case, the reduced basicity of a benzopyran oxygen compared to a pyran as well as the reduced MsOH loading likely retard isomerization, leading to poor site-selectivity that represents kinetic control.

2.3. Influence of Tether Length. On the basis of the observed characteristics of the sulfenofunctionalization reaction, changes in the tether length were primarily expected to affect the rate- and site-selectivity of the process. As the alkene environment is constant among the various substrates, the enantioselectivity was not expected to vary. Indeed, comparable substrates displayed similar enantioselectivities irrespective of tether length (**3a** and **3n**, **3p** and **3q**).

2.3.1. Rate. The free energy barrier to cyclization for medium-sized rings is highly dependent on ring size.[36] Consequently, the relative rates of *endo* and *exo* capture of the thiiranium ions are dependent on the sizes of the rings being formed. The rate of cyclization of substrate **3n**, bearing one more atom in the tether than **3a**, is similar to the rate of **3a** (cf. Table 4, entry 1, and Table 5, entry 5, Scheme 6a). Similarly, the rates of cyclization of dialkyl-substituted substrates **3l** and **3s** are comparable (Table 5, entries 3 and 10, Scheme 6b,c). Overall, for *5-exo*, *6-endo*, *6-exo*, and *7-endo* capture, thiiranium ion formation appears to be turnover-limiting, and no effect on rate as a function of tether length is observed. In contrast, substantially different rates are observed for the cyclization of **3p** and **3q** (12 h vs 48 h) which have, respectively, two and three methylene units in their tethers (Table 5, entries 7 and 8, Scheme 6d). The cyclization of **3o**,

Scheme 6. Influence of Tether Length and Substituents on Constitutional Site Selectivity

3a: n=1
3n: n=2
3o: n=3

1a (1.0 equiv)
2b (0.1 equiv)
MsOH (X equiv)
CH₂Cl₂, -20 °C

4a: n=6, 0.25 equiv MsOH, 84%
4n: n=7, 0.5 equiv MsOH, 92%
4o: n=8, 0.5 equiv MsOH, 0%

3l

1c (1.0 equiv)
2b (0.1 equiv)
MsOH (0.25 equiv)
CH₂Cl₂, -20 °C

4l/5l
24 h, 74%, 1.5:1 *endo:exo*

3s

1c (1.0 equiv)
2b (0.1 equiv)
MsOH (0.5 equiv)
CH₂Cl₂, -20 °C

4s
24 h, 85%, <1:30 *endo:exo*

3p: n=1
3q: n=2

1c (1.0 equiv)
2b (0.1 equiv)
MsOH (0.5 equiv)
CH₂Cl₂, 0 °C

4p: n=6, 12 h, 91%
4q: n=7, 48 h, 84%
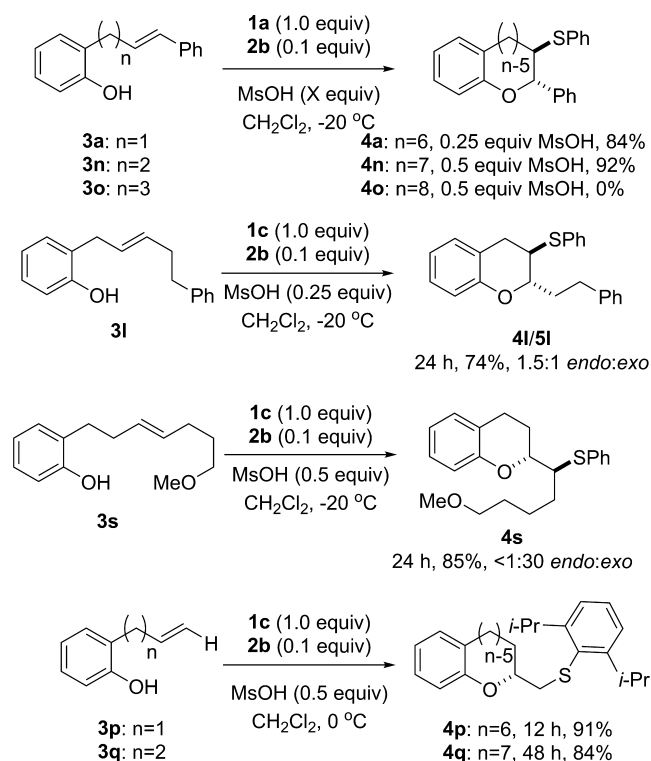
also bearing a three-carbon tether, with **1c**, required elevated temperature compared to the shorter **3n** (22 °C vs −20 °C, Table 5, entries 5 and 6). Attempts to cyclize **3o** with **1a** for comparison purposes failed, with primarily decomposition products being formed (Scheme 6a). Thus, both *7-exo* and *8-endo* cyclizations are generally disfavored in comparison to the aforementioned modes. The overall relative rates as a function of cyclization mode can then be expressed as *8-endo* ≪ *7-exo* < *7-endo* ~ *6-exo* ~ *6-endo* ~ *5-exo*. In conjunction with these rates, a structural feature for change of the rate-determining step can be established. For *7-endo* and more facile closures, thiiranium formation remains turnover-limiting; however, for less favored closures such as *7-exo* and *8-endo*, capture becomes turnover-limiting. The importance of sterically shielding the thiiranium ion reactions with turnover-limiting capture is clearly illustrated by the failure of **1a** to promote the cyclization of **3o**.

2.3.2. Site-Selectivity. Changing the tether length introduces substantial bias into the cyclization due to the higher energy associated with forming 7-membered and larger rings.[36,37] The cyclization of electronically unbiased alkenes with two-carbon tethers (**3s** and **3r**) shows that the intrinsic selectivity for *6-exo* over *7-endo* highly favors the *6-exo* product. However, **3n**, which bears a phenyl substituent, cyclized selectively to the benzoxepane **4n**. Thus, a kinetic preference exists for cyclization following the Markovnikov rule. Surprisingly, the cyclization of **3o** did not follow the expected trend. Under standard reaction conditions, decomposition was observed. The increased kinetic barrier to either *8-endo* or *7-exo* cyclization extends the lifetime of the thiiranium ion such that decomposition processes intervene. The use of the electrophile **1c** led to preferential *7-exo* cyclization. In this case, the increased stability imparted to the thiiranium ion is sufficient to prevent decomposition, whereupon successful capture can take

place. The observed site-selectivity is dominated by the kinetic preference for formation of a seven- vs eight-membered ring. The subtle interplay between enthalpic and entropic contributions is similar to that exhibited with epoxide substrates wherein the cyclization of an electronically unbiased epoxide affords the 5-*exo* isomer vs the 6-*endo* isomer with high selectivity whereas an electronically biased epoxide opens with opposite selectivity (eq 11).[38]

$$
\begin{array}{ll}
\text{R = Me} & 74\% (85{:}15\ d.r.) \quad 0\% \\
\text{R = Ph} & 0\% \qquad\qquad\quad\ 58\%
\end{array}
\tag{11}
$$
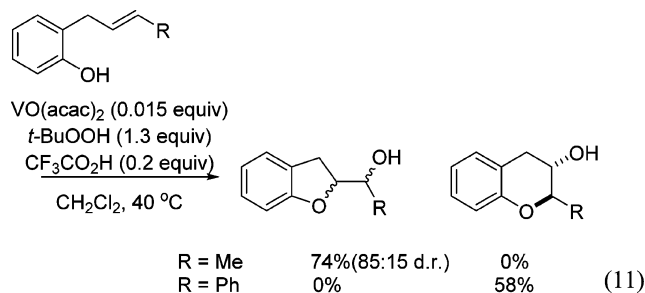
2.4. Influence of Lewis Basic Functional Groups. The sulfenofunctionalization process relies on a moderately Lewis basic selenophosphoramide to promote the catalytic process. Therefore, the sensitivity of the reaction to other Lewis basic functional groups that may be present in the reaction was of interest. In comparison with the reaction of **3a**, no effect on rate was observed for any of the four Lewis basic groups tested (alcohol, acid, ester, ether), although in these cases 0.5 equiv of acid was used to counteract any potential buffering effects.

The enantioselectivity of the reactions was consistently high except for **4r** and **8t**, which showed slight erosion. The interaction of the carbonyl group either directly with the thiiranium ion during its formation or with the complex during its capture may lead to this erosion. Given the small magnitude of the change, the interaction appears to be weak. The site-selectivity for ester **4r** was slightly lower than for **3s**, which also suggests an interaction not present with the ether functional group.

If two competent nucleophiles are present in the molecule, such as in **3t** and **3u**, capture with either nucleophile is possible. The chemoselectivity of the reaction is then dependent on, in addition to the ring size as discussed, the relative rates of cyclization for either nucleophile. Both a carboxylic acid and an alcohol outcompeted the phenolic hydroxyl group for thiiranium capture.[39] Clearly, the lesser nucleophilicity of the phenolic hydroxyl group with respect to other oxygen nucleophiles is sufficient to disfavor aryl ether formation.[30]

Interestingly, the chemoselectivity does not correlate with proton affinity, as the pK_a of a protonated carboxylic acid is somewhat higher than that for a protonated phenol (p$K_{a,aq}$: PhCO$_2$H$_2^+$ −7.8 vs PhOH$_2^+$ −6.5).[31] The discrepancy suggests that the kinetic preference for formation of a five-membered ring via 5-*exo* closure dominates the reaction of **3t**.[16] In contrast, alcohol **3u** formed **8u** and **9u** in almost equimolar ratio, compared to previous results where a 5:1 isomer ratio favoring the pyran was observed (Schemes 7a,b).[16] There appears to be no intrinsic kinetic preference for 5-*exo* vs 6-*endo* cyclization for alcohols with three carbon tethers, though the product ratio for the aliphatic alcohol may not represent kinetic control.

■ CONCLUSIONS

A highly enantioselective sulfenocyclization of alkenes with tethered phenolic hydroxyl groups to afford substituted chromans has been developed. A systematic variation of the nucleophile component and tether length allowed further trends in sulfenofunctionalization to be identified. The reaction was insensitive to changes in the steric properties of the nucleophile. The nucleophile electron density only made a difference for highly electron-deficient phenols. The reaction rate did not change for one- and two-methylene tethers, and both benzopyrans and benzoxepanes were readily prepared, whereas further increases in tether length resulted in slower reactions. Enantioselectivity was unaffected by changes in the nucleophile component or tether length. Nucleophilic capture occurred at the more electronically biased location of the thiiranium ion. In the absence of electronic bias, the intrinsic site-selectivity of sulfenofunctionalization was low for one-methylene tethers but high for two-methylene tethers. Carboxylic acids and alcohols were more reactive toward thiiranium ions than phenolic hydroxyl groups, and high chemoselectivity was observed in competition experiments. Substrates which displayed low reactivity at −20 °C were amenable to sulfenofunctionalization with hindered electrophile **1c** at higher temperatures. The increased thiiranium ion stability as a result of shielding prevented erosion of enantioselectivity that had previously plagued reactions at such temperatures. The effects and influences identified here are predicted to be general for capture of thiiranium ions by other nucleophiles. Expansion of both scope and selectivity to other nucleophiles will be reported in due course.

Scheme 7. Constitutional Site Selectivity for 4-Pentenols
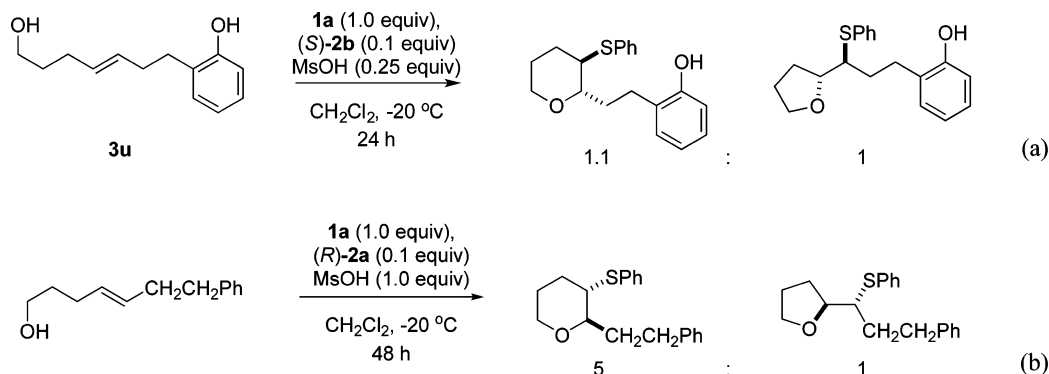
■ EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed in oven- (160 °C) and/or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. All reaction temperatures correspond to internal temperatures measured with Teflon-coated thermocouples. A ThermoNesLab CC-100 or a ThermoNesLab IBC-4A Cryocool with an attached Cryotrol was used for reactions at subambient temperatures.

^{1}H and ^{13}C NMR spectra were recorded on Varian Unity (400 MHz, ^{1}H; 101 MHz, ^{13}C) or Inova (500 MHz, ^{1}H; 126 MHz, ^{13}C) spectrometers. ^{31}P and ^{19}F NMR spectra were recorded on Inova (202 MHz) and Inova (470 MHz) spectrometers, respectively. Acquisition times were 4.096 s for ^{1}H NMR, 1.024 s for ^{13}C NMR, 0.655 s for ^{31}P NMR, and 0.328 s for ^{19}F NMR. Spectra are referenced to residual chloroform ($\delta = 7.26$ ppm, ^{1}H; 77.0 ppm, ^{13}C). Chemical shifts are reported in parts per million; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), sept (septet), m (multiplet), and br (broad). Coupling constants, J, are reported in hertz, integration is provided, and assignments are indicated. Assignments were confirmed through 2-D COSY and HMQC experiments. Elemental analysis for was performed by the University of Illinois Microanalysis Laboratory or Robertson Microlit Laboratories. Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electron Impact (EI) spectra were performed at 70 eV using methane as the carrier gas on a Finnegan-MAT C5 spectrometer. Chemical Ionization (CI) spectra were performed with methane reagent gas on a Micromass 70-VSE spectrometer. Electrospray Ionization (ESI) spectra were performed on a Micromass Q-Tof Ultima spectrometer. Data are reported in the form of m/z (intensity relative to the base peak = 100). Infrared spectra (IR) were recorded on a PerkinElmer FT-IR system, and peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0−33% T); m (medium, 34−66% T), w (weak, 67−100% %), and br (broad). Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus in sealed tubes under vacuum and are corrected.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 or Merck silica gel 60 RP-18 F254s plates. Silver-impregnated silica was prepared by first dissolving 5 g of AgNO$_3$ in 30 mL of deionized water. The resulting homogeneous solution was added to 50 g of SiO$_2$ in a mortar. The clumpy silica paste was ground with a pestle until free-flowing. The mortar was then covered in aluminum foil and placed in an oven (160 °C) for 3 h. The vessel was then removed from the oven and allowed to cool in a desiccator. No special precautions were necessary during the chromatography process; however, prolonged (>6 h) exposure to visible light resulted in the formation of black Ag nanoparticles and a loss of column separation power. Visualization was accomplished with UV light and/ or ceric ammonium molybdate (CAM) solution. R_f values reported were measured using a 10 × 2 cm TLC plate in a developing chamber containing the solvent system described. Flash chromatography was performed using Merck silica gel 60 230−400 mesh (60−63 μ, 60 Å pore size). Analytical chiral stationary phase supercritical fluid chromatography (CSP-SFC) was performed on an Agilent 1100 HPLC equipped with an Aurora Systems A-5 supercritical CO$_2$ adapter for supercritical fluid chromatography and a UV detector (220 or 254 nm) using Daicel Chiralcel OD, OJ, OB or Chiralpak AD, and AS columns as well as a Regis Whelk-O1 column. Normal-phase HPLC was performed on an Agilent 1100 HPLC equipped with AD-H, OJ-H, IB-3, naphthylleucine, and R,R-Beta-Gem columns. Reversed-phase HPLC was performed on an Agilent 1100 HPLC using a Chiralpak AD-RH or Chiralcel OJ-RH column.

Literature Preparations. *Synthesis of Reagents.* The following compounds were prepared according to literature procedures: *N*-(phenylthio)phthalimide (**1a**),[16] *N*-[(2,6-diisopropylphenyl)thio]-phthalimde (**1c**),[21] 4-(*N*-azepano)-3,5-dimethyl-3,5-dihydrodinaphtho[2,1-*d*:1′,2′]-[1,3,2]diazaphosphepine 4-selenide (**2a**),[16] 4-(diisopropylamino)-3,5-dimethyl-3,5-dihydrodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]diazaphosphepine 4-selenide (**2b**),[17] and 4-(diisobu-tyl-1-amino)-3,5-dimethyl-3,5-dihydrodinaphtho[2,1-*d*:1′,2′-*f*]-diazaphosphepine 4-selenide (**2c**).[18] Methanesulfonic acid and ethanesulfonic acid were dried as described in the literature.[22] Substrates 2-((*E*)-3-thiophene-ylprop-2-en-1-yl)phenol (**3k**),[40] 2-(but-3-en-1-yl)phenol (**3p**)[41] and 2-(pent-4-en-1-yl)phenol (**3q**)[42] were prepared as described. Intermediates (*E*)-3-(furan-2-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**S2**)[43] and diethyl (*E*)-2-(5-(2-hydroxyphenyl)pent-2-en-1-yl)malonate (**S3**)[44] were prepared as described.

**Preparation of 2-Substituted Phenols with One Methylene Tether.**
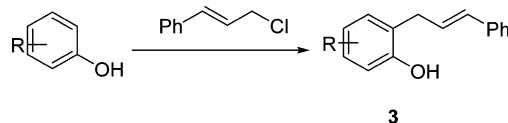
General Procedure 1. To a 50 mL, oven-dried Schlenk flask was added washed, dry NaH (1.05 equiv) in a glovebox. The flask was transferred to a Schlenk line. Solvent (0.5 M) was added to afford a cloudy mixture. The mixture was placed in an ice bath and the corresponding phenol (1 equiv) was added portion wise. During this phase, substantial gas evolution was observed. The insoluble material appeared to change in texture from an amorphous, cloudy particulate matter to a finely distributed crystallized solid. The reaction was removed from the ice bath and then allowed to stir at rt for 30 min. Subsequently, cinnamyl chloride (1.1 equiv) was added dropwise via syringe. After the addition was complete, the reaction was placed in an oil bath and then heated to reflux for the specified amount of time. After completion of the reaction as judged by TLC, the flask was removed from the heat source and allowed to cool to rt. The mixture was then transferred to a separatory funnel, diluted with water (20 mL) and dichloromethane (20 mL), and then acidified to pH < 1 with slow addition of a 6 M HCl solution. The aqueous layer was separated and then back-extracted with a further 30 mL of dichloromethane. The combined organic layers were then washed with brine, dried over MgSO$_4$, and then filtered through glass wool. The filtrate was dried under reduced pressure (~3 mmHg, rotary evaporator). The residue was then taken up in 10 mL of dichloromethane. Celite was added, and the mixture was concentrated to afford a white powder, which was then subjected to flash column chromatography. A second flash column chromatography operation was then performed using silica impregnated with 10% AgNO$_3$ (w/w).
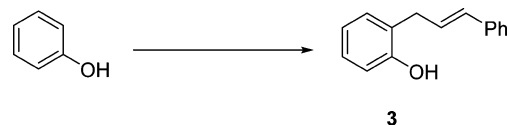
Preparation of (E)-2-(3-Phenyl-2-propen-1-yl)phenol (3). Following general procedure 1, NaH (252 mg, 10.5 mmol), CCl$_4$ (20 mL), phenol (0.94 g, 10 mmol), and cinnamyl chloride (1.53 mL, 11 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1 hexanes/toluene, 30 mm diameter, 14 cm of SiO$_2$) followed by a second silica gel flash column chromatography (9:1, hexanes/ethyl acetate, 30 mm diameter, 50 g of SiO$_2$ (10% AgNO$_3$ w/w)) afforded a pale oil. Distillation afforded 1.49 g of **3** (71%) as a pale oil that solidified upon standing. The spectroscopic data matched those reported in the literature.[45] Data for **3**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39−7.35 (m, 2H), 7.33−7.28 (m, 2H), 7.25−7.14 (m, 3H), 6.92 (td, J = 7.4, 1.2 Hz, 1H), 6.83 (dd, J = 7.9, 1.2 Hz, 1H), 6.52 (d, J = 15.9 Hz, 1H), 6.40 (dt, J = 15.9, 6.5 Hz, 1H), 3.59 (d, J = 6.0 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.2, 137.3, 131.8, 130.7, 128.8, 128.2, 128.1, 127.6, 126.5, 125.9, 121.3, 116.0, 34.4; MS (EI, 70 eV, m/z) 210 (100, M$^+$), 119 (33), 115 (38),104 (66), 91 (82), 69 (45).
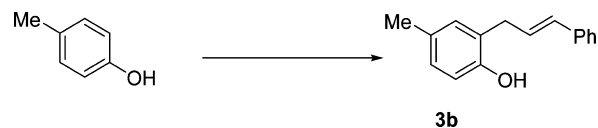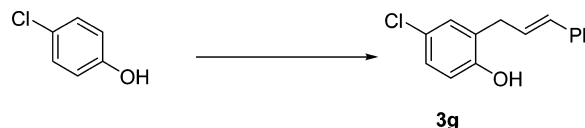
Preparation of (E)-2-(3-Phenyl-2-propen-1-yl)-4-methylphenol (3b). Following general procedure 1, NaH (252 mg, 10.5 mmol), CCl₄ (20 mL), *p*-cresol (1.08 g, 10 mmol), and cinnamyl chloride (1.53 mL, 11 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1 hexanes/toluene, 30 mm diameter, 16 cm of SiO₂) followed by a second silica gel flash column chromatography (9:1, hexanes/ethyl acetate, 50 g of SiO₂ (10% AgNO₃ w/w)) afforded a pale oil. Distillation afforded 1.05 g of **3b** (47%) as a pale oil that solidified upon standing. The spectral data matched those reported in the literature.[46] Data for **3b**: ^{1}H NMR (500 MHz, CDCl₃) δ 7.40–7.35 (m, 2H), 7.32 (td, *J* = 7.6, 1.1 Hz, 2H), 7.26–7.21 (m, 1H), 7.06 (t, *J* = 8.3 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 0H), 6.41 (dtd, *J* = 15.8, 6.6, 1.0 Hz, 1H), 4.96 (s, 1H), 3.59 (dd, *J* = 6.7, 1.6 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, CDCl₃) δ 149.7, 135.1, 129.3, 128.9, 128.2, 126.5, 126.2, 126.1, 125.2, 124.2, 124.1, 123.4, 113.6, 32.1, 18.5; MS (EI, 70 eV, *m/z*) 224 (100, M⁺), 209 (30), 133 (55), 115 (30), 104 (35), 91 (69), 77 (22).

3c
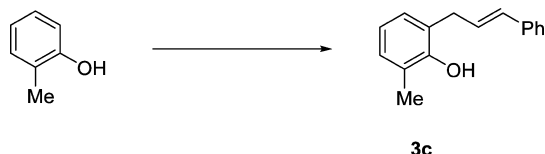
Preparation of (E)-2-(3-Phenyl-2-propen-1-yl)-6-methylphenol (3c). Following general procedure 1, NaH (252 mg, 10.5 mmol), CCl₄ (20 mL), *o*-cresol (1.08 g, 10 mmol), and cinnamyl chloride (1.53 mL, 11 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1 hexanes/toluene, 30 mm diameter, 14 cm of SiO₂) followed by a second silica gel flash column chromatography (9:1, hexanes/ethyl acetate, 30 mm diameter 50 g of SiO₂ (10% AgNO₃ w/w)) afforded a pale oil. Distillation afforded 1.38 g of **3c** (62%) as a pale oil that solidified upon standing. The spectral data matched those reported in the literature.[47] Data for **3c**: ^{1}H NMR (500 MHz, CDCl₃) δ 7.41–7.35 (m, 2H), 7.34–7.30 (m, 2H), 7.23 (ddd, *J* = 12.8, 6.5, 1.7 Hz, 1H), 7.06 (t, *J* = 8.7 Hz, 1H), 6.90–6.80 (m, 1H), 6.56 (d, *J* = 16.0 Hz, 0H), 6.41 (ddd, *J* = 15.9, 8.0, 5.6 Hz, 1H), 3.59 (dd, *J* = 6.6, 1.7 Hz, 2H); ^{13}C NMR (126 MHz, CDCl₃) δ 152.5, 136.9, 131.6, 129.4, 128.5, 128.1, 127.9, 127.4, 126.2, 124.9, 124.0, 120.4, 34.6, 15.9; MS (EI, 70 eV, *m/z*) 224 (100, M⁺), 209 (33), 168 (26), 141 (28), 120 (29), 115 (52), 105 (47), 91 (71), 77 (76), 69 (41).
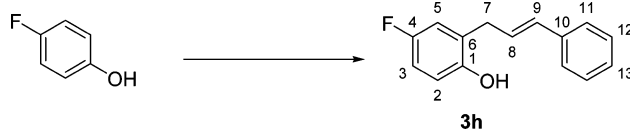

3e

Preparation of (E)-2-(3-Phenyl-2-propen-1-yl)-4-methoxyphenol (3e). Following general procedure 1, NaH (252 mg, 10.5 mmol), CCl₄ (20 mL), 4-methoxyphenol (1.24 g, 10 mmol), and cinnamyl chloride (1.53 mL, 11 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1, hexanes/toluene, 30 mm diameter, 14 cm of SiO₂) followed by a second silica gel flash column chromatography (9:1 hexanes/ethyl acetate, 30 mm diameter, 50 g of SiO₂ (10% AgNO₃ w/w)) afforded a pale oil. Distillation afforded 1.17 g of **3e** (49%) as a pale oil that solidified upon standing. The spectral data matched those reported in the literature.[48] Data for **3e**: ^{1}H NMR (500 MHz, CDCl₃) δ 7.39–7.14 (m, 5H), 6.81–6.65 (m, 3H), 6.48 (d, 1H, *J* = 15.9 Hz), 6.35 (dt, *J* = 15.9, 6.5 Hz, 1H), 3.74 (s, 3H), 3.52 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl₃) δ 153.8, 147.9, 137.0, 131.5, 128.5, 127.7, 127.3, 126.8, 126.2, 116.4, 116.0, 112.6, 55.7, 34.3; MS (EI, 70 eV, *m/z*) 240 (100, M⁺), 149 (66), 136 (99), 121 (25), 115 (31), 108 (44), 91 (79), 77 (21).

3f

Preparation of (E)-2-(3-Phenyl-2-propen-1-yl)-4-bromophenol (3f). Following general procedure 1, NaH (252 mg, 10.5 mmol), CCl₄ (20 mL), 4-bromophenol (1.73 g, 10 mmol), and cinnamyl chloride (1.53 mL, 11 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1 hexanes/toluene, 30 mm diameter, 16 cm of SiO₂) followed by a second silica gel flash column chromatography (9:1, hexanes/ethyl acetate, 30 mm diameter, 50 g of SiO₂ (10% AgNO₃ w/w)) afforded a pale oil. Distillation afforded 1.62 g of **3f** (56%) as a pale oil that solidified upon standing. The spectroscopic data matched those reported in the literature.[49] Data for **3f**: ^{1}H NMR (500 MHz, CDCl₃) δ 7.42–7.19 (m, 5H), 6.74 (ddd, *J* = 9.9, 8.5, 1.3 Hz, 1H), 6.53 (dd, *J* = 15.9, 1.7 Hz, 1H), 6.36 (dt, *J* = 15.9, 6.6 Hz, 0H), 4.99 (d, *J* = 1.3 Hz, 0H), 3.55 (dd, *J* = 6.6, 1.6 Hz, 2H); ^{13}C NMR (126 MHz, CDCl₃) δ 153.4, 150.1, 137.1, 133.2, 132.4, 130.8, 128.8, 128.3, 127.8, 127.1, 126.5, 117.7, 113.2, 34.1; MS (EI, 70 eV, *m/z*) 290 (71, M⁺ + 2), 288 (76, M⁺), 209 (93), 131 (24), 118 (39), 115 (45), 104 (100), 91 (82), 77 (41).


3g

Preparation of (E)-2-(3-Phenyl-2-propen-1-yl)-4-chlorophenol (3g). Following general procedure 1, NaH (252 mg, 10.5 mmol), CCl₄ (20 mL), 4-chlorophenol (1.28 g, 10 mmol), and cinnamyl chloride (1.53 mL, 11 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1 hexanes/toluene, 30 mm diameter, 16 cm of SiO₂) followed by a second silica gel flash column chromatography (9:1, hexanes/ethyl acetate, 50 g of SiO₂ (10% AgNO₃ w/w)) afforded a pale oil. Distillation afforded 1.49 g of **3g** (61%) as a yellow oil that solidified upon standing. The spectroscopic data matched those reported in the literature.[50] Data for **3g**: ^{1}H NMR (500 MHz, CDCl₃) δ 7.43–7.07 (m, 5H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.57–6.49 (m, 1H), 6.36 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.97 (s, 1H), 3.60–3.47 (m, 2H); ^{13}C NMR (126 MHz, CDCl₃) δ 159.4, 152.8, 137.1, 132.4, 130.3, 128.8, 127.8, 127.7, 127.1, 126.5, 117.2, 34.1; MS (EI, 70 eV, *m/z*) 246 (33, M⁺+2), 244 (96, M⁺), 209 (75), 165 (19), 153 (42), 115 (42), 105 (60), 104 (100), 91 (87), 81 (40), 77 (59), 69 (81).
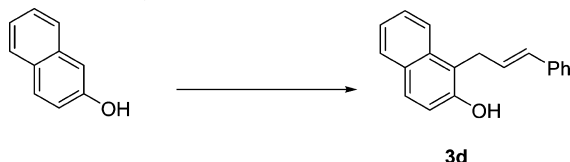

3h

Preparation of (E)-2-(3-Phenyl-2-propen-1-yl)-4-fluorophenol (3h). Following general procedure 1, NaH (252 mg, 10.5 mmol), CCl₄ (20 mL), 4-fluorophenol (1.12 g, 10 mmol), and cinnamyl chloride (1.53 mL, 11 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1 hexanes/toluene, 30 mm diameter, 16 cm of SiO₂) followed by a second silica gel flash column chromatography (9:1, hexanes/ethyl acetate, 30 mm diameter, 50 g of SiO₂ (10% AgNO₃ w/w)) afforded a pale oil. Distillation afforded 1.73 g of **3h** (76%) as a yellow oil that solidified upon standing.[51] Data for **3h**: bp 100 °C (ABT, 3 × 10⁻⁵ mm Hg); ^{1}H NMR (500 MHz, CDCl₃) δ 7.40–7.32 (m, 2H, HC(12)), 7.29 (ddd, *J* = 7.9, 6.2, 1.3 Hz, 2H, HC(11)), 7.24–7.18 (m, 1H, HC(13)), 6.88 (dd, *J* = 9.0, 3.0 Hz, 1H, HC(5)), 6.82 (td, *J* = 8.3, 3.1 Hz, 1H, HC(3)), 6.74 (dd, *J* = 8.7, 4.7 Hz, 1H, HC(2)), 6.49 (dt, *J* = 15.7, 1.5 Hz, 1H, HC(9)), 6.33 (dt, *J* = 15.9, 6.6 Hz, 1H, HC(8)), 3.52 (dd, *J* = 6.6, 1.5 Hz, 2H, HC(7)); ^{13}C NMR (126 MHz, CDCl₃) δ 157.2 (d, *J* = 232 Hz, C4), 149.8 (C1), 136.9 (C10), 132.0 (C9), 128.6 (C12), 127.5 (C13), 127.3 (d, *J* = 7 Hz, C6), 126.9 (C9), 126.2 (C11), 116.6 (d, *J* = 23 Hz, C5)), 116.5 (d, *J* = 8.5 Hz, C2), 113.9 (d, *J* = 25 Hz, C3), 34.0 (C7); ^{19}F NMR (470 MHz, CDCl₃) δ −123.9 (m); IR (ATR, cm⁻¹) 3429 (br), 3027 (w), 1619 (w), 1598 (w), 1494 (s), 1438 (s), 1327 (w), 1254 (w), 1176 (s), 1141 (m), 1090 (w), 1028 (w), 958 (m), 928 (w), 872

(w), 809 (m), 748 (s), 731 (m), 716 (w), 692 (s); MS (EI, 70 eV, m/z) 228 (100, M$^+$), 137 (46), 115 (21), 109 (21), 104 (85), 91 (57) HRMS calcd for $C_{15}H_{13}OF$ 228.0950, found 228.0952, error 0.7; TLC R_f 0.30 (4:1, hexanes/ethyl acetate) [UV,CAM].


3i
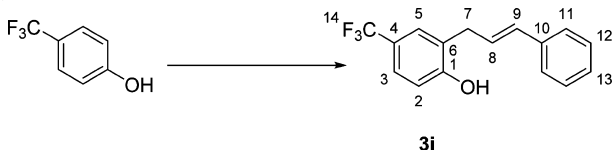
Preparation of (E)-2-(3-Phenyl-2-propen-1-yl)-4-(trifluoromethyl)phenol (3i). Following general procedure 1, NaH (126 mg, 5.25 mmol), toluene (10 mL), 4-(trifluoromethyl)phenol (810 mg, 5 mmol), and cinnamyl chloride (715 µL, 5.5 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1 hexanes/toluene, 30 mm diameter, 16 cm of SiO$_2$) followed by a second silica gel flash column chromatography (9:1, hexanes/ethyl acetate, 30 mm diameter, 50 g of SiO$_2$ (10% AgNO$_3$ w/w)) afforded a pale oil. Distillation afforded 885 mg of **3i** (64%) as a clear oil that solidified upon standing. Data for **3i**: bp 120 °C (ABT, 3.2 × 10^{-5} mm Hg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.47−7.28 (m, 5H, HC(aryl)), 7.28−7.21 (m, 2H, HC(11)), 6.88 (d, J = 8.2 Hz, 1H, HC(2)), 6.54 (dt, J = 15.8, 1.6 Hz, 1H, HC(9)), 6.36 (dt, J = 15.9, 6.6 Hz, 1H, HC(8)), 5.26 (s, 1H, OH), 3.61 (d, J = 6.6 Hz, 2H, HC(7)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.9 (C1), 136.9 (C10), 132.5 (C9), 128.9 (C-aryl), 127.9 (q, J = 3.8 Hz, C5), 127.8 (C-aryl), 126.9, (C8), 126.50 (C-aryl), 125.5 (q, J = 3.9 Hz, C3), 116.0 (C2), 34.3 (C7); ^{19}F NMR (470 MHz, CDCl$_3$) δ −61.56 (s); IR (ATR, cm^{-1}) 3498 (br), 3027 (w), 2923 (w), 1614 (w), 1496 (w), 1485 (w), 1448 (w), 1355 (s), 1335 (s), 1250 (w), 1201 (s), 1152 (s), 1114 (s), 1028 (w), 967 (m), 928 (w), 889 (w), 805 (w), 743 (m), 692 (s); MS (EI, 70 eV, m/z) 278 (4, M$^+$), 260 (83), 223 (30),184 (23), 168 (60), 156 (35), 149 (40), 141 (60), 128 (51), 115 (74), 104 (40), 91 (69), 77 (100); HRMS calcd for $C_{16}H_{13}OF_3$ 278.0919, found 278.0912, error −2.4; TLC R_f 0.33 (4:1, hexanes/ethyl acetate) [UV,CAM].


3d

Preparation of (E)-1-(3-Phenyl-2-propen-1-yl)naphthalen-2-ol (3d). Following general procedure 1, NaH (252 mg, 10.5 mmol), CCl$_4$ (20 mL), 2-naphthol (1.44g, 10 mmol), and cinnamyl chloride (1.53 mL, 11 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1 hexanes/toluene, 30 mm diameter, 16 cm of SiO$_2$) followed by a second silica gel flash column chromatography (9:1, hexanes/ethyl acetate, 30 mm diameter, 50 g of SiO$_2$ (10% AgNO$_3$ w/w)) afforded 2.05 g (79%) of **3d** as a pale pink solid. The spectroscopic data matched those reported in the literature.[52] Data for **3d**: mp 62−64 °C (hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.00 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.52 (ddt, J = 8.2, 6.9, 1.3 Hz, 1H), 7.39−7.35 (m, 1H), 7.34−7.29 (m, 2H), 7.30−7.24 (m, 2H), 7.22−7.18 (m, 1H), 7.16−7.09 (m, 2H), 6.47 (p, J = 1.9 Hz, 2H), 4.01 (dd, J = 3.1, 1.4 Hz, 2H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 151.1, 137.2, 133.3, 130.9, 129.4, 128.6, 128.4, 128.3, 127.6, 127.1, 126.6, 126.1, 126.0, 123.2, 123.1, 117.9, 117.1, 28.43; MS (EI, 70 eV, m/z) 260 (100, M$^+$), 169 (59), 156 (36), 128 (38), 117 (25), 115 (24), 104 (44), 91 (38).

3l
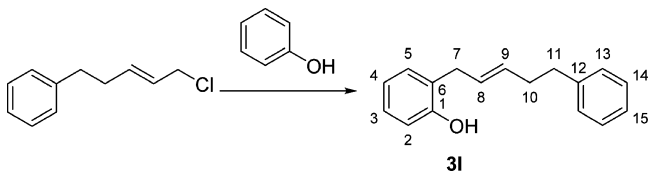
Preparation of (E)-2-(5-Phenylpent-2-en-1-yl)phenol (3l). Following general procedure 1, NaH (126 mg, 5.25 mmol), toluene (10 mL), phenol (470 mg, 5 mmol), and (E)-(5-chloro-3-penten-1-yl)benzene[53] (990 mg, 5.5 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1, hexanes/toluene, 30 mm diameter, 16 cm of SiO$_2$) followed by a second silica gel flash column chromatography (9:1, hexanes/ethyl acetate, 30 mm diameter SiO$_2$ (10% AgNO$_3$ w/w)) afforded a pale oil. Distillation afforded 940 mg of **3l** (79%) as a clear oil. Data for **3l**: bp 160 °C (ABT, 0.05 mmHg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30−7.26 (m, 2H, HC(aryl)), 7.21−7.10 (m, 5H, HC(aryl)), 7.05 (dd, J = 7.5, 1.7 Hz, 1H, HC(5)), 6.87 (td, J = 7.4, 1.2 Hz, 1H, HC(4)), 6.82 (dd, J = 8.0, 1.2 Hz, 1H, HC(2)), 5.64 (ddd, J = 5.5, 3.9, 1.7 Hz, 2H, HC(8), HC(9)), 5.01 (s, 1H, OH), 3.35 (dd, J = 4.5, 1.8 Hz, 2H, HC(7)), 2.70 (dd, J = 8.8, 6.7 Hz, 2H, HC(11)), 2.42−2.32 (m, 2H, HC(10)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.2 (C1), 141.7 (C12), 131.9 (C9), 130.2 (C5), 128.4 (C13), 128.3 (C8), 128.2 (C14), 127.8 (C15), 125.8 (C3, C6), 120.8 (C4), 115.8 (C2), 35.7 (C11), 34.2 (C10), 34.0 (C7); IR (ATR, cm^{-1}) 3531 (br), 3083 (w), 3062 (w), 3026 (w), 2922 (w), 2852 (w), 1602 (w), 1591 (w), 1585 (w), 1489 (m), 1453 (s), 1435 (w), 1328 (w), 1254 (m), 1212 (m), 1169 (m), 1152 (w), 1097 (m), 1038 (w), 1030 (w), 970 (m), 936 (w), 916 (w), 842 (w), 798 (w), 749 (s), 697 (s); MS (EI, 70 eV, m/z) 238 (95, M$^+$), 147 (100), 131 (21), 107 (42), 91 (62); TLC R_f 0.27 (4:1, hexanes/ethyl acetate) [UV,CAM]. Anal. Calcd for $C_{17}H_{18}O$ (238.33): C, 85.67; H, 7.61. Found: C, 85.31; H, 7.63.


3m
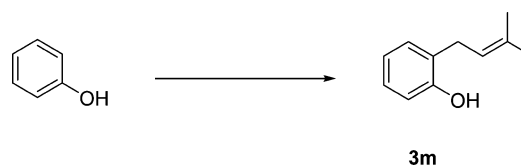
Preparation of 2-(3-Methylbut-2-en-1-yl)phenol (3m). Following general procedure 1, NaH (126 mg, 5.25 mmol), CCl$_4$ (10 mL), phenol (470 mg, 5 mmol), and prenyl chloride (605 µL, 5.5 mmol) were combined in a 50 mL Schlenk flask. The reaction was worked up according to the general procedure. Silica gel flash column chromatography (3:1, hexanes/toluene, 30 mm diameter, 16 cm of SiO$_2$) followed by a second silica gel flash column chromatography (9:1, hexanes/ethyl acetate, 30 mm diameter, 50 g of SiO$_2$ (10% AgNO$_3$ w/w)) afforded a pale oil. Distillation afforded 525 mg (65%) of **3m** as a clear oil. The spectroscopic data matched those reported in the literature.[54] Data for **3m**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14 (t, J = 7.4 Hz, 1H), 6.89 (td, J = 7.5, 1.2 Hz, 1H), 6.83 (dt, J = 7.6, 1.3 Hz, 1H), 5.35 (dddd, J = 7.3, 5.8, 2.9, 1.5 Hz, 1H), 5.09 (s, 1H), 3.38 (d, J = 7.2 Hz, 2H), 1.80 (dd, J = 5.1, 1.4 Hz, 6H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.1, 129.8, 127.3, 121.8, 120.6, 115.5, 29.4, 25.7, 17.7; MS (EI, 70 eV, m/z) 162 (21, M$^+$), 145 (39), 133 (38), 115 (33), 107 (100), 91 (77), 77 (47).

S2

3j
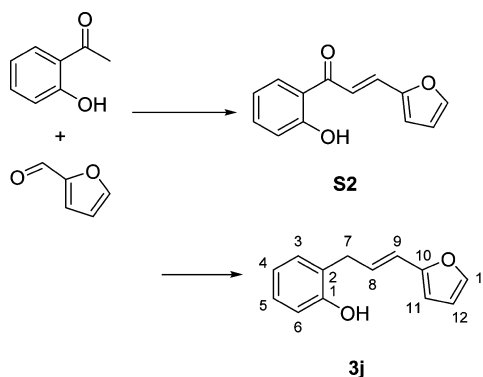
Preparation of (E)-2-(3-(Furan-2-yl)allyl)phenol (3j). To a 5 mL Schlenk flask equipped with a stir bar were added, under argon, (E)-3-(furan-2-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one **S2** (749 mg, 3.5 mmol), THF (3.5 mL), and triethylamine (535 µL, 3.85 mmol, 1.1 equiv). To this solution was added with vigorous stirring ethyl

chloroformate (370 μL, 3.85 mmol, 1.1 equiv). The color of the solution changed from dark brown to light gold with concomitant precipitation of solid triethylammonium chloride. The mixture was stirred for a further 30 min, and the reaction was assayed for completion by TLC. To a separate 50 mL flask, under argon and equipped with a stir bar, were added ethanol (15 mL) and cerium chloride heptahydrate (1.56 g, 4.2 mmol, 1.2 equiv), and the resulting clear solution was stirred for 20 min. The solution containing the ethyl carbonate of the starting material was then filtered into the second flask through glass wool. THF (2 × 5 mL) was used to wash the flask and filter cake. To the resulting light yellow solution was added NaBH$_4$ (160 mg, 4.2 mmol, 1.2 equiv), and the solution was stirred for a further 1 h. Water (1 mL) was added to quench the reaction, and the solution was then stirred for a further 15 min. The resulting heterogeneous mixture was transferred to a 125 mL separatory funnel and diluted with water (15 mL) and CH$_2$Cl$_2$ (30 mL). The layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 30 mL). The organic layers were combined, dried over MgSO$_4$, and concentrated by rotary evaporation (30 °C, 3 mmHg). The crude material thus obtained was redissolved in 10 mL of CH$_2$Cl$_2$ and adsorbed onto Celite. Purification by silica gel flash column chromatography (12:1 hexanes/ethyl acetate, 20 mm diameter, 18 cm of SiO$_2$) followed by bulb-to-bulb diffusion pump distillation afforded 112 mg (16%) of **3j** as a pale yellow oil. Data for **3j**: bp 70 °C (ABT, 2 × 10^{-4} mm Hg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.33 (d, J = 1.8 Hz, 1H, HC(11)), 7.17 (m, 2H, HC(3), HC(5)), 6.93 (t, J = 7.5 Hz, 1H, HC(4)), 6.83 (d, J = 7.9 Hz, 1H, HC(6)), 6.41−6.31 (m, 2H, HC(8), HC(12)), 6.28 (d, J = 15.9 Hz, 1H, HC(9)), 6.18 (d, J = 3.3 Hz, 1H, HC(13)), 4.87 (s, 1H, OH), 3.55 (d, J = 6.3 Hz, 2H, HC(7)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.1 (C1), 141.9 (C2), 130.8 (C3), 128.2 (C5), 127.0 (C8), 121.3 (C9), 120.2 (C4), 115.9 (C6), 111.4, 107.3 (C13), 33.9 (C7); IR (ATR, cm^{-1}) 3409 (br), 1593 (w), 1489 (m), 1455 (s), 1232 (m), 1095 (w), 1012 (m), 964 (m), 753 (s); MS (EI, 70 eV, m/z) 200 (100, M$^+$), 171 (16), 131 (19), 107 (16), 94 (54), 81 (24); HRMS calcd for C$_{13}$H$_{12}$O$_2$ 200.0837, found 200.0842, error 2.3; TLC R_f 0.36 (4:1, hexanes/ethyl acetate) [UV,CAM].

**Preparation of 2-Substituted Phenols with Two or More Methylene Tethers.**

3p   **3n**
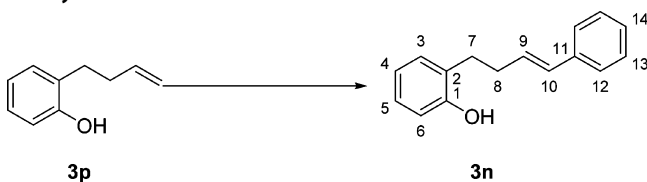
Preparation of (E)-2-(4-Phenylbut-3-en-1-yl)phenol[55] **(3n)**. To a 50 mL Schlenk flask under argon was added BuLi (2.23 M in hexanes, 9.5 mL, 21 mmol, 2.1 equiv) followed by a further 4 mL of hexanes. Tetramethylethylenediamine (TMEDA, 2.44 g, 21 mmol, 2.1 equiv) was added via syringe, and the flask was placed in a −78 °C bath (dry ice/i-PrOH). The internal temperature was monitored until it dropped below −40 °C. Cresol (1.08 g, 10 mmol) was dissolved in hexanes (6 mL) and added to the cold mixture as a solution. To this cold mixture was then added solid KO-t-Bu (2.36 g, 21 mmol, 2.1 equiv). The formation of a yellow suspension was observed. The flask was then removed from the −78 °C bath and placed in a −20 °C bath (i-PrOH, IBC-4A Cryocool), and the solution within was allowed to stir for 30 min. The flask was then removed and allowed to warm to rt over 15 min. THF (10 mL) was added. The flask was then returned to the aforementioned −78 °C bath, and the internal temperature was monitored until it was below −60 °C and then allowed to equilibrate for a further 20 min. Cinnamyl chloride (1.98 g, 13 mmol, 1.3 equiv) was dissolved in THF (2 mL) and added to the mixture. The solution was then allowed to warm to rt and stirred for 1 h. The reaction was quenched by the addition of aq satd NH$_4$Cl (10 mL). The mixture was transferred to a 250 mL separatory funnel and the pH adjusted to <1 with 6 M HCl. The layers were separated, and the aqueous layer was extracted with ether (2 × 30 mL). The organic layers were combined, dried over MgSO$_4$, filtered, and concentrated (30 °C, 3 mmHg). The product was purified by two successive silica gel flash column

chromatography operations (1, 9:1 hexanes/ethyl acetate, 30 mm diameter, 15 cm of SiO$_2$; 2, 50:1 toluene/ethyl acetate, 30 mm diameter, 14 cm of SiO$_2$) and then distilled under vacuum to afford 330 mg (15%) of **3n** as a clear oil. The spectroscopic data match those reported in the literature.[55] Data for **3n**: ^{1}H NMR: (400 MHz, CDCl$_3$) δ 7.38 (d, J = 6.9 Hz, 2H, HC(12)), 7.33 (t, J = 7.7 Hz, 2H, HC(13)), 7.24 (t, J = 7.2 Hz, 1H, HC(14)), 7.20 (dd, J = 7.5, 1.6 Hz, 1H, HC(3)), 7.14 (td, J = 7.7, 1.7 Hz, 1H, HC(5)), 6.93 (td, J = 7.4, 1.1 Hz, 1H, HC(4)), 6.81 (dd, J = 8.0, 1.2 Hz, 1H, HC(6)), 6.48 (dt, J = 15.9, 1.4 Hz, 1H, HC(10)), 6.33 (dt, J = 15.8, 6.9 Hz, 1H, HC(9)), 4.69 (s, 1H, OH), 2.84 (dd, J = 8.8, 6.6 Hz, 2H, HC(7)), 2.62−2.54 (app q, J = 7.5 Hz, 2H, HC(8)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.7, 137.9, 130.7, 130.6, 130.4, 128.7, 127.5, 127.2, 126.2, 121.1, 115.5, 115.1, 33.5, 30.4; MS (EI, 70 eV, m/z) 224 (59, M$^+$), 117 (100), 115 (26), 107 (97), 91 (20), 77 (20).


3q   **3o**
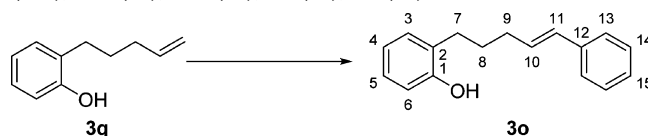
Preparation of (E)-2-(5-Phenylpent-4-en-1-yl)phenol **(3o)**. Dichloromethane was degassed by being purged with argon for 30 min. To a 10 mL flask was added Grubbs-I-indenylidene catalyst (46 mg, 0.05 mmol, 0.033 equiv) in a glovebox. The flask was transferred to a Schlenk line, and degassed dichloromethane (3 mL), **3q** (241 mg, 1.5 mmol) and styrene (890 μL, 7.5 mmol, 5 equiv) were added in order. The solution was stirred for 24 h, whereupon a second portion of catalyst (23 mg, 0.025 mmol, 0.016 equiv) was added. The solution was then stirred for a further 24 h. The solution was then transferred to a 100 mL RB flask, and the volatiles were removed by rotary evaporation (30 °C. Three mm Hg). The material was redissolved in 10 mL of CH$_2$Cl$_2$ and adsorbed onto Celite. Purification by silica gel flash column chromatography (12:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO$_2$) followed by distillation afforded 150 mg (42%) of **3o** as a clear oil. Data for **3o**: bp 150 °C (ABT, 0.05 mmHg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 (d, J = 8.1 Hz, 2H, HC(13)), 7.30 (t, J = 7.6 Hz, 2H, HC(14)), 7.20 (t, J = 7.2 Hz, 1H, HC(15)), 7.14 (d, J = 7.4 Hz, 1H, HC(3)), 7.09 (t, J = 7.7 Hz, 1H, HC(5)), 6.88 (t, J = 7.4 Hz, 1H, HC(4)), 6.76 (d, J = 8.0 Hz, 1H, HC(6)), 6.42 (d, J = 16.1 Hz, 1H, HC(11)), 6.26 (dt, J = 15.9, 6.7 Hz, 1H, HC(10), 4.65 (s, 1H, OH), 2.68 (t, J = 7.7 Hz, 1H, HC(7)), 2.29 (q, J = 6.9 Hz, 1H, HC(9)), 1.82 (p, J = 7.4 Hz, 1H, HC(8)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.8 (C1), 138.1 (C12), 130.9 (C3), 130.6 (C11), 130.5 (C10), 128.8 (C14), 128.6 (C2), 127.4 (C5), 127.2 (C15), 126.3 (C13), 121.1 (C4), 115.6 (C6), 33.0 (C9), 29.7 (C7), 29.6 (C8); IR (ATR, cm^{-1}) 3401 (br), 3059 (w), 3025 (w), 2926 (w), 2857 (w), 1650 (w), 1592.1 (w), 1490 (m), 1454 (s), 1327 (m), 1234 (m), 1169 (w), 1104 (w), 1068 (w), 1042 (w), 1028 (w), 963 (s), 933 (w), 911 (w), 842 (w), 747 (s), 691 (s); MS (EI, 70 eV, m/z) 238 (100, M$^+$), 147 (45), 131 (34), 117 (42), 107 (74), 91 (43), 77 (25); TLC R_f 0.44 (4:1 hexanes/ethyl acetate) [UV,CAM]. Anal. Calcd for C$_{16}$H$_{16}$O (224.34): C, 85.67; H, 7.61. Found: C, 85.27; H, 7.43.


S3

3r
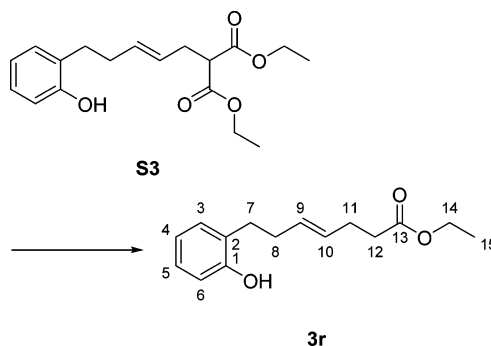
Preparation of Ethyl (E)-7-(2-Hydroxyphenyl)hept-4-enoate **(3r)**. To a 50 mL RB flask equipped with a stir bar were added, under argon, LiI (1.87 g, 14 mmol, 4 equiv) and NaCN (189 mg, 3.85 mmol, 1.1 equiv). To this was added DMSO (10 mL), and the solution was

stirred for 15 min. The diester **S3** (1.12 g, 3.5 mmol) was then dissolved in DMSO (10 mL) and added to the stirring solution. The solution was heated to 160 °C (internal temperature, oil bath) for 3 h. Consumption of starting material was monitored by TLC. The flask was then removed from the heat source and allowed to cool to rt. The solution was transferred to a 125 mL separatory funnel and diluted with water (50 mL) and ethyl acetate (50 mL). Use of other solvent ratios occasionally resulted in persistent emulsions. The layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The organic layers were washed thoroughly (5 × 30 mL water) and then washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). The material was then redissolved in 10 mL of diethyl ether and adsorbed onto Celite. Purification by silica gel flash chromatography (7:1 hexanes/ethyl acetate, 20 mm diameter, 18 cm of SiO_2) followed by bulb-to-bulb vacuum distillation afforded 476 mg (57%) of **3r** as a clear oil. Data for **3r**: bp 130 °C (ABT, 0.05 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15−7.05 (m, 2H, HC(3), HC(5)), 6.87 (t, J = 7.4 Hz, 1H, HC(4)), 6.78 (d, J = 7.9 Hz, 1H, HC(6)), 5.57 (dt, J = 15.3, 6.7 Hz, 1H, HC(9)), 5.47 (dt, J = 15.3, 6.0 Hz, 1H, HC(10)), 5.24 (s, 1H, OH), 4.16 (q, J = 7.1 Hz, 2H, HC(14)), 2.68 (dd, J = 8.7, 6.7 Hz, 2H, HC(11)), 2.42−2.26 (m, 6H, HC(7), HC(8), HC(10)), 1.28 (t, J = 7.1 Hz, 3H, HC(15)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8 (C13), 153.9 (C1), 131.2 (C9), 130.5 (C3), 129.1 (C10), 128.2 (C2), 127.4 (C5), 120.9 (C4), 115.6 (C6), 60.7 (C14), 34.5 (C7/C8/C10), 32.9 (C7/C8/C10), 30.4(C11), 28.1 (C7/C8/C10), 14.5 (C15); IR (ATR, cm^{-1}) 3416 (br), 2981 (w), 2926 (w), 2854 (w), 1706 (s), 1608 (w), 1593 (w), 1504 (w), 1490 (w), 1455 (s), 1372 (m), 1344 (w), 1299 (w), 1232 (s), 1176 (s), 1150 (s), 1101 (m), 1033 (m), 968 (m), 850 (m), 751 (s); MS (EI, 70 eV, m/z) 248 (29, M⁺), 107 (100); TLC R_f 0.31 (4:1, hexanes/ethyl acetate) [UV,CAM]. Anal. Calcd for $C_{15}H_{20}O_3$ (248.32): C, 72.55; H, 8.12. Found: C, 72.43; H, 8.14.


3r

3t
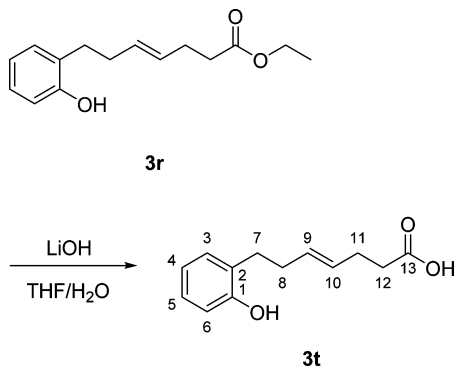
Preparation of (E)-7-(2-Hydroxyphenyl)hept-4-enoic Acid (3t). To a 10 mL Schlenk flask under argon were added ester **3r** (447 mg, 1.8 mmol) and THF (10 mL). Water was added via syringe (2.5 mL) followed by solid LiOH·H2O (272 mg, 6.48 mmol, 3.6 equiv). The solution was allowed to stir 16 h at rt. The mixture was transferred to a 60 mL separatory funnel and diluted with ether (30 mL) and water (20 mL). The biphasic mixture was acidified with 1 M HCl to pH < 2, whereupon a white precipitate formed, which disappeared upon thorough shaking. The layers were separated, and the aqueous layer was extracted with ether (2 × 15 mL). The organic layers were combined, washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). The material was redissolved in 10 mL of diethyl ether and then was adsorbed onto Celite. Purification by silica gel flash column chromatography (4:1 hexanes/ethyl acetate, 30 mm diameter, 16 cm of SiO_2) followed by recrystallization from hexanes (5 mL) afforded 326 mg (83%) of **3t** as white spindles. Data for **3t**: mp 108−110 °C (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17−7.08 (m, 2H, HC(3), HC(5)), 6.91 (t, J = 7.4 Hz, 1H, HC(4)), 6.80 (d, J = 7.9 Hz, 1H, HC(2)), 5.60 (dt, J = 15.6, 6.5 Hz, 1H, HC(9)), 5.50 (dt, J = 15.4, 6.3 Hz, 1H, HC(10)), 2.70 (dd, J = 8.5, 6.6 Hz, 2H, HC(8)), 2.45 (t, J = 7.1 Hz, 2H, HC(11)), 2.35 (app p, J = 6.8 Hz, 4H, HC(7), HC(12)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.0 (C13), 153.6 (C1), 131.4

(C10), 130.6 (C5), 128.8 (C9), 128.0 (C2), 127.4 (C3), 121.1 (C4),115.6 (C6), 34.1 (C11), 32.9 (C7), 30.3 (C8), 27.8 (C12); IR (ATR, cm^{-1}) 3184 (br), 3042 (w), 2934 (w), 2908 (w), 1703 (s), 1613 (w), 1591 (m), 1503 (w), 1455 (s), 1441 (m), 1425 (m), 1409 (m), 1373 (m), 1280 (m), 1262 (w), 1236 (s), 1192 (s), 1109 (w), 1041 (w), 990 (w), 974 (s), 930 (w), 909 (w), 845 (w), 821 (m), 747 (s), 688 (w); MS (EI, 70 eV, m/z) 220 (16, M⁺), 137 (16), 107 (100); TLC R_f 0.06 (4:1, hexanes/ethyl acetate) [UV,CAM]. Anal. Calcd for $C_{13}H_{16}O_3$ (220.27): C, 70.89; H, 7.32. Found: C, 71.12; H, 7.24.


3r

3u
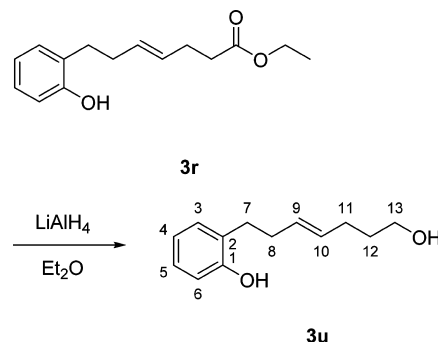
Preparation of (E)-2-(7-Hydroxyhept-3-en-1-yl)phenol (3u). To a 50 mL Schlenk flask under argon were added lithium aluminum hydride (126 mg, 3.3 mmol, 1.5 equiv) and THF (4 mL). The flask was placed in an ice bath for 10 min. Ester **3r** (520 mg, 2.2 mmol) was dissolved in THF (4 mL) and added dropwise to the cold solution. The solution was then allowed to stir at 0 °C for 2 h. The flask was then once again placed in an ice bath for 15 min. The reaction was quenched by the addition of water (2 mL, dropwise) with substantial gas evolution and the formation of copious amounts of solids. After addition of water was complete, a further 5 mL of water was added, followed by dropwise addition of 6 M HCl to pH < 2. The resulting biphasic mixture was transferred to a 125 mL separatory funnel and then shaken well. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The organic layers were combined, washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). The resulting material was dissolved in 10 mL of ether and adsorbed onto Celite. Purification by silica gel flash column chromatography (3:1 hexanes/ethyl acetate, 20 mm diameter, 17 cm of SiO_2) followed by bulb-to-bulb distillation afforded 416 mg (91%) of **3u** as a clear oil. Data for **3u**: bp 140 °C (ABT, 0.05 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17−7.07 (m, 2H, HC(3), HC(5)), 6.90 (t, J = 8.0 Hz, 1H, HC(4)), 6.79 (d, J = 8.2 Hz, 1H, HC(6)), 5.56 (dt, J = 15.1, 6.5 Hz, 1H, HC(9)), 5.48 (dt, J = 15.6, 6.5 Hz, 1H, HC(10)), 3.65 (t, J = 6.5 Hz, 2H, HC(13)), 2.71 (dd, J = 8.3, 6.8 Hz, 2H, HC(7)), 2.35 (q, J = 7.4 Hz, 2H, HC(8)), 2.12 (q, J = 6.8 Hz, 2H, HC(11)), 1.65 (p, J = 6.8 Hz, 2H, HC(12)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2 (C1), 130.8 (C10), 130.5 (C5), 130.3 (C9), 128.5 (C2), 127.3 (C3), 120.7 (C4), 115.7 (C6), 62.6 (C13), 33.1 (C8), 32.2 (C12), 30.3 (C7), 29.0 (C11); IR (ATR, cm^{-1}) 3307 (br), 3033 (w), 2932 (w), 2851 (w), 1607 (w), 1592 (w), 1504 (w), 1489 (w), 1455 (m), 1354 (w), 1238 (m), 1178 (w), 1153 (w), 1094 (w), 1042 (m), 1015 (w), 968 (w), 929 (w), 847 (w), 750 (s); MS (EI, 70 eV, m/z) 206 (20, M⁺), 120 (14), 107 (100); TLC R_f 0.1 (4:1 hexanes/ethyl acetate) [UV,CAM]. Anal. Calcd for $C_{13}H_{18}O_2$ (206.29): C, 75.69; H, 8.80. Found: C, 75.48; H, 8.56.

3u

S4

3s
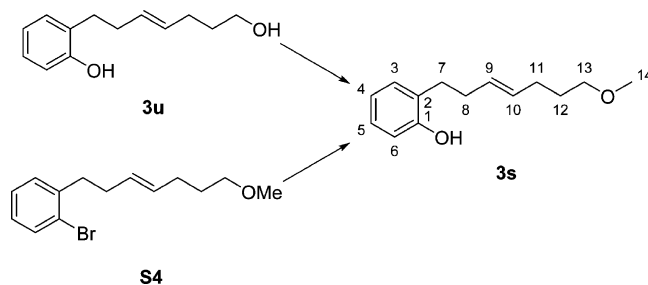
Preparation of (E)-2-(7-Methoxyhept-3-en-1-yl)phenol (3s). This compound was prepared in two ways. Method A: To a 10 mL Schlenk flask in a glovebox was added NaH (27 mg, 1.1 mmol, 2.1 equiv). The flask was transferred to the Schlenk line, and THF (1.5 mL) was added. To this was added the alcohol **3u** (103 mg, 0.5 mmol) in THF (0.5 mL). The solution was stirred for 15 min at rt, and MeI (34 μL, 0.55 mmol, 1.1 equiv) was added dropwise. The solution was then allowed to stir at rt for 16 h. The reaction was quenched by the addition of water (1 mL) and 1 M HCl (0.5 mL). The mixture was transferred to a 60 mL separatory funnel and diluted with ether (10 mL) and water (10 mL) and the pH adjusted to <2 with 3 M HCl. The layers were separated, and the aqueous layer was extracted with ether (2 × 10 mL). The organic layers were combined, washed with brine (15 mL), dried over MgSO$_4$, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (12:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO$_2$) afforded 63 mg (57%) of **3s** as a clear oil. Method B: To a 10 mL Schlenk flask were added **S4** (368 mg, 1.3 mmol) and THF (15 mL). The flask was cooled to −76 °C (internal temperature, dry ice/*i*-PrOH). BuLi (2.3 M, 620 μL, 1.43 mmol, 1.1 equiv) was added via syringe, and the solution was allowed to stir for 1 h. Triisopropyl borate (489 mg, 2.6 mmol, 2.0 equiv) was added via syringe, and the solution was allowed to warm to rt. After the solution was stirred for 6 h at rt, the flask was placed in an ice bath. In a separate 25 mL RB flask, a basic hydrogen peroxide solution was prepared by combining 20 mL of 30% H$_2$O$_2$ with 2 g of NaOH. A portion of this solution (2 mL) was then added dropwise to the flask containing the borate (strong exotherm) followed by the remaining 8 mL of basic peroxide, and the solution was allowed to stir for 5 h at rt. The excess peroxide solution was quenched with satd aq Na$_2$S$_2$O$_3$. After the allotted time had passed, the mixture was transferred to a 125 mL separatory funnel, and satd aq Na$_2$S$_2$O$_3$ was added until no more peroxide was evident (Quantifix test strip). The mixture was then diluted with ether (15 mL) and water (15 mL) and acidified with 1 M HCl to pH < 2. The layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (12:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO$_2$) followed by bulb-to-bulb vacuum distillation afforded 213 mg (76%) of **3s** as a clear oil (76%). Data for **3s**: bp 100 °C (ABT, 0.05 mmHg); ^{1}H NMR: (500 MHz, CDCl$_3$) δ 7.15−7.05 (m, 2H, HC(3), HC(5)), 6.88 (t, J = 7.6 Hz, 1H, HC(4)), 6.77 (d, J = 8.0 Hz, 1H, HC(6)), 5.62−5.38 (m, 2H, HC(9), HC(10)), 3.45−3.32 (m, 5H, HC(13), HC(14)), 2.68 (dd, J = 8.6, 6.7 Hz, 2H, HC(7)), 2.32 (app q, J = 7.8 Hz, 2H, HC(8)), 2.11−2.01 (app q, J = 7.7 Hz, 2H, HC(11)), 1.64 (app p, J = 7.2, 6.8 Hz, 2H, HC(12)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.8 (C1), 130.7 (C9), 130.5 (C5), 130.3 (C10), 128.2 (C2), 127.4 (C3), 120.9 (C4), 115.6 (C6), 72.4 (C13), 58.7 (C14), 33.0 (C8), 30.5 (C7), 29.5 (C11), 29.3 (C12); IR (ATR, cm^{-1}) 3308 (br), 2930 (w), 2852 (w), 1607 (w), 1593 (w), 1504 (w), 1489 (w), 1455 (s), 1353 (w), 1234 (m), 1179 (m), 1099 (m), 1042 (w), 968 (m), 931 (w), 847 (w), 765 (s); MS (EI, 70 eV, m/z) 220 (17, M$^+$), 149 (15), 107 (100), 81 (35); TLC R_f 0.33 (4:1 hexanes/ethyl acetate) [UV,CAM]. Anal. Calcd for C$_{14}$H$_{20}$O$_2$ (220.31): C, 76.33; H, 9.15. Found: C, 76.10; H, 8.91.

Sulfenocyclizations of Substituted (*E*)-2-Cinnamylphenols. General Procedure 2. To a 10 mL, oven-dried flask equipped with a magnetic stir bar under an argon atmosphere were added substrate and CH$_2$Cl$_2$. The catalyst and the electrophile were added as solids and allowed to dissolve to obtain a clear or pale yellow solution. The reaction vessel was placed in an *i*-PrOH bath kept at constant temperature by means of a Neslab IBC-4A Cryocool with probe. The reaction mixture was cooled to the appropriate reaction temperature, and the internal temperature was checked. After the temperature stabilized to ±2 °C, MsOH was added to the stirring reaction mixture via syringe. (Note: It is important to not let the acid touch the walls of the reaction vessel as it may immediately freeze.) After addition of the acid, rapid formation of a yellow color was observed. The reaction mixture was then stirred for the appropriate time. Over the course of the reaction, white crystals of phthalimide precipitate out of the

mixture. After the reaction was complete as judged by TLC and ^{1}H NMR spectroscopy, Et$_3$N was added directly to the cold reaction mixture. The flask was then allowed to warm to rt, whereupon the white crystals slowly dissolved to afford a homogeneous solution. This solution was then either (1) poured into a separatory funnel containing 1 M NaOH solution, shaken well, extracted with dichloromethane, dried, and concentrated or (2) directly concentrated. Subsequently, ^{1}H NMR spectra of the crude residue were recorded. Products were purified by silica flash chromatography, and analytically pure samples were obtained by recrystallization or distillation as specified.
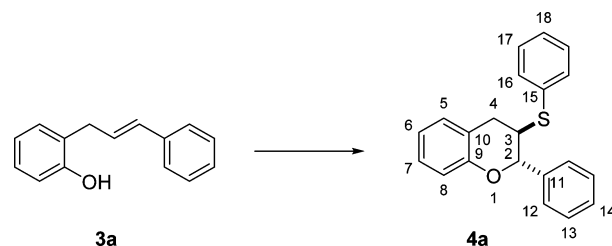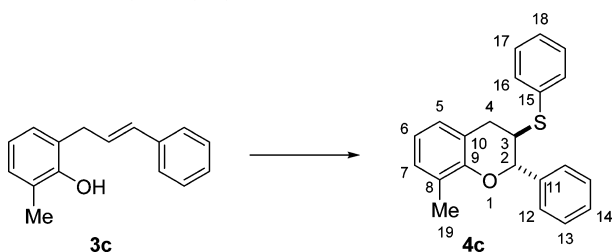

Preparation of (2S,3R)-2-Phenyl-3-(phenylthio)chromane (4a). Following general procedure 2, **3a** (210 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH$_2$Cl$_2$ (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv) and catalyst (*S*)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL) and allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and then was diluted with CH$_2$Cl$_2$ (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH$_2$Cl$_2$. The organic phases were combined, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (40:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO$_2$) followed by recrystallization from hexanes (3 mL) afforded, in two crops, 268 mg (84%) of **4a** as white needles. Data for **4a**: mp 121−122 °C (hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41−7.32 (m, 5 H, HC(aryl)), 7.30 (m, 2H, HC(aryl)), 7.26 (m, 3 H, HC(aryl)), 7.20 (t, J = 7.8 Hz, 1H, HC(7)), 7.08 (d, J = 7.5 Hz, 1H, HC(5)), 6.97 (d, J = 8 Hz, 1H, HC(8)), 6.94 (t, J = 8 Hz, 1H, HC(6)), 5.09 (d, J = 7.8 Hz, 1H, HC(2)), 3.81 (ddd, J = 9.5, 7.7, 5.2 Hz, 1H, HC(3)), 3.15 (dd, J = 16.6, 5.1 Hz, 1H, HC(4)), 2.99 (dd, J = 16.6, 9.1 Hz, 1H, HC(4)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.3 (C9), 139.4 (C15), 133.7 (C11), 133.3 (C17), 129.5 (C5), 129.1 (C13), 128.6 (C12), 128.6 (C14), 128.1 (C7), 127.7 (C18), 127.3 (C16), 121.0 (C6), 120.7 (C10), 116.8 (C8), 81.2 (C2), 47.2 (C3), 31.8 (C4); IR (ATR, cm^{-1}) 2912 (w), 1583 (w), 1487 (m), 1449 (w), 1439 (w), 1427 (w), 1306 (w), 1277 (w), 1222 (m), 1205 (w), 1193 (w), 1150 (w), 1111 (w), 1086 (w), 1069 (w), 1024 (w), 1000 (m), 969 (w), 904 (w), 851 (w), 831 (w), 797 (w), 757 (s), 750 (s), 727 (w), 716 (m), 700 (s); MS (EI, 70 eV, m/z) 318 (36, M$^+$), 208 (40), 200 (100), 199 (98), 119 (19); TLC R_f 0.48 (1:1, hexanes/CH$_2$Cl$_2$) [UV,CAM]; $[\alpha]_D^{23}$ = −40.0 (c = 0.87, CHCl$_3$); CD, (−), Cotton sign, 230−280 nm; CSP-SFC, (2R,3S)-**4a** t_{min} 13.4 min, (5.1%), (2S,3R)-**4a** t_{maj} 18.5 min, (94.9%) (Chiralpak AD, 220 nm, 200 bar, 40 °C, 95:5, sCO$_2$/MeOH, 2 mL/min). Anal. Calcd for C$_{21}$H$_{18}$OS (318.43): C, 79.21; H, 5.70. Found: C, 78.91; H, 5.62.
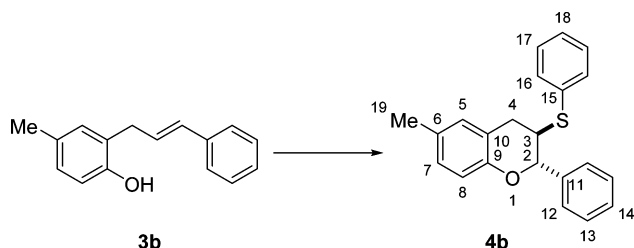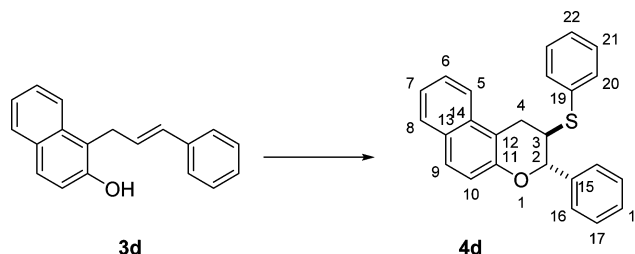
Preparation of (2S,3R)-6-Methyl-2-phenyl-3-(phenylthio)-chromane (4b). Following general procedure 2, **3b** (224 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ¹H NMR), the reaction was quenched with triethylamine (300 μL), and the mixture was then allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and then was diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (4:1 hexanes/$CHCl_3$ to 3:1 hexanes/$CHCl_3$, 20 mm diameter, 20 cm of SiO_2) followed by recrystallization from hexanes (3 mL) afforded, in two crops, 272 mg (82%) of **4b** as white needles. Data for **4b**: mp 114−115 °C (hexanes); ¹H NMR (500 MHz, $CDCl_3$) δ 7.40−7.29 (m, 7H, HC(aryl)), 7.27−7.23 (m, 3H, HC(aryl))), 7.00 (d, J = 8.5 Hz, 1H, HC(7)), 6.88, (s, 1H, HC(5)), 6.87 (d, J = 8.5 Hz, 1H, HC(8)), 5.06 (d, J = 7.7 Hz, 1H, HC(2)), 3.80 (ddd, J = 8.8, 7.6, 5.2 Hz, 1H, HC(3)), 3.09 (dd, J = 16.6, 5.2 Hz, 1H, HC(4)), 2.95 (dd, J = 16.6, 8.9 Hz, 1H, HC(4)), 2.31 (s, 3H, HC(19)); ¹³C NMR (126 MHz, $CDCl_3$) δ 152.1 (C9), 139.6 (C15), 133.8 (C11), 133.2 (C17), 130.2 (C6), 129.9 (C5), 129.1 (C13), 128.7 (C7), 128.6 (C12), 128.5 (C14), 127.7 (C18), 127.3 (C16), 120.3 (C10), 116.5 (C8), 81.1 (C2), 47.3 (C3), 31.7 (C4), 20.8 (C19); IR (ATR, cm⁻¹) 2923 (w), 1588 (w), 1497 (m), 1474 (w), 1457 (w), 1436 (w), 1301 (w), 1239 (m), 1227 (s), 1148 (w), 1127 (w), 1027 (w), 988 (m), 937 (w), 909 (w), 880 (w), 852 (w), 831 (m), 818 (w), 798 (w), 745 (s), 729 (w), 691 (s); MS (EI, 70 eV, *m/z*) 332 (60, M⁺), 200 (88), 199 (80), 133 (60), 91 (100); TLC R_f 0.67 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23}$ = −32.9 (*c* = 0.88 in $CHCl_3$); CD, (−), Cotton sign, 230−280 nm; CSP-SFC, (2R,3S)-**4b** t_{min} 10.2 min (5.0%), (2S,3R)-**4b** t_{maj} 14.3 min (95.0%) (Chiralpak AD, 220 nm, 200 bar, 40 °C, 85:15 sCO₂/MeOH, 2 mL/min). Anal. Calcd for $C_{22}H_{20}OS$ (332.46): C, 79.48; H, 6.06. Found: C, 79.15; H, 5.97.
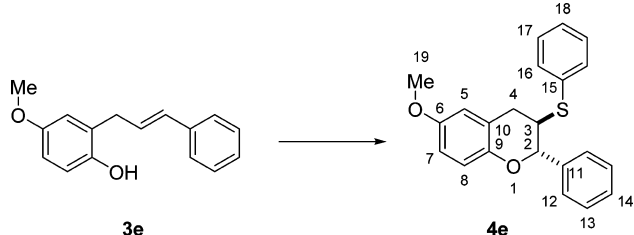

Preparation of (2S,3R)-8-Methyl-2-phenyl-3-(phenylthio)-chromane (4c). Following general procedure 2, **3c** (224 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ¹H NMR), the

reaction was quenched with triethylamine (300 μL), and the mixture was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (60:1 hexanes/ethyl acetate then 40:1 hexanes/ethyl acetate, 30 mm diameter, 16 cm of SiO_2) afforded a white solid. Recrystallization from hexanes (3 mL) afforded, in two crops, 259 mg (78%) of **4c** as white needles. Data for **4c**: mp 89−90 °C (hexanes); ¹H NMR (500 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H, HC(aryl)), 7.28 (d, J = 2.1 Hz, 2H, HC(aryl)), 7.25−7.19 (m, 3H, HC(aryl)), 7.05 (d, J = 7.5 Hz, 1H, HC(5)), 6.88 (dd, J = 7.7, 1.9 Hz, 1H, HC(7)), 6.81 (t, J = 7.4 Hz, 1H, HC(6)), 5.11 (d, J = 7.6 Hz, 1H, HC(2)), 3.75 (ddd, J = 8.9, 7.5, 5.0 Hz, 1H, HC(3)), 3.08 (dd, J = 16.6, 5.1 Hz, 1H, HC(4)), 2.95 (dd, J = 16.5, 8.8 Hz, 1H, HC(4)), 2.23 (s, 3H, HC(19)); ¹³C NMR (101 MHz, $CDCl_3$) δ 152.4 (C9), 139.9 (C15), 133.9 (C11), 133.0 (C17), 129.2 (C5), 129.2 (C16), 128.6 (C13), 128.4 (C18), 127.6 (C14), 127.1 (C7, C16), 126.0 (C10), 120.4 (C6), 120.1 (C8), 81.0 (C2), 47.3 (C3), 31.8 (C4), 16.4 (C19); IR (ATR, cm⁻¹) 1594 (w), 1467 (m), 1432 (w), 1379 (w), 1304 (w), 1259 (w), 1239 (w), 1204 (s), 1101 (w), 1072 (w), 1026 (w), 985 (m), 959 (w), 924 (w), 910 (w), 828 (w), 798 (w), 757 (s), 744 (s), 728 (m), 699 (s); MS (EI, 70 eV, *m/z*) 332 (43, M⁺), 222 (48), 200 (100), 199 (60), 149 (20), 133 (41); TLC R_f 0.77 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23}$ = −4.5 (*c* = 0.88 in $CHCl_3$); CD, (−), Cotton sign, 230−280 nm; CSP-SFC, (2R,3S)-**4c** t_{min} 10.5 (4.0%), (2S,3R)-**4c** t_{maj} 11.8 (96.0%) (Chiralpak AD, 220 nm, 200 bar, 40 °C, 95:5, sCO₂/MeOH, 2 mL/min). Anal. Calcd for $C_{22}H_{20}OS$ (332.46): C, 79.48; H, 6.06. Found: C, 79.54; H, 6.19.

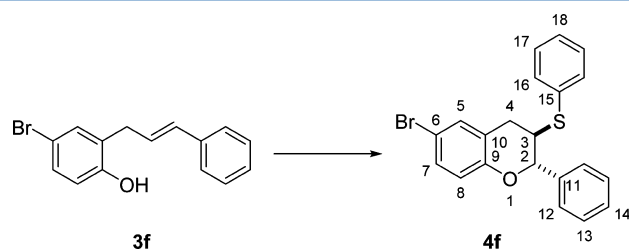*Preparation of (2R,3S)-3-Phenyl-2-(phenylthio)-2,3-dihydro-1H-benzo[f]chromene (4d).* Following general procedure 2, **3d** (260 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ¹H NMR), the reaction was quenched with triethylamine (300 μL) and then was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (60:1 hexanes/ethyl acetate then 40:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO_2) followed by recrystallization (hexanes, 3 mL, ether, 0.2 mL) afforded, in two crops, 290 mg (79%) of **4d** as pale pink prisms. Data for **4d**: mp 136−138 °C (hexanes/ether); ¹H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 7.8 Hz, 1H, HC(5)), 7.77 (d, J = 8.5, 1H, HC(8)), 7.72 (d, J = 8.9 Hz, 1H, HC(9)), 7.53 (dd, J = 8.3, 7.0 Hz, 1H, HC(7)), 7.46−7.38 (m, 4H, HC(aryl), HC(6)), 7.38−7.27 (m, 4H, HC(aryl)), 7.27−7.22 (m, 3H HC(aryl)), 7.19 (d, 1H, 8.9 Hz, HC(10)), 5.15 (d, J = 8.0 Hz, 1H, HC(2)), 3.95 (ddd, J = 8.9, 8.0, 5.6, 1H, HC(3)), 3.49 (dd, J = 16.8, 5.6 Hz, 1H, HC(4)), 3.26 (dd, J = 16.8, 8.9 Hz, 1H, HC(4)); ¹³C NMR (101 MHz, $CDCl_3$) δ 152.0 (C11), 139.1 (C19), 133.9 (C14),

133.3 (C21), 132.9 (C12), 129.4 (C13), 129.2 (C17), 128.8 (C18), 128.7 (C5), 128.7 (C16), 128.6 (C9), 127.8 (C22), 127.5 (C20), 126.9 (C7), 123.8 (C6), 122.0 (C8), 118.9 (C10), 112.7 (C12), 81.2 (C2), 47.4 (C3), 28.9 (C4); IR (ATR, cm^{-1}) 3054 (w), 1621 (w), 1596 (m), 1508 (w), 1466 (m), 1456 (w), 1433 (m), 1397 (m), 1259 (w), 1227 (s), 1166 (m), 1140 (w), 1080 (w), 1066 (m), 1024 (w), 991 (s), 971 (s), 913 (w), 862 (w), 847 (w), 818 (s), 801 (m), 767 (s), 746 (s), 736 (s), 703 (s); MS (EI, 70 eV, m/z) 368 (65, M$^+$), 318 (25), 258 (44), 208 (32), 200 (97), 199 (100), 169 (49), 168 (46); TLC R_f 0.74 (1:1, hexanes/CH$_2$Cl$_2$) [UV,CAM]; $[\alpha]_D^{23} = -89.4$ ($c = 0.86$ in CHCl$_3$); CD, ($-$), Cotton sign, 230$-$280 nm; CSP-HPLC, (2R,3S)-**4d** t_{min} 11.3 (6.8%), (2S,3R)-**4d** t_{maj} 17.6 (93.2%) (Chiralpak AD, 220 nm, 95:5, hexanes/i-PrOH, 0.8 mL/min). Anal. Calcd for C$_{25}$H$_{20}$OS (368.49): C, 81.49; H, 5.47. Found: C, 81.32; H, 5.50.

3e

Preparation of (2S,3R)-6-Methoxy-2-phenyl-3-(phenylthio)-chromane (4e). Following general procedure 2, **3e** (240 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH$_2$Cl$_2$ (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an i-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL), and the mixture was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and then was diluted with CH$_2$Cl$_2$ (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH$_2$Cl$_2$. The organic phases were combined, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (60:1 hexanes/ethyl acetate to 40:1 hexanes/ethyl acetate, 30 mm diameter, 18 cm of SiO$_2$) followed by recrystallization from hexanes (3 mL) afforded, in two crops, 293 mg (84%) of **4e** as white needles. Data for **4e**: mp 128$-$129 °C (hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.42$-$7.26 (m, 7H, HC(aryl)), 7.25$-$7.19 (m, 3H, HC(aryl)), 6.87 (d, $J = 8.9$ Hz, 1H, HC(8)), 6.75 (dd, $J = 8.9, 2.8$ Hz, 1H, HC(7)), 6.58 (d, $J = 3.1$, 1H, HC(5)), 5.02 (dd, $J = 7.7, 1.2$ Hz, 1H, HC(2)), 3.83$-$3.72 (m, 4H, HC(3), HC(19)), 3.09 (dd, $J = 16.7, 5.2$ Hz, 1H, HC(4)), 2.95 (dd, $J = 16.7, 8.9$ Hz, 1H, HC(4)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.9 (C9), 148.3 (C6), 139.5 (C15), 133.7 (C11), 133.2 (C17), 129.1 (C13), 128.6 (C12), 128.6 (C14), 127.7 (C18), 127.3 (C16), 121.3 (C10), 117.5 (C8), 114.2 (C7), 113.9 (C5), 81.1 (C2), 56.0 (C19), 47.2 (C3), 32.1 (C4); IR (ATR, cm^{-1}) 2835 (w), 1583 (w), 1496 (m), 1457 (w), 1429 (m), 1293 (w), 1245 (w), 1224 (s), 1209 (s), 1151 (m), 1122 (w), 1086 (w), 1040 (s), 994 (s), 934 (w), 909 (w), 875 (w), 851 (w), 820 (m), 787 (w), 742 (s), 727 (s); MS (EI, 70 eV, m/z) 348 (69, M$^+$), 199 (42), 149 (56), 91 (100); TLC R_f 0.44 (1:1, hexanes/CH$_2$Cl$_2$) [UV,CAM]; $[\alpha]_D^{23} = -36.2$ ($c = 0.96$ in CHCl$_3$); CD, ($-$), Cotton sign, 230$-$280 nm; CSP-SFC, (2R,3S)-**4e** t_{min} 13.9 min (5.6%), (2S,3R)-**4e** t_{maj} 16.0 min (94.4%) (Chiralpak AD, 220 nm, 200 bar, 40 °C, 85:15, sCO$_2$/MeOH, 2 mL/min). Anal. Calcd for C$_{22}$H$_{20}$O$_2$S (348.46): C, 75.83; H, 5.79. Found: C, 76.04; H, 5.57.
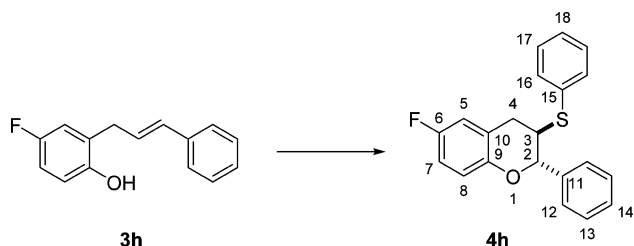

3f   **4f**

Preparation of (2S,3R)-6-Bromo-2-phenyl-3-(phenylthio)-chromane (4f). Following general procedure 2, **3f** (289 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH$_2$Cl$_2$ (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an i-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 36 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL), and the mixture was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and then was diluted with CH$_2$Cl$_2$ (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH$_2$Cl$_2$. The organic phases were combined, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (60:1 hexanes/ethyl acetate, then 40:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO$_2$) followed by recrystallization (hexanes, 3 mL, ether, 0.2 mL) afforded, in two crops, 320 mg (81%) of **4f** as white needles. Data for **4f**: mp 138$-$139 °C (hexanes/ether); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40$-$7.24 (m, 11H, HC(aryl), HC(7)), 7.19 (d, $J = 2.4$ Hz, 1H, HC(5)), 6.85 (d, $J = 8.7$ Hz, 1H, HC(8)), 5.10 (d, $J = 7.3$ Hz, 1H, HC(2)), 3.77 (ddd, $J = 8.7, 7.3, 5.1$ Hz, 1H, HC(3)), 3.07 (dd, $J = 16.8, 5.1$ Hz, 1H, HC(4)), 2.92 (dd, $J = 16.7, 8.5$ Hz, 1H, HC(4)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.4 (C9), 139.1 (C15), 133.4 (C17), 133.3 (C11), 132.1 (C5), 131.0 (C7), 129.2 (C13), 128.7 (C12, C14), 128.0 (C18), 127.0 (C16), 122.8 (C6), 118.6 (C8), 113.0 (C10), 81.0 (C2), 46.7 (C3), 31.0 (C4); IR (ATR, cm^{-1}) 3037 (w), 1573 (w), 1473 (m), 1432 (w), 1405 (w), 1288 (w), 1232 (s), 1182 (m), 1121 (m), 1088 (w), 1067 (w), 1027 (w), 977 (m), 935 (w), 911 (w), 890 (m), 866 (m), 844 (w), 830 (w), 815 (w), 799 (w), 776 (w), 743 (s), 699 (s); MS (EI, 70 eV, m/z) 397 (18, M$^+$), 395 (18, M$^+$), 199 (100), 91 (88); TLC R_f 0.44 (1:1, hexanes/CH$_2$Cl$_2$) [UV,CAM]; $[\alpha]_D^{23} = -49.2$ ($c = 0.84$ in CHCl$_3$); CD, ($-$), Cotton sign, 230$-$280 nm; CSP-HPLC, (2R,3S)-**4f**, t_{min} 9.3 (6.2%), (2S,3R)-**4f**, t_{maj} 12.2 (93.8%) (Chiralpak AD, 220 nm, 95:5, hexanes/i-PrOH, 0.8 mL/min). Anal. Calcd for C$_{21}$H$_{17}$BrOS (397.33): C, 63.48; H, 4.31. Found: C, 63.38; H, 4.30.
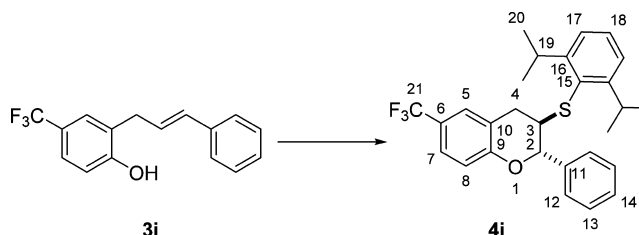

3g   **4g**
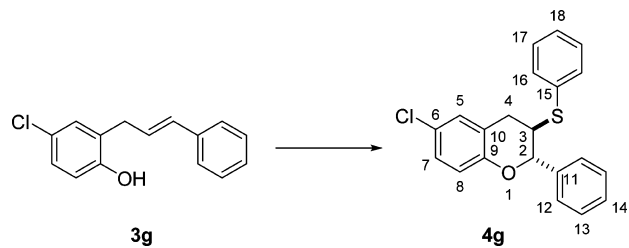
Preparation of (2S,3R)-6-Chloro-2-phenyl-3-(phenylthio)-chromane (4g). Following general procedure 2, **3g** (245 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH$_2$Cl$_2$ (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an i-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 36 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL), and the mixture

was allowed to warm to rt, whereupon the white solid dissolved. The material was transferred to a 250 mL RB flask using 20 mL of CH_2Cl_2 and concentrated by rotary evaporation (30 °C, 3 mmHg). The material was then redissolved in 10 mL of CH_2Cl_2 and then adsorbed onto Celite. Purification by silica gel flash column chromatography (5:1 hexanes/CH_2Cl_2, 20 mm diameter, 16 cm of SiO_2) followed by recrystallization from hexanes (3 mL) afforded, in two crops, 248 mg (70%) of **4g** as white needles. Data for **4g**: mp 144−145 °C (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.29 (m, 7H, HC(aryl)), 7.29− 7.25 (m, 3H, HC(aryl)), 7.15 (dd, J = 8.7, 2.5 Hz, 1H, HC(7)), 7.04 (d, J = 2.6 Hz, 1H, HC(5)), 6.90 (d, J = 8.7, 1H, HC(8)), 5.09 (d, J = 7.3 Hz, 1H, HC(2)), 3.77 (ddd, J = 8.5, 7.3, 5.1 Hz, 1H, HC(3)), 3.07 (dd, J = 16.8, 5.1 Hz, 1H, HC(4)), 2.92 (dd, J = 16.8, 8.5 Hz, 1H, HC(4)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9 (C9), 148.7 (C6) 139.1 (C15), 133.4 (C17), 133.3 (C11), 129.2 (C13), 129.1 (C5), 128.7 (C12), 128.1 (C7), 128.0 (C14/C18), 127.0 (C16), 125.7 (C14/C18), 122.2 (C10), 118.1 (C8), 81.0 (C2), 46.7 (C3), 31.2 (C4); IR (ATR, cm^{-1}) 3059 (w), 1578 (w), 1476 (m), 1432 (w), 1411 (w), 1290 (w), 1235 (s), 1187 (m), 1123 (m), 1068 (w), 1027 (w), 981 (m), 935 (m), 898 (m), 875 (s), 849 (w), 831 (m), 794 (w), 781 (w), 743 (s), 699 (s); MS (EI, 70 eV, m/z) 354 (12, M^+), 352 (20, M^+),247 (44),199 (89), 149 (36),133 (41),107 (23), 91 (80); TLC R_f 0.45 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23} = -42.6$ (c = 1.12 in $CHCl_3$); CD, (−), Cotton sign, 230−280 nm; CSP-HPLC, (2R,3S)-**4g** t_{min} 9.2 (6.2%), (2S,3R)-**4g** t_{maj} 12.4 (93.8%) (Chiralpak AD, 220 nm, 95:5, hexanes/i-PrOH, 0.8 mL/min). Anal. Calcd for $C_{21}H_{17}ClOS$ (352.88): C, 71.48; H, 4.86. Found: C, 71.73; H, 5.11.
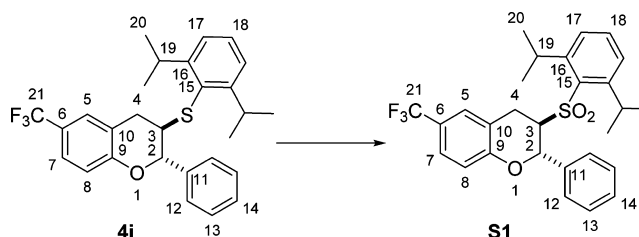

Preparation of (2S,3R)-6-Fluoro-2-phenyl-3-(phenylthio)-chromane (4h). Following general procedure 2, **3h** (228 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an i-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 36 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL), and the mixture was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (6:1 hexanes/$CHCl_3$ then 4:1 then 3:1 hexanes/$CHCl_3$, 20 mm diameter, 17 cm of SiO_2) followed by recrystallization from hexanes (3 mL) afforded, in two crops, 289 mg (86%) of **4h** as white needles. Data for **4h**: mp 111−112 °C (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.32 (m, 5H, HC(aryl)), 7.30 (m, 2H, HC(aryl)), 7.28−7.24 (m, 3H, HC(aryl)), 6.93−6.88 (m, 2H, HC(8), HC(5)), 6.81−6.74 (d, J = 8.4 Hz, 1H, HC(7)), 5.07 (d, J = 7.6 Hz, 1H, HC(2)), 3.78 (ddd, J = 8.6, 7.5, 5.2 Hz, 1H, (HC(3)), 3.10 (dd, J = 16.9, 5.2 Hz, 1H, HC(4)), 2.95 (dd, J = 16.8, 8.8 Hz, 1H, HC(4)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2 (d, J = 238.9 Hz, C6), 150.3 (C9), 139.2 (C15), 133.4 (C11), 133.4 (C17), 129.2 (C13), 128.7 (C12,C14), 127.9 (C18), 127.2 (C16), 121.8 (d, J = 7.4 Hz, C10), 117.7 (d, J = 8.1 Hz, C8), 115.4 (d, J = 22.8 Hz, C7), 114.9 (d, J = 23.2 Hz, C5), 81.1 (C2), 46.8 (C3), 31.7 (C4); ^{19}F NMR (470 MHz, $CDCl_3$) δ −124.03 (app q, J = 7.3 Hz); IR (ATR, cm^{-1}) 3072 (w), 1580 (w), 1491 (s), 1473 (m), 1458 (w),

1438 (w), 1429 (m), 1374 (w), 1332 (w), 1283 (w), 1240 (m), 1222(s), 1203 (s), 1140 (m), 1103 (w), 1087 (w), 1067 (w), 1036 (w), 984 (s), 948 (m), 933 (m), 911 (w), 873 (m), 850 (m), 827 (m), 792 (m), 744 (s), 730 (s); MS (EI, 70 eV, m/z) 336 (33, M^+), 226 (27), 199 (100), 91 (93); TLC R_f 0.49 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23} = -23.4$ (c = 0.94 in $CHCl_3$); CD, (−), Cotton sign, 230−280 nm; CSP-SFC, (2R,3S)-**4h** t_{min} 9.0 min (6.8%), (2S,3R)-**4h** t_{maj} 11.6 min (93.2%) (Chiralpak AD, 220 nm, 95:5, hexanes/i-PrOH, 0.8 mL/min). Anal. Calcd for $C_{21}H_{17}FOS$ (336.42): C, 74.97; H, 5.09. Found: C, 74.73; H, 5.02.


Preparation of (2S,3R)-3-((2,6-Diisopropylphenyl)thio)-2-phenyl-6-(trifluoromethyl)chromane (4i). Following general procedure 2, **3i** (276 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1c** (339 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an i-PrOH bath and stirred at rt. MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 12 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL), and the mixture was allowed to warm to rt, whereupon the white solid dissolved. The material was transferred to a 250 mL RB flask using 20 mL of CH_2Cl_2 and concentrated by rotary evaporation (30 °C, 3 mmHg) to afford a pale yellow residue. The material was then redissolved in 10 mL of CH_2Cl_2 and adsorbed onto Celite. Purification by silica gel flash column chromatography of the adsorbed material (5:1 hexanes/CH_2Cl_2, 20 mm diameter, 16 cm of SiO_2) followed by recrystallization from hexanes (3 mL) afforded, in two crops, 416 mg (89%) of **4i** as white prisms. Data for **4i**: mp 137− 140 °C (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.5 Hz, 2.2 Hz, 1H, HC(7)), 7.34 (m, 4H, HC(aryl)), 7.25 (m, 2H, HC(aryl)), 7.22−7.20 (br s, 1H, HC(5)), 7.18 (d, J = 7.7 Hz, 2H, HC(17)), 7.04 (d, J = 8.6 Hz, 1H, HC(8)), 5.19 (d, J = 5.5 Hz, 1H, HC(2)), 3.75 (p, J = 6.9 Hz, 2H, HC(19)), 3.50 (q, J = 5.6 Hz, 1H, HC(3)), 2.77 (d, J = 5.5 Hz, 2H, HC(4)), 1.18 (d, J = 6.9 Hz, 12H, HC(20)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6 (C15), 154.2 (C9), 139.6 (C11), 130.0 (C14), 128.8 (C13), 128.7 (C16), 128.6 (C18), 127.1 (C5), 126.2 (C12), 125.5 (C7), 124.1 (C17), 120.6 (C4), 117.0 (C8), 79.8 (C2), 47.2 (C3), 31.8 (C19), 29.1 (C4), 24.7 (m, C20); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.87 (s); IR (ATR, cm^{-1}) 2961 (w), 2926 (w), 1738(w), 1620 (w), 1594 (w), 1507 (w), 1455 (w), 1380 (w), 1361 (w), 1330 (s), 1292 (m), 1241 (s), 1188 (w), 1159 (s), 1115 (s), 1070 (w), 1050 (w), 1032 (w), 990 (m), 971(m), 936 (w), 905 (m), 889 (m), 846 (m), 799 (m), 781 (w), 748 (m), 740 (m), 696 (s); MS (EI, 70 eV, m/z) 470 (25, M^+), 283 (100),276 (21),194 (22), 149 (51); TLC R_f 0.65 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23} = -7.0$ (c = 0.9 in $CHCl_3$); CD, (−), Cotton sign, 230−280 nm. Anal. Calcd for $C_{28}H_{29}F_3OS$ (470.59): C, 71.46; H, 6.21. Found: C, 71.38; H, 6.22.

Preparation of (2S,3R)-3-((2,6-Diisopropylphenyl)sulfonyl)-2-phenyl-6-(trifluoromethyl)chromane (S1). To determine enantiomeric

composition, **4i** was oxidized to the sulfone **S1**. To a 4 dram vial under nitrogen was added solid **4i** (20 mg, 0.04 mmol, 1 equiv) followed by CH_2Cl_2 (1 mL) and solid *m*-CPBA (18 mg, 0.11 mmol, 2.5 equiv). The resulting solution was stirred at rt for 3 h. The solution was then diluted with hexanes (3 mL) and directly purified by silica gel flash column chromatography (9:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO_2) to afford 22 mg of a white solid. The product sulfone was then analyzed by chiral stationary phase HPLC. Data for **S1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56−7.44 (m, 2H, HC(7), HC(5)), 7.35 (d, *J* = 7.7 Hz, 3H, HC(aryl)), 7.31−7.27 (m, 5H, HC(aryl)), 7.19 (dd, *J* = 6.7, 2.9 Hz, 2H, HC(aryl)), 7.08 (d, *J* = 8.5 Hz, 1H, HC(8)), 5.82 (d, *J* = 4.4 Hz, 1H, HC(2)), 4.04 (p, *J* = 6.7 Hz, 2H, HC(19)), 3.86 (app q, *J* = 5.8 Hz, 1H, HC(3)), 3.30 (dd, *J* = 17.5, 5.5 Hz, 1H, HC(4)), 3.03 (dd, *J* = 17.5, 6.4 Hz, 1H, HC(4)), 1.30 (d, *J* = 6.7 Hz, 6H, HC(20)), 1.25 (d, *J* = 6.7 Hz, 6H, HC(21)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 138.2, 133.6, 129.1, 128.9, 126.6, 126.4, 126.2, 119.1, 117.4, 74.9, 62.5, 30.0, 25.3, 25.2, 22.6; CSP-HPLC, (2*S*,3*R*)-**S1** t_{maj} 6.9 min (95.2%) (2*R*,3*S*)-**S1** t_{min} 7.7 min (4.8%) (Chiralpak AD, 220 nm, 95:5, hexanes/*i*-PrOH, 0.8 mL/min).

**Sulfenocyclizations of Other Substituted (*E*)-2-(2-Propenyl)-phenols.**
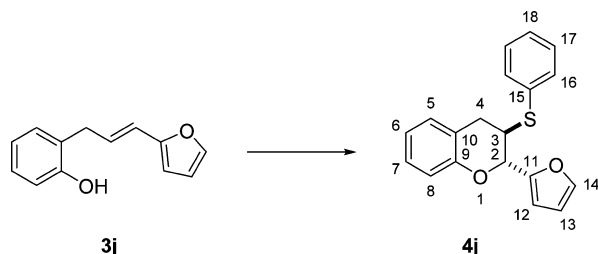
Preparation of (2S,3R)-2-(Furan-2-yl)-3-(phenylthio)chromane (4j). For compound **4j**, general procedure 2 was modified as follows: To a dried 10 mL Schlenk flask were added CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (*S*)-**2b** (52 mg, 0.1 mmol, 0.1 equiv). The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe, and the solution was allowed to stir for 5 min. Substrate **3j** (200 mg, 1.0 mmol) was then added directly to the cold solution. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL) and then was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). The material was dissolved in CH_2Cl_2 (10 mL) and adsorbed onto Celite. Purification by silica gel flash column chromatography (5:1 hexanes/CH_2Cl_2, 20 mm diameter, 16 cm of SiO_2) followed by recrystallization from hexanes (3 mL) afforded, in two crops, 271 mg (88%) of **4j** as white needles. Data for **4j**: mp 72−73 °C (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.38 (m, 2H, HC(17)), 7.36−7.26 (m, 4H, HC(14), HC(16), HC(18)), 7.16 (dd, *J* = 8.4, 7.4, 1H, HC(7)), 7.06 (d, *J* = 7.2 Hz, 1H, HC(5)), 6.96−6.88 (m, 2H, HC(8), HC(6)), 6.45−6.39 (m, 1H, HC(12), 6.35 (ddd, *J* = 3.2, 1.8, 1.0 Hz, 1H, HC(13), 5.09 (dd, *J* = 8.1, 1.1 Hz, 1H, HC(2)), 3.98 (ddd, *J* = 9.2, 8.1, 5.4, 1H, HC(3)), 3.21 (dd, *J* = 16.6, 5.4 Hz, 1H, HC(4)), 3.03−2.89 (dd, *J* = 16.6, 9.2 Hz, 1H HC(4)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7 (C9), 151.5 (C11), 142.9 (C14), 133.6 (C117), 132.9 (C15), 129.5 (C5), 129.1 (C16), 128.0 (C7), 127.9 (C18), 121.2 (C6), 120.5 (C10), 116.9 (C8), 110.6 (C13), 109.9 (C12), 74.6 (C2), 44.3 (C3), 31.7 (C4); IR (ATR, cm^{-1}) 3058 (w), 1733 (w), 1583 (m), 1504 (w), 1487 (m), 1476 (m), 1453 (m), 1439 (w), 1349 (w), 1331 (w), 1301 (w), 1279 (w), 1234 (s), 1217 (m), 1190 (w), 1170 (w), 1150 (m), 1111 (w), 1079 (w), 1033 (m), 1013 (m), 978 (s), 931 (m), 902 (m), 885 (m), 876 (m), 846 (w), 820 (m), 778 (w), 747 (s), 728 (s), 703 (m); MS (EI, 70 eV, *m/z*) 308 (31, M$^+$), 199 (29), 190 (46), 81

(100); TLC R_f 0.42 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23}$ = −55.5 (*c* = 0.96 in $CHCl_3$); CD, (−), Cotton sign, 230−280 nm; CSP-HPLC, (2*R*,3*S*)-**4j** t_{min} 8.7 min (7.5%), (2*S*,3*R*)-**4j** t_{maj} 9.7 min (92.5%) (Chiralpak AD, 220 nm, 95:5, hexanes/*i*-PrOH, 0.8 mL/min). Anal. Calcd for $C_{19}H_{16}O_2S$ (308.40): C, 74.00; H, 5.23. Found: C, 73.83; H, 5.16.
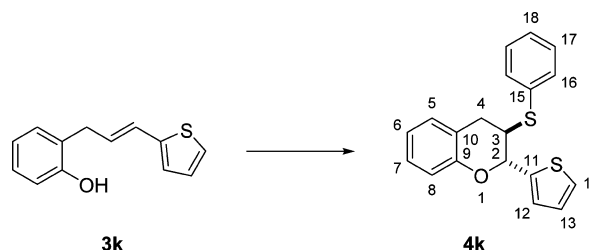
Preparation of (2R,3R)-3-(Phenylthio)-2-(thiophene-2-yl)-chromane (4k). Following general procedure 2, **3k** (216 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (*S*)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL) and then was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel, diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (60:1 hexanes/ethyl acetate then 40:1 hexanes/ethyl acetate, 30 mm diameter, 15 cm of SiO_2) afforded 278 mg (86%) of **4k** as a white, analytically pure solid. Data for **4k**: mp 98−99 °C (hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 2H, HC(17)), 7.30 (m, 4H, HC(16), HC(18), HC(7)), 7.19 (t, *J* = 8.3 Hz, 1H, HC(6)), 7.13 (d, *J* = 3.5 Hz, 1H, HC(12)), 7.06 (d, *J* = 7.5 Hz, 1H, HC(5)), 6.99 (t, *J* = 4.0 Hz, 1H, HC(13)), 6.94 (m, 2H, HC(14), HC(8)), 5.36 (d, *J* = 7.6 Hz, 1H, HC(2)), 3.80 (td, *J* = 8.1, 5.4 Hz, 1H, HC(3)), 3.21 (dd, *J* = 16.7, 5.3 Hz, 1H, HC(4)), 2.99 (dd, *J* = 16.7, 8.7 Hz, 1H, HC(4)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6 (C9), 142.6 (C15), 133.4 (C17), 133.3 (C11), 129.5 (C13), 129.2 (C16), 128.1 (C12), 127.9 (C18), 126.8 (C6), 126.5 (C5), 126.0 (C7), 121.3 (C14), 120.4 (C10), 117.0 (C8), 77.0 (C2), 47.7 (C3), 31.6 (C4); IR (ATR, cm^{-1}) 2923 (w), 1582 (w), 1485 (m), 1456 (w), 1437 (w), 1345 (w), 1305 (w), 1275 (w), 1233 (w), 1219 (s), 1191 (m), 1149 (w), 1120 (w), 1104 (w), 1078 (m), 1042 (w), 1026 (w), 991 (m), 965 (m), 900 (w), 846 (m), 839 (m), 757 (s), 747 (s), 710 (s); MS (EI, 70 eV, *m/z*) 324 (15, M$^+$), 215 (30), 205 (26), 97 (100); TLC: R_f 0.42 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23}$ = −49.8 (*c* = 0.95 in $CHCl_3$); CD, (−), Cotton sign, 230−280 nm; CSP-HPLC, (2*R*,3*R*)-**4k** t_{maj} 26.6 min (93.9%), (2*S*,3*S*)-**4k** t_{min} 34.2 min (6.1%) (Reverse-Phase Chiralpak OJ-RH, 220 nm, 65:35, MeCN/H_2O, 0.5 mL/min). Anal. Calcd for $C_{19}H_{16}OS_2$ (324.46): C, 70.33; H, 4.97. Found: C, 69.93; H, 4.83.
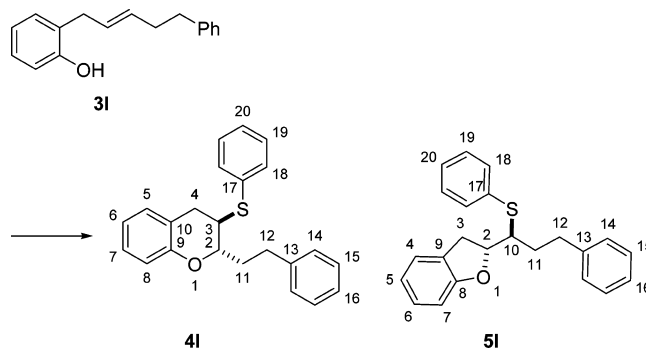
Preparation of (2S,3R)-2-Phenethyl-3-(phenylthio)chromane (4l) and (R)-2-((S)-3-Phenyl-1-(phenylthio)propyl)-2,3-dihydrobenzofuran (5l). Following general procedure 2, **3l** (238 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an i-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ¹H NMR), the reaction was quenched with triethylamine (300 μL) and then was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and then was diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated (30 °C, 3 mmHg). The crude **4l/5l** ratio (1.5:1) was established by ¹H NMR spectroscopy. The material was dissolved in 10 mL of CH_2Cl_2 and adsorbed onto Celite. Purification by silica gel flash column chromatography of this material (60:1 hexanes/ethyl acetate then 40:1 hexanes/ethyl acetate, 30 mm diameter, 14 cm of SiO_2) followed by bulb-to-bulb distillation afforded 258 mg (74%) of the mixture as a clear oil. Data for mixture: bp 120 °C (ABT, 0.05 mmHg); ¹H NMR (500 MHz, $CDCl_3$) δ 7.51−7.40 (m, 5H, HC(aryl)), 7.32 (m, 13H, HC(aryl)), 7.25 (m, 7H, HC(aryl)), 7.21−7.09 (m, 4H, HC(aryl)), 7.02 (d, J = 7.6 Hz, 1H, HC(aryl)), 6.97−6.81 (m, 4H), 6.74 (d, J = 8.0 Hz, 1H); diagnostic for **5l** ¹H NMR (500 MHz, $CDCl_3$) δ 4.86 (dt, J = 9.1, 7.4 Hz, 1H, HC(2)), 3.35 (dd, J = 15.9, 9.2 Hz, 1H, HC(3)), 3.29 (ddd, J = 10.2, 7.0, 3.6 Hz, 1H, HC(10)), 3.22−3.15 (m, 2H, HC(3), HC(12)), 2.88 (m, HC(12)), 2.26 (dddd, J = 14.3, 9.6, 7.1, 3.6 Hz, 1H, HC(11)), 1.95 (dtd, J = 14.4, 9.6, 4.9 Hz, 1H, HC(11)); ¹³C NMR (126 MHz, CDCl3) δ 85.1 (C2), 53.9 (C10), 34.2 (C3), 33.1 (C12), 32.7 (C11); diagnostic for **4l** ¹H NMR (500 MHz, $CDCl_3$) δ 4.06 (td, J = 8.4, 2.9 Hz, 1H, HC(2)), 3.45 (ddd, J = 9.0, 7.9, 5.3 Hz, 1H, HC(3)), 3.15−3.08 (m, 1H, HC(4)), 3.00−2.91 (m, 1H, HC(4)), 2.91−2.82 (m, 2H, HC(12)), 2.36 (dddd, J = 14.0, 10.0, 7.3, 3.0 Hz, 1H, HC(11)), 2.10 (dtd, J = 14.0, 9.0, 5.0 Hz, 1H, HC(11)); ¹³C NMR (126 MHz, CDCl3) δ 77.4 (C2), 45.0 (C3), 35.0 (C11), 31.7 (C4), 31.4 (C12); IR (ATR, cm⁻¹) 3025 (w), 2923 (w), 1599 (w), 1584 (m), 1488 (m), 1479 (m), 1455 (m), 1437 (m), 1303 (w), 1231 (s), 1174 (w), 1111 (w), 1088 (w), 1066 (w), 1024 (w), 964 (w), 942 (w), 872 (w), 796 (w), 744 (s); MS (EI, 70 eV, m/z) 346 (73, M⁺), 145 (30), 131 (41), 117 (65), 91 (100), 69 (29); TLC R_f 0.49 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; CSP-SFC, (2R,3S)-**4l**, t_{min} 16.2 (3.4%), (2S,3R)-**4l** t_{maj} 17.7 (96.6%), (2S,10R)-**5l** t_{min} 13.3 (3.7%), (2S,10R)-**5l** t_{maj} 14.7 (96.3%) (Chiralpak AD, 220 nm, 95:5 sCO₂/MeOH, 2 mL/min). Anal. Calcd for $C_{23}H_{22}OS$ (346.49): C, 79.73; H, 6.40. Found: C, 79.87; H, 6.51.
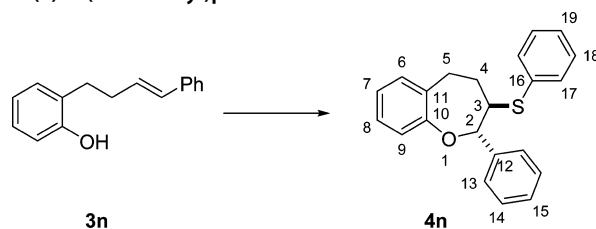

3m → **4m**
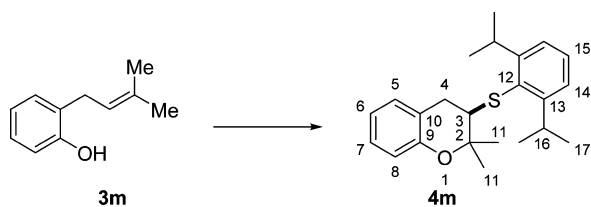
Preparation of (S)-3-((2,6-Diisopropylphenyl)thio)-2,2-dimethylchromane (4m). Following general procedure 2, **3m** (162 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1c** (339 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an i-PrOH bath and cooled to 0 °C (probe). MsOH (17 μL, 0.25 mmol, 0.25 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ¹H NMR), the reaction was quenched with triethylamine (300 μL) and then was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a

60 mL separatory funnel and diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated (30 °C, 3 mmHg). The material was then dissolved in 10 mL of CH_2Cl_2 and adsorbed onto Celite. Purification by silica gel flash column chromatography of this material (5:1 hexanes/CH_2Cl_2, 20 mm diameter, 16 cm of SiO_2) followed by recrystallization (EtOH, 5 mL), afforded, in two crops, 330 mg (93%) of **4m** as white needles. Data for **4m**: mp 74−75 °C (EtOH); ¹H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 7.8 Hz, 1H, HC(15)), 7.18 (d, J = 7.7 Hz, 2H, HC(14)), 7.08 (t, J = 8.1 Hz, 1H, HC(7)), 6.89 (d, J = 7.3 Hz, 1H, HC(5)), 6.83−6.75 (m, 2H, HC(6), HC(8)), 3.89 (p, J = 6.8 Hz, 2H, HC(16)), 3.16 (dd, J = 8.1, 6.9 Hz, 1H, HC(3)), 2.72 (d, J = 7.2 Hz, 2H, HC(4)), 1.55 (s, 3H, HC(11)), 1.49 (s, 3H, HC(11)), 1.24 (d, J = 6.8 Hz, 6H, HC(17)), 1.18 (d, J = 6.8 Hz, 6H, HC(17)); ¹³C NMR (101 MHz, $CDCl_3$) δ 154.2 (C12), 153.2 (C9), 129.7 (C15), 129.5 (C13), 129.4 (C7), 127.9 (C5), 124.1 (C14), 120.6 (C13), 120.4 (C6), 117.4 (C8), 77.5 (C2), 52.1 (C3), 31.8 (C16), 31.7 (C16), 29.8 (C4), 27.9 (C11), 25.0 (C17), 24.5 (C17), 22.2 (C11); IR (ATR, cm⁻¹) 3058 (w), 2962 (m), 2928 (m), 2867 (w), 1609 (w), 1583 (m), 1489 (s), 1455 (s), 1420 (w), 1382 (m), 1368 (m), 1360 (w), 1315 (w), 1301 (m), 1265 (s), 1252 (m), 1236 (s), 1178 (m), 1150 (s), 1127 (s), 1099 (s), 1052 (m), 1033 (m), 974 (w), 944 (s), 927 (m), 896 (w), 858 (s), 847 (w), 825 (w), 804 (m), 748 (s), 741 (s), 713 (m); MS (EI, 70 eV, m/z) 354 (69, M⁺), 235 (98), 194 (28), 161 (100), 149 (33), 145 (60), 119 (71), 91 (41); TLC R_f 0.60 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23}$ = −104.8 (c = 0.79 in $CHCl_3$); CD, (+), Cotton sign, 230−280 nm. Anal. Calcd for $C_{23}H_{30}OS$ (354.55): C, 77.92; H, 8.53. Found: C, 77.71; H, 8.31.


4m → **S5**
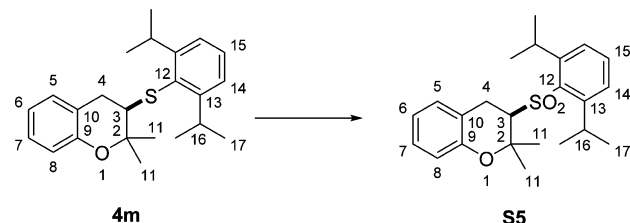
Preparation of (S)-3-((2,6-Diisopropylphenyl)thio)-2,2-dimethylchromane (S5). To determine enantiomeric composition, **4m** was oxidized to the sulfone. To a 4 dram vial was added solid **4m** (20 mg, 0.055 mmol, 1 equiv), followed by CH_2Cl_2 (1 mL) and m-CPBA (25 mg, 0.15 mmol, 2.5 equiv). The solution was stirred at rt for 3 h. The solution was diluted with hexanes (3 mL) and then directly purified by silica gel flash column chromatography (9:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO_2) to afford 21 mg of a white solid. The product was analyzed by chiral stationary phase HPLC. Data for **S5**: ¹H NMR (500 MHz, $CDCl_3$) δ 7.55 (t, J = 7.8 Hz, 1H, HC(15)), 7.41 (d, J =7.8 Hz, 2H, HC(14)), 7.14 (t, J = 7.7 Hz, 1H, HC(7)), 6.97 (d, J = 7.6 Hz, 1H, HC(6)), 6.91−6.79 (m, 2H, HC(5), HC(8)), 4.26 (q, J = 7.0 Hz, 2H, HC(16)), 3.54 (ddd, J = 13.0, 5.3, 2.0 Hz, 1H, HC(3)), 3.36 (dd, J = 16.2, 12.7 Hz, 1H, HC(4)), 2.73 (dd, J = 16.2, 5.2 Hz, 1H, HC(4)), 1.84 (s, 3H, HC(11)), 1.56 (s, 3H, HC(11)), 1.36 (d, J = 6.9, 6H, HC(17)), 1.29 (d, J = 6.7 Hz, 6H, HC(17)); ¹³C NMR (126 MHz, $CDCl_3$) δ 151.6, 133.5, 129.2, 128.3, 126.6, 121.0, 118.9, 117.6, 76.5, 66.6, 30.0, 29.3, 25.2, 21.8; CSP-HPLC, (R)-**S5** t_{min} 55.9 min (4.6%), (S)-**S5** t_{maj} 60.0 min (95.4%) (reversed-phase Chiralpak AD-RH, 220 nm, 45:55, MeCN/H_2O, 0.15 mL/min).

**Sulfenocyclizations of Substituted (E)-2-(3-Butenyl)phenols and (E)-2-(4-Pentenyl)phenols.**

3n → **4n**

Preparation of (2S,3R)-2-Phenyl-3-(phenylthio)-2,3,4,5-tetrahydrobenzo[b]oxepine (4n). Following general procedure 2, **3n** (224 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (*S*)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (33 µL, 0.5 mmol, 0.5 equiv) was added directly via syringe. The solution was allowed to stir for 18 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 µL) and then was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and then was diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). The residue was taken up in 10 mL of CH_2Cl_2 and then adsorbed onto Celite. Purification by silica gel flash column chromatography of this material (5:1 hexanes/CH_2Cl_2, 20 mm diameter, 16 cm of SiO_2) followed by bulb-to-bulb distillation afforded 304 mg (92%) of **4n** as a clear oil. Data for **4n**: bp 150 °C (ABT, 0.05 mmHg; ^{1}H NMR (500 MHz, CDCl₃) δ 7.49 (m, 2H, HC(aryl)), 7.43–7.34 (m, 3H, HC(aryl)), 7.25–7.12 (m, 7H), 7.05 (t, *J* = 7.4, 1H, HC(7)), 6.97 (d, *J* = 7.9, 1H, HC(9)), 4.61 (dd, *J* = 10.6, 1H, HC(2)), 3.85 (ddd, *J* = 10.6, 8.6, 4.2, 1H, HC(3)), 3.05 (dt, *J* = 6.9, 2.8 Hz, 2H, HC(5)), 2.63 (ddd, *J* = 12.1, 10.4, 4.2 Hz, 1H, HC(4)), 1.91 (dt, *J* = 14.5, 8.7 Hz, 1H, HC(4)); ^{13}C NMR (126 MHz, CDCl₃) δ 159.25 (C10), 140.66 (C16), 134.32 (C12), 134.25 (C11), 132.92 (C18), 130.22 (C15), 128.96 (C14), 128.49 (C13), 128.44 (C8), 127.68 (C17), 127.64 (C6), 127.36 (C19), 123.99 (C7), 121.62 (C9), 88.36 (C2), 55.46 (C3), 33.38 (C4), 30.88 (C5); IR (ATR, cm⁻¹) 3060 (w), 3031 (w), 2930 (w), 1603 (w), 1581 (w), 1487 (s), 1453 (m), 1438 (m), 1350 (w), 1303 (w), 1260 (w), 1232 (s), 1187 (m), 1155 (w), 1106 (w), 1090 (w), 1042 (m), 1024 (w), 978 (m), 939 (w), 914 (m), 887 (w), 754 (s), 738 (s); MS (EI, 70 eV, *m/z*) 340 (25, M⁺), 199 (56), 133 (100), 115 (26), 107 (24); TLC R_f 0.50 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23}$ = +39.6 (0.96 in CHCl₃); CD, (−), Cotton sign, 230–280 nm; CSP-SFC, (2*R*,3*S*)-**4n** t_{min} 7.6 (5.6%), (2*S*,3*R*)-**4n** t_{maj} 8.1 min (94.4%) (Chiralpak AD, 220 nm, 97:3, hexanes/*i*-PrOH, 0.8 mL/min). Anal. Calcd for $C_{22}H_{20}OS$ (332.46): C, 79.48; H, 6.06%; Found: C, 79.53; H, 6.09.

3o   **5o**
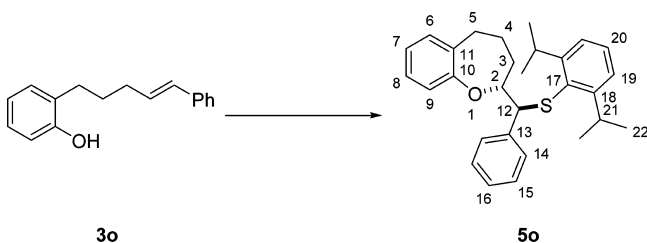
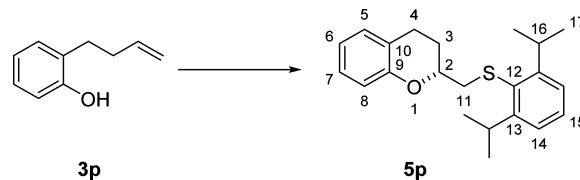*Preparation of (R)-2-((S)-((2,6-Diisopropylphenyl)thio)(phenyl)-methyl)-2,3,4,5-tetrahydrobenzo[b]oxepine (5o).* Following general procedure 2, **3o** (238 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1c** (339 mg, 1.0 mmol, 1.0 equiv), and catalyst (*S*)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to 0 °C (probe). After equilibration (ca. 20 min), MsOH (33 µL, 0.5 mmol, 0.5 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 µL) and then was allowed to warm to rt, whereupon the white solid dissolved. The material was transferred to a 250 mL RB flask using CH_2Cl_2 (20 mL) and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (5:1 hexanes/CH_2Cl_2, 20 mm diameter, 17 cm of SiO_2) followed by recrystallization (MeOH, 3 mL) afforded, in two crops, 327 mg (76%) of **5o** as white needles. Data for **5o**: mp 52–55 °C (methanol); ^{1}H NMR (500 MHz, CDCl₃) δ 7.31–7.29 (m, 1H, HC(20)), 7.28–7.24

(m, 5H, H-aryl), 7.14 (ddd, *J* = 7.0, 4.2 Hz, 2H, H-aryl, HC(6), HC(8)), 7.11 (d, *J* = 7.7 Hz, 2H, HC(19)), 7.01 (t, *J* = 7.4 Hz, 1H, HC(7)), 6.86 (d, *J* = 8.2 Hz, 1H, HC(9)), 4.15 (ddd, *J* = 11.0, 6.2, 1.5 Hz, 1H, HC(2)), 3.81–3.67 (m, 3H, HC(12), HC(21)), 2.89 (dd, *J* = 14.4, 12.1, 1H, HC(5)), 2.78–2.67 (m, 1H, HC(5)), 2.31–2.19 (m, 1H, HC(3)), 2.12–1.98 (m, 1H, HC(4)), 1.76 (dddd, *J* = 14.2, 12.0, 10.9, 3.6 Hz, 1H, HC(3)), 1.66–1.47 (m, 1H, HC(4)), 1.16 (d, *J* = 6.9 Hz, 6H, HC(22)), 0.97 (d, *J* = 6.8 Hz, 6H, HC(22)); ^{13}C NMR (126 MHz, CDCl₃) δ 159.62 (C17), 153.91 (C10), 140.17 (C18), 136.01 (C18), 131.07 (C13), 130.25 (C8), 129.37 (C20), 129.27 (C15), 128.06 (C14), 127.53 (C6), 127.26 (C16), 123.84 (C7), 123.77 (C19), 121.83 (C9), 85.71 (C2), 62.24 (C12), 36.19 (C3), 33.96 (C5), 31.70 (C21), 26.28 (C4), 24.77 (C22), 24.16 (C22); IR (ATR, cm⁻¹) 3057 (w), 3026 (w), 2960 (m), 2924 (m), 2865 (w), 1602 (w), 1580 (w), 1487 (s), 1453 (m), 1382 (w), 1360 (m), 1305 (w), 1231 (s), 1209 (w), 1178 (w), 1107 (w), 1075 (w), 1052 (m), 953 (m), 924 (w), 861 (w), 801 (m), 755 (s), 743 (s), 733 (s), 720 (m); MS (EI, 70 eV, *m/z*) 430 (39, M⁺), 283 (72), 237 (61), 147 (41), 107 (62), 91 (100); TLC R_f 0.8 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23}$ = −144.2 (*c* = 0.74 in CHCl₃); CD, (−), Cotton sign, 230–280 nm. Anal. Calcd for $C_{29}H_{34}OS$ (430.65): C, 80.88; H, 7.96. Found: C, 80.79; H, 7.91.
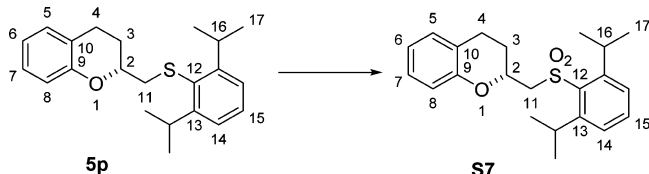

5o → **S6**
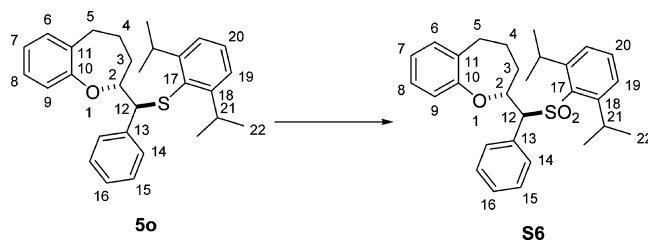
Preparation of (R)-2-((S)-((2,6-Diisopropylphenyl)sulfonyl)-(phenyl)methyl)-2,3,4,5-tetrahydrobenzo[b]oxepine (S6). To determine enantiomeric composition, **5o** was oxidized to the sulfone **S6**. To a 4 dram vial was added solid **5o** (20 mg, 0.05 mmol 1 equiv) followed by CH_2Cl_2 (1 mL) and *m*-CPBA (22 mg, 0.13 mmol, 2.7 equiv) The solution was stirred at rt for 3 h. The solution was diluted with hexanes (3 mL) and then directly purified by silica gel flash column chromatography (9:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO_2) to afford 21 mg of a white solid which was analyzed by chiral stationary phase HPLC. Data for **S6**: ^{1}H NMR: (400 MHz, CDCl₃) δ 7.40 (t, *J* = 7.9 Hz, 2H, HC(aryl)), 7.34–7.04 (m, 10H, HC(aryl)), 7.04–6.90 (m, 1H, HC(aryl)), 4.86 (ddd, *J* = 11.0, 4.3, 1.5 Hz, 1H, HC(2)), 4.19 (d, *J* = 4.3 Hz, 1H, HC(12)), 2.91–2.78 (m, 1H, HC(5)), 2.68 (dd, *J* = 14.3, 5.9 Hz, 1H, HC(5)), 1.99 (tdd, *J* = 10.6, 7.9, 4.3 Hz, 2H, HC(4)), 1.82–1.46 (m, 2H, HC(3)), 1.43–1.00 (m, 12H, HC(22)); ^{13}C NMR: (126 MHz, CDCl₃) δ 159.3, 135.8, 134.1, 133.0, 132.3, 130.7, 130.3, 130.1, 129.2, 128.5, 127.9, 126.0, 124.2, 122.5, 80.5, 79.7, 76.6, 36.6, 33.8, 30.0, 26.3; CSP-HPLC, (2*S*,12*R*)-**S6** t_{min} 6.7 min (7.4%), (2*R*,12*S*)-**S6** t_{maj} 7.2 min (92.6%) (BG, 220 nm, 95:5, hexanes/*i*-PrOH, 0.8 mL/min).
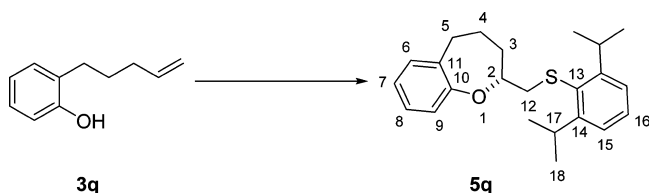

3p   **5p**

Preparation of (R)-2-(((2,6-Diisopropylphenyl)thio)methyl)-chromane (5p). Following general procedure 2, **3p** (148 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1c** (339 mg, 1.0 mmol, 1.0 equiv), and catalyst (*S*)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to 0 °C (probe). After equilibration (ca. 20 min), MsOH (33 µL, 0.5 mmol, 0.5 equiv) was added directly via syringe. The solution was allowed to stir for 12 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 µL) and then was

allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and diluted with CH$_2$Cl$_2$ (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (15 mL). The organic phases were combined, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). The residue was dissolved in 10 mL of CH$_2$Cl$_2$ and adsorbed onto Celite. Purification by silica gel flash column chromatography (5:1 hexanes/CH$_2$Cl$_2$, 20 mm diameter, 16 cm of SiO$_2$) followed by bulb-to-bulb distillation afforded 308 mg (91%) of **5p** as a clear oil. Data for **5p**: bp 160 °C (ABT, 0.05 mmHg); ^{1}H NMR: (500 MHz, CDCl$_3$) δ 7.37 (t, J = 7.7 Hz, 1H, HC(15)), 7.23 (d, J = 7.7 Hz, 2H, HC(14)), 7.17−7.11 (t, J = 7.6 Hz, 1H, HC(7)), 7.09 (d, J = 7.7, 1H, HC(5)), 6.89 (t, J = 7.4, 1H, HC(6)), 6.85 (d, J = 8.3, 1H, HC(8)), 4.16−3.99 (m, 3H, HC(2), HC(16)), 3.06 (dd, J = 12.9, 6.2 Hz, 1H, HC(11)), 2.92 (dd, J = 12.9, 6.6 Hz, 1H, HC(11)), 2.90−2.80 (m, 2H, HC(4)), 2.24 (dddd, J = 13.4, 6.0, 3.7 Hz, 1H, HC(3)), 1.88 (dddd, J = 13.4, 10.7, 9.7, 5.7 Hz, 1H, HC(3)), 1.30 (dd, J = 6.9, 3.9 Hz, 12H, HC(17)); ^{13}C NMR (101 MHz, CDCl$_3$) δ 154.8 (C12), 153.6 (C9), 131.6 (C4), 129.7 (C7), 129.5 (C14), 127.5 (C5), 124.0 (C10), 122.0 (C13), 120.5 (C6), 117.1 (C8), 74.8 (C2), 42.6 (C11), 31.8 (C3), 27.1 (C4), 24.8 (C17), 24.7 (C17); IR (ATR, cm^{-1}) 3054 (w), 2960 (m), 2924 (m), 2866 (w), 1610 (w), 1582 (m), 1487 (s), 1456 (s), 1420 (w), 1382 (w), 1361 (w), 1339 (w), 1301 (m), 1274 (w), 1232 (s), 1113 (m), 1075 (w), 1050 (s), 1029 (w), 996 (m), 930 (w), 886 (w), 842 (w), 800 (m), 750(s), 710 (w); MS (EI, 70 eV, m/z) 340 (88, M$^+$), 194 (29), 161 (49), 147 (47), 133 (100); TLC R_f 0.61 (1:1, hexanes/CH$_2$Cl$_2$) [UV,CAM]; $[\alpha]_D^{23}$ = +69.7 (c = 1.01 in CHCl$_3$); CD (−), Cotton sign, 230−280 nm. Anal. Calcd for C$_{22}$H$_{28}$OS (340.53): C, 77.60; H, 8.29. Found: C, 77.54; H, 7.93%.
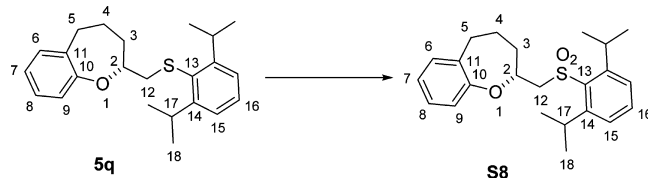

Preparation of (R)-2-(((2,6-Diisopropylphenyl)sulfonyl)methyl)-chromane (S7). To determine enantiomeric composition, **5p** was oxidized to the sulfone. To a 4 dram vial was added solid **5p** (20 mg, 0.06 mmol 1 equiv), followed by CH$_2$Cl$_2$ (1 mL) and *m*-CPBA (26 mg, 0.15 mmol, 2.5 equiv) The solution was stirred at rt for 3 h. The material was then diluted with hexanes (3 mL) and directly purified by silica gel flash column chromatography (9:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO$_2$) to afford 22 mg of a white solid. The product was analyzed by chiral stationary phase HPLC. Data for **S7**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.53 (t, J = 7.8 Hz, 1H, HC(15)), 7.37 (d, J = 7.8 Hz, 2H, HC(14)), 7.01 (d, J = 7.5, 1H, HC(5)), 6.95 (t, J = 7.8 Hz, 1H, HC(7)), 6.81 (t, J = 7.4, 1H, HC(7)), 6.20 (d, J = 8.2, 1H, HC(8)), 4.77 (dddd, J = 8.8, 7.3, 4.4, 2.7 Hz, 1H, HC(2)), 4.21 (p, J = 6.7 Hz, 2H, HC(16)), 3.74 (dd, J = 14.3, 7.4 Hz, 1H, HC(11)), 3.37 (dd, J = 14.4, 4.4 Hz, 1H, HC(11)), 2.88 (ddd, J = 16.0, 9.5, 6.1 Hz, 1H, HC(4)), 2.77 (dt, J = 16.7, 5.4 Hz, 1H, HC(4)), 2.25 (dddd, J = 13.8, 6.2, 5.1, 2.7 Hz, 1H, HC(3)), 1.90 (dddd, J = 13.5, 9.5, 8.8, 5.7 Hz, 1H, HC(3)), 1.28 (d, J = 6.7 Hz, 6H, HC(17)), 1.23 (d, J = 6.8 Hz, 6H, HC(17)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.3, 151.3, 136.2, 133.1, 129.6, 127.6, 126.2, 121.2, 121.0, 117.0, 70.3, 62.4, 29.9, 27.4, 25.2, 25.0, 23.7; CSP-HPLC, (R)-**S7** t_{maj} 8.4 (97.2%), (S)-**S7** t_{maj} 9.0 min (2.8%) (Chiralpak AD, 220 nm, 95:5, hexanes/*i*-PrOH, 0.8 mL/min).


Preparation of (R)-2-(((2,6-Diisopropylphenyl)thio)methyl)-2,3,4,5-tetrahydrobenzo[b]oxepine (5q). Following general proce-

dure 2, **3q** (162 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH$_2$Cl$_2$ (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst **2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to 0 °C (probe). After equilibration (ca. 20 min), MsOH (33 μL, 0.5 mmol, 0.5 equiv) was added directly via syringe. The solution was allowed to stir for 48 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL) and then was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and diluted with CH$_2$Cl$_2$ (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH$_2$Cl$_2$. The organic phases were combined, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (5:1 hexanes/CH$_2$Cl$_2$, 20 mm diameter, 20 cm of SiO$_2$) followed by bulb-to-bulb distillation afforded 296 mg (84%) of **5q** as a clear, viscous oil. Data for **5q**: bp 180 °C (ABT, 0.05 mmHg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 (t, J = 7.7 Hz, 1H, HC(16)),7.21−7.17 (m, 3H, HC(8), HC(15)), 7.17−7.12 (m, 2H, HC(6), HC(9)), 7.03 (ddt, J = 8.9, 7.2 Hz, 1H, HC(7)), 4.02 (p, J = 6.8 Hz, 2H, HC(17)), 3.79 (ddd, J = 10.2, 8.0, 4.0 Hz, 1H, HC(2)), 3.15 (dd, J = 12.0 Hz, 8.0 Hz, 1H, HC(12)), 2.93 (dd, J = 14.4, 12.0 Hz, 1H, HC(5)), 2.74 (ddd, J = 14.9, 12.6, 5.3 Hz, 2H, HC(12), HC(5)), 2.12−1.97 (m, 2H, HC(4), HC(3)), 1.91−1.79 (m, 1H, HC(3)), 1.60−1.48 (m, 1H, HC(4)) 1.28 (d, J = 6.8 Hz, 6H, HC(18)), 1.23 (d, J = 6.8 Hz, 6H, HC(18)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.1 (C13), 153.5 (C10), 135.8 (C14), 132.3 (C14), 130.3 (C6), 129.3 (C16), 127.6 (C8), 123.9 (C15), 123.8 (C7), 121.9 (C9), 110.0 (C11), 82.6 (C2), 44.7 (C12), 37.0 (C3), 33.9 (C5), 31.8 (C17), 25.9 (C4), 24.7 (C18), 24.6 (C18); IR (ATR, cm^{-1}) 3055 (w), 2960 (m), 2924 (m), 2865 (w), 1602 (w), 1579 (w), 1487 (s), 1454 (m), 1382 (w), 1360 (m), 1306 (w), 1231(s), 1194 (w), 1178 (w), 1105 (w), 1065 (m), 1052 (m), 1035 (m), 1019 (m), 955 (s), 926 (m), 864 (w), 830 (w), 799 (s), 762 (s), 736 (s), 718 (w); MS (EI, 70 eV, m/z) 354 (82, M$^+$), 194 (100), 160 (81), 153 (51), 151 (51), 107 (98); TLC R_f 0.56 (1:1 hexanes:CH$_2$Cl$_2$) [UV,CAM]; $[\alpha]_D^{23}$ = +36.9 (c = 1.1 in CHCl$_3$); CD, (+), Cotton sign, 230−280 nm. Anal. Calcd for C$_{23}$H$_{30}$OS (354.55): C, 77.92; H, 8.53. Found: C, 77.75; H, 8.25.


Preparation of (R)-2-(((2,6-Diisopropylphenyl)sulfonyl)methyl)-2,3,4,5-tetrahydrobenzo[b]oxepine (S8). To determine enantiomeric composition, **5q** was oxidized to the sulfone. To a 4 dram vial was added neat **5q** (20 mg, 0.06 mmol 1 equiv) followed by CH$_2$Cl$_2$ (1 mL) and *m*-CPBA (26 mg, 0.15 mmol, 2.5 equiv). The solution was stirred at rt for 3 h. The material was diluted with hexanes (3 mL) and then directly purified by silica gel flash column chromatography (9:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO$_2$) to afford 20 mg of a white solid which was analyzed by chiral stationary phase HPLC. Data for **S8**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.54 (t, J = 7.8 Hz, 1H, HC(16)), 7.39 (d, J = 7.7 Hz, 2H, HC(15)), 7.08 (d, J = 7.3 Hz, 1H, HC(6)), 7.02 (t, J = 7.6, 1H, HC(8)), 6.96 (t, J = 7.3, 1H, HC(7)), 6.51 (d, J = 7.8 Hz, 1H, HC(9)), 4.32 (dt, J = 9.0, 3.6, 1H, HC(2)), 4.22 (p, J = 6.7 Hz, 2H, HC(17)), 3.85 (dd, J = 14.4, 7.1 Hz, 1H, HC(12)), 3.32 (dd, J = 14.3, 3.5 Hz, 1H, HC(12)), 2.94−2.80 (m, 1H, HC(5)), 2.80−2.68 (m, 1H, HC(5)), 2.15−1.90 (m, 3H, HC(3), HC(4)), 1.72−1.46 (m, 1H, HC(3), HC(4)), 1.30 (d, J = 6.7 Hz, 6H, HC(18), 1.24 (d, J = 6.7 Hz, 6H, HC(18)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.4, 151.4, 136.0, 135.4, 133.2, 130.2, 127.6, 126.4, 126.4, 124.2, 121.9, 76.8, 64.6, 38.2, 33.6, 29.9, 25.9, 25.3, 24.9; CSP-HPLC, (S)-**S8** t_{min} 10.5 min (2.3%), (R)-**S8** t_{maj} 11.1 min (97.7%) (Chiralpak AD, 220 nm, 95:5, hexanes/*i*-PrOH, 0.8 mL/min).

Preparation of Ethyl (S)-1-((R)-Chroman-2-yl)-1-(phenylthio)-butanoate (5r). Following general procedure 2, **3r** (248 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (33 μL, 0.5 mmol, 0.5 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL) and then was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and then was diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). The material was dissolved in ethyl acetate (10 mL) and adsorbed onto Celite. Purification by silica gel flash column chromatography (20:1 hexanes/ethyl acetate, 20 mm diameter, 16 cm of SiO_2) followed by bulb-to-bulb distillation afforded 286 mg (80%) of **5r** as a clear, viscous oil. Data for **5r**: bp 180 °C (ABT, 0.05 mmHg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.52 (d, J = 7.3 Hz, 2H, HC(19)), 7.37−7.31 (m, 2H, HC(16)), 7.30−7.28 (m, 1H, HC(20)), 7.11 (dd, J = 8.2, 7.4, 1H, HC(7)), 7.07 (d, J = 7.5 Hz, 1H, HC(5)), 6.87 (t, J = 7.3 Hz, 1H, HC(6)), 6.81 (d, J = 8.2 Hz, 1H, HC(8)), 4.22−4.07 (m, 3H, HC(2), HC(15)), 3.38−3.28 (m, 1H, HC(11)), 2.91−2.73 (m, 3H, HC(13), HC(4)), 2.71−2.63 (m, 1H, HC(13)), 2.42−2.32 (m, 2H, HC(3), HC(12)), 2.06−1.90 (m, 2H, HC(12), HC(3)), 1.28 (t, J = 7.2 Hz, 3H, HC(16)); ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.7 (C14), 154.8 (C9), 135.4 (C17), 132.7 (C19), 129.7 (C5), 129.3 (C18), 127.5 (C7,C20), 122.2 (C10), 120.6 (C6), 117.1 (C8), 78.4 (C2), 60.7 (C15), 53.5 (C11), 32.0 (C13), 26.4 (C3), 25.1 (C4), 24.9 (C12), 14.5 (C16); IR (ATR, cm^{-1}) 2930 (w), 1729 (s), 1609 (w), 1582 (m), 1487 (s), 1457 (m), 1438 (m), 1373 (m), 1302 (m), 1273 (m), 1231 (s), 1183 (s), 1150 (m), 1103 (m), 1067 (m), 1024 (m), 995 (m), 935 (w), 883 (w), 852 (w), 832 (w), 749 (s); MS (EI, 70 eV, m/z) 356 (36, M$^+$), 311 (22), 247 (100), 201 (58), 177 (43), 159 (65), 149 (81), 133 (100), 107 (62); TLC R_f 0.22 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23}$ = +92.0 (c = 0.70 in CHCl$_3$); CD, (+), Cotton sign, 230−280 nm; CSP-HPLC, (2S,11R)-**5r** t_{min} 16.5 min (6.8%), (2R,11S)-**5r** t_{maj} 24.7 min (93.2%) (Chiralcel OJ, 220 nm, 95:5 hexanes/*i*-PrOH, 0.8 mL/min). Anal. Calcd for $C_{21}H_{24}O_3S$ (356.48): C, 70.76; H, 6.79. Found: C, 70.82; H, 6.67.
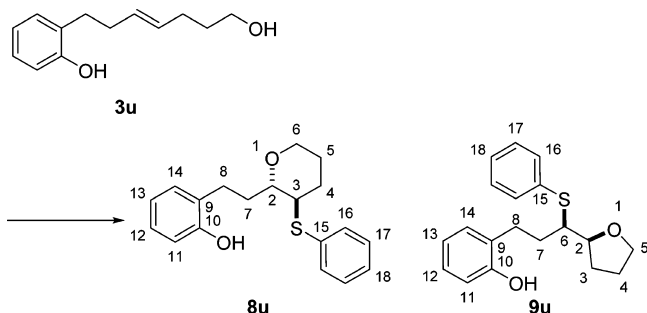
3s   **5s**
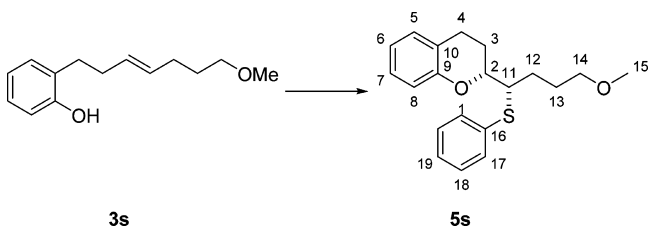
Preparation of (R)-2-((S)-4-Methoxy-1-(phenylthio)butyl)-chromane (5s). Following general procedure 2, **3s** (220 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst (S)-**2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (33 μL, 0.5 mmol, 0.5 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL) and then was allowed to warm to rt, whereupon the white solid dissolved. The material was transferred to a 250 mL RB flask using 20 mL of CH_2Cl_2 and concentrated by rotary evaporation (30 °C, 3 mmHg). The material was dissolved in 10 mL of CH_2Cl_2 and adsorbed onto Celite. Purification by silica gel flash column chromatography (5:1 hexanes/CH_2Cl_2, 20 mm diameter, 18 cm of SiO_2) followed by bulb-to-bulb

distillation afforded 287 mg (88%) of **5s** as a clear, viscous oil. Data for **5s**: bp 150 °C (ABT, 0.05 mmHg); ^{1}H NMR: (500 MHz, CDCl$_3$) δ 7.56−7.48 (m, 2H, HC(18)), 7.32 (t, J = 6.8, 2H, HC(17)), 7.29−7.25 (m, 1H, HC(19)), 7.11 (t J = 7.3 Hz, 1H, HC(7)), 7.06 (d, J = 7.3 Hz, 1H, HC(5)), 6.86 (t, J = 7.4 Hz, 1H, HC(6)), 6.79 (d, J = 8.1 Hz, 1H, HC(8)), 4.12 (ddd, J = 9.9, 6.5, 2.2 Hz, 1H, HC(2)), 3.52−3.41 (m, 2H, HC(14)), 3.37 (s, 3H, HC(15)), 3.33 (ddd, J = 8.9, 6.5, 3.3 Hz, 1H, HC(11)), 2.90−2.81 (m, 1H, HC(4)), 2.80−2.72 (m, 1H, HC(4)), 2.26 (dddd, J = 13.4, 5.8, 3.5, 2.3 Hz, 1H, HC(3)), 2.13−1.92 (m, 3H, HC(3), HC(12), HC(13)), 1.88−1.76 (m, 1H, HC(13)), 1.76−1.67 (m, 1H, HC(12)); ^{13}C NMR (101 MHz, CDCl$_3$) δ 154.9 (C9), 136.1 (C16), 132.4 (C18), 129.7 (C5), 129.2 (C17), 127.5 (C7), 127.2 (C19), 122.3 (C10), 120.4 (C6), 117.0 (C8), 78.5 (C2), 72.9 (C14), 58.9 (C15), 54.1 (C11), 28.0 (C3), 27.5 (C12), 25.0 (C4), 24.9 (C11); IR (ATR, cm^{-1}) 2924 (w), 2855 (w), 1736 (w), 1609 (w), 1582 (m), 1487 (s), 1456 (m), 1438 (m), 1374 (w) 1302 (m), 1273 (w), 1232 (s), 1194 (m), 1114 (s), 1051 (m), 1024 (m), 995 (m), 886 (m), 850 (w), 830 (w), 748 (s); MS (EI, 70 eV, m/z) 328 (58, M$^+$), 219 (69), 195 (52), 187 (36), 163 (84), 133 (97), 107 (100), 85 (50), 69 (66); TLC R_f 0.15 (1:1, hexanes/CH_2Cl_2) [UV,CAM]; $[\alpha]_D^{23}$ = +81.4 (c = 0.68 in CHCl$_3$); CD, (+), Cotton sign, 230−280 nm; CSP-HPLC, (2S,11R)-**5s** t_{min} 10.4 (3.3%), (2R,11S)-**5s** t_{maj} 13.4 min (96.7%) (Chiralcel OJ, 220 nm, 95:5, hexanes/*i*-PrOH, 0.8 mL/min). Anal. Calcd for $C_{20}H_{24}O_2S$ (328.47): C, 73.13; H, 7.37. Found: C, 73.41; H, 7.28.

3t   **8t**
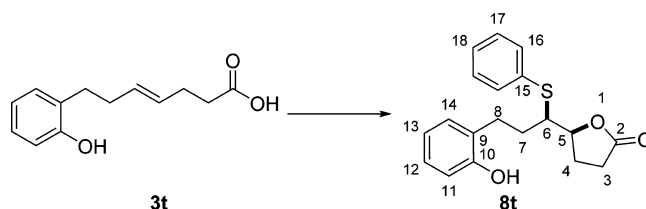
Preparation of (S)-5-((R)-3-(2-Hydroxyphenyl)-1-(phenylthio)-propyl)dihydrofuran-2(3H)-one (8t). Following general procedure 2, **3t** (220 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH_2Cl_2 (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv), and catalyst **2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (33 μL, 0.5 mmol, 0.5 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL) and then was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and then was diluted with CH_2Cl_2 (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (6:1 hexanes/ethyl acetate, then 3:1 hexanes/ethyl acetate then 2:1 hexanes/ethyl acetate, 30 mm diameter, 16 cm of SiO_2) followed by bulb-to-bulb distillation afforded 300 mg (92%) of **8t** as a clear, viscous oil. Data for **8t**: bp 120 °C (ABT, 2.4 × 10^{-5} mm Hg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.53−7.48 (m, 2H, HC(17)), 7.37−7.31 (m, 3H, HC(16), HC(18)), 7.17−7.11 (m, 2H, HC(12), HC(14)), 6.90 (t, J = 7.5 Hz, 1H, HC(13)), 6.82 (d, J = 8.2, 1H, HC(11)), 5.09 (s, 1H, OH)), 4.59 (q, J = 7.3 Hz, 1H, HC(5)), 3.26−3.15 (m, 1H, HC(6)), 3.08 (ddd, J = 13.9, 9.2, 4.9 Hz, 1H, HC(8)), 2.88 (ddd, J = 14.1, 9.1, 7.1 Hz, 1H, HC(8)), 2.68−2.49 (m, 2H, HC(3)), 2.41 (dddd, J = 13.1, 9.6, 7.1, 4.9 Hz, 1H, HC(4)), 2.28−2.18 (m, 1H, HC(7)), 2.14−2.01 (m, 1H, HC(4)), 1.87 (dtd, J = 14.2, 9.5, 4.9 Hz, 1H, HC(7)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 176.9 (C2), 153.9 (C10), 133.9 (C15), 133.0 (C17), 130.7 (C12), 129.4 (C16), 128.1 (C18), 127.9 (C14), 127.1 (C9), 121.2 (C13), 115.8 (C11), 82.6 (C5), 54.2 (C6), 31.8 (C8), 29.0 (C3), 27.4 (C4), 26.1 (C7); IR (ATR, cm^{-1}) 3360 (br), 2924 (w), 1749 (s), 1582 (w), 1504 (w), 1488 (w), 1455 (s), 1438 (w), 1345 (w), 1303 (w), 1230 (s), 1180 (s), 1100 (w), 1068 (w), 1023 (w), 913 (w), 846 (w), 748 (s); MS (EI, 70 eV, m/z) 328 (9), 249 (21),247

(83), 201 (38),177 (27),159 (44), 149 (60),133 (100), 107 (68); TLC R_f 0.05 (4:1, hexanes/ethyl acetate) [UV,CAM]; $[\alpha]_D^{23}$ = +35.4 (c = 0.68 in CHCl$_3$); CD, (−), Cotton sign, 230−280 nm; CSP-HPLC, (5R,6S)-**8t** t_{min} 20.2 min (7.8%), (5S,6R)-**8t** t_{maj} 23.5 min (92.2%), (Chiralpak AD-RH, 220 nm, 48:52, H$_2$O/MeCN, 0.3 mL/min). Anal. Calcd for C$_{19}$H$_{20}$O$_3$S (328.43): C, 69.49; H, 6.14. Found: C, 69.56; H, 6.08.

3u

8u   **9u**

*Preparation of ((R)-3-(Phenylthio)-3-((S)-tetrahydrofuran-2-yl)-propyl)phenol (8u) and 2-((R)-3-(Phenylthio)-3-((S)-tetrahydrofuran-2-yl)propyl)phenol (9u).* Following general procedure 2, **3u** (206 mg, 1.0 mmol) was weighed into a dried 10 mL Schlenk flask. Subsequently, CH$_2$Cl$_2$ (7 mL), electrophile **1a** (255 mg, 1.0 mmol, 1.0 equiv) and catalyst **2b** (52 mg, 0.1 mmol, 0.1 equiv) were added. The flask was placed in an *i*-PrOH bath and cooled to −20 °C (probe). After equilibration (ca. 20 min), MsOH (33 μL, 0.5 mmol, 0.5 equiv) was added directly via syringe. The solution was allowed to stir for 24 h at constant temperature during which time phthalimide precipitated. Upon consumption of the starting material (TLC, ^{1}H NMR), the reaction was quenched with triethylamine (300 μL) and then was allowed to warm to rt, whereupon the white solid dissolved. The solution was transferred to a 60 mL separatory funnel and then was diluted with CH$_2$Cl$_2$ (10 mL) and 1 M NaOH (15 mL). The phases were separated, and the aqueous layer was extracted with 15 mL of CH$_2$Cl$_2$. The organic phases were combined, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). The crude ratio of **8u/9u** (1.1:1) was established by ^{1}H NMR spectroscopy. Purification by silica gel flash column chromatography (12:1 hexanes/ethyl acetate, 30 mm diameter, 16 cm of SiO$_2$) followed by bulb-to-bulb distillation afforded 276 mg (88%) of the mixture as a clear oil. Data for **8u**: bp 180 °C (ABT, 0.05 mmHg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41−7.37 (m, 2H, HC(17)), 7.34−7.22 (m, 3H, HC(16), HC(18)), 7.16 (dd, J = 7.9, 7.3 Hz, 1H, HC(12)), 7.07 (dd, J = 7.5 Hz, 1H, HC(14)), 6.89 (d, J = 8.1 Hz, 1H, HC(11)), 6.85 (t, 7.8 Hz, 1H, HC(13)), 6.82 (br s, 1H, OH), 4.06 (ddd, J = 8.7, 7.7, 6.4 Hz, 1H, HC(2)), 4.01 (dt, J = 8.0, 6.9 Hz, 1H, HC(5)), 3.90 (td, J = 7.9, 6.2 Hz, 1H, HC(5)), 3.12 (dt, J = 8.9, 5.5 Hz, 1H, HC(6)), 2.93 (ddd, J = 13.9, 9.0, 6.8 Hz, 1H, HC(8)), 2.79 (ddd, J = 14.4, 9.1, 6.1 Hz, 1H, HC(8)), 2.21 (dddd, J = 12.6, 7.9, 6.4, 5.0 Hz, 1H, HC(3)), 2.16−1.89 (m, 4H, HC(4), HC(8)), 1.77 (ddt, J = 12.5, 8.4, 7.6 Hz, 1H, HC(7)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.8 (C10), 134.7 (C15), 132.0 (C17), 130.5 (C14), 129.2 (C16), 127.9 (C12), 127.3 (C18), 127.1 (C9), 120.4 (C13), 116.3 (C11), 82.7 (C2), 68.8 (C5), 52.3 (C6), 34.1 (C7), 31.4 (C3), 27.6 (C8), 25.9 (C4); IR (ATR, cm^{-1}) 3306 (br), 2927 (w), 2866 (w), 1737 (w), 1582 (m), 1488 (m), 1455 (s), 1438 (m), 1359 (m), 1232 (s), 1177 (m), 1088 (m), 1041 (s), 921 (m), 843 (w), 746 (s); MS (EI, 70 eV, m/z) 314 (47, M$^+$), 133 (67), 107 (100), 71 (62); TLC R_f 0.25 (4:1, hexanes/ethyl acetate) [UV,CAM]; $[\alpha]_D^{23}$ = −17.3 (c = 0.52 in CHCl$_3$); CD, (−), Cotton sign, 230−280 nm. Data for **9u**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 (m, 3H, HC(aryl)), 7.24 (m, 3H, HC(aryl)), 7.17−7.05 (m, 2H, HC(12), H(C14)), 6.86 (m, 2H, HC(11), HC(13)), 4.04 (dd, J = 11.4, 4.0, 1H, HC(2)), 3.41 (td, J = 11.7, 2.7 Hz, 1H, HC(5)), 3.16 (td, J = 9.9, 2.8 Hz, 1H, HC(5)), 2.91−2.67 (m, 2H, HC(3), HC(8)), 2.62 (ddd, J = 14.3, 6.1, 4.2 Hz, 1H, HC(8)), 2.45 (dddd, J = 13.9, 10.9, 6.1, 2.8 Hz, 1H, HC(3)), 2.17−2.01 (m, 1H, HC(4)), 2.01−1.57 (m, 3H, HC(3), HC(4), HC(7)), 1.53−1.34 (m, 1H, HC(7)); ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.0 (C10), 135.0 (C15), 133.7 (C17), 130.7 (C14), 129.2 (C16), 128.0 (C12), 124.4 (C9), 120.7 (C13),

116.4 (C11), 79.7 (C2), 68.3 (C5), 49.3 (9), 34.6 (C8), 31.7 (C4), 27.0 (C3), 25.2 (C7); CSP-HPLC (2R,6S)-**9u** t_{maj} 19.2 min (97.1%), (2S,6R)-**9u** t_{min} 20.83 min (2.9%) (Chiralpak AD, 220 nm, 90:10, hexanes/*i*-PrOH, 0.6 mL/min); (2R,3S)-**8u**, t_{maj} 14.6 min (96.9%), (2S,3R)-**8u**, t_{min} 18.1 min (3.1%) (Chiralpak AD 220 nm, 90:10 hexanes/*i*-PrOH, 0.6 mL/min). Anal. Calcd for C$_{19}$H$_{22}$O$_2$S (314.44): C, 72.58; H, 7.05. Found: C, 72.64; H, 6.95.


S9
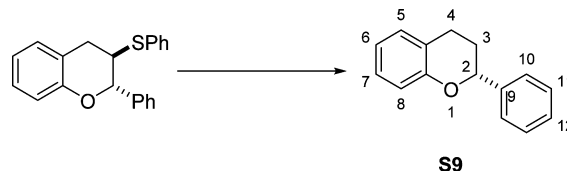
Manipulations of 4a. *Preparation of (R)-2-Phenylchromane (S9).* To a 50 mL Schlenk flask under argon was added *i*-PrOH (20 mL) followed by solid **4a** (238 mg, 0.75 mmol). The solid was dissolved by heating, and the flask was then cooled in an ice bath (internal temperature <5 °C). Solid NiCl$_2$·6H$_2$O (600 mg, 2.5 mmol, 3.3 equiv) was added to form a green solution. In a separate flask, NaBH$_4$ (300 mg, 7.9 mmol, 10.5 equiv) was dissolved in EtOH (20 mL) with stirring. This flask was then also cooled in an ice bath (internal temperature 3 °C). The cold borohydride solution in ethanol was cannula transferred into the flask containing the substrate and the nickel chloride. The solution turned black, and gas evolution was observed. The flask was maintained in the ice bath for a further 4 h. The resulting black suspension was filtered through Celite while cold, and the filter cake was washed with CH$_2$Cl$_2$ (2 × 25 mL). The filtrate was then concentrated by rotary evaporation (30 °C, 3 mmHg). Purification of the residue by silica gel flash column chromatography (9:1, hexanes/CH$_2$Cl$_2$, 20 mm diameter, 15 cm of SiO$_2$) afforded 111 mg (71%) of **S9** as a white solid. The spectroscopic data match those reported in the literature.[56] Absolute configuration was established by correlation with the known optical rotation.[47] Data for **S9**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.47 (d, J = 7.5 Hz, 2H, HC((11)), 7.43 (t, J = 7.4 Hz, 2H, HC(10)), 7.36 (t, J = 7.2 Hz, 1H, HC(12)), 7.17 (t, J = 7.7 Hz, 1H, HC(7)), 7.13 (d, J = 7.1 Hz, 1H, HC(5)), 6.95 (d, J = 7.5 Hz, 1H, HC(8)), 6.92 (t, J = 7.4 Hz, 1H, HC(6)), 5.11 (dd, J = 10.2, 2.5 Hz, 1H, HC(2)), 3.05 (ddd, J = 17.0, 11.4, 5.9 Hz, 1H, HC(4)), 2.85 (ddd, J = 16.5, 5.3, 3.3 Hz, 1H, HC(4)), 2.26 (dddd, J = 13.7, 5.9, 3.3, 2.4 Hz, 1H, HC(3)), 2.14 (dddd, J = 13.7, 11.2, 10.2, 5.3 Hz, 1H, HC(3)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.1, 141.7, 129.5, 128.5, 128.4, 127.8, 127.3, 125.9, 121.8, 120.3, 116.9, 77.7, 29.9, 25.0; MS (EI, 70 eV, m/z) 210 (100, M$^+$), 129 (32), 171 (14), 119 (14), 104 (27), 77 (12); $[\alpha]_D^{23}$ = +16.6 (c = 1.05 in CHCl$_3$).


4a   **6a, 6b**
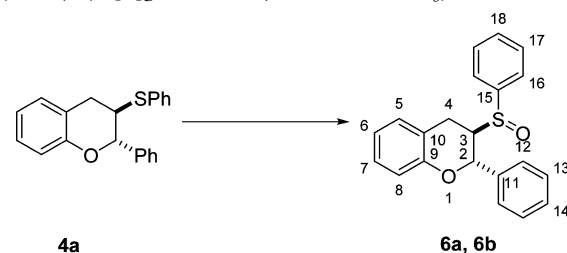
Preparation of (2S,3R)-2-Phenyl-3-((R,S)-phenylsulfinyl)-chromane (6a and 6b). To a 250 mL RB flask under argon were added MeOH (100 mL) and **4a** (2.23 g, 7.0 mmol). Sodium periodate (1.65 mg, 7.7 mmol, 1.1 equiv) was added as a solid, resulting in a heterogeneous solution. The mixture was then heated to 50 °C for 16 h. TLC analysis showed trace amounts of remaining starting material; however, formation of the corresponding sulfone was also observed and the flask then removed from heat. After the solution cooled to rt, water (100 mL) and CH$_2$Cl$_2$ (100 mL) were added to afford a clear, biphasic mixture. The mixture was transferred to a 500 mL separatory funnel and shaken thoroughly, and the layers were separated. The aqueous layer was extracted with further CH$_2$Cl$_2$ (2 × 50 mL). The organic layers were combined, washed with water (25 mL) and brine (25 mL), dried over MgSO$_4$, filtered, and concentrated by rotary evaporation (30 °C, 3 mmHg). Analysis of the crude material by ^{1}H

NMR spectroscopy revealed a 2:1 diastereomeric mixture. Purification by silica gel flash column chromatography (9:1 hexanes/ethyl acetate, then 4:1 hexanes/ethyl acetate, 30 mm diameter, 16 cm of SiO$_2$) separated the diastereomers. Recombination of the diastereomers **6a** and **6b** followed by recrystallization (EtOH, 2 mL) afforded, in two crops, 284 mg (85% combined yield) of the mixture as white to pale yellow prisms. Data for **6a**: mp 138−140 °C (ethanol); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59−7.39 (m, 10H, HC(aryl)), 7.12 (t, J = 8.4 Hz, 1H, HC(7)), 7.03 (d, J = 8.4 Hz, 1H, HC(5)), 6.95−6.84 (m, 2H, HC(6), HC(8)), 5.12 (d, J = 9.1 Hz, 1H, HC(2)), 3.50 (dd, J = 16.9, 10.2 Hz, 1H, HC(4)), 3.12 (ddd, J = 10.3, 9.1, 5.4 Hz, 1H, HC(3)), 2.31 (dd, J = 16.8, 5.4 Hz, 1H, HC(4)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.2 (C9), 141.4 (C15), 138.2 (C11), 131.3 (C18), 130.2 (C7), 129.5 (C17), 129.4 (C14), 129.3 (C13), 127.9 (C5), 127.6 (C16), 124.6 (C12), 121.5 (C6), 120.2 (C10), 117.0 (C8), 77.7 (C2), 63.5 (C3), 20.4 (C4); IR (ATR, cm^{-1}) 3050 (w), 1609 (w), 1583 (w), 1487 (m), 1455 (m), 1443 (m), 1369 (w), 1298 (w), 1232 (s), 1194 (w), 1177 (w), 1110(w), 1085 (m), 1034 (s), 999 (m), 931 (m), 910 (m), 873 (w), 840 (w), 830 (w), 788 (m), 747 (s), 698 (s), 686 (s); MS (ESI, m/z) 335 (M + H$^+$, 100), 209 (66); TLC R_f 0.2 (4:1 hexanes/ethyl acetate) [UV,CAM]. Anal. Calcd for C$_{21}$H$_{18}$O$_2$S (334.43): C, 75.42; H, 5.43. Found: C, 75.06; H, 5.23. Data for **6b**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.72−7.65 (m, 2H, HC(aryl)), 7.61−7.53 (m, 3H, HC(aryl)), 7.37−7.33 (m, 4H, HC(aryl)), 7.27 (m, 2H, HC(aryl)), 7.10 (d, J = 8.4 Hz, 1H, HC(5)), 6.97−6.92 (m, 2H, HC(6), HC(8)), 6.09 (dd, J = 3.1, 1.5 Hz, 1H, HC(2)), 3.42 (dt, J = 5.2, 3.2 Hz, 1H, HC(3)), 2.82 (dd, J = 17.7, 5.2 Hz, 1H, HC(4)), 2.38 (ddd, J = 17.7, 2.9, 1.2 Hz, 2H, HC(4)).
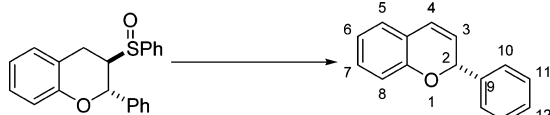
6a,6b   **S10**

Preparation of (S)-2-Phenyl-2H-chromene (S10). To a 10 mL Schlenk flask under argon was added a 1:1 diastereomeric mixture of sulfoxides **6a/6b** (334 mg, 1.0 mmol) and toluene (10 mL). Trimethyl phosphite (236 μL, 2.0 mmol, 2 equiv) was added via syringe. The solution was then refluxed for 4 h. After the reaction was complete (TLC), the flask was removed from the oil bath and allowed to cool to rt. The solution was concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (9:1 hexanes/CH$_2$Cl$_2$ then 5:1 hexanes/CH$_2$Cl$_2$, 20 mm diameter, 16 cm of SiO$_2$) afforded 193 mg (92%) of **S10** as a clear oil. The spectroscopic data match those reported in the literature.[47] The rotation is in agreement with the absolute configuration shown.[47] Data for **S10**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.53−7.46 (m, 2H, HC(aryl)), 7.47−7.33 (m, 3H, HC(aryl)), 7.16 (t, J = 7.8 Hz, 1H, HC(7)), 7.06 (d, J = 7.5 Hz, 1H, HC(5)), 6.91 (t, J = 7.4 Hz, 1H, HC(6)), 6.84 (d, J = 8.0 Hz, 1H, HC(8)), 6.58 (d, J = 9.8 Hz, 1H, HC(4)), 5.97 (d, J = 2.1 Hz, 1H, HC(2)), 5.85 (dd, J = 9.9, 3.3 Hz, 1H, HC(3)); ^{13}C NMR δ 153.2, 140.9, 129.5, 128.6, 128.3, 127.0, 126.6, 124.8, 124.0, 121.3, 121.2, 116.0, 77.2; MS (EI, 70 eV, m/z) 208 (90, M$^+$), 207 (100), 178 (15), 131 (41); $[α]_D^{23}$ = +97.6 (c = 1.1 in CHCl$_3$).
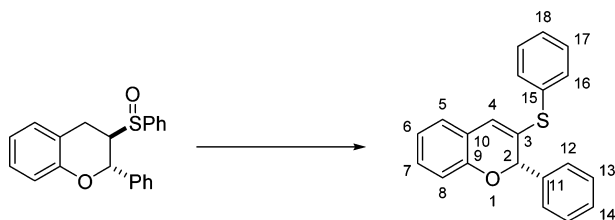
6a, 6b   **7**

Preparation of (S)-2-Phenyl-3-(phenylthio)-2H-chromene (7). To a 50 mL Schlenk flask under argon was added a 1:1 mixture of **6a/6b** (334 mg, 1 mmol) and toluene (8 mL). To this was added pyridine (805 μL, 10 mmol, 10 equiv) via syringe followed by trifluoroacetic

anhydride (278 μL, 2.0 mmol, 2.0 equiv). The solution was then heated to 80 °C (internal temperature, oil bath) for 4 h. The flask was then removed from the heat source and allowed to cool to rt. The mixture was transferred to a 60 mL separatory funnel and diluted with water (10 mL) and ether (15 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 10 mL). The organic layers were combined, dried over MgSO$_4$, and concentrated by rotary evaporation (30 °C, 3 mmHg). Purification by silica gel flash column chromatography (9:1 hexanes/CH$_2$Cl$_2$ then 5:1 hexanes/CH$_2$Cl$_2$, 20 mm diameter, 16 cm of SiO$_2$) followed by recrystallization (hexanes, 2 mL) afforded 292 mg (92%) of **7** as white prisms. Data for **7**: mp 86−88 °C (hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.49 (d, J = 6.6 Hz, 2H, HC(aryl)), 7.43−7.32 (m, 8H, HC(aryl)), 7.12 (t, J = 7.7 Hz, 1H, HC(7)), 7.00 (d, J = 7.6, Hz, 1H, HC(5)), 6.90 (t, J = 7.5 Hz, 1H, HC(6)), 6.78 (d, J = 8.0 Hz, 1H, HC(8)), 6.66 (s, 1H, HC(4)), 5.75 (s, 1H, HC(2)); ^{13}C NMR (126 MHz, CDCl$_3$) δ 151.8 (C9), 138.5 (C15), 132.5 (C17), 132.3 (C11), 131.4 (C13), 129.7 (C9), 129.6 (C16), 129.1 (C18), 128.7 (C13), 128.3 (C14), 128.0 (C12), 126.3 (C7), 125.4 (C4), 122.4 (C10), 121.8 (C6), 116.5 (C8), 79.6 (C2); IR (ATR, cm^{-1}) 3047 (w), 3028 (w), 2942 (w), 1902 (w), 1736 (w), 1704 (w), 1625 (w), 1600 (w), 1581 (w), 1570 (w), 1483 (m), 1473 (m), 1450 (m), 1437 (m), 1348 (w), 1326 (m), 1301 (w), 1258 (m), 1223 (m), 1206 (m), 1194 (m), 1160 (w), 1148 (w), 1115 (m), 1078 (w), 1065 (m), 1045 (m),1022 (m), 1000 (w), 962 (m), 937 (m), 924 (m), 905 (m), 889 (m), 854 (m), 832 (w), 776 (m), 764 (m), 747 (s), 737 (s), 697 (s), 688 (s); MS (EI, 70 eV, m/z) 316 (40, M$^+$), 207 (100),178 (23); TLC R_f 0.57 (4:1 hexanes/ethyl acetate) [UV,CAM]. Anal. Calcd for C$_{21}$H$_{16}$OS (316.42): C, 79.71; H, 5.10. Found: C, 79.31; H, 4.97.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00295.

General experimental details, optimization experiments, ^{1}H and ^{13}C spectra for new compounds, LC and SFC chromatograms for enantioenriched compounds, and CD spectra for enantioenriched compounds (PDF)

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Notes

The authors declare no competing financial interest.

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