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Nucleophilic Substitution Reactions of Sulfur-Substituted Cyclohexanone Acetals: An Analysis of the Factors Controlling Stereoselectivity

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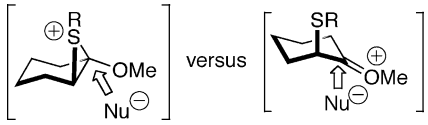
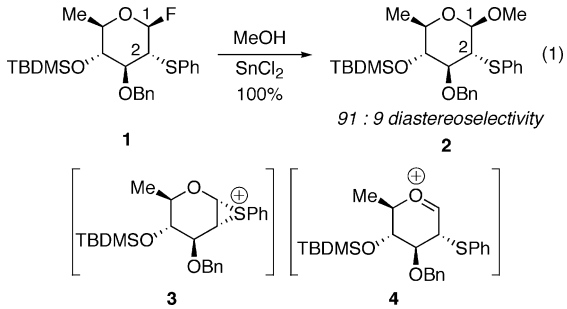


The reactions of cyclohexanone acetals substituted with thiophenyl groups (and other heteroatoms) at C-2 demonstrate the powerful influence that these substituents have on the stereoselectivity of nucleophilic substitution reactions. The trans selectivities of these reactions correlate with the behavior of the corresponding ketones. These experiments lend support to the possibility that the reactions of the acetals, which proceed via oxocarbenium ions, are operating under Felkin−Anh control.

Introduction

The stereoselective synthesis of 2-deoxysugars remains an important challenge in carbohydrate chemistry.[1] Because substitution reactions of 2-deoxyglycosyl donors are poorly stereoselective,[1] control of diastereoselectivity is achieved by incorporation of a heteroatom, usually sulfur[1] or iodine,[2−5] at C-2 to control the stereochemical outcome of glycosylation, followed by removal of the directing substituent. Nucleophilic attack onto the carbocationic reactive intermediate typically occurs anti to the heteroatom at C-2, providing the trans product with high selectivity (eq 1).[6] These nucleophilic substitution reactions are believed to be controlled by the stereospecific ring opening of the three-membered ring episulfonium ion intermediate **3** rather than a stereoselective reaction of thiophenyl-substituted oxocarbenium ion **4**.



(1)

Although three-membered ring onium ions resembling **3** are intermediates in many reactions,[7,8] these intermediates may not be involved when an oxygen substituent is attached to the cation (as in oxocarbenium ion **4**). Glycosylation reactions that should proceed through episulfonium ions[9−11] (and their related episelenonium[11,12] or iodonium ions[3,4]) do not always provide trans products exclusively, raising the possibility that oxocarbenium ions such as **4** are involved. This analysis is supported by the observation that benzylic episulfonium ions open rapidly at low temperatures.[13] Experimental studies of carbocation stability also indicate that episulfonium ions are less stable than oxocarbenium ions.[14] Computational studies of processes such as those shown in eq 1 do not locate episulfonium ions as low-energy

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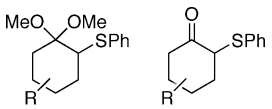
structures.[15−17] In cases where five-[18] and six-membered[19] ring sulfonium ions related to **3** were observed, the stereochemical courses of their substitution reactions may[19] or may not[18] be consistent with direct displacement reactions of the sulfonium ion. The reactions of acyclic acetals bearing sulfur or related substituents are also not consistent with the intermediacy of episulfonium ions.[20,21]

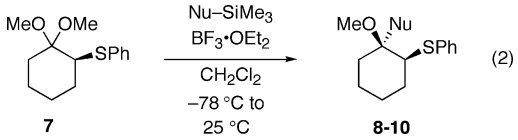
In this paper, we examine the reactions of substituted cyclohexanone acetals **5** and provide an explanation for the stereoselectivities of their reactions. The use of exocyclic acetals permits a comparison of the behavior of an oxocarbenium ion electrophile to its ketone analogue **6**,[22−25] a comparison that cannot be made in the case of carbohydrate-derived acetals. The parallels between the behavior of the ketones and their derived acetals suggest that similar forces likely control the conformational biases and facial preferences for nucleophilic attack in both cases. We propose that the outcomes of these reactions can be understood without invoking episulfonium ions as reactive intermediates.



5 **6**

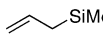
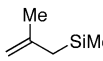
Results and Discussion

The stereochemical courses of substitution reactions of sulfur-substituted cyclohexanone acetal **7**[26−28] are consistent with observations of *C*-glycosylation reactions.[8] In all cases, nucleophilic substitutions under Lewis acid mediated conditions provided the 1,2-trans products (eq 2 and Table 1).[29] Control



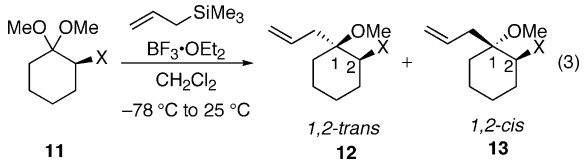
7 **8-10**

TABLE 1. Nucleophilic Substitution Reactions of Sulfur-Substituted Acetal 7 (Eq 2)

entry	Nu–SiMe$_3$	product	dr	yield (%)
1		**8**	≥ 97 : 3	70
2		**9**	≥ 97 : 3	63
3	NC–SiMe$_3$	**10**	≥ 97 : 3	93

experiments suggested that the addition of cyanotrimethylsilane proceeded under kinetic control.

The reactions of 2-heteroatom-substituted cyclohexanone acetals revealed consistent periodic trends in selectivity for both the chalcogens and the halogens (eq 3 and Table 2). Proceeding



11 **12** **13**

TABLE 2. Influence of C-2 Heteroatom on Stereoselectivity (Eq 3)

entry	acetal	X	**12**:**13**	yield (%)
1	**11a**	F	55:45	42
2	**11b**	Cl	83:17	73
3	**11c**	I	≥97:3	79
4	**11d**	OPh	65:35	87

down the group, trans selectivity increased (OPh < SPh and F < Cl < I). Similar to the observations of endocyclic acetals, substrates containing sulfur and iodine substituents at C-2 resulted in the highest selectivities.[1−4]

The highly selective formation of the trans products bearing sulfur substituents at C-2 are consistent with three transition states. Backside displacement on episulfonium[7] ion **14** would provide the observed trans product. This rationalization, however, ignores the concerns of the stability and reactivity of these intermediates raised in the Introduction (vide supra). It is also unnecessary to invoke an episulfonium ion intermediate to explain trans selectivity; addition to the 2-methyl-substituted oxocarbenium ion also proceeded with high trans selectivity,[30] and, in that case, anchimeric assistance is impossible. Consequently, the trans product could result from equatorial addition to equatorial oxocarbenium ion **15eq** (eq 4). This explanation would be consistent with observations that additions of larger nucleophiles to cyclohexanone and its related oxocarbenium ion occur from equatorial trajectories.[31,32] A third possibility involves axial attack on the axial conformer **15ax**. An approach anti to the sulfur atom of **15ax** could be the result of either steric protection of the top face[16] or by a stereoelectronically preferred Felkin−Anh-type addition.[33−36] The Felkin−Anh mode of addition has been invoked to explain the high

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(29) The syntheses of all substrates are provided as Supporting Information. The nucleophiles allyltrimethylsilane and methallyltrimethylsilane were generally employed with acetals, because nucleophilic attack provided clean reactions in high yields. The diastereoselectivities of all reactions were determined by gas chromatography and confirmed by ^{1}H NMR spectroscopy. The stereochemical courses of the reactions were assigned either by X-ray crystallographic analysis of the product (or a derivative) or by spectroscopic analysis (NOE measurements and ^{1}H NMR coupling constants); details of stereochemistry proofs are provided as Supporting Information.
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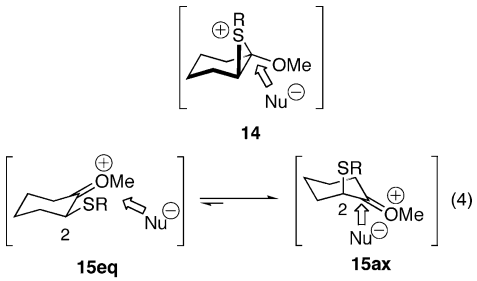
selectivities of nucleophilic additions to 2-thioalkyl-substituted ketones.[24,37,38]



The explanation invoking the equatorial cation **15eq** is unconvincing because it likely does not coincide with the conformational preference of the cation. Cyclohexanone-derived oxocarbenium ions **15eq** and **15ax** should exhibit conformational preferences similar to those of the corresponding cyclohexanones. A correlation can be found between the preference for the axial conformer of the ketones[39−47] (eq 5, Table 3) and the

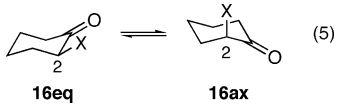


TABLE 3. Conformational Preferences of C-2 Heteroatom-Substituted Cyclohexanones (Eq 5)[45]

entry	X	equatorial/axial ($CDCl_3$)
1	OMe	72:28
2	SMe	15:85
3	F	83:17
4	Cl	55:45
5	I	12:88

selectivity of the reactions of the derived oxocarbenium ions (Tables 1 and 2): the two cyclohexanones with the highest preference for axial conformers **16ax** (bearing SMe and I substituents) exhibit the highest trans selectivities for reactions of the corresponding acetals. If a hyperconjugative interaction between σ_{C-S} and π^*_{C-O} contributes to the conformational preference of the sulfur-substituted ketone,[45−48] an oxocarbenium ion should have a much higher preference for an axial conformer because its π^* is lower in energy than for a carbonyl group.[48−50] Because a σ_{C-H} bond is more electron-donating than σ_{C-O} and σ_{C-F} bonds,[50,51] in the case of cations bearing fluorine and oxygen substituents, the equatorial conformer **15eq** may be more favored in the oxocarbenium ion.[52−54]

Computational studies provided insight into the viability of the three possible reactive intermediates (episulfonium ion **14** and oxocarbenium ions **15eq** and **15ax**). The analysis for the hyperconjugative donation of σ_{C-S} in **15ax** is supported by ab initio calculations (HF/6-31G*): for the thiomethyl analogue of this cation, the axial conformer **15ax** is considerably lower in energy (by 7.6 kcal/mol) than the equatorial isomer **15eq** (eq 4). These calculations do not support the explanation involving episulfonium ion **14**. In accord with previous computational studies,[15−17] episulfonium ion **14** was not found to be an energy minimum, so it must be less stable than the equatorial oxocarbenium ion **15eq**. Consequently, of the three possible reactive intermediates, the axially substituted oxocarbenium ion **15ax** is the most plausible.

The preference for Felkin−Anh attack on the axial oxocarbenium ion **15ax** is also consistent with the trends in selectivity illustrated in Tables 1 and 2. For the chalcogens, Felkin−Anh effects in additions to ketones are stronger for sulfur[24,37] than for oxygen.[38,55] In the sulfur-substituted acetal, the strong preference for the axial conformer of the oxocarbenium ion (**15ax**) and the inherent Felkin−Anh selectivity are complementary, leading to high trans selectivity. Halogenated cyclohexanones and related compounds also undergo Felkin−Anh-selective additions.[56−59] In constrained cyclohexanones, the heavier halogens exerted higher selectivity: a chlorine atom increased anti reduction, whereas fluorine (and oxygen) atoms exerted little influence on selectivity.[60]

The inherent Felkin−Anh bias of a fluorine atom,[35] which has been questioned,[61] was confirmed. Nucleophilic addition to cyclohexanone[62] **17** proceeded with high diastereoselectivity (eq 6). In the case of the fluorine-substituted acetal, the

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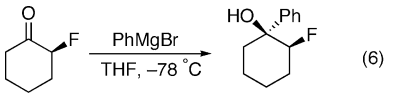
conformational effects,[45,47] favoring the equatorial conformer (Table 3, entry 3), and the Felkin−Anh effects oppose each other, so the selectivity for the reaction of the oxocarbenium ion is attenuated.



The powerful influence of a sulfur atom on the facial preference of nucleophilic attack is illustrated by the reaction of conformationally constrained exocyclic acetal **19**.[60] When three different nucleophiles were employed, nucleophilic substitution was highly stereoselective (eq 7 and Table 4). The *tert*-

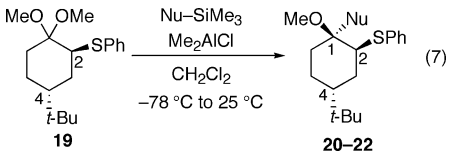
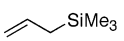
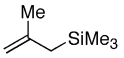
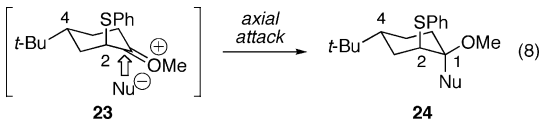


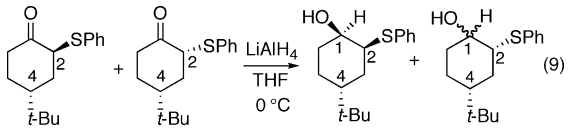
TABLE 4. Nucleophilic Substitution Reactions of Sulfur-Substituted Acetal 19 (Eq 7)

entry	Nu–$SiMe_3$	product	dr	yield (%)
1		**20**	97 : 3	87
2		**21**	≥ 97 : 3	86
3	NC–$SiMe_3$	**22**	≥ 97 : 3	90

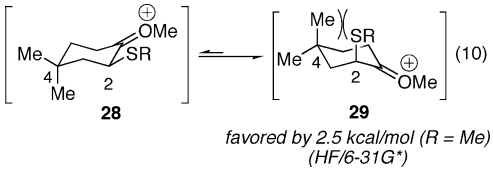
butyl substituent at C-4 of intermediate **23** should strongly bias the ring to a conformation where the *tert*-butyl group adopts an equatorial orientation,[63] positioning the sulfur substituent in its favored axial orientation. Consequently, the nucleophile approached from an axial trajectory to give the product **24**, where the nucleophile was introduced cis to the *tert*-butyl group (eq 8). This facial selectivity is diametrically opposed to the high (95:5) 1,4-trans selectivity exhibited by the reactions of 4-*tert*-butylcyclohexanone acetals,[32] which results from equatorial attack.[30] The results shown in Table 4 reveal that a sulfur atom is capable of completely reversing the approach of a nucleophile onto an oxocarbenium ion.[64]

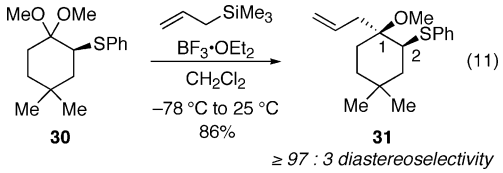


Reduction reactions of the conformationally constrained ketones *trans*-**25** and *cis*-**25** provided additional support for the involvement of Felkin−Anh selectivity (eq 9). In the course of preparing the 2,4-trans disubstituted acetal **19**, we reduced a mixture of the ketones *trans*-**25** and *cis*-**25** (3:1) to resolve the stereoisomers. This reduction proceeded with exclusive trans selectivity for the axial sulfide *trans*-**25**, consistent with the Felkin−Anh model and results with other 2-substituted 4-*tert*-butylcyclohexanones with the substituent oriented axially.[60] Conversely, the equatorial sulfide *cis*-**25** underwent nucleophilic addition with low selectivity, consistent with reactions of cyclohexanones with substituents constrained equatorially.[60] These results reinforce the fact that diastereoselective additions to 2-thiophenylcyclohexanone[24,37] likely involve addition to the preferred axial conformer[45,46] through Felkin−Anh transition states.[33,34]



Because epimerization at C-2 occurred during preparation of the acetal for the equatorial ketone *cis*-**25**,[65] a substrate that would shift the bias of the ketone to the equatorial conformer was designed. Geminal substitution at C-4 of a cyclohexanone[28,66] would develop an unfavorable *syn*-pentane interaction between the methyl group at C-4 and the sulfur substituent at C-2, destabilizing the axial conformer **29** (eq 10).[67,68] This effect may not be significant enough to force the equilibrium toward the equatorial conformer **28**, however, because the axial conformer **29** was calculated (HF/6-31G*) to be lower in energy by 2.5 kcal/mol. The computational result was supported by the experiment: nucleophilic substitution of acetal **30** proceeded with high 1,2-trans selectivity (eq 11), suggesting that the axial conformer **29** was favored.[69]





The high 1,2-trans selectivity of nucleophilic addition was also observed for a sterically encumbered substrate that incorporated geminal substitution at C-5 to impede steric approach from the axial face. Nucleophilic substitutions of acetal **32**[70,71] occurred with high selectivity, favoring the trans stereoisomer (eq 12 and Table 5). The trans products could arise from the preferential formation of the axial conformer **35**, followed by axial attack of the incoming nucleophile (eq 13). The destabilizing *syn*-pentane interaction[72] that would develop in the transition state is not destabilizing enough to dominate the axial preference

(60) For a discussion comparing the models for nucleophilic attack to cyclohexanones and an examination of the reactions of conformationally constrained 2-substituted cyclohexanones, see: Rosenberg, R. E.; Abel, R. L.; Drake, M. D.; Fox, D. J.; Ignatz, A. K.; Kwiat, D. M.; Schaal, K. M.; Virkler, P. R. *J. Org. Chem.* **2001**, *66*, 1694−1700.

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(65) Attempts to equilibrate the mixture to one diastereomer were unsuccessful, because the 3:1 ratio is the thermodynamic ratio.

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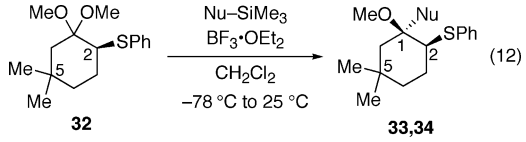
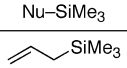
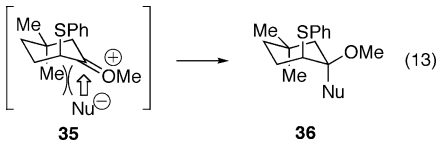


32 **33,34**

TABLE 5. Nucleophilic Substitution Reactions of Sulfur-Substituted Acetal 32 (Eq 12)

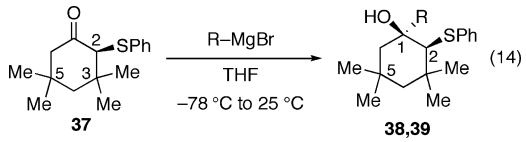
entry	Nu–SiMe$_3$	product	dr	yield (%)
1		**33**	≥ 97 : 3	94
2	NC–SiMe$_3$	**34**	92 : 8	89

of the cation (7.6 kcal/mol, as shown in eq 4) and the inherent Felkin−Anh selectivity. For comparison, similar geminal substitution alters the diastereoselectivity of nucleophilic additions to ketones, but product ratios indicated that axial attack still occurred.[73−75]



35 **36**

A control experiment demonstrated the powerful influence of a sulfur atom on the nucleophilic addition to sterically congested ketones. Although the acetal of 3,3,5,5-tetramethylcyclohexanone (**37**)[76] was synthetically inaccessible due to formation of the enol ether, nucleophilic addition reactions of Grignard reagents proceeded cleanly to provide the trans products with high selectivity (eq 14 and Table 6). These

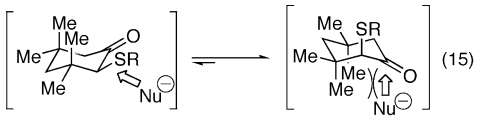


37 **38,39**

TABLE 6. Nucleophilic Additions to Sulfur-Substituted Ketone 37 (Eq 14)

entry	nucleophile	product	dr	yield (%)
1	PhMgBr	**38**	≥97:3	88
2	MeMgBr	**39**	≥97:3	77

products could arise from equatorial attack on the higher energy equatorial conformer **40eq** to avoid steric interactions with the two axial methyl groups in the transition state of nucleophilic attack (eq 15). Alternatively, axial attack on the more populated axial conformer **40ax** would be favored by Felkin−Anh effects. In either case, the selective addition can be explained without invoking cyclic onium ions, so the same arguments likely hold for the selectivity exhibited by acetal **32** (Table 5, vide supra).



40eq **40ax**

favored by 1.6 kcal/mol (R = Me) (HF/3-21G)*

Conclusion

The nucleophilic substitution reactions of 2-thiophenyl-substituted acetals are strongly influenced by the sulfur substituent. In all cases, the nucleophile was introduced trans to the sulfur substituent, regardless of the steric congestion present. Because the behavior of the oxocarbenium ions and their related ketones correlate, similar factors likely operate for both electrophiles. Ketones with sulfur substituents at C-2 prefer axial conformers,[45,46] and these ketones react with nucleophiles in accord with the Felkin−Anh model. Sulfur-substituted oxocarbenium ions should show a similar conformational preference, as demonstrated by computational data. In analogy to the behavior of the ketones, nucleophilic addition to these oxocarbenium ions through Felkin−Anh-type transition states would lead to the observed products. Although explanations involving episulfonium ions are consistent with the stereochemistry of the reactions of sulfur-substituted acetals, such explanations do not reconcile other data (vide supra) and cannot be applied to explain the behavior of the sulfur-substituted ketones. This paper provides an alternative explanation of stereochemistry that acknowledges the similarities between the reactivities of ketones and the reactivities of their related acetals.

Experimental Section

Details of the syntheses of previously reported ketones **17**[62] and **37**,[76] in addition to acetals **7**,[26−28,77] **11b**,[78] and **11c**,[79,80] are provided as Supporting Information.

General Procedure for Acetalization of Cyclohexanones:[81] A solution of cyclohexanone in MeOH (0.15 M) was treated with trimethyl orthoformate (4.00 equiv) and 3 drops of concentrated H_2SO_4. The reaction mixture was heated to 50 °C and stirred for 12 h before it was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (1 mL per mmol of cyclohexanone). The aqueous layer was extracted with 3 portions of CH_2Cl_2 (1 mmol per cyclohexanone). The combined organic layers were washed with a saturated sodium chloride solution, dried (Na_2SO_4), and concentrated in vacuo to provide a pale yellow residue.

***tert*-Butyl Acetal 19.** The standard acetalization procedure was followed with **25**[26,82] (2.50 g, 9.60 mmol) in 32 mL of MeOH with

(68) The coupling constants (6.0 and 12.0 Hz) at C-2 of the ketone corresponding to acetal **30** indicate that the thiophenyl group is predominantly equatorial. The coupling values are consistent with those observed for equatorially substituted ketone *cis*-**25**, not the axially constrained isomer *trans*-**25** (ref 45). The preference for the equatorial conformer corresponds to Corey's observations of the analogous bromine-substituted ketone (ref 67). Calculations (HF/6-31G*) of the ketone corresponding to acetal **30** suggest that the equatorial conformer is favored by 0.5 kcal/mol.

(69) Additions of Grignard reagents to the ketone corresponding to **30** were highly diastereoselective, but we were unable to obtain crystals suitable for X-ray crystallographic analysis. Therefore, we do not know the stereochemical courses of those reactions.

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trimethyl orthoformate (11.0 mL, 96.0 mmol) and H_2SO_4 (3 drops). Purification of the resultant residue by silica gel chromatography (0:100 to 5:95 EtOAc/hexanes) yielded product **19** as a yellow oil (2.25 g, 77%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21−7.46 (m, 5H), 3.63 (m, 1H), 3.25 (s, 3H), 3.21 (s, 3H), 1.91 (m, 1H), 1.68 (m, 4H), 1.53 (m, 1H), 1.14 (m, 1H), 0.77 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 132.9, 129.2, 127.3, 101.2, 51.2, 48.0, 47.8, 40.8, 32.2, 28.9, 28.6, 27.8, 23.5; IR (thin film) 2960, 1478, 1208, 1023 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{18}H_{28}NaO_2S$ [M + Na]$^+$, 331.1708; found, 331.1705. Anal. Calcd for $C_{18}H_{28}O_2S$: C, 70.08; H, 9.15. Found: C, 70.31; H, 9.09.

Acetal 30. The standard acetalization procedure was followed with 4,4-dimethyl-2-thiophenylcyclohexanone[26,28] (0.160 g, 0.68 mmol) in 2.2 mL of MeOH with trimethyl orthoformate (0.373 mL, 3.41 mmol) and H_2SO_4 (3 drops). Purification of the resultant residue by silica gel chromatography (5:95 EtOAc/hexanes) yielded product **30** as a yellow oil (0.147 g, 77%): ^{1}H (500 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.26 (m, 2H), 7.18 (m, 1H), 3.50 (dd, J = 9.4, 4.6 Hz, 1H), 3.35 (s, 3H), 3.30 (s, 3H), 1.93 (ddd, J = 13.7, 7.2, 3.8 Hz, 1H), 1.70 (m, 3H), 1.41 (ddd, J = 13.6, 10.2, 3.8 Hz, 1H), 1.31 (m, 1H), 1.01 (s, 3H), 0.90 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 137.0, 130.7, 129.1, 126.4, 101.3, 50.9, 50.0, 49.2, 43.7, 35.7, 31.4, 30.8, 27.7, 27.4; IR (thin film) 2952, 1584, 1439 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{24}NaO_2S$ [M + Na]$^+$, 303.1395; found, 303.1403. Anal. Calcd for $C_{14}H_{18}OS$: C, 68.53; H, 8.63. Found: C, 68.35; H, 8.37.

Acetal 32. The standard acetalization procedure was followed with 5,5-dimethyl-2-thiophenylcyclohexanone[83] (0.355 g, 1.51 mmol) in 15 mL of MeOH with trimethyl orthoformate (1.20 mL, 10.6 mmol) and H_2SO_4 (3 drops). Purification of the resultant residue by silica gel chromatography (2:98 EtOAC/hexanes) yielded product **32** as a yellow oil (0.380 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.45 (m, 5H), 3.62 (br s, 1H), 3.26 (s, 3H), 3.21 (s, 3H), 1.93 (dddd, J = 12.5, 12.0, 3.5, 3.3 Hz, 1H), 1.81 (ddd, J = 13.3, 13.0, 3.2 Hz, 1H), 1.68 (dt, J = 14.6, 1.8 Hz, 1H), 1.57 (m, 1H), 1.48 (d, J = 14.6 Hz, 1H), 1.06 (m, 1H), 1.02, (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 132.0, 129.2, 126.9, 101.7, 50.8, 48.7, 47.5, 40.1, 33.6, 33.5, 31.6, 26.5, 24.2; IR (thin film) 3059, 2938, 2829 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{15}H_{20}OS$ [M − MeOH]$^+$, 249.1313; found, 249.1309. Anal. Calcd for $C_{16}H_{24}O_2S$: C, 68.53; H, 8.63. Found: C, 68.78; H, 8.78.

Fluoro Acetal 11a. The standard acetalization procedure was followed with 2-fluorocyclohexanone **17**[62] (1.81 g, 15.7 mmol) in 50 mL of MeOH with trimethyl orthoformate (14.0 mL, 94.7 mmol) and H_2SO_4 (3 drops). Purification of the resultant residue by silica gel chromatography (0:100 to 3:97 EtOAc/hexanes) yielded the product **11a** as a pale yellow oil (0.960 g, 38%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (dt, J = 48.9, 2.1, 1H), 3.25 (d, J = 1.7 Hz, 3H), 3.19 (d, J = 1.7 Hz, 3H), 1.94 (m, 1H), 1.68 (m, 3H), 1.52 (m, 2H), 1.42 (m, 1H), 1.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.9 (J = 21.5 Hz), 88.2 (d, J = 175.3 Hz), 47.8, 28.7, 28.4 (J = 13.3 Hz), 21.8, 20.0 (J = 2.1 Hz); IR (thin film) 2927, 1063 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_8H_{15}FNaO_2$ [M + Na]$^+$, 185.0954; found, 185.0947. Anal. Calcd for $C_8H_{15}O_2F$: C, 59.24; H, 9.32. Found: C, 59.54; H, 9.30.

Phenoxy Acetal 11d. The standard acetalization procedure was followed with 2-phenoxycyclohexanone[84] (0.363 g, 1.92 mmol) in 19 mL of MeOH with trimethyl orthoformate (1.05 mL, 9.60 mmol) and H_2SO_4 (3 drops). Purification of the resultant residue by silica gel chromatography (3:97 EtOAc/hexanes) yielded product **11d** as a colorless oil (0.44 g, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.94 (m, 3H), 4.44 (t, J = 3.1 Hz, 1H), 3.24 (s, 3H), 3.17 (s, 3H), 1.96 (m, 1H), 1.85 (m, 2H), 1.67 (m, 1H), 1.59 (m, 1H), 1.53 (m, 1H), 1.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 129.7, 121.2, 116.4, 100.3, 73.7, 47.9, 47.8, 28.5, 26.5, 22.2, 20.1; IR (thin film) 3040, 2862, 1240 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{13}H_{17}O_2$ [M − CH_3O]$^+$, 205.1228; found, 205.1222. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.26; H, 8.61.

General Procedure for Allylation of Acetals: A solution of acetal in CH_2Cl_2 (0.10 M) was treated with allyltrimethylsilane or 2-methylpropenyltrimethylsilane (4.0 equiv) and then cooled to −78 °C. The appropriate Lewis acid (1.2 equiv, 1.0 M in CH_2Cl_2) was added dropwise, and the reaction mixture was allowed to warm to 22 °C for 24 h. The reaction mixture was poured into a separatory funnel containing saturated aqueous Na_2HPO_4 (1 mL per mmol acetal). The aqueous layer was extracted with three portions of CH_2Cl_2 (1 mL per mmol acetal). The combined organic layers were washed with a saturated sodium chloride solution, dried (Na_2SO_4), and concentrated in vacuo. The unpurified mixture was analyzed by GC and ^{1}H NMR spectroscopy and then purified as indicated.

Allyl Product 8. The standard allylation procedure was followed with acetal **7**[26−28,77] (0.11 g, 0.47 mmol), allyltrimethylsilane (0.30 mL, 1.90 mmol), and $BF_3{\cdot}OEt_2$ (0.072 mL, 0.56 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer. Purification of the resultant residue by silica gel chromatography (0:100 to 2:98 EtOAc/hexanes) yielded product as a colorless oil (0.071 g, 61%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.26 (t, J = 7.5 Hz, 2H), 7.18 (m, 1H), 5.82 (ddt, J = 17.0, 12.4, 4.9 Hz, 1H), 5.16 (dd, J = 17.0, 1.8 Hz, 1H), 5.10 (dd, J = 10.1, 2.0 Hz, 1H), 3.25 (s, 3H), 3.10 (dd, J = 11.1, 4.1 Hz, 1H), 2.80 (dd, J = 13.3, 7.6 Hz, 1H), 2.41 (dd, J = 13.3, 7.3 Hz, 1H), 1.90 (m, 2H), 1.78 (m, 1H), 1.70 (m, 1H), 1.47 (m, 3H), 1.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 134.0, 131.6, 129.1, 126.5, 118.9, 77.8, 54.7, 48.8, 40.3, 30.9, 30.0, 25.9, 21.4; IR (thin film) 3074, 2935, 2858, 1444 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{16}H_{22}OS$ [M]$^+$, 262.1391; found, 262.1393. Anal. Calcd for $C_{16}H_{22}OS$: C, 73.23; H, 8.45. Found: C, 73.50; H, 8.68.

Methallyl Product 9. The standard allylation procedure was followed with acetal **7**[26−28,77] (0.376 g, 1.50 mmol), 2-methylpropenyltrimethylsilane (1.02 mL, 5.96 mmol), and $BF_3{\cdot}OEt_2$ (0.225 mL, 1.80 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer was present. Purification by silica gel chromatography (0:100 to 2:98 EtOAc/hexanes) yielded the product as a colorless solid (0.260 g, 63%). X-ray quality crystals were grown from a 3:1 mixture of $CHCl_3$ and hexanes in which slow evaporation provided the crystal: mp 35−38 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 7.3 Hz, 2H), 7.26 (m, 2H), 7.16 (t, J = 7.3 Hz, 1H), 4.91 (m, 1H), 4.89 (m, 1H), 3.30 (dd, J = 4.2, 10.1 Hz, 1H), 3.28 (s, 3H), 2.77 (d, J = 13.3 Hz, 1H), 2.39 (d, J = 13.3 Hz, 1H), 1.93 (m, 2H), 1.86 (s, 3H), 1.86 (m, 1H), 1.80 (m, 1H), 1.47 (m, 3H), 1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 136.6, 130.7, 129.1, 126.2, 115.8, 78.6, 53.8, 48.9, 41.6, 31.9, 31.9, 30.1, 25.3, 21.9; IR (thin film) 3074, 2928, 2855, 1444 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{17}H_{24}OS$ [M]$^+$, 276.1548; found, 276.1549. Anal. Calcd for $C_{17}H_{24}OS$: C, 73.86; H, 8.75. Found: C, 73.89; H, 8.73.

Chlorocyclohexanes 12b and 13b. The standard allylation procedure was followed with chloroacetal **11b**[78] (0.212 g, 1.20 mmol), allyltrimethylsilane (0.754 mL, 4.70 mmol), and $BF_3{\cdot}OEt_2$ (0.179 mL, 1.42 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 17:83 ratio. Purification of the resultant residue by silica gel chromatography (0:100 to 2:98 EtOAc/hexanes) yielded the product as a clear oil (0.160 g, 73%). The major isomer **12b** was isolated as a pure sample, while the minor isomer **13b** was isolated as a mixture of **12b** and **13b**. IR, mass spectrometry, and combustion analysis data were obtained for the major isomer (**12b**) and the minor isomer (**13b**) as a mixture of diastereomers. IR (thin film) 2956, 1075, 742 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{17}ClNaO$ [M + Na]$^+$, 211.0866; found, 211.0871. Anal. Calcd for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08. Found: C, 63.35; H, 9.13.

Major Isomer (12b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt,

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J = 17.2, 10.4, 7.5 Hz, 1H), 5.19 (d, J = 17.0 Hz, 1H), 5.14 (d, J = 10.1 Hz, 1H), 3.94 (dd, J = 10.7, 3.8 Hz, 1H), 3.28 (s, 3H), 2.57 (dd, J = 13.4, 7.7 Hz, 1H), 2.37 (dd, J = 13.3, 7.5 Hz, 1H), 2.11 (dq, J = 4.2, 12.1 Hz, 1H), 1.91 (m, 2H) 1.41 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.4, 119.2, 77.1, 65.5, 48.9, 39.2, 32.2, 30.6, 25.5, 20.9.

Minor Isomer (13b). ^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.08 (m, 1H), 3.25 (s, 3H), 2.44 (dd, J = 15.0, 7.5 Hz, 1H), 2.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, distinctive peaks) δ 132.6, 118.6, 62.1, 49.1, 37.4, 20.9.

Iodocyclohexane 12c. The standard allylation procedure was followed with iodo acetal **11c**[79,80] (0.168 g, 0.62 mmol), allyltrimethylsilane (0.395 mL, 2.48 mmol), and $TiCl_4$ (0.746 mL, 0.746 mmol, 1.0 M in CH_2Cl_2). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer was present. Purification of the resultant residue by silica gel chromatography (2:98 EtOAc/hexanes) yielded the product as a colorless oil (0.137 g, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddt, J = 17.0, 12.4, 5.0 Hz, 1H), 5.22 (d, J = 16.9 Hz, 1H), 5.14 (d, J = 10.1 Hz, 1H), 4.23 (dd, J = 10.2, 4.2 Hz, 1H), 3.24 (s, 3H), 2.39 (m, 3H), 2.13 (m, 1H), 1.97 (m, 1H), 1.52 (m, 4H), 1.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.2, 119.4, 76.2, 49.0, 43.8, 36.1, 29.7, 21.5; IR (thin film) 3076, 1440, 2935, 669 cm^{-1}; HRMS (CI) *m/z* calcd for $C_{10}H_{17}INaO$ $[M + Na]^+$, 303.0222; found, 303.0127. Anal. Calcd for $C_{10}H_{17}OI$: C, 42.87; H, 6.12. Found: C, 43.12; H, 5.95.

Phenoxycyclohexanes 12d and 13d. The standard allylation procedure was followed with acetal **11d** (0.190 g, 0.81 mmol), allyltrimethylsilane (0.511 mL, 3.20 mmol), and $BF_3{\cdot}OEt_2$ (0.121 mL, 0.97 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 34:66 ratio. Separation of the diastereomers was achieved by purification of the resultant residue by silica gel chromatography (3:97 EtOAc/hexanes) to yield the product as a colorless oil (0.171 g, 87%). Mass spectrometry data was obtained for major isomer (**12d**) and minor isomer (**13d**) as a mixture of diastereomers: HRMS (ESI) *m/z* calcd for $C_{16}H_{22}NaO_2$ $[M + Na]^+$, 269.1518; found, 269.1513.

Major Isomer (12d). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (m, 2H), 6.83 (m, 3H), 5.78 (ddt, J = 17.2, 12.2, 5.2 Hz, 1H), 4.99 (d, J = 10.1 Hz, 1H), 4.98 (d, J = 17.1 Hz, 1H), 4.08 (dd, J = 10.5, 3.7 Hz, 1H), 3.37 (s, 3H), 2.54 (dd, J = 13.6, 7.5 Hz, 1H), 2.47 (dd, J = 13.6, 7.2 Hz, 1H), 1.94 (m, 1H), 1.76 (m, 2H), 1.58 (m, 2H), 1.24 (m, 1H), 1.13 (ddd, J = 13.9, 12.1, 4.1 Hz, 1H), 1.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 133.9, 129.7, 120.9, 118.5, 116.1, 80.3, 77.6, 49.8, 38.2, 31.7, 26.1, 24.2, 21.0; IR (thin film) 2929, 2860, 1597, 1493 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.18; H, 9.07.

Minor Isomer (13d). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (m, 2H), 6.90 (m, 3H), 5.78 (ddt, J = 21.1, 12.8, 8.6 Hz, 1H), 5.03 (d, J = 12.8 Hz, 1H), 4.95 (d, J = 21.2 Hz, 1H), 4.26 (t, J = 3.6 Hz, 1H), 3.25 (s, 3H), 2.44 (dd, J = 18.5, 9.6 Hz, 1H), 2.36 (dd, J = 18.1, 8.5 Hz, 1H), 1.78 (m, 4H), 1.48 (m, 3H), 1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 133.4, 129.7, 120.9, 118.3, 116.2, 77.6, 75.1, 48.6, 36.8, 28.9, 24.6, 21.1, 20.2; IR (thin film) 2933, 2826, 1598, 1495 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.16; H, 9.19.

Allyl Product 20. The standard allylation procedure was followed with acetal **19** (0.070 g, 0.23 mmol), allyltrimethylsilane (0.144 mL, 0.91 mmol), and $MeAlCl_2$ (0.27 mL, 0.27 mmol, 1.0 M in hexane). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer was present. Purification of the resultant residue by silica gel chromatography (0:100 to 2:98 EtOAc/hexanes) yielded the product as a pale yellow oil (0.062 g, 87%): ^{1}H NMR (500 MHz, C_6D_6) δ 7.48 (m, 2H), 7.05 (t, J = 7.5 Hz, 2H), 6.97 (m, 1H), 5.92 (ddt, J = 17.2, 10.2, 6.97 Hz, 1H), 5.10 (m, 2H), 3.58 (m, 1H), 3.33 (s, 3H), 2.31 (dd, J = 15.0, 7.5 Hz, 1H), 2.22 (dd, J = 15.0, 7.1 Hz, 1H), 2.00 (td, J = 13.3, 3.8 Hz, 1H), 1.82 (tt, J = 12.5, 3.7 Hz, 1H), 1.76 (dq, J = 13.1, 1.8 Hz, 1H), 1.67 (ddt, J = 15.2, 3.1 Hz, 1H), 1.56 (m, 1H), 1.15 (ddd, J = 14.3, 12.4, 3.4 Hz, 1H), 1.01 (dq, J = 3.8, 13.4 Hz, 1H), 0.77 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 133.4, 133.4, 129.1, 127.2, 118.1, 53.9, 48.8, 40.5, 36.3, 32.2, 30.8, 28.1, 27.8, 27.5, 23.7; IR (thin film) 2948, 2869, 1480, 1077 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{30}ONaS$ $[M + Na]^+$, 341.1915; found, 341.1921. Anal. Calcd for for $C_{20}H_{30}OS$: C, 75.42; H, 9.49. Found: C, 75.02; H, 9.67.

Methallyl Product 21. The standard allylation procedure was followed with acetal **19** (0.072 g, 0.23 mmol), 2-methylpropenyltrimethylsilane (0.160 mL, 0.93 mmol), and $TiCl_4$ (0.28 mL, 0.28 mmol, 1.0 M in CH_2Cl_2). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer was present. Purification of the resultant residue by silica gel chromatography (0:100 to 2:98 EtOAc/hexanes) yielded the product as a pale yellow oil (0.066 g, 86%): ^{1}H NMR (500 MHz, C_6D_6) δ 7.49 (m, 2H), 7.05 (m, 2H), 6.97 (tt, J = 2.0, 1.2 Hz, 1H), 4.95 (s, 1H), 4.87 (s, 1H), 3.60 (m, 1H), 3.23 (s, 3H), 2.28 (ddd, J = 14.0, 11.7, Hz, 2H), 2.01 (td, J = 13.5, 4.3 Hz, 1H), 1.89 (s, 3H), 1.87 (dt, J = 12.6, 3.6 Hz, 1H), 1.80 (dq, J = 13.0, 2.8 Hz, 1H), 1.75 (ddt, J = 15.0, 3.5 Hz, 1H), 1.59 (ddt, J = 13.4, 6.5, 3.4 Hz, 1H), 1.24 (ddd, J = 14.4, 12.5, 3.3 Hz, 1H), 1.08 (dq, J = 3.8, 13.2 Hz, 1H), 0.79 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 136.3, 133.4, 129.2, 127.3, 115.0, 78.5, 54.3, 48.9, 40.5, 38.3, 32.4, 32.2, 28.5, 27.9, 24.2, 24.1; IR (thin film) 3059, 2949, 1468 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{32}OS$ $[M]^+$, 332.2174; found, 332.2180.

Allyl Product 31. The standard allylation procedure was followed with acetal **30** (0.071 g, 0.25 mmol), allyltrimethylsilane (0.161 mL, 1.01 mmol), and $BF_3{\cdot}OEt_2$ (0.038 mL, 0.30 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer was present. Purification of the resultant residue by silica gel chromatography (0:100 to 2:98 EtOAc/hexanes) yielded the product as a colorless oil (0.067 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.28 (m, 2H), 7.15 (m, 1H), 5.82 (ddt, J = 17.2, 12.4, 7.5 Hz, 1H), 5.18 (d, J = 17.0 Hz, 1H), 5.11 (d, J = 12.2 Hz, 1H), 3.27 (m, 1H), 3.26 (s, 3H), 2.80 (dd, J = 12.9, 7.7 Hz, 1H), 2.41 (dd, J = 12.9, 7.4 Hz, 1H), 1.89 (t, J = 12.9 Hz, 1H), 1.80 (dt, J = 15.0, 3.3 Hz, 1H), 1.60 (td, J = 14.5, 3.9 Hz, 1H), 1.49 (ddd, J = 13.3, 4.1, 2.5 Hz, 1H), 1.42 (td, J = 13.2, 3.7 Hz, 1H), 1.12 (ddd, J = 12.9, 6.0, 2.9 Hz, 1H), 0.89 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 134.1, 130.4, 129.1, 126.2, 119.2, 76.8, 50.8, 48.9, 43.1, 40.4, 33.9, 32.6, 31.8, 26.7, 24.1; IR (thin film) 3074, 2951, 1481 cm^{-1}; HRMS (CI) *m/z* calcd for $C_{18}H_{26}NaOS$ $[M + Na]^+$, 313.1602; found, 313.1608. Anal. Calcd for $C_{18}H_{26}OS$: C, 74.43; H, 9.02. Found: C, 74.69; H, 9.26.

Allyl Product 33. The standard allylation procedure was followed with acetal **32** (0.091 g, 0.33 mmol), allyltrimethylsilane (0.206 mL, 1.33 mmol), and $BF_3{\cdot}OEt_2$ (0.050 mL, 0.39 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer was present. Purification of the resultant residue by silica gel chromatography (0:100 to 2:98 EtOAc/hexanes) yielded the product as a pale yellow oil (0.084 g, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.28 (m, 2H), 7.19 (m, 1H), 5.81 (ddt, J = 17, 12, 4.8 Hz, 1H), 5.19 (m, 1H), 5.12 (m, 1H), 3.24 (s, 3H), 2.98 (dd, J = 12.2, 4.2 Hz, 1H), 2.79 (dd, J = 13.0, 7.6 Hz, 1H), 2.34 (dd, J = 13.0, 7.4 Hz, 1H), 2.10 (m, 1H), 1.78 (dd, J = 15.1, 2.7 Hz, 1H), 1.73 (m, 1H), 1.41 (m, 1H), 1.20 (d, J = 15.1 Hz, 1H), 1.10 (m, 1H), 1.10 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 134.4, 131.4, 129.1, 126.5, 119.2, 78.8, 54.9, 49.2, 41.7, 40.9, 40.0, 34.1, 30.9, 26.9, 25.8; IR (thin film) 3075, 2951, 2868, 1438 cm^{-1}; HRMS (CI) *m/z* calcd for $C_{18}H_{26}NaOS$ $[M + Na]^+$, 313.1602; found, 313.1613. Anal. Calcd for $C_{18}H_{26}OS$: C, 74.43; H, 9.02. Found: C, 74.32; H, 9.06.

General Procedure for Cyanation of 2-Phenylsulfanylcyclohexanone Dimethyl Acetals: A solution of the acetal in CH_2Cl_2 (0.10 M) was treated with Me_3SiCN (4.0 equiv) and then cooled to −78 °C. The appropriate Lewis acid (1.2 equiv) was added dropwise, and the reaction mixture was allowed to warm to 22 °C. After 18 h, the reaction mixture was cooled to −78 °C and treated

with a 1:1:1 solution of Et_3N, MeOH, and CH_2Cl_2 (1 mL per mL of reaction volume). The reaction mixture was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (1 mL per mL of reaction volume) and extracted with 3 portions of CH_2Cl_2 (1 mL per mL of acetal). The organic layers were washed with a saturated sodium chloride solution, dried (Na_2SO_4), and concentrated in vacuo. The unpurified mixture was analyzed by GC and ^{1}H NMR spectroscopy and then purified as indicated.

Nitrile 10. The standard cyanation procedure was followed with acetal **7**,[26−28,77] Me_3SiCN (0.198 mL, 1.50 mmol), and $BF_3{\cdot}OEt_2$ (0.056 mL, 0.45 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer was present. Purification of the resultant residue by silica gel chromatography (0:100 to 5:95 EtOAc/hexanes) yielded the product as a white solid (0.086 g, 93%). X-ray quality crystals were grown from a 3:1 mixture of $CHCl_3$ and hexanes in which slow evaporation provided the crystal: mp 80−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.53 (m, 5H), 3.46 (s, 3H), 3.34 (m, 1H), 2.32 (m, 1H), 1.94 (m, 2H), 1.73 (m, 2H), 1.57 (m, 2H), 1.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 133.3, 129.4, 128.0, 119.4, 78.2, 55.2, 53.1, 32.7, 29.6, 23.8, 20.5; IR (thin film) 2943, 2082, 2866, 2260, 1444 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{14}H_{18}NOS$ [M + H]$^+$, 248.1071; found, 248.1073. Anal. Calcd for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66. Found: C, 67.97; H, 7.00; N, 5.63.

Nitrile 22. The standard cyanation procedure was followed with acetal **19** (0.366 g, 1.41 mmol), Me_3SiCN (0.750 mL, 5.63 mmol), and $BF_3{\cdot}OEt_2$ (0.213 mL, 1.68 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer was present. Purification of the resultant residue by silica gel chromatography (0:100 to 2:98 EtOAc/hexanes) yielded the product as a white solid (0.321 g, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.30 (m, 3H), 3.87 (m, 1H), 3.45 (s, 3H), 2.07 (m, 1H), 2.03 (dd, J = 13.2, 3.9 Hz, 1H), 1.99 (m, 1H), 1.89 (m, 1H), 1.70 (ddd, J = 14.2, 12.3, 3.3 Hz, 1H), 1.60 (m, 1H), 1.40 (ddd, J = 25.8, 13.3, 4.2 Hz, 1H), 0.83 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 133.7, 129.4, 128.2, 119.1, 78.9, 53.0, 52.6, 40.8, 32.2, 31.7, 30.2, 27.7, 24.4; IR (thin film) 3060, 2960, 2870, 2260 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{18}H_{25}NOS$ [M]$^+$, 303.1657; found, 303.1659. Anal. Calcd for $C_{18}H_{25}NOS$: C, 71.24; H, 8.30; N, 4.62. Found: C, 71.51; H, 8.46; N, 4.68.

Nitrile 34. The standard cyanation procedure was followed with acetal **32** (0.222 g, 0.79 mmol), Me_3SiCN (0.423 mL, 3.17 mmol), and $BF_3{\cdot}OEt_2$ (0.120 mL, 0.95 mmol). GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a ratio of 92:8. Purification of the resultant residue by silica gel chromatography (3:97 EtOAc/hexanes) yielded the product as a white solid (0.198 g, 91%). The purified products were characterized as a mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2.3H), 7.31 (m, 3.3H), 3.50 (s, 3H), 3.47 (s, 0.4H), 3.19 (dd, J = 11.1, 4.4 Hz, 1.1H), 2.23 (dd, J = 14.8, 2.2 Hz, 1H), 2.01 (m, 2.4H), 1.24 (m, 1.7H), 1.09 (s, 0.5H), 1.06 (s, 3H), 1.01 (s, 0.5H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 133.3, 133.2, 129.4, 129.2, 128.0, 127.9, 119.6, 56.5, 53.7, 53.2, 43.4, 38.4, 32.2, 31.4, 26.7, 26.5; IR (thin film) 3059, 2953, 2866, 2850 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{21}NNaOS$ [M + Na]$^+$, 298.1241; found, 298.1248. Anal. Calcd for $C_{16}H_{21}NOS$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.92; H, 7.76; N, 5.06.

General Procedure for Grignard Addition to Cyclohexanones: A cooled (−78 °C) solution of cyclohexanone derivative (1.00 equiv) in THF (0.10 M) was treated with Grignard nucleophile (2.40 equiv). The reaction mixture was warmed to 22 °C and stirred for 1.5 h before it was cooled to 0 °C and treated with H_2O (1 mL per mmol cyclohexanone). The aqueous layer was extracted with 3 portions of Et_2O (1 mL per mmol cyclohexanone). The combined organic layers were washed with a saturated sodium chloride solution (1 mL per mL of Et_2O), dried (Na_2SO_4), and concentrated in vacuo. The unpurified mixture was analyzed by GC and ^{1}H NMR spectroscopy and then purified as indicated.

Fluorocyclohexanol 18. The standard Grignard addition procedure was followed with **17**[62] (0.036 g, 0.31 mmol) and phenylmagnesium bromide (0.75 mL, 0.75 mmol, 1.0 M in THF). GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a single isomer was present. Purification of the resultant residue by silica gel chromatography (2:98 EtOAc/hexanes) yielded the product as a white solid (0.057 g, 95%). X-ray quality crystals were grown from $CHCl_3$ in which slow evaporation provided the crystal: mp 74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 7.5 Hz, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.28 (m, 1H), 4.98 (dt, J = 40.4, 8.4 Hz, 1H), 2.27 (t, J = 2.3 Hz, 1H), 2.02 (tdd, J = 9.0, 8.9, 3.8 Hz, 2H), 1.94 (m, 1H), 1.83 (m, 1H), 1.73 (ddt, J = 25.8, 12.9, 3.6 Hz, 1H), 1.60 (m, 1H), 1.52 (m, 1H), 1.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 128.7, 127.5, 125.2, 95.2 (d, J = 176.3 Hz), 75.2 (d, J = 17.5 Hz), 39.3 (d, J = 15.0 Hz), 27.8 (d, J = 70.0 Hz), 23.9 (d, J = 45.0 Hz), 21.1 (d, J = 5.0 Hz); IR (thin film) 3419, 2924, 1458 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{15}FNaO$ [M + Na]$^+$, 217.1005; found, 217.1004. Anal. Calcd for $C_{12}H_{15}FO$: C, 74.97; H, 8.23. Found: C, 74.90; H, 8.16.

Cyclohexanol 38. The standard Grignard addition procedure was followed with **37**[76] (0.044 g, 0.19 mmol) and phenylmagnesium bromide (0.45 mL, 0.45 mmol, 1.0 M in THF). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer was present. Purification of the resultant residue by silica gel chromatography (3:97 EtOAc/hexanes) yielded the product as a white solid (0.054 g, 84%). X-ray quality crystals were grown from a 3:1 mixture of hexanes and CH_2Cl_2 in which slow evaporation provided the crystal: mp 108−110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (m, 2H), 6.98 (m, 4H), 6.89 (m, 2H), 6.79 (m, 2H), 3.35 (s, 1H), 3.00 (d, J = 2.6 Hz, 1H), 1.81 (dd, J = 14.8, 2.9 Hz, 1H), 1.66 (dd, J = 14.1, 2.9 Hz, 1H), 1.63 (dd, J = 14.8, 2.5 Hz, 1H), 1.52 (d, J = 14.1 Hz, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 0.90 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 148.4, 136.8, 133.1, 128.4, 127.6, 126.6, 126.4, 125.3, 79.1, 71.1, 54.5, 52.3, 36.9, 36.6, 35.4, 31.3, 27.9, 24.8; IR (thin film) 3505, 3030, 2951, 1445 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{28}NaOS$ [M + Na]$^+$, 363.1758; found, 363.1751. Anal. Calcd for $C_{22}H_{28}OS$: C, 77.60; H, 8.29. Found: C, 77.41; H, 8.43.

Cyclohexanol 39. The standard Grignard addition procedure was followed with **37**[76] (0.033 g, 0.13 mmol) and methylmagnesium bromide (0.10 mL, 0.30 mmol, 3.0 M in Et_2O). GC and ^{1}H NMR spectroscopic analysis of the unpurified product detected only a single isomer was present. Purification of the resultant residue by silica gel chromatography (3:97 EtOAc/hexanes) yielded the product as a colorless oil (0.027 g, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.28 (m, 2H), 7.18 (m, 1H), 2.89 (s, 1H), 2.17 (d, J = 2.2 Hz, 1H), 1.82 (dd, J = 14.4, 2.9 Hz, 1H), 1.57 (dd, J = 14.0, 2.9 Hz, 1H), 1.29 (m, 2H), 1.32 (s, 3H), 1.24 (s, 6H), 1.14 (s, 3H), 0.89 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 139.3, 130.6, 129.3, 126.5, 69.8, 54.6, 50.8, 37.1, 36.5, 35.3, 33.6, 30.9, 27.7, 24.4, 22.7; IR (thin film) 3529, 2951, 1481 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{17}H_{25}S$ [M − OH]$^+$, 261.1677; found, 261.1674. Anal. Calcd for $C_{17}H_{26}OS$: C, 73.33; H, 9.41. Found: C, 73.14; H, 9.65.

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Supporting Information Available: Complete experimental procedures, product characterization, stereochemical proofs, X-ray crystallographic data, and GC and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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