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Palladium(II)-Catalyzed Enantioselective Synthesis of 2-Vinyl Oxygen Heterocycles

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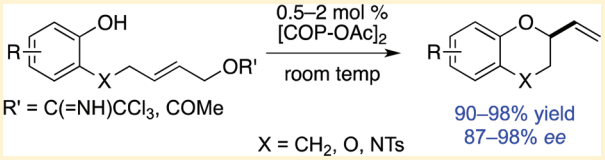
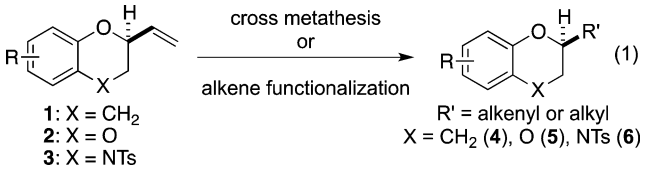
Supporting Information

ABSTRACT: 2-Vinylchromanes (**1**), 2-vinyl-1,4-benzodioxanes (**2**), and 2,3-dihydro-2-vinyl-2*H*-1,4-benzoxazines (**3**) can be prepared in high yields (90−98%) and excellent enantiomeric purities (87−98% ee) by $[COP\text{-}OAc]_2$-catalyzed cyclization of phenolic (*E*)-allylic trichloroacetimidate precursors. Deuterium-labeling and computational experiments are consistent with these cyclization reactions taking place by an *anti*-oxypalladation/*syn*-deoxypalladation mechanism. 2-Vinylchromanes can also be prepared in good yields and high enantiomeric purities from analogous (*E*)-allylic acetate precursors, which constitutes the first report that acetate is a competent leaving group in COP-catalyzed enantioselective S_N2' substitution reactions.



INTRODUCTION

2-Alkenyl- and 2-alkylchromanes (**4**),[1] 1,4-benzodioxanes (**5**), and 2,3-dihydro-2*H*-1,4-benzoxazines (**6**) are heterocyclic fragments found in many molecules exhibiting useful therapeutic properties.[2] The corresponding enantioenriched 2-vinyl heterocycles—2-vinylchromanes (**1**), 2-vinyl-1,4-benzodioxanes (**2**), and 2,3-dihydro-2-vinyl-2*H*-1,4-benzoxazines (**3**)—would be attractive precursors for the enantioselective synthesis of many heterocycles **4**−**6** (eq 1).[3] Previously



(1)

reported catalytic enantioselective methods for preparing 2-vinyl heterocycles **1**−**3** involve Pd(0)- or Ir(I)-catalyzed cyclization reactions that proceed via η^3-allyl intermediates to form the allylic C−O σ-bond.[4−6] The development of an alternative palladium(II)-catalyzed construction of enantioenriched 2-vinyl heterocycles **1**−**3** is the subject of this account.

Our investigations in this area are an outgrowth of the recently reported enantioselective synthesis of 3-phenoxy-1-alkenes from the reaction of phenols and allylic trichloroacetimidates using palladium(II) catalysts of the COP family (Figure 1).[7−9] Herein we disclose our studies of the intramolecular variant of this chemistry, in which tethered (*E*)-allylic imidates yield 2-vinylchromanes (**1**), 2-vinyl-1,4-benzodioxanes (**2**), and 2,3-dihydro-2-vinyl-2*H*-1,4-benzoxazines (**3**) in good yields and high enantiomeric purities (eq 2). We report also that the enantioselective synthesis of chromane **1** can be accomplished with substrates having an acetate rather than a trichloroacetimidate leaving group.

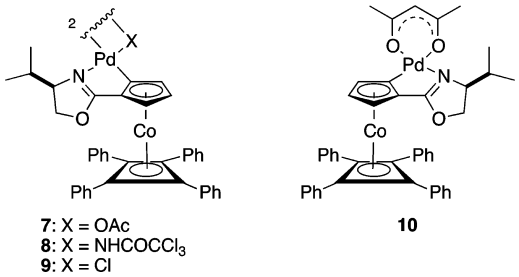
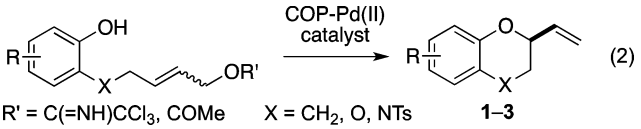


Figure 1. Selected palladium(II) catalysts of the COP family.



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RESULTS AND DISCUSSION

Enantioselective Synthesis of 2-Vinylchromanes, 2-Vinyl-1,4-benzodioxanes, and 2,3-Dihydro-2-vinyl-2*H*-1,4-benzoxazines from Allylic Trichloroacetimidate Precursors. Our studies began by examining the cyclization of phenolic (*E*)-allylic imidate **11a**[10] in the presence of 2 mol % of various palladium(II) catalysts (Table 1). At 38 °C in CH_2Cl_2, the COP complexes $[(S_p,R)\text{-}COP\text{-}OAc]_2$ (**7**) and (R_p,*S*)-COP-acac (**10**) catalyzed the formation of 2-vinylchromane (**1a**) in high yields and 89 and 80% ee, respectively (entries 1 and 2). As expected, allylic imidate rearrangement to form transposed allylic amide **12** was a significant competing process when chloride-bridged complex *ent*-**9** was employed (entry 3).[11] Trichloroacetamidate-bridged dimer **8**, previously reported by our group to be a kinetically poor catalyst for allylic trichloroacetimidate rearrangements,[8] did not suppress com-

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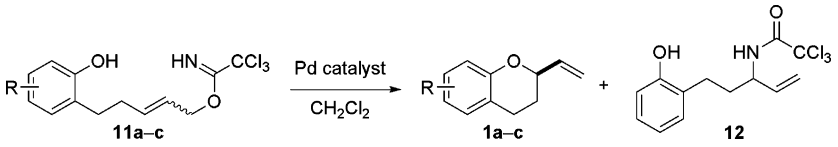
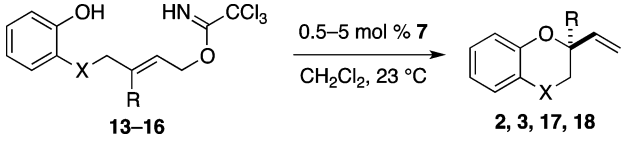
Table 1. Catalytic Enantioselective Synthesis of 2-Vinylchromanes 1a−c



entry[a]	substrate	R	catalyst (mol %)	temp (°C)	yield[b] (%) **12**	yield[b] (%)**1**	ee[c] (%) **1**
1	(*E*)-**11a**	H	**7** (2)	38		86	89 (*R*)[d]
2	(*E*)-**11a**	H	**10** (2)	38		72	80 (*S*)
3	(*E*)-**11a**	H	*ent*-**9** (2)	38	43	41	80 (*S*)
4	(*E*)-**11a**	H	**8** (2)	38	13	81	87 (*R*)
5	(*E*)-**11a**	H	**7** (0.5)	23		91[e]	94 (*R*)[e]
6	(*E*)-**11a**	H	*ent*-**7** (0.5)	23		97[e]	92 (*S*)[e]
7	(*E*)-**11b**	4-Br	**7** (0.5)	23		96[e]	80[e]
8[f]	(*E*)-**11b**	4-Br	**7** (0.5)	23		94[e]	90[e]
9[g]	(*E*)-**11c**	4-OMe	**7** (0.5)	23		92[e]	91 (*R*)[d,e]
10	(*Z*)-**11a**	H	*ent*-**7** (0.5)	23		92[e]	9 (*R*)[e]

[a][**11**] = 0.2 M; reaction time 8−18 h. [b]Isolated yield after purification on silica gel. [c]Determined by HPLC analysis using an enantioselective stationary phase. [d]Absolute configuration determined by comparison of optical rotation data with that reported in the literature.[4b] [e]Mean values of duplicate reactions. [f]The solvent was $CHCl_3$. [g]Reaction time was 30 h.

Table 2. Catalytic Enantioselective Synthesis of 2-Vinyl-1,4-benzodioxanes (2, 17) and 2-Vinyl-2*H*-1,4-benzoxazines (3)



entry	X	R	imidate	catalyst (mol %)	time (h)	product	yield[a] (%)	ee[b] (%)
1	O	H	**13**	**7** (0.5)	72	**2**	92	92 (*S*)[c]
2	O	H	**13**	**7** (2)	18	**2**	90	94 (*S*)[c]
3	NTs	H	**14**	**7** (2)	15	**3**	98	98 (*S*)[c]
4	O	Me	**15**	*ent*-**7** (5)	72	**17**	30	85[d]
5	S	H	**16**	**7** (5)	18	**18**	0	

[a]Mean yields after purification on silica gel of reactions performed in duplicate. [b]Determined by HPLC analysis using a enantioselective stationary phase (mean value of duplicate reactions). [c]Absolute configuration determined by comparison of optical rotation data with those reported in the literature.[6c,d] [d]Absolute configuration was not established.

pletely the competitive formation of allylic amide **12** (entry 4). Reactions were sufficiently rapid that a catalyst loading of 0.5 mol % could be employed in reactions carried out at room temperature where enantioselectivity was improved to 92−94% ee (entries 5 and 6). With [COP-OAc]$_2$ identified as the most effective catalyst, several additional solvents were examined. Enantioselectivity was enhanced to 98% ee in toluene-d_8; however, competitive formation of amide **12** was observed in this solvent.[12] The best combination of catalyst rate and enantioselectivity was obtained in CH_2Cl_2 at room temperature, conditions that we utilized in most subsequent experiments. The 4-bromo- and 4-methoxyphenol analogues cyclized similarly, although enantioselection was lower with the bromophenol precursor, and catalysis rate lower with the methoxy congener (entries 7−9). As observed in related bimolecular reactions,[8] enantioselectivity in the cyclization of the 4-bromophenol precursor was increased when $CHCl_3$ was employed as the solvent (entry 8). In marked contrast, the *Z* allylic imidate stereoisomer cyclized to form 2-vinylchromane (**1a**) of negligible enantiomeric purity (entry 10).

2-Vinyl-1,4-benzodioxane (**2**) and 2,3-dihydro-2-vinyl-2*H*-1,4-benzoxazine (**3**) can be prepared in similar fashion in high yield and enantiopurity, although the catalysis rate is somewhat slower (Table 2). For example, in the presence of 0.5 mol % of COP catalyst **7**, 2-vinylbenzodioxane **2** was formed in 92% ee; however, a reaction time of 72 h was required (entry 1). Increasing the catalyst loading to 2 mol % gave **2** and **3** in high yield and 94% and 98% ee, respectively, after reaction times of 15−18 h (entries 2 and 3). The *E*-trisubstituted allylic precursor **15** provided benzodioxane **17** in 85% ee, albeit in only 30% yield after a reaction time of 72 h (entry 4). Although the yield of **17** was modest, this transformation is notable because it represented the first example of COP-catalyzed formation of a tetrasubstituted stereocenter.[13] The reaction could not be extended to the formation of 2,3-dihydro-2-vinyl-2*H*-1,4-benzothiopyran (**18**), presumably as a result of coordination of the palladium(II) catalyst to sulfur.[12]

Enantioselective Synthesis of 2-Vinylchromanes from Allylic Acetate Precursors. Trichloroacetimidates are widely used leaving groups, largely because they can be prepared in high yields from trichloroacetonitrile and most alcohols—including quite labile ones—under mild conditions (catalytic DBU at room temperature).[14,15] The disadvantage in their use is the production of trichloroacetamide (MW = 144) as a byproduct. In a preliminary survey, we found that acetate was an adequate leaving group for the [COP-OAc]$_2$-catalyzed cyclization of phenolic (*E*)-allylic acetate **19a** to form 2-vinylchromane (Table 3).[16] In CH_2Cl_2, cyclohexane, or

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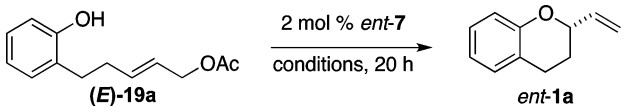
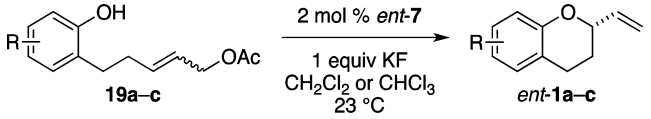
Table 3. Catalytic Enantioselective Synthesis of 2-Vinylchromane *ent*-1a from Allylic Acetate Precursor (*E*)-19a[18]



entry[a]	solvent	temp (°C)	additive[b]	conversion[c] (%)	ee[d] (%)
1	CH_2Cl_2	40	none	33	84
2	toluene	40	none	27	85
3	cyclohexane	40	none	43	84
4[e]	MeOH	60	none	71	91
5[e,f]	CH_2Cl_2	23	K_2CO_3	73	91
6[e,f]	cyclohexane	23	K_2CO_3	>95	82
7[e]	CH_2Cl_2	23	K_3PO_4	93	73
8	CH_2Cl_2	23	Et_3N	41	84
9[e]	CH_2Cl_2	23	CsF	26	94
10[e,f]	CH_2Cl_2	23	KF	55	93
11[e,g]	CH_2Cl_2	23	KF	88	92
12[e,h]	CH_2Cl_2	23	KF	64	93

[a][(*E*)-19a] = 0.2 M, unless otherwise indicated. [b]1 equiv was used. [c]Determined by ^{1}H NMR analysis using an internal standard. [d]Determined by HPLC analysis using a enantioselective stationary phase. [e]Reaction was heterogeneous. [f]When the identical reaction was performed in the absence of *ent*-7, only (*E*)-19a was observed by ^{1}H NMR analysis. [g][(*E*)-19a] = 1.0 M. [h]1 mol % of $[(R_p,S)$-COP-OAc$]_2$ (*ent*-7) was employed.

Table 4. Catalytic Enantioselective Synthesis of 2-Vinylchromane *ent*-1a from Allylic Acetate Precursors 19[a]



entry[b]	R	19	solvent	time (h)	yield[c] (%)	ee[d] (%)
1	H	(*E*)-19a	CH_2Cl_2	24	89	94 (*S*)
2	4-Br	(*E*)-19b	CH_2Cl_2	6	82	88
3	4-Br	(*E*)-19b	$CHCl_3$	10	92	90
4	4-OMe	(*E*)-19c	CH_2Cl_2	36	95	95 (*S*)
5	H	(*Z*)-19a	CH_2Cl_2	24	91	18–51 (*S*)

[a]All reactions reported in this table were heterogeneous. [b][19] = 1.0 M. [c]Mean yields after purification on silica gel of reactions performed in duplicate. [d]Determined by HPLC analysis using a enantioselective stationary phase (mean value of duplicate reactions).

toluene, acetate (*E*)-19a cyclized in the presence of 2 mol % of $[COP\text{-}OAc]_2$ to form *ent*-1a in 84–85% ee (entries 1–3), whereas significantly lower enantioselectivity was observed in CH_3CN, DMF, and THF. Though the use of the alcoholic solvents EtOH, *i*-PrOH, cyclohexanol, or *t*-BuOH typically resulted in low conversions (5–20%) and moderate enantioselectivities (72–84% ee), to our surprise, excellent enantioselectivity was obtained in MeOH. Increasing the reaction temperature to 60 °C gave rise to chromane *ent*-1a in 71% yield and 91% ee after 20 h using 2 mol % of $[(R_p,S)$-COP-OAc$]_2$ (*ent*-7) (entry 4). However, enantiomeric purity of the product *ent*-1a begins to erode at ~15–20 h, which is attributed to protodemetalation of $[COP\text{-}OAc]_2$ at 60 °C to generate an achiral palladium(II) catalyst. More success was realized by adding bases. For example, adding K_2CO_3 (1 equiv) increased conversion in reactions carried out at room temperature in CH_2Cl_2 or cyclohexane to 73% and >95%, respectively (entries 5 and 6). Since enantioselectivity was higher in CH_2Cl_2, further optimization of the base was carried out in this solvent (entries 7–12). Heterogeneous bases performed better than Et_3N (entry 8). As expected in the heterogeneous reactions,[17] conversions and enantioselectivities were highly dependent upon the physical state of the solid bases employed. Conversions were generally highest when K_2CO_3 was used; however, reproducible yields and enantioselectivities were best achieved using powdered, dried KF with rapid stirring. The optimal conditions for the conversion of 19 to *ent*-1a were found to be 2 mol % of $[(R_p,S)$-COP-OAc$]_2$ (*ent*-7), 1 equiv of KF, [19] = 1.0 M CH_2Cl_2, 23 °C (entry 11).

The results of the synthesis of 2-vinylchromanes *ent*-1a–c from the corresponding allylic acetate precursors under these optimized conditions are summarized in Table 4. In all three cases, yields (89–95%) and enantioselectivities (88–95%) were excellent. The (*Z*)-allylic ester (*Z*)-19a was also transformed to chromane *ent*-1a under these conditions, although as observed with the corresponding trichloroacetimidate precursor, enantioselectivity was low (entry 5).

Geometry of the Intramolecular S_N2' Reaction. To gain insight into the mechanism of the $[COP\text{-}OAc]_2$-catalyzed cyclization reactions in both the imidate and acetate series, the cyclization of two enantioenriched deuterium-labeled substrates was examined (eqs 3 and 4). As in our study of the geometry of related bimolecular S_N2' reactions,[7b] the allylic alcohol precursors of deuterated enantioenriched imidate and acetate cyclization substrates were prepared by enantioselective Keck reduction of the corresponding enal.[12,19] In both series, chirality transfer was complete within experimental error and in accord with an antarafacial S_N2' geometry.

The antarafacial geometry of the S_N2' cyclization to form 2-vinylchromane (1a) from both the (*E*)-allylic trichloroacetimi-

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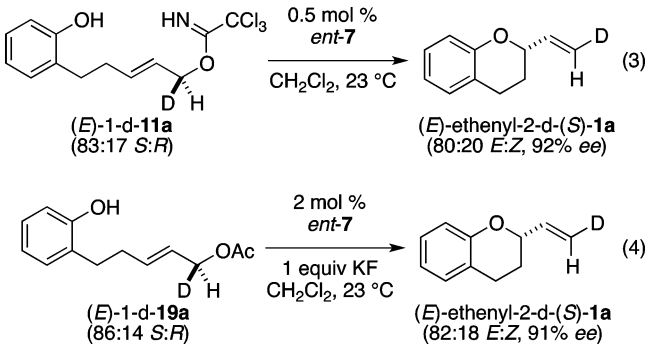
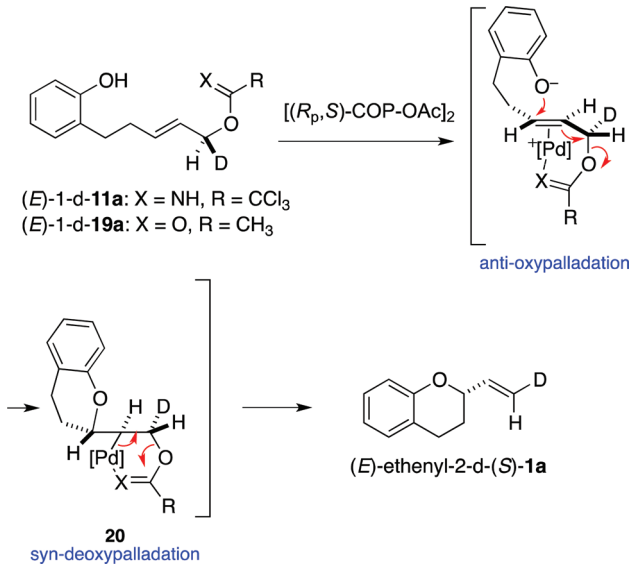


date and (*E*)-allylic acetate precursors is identical to the geometry of the bimolecular reaction of (*E*)-allylic imidates and phenol in the presence of COP catalyst **8**.[7b] In the context of an oxypalladation/deoxypalladation mechanism, this result requires that the two steps occur with opposite geometries. In our earlier study of $[COP\text{-}OAc]_2$-catalyzed allylic esterification of (*Z*)-allylic imidates, computational modeling provided evidence for an anti-oxypalladation/syn-deoxypalladation mechanism.[7b,20] Such a sequence for the formation of vinylchromane (***S***)-**1a** is illustrated in Scheme 1.

Scheme 1. anti-oxypalladation/syn-deoxypalladation Sequence for Forming (*S*)-1a



Computational Studies. As the oxypalladation step has been determined to be both rate- and enantiodetermining in the $[COP\text{-}OAc]_2$-catalyzed bimolecular reaction of (*Z*)-allylic trichloroacetimidates with carboxylic acid nucleophiles,[7b] this step of the $[COP\text{-}OAc]_2$-catalyzed cyclization of (*E*)- and (*Z*)-imidates **11a** to form 2-vinylchromane was studied computationally. The objective was to ascertain whether or not an anti-oxypalladation/syn-deoxypalladation mechanism would: (a) explain the observation that stereoinduction was much higher in the $[COP\text{-}OAc]_2$-catalyzed cyclization of *E* allylic imidate (***E***)-**11a** than the corresponding *Z* stereoisomer, and (b) rationalize preferential formation of the *S* enantiomer of dihydrobenzopyran **1a** from the cyclization of (***E***)-**11a** catalyzed by $[(R_p,S)\text{-COP-OAc}]_2$ (*ent*-**7**). The TURBOMOLE v6.2[21] program at the B3-LYP level of theory[22] with a continuum solvation model (COSMO)[23] was utilized for this study. All atoms were represented by the def2-TZVP basis set[24] except for the carbon and hydrogen atoms of the tetraphenylcyclobutadiene unit of catalyst *ent*-**7**, which were represented by the SZ.benzene basis set.[25]

For each double-bond isomer, two pathways were investigated: anti-oxypalladation where the catalyst *ent*-**7** was bound to the imidate nitrogen and the *Re* (pathways (***E***)-**I** or (***Z***)-**I**) or *Si* face (pathways (***E***)-**II** or (***Z***)-**II**) of the double bond (Figure 2).[7b] Oxypalladation of *Re*-bound catalyst complex **24** occurs by transition structure **25** to provide palladated benzopyran complex **26** (Figure 2, pathway (***E***)-**I**); this elementary step requires 0.3 kcal/mol in activation energy and is exergonic by 21.0 kcal/mol. Deoxypalladation of **26** would yield (*S*)-2-vinylchromane. The *Si*-bound complex **21** undergoes oxypalladation with an activation energy of 1.4 kcal/mol by transition structure **22** to give palladated-chromane complex **23** with the overall release of 20.1 kcal/mol (Figure 2, pathway (***E***)-**II**). Further reaction of this intermediate would form (*R*)-2-vinylchromane. Oxypalladation via pathway (***E***)-**I** to form the observed *S* enantiomer of **1a** is calculated to be favored by $\Delta\Delta E^{\ddagger}$ of 3.7 kcal/mol. In contrast, the transition-state energy differences for oxypalladation of the two (*Z*)-imidate complexes (pathways (***Z***)-**I** and (***Z***)-**II**) are calculated to differ in energy by only 0.8 kcal/mol, consistent with the low selectivity observed in the cyclization of the (*Z*)-imidate precursor.

Analysis of the two calculated transition structures, **22** and **25**, for cyclization of the (*E*)-allylic imidate substrate provided some insight into the factors contributing to the high levels of enantioselectivity observed in the $[COP\text{-}OAc]_2$-catalyzed cyclization reaction (Figure 3).[26] The closest contact (2.36 Å) seen in low energy transition structure **25** is between H_4 and the cyclopentadiene fragment (H_{Cp}), with the remaining interatomic distances being outside of van der Waals contact. In contrast, oxypalladation transition structure **22** that leads to the minor observed enantiomer shows several destabilizing steric interactions. In particular, imidate hydrogen H_4 is 2.26 Å from the cyclopentadiene fragment (H_{Cp}), and H_5 is 2.73 Å from the tetraphenylcyclobutadiene fragment (C_{floor}). Unlike transition structure **25**, structure **22** has van der Waals contacts between the hydrogens of the methylene chain (H_4 and H_5) of the substrate and the COP ligand (C_{floor} and H_{Cp}).[27]

CONCLUSION

Using phenol-tethered (*E*)-allylic trichloroacetimidate precursors, the catalytic enantioselective synthesis of 2-vinylchromanes, 2-vinyl-1,4-benzodioxanes, and 2,3-dihydro-2-vinyl-2*H*-1,4-benzoxazines depicted in eq 2 takes place at room temperature in 90−98% yield and 87−98% ee under neutral conditions using 0.5 mol % of the palladacyclic catalyst $[COP\text{-}OAc]_2$. For the preparation of 2-vinylchromane (**1a**), 2-vinyl-1,4-benzodioxane (**2**), and 2,3-dihydro-4-(4-toluenesulfonyl)-2-vinyl-2*H*-1,4-benzoxazine (**3**), the catalytic enantioselective syntheses reported herein are the first to provide these products in both >90% yield and >90% ee.[4−6] We also demonstrate for the first time that acetate is a competent leaving group in COP-catalyzed enantioselective S_N2' substitution reactions. In this way, 2-vinylchromanes **1a−c** were prepared in 82−95% yield and 88−95% ee.

Deuterium-labeling experiments establish that the catalytic enantioselective cyclizations of both the (*E*)-allylic trichloroacetimidate and acetate precursors proceed by an antarafacial geometry identical to that of the bimolecular reaction of (*E*)-allylic trichloroacetimidates with phenols.[7b] DFT-modeling

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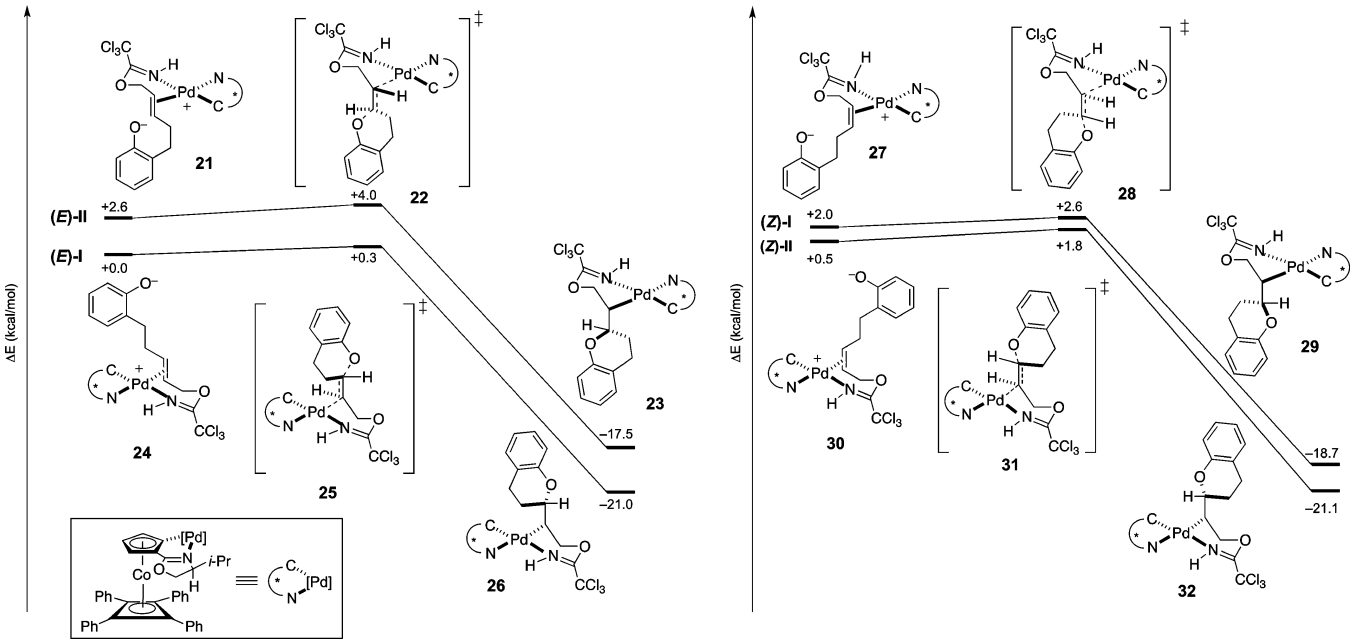

Figure 2. Calculated reaction coordinate diagrams for oxypalladation of (*E*)- and (*Z*)-allylic trichloroacetimidates **11a** with COP catalyst *ent*-**7**.

studies of the synthesis of 2-vinylchromane from the allylic imidate precursor are consistent with an anti-oxypalladation/syn-deoxypalladation identical to that of the corresponding bimolecular reaction. We speculate that cyclization of the allylic acetate precursor takes place in a similar fashion (Scheme 1), although additional experimentation will be required to establish this point. The computational studies rationalize the observation that enantioselection is significantly higher with the *E* than the *Z* allylic trichloroacetimidate substrate as well as the overall sense of stereoinduction. This model for stereoinduction supports earlier findings that the positioning of the tetraphenylcyclobutadiene group beneath the palladium square-plane is a key factor in achieving high levels of enantioselection in reactions catalyzed by COP complexes.[7b]

EXPERIMENTAL SECTION

General Procedure for Synthesis of 2-Vinylheterocycles from Allylic Trichloroacetimidate Precursors. A sealable 0.5-dram glass vial equipped with a Teflon cap was charged with the trichloroacetimidate precursor (0.077 mmol). A solution of [(S_p,*R*)-COP-OAc]$_2$ (**7**) or its enantiomer (*ent*-**7**) (0.001 M in CH_2Cl_2 or $CHCl_3$, 0.4 mL, 0.0004 mmol) was added via syringe. The reaction vial was sealed under an Ar atmosphere, and the orange solution was maintained at room temperature. After the reported reaction time, the solution was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel to afford the 2-vinylheterocycle product.

(*R*)-2,3-Dihydro-2-vinyl-2*H*-1-benzopyran (1a). Following the general procedure for imidate cyclization with catalyst **7** (0.001 M in CH_2Cl_2, 0.4 mL, 0.0004 mmol), imidate (*E*)-**11a** (25 mg, 0.077 mmol) was converted to **1a** (11 mg, 0.070 mmol, 91%), a clear colorless oil: 94% ee by enantioselective HPLC analysis [OJ column + OJ guard; flow: 0.5 mL/min; 100% *n*-hexane; λ = 280 nm; major enantiomer t_R = 22.56 min, minor enantiomer t_R = 25.41 min]; $[\alpha]_D^{25}$ −76.5, $[\alpha]_{577}^{25}$ −85.0, $[\alpha]_{546}^{25}$ −95.4, $[\alpha]_{435}^{25}$ −168.8, $[\alpha]_{405}^{25}$ −202.3 (*c* 0.27, $CHCl_3$). ^{1}H NMR and optical rotation data were consistent with previously reported values.[4b]

(*R*)-6-Bromo-2,3-dihydro-2-vinyl-2*H*-1-benzopyran (1b).[28] Following the general procedure for imidate cyclization with catalyst **7** (0.001 M in $CHCl_3$, 0.4 mL, 0.0004 mmol), imidate (*E*)-**11b** (30 mg, 0.075 mmol) was converted to **1b** (17 mg, 0.070 mmol, 94%), a clear colorless oil: 90% ee by enantioselective HPLC analysis [OJ column; flow: 0.5 mL/min; 100% *n*-hexane; λ = 230 nm; major enantiomer t_R = 28.85 min, minor enantiomer t_R = 32.63 min]; $[\alpha]_D^{25}$ −63.4, $[\alpha]_{577}^{25}$ −67.7, $[\alpha]_{546}^{25}$ −78.5, $[\alpha]_{435}^{25}$ −133.1 (*c* 0.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.18 (m, 2H), 6.74 (d, *J* = 8.3, 1H), 5.96 (ddd, *J* = 16.3, 10.6, 5.6, 1H), 5.37 (d, *J* = 17.3, 1H), 5.25 (d, *J* = 10.6, 1H), 4.57−4.53 (m, 1H), 2.87−2.80 (m, 1H), 2.77−2.72 (m, 1H), 2.09−2.04 (m, 1H), 1.87−1.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 137.2 (CH), 132.1 (CH), 130.3 (CH), 124.1 (C), 118.7 (CH), 116.7 (CH), 112.3 (C), 76.3 (CH), 27.1 (CH_2), 24.1 (CH_2); IR (thin film) 3083, 2927, 1648, 1236, 1040, 992 cm^{-1}; HRMS (GC−MS) *m*/*z* calcd for $C_{11}H_{11}BrO$, $(M)^+$ 237.9993, found 237.9985.

(*R*)-2,3-Dihydro-6-methoxy-2-vinyl-2*H*-1-benzopyran (1c). Following the general procedure for imidate cyclization with catalyst **7** (0.001 M in CH_2Cl_2, 0.6 mL, 0.0006 mmol), imidate (*E*)-**11c** (40 mg, 0.11 mmol) was converted to **1c** (19 mg, 0.10 mmol, 92%), a clear colorless oil: 91% ee by enantioselective HPLC analysis [OJ column + OJ guard; flow: 0.5 mL/min; 99:1 *n*-hexane/2-propanol; λ = 210 nm; major enantiomer t_R = 24.82 min, minor enantiomer t_R = 27.55 min]; $[\alpha]_D^{25}$ −83.7, $[\alpha]_{577}^{25}$ −86.6, $[\alpha]_{546}^{25}$ −99.3, $[\alpha]_{435}^{25}$ −161.5, $[\alpha]_{405}^{25}$ −188.8 (*c* 0.54, $CHCl_3$). ^{1}H NMR and optical rotation data were consistent with previously reported values.[4b]

(*S*)-2,3-Dihydro-2-vinyl-2*H*-1,4-benzodioxane (2).[29] Following the general procedure for imidate cyclization with catalyst **7** (0.004 M in CH_2Cl_2, 0.6 mL, 0.0023 mmol), imidate **13** (38 mg, 0.12 mmol) was converted to **2** (17 mg, 0.11 mmol, 90%), a clear colorless oil: 94% ee by enantioselective HPLC analysis [OJ column + OJ guard; flow: 0.5 mL/min; 99:1 *n*-hexane/2-propanol; λ = 280 nm; major enantiomer t_R = 18.90 min, minor enantiomer t_R = 20.19 min]; $[\alpha]_D^{25}$ −6.5, $[\alpha]_{577}^{25}$ −3.7, $[\alpha]_{546}^{25}$ −4.1 (*c* 0.16, $CHCl_3$). ^{1}H NMR and optical rotation data were consistent with previously reported values.[6c]

(*S*)-2,3-Dihydro-4-(4-toluenesulfonyl)-2-vinyl-2*H*-1,4-benzoxazine (3).[29] Following the general procedure for imidate cyclization with catalyst **7** (0.004 M in CH_2Cl_2, 0.5 mL, 0.00021 mmol), imidate **14** (50 mg, 0.10 mmol) was converted to **3** (32 mg, 0.10 mmol, 98%), a pale yellow oil: 98% ee by enantioselective HPLC analysis [AD column; flow: 1.0 mL/min; 80:20 *n*-hexane:isopropanol; λ = 280 nm; minor enantiomer t_R = 6.09 min, major enantiomer t_R = 6.49 min]; $[\alpha]_D^{25}$ +72.8, $[\alpha]_{577}^{25}$ +70.9, $[\alpha]_{546}^{25}$ +75.0, $[\alpha]_{435}^{25}$ +195.3, (*c* 0.25, $CHCl_3$). ^{1}H NMR and optical rotation data were consistent with previously reported values.[6d]

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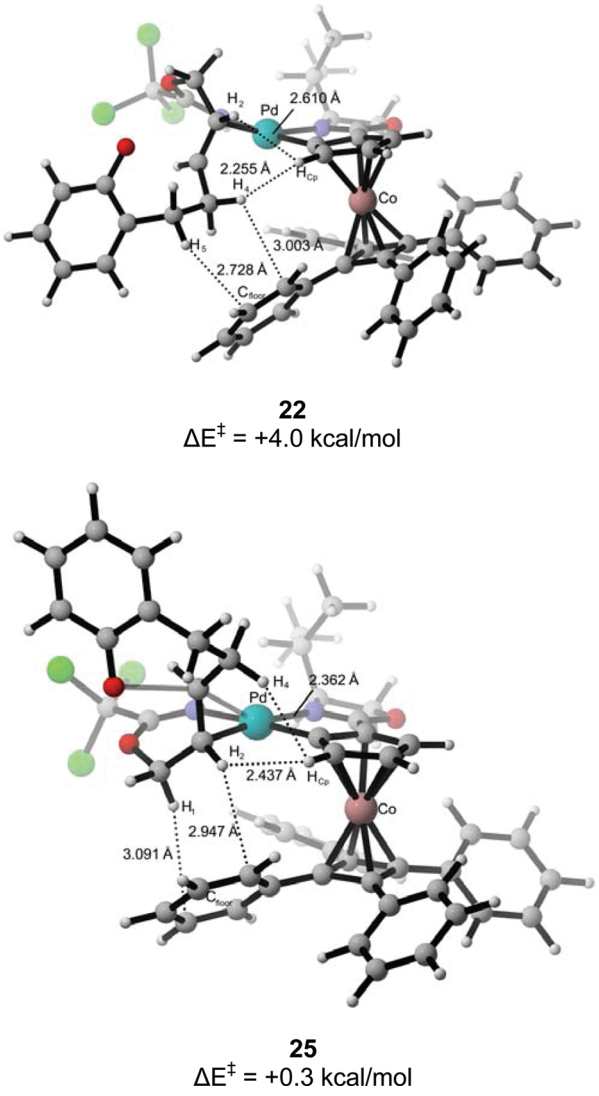

Figure 3. Calculated transition structures for intramolecular oxypalladation of (*E*)-allylic trichloroacetimidates.

(*R*)-2,3-Dihydro-2-methyl-2-vinyl-1,4-benzodioxane (17).[28,29] Following the general procedure for imidate cyclization with catalyst *ent*-**7** (0.01 M in CH_2Cl_2, 0.3 mL, 0.0030 mmol), imidate **15** (20 mg, 0.059 mmol) was converted to **17** (3.2 mg, 0.018 mmol, 30%), a pale yellow oil: 85% ee by enantioselective HPLC analysis [OJ column; flow: 0.5 mL/min; 99.5:0.5 *n*-hexane/2-propanol; λ = 280 nm; major enantiomer t_R = 13.59 min, minor enantiomer t_R = 14.95 min]; $[\alpha]_D^{25}$ −3.6, $[\alpha]_{577}^{25}$ −3.0, $[\alpha]_{546}^{25}$ −8.1, $[\alpha]_{435}^{25}$ −6.0, (*c* 0.05, $CHCl_3$). ^{1}H NMR data were consistent with previously reported values.[30]

(*S*,*E*)-2-(2-Deuterovinyl)-1-benzopyran ((*E*)-ethenyl-2-*d*-(*S*)-1a).[31,32] Following the general procedure for imidate cyclization with catalyst *ent*-**7** (0.001 M in CH_2Cl_2, 0.4 mL, 0.0004 mmol), imidate (*E*)-**1-*d*-11a** (25 mg, 0.077 mmol) was converted to (*E*)-**ethenyl-2-*d*-(*S*)-1a** (9 mg, 0.058 mmol, 75%), a clear colorless oil. Analysis by electrospray mass spectrometry indicated a >96:4 ratio of ***d*$_1$-2-*d*-(*S*)-1a:*d*$_0$-2-*d*-(*S*)-1a**. The *E*:*Z*-ratio was calculated to be 80:20 using ^{1}H NMR spectroscopy: 92% ee by enantioselective HPLC analysis [OJ column + OJ guard; flow: 0.5 mL/min; 100% *n*-hexane; λ = 280 nm; minor enantiomer t_R = 22.23 min, major enantiomer t_R = 24.51 min]; $[\alpha]_D^{25}$ 2.5, (*c* 0.33, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12−7.09 (m, 1H), 7.06 (d, *J* = 7.4, 1H), 6.87−6.84 (m, 2H), 5.38 (d, *J* = 17.2, 1H), 4.58−4.56 (m, 1H), 2.91−2.84 (m, 1H), 2.81−2.76 (m, 1H), 2.11−2.06 (m, 1H), 1.90−1.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6 (C), 137.6 (CH), 129.6 (CH), 127.4 (CH), 121.9 (C), 120.3 (CH), 117.0 (CH), 116.1 (t, J_{CD} = 23.8, CDH), 76.2 (CH), 27.6 (CH_2), 24.3 (CH_2); IR (thin film) 3081, 2919, 1231, 1048, 975 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{11}H_{12}DO$, $(M + H)^+$ 162.1029, found 162.1023.

General Procedure for Synthesis of 2-Vinylchromanes from Allylic Acetate Precursors. A sealable, oven-dried 0.5-dram glass vial equipped with a stir bar and a Teflon cap was charged with [(R_p,*S*)-COP-OAc]$_2$ (*ent*-**7**) or its enantiomer (**7**) (2.7 mg, 0.0018 mmol) and KF (5.3 mg, 0.091 mmol). The vial was sealed with a Teflon cap then flame-dried and backfilled with Ar twice. Once the vial cooled to room temperature, acetate (0.091 mmol) in CH_2Cl_2 or $CHCl_3$ (0.09 mL, 1.0 M) was added via syringe. The reaction vial was sealed under an Ar atmosphere and placed in an aluminum block, and the reaction was stirred vigorously at room temperature. After the reported reaction time, the heterogeneous brown reaction mixture was filtered, the filtrate was concentrated in vacuo, and then the residue was purified by flash chromatography on silica gel to afford the 2-vinylchromane product.

(*S*)-2,3-Dihydro-2-vinyl-2*H*-1-benzopyran (*ent*-1a). Following the general procedure for acetate cyclization with catalyst *ent*-**7** (2.7 mg, 0.0018 mmol), acetate (*E*)-**19a** (1.0 M in CH_2Cl_2, 0.09 mL, 0.091 mmol) was converted to *ent*-**1a** (13 mg, 0.081 mmol, 89%), a clear colorless oil: 94% ee by enantioselective HPLC analysis [OJ column + OJ guard; flow: 0.5 mL/min; 100% *n*-hexane; λ = 280 nm; minor enantiomer t_R = 20.94 min, major enantiomer t_R = 22.92 min]. ^{1}H NMR data were consistent with previously reported values.[4b]

(*S*)-6-Bromo-2,3-dihydro-2-vinyl-2*H*-1-benzopyran (*ent*-1b).[28] Following the general procedure for acetate cyclization with catalyst *ent*-**7** (2.0 mg, 0.0013 mmol), acetate (*E*)-**19b** (1.0 M in $CHCl_3$, 0.07 mL, 0.067 mmol) was converted to *ent*-**1b** (15 mg, 0.061 mmol, 92%), a clear colorless oil: 90% ee by enantioselective HPLC analysis [OJ column; flow: 0.5 mL/min; 100% *n*-hexane; λ = 230 nm; minor enantiomer t_R = 30.55 min, major enantiomer t_R = 32.78 min]. See characterization data for **1b** for spectral details.

(*S*)-2,3-Dihydro-6-methoxy-2-vinyl-2*H*-1-benzopyran (*ent*-1c). Following the general procedure for acetate cyclization with catalyst *ent*-**7** (1.8 mg, 0.0012 mmol), acetate (*E*)-**19c** (1.0 M in CH_2Cl_2, 0.06 mL, 0.060 mmol) was converted to *ent*-**1c** (10.8 mg, 0.057 mmol, 95%), a clear colorless oil: 95% ee by enantioselective HPLC analysis [OJ column + OJ guard; flow: 0.5 mL/min; 99:1 *n*-hexane/2-propanol; λ = 210 nm; minor enantiomer t_R = 22.64 min, major enantiomer t_R = 24.19 min]. ^{1}H NMR data were consistent with previously reported values.[4b]

(*S*,*E*)-2-(2-Deuterovinyl)-1-benzopyran ((*E*)-ethenyl-2-*d*-(*S*)-1a).[31,32] Following the general procedure for acetate cyclization with catalyst *ent*-**7** (2.7 mg, 0.0018 mmol), acetate (*E*)-**1-*d*-19a** (20 mg, 0.090 mmol) was converted to (*E*)-**ethenyl-2-*d*-(*S*)-1a** (14 mg, 0.083 mmol, 92%), a clear colorless oil. Analysis by electrospray mass spectrometry indicated a >96:4 ratio of ***d*$_1$-2-*d*-(*S*)-1a:*d*$_0$-2-*d*-(*S*)-1a**. The *E*/*Z* ratio was calculated to be 82:18 using ^{1}H NMR spectroscopy: 91% *ee* by enantioselective HPLC analysis [OJ column + OJ guard; flow: 0.5 mL/min; 100% *n*-hexane; λ = 280 nm; minor enantiomer t_R = 20.82 min, major enantiomer t_R = 22.48 min]. See characterization data above for spectral details.

Synthesis of Cyclization Precursors. 2-(4,4-Dibromobut-3-enyl)phenol (34). Using a procedure by Kinoshita,[33] chroman-2-ol (**33**) (2.00 g, 13.3 mmol) was treated with CBr_4 (8.83 g, 26.6 mmol) and PPh_3 (13.9 g, 53.3 mmol). The crude light yellow residue was purified by flash chromatography (99.5:0.5 CH_2Cl_2−acetone) to provide dibromide **34** (3.65 g, 11.9 mmol, 90%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13−7.11 (m, 2H), 6.90 (t, *J* = 7.4, 1H), 6.75 (d, *J* = 7.9, 1H), 6.47 (t, *J* = 7.2, 1H), 4.74−4.70 (m, 1H), 2.75 (t, *J* = 7.7, 2H), 2.44 (app q, *J* = 7.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6 (C), 138.1 (CH), 130.5 (CH), 127.7 (CH), 126.9 (C), 121.0 (CH), 115.4 (CH), 89.3 (C), 33.2 (CH_2), 28.3 (CH_2); IR (thin film) 3541, 3032, 2927, 1591, 753 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{10}H_{11}Br_2O$, $(M + H)^+$ 305.9078, found 305.9074.

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2-(5-Hydroxypent-3-ynyl)phenol (35). Using a modification of the procedure by Kinoshita,[33] a solution of **34** (3.55 g, 11.6 mmol) in THF (39 mL) was cooled to −78 °C in a 100-mL round-bottomed flask. A solution of *n*-BuLi (2.0 M in hexane, 21 mL, 42.0 mmol) was added via syringe over 20 min. The reaction mixture was stirred at −78 °C for 40 min, and then paraformaldehyde (1.04 g, 34.8 mmol) was added in a single portion. The reaction mixture was allowed to warm to 0 °C, stirred for 1 h, allowed to warm to ambient temperature, and then stirred for 1 h. Saturated aqueous NH_4Cl (60 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a pale yellow residue that was purified by flash chromatography (97.5:2.5 to 92:8 CH_2Cl_2−acetone) to provide propargyl alcohol **35** (1.33 g, 7.6 mmol, 65%) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16−7.11 (m, 2H), 6.90 (t, J = 7.4, 1H), 6.79 (d, J = 7.9, 1H), 4.96 (s, 1H), 4.25 (s, 2H), 2.87 (t, J = 7.3, 2H), 2.55 (t, J = 7.3, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8 (C), 130.7 (CH), 128.0 (CH), 127.0 (C), 121.0 (CH), 115.8 (CH), 86.5 (C), 79.3 (C), 51.5 (CH_2), 29.8 (CH_2), 19.6 (CH_2); IR (thin film) 3364, 2929, 2223, 1181, 1006 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{12}O_2Na$, $(M + Na)^+$ 199.0735, found 199.0730.

(*E*)-2-(5-Hydroxypent-3-enyl)phenol ((*E*)-36). Using a modification of a procedure by Denmark,[34] Red-Al (65% in toluene, 0.66 mL, 2.1 mmol) and Et_2O (0.6 mL) were cooled to 0 °C in a 10-mL round-bottomed flask. A solution of alkyne **35** (150 mg, 0.85 mmol) in Et_2O (0.6 mL) was added via syringe over 5 min, and then the solution was allowed to warm to room temperature. After 16 h, the solution was cooled to 0 °C, and saturated aqueous Rochelle's salt (5 mL) was added slowly. The mixture was stirred for 1 h, extracted with EtOAc (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (94:6 CH_2Cl_2−acetone) to yield alkene **(*E*)-36** (107 mg, 0.600 mmol, 71%) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12−7.07 (m, 2H), 6.87 (t, J = 7.4, 1H), 6.76 (d, J = 8.0, 1H), 5.78 (dt, J = 15.4, 6.6, 1H), 5.68 (dt, J = 15.4, 5.8, 1H), 5.48 (br s, 1H), 4.10 (d, J = 5.4, 2H), 2.72 (t, J = 7.4, 2H), 2.38 (app q, J = 7.3, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8 (C), 133.1 (CH), 130.4 (CH), 129.4 (CH), 128.0 (C), 127.4 (CH), 120.8 (CH), 115.5 (CH), 63.9 (CH_2), 32.5 (CH_2), 29.9 (CH_2); IR (thin film) 3307, 3035, 2850, 1668, 966 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{14}O_2Na$, $(M + Na)^+$ 201.0892, found 201.0892.

(*E*)-5-(2-Hydroxyphenyl)pent-2-enyl 2′,2′,2′-trichloroacetimidate ((*E*)-11a). In a 10-mL round-bottomed flask, alcohol **(*E*)-36** (25 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (0.56 mL), and then DBU (24 μL, 0.17 mmol) was added via syringe. Trichloroacetonitrile (17 μL, 0.17 mmol) was added via syringe, and the solution was maintained at room temperature. After 1 h, the reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (98.5:0.5:1 CH_2Cl_2−acetone−Et_3N) to provide imidate **(*E*)-11a** (43 mg, 0.13 mmol, 96%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.12−7.08 (m, 2H), 6.88 (t, J = 7.4, 1H), 6.76 (d, J = 7.9, 1H), 5.95 (dt, J = 15.4, 6.6, 1H), 5.73 (dt, J = 15.3, 6.2, 1H), 4.82 (br s, 1H), 4.76 (d, J = 5.9, 2H), 2.74 (t, J = 7.7, 2H), 2.45−2.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (C), 153.7 (C), 136.2 (CH), 130.5 (CH), 127.8 (C), 127.4 (CH), 123.7 (CH), 120.9 (CH), 115.5 (CH), 91.6 (C), 70.1 (CH_2), 32.5 (CH_2), 29.7 (CH_2); IR (thin film) 3328, 3067, 2927, 1658, 1607, 1592 cm^{-1}; HRMS (CI) m/z calcd for $C_{13}H_{18}Cl_3N_2O_2$, $(M + NH_4)^+$ 339.0434, found 339.0436.

(*Z*)-2-(5-Hydroxypent-3-enyl)phenol ((*Z*)-36). Using a modification of a procedure by Taber,[35] a 10-mL round-bottomed flask was evacuated and refilled with nitrogen three times. The flask was charged with $Ni(OAc)_2{\cdot}4H_2O$ (106 mg, 0.426 mmol) and evacuated and refilled with nitrogen three additional times before degassed EtOH (1.5 mL) and $NaBH_4$ (20 mg, 0.54 mmol) were added to form a black suspension. Ethylenediamine (0.11 mL, 1.7 mmol) was added via syringe, followed by a degassed aqueous solution of NaOH (2.0 M, 7 μL, 0.01 mmol). Alkyne **35** (500 mg, 2.84 mmol) was dissolved in degassed EtOH (1.5 mL) and added via syringe to the black suspension. Hydrogen gas was bubbled vigorously through the reaction mixture for 5 min, then a balloon of H_2 was placed over the reaction mixture, which was allowed to stir for 18 h then filtered through a short pad of silica gel using EtOH as the eluent. The organic layer was concentrated in vacuo to yield alkene **(*Z*)-36** (506 mg, 2.84 mmol, 100%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10−7.07 (m, 2H), 6.86 (t, J = 7.4, 1H), 6.78 (d, J = 7.9, 1H), 5.70−5.66 (m, 2H), 4.07 (d, J = 6.2, 2H), 2.71 (t, J = 7.4, 2H), 2.43 (app q, J = 7.3, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1 (C), 133.2 (CH), 130.8 (CH), 128.8 (CH), 127.8 (C), 127.6 (CH), 120.5 (CH), 115.6 (CH), 58.3 (CH_2), 30.6 (CH_2), 27.8 (CH_2); IR (thin film) 3367, 2932, 1592, 1180, 1017, 721 cm^{-1}; HRMS (CI) m/z calcd for $C_{11}H_{16}NO$, $(M + NH_4 - H_2O)^+$ 178.1232, found 178.1240.

(*Z*)-5-(2-Hydroxyphenyl)pent-2-enyl 2′,2′,2′-trichloroacetimidate ((*Z*)-11a). Following the procedure described for the preparation of **(*E*)-11a**, alcohol **(*Z*)-36** (100 mg, 0.561 mmol) was treated with DBU and Cl_3CCN. After 2 h, the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (98.5:0.5:1 CH_2Cl_2−acetone−Et_3N) to provide imidate **(*Z*)-11a** (136 mg, 0.424 mmol, 76%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 7.12−7.09 (m, 2H), 6.87 (t, J = 7.4, 1H), 6.78 (d, J = 8.1, 1H), 5.91 (br s, 1H), 5.83 (dt, J = 10.6, 7.9, 1H), 5.67 (dt, J = 10.8, 6.8, 1H), 4.87 (d, J = 6.8, 2H), 2.73 (t, J = 7.8, 2H), 2.48 (app q, J = 7.7, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2 (C), 154.0 (C), 135.2 (CH), 130.5 (CH), 128.6 (CH), 127.5 (C), 123.3 (CH), 120.8 (CH), 115.6 (CH), 91.6 (C), 65.4 (CH_2), 30.5 (CH_2), 28.0 (CH_2); IR (thin film) 3333, 3029, 2944, 1650, 1608, 1593 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{14}Cl_3NO_2Na$, $(M + Na)^+$ 343.9988, found 343.9981.

6-Bromochroman-2-ol (38). A 250-mL round-bottomed flask was charged with 6-bromochroman-2-one (**37**)[36] (9.9 g, 44 mmol) and toluene (110 mL). The solution was cooled to −78 °C, and DIBAL (25% in toluene, 30 mL, 48 mmol) was added over 10 min via syringe. The reaction mixture was stirred at −78 °C for 4 h and then allowed to warm to 0 °C. Water (50 mL) and saturated aqueous Rochelle's salt (75 mL) were added, and the resultant mixture was allowed to warm to room temperature and stirred for 1 h. The biphasic mixture was extracted with Et_2O (3 × 70 mL), and the organic layer was dried over Na_2SO_4, filtered, then concentrated in vacuo to yield a residue that was purified by flash chromatography (98.5:1.5 CH_2Cl_2−acetone) to provide lactol **38** (8.2 g, 36 mmol, 82%) as a pale yellow oil. Product was of sufficient purity to be carried on to the next step. ^{1}H NMR data were consistent with previously reported values.[37]

(*E*)-Ethyl 5-(5-bromo-2-hydroxyphenyl)pent-2-enoate (39). In a 250-mL round-bottomed flask, lactol **38** (8.19 g, 35.6 mmol) was dissolved in benzene (100 mL) and then treated with carbethoxymethylenetriphenylphosphorane (13.1 g, 37.5 mmol) in benzene (100 mL), and the solution was maintained at room temperature for 15 h. Evaporation of solvent using a rotary evaporator left a viscous oil that was dissolved in CH_2Cl_2 (70 mL). Celite (2 g) was added to the suspension, and the organic solvent was removed in vacuo to yield a powder that was loaded on silica gel and purified by flash chromatography (92:8 to 0:100 hexanes−EtOAc) to provide ester **39** (6.95 g, 24.5 mmol, 67%) as a white solid: mp 87−89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.18 (dd, J = 8.5, 2.4, 1H), 7.06−7.00 (m, 1H), 6.65 (d, J = 8.5, 1H), 5.87 (dd, J = 15.6, 1.4, 1H), 5.75 (br s, 1H), 4.21 (q, J = 3.4, 2H), 2.74 (t, J = 7.3, 2H), 2.54−2.49 (m, 2H), 1.30 (t, J = 4.4, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3 (C), 153.0 (C), 148.6 (CH), 132.9 (CH), 130.3 (CH), 129.7 (C), 121.8 (CH), 117.1 (CH), 112.7 (C), 60.6 (CH_2), 32.2 (CH_2), 28.7 (CH_2), 14.4 (CH_3); IR (thin film) 3381, 2983, 1693, 1272, 1039 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{15}BrO_3Na$, $(M + Na)^+$ 321.0102, found 321.0098.

(*E*)-4-Bromo-2-(5-hydroxypent-3-enyl)phenol ((*E*)-40). A 25-mL round-bottomed flask was charged with ester **39** (500 mg, 1.76 mmol) and toluene (4.4 mL). The solution was cooled to −78 °C, and DIBAL (25% in toluene, 2.2 mL, 3.5 mmol) was added over 5 min via syringe. The reaction mixture was stirred at −78 °C for 3.5 h and then allowed to warm to 0 °C. Water (5 mL) and saturated aqueous Rochelle's salt (5 mL) were added, and the resultant mixture was allowed to warm to room temperature and stirred for 1 h. The biphasic mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the organic layer

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was dried over Na_2SO_4, filtered, and then concentrated in vacuo to yield a residue that was purified by flash chromatography (98:2 to 96:4 CH_2Cl_2–MeOH) to provide alcohol (*E*)-**40** (243 mg, 0.945 mmol, 54%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.17 (dd, J = 8.5, 2.4, 1H), 6.64 (d, J = 8.5, 1H), 5.75 (dt, J = 15.3, 6.5, 1H), 5.67 (dt, J = 18.0, 6.4, 1H), 4.11 (d, J = 5.8, 2H), 2.67 (t, J = 7.7, 2H), 2.37–2.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0 (C), 133.0 (CH), 132.6 (CH), 130.4 (C), 130.0 (CH), 129.6 (CH), 117.2 (CH), 112.7 (C), 63.8 (CH_2), 32.3 (CH_2), 29.7 (CH_2); IR (thin film) 3325, 3029, 2927, 1669, 812 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{13}BrO_2Na$, (M + Na)$^+$ 278.9997, found 278.9995.

(*E*)-5-(5-Bromo-2-hydroxyphenyl)pent-2-enyl 2′,2′,2′-trichloroacetimidate ((*E*)-11b). Following the procedure described for the preparation of (*E*)-**11a**, alcohol (*E*)-**40** (243 mg, 0.945 mmol) was treated with DBU and Cl_3CCN. After 1 h, the reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (98.5:0.5:1 CH_2Cl_2–acetone–Et_3N) to provide imidate (*E*)-**11b** (272 mg, 0.677 mmol, 72%) as a pale yellow powder: mp 108–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 7.23 (s, 1H), 7.18 (dd, J = 8.4, 2.4, 1H), 6.64 (d, J = 8.5, 1H), 5.91 (dt, J = 15.5, 6.7, 1H), 5.70 (dt, J = 15.4, 6.1, 1H), 4.94 (br s, 1H), 4.76 (d, J = 6.0, 2H), 2.70 (t, J = 7.2, 2H), 2.42–2.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (C), 152.9 (C), 135.5 (CH), 133.1 (CH), 130.3 (C), 130.1 (CH), 124.0 (CH), 117.2 (CH), 112.8 (C), 91.6 (C), 70.0 (CH_2), 32.3 (CH_2), 29.5 (CH_2); IR (thin film) 3326, 3033, 2922, 1657, 971 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{13}BrCl_3NO_2Na$, (M + Na)$^+$ 421.9093, found 421.9083.

(*E*)-2-(5-Hydroxypent-3-enyl)-4-methoxyphenol ((*E*)-42). A 50-mL round-bottomed flask was charged with (*E*)-5-(2-((*tert*-butyldimethylsilyl)oxy)-5-methoxyphenyl)pent-2-en-1-ol (**41**)[4a] (1.63 g, 5.05 mmol) and THF (25 mL), and then TBAF (1.0 M in THF, 7.6 mL, 7.6 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, and then the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (70:30 to 50:50 to 40:60 hexanes–EtOAc) to provide diol (*E*)-**42** (714 mg, 3.43 mmol, 85%) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70–6.69 (m, 2H), 6.64–6.62 (m, 1H), 5.78 (dt, J = 15.4, 6.5, 1H), 5.69 (dt, J = 15.4, 5.8, 1H), 4.10 (d, J = 5.1, 2H), 3.76 (s, 3H), 2.69 (t, J = 7.4, 2H), 2.40–2.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3 (C), 148.0 (C), 133.0 (CH), 129.5 (C), 129.1 (CH), 116.2 (CH), 116.0 (CH), 111.9 (CH), 63.6 (CH_2), 55.9 (CH_3) 32.4 (CH_2), 30.0 (CH_2); IR (thin film) 3366, 2935, 1611, 1509, 971 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{16}O_3Na$, (M + Na)$^+$ 231.0997, found 231.0994.

(*E*)-5-(2-Hydroxy-5-methoxyphenyl)pent-2-enyl 2′,2′,2′-trichloroacetimidate ((*E*)-11c). A 0.5-dram glass vial equipped with a Teflon cap was charged with NaH (60% dispersion in mineral oil, 11 mg, 0.26 mmol) and Et_2O (0.2 mL). The suspension was cooled to 0 °C and stirred for 15 min. Diol (*E*)-**42** (50 mg, 0.24 mmol) was added in 0.28 mL of Et_2O via syringe. Trichloroacetonitrile (25 μL, 0.25 mmol) was added via syringe, and the reaction mixture was stirred at 0 °C for 1 h. The suspension was allowed to warm to room temperature and stirred for 15 min. The reaction mixture was filtered through silica gel using 50:50:1 CH_2Cl_2–acetone–Et_3N as the eluent. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (98.5:0.5:1 CH_2Cl_2–acetone–Et_3N) to yield imidate (*E*)-**11c** (60 mg, 0.17 mmol, 71%) as a clear colorless oil. Imidate (*E*)-**11c** was used directly in the [COP-OAc]$_2$ (**7**)-catalyzed cyclization reactions: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 6.70–6.69 (m, 2H), 6.64–6.62 (m, 1H), 5.94 (dt, J = 15.4, 6.7, 1H), 5.72 (dt, J = 15.4, 6.2, 1H), 4.76 (d, J = 6.2, 2H), 4.61 (br s, 1H), 3.76 (s, 3H), 2.71 (t, J = 7.3, 2H), 2.44–2.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (C), 153.9 (C), 147.5 (C), 135.9 (CH), 129.1 (C), 123.9 (CH), 116.3 (CH), 116.1 (CH), 112.0 (CH), 91.6 (C), 70.0 (CH_2), 55.8 (CH_3), 32.6 (CH_2), 30.0 (CH_2); IR (thin film) 3372, 3334, 2924, 1660, 1080, 971 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{16}Cl_3NO_3Na$, (M + Na)$^+$ 374.0093, found 374.0082.

(*E*)-2-(4-Tetrahydro-2*H*-pyran-2-yloxy)but-2-enyloxy)phenol (48). In a 5-mL round-bottomed flask, catechol (**45**) (0.400 g, 3.63 mmol) in DMF (11 mL) was cooled to 0 °C. In a single portion, K_2CO_3 (0.100 g, 0.726 mmol) was added, and the suspension was stirred for 5 min. (*E*)-2-((4-Bromobut-2-en-1-yl)oxy)tetrahydro-2*H*-pyran (**47**)[38] (0.170 g, 0.726 mmol) in DMF (1.1 mL) was added via syringe, and the reaction mixture was allowed to warm to room temperature. After 20 h, water (20 mL) and brine (10 mL) were added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a residue that was purified by flash chromatography (75:25 hexanes–Et_2O) to provide ether **48** (147 mg, 0.557 mmol, 77%) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95–6.81 (m, 4H), 6.04–5.95 (m, 2H), 5.67 (s, 1H), 4.66 (t, J = 3.5, 1H), 4.62 (d, J = 4.1, 2H), 4.31 (dd, J = 13.4, 4.2, 1H), 4.05 (dd, J = 13.6, 4.9, 1H), 3.88 (td, J = 11.0, 2.8, 1H), 3.54–3.51 (m, 1H), 1.89–1.83 (m, 1H), 1.78–1.72 (m, 1H), 1.64–1.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0 (C), 145.7 (C), 131.1 (CH), 127.0 (CH), 121.9 (CH), 120.2 (CH), 114.8 (CH), 112.3 (CH), 98.3 (CH), 69.1 (CH_2), 66.9 (CH_2), 62.4 (CH_2), 30.7 (CH_2), 25.5 (CH_2), 19.6 (CH_2); IR (thin film) 3393, 2942, 1609, 1115, 972 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{20}O_4Na$, (M + Na)$^+$ 287.1259, found 287.1261.

(*E*)-4-(2-Hydroxyphenoxy)but-2-enyl 2′,2′,2′-trichloroacetimidate (13). In a 5-mL round-bottomed flask, protected alcohol **48** (30 mg, 0.11 mmol) and *p*-TsOH·H_2O (4 mg, 0.02 mmol) were dissolved in MeOH (3.0 mL). The solution was refluxed for 3 h and then allowed to cool to room temperature. The solvent was removed in vacuo to yield a viscous oil that was dissolved in CH_2Cl_2 (0.57 mL), and then DBU (23 μL, 0.16 mmol) was added via syringe. Trichloroacetonitrile (14 μL, 0.14 mmol) was added via syringe, and the solution was maintained at room temperature. After 10 min, the reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (60:40:1 pentane–Et_2O–Et_3N) to provide imidate **13** (28 mg, 0.086 mmol, 76%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 6.96 (d, J = 7.8, 1H), 6.91–6.82 (m, 3H), 6.13 (dt, J = 15.8, 5.1, 1H), 6.06 (dt, J = 16.1, 4.9, 1H), 5.65 (s, 1H), 4.87 (d, J = 5.1, 2H), 4.66 (d, J = 5.0, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 (C), 146.0 (C), 145.5 (C), 129.1 (CH), 127.3 (CH), 122.1 (CH), 120.3 (CH), 115.0 (CH), 112.3 (CH), 91.4 (C), 68.8 (CH_2), 68.5 (CH_2); IR (thin film) 3411, 3338, 2926, 1663, 1473, 982 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{12}Cl_3NO_3Na$, (M + Na)$^+$ 345.9781, found 345.9787.

(*E*)-*N*-(4-Hydroxybut-2-enyl)-*N*-(2-hydroxyphenyl)-4-methylbenzenesulfonamide (50). In a 250-mL round-bottomed flask, PPh_3 (889 mg, 3.39 mmol) was added to a mixture of *N*-(2-hydroxyphenyl)-4-methylbenzenesulfonamide (**43**) (0.800 g, 3.39 mmol), (*E*)-4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-en-1-ol (**44**)[38] (583 mg, 3.39 mmol), and diethyl azodicarboxylate (40% in toluene, 1.5 mL, 3.4 mmol) in THF (39 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature. After 18 h, the reaction mixture was concentrated in vacuo to give a residue that was filtered through silica gel using 75:25 petroleum ether–EtOAc as eluent. The pale yellow oil and *p*-TsOH·H_2O (77 mg, 0.41 mmol) were dissolved in MeOH (12 mL) and refluxed for 18 h. The solution was allowed to cool to room temperature, and the solvent was removed in vacuo. The residue was purified by flash chromatography (70:30 to 60:40 petroleum ether-EtOAc) to provide diol **50** (437 mg, 1.31 mmol, 64%) as a pale yellow oil: ^{1}H NMR (500 MHz, DMSO) δ 9.53 (s, 1H), 7.56 (d, J = 8.2, 2H), 7.35 (d, J = 8.1, 2H), 7.11 (td, J = 8.0, 1.5, 1H), 6.93 (dd, J = 7.8, 1.5, 1H), 6.79 (dd, J = 8.1, 1.1, 1H), 6.72 (td, J = 7.6, 1.1, 1H), 5.57 (dt, J = 15.5, 4.6, 1H), 5.50 (dt, J = 15.5, 5.9, 1H), 4.64 (t, J = 5.4, 1H), 4.13 (d, J = 5.5, 2H), 3.78 (t, J = 4.2, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 154.9 (C), 142.8 (CH), 137.2 (CH), 133.9 (CH), 132.0 (C), 129.4 (2C), 127.3 (CH), 124.8 (CH), 124.2 (CH), 118.6 (CH), 116.4 (CH), 60.6 (CH_2), 50.9 (CH_2), 21.0 (CH_3); IR (thin film) 3416, 3049, 2923, 1598, 1337, 1090 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{19}NO_4SNa$, (M + Na)$^+$ 356.0933, found 356.0931.

(*E*)-4-(*N*-(2-Hydroxyphenyl)-4-methylphenylsulfonamido)-but-2-enyl 2′,2′,2′-trichloroacetimidate (14). Following the procedure described for the preparation of (*E*)-**11a**, alcohol **50** (193 mg, 0.579 mmol) was treated with DBU and Cl_3CCN. After 1 h, the reaction mixture was concentrated in vacuo and the residue was

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purified by flash chromatography (99.5:0.5:1 CH_2Cl_2−acetone−Et_3N) to provide imidate **14** (249 mg, 0.521 mmol, 90%) as a pale yellow oil: ^{1}H NMR (500 MHz, DMSO) δ 9.57 (br s, 1H), 9.25 (br s, 1H), 7.57 (d, J = 8.2, 2H), 7.35 (d, J = 8.2, 2H), 7.10 (td, J = 8.1, 1.3, 1H), 6.92 (d, J = 7.8, 1H), 6.79 (d, J = 8.1, 1H), 6.70 (t, J = 7.7, 1H), 5.78−5.68 (m, 2H), 4.62 (d, J = 4.5, 2H), 4.19 (d, J = 4.0, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 159.7 (C), 154.9 (C), 142.8 (C), 137.2 (C), 132.0 (CH), 129.6 (CH), 129.4 (CH), 129.3 (CH), 127.3 (CH), 126.6 (CH), 124.8 (C), 118.7 (CH), 116.5 (CH), 90.7 (C), 67.6 (CH_2), 50.6 (CH_2), 21.0 (CH_3); IR (thin film) 3436, 3336, 2924, 1664, 1344, 1090 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{19}Cl_3N_2O_4SNa$, $(M + Na)^+$ 499.0029, found 499.0024.

(*E*)-*tert*-Butyldimethyl(3-methyl-4-(2-triisopropylsilyloxy)-phenoxy)but-2-enyloxy)silane (54). In a 200-mL round-bottomed flask, PPh_3 (1.34 g, 5.11 mmol) was added to a mixture of 2-((triisopropylsilyl)oxy)phenol (**52**) (1.30 g, 4.87 mmol), (*E*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-ol (**53**)[39] (1.12 mg, 5.17 mmol), and diethyl azodicarboxylate (40% in toluene, 2.3 mL, 5.2 mmol) in THF (54 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature. After 3 h, the reaction mixture was concentrated in vacuo to give a residue that was purified by flash chromatography (99.5:0.5 to 98.5:1.5 pentane−Et_2O) to provide ether **54** (1.61 g, 3.17 mmol, 65%) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90−6.86 (m, 3H), 6.83−6.81 (m, 1H), 5.72 (m, 1H), 4.41 (s, 2H), 4.28 (d, J = 6.2, 2H), 1.77 (s, 3H), 1.32−1.26 (m, 3H), 1.13 (d, J = 6.1, 18H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3 (C), 145.9 (C), 132.6 (C), 128.3 (CH), 121.4 (CH), 121.1 (CH), 120.5 (CH), 114.2 (CH), 74.3 (CH_2), 60.1 (CH_2), 26.1 (CH_3), 18.1 (C, CH_3), 14.3 (CH_3), 13.0 (CH), −5.0 (CH_3); IR (thin film) 3064, 2947, 1267, 1116, 1073, 921 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{48}O_3Si_2Na$, $(M + Na)^+$ 487.3040, found 487.3038.

(*E*)-2-(4-Hydroxy-2-methylbut-2-enyloxy)phenol (55). A 50-mL round-bottomed flask was charged with bis-silyl ether **54** (1.61 g, 3.17 mmol) and THF (16 mL), and then TBAF (1.0 M in THF, 7.0 mL, 7.0 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, and then the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (94:6 CH_2Cl_2−acetone) to provide diol **55** (616 mg, 3.17 mmol, 100%) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, J = 7.7, 1H), 6.94−6.80 (m, 3H), 6.23 (br s, 1H), 5.77 (t, J = 6.6, 1H), 4.44 (s, 2H), 4.23 (d, J = 6.9, 2H), 2.60 (br s, 1H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9 (C), 145.8 (C), 133.8 (C), 127.2 (CH), 121.8 (CH), 120.1 (CH), 115.1 (CH), 112.5 (CH), 73.8 (CH_2), 58.8 (CH_2), 14.0 (CH_3); IR (thin film) 3418, 2924, 1679, 1596, 845 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{14}O_3Na$, $(M + Na)^+$ 217.0841, found 217.0841.

(*E*)-4-(2-Hydroxyphenoxy)-3-methylbut-2-enyl 2′,2′,2′-trichloroacetimidate (15). Following the procedure described for the preparation of (*E*)-**11a**, alcohol **55** (26 mg, 0.13 mmol) was treated with DBU and Cl_3CCN. After 5 min, the reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (97.5:1.5:1 CH_2Cl_2−acetone−Et_3N) to provide imidate **15** (41 mg, 0.12 mmol, 91%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (br s, 1H), 6.95 (dd, J = 7.8, 1.5, 1H), 6.91−6.80 (m, 3H), 5.88−5.85 (m, 1H), 5.64 (s, 1H), 4.91 (d, J = 6.7, 2H), 4.54 (s, 2H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 (C), 145.9 (C), 145.6 (C), 137.3 (C), 121.9 (CH), 121.4 (CH), 120.11 (CH), 115.0 (CH), 112.4 (CH), 91.4 (C), 73.6 (CH_2), 65.4 (CH_2), 14.3 (CH_3); IR (thin film) 3414, 3337, 2923, 1662, 1501, 988 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{14}Cl_3NO_3Na$, $(M + Na)^+$ 359.9937, found 359.9928.

(*E*)-2-(4-(Tetrahydro-2*H*-pyran-2-yloxy)but-2-enylthio)-phenol (49). Following the procedure described for the preparation of **48**, 2-mercaptophenol (**46**) (902 mg, 7.15 mmol) was alkylated using (*E*)-2-((4-bromobut-2-en-1-yl)oxy)tetrahydro-2*H*-pyran (**47**).[38] After 24 h, water (20 mL) and brine (10 mL) were added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a residue that was purified by flash chromatography (70:30 hexanes−Et_2O) to provide thioether **49** (319 mg, 1.14 mmol, 80%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, J = 7.7, 1.6, 1H), 7.28−7.23 (m, 1H), 6.98 (dd, J = 8.1, 1.1, 1H), 6.88−6.84 (m, 1H), 6.68 (s, 1H), 5.73 (dt, J = 15.2, 7.5, 1H), 5.41 (dt, J = 15.2, 5.5, 1H), 4.56 (t, J = 2.9, 1H), 4.11 (dd, J = 12.9, 4.8, 1H), 3.89 (dd, J = 13.0, 6.3, 1H), 3.83 (td, J = 11.0, 3.0, 1H), 3.52−3.46 (m, 1H), 3.32 (d, J = 7.5, 2H), 1.85−1.79 (m, 1H), 1.73−1.68 (m, 1H), 1.62−1.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3 (C), 136.7 (CH), 136.4 (C), 131.5 (CH), 130.7 (CH), 127.6 (CH), 120.8 (CH), 114.9 (CH), 97.8 (CH), 66.7 (CH_2), 62.2 (CH_2), 38.8 (CH_2), 30.7 (CH_2), 25.6 (CH_2), 19.5 (CH_2); IR (thin film) 3404, 2940, 1470, 1119, 966 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{20}O_3SNa$, $(M + Na)^+$ 303.1031, found 303.1029.

(*E*)-2-(4-Hydroxybut-2-enylthio)phenol (51). In a 25-mL round-bottomed flask, protected alcohol **49** (319 mg, 1.14 mmol) and *p*-TsOH·H_2O (43 mg, 0.23 mmol) were dissolved in MeOH (9.5 mL), and the solution was refluxed for 6 h and then allowed to cool to room temperature. After 18 h, the solvent was removed in vacuo, and the residue was purified by flash chromatography to yield alcohol **51** (142 mg, 0.723 mmol, 64%) as a clear colorless oil. ^{1}H NMR data were consistent with those previously reported.[40]

(*E*)-4-(2-Hydroxyphenylthio)but-2-enyl 2′,2′,2′-trichloroacetimidate (16). Following the procedure described for the preparation of (*E*)-**11a**, alcohol **51** (132 mg, 0.673 mmol) was treated with DBU and Cl_3CCN. After 5 min, the reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (98.5:0.5:1 CH_2Cl_2−acetone−Et_3N) to provide imidate **16** (191 mg, 0.563 mmol, 84%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.42 (dd, J = 7.7, 1.4, 1H), 7.29−7.25 (m, 1H), 6.99 (d, J = 8.2, 1H), 6.86 (t, J = 7.6, 1H), 6.66 (s, 1H), 5.87 (dt, J = 15.3, 7.5, 1H), 5.48 (dt, J = 15.3, 5.8, 1H), 4.69 (d, J = 5.8, 2H), 3.33 (d, J = 7.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4 (C), 157.3 (C), 136.7 (CH), 131.5 (CH), 129.8 (CH), 127.0 (CH), 120.7 (CH), 117.7 (C), 114.9 (CH), 91.4 (C), 68.6 (CH_2), 38.4 (CH_2); IR (thin film) 3408, 3337, 2916, 1662, 1470, 984 cm^{-1}; HRMS (GC−MS) m/z calcd for $C_{12}H_{16}Cl_3N_2O_2S$, $(M + NH_4)^+$ 356.9998, found 357.0004.

(*E*)-5-(2-Hydroxyphenyl)pent-2-enyl acetate ((*E*)-19a). In a 25-mL round-bottomed flask, alcohol (*E*)-**36** (700 mg, 3.93 mmol) in THF (5.9 mL) was cooled to 0 °C, and then acetic anhydride (1.1 mL, 12 mmol) was added via syringe. BF_3·OEt_2 (0.12 mL, 0.98 mmol) was added via syringe, and the solution was maintained at 0 °C. After 1.5 h, cold aqueous $NaHCO_3$ (5% solution, 10 mL) was added, the mixture was stirred for 2 min, extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a residue that was purified by flash chromatography (80:20 hexanes−Et_2O) to give acetate (*E*)-**19a** (691 mg, 3.14 mmol, 80%) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12−7.08 (m, 2H), 6.87 (t, J = 7.4, 1H), 6.76 (d, J = 7.9, 1H), 5.86 (dt, J = 15.4, 7.7, 1H), 5.61 (dt, J = 15.4, 6.6, 1H), 5.16 (br s, 1H), 4.53 (d, J = 6.5, 2H), 2.72 (t, J = 7.4, 2H), 2.41−2.37 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (C), 153.7 (C), 135.9 (CH), 130.4 (CH), 127.8 (C), 127.4 (CH), 124.4 (CH), 120.9 (CH), 115.5 (CH), 65.4 (CH_2), 32.5 (CH_2), 30.0 (CH_2), 21.2 (CH_3); IR (thin film) 3411, 2925, 1739, 1672, 1235, 965 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{16}O_3Na$, $(M + Na)^+$ 243.0997, found 243.0992.

(*Z*)-5-(2-Hydroxyphenyl)pent-2-enyl acetate ((*Z*)-19a). Following the procedure described for the preparation of (*E*)-**19a**, alcohol (*Z*)-**36** (100 mg, 0.561 mmol) was acetylated using acetic anhydride (0.16 mL, 1.7 mmol) to give a residue that was purified by flash chromatography (80:20 hexanes−Et_2O) to provide acetate (*Z*)-**19a** (93 mg, 0.42 mmol, 75%) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11−7.08 (m, 2H), 6.88 (t, J = 7.4, 1H), 6.80 (d, J = 7.7, 1H), 5.78−5.68 (br m, 2H), 5.58−5.53 (m, 1H), 4.59 (d, J = 7.2, 2H), 2.69 (t, J = 7.4, 2H), 2.45 (app q, J = 8.0, 2H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6 (C), 154.0 (C), 134.8 (CH), 130.5 (CH), 127.6 (CH), 127.4 (C), 123.9 (CH), 120.7 (CH), 115.7 (CH), 60.5 (CH_2), 30.4 (CH_2), 28.1 (CH_2), 21.2 (CH_3); IR (thin film) 3306, 3026, 2929, 1731, 1609, 754 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{16}O_3Na$, $(M + Na)^+$ 243.0997, found 243.0997.

(*E*)-5-(5-Bromo-2-hydroxyphenyl)pent-2-enyl acetate ((*E*)-19b). Following the procedure described for the preparation of (*E*)-

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19a, allylic alcohol (*E*)-**40** (100 mg, 0.389 mmol) was acetylated using acetic anhydride (0.11 mL, 1.2 mmol) to give a residue that was purified by flash chromatography (80:20 to 75:25 pentane−Et_2O) to provide acetate (*E*)-**19b** (89 mg, 0.30 mmol, 77%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.18−7.16 (m, 1H), 6.65 (d, J = 8.4, 1H), 5.82 (dt, J = 15.4, 6.8, 1H), 5.59 (dt, J = 15.4, 6.5, 1H), 5.28 (br s, 1H), 4.52 (d, J = 6.4, 2H), 2.68 (t, J = 7.4, 2H), 2.36 (app q, J = 7.3, 2H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (C), 152.9 (C), 135.3 (CH), 133.0 (CH), 130.4 (C), 130.0 (CH), 124.8 (CH), 117.2 (CH), 112.8 (C), 65.4 (CH_2), 32.3 (CH_2), 29.5 (CH_2), 21.2 (CH_3); IR (thin film) 3459, 3021, 2924, 1710, 1269, 966 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{15}BrO_3Na$, $(M + Na)^+$ 321.0102, found 321.0105.

(*E*)-5-(2-Hydroxy-5-methoxyphenyl)pent-2-enyl acetate ((*E*)-19c). Following the procedure described for the preparation of (*E*)-**19a**, allylic alcohol (*E*)-**42** (60 mg, 0.29 mmol) was acetylated using acetic anhydride (54 μL, 0.58 mmol) to give a residue that was purified by flash chromatography (90:10 hexanes−EtOAc) to provide acetate (*E*)-**19c** (52 mg, 0.21 mmol, 72%) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71−6.62 (m, 3H), 5.85 (dt, J = 15.3, 6.7, 1H), 5.60 (dt, J = 15.3, 6.4, 1H), 4.60 (br s, 1H), 4.52 (d, J = 6.4, 2H), 3.76 (s, 3H), 2.69 (t, J = 7.5, 2H), 2.38 (app q, J = 7.2, 2H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2 (C), 153.8 (C), 147.6 (C), 135.7 (CH), 129.1 (C), 124.6 (CH), 116.2 (CH), 116.0 (CH), 112.0 (CH), 65.4 (CH_2), 55.8 (CH_3), 32.6 (CH_2), 30.0 (CH_2), 21.2 (CH_3); IR (thin film) 3397, 3028, 2917, 1708, 1611, 801 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{18}O_4Na$, $(M + Na)^+$ 273.1103, found 273.1109.

Synthesis of Deuterium-Labeled Cyclization Precursors (*E*)-1-*d*-11a and (*E*)-1-*d*-19a. *tert*-Butyl (2-(4,4-dibromobut-3-enyl)phenoxy)dimethylsilane (56). A. 250-mL round-bottomed flask was charged with alcohol **34** (12.0 g, 39.2 mmol). Dimethylformamide (26 mL) was added by syringe, followed by imidazole (5.34 g, 78.4 mmol), then TBSCl (6.80 g, 45.1 mmol). The reaction mixture was stirred for 2 h, then water (100 mL) was added. The resulting mixture was extracted with Et_2O (4 × 75 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and then concentrated in vacuo to give a light yellow residue that was purified by flash chromatography (99.75:0.25 hexanes−Et_2O) to provide silyl ether **56** (14.2 g, 33.7 mmol, 86%) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16−7.11 (m, 2H), 6.94 (t, J = 6.6, 1H), 6.83 (d, J = 8.0, 1H), 6.44 (t, J = 7.1, 1H), 2.75 (t, J = 7.5, 2H), 2.42 (app q, J = 7.5, 2H), 1.06 (s, 9H), 0.29 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8 (C), 138.3 (CH), 131.2 (C), 130.4 (CH), 127.5 (CH), 121.3 (CH), 118.6 (CH), 89.1 (C), 33.6 (CH_2), 28.8 (CH_2), 26.0 (CH_3), 18.4 (C), −4.0 (CH_3); IR (thin film) 3020, 2955, 1600, 922, 810 cm^{-1}; HRMS (CI) m/z calcd for $C_{16}H_{28}Br_2NOSi$, $(M + NH_4)^+$ 436.0307, found 436.0291.

Methyl 5-(2-(*tert*-butyldimethylsilyloxy)phenyl)pent-2-ynoate (57). Using a modification of a procedure by Kinoshita,[33] a solution of bromide **56** (14.2 g, 33.7 mmol) in THF (110 mL) was cooled to −78 °C in a 1-L round-bottomed flask. A solution of *n*-BuLi in hexane (1.6 M, 52 mL, 84 mmol) was added to the clear solution via syringe over 20 min. The pale yellow reaction mixture was stirred at −78 °C for 30 min, and then methyl chloroformate (7.80 mL, 101 mmol) was added via syringe over 5 min. The reaction mixture was allowed to warm to 0 °C, stirred for 10 min, and then allowed to warm to ambient temperature and stirred for 15 min. Saturated aqueous NH_4Cl (120 mL) was added, and the resulting mixture was extracted with Et_2O (3 × 75 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a pale yellow residue that was purified by flash chromatography (99:1 hexanes−Et_2O) to provide ynoate **57** (10.6 g, 33.3 mmol, 99%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 7.5, 1H), 7.14−7.11 (m, 1H), 6.91 (t, J = 7.5, 1H), 6.80 (d, J = 8.1, 1H), 3.76 (s, 3H), 2.88 (t, J = 7.7, 2H), 2.61 (t, J = 7.7, 2H), 1.03 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4 (C), 153.7 (C), 130.5 (CH), 130.2 (C), 127.9 (CH), 121.2 (CH), 118.5 (CH), 89.5 (C), 73.2 (C), 52.7 (CH_3), 29.4 (CH_2), 25.9 (CH_3), 19.3 (CH_2), 18.3 (C), −4.0 (CH_3); IR (thin film) 3011, 2931, 2239, 1718, 1435, 1108 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{26}O_3SiNa$, $(M + Na)^+$ 341.1549, found 341.1544.

5-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-1,1-dideuteropent-2-yn-1-ol (58). In a 1-L round-bottomed flask, a solution of ynoate **57** (9.0 g, 28 mmol) in Et_2O (140 mL) was cooled to 0 °C. Lithium aluminum deuteride (1.76 g, 42.0 mmol) was added portionwise over 30 min, and gas evolution was observed. After the reaction mixture was stirred at 0 °C for 45 min, water (50 mL) was added slowly, followed by aqueous NaOH solution (0.1 N, 20 mL), followed by more water (50 mL). The resulting mixture was allowed to warm to ambient temperature, extracted with Et_2O (4 × 75 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a residue that was purified by flash chromatography (90:10 hexanes−EtOAc) to provide propargyl alcohol **58** (6.23 g, 21.1 mmol, 75%) as a clear colorless oil. Analysis by electrospray mass spectrometry indicated a 327:5:1 ratio of d_2-**58**:d_1-**58**:d_0-**58**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 7.5, 1H), 7.13−7.10 (m, 1H), 6.91 (t, J = 7.4, 1H), 6.81 (d, J = 8.1, 1H), 2.83 (t, J = 7.7, 2H), 2.50 (t, J = 7.6, 2H), 1.05 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 131.2 (C), 130.5 (CH), 127.5 (C), 121.1 (CH), 118.5 (CH), 86.2 (C), 78.8 (C), 50.9 (quintet, J_{CD} = 22.4, CD_2), 30.3 (CH_2), 26.0 (CH_2), 19.4 (CH_3), 18.3 (C), −4.0 (CH_3); IR (thin film) 3243, 3030, 2929, 2248, 1453, 1175 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{24}D_2O_2SiNa$, $(M + Na)^+$ 315.1725, found 315.1725.

(*Z*)-5-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-1,1-dideuteropent-2-en-1-ol (59). Following the procedure described for the preparation of (*Z*)-**36**,[35] propargyl alcohol **58** (3.65 g, 12.5 mmol) was reduced using catalytic $Ni(OAc)_2{\cdot}4H_2O$ (466 mg, 1.87 mmol) to give a residue that was purified by filtering the reaction mixture through a short pad of silica gel using EtOH as the eluent. The organic layer was concentrated in vacuo to yield alkene **59** (3.68 g, 12.5 mmol, 100%) as a pale yellow oil. Analysis by electrospray mass spectrometry indicated a 226:4:1 ratio of d_2-**59**:d_1-**59**:d_0-**59**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13−7.08 (m, 2H), 6.90 (t, J = 7.4, 1H), 6.82 (d, J = 7.9, 1H), 5.61−5.59 (m, 2H), 2.69 (t, J = 7.5, 2H), 2.39 (app q, J = 7.2, 2H), 1.05 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 132.1 (CH), 132.1 (C), 130.7 (CH), 129.1 (C), 127.2 (CH), 120.9 (CH), 118.5 (CH), 57.8 (quintet, J_{CD} = 21.5, CD_2), 30.5 (CH_2), 27.8 (CH_2), 25.9 (CH_3), 18.3 (C), −4.0 (CH_3); IR (thin film) 3338, 3017, 2930, 1107, 755, 701 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{26}D_2O_2SiNa$, $(M + Na)^+$ 317.1882, found 317.1884.

(*Z*)-5-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-1-deuteropent-2-enal ((*Z*)-60). In a 100-mL round-bottomed flask, a solution of **59** (1.0 g, 3.4 mmol) in CH_2Cl_2 (34 mL) was cooled to 0 °C. *N*,*N*-Diisopropylethylamine (4.1 mL, 24 mmol) was added via syringe, and the solution was maintained at 0 °C for 10 min. DMSO (2.4 mL, 34 mmol) was added via syringe, the solution was maintained at 0 °C for 10 min, and then SO_3·pyridine (2.16 g, 13.6 mmol) was added in a single portion. The reaction mixture was stirred at 0 °C for 45 min, saturated aqueous $NaHCO_3$ (40 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with water (2 × 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a pale yellow residue. After azeotropic removal of pyridine with toluene (2 × 100 mL), the residue (988 mg, 3.37 mmol, 99%, 90:10 *Z*:*E* by ^{1}H NMR analysis) was carried directly to the next synthetic step. Analysis by electrospray mass spectrometry indicated a >96:4 ratio of d_1-(*Z*)-**60**:d_0-(*Z*)-**60**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13−7.05 (m, 2H), 6.89 (t, J = 7.3, 1H), 6.82 (d, J = 8.3, 1H), 6.69−6.63 (m, 1H), 5.94 (d, J = 11.2, 1H), 2.89 (app q, J = 7.5, 2H), 2.81 (t, J = 7.3, 2H), 1.03 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6 (t, J_{CD} = 25.7, CDO), 153.7 (C), 152.3 (CH), 130.6 (CH), 130.6 (C), 130.5 (CH), 127.7 (CH), 121.2 (CH), 118.6 (CH), 30.3 (CH_2), 28.4 (CH_2), 25.9 (CH_3), 18.3 (C), −4.0 (CH_3); IR (thin film) 3023, 2955, 2857, 1668, 1252, 927 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{25}DO_2SiNa$, $(M + Na)^+$ 314.1663, found 314.1659.

(*E*)-5-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-1-deuteropent-2-enal ((*E*)-60). In a 25-mL round-bottomed flask, (*Z*)-**60** (938 mg, 3.22 mmol) was dissolved in hexanes (10 mL). Silica gel (500 mg) and pyridine (0.20 mL, 2.5 mmol) were added in a single portion and the slurry was stirred at ambient temperature for 15 h. The reaction

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mixture was filtered and concentrated in vacuo, then pyridine was azeotropically removed with toluene (2 × 25 mL) to give aldehyde (*E*)-**60** (938 mg, 3.22 mmol, 100%, >20:1 *E*:*Z* by ^{1}H NMR analysis) as a clear colorless oil. Analysis by electrospray mass spectrometry indicated a >96:4 ratio of d_1-(*E*)-**60**:d_0-(*E*)-**60**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13−7.10 (m, 2H), 6.91−6.82 (m, 2H), 6.81 (d, J = 7.8, 1H), 6.14 (d, J = 15.5, 1H), 2.80 (t, J = 7.3, 2H), 2.63 (app q, J = 6.8, 2H), 1.02 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9 (t, J_{CD} = 26.3, CDO), 158.2 (CH), 153.7 (C), 133.1 (t, J_{CD} = 3.8, CH), 131.0 (C), 130.2 (CH), 127.6 (CH), 121.3 (CH), 118.6 (CH), 33.1 (CH_2), 29.2 (CH_2), 25.9 (CH_3), 18.3 (C), −4.0 (CH_3); IR (thin film) 3033, 2930, 2857, 1711, 1491, 1146 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{25}DO_2SiNa$, $(M + Na)^+$ 314.1663, found 314.1655.

(*S*,*E*)-5-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-1-deutero-pent-2-en-1-ol ((*E*)-61).[31] Using a modification of a procedure by Keck,[19] titanium isopropoxide (89 μL, 0.32 mmol) was added to a stirring mixture of (*R*)-BINOL (184 mg, 0.644 mmol), trifluoroacetic acid (0.5 M in CH_2Cl_2, 0.13 mL, 0.064 mmol), molecular sieves (4 Å, 1.7 g), and diethyl ether (12 mL) in a 100-mL round-bottomed flask. The red-orange mixture was heated to reflux for 1 h and allowed to cool to room temperature, and α,β-unsaturated aldehyde (*E*)-**60** (938 mg, 3.22 mmol) in Et_2O (10 mL) was added. The resulting mixture was stirred at room temperature for 10 min and then cooled to −78 °C, and Bu_3SnH (1.0 mL, 3.9 mmol) was added dropwise. The reaction mixture was then transferred to a −20 °C freezer and left for 18 h, without stirring. The mixture was removed from the freezer, and saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was stirred for 1 h at room temperature and then filtered through a pad of Celite. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with water (2 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a residue that was purified by flash chromatography (88:12 hexanes−Et_2O) to provide allylic alcohol (*E*)-**61** (488 mg, 1.67 mmol, 62% brsm) as a clear colorless oil. A modified Mosher's ester analysis[12] of the product showed it to be of 65% enantiomeric excess and predominantly the (*S*) enantiomer. Analysis by electrospray mass spectrometry indicated a >96:4 ratio of d_1-(*E*)-**61**:d_0-(*E*)-**61**: $[\alpha]_D^{23}$ −2.7, $[\alpha]_{577}^{24}$ −3.6, $[\alpha]_{546}^{24}$ −3.8, $[\alpha]_{435}^{24}$ −3.3, (c = 0.33, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, J = 7.4, 1H), 7.08 (t, J = 7.9, 1H), 6.88 (t, J = 7.3, 1H), 6.79 (d, J = 7.9, 1H), 5.75 (dt, J = 15.5, 6.5, 1H), 5.66 (dd, J = 15.4, 5.8, 1H), 4.07 (br s, 1H), 2.68 (t, J = 7.6, 2H), 2.34 (app q, J = 7.8, 2H), 1.03 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 133.1 (CH), 132.4 (C), 130.4 (CH), 129.4 (CH), 127.1 (CH), 121.1 (CH), 118.5 (CH), 63.6 (t, J_{CD} = 22.5, CDH), 32.8 (CH_2), 30.5 (CH_2), 26.0 (CH_3), 18.4 (C), −4.0 (CH_3); IR (thin film) 3338, 3022, 2929, 1105, 755, 701 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{27}DO_2SiNa$, $(M + Na)^+$ 316.1819, found 316.1818.

(*S*,*E*)-2-(5-Deutero-5-hydroxypent-3-enyl)phenol ((*E*)-62). In a 25-mL round-bottomed flask, silyl ether (*E*)-**61** (468 mg, 1.59 mmol) was dissolved in THF (8.0 mL). A solution of TBAF (1.0 M in THF, 1.9 mL, 1.9 mmol) was added via syringe. After 18 h, the reaction mixture was concentrated in vacuo to give a pale yellow residue that was purified by flash chromatography (90:10 to 85:15 CH_2Cl_2−acetone) to provide diol (*E*)-**62** (285 mg, 1.59 mmol, 100%) as a clear colorless oil. Analysis by electrospray mass spectrometry indicated a >96:4 ratio of d_1-(*E*)-**62**:d_0-(*E*)-**62**: $[\alpha]_D^{24}$ −8.3, $[\alpha]_{577}^{24}$ −8.5, $[\alpha]_{546}^{24}$ −10.7, $[\alpha]_{435}^{24}$ −3.9, (c = 0.11, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12−7.06 (m, 2H), 6.86 (t, J = 7.9, 1H), 6.78 (d, J = 7.7, 1H), 6.62 (br s, 1H), 5.77 (dt, J = 15.4, 6.5, 1H), 5.65 (dd, J = 15.5, 5.8, 1H), 4.07 (d, J = 5.4, 1H), 2.72 (t, J = 7.8, 2H), 2.51 (br s, 1H), 2.38 (app q, J = 7.2, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0 (C), 133.4 (CH), 130.3 (CH), 128.8 (CH), 128.2 (C), 127.3 (CH), 120.5 (CH), 115.5 (CH), 63.4 (t, J_{CD} = 21.3, CDH), 32.5 (CH_2), 29.8 (CH_2); IR (thin film) 3336, 3070, 2922, 1180, 1042, 973 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{13}DO_2Na$, $(M + Na)^+$ 202.0954, found 202.0951.

(*S*,*E*)-1-Deutero-5-(2-hydroxyphenyl)pent-2-enyl 2′,2′,2′-trichloroacetimidate ((*E*)-1-*d*-11a). Following the procedure described for the preparation of (*E*)-**11a**, alcohol (*E*)-**62** (100 mg, 0.558 mmol) was treated with DBU and Cl_3CCN. After 30 min, the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (97:2:1 toluene−acetone−Et_3N) to provide imidate (*E*)-**1-*d*-11a** (101 mg, 0.312 mmol, 56%) as a pale yellow oil. Analysis by electrospray mass spectrometry indicated a >96:4 ratio of d_1-(*E*)-**1-*d*-11a**:d_0-(*E*)-**1-*d*-11a**: $[\alpha]_D^{24}$ −43.8, $[\alpha]_{577}^{24}$ −40.2, $[\alpha]_{546}^{23}$ −27.2, $[\alpha]_{435}^{23}$ −24.6, (c = 0.17, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.13−7.08 (m, 2H), 6.88 (t, J = 7.5, 1H), 6.76 (d, J = 8.0, 1H), 5.96 (dt, J = 15.4, 6.7, 1H), 5.86 (br s, 1H), 5.73 (dd, J = 15.5, 6.1, 1H), 4.76 (d, J = 5.4, 1H), 2.75 (t, J = 7.8, 2H), 2.43 (app q, J = 7.3, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 (C), 153.8 (C), 136.4 (CH), 130.4 (CH), 127.9 (C), 127.3 (CH), 123.4 (CH), 120.7 (CH), 115.4 (CH), 91.6 (C), 69.9 (t, J_{CD} = 21.3, CDH), 32.5 (CH_2), 29.6 (CH_2); IR (thin film) 3332, 3036, 2928, 1660, 1593, 972 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{13}DCl_3NO_2Na$, $(M + Na)^+$ 345.0051, found 345.0056.

(*S*,*E*)-1-Deutero-5-(2-hydroxyphenyl)pent-2-enyl acetate ((*E*)-1-*d*-19a). Following the procedure described for the preparation of acetate (*E*)-**19a**, allylic alcohol (*E*)-**62** (50 mg, 0.28 mmol) was acetylated using acetic anhydride (80 μL, 0.84 mmol) to give a residue that was purified by flash chromatography (85:15 to 80:20 pentane-Et_2O) to provide acetate (*E*)-**1-*d*-19a** (55 mg, 0.25 mmol, 89%) as a clear colorless oil. Analysis by electrospray mass spectrometry indicated a >96:4 ratio of d_1-(*E*)-**1-*d*-19a**:d_0-(*E*)-**1-*d*-19a**: $[\alpha]_D^{25}$ −16.8, $[\alpha]_{577}^{25}$ −18.4, $[\alpha]_{546}^{25}$ −15.3, (c = 0.16, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12−7.06 (m, 2H), 6.88 (t, J = 7.4, 1H), 6.76 (d, J = 7.9, 1H), 5.86 (dt, J = 15.6, 6.5, 1H), 5.60 (dd, J = 15.6, 6.4, 1H), 4.74 (br s, 1H), 4.50 (d, J = 5.8, 1H), 2.72 (t, J = 7.5, 2H), 2.39 (app q, J = 7.0, 2H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2 (C), 153.6 (C), 135.9 (CH), 130.4 (CH), 127.8 (C), 127.4 (CH), 124.5 (CH), 121.0 (CH), 115.5 (CH), 65.1 (t, J_{CD} = 21.3, CDH), 32.6 (CH_2), 29.7 (CH_2), 21.2 (CH_3); IR (thin film) 3408, 3035, 2918, 1708, 1242, 969 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{15}DO_3Na$, $(M + Na)^+$ 244.1060, found 244.1054.

(*S*,*E*)-5-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-1-deutero-pent-2-enyl (*R*)-3′,3′,3′-trifluoro-2′-methoxy-2′-phenylpropanoate ((1*S*,2′*R*)-(*E*)-63). In a 5-mL round-bottomed flask, allylic alcohol (*E*)-**61** (5 mg, 0.02 mmol), DMAP (0.2 mg, 0.002 mmol), and (*R*)-2-trifluoromethyl-2-methoxy-2-phenylacetic acid (5 mg, 0.02 mmol) were dissolved in CH_2Cl_2 (0.34 mL). *N*,*N*′- Dicyclohexylcarbodiimide (5 mg, 0.02 mmol) was added at room temperature, and the reaction mixture was stirred for 18 h. Saturated aqueous $NaHCO_3$ (1 mL) was added, and the resulting mixture was extracted with Et_2O (3 × 0.5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a residue that was purified by flash chromatography (95:5 pentane-Et_2O). The ester product (7 mg, 0.01 mmol, 80%) was obtained as a 82.5:17.5 mixture of (**1*S*,2′*R***)-(*E*)-**63**:(**1*R*,2′*R***)-(*E*)-**63** as a clear colorless oil. Analysis by electrospray mass spectrometry indicated a >96:4 ratio of d_1-(**1*S*,2′*R***)-(*E*)-**63**:d_0-(**1*S*,2′*R***)-(*E*)-**63**. Major diastereomer (**1*S*,2′*R***)-(*E*)-**63**: $[\alpha]_D^{25}$ 28.1, $[\alpha]_{577}^{25}$ 28.7, $[\alpha]_{546}^{25}$ 31.9, (c = 1.10, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53−7.52 (m, 2H), 7.41−7.40 (m, 3H), 7.10−7.06 (m, 2H), 6.87 (d, J = 6.7, 1H), 6.78 (d, J = 7.9, 1H), 5.90 (dt, J = 15.3, 6.7, 1H), 5.62 (dd, J = 15.4, 6.6, 1H), 4.71 (d, J = 6.5, 1H), 3.55 (s, 3H), 2.67 (t, J = 7.5, 2H), 2.35 (app q, J = 7.1, 2H), 1.01 (s, 9H), 0.24 (s, 6H); ^{2}H NMR (61 MHz, $CDCl_3$) δ 4.81 (s, ^{1}²H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5 (C), 153.7 (C), 138.0 (CH), 132.5 (C), 132.0 (C), 130.3 (CH), 129.7 (CH), 128.5 (CH), 127.5 (CH), 127.2 (CH), 124.6 (C), 122.8 (CH), 122.3 (C), 121.1 (CH), 118.5 (CH), 66.8 (t, J_{CD} = 23.5, CDH), 55.6 (CH_3), 32.7 (CH_2), 30.2 (CH_2), 25.9 (CH_3), 18.3 (C), −4.0 (CH_3); IR (thin film) 3034, 2930, 1748, 1453, 1253, 1169 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{34}DF_3O_4SiNa$, $(M + Na)^+$ 532.2217, found 532.2202.

(*S*,*E*)-5-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-1-deutero-pent-2-enyl (*S*)-3′,3′,3′-trifluoro-2′-methoxy-2′-phenylpropanoate ((1*S*,2′*S*)-(*E*)-63). Following the procedure described for the preparation of (**1*S*,2′*R***)-(*E*)-**63**, allylic alcohol (*E*)-**61** (5 mg, 0.02 mmol) was acylated using (*S*)-2-trifluoromethyl-2-methoxy-2-phenylacetic acid (5 mg, 0.02 mmol) to give a residue that was purified by flash chromatography (95:5 pentane-Et_2O). The ester product (6 mg, 0.01 mmol, 69%) was obtained as a 82.5:17.5 mixture of (**1*S*,2′*S***)-(*E*)-

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63:(1*R*,2′*S*)-(*E*)-**63** as a clear colorless oil. Analysis by electrospray mass spectrometry indicated a >96:4 ratio of d_1-(1*S*,2′*S*)-(*E*)-**63**:d_0-(1*S*,2′*S*)-(*E*)-**63**. Major diastereomer (1*S*,2′*S*)-(*E*)-**63**: $[\alpha]_D^{25}$ −28.6, $[\alpha]_{577}^{25}$ −30.8, $[\alpha]_{546}^{24}$ −35.7, (*c* = 1.60, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.52 (m, 2H), 7.41−7.40 (m, 3H), 7.10−7.06 (m, 2H), 6.87 (d, *J* = 7.3, 1H), 6.79 (d, *J* = 7.9, 1H), 5.90 (dt, *J* = 15.3, 6.6, 1H), 5.62 (dd, *J* = 15.3, 6.5, 1H), 4.77 (d, *J* = 6.2, 1H), 3.55 (s, 3H), 2.67 (t, *J* = 7.5, 2H), 2.35 (app q, *J* = 7.0, 2H), 1.01 (s, 9H), 0.24 (s, 6H); ^{2}H NMR (61 MHz, $CDCl_3$) δ 4.74 (s, 1^2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5 (C), 153.7 (C), 138.0 (CH), 132.5 (C), 132.0 (C), 130.3 (CH), 129.7 (CH), 128.5 (CH), 127.5 (CH), 127.2 (CH), 124.6 (C), 122.8 (CH), 122.3 (C), 121.1 (CH), 118.5 (CH), 66.8 (t, J_{CD} = 21.9, CDH), 55.6 (CH_3), 32.7 (CH_2), 30.2 (CH_2), 25.9 (CH_3), 18.4 (C), −4.0 (CH_3); IR (thin film) 3032, 2930, 1748, 1453, 1254, 1169 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{34}DF_3O_4SiNa$, $(M + Na)^+$ 532.2217, found 532.2198.

■ ASSOCIATED CONTENT

Supporting Information

General experimental methods, tables of additional optimization experiments and reaction of imidate **16** with $Pd(OAc)_2$, synthetic schemes for the synthesis of cyclization precursors, ^{1}H and ^{13}C NMR data for new compounds, and copies of chromatography traces used to determine enantiomeric purity. General computational details, calculated close contacts in transition structures **22**, **25**, **28**, and **31**, three-dimensional models of **28** and **31**, and *XYZ* coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(25) For further computational details, see the Supporting Information.
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