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Unusual Kinetic Profiles for Lewis Base-Catalyzed Sulfenocyclization of *ortho*-Geranylphenols in Hexafluoroisopropyl Alcohol

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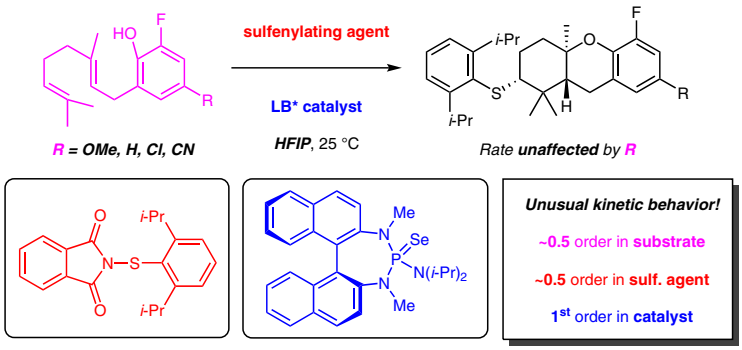

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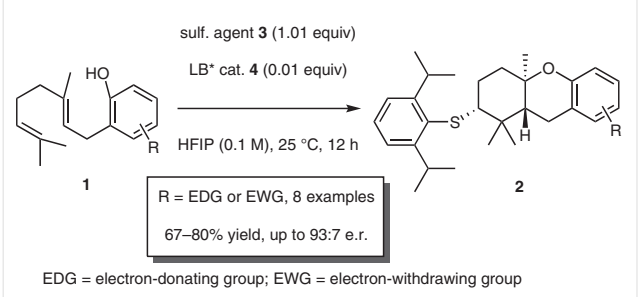
Abstract The kinetic behavior of the Lewis base-catalyzed sulfenocyclization of polyenes in hexafluoroisopropyl alcohol (HFIP) was explored. The rate of reaction is not dependent on the electronic properties of the terminal nucleophile, suggesting that this capture step is not rate limiting. Additionally, fractional orders were observed for two of the reaction components. This intriguing profile appears unique to the polyene sulfenocyclization reaction and is not merely due to solvent effects.

Key words polyenes, cyclization, sulfenocyclization, kinetics, Lewis base catalysis, hexafluoroisopropyl alcohol

Polyene cyclizations constitute key biosynthetic pathways that rapidly generate structurally complex metabolites from linear olefin precursors. These fascinating transformations, which can construct multiple rings and stereogenic centers from simple achiral starting materials in a single step, have inspired the development of nonenzymatic approaches for the synthesis of polycyclic terpenoids. Polyene cyclizations have been used as strategy-level disconnections in the laboratory syntheses of numerous natural products.[1] Early investigations of enantioselective variants of polyene cyclizations involved high catalyst loadings and stoichiometric amounts of chiral Lewis or Brønsted acids.[2] Examples of truly catalytic enantioselective cyclizations have been reported only recently. In 2017, Samanta and Yamamoto disclosed an enantioselective bromocyclization of polyenes with a BINOL-derived chiral Lewis basic catalyst.[3] Organometallic catalysts have also been employed by the groups of Gagne (Pt),[4] Toste (Au),[5] Carreira (Ir),[6] and Snyder (Hg, stoichiometric).[7] Halides, olefins, or vinyl groups in the products can be used for further functional elaboration. Highly selective organocatalytic methods introduced by Jacobsen,[8] MacMillan,[9] and Zhao[10] and their respective co-workers require specifically engineered substrates that are not amenable to easy postcyclization functionalization.

A recent disclosure from this laboratory reported a Lewis base-catalyzed enantioselective sulfenocyclization of polyenes, enabled by the use of 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) as the reaction solvent (Scheme 1).[11] Electron-rich homogeranylarenes, as well as electronically diverse *ortho*-geranylphenols **1**, are competent substrates for this transformation, affording tricyclic products **2** in good yields and high enantioselectivities with an operationally simple protocol. The resulting thioethers can be subjected to a range of transformations to install useful A-ring functionality.



Scheme 1 Chiral Lewis base-catalyzed enantioselective sulfenocyclization of polyenes in HFIP

The mechanism for the Lewis base-catalyzed sulfenofunctionalization of olefins has been extensively studied in these laboratories, and the catalytic cycle shown in Scheme 2 has been proposed.[12,13] Initially, acid-mediated transfer of a sulfenyl group from **3** to **4** generates a cationic donor–acceptor complex ***i***. This highly electrophilic complex reacts with a nonactivated olefin **1** to generate an enantiomerically enriched thiiranium-ion intermediate ***ii***. This thiiranium

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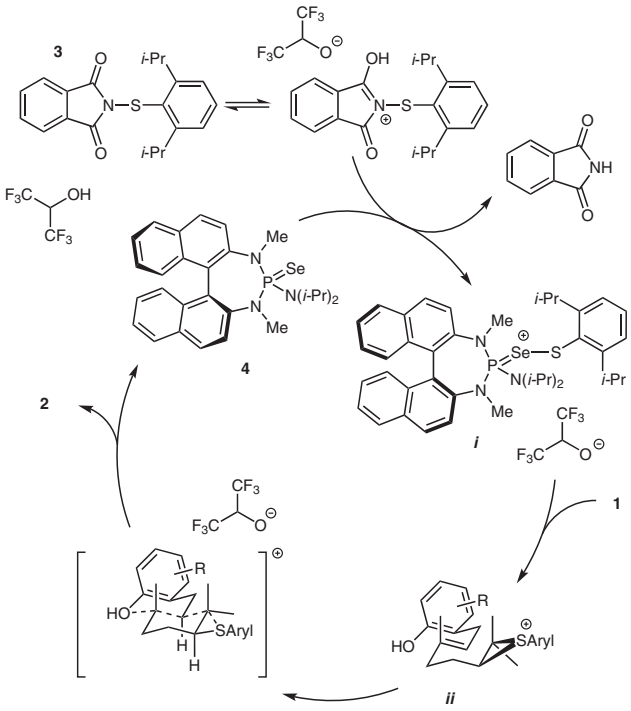
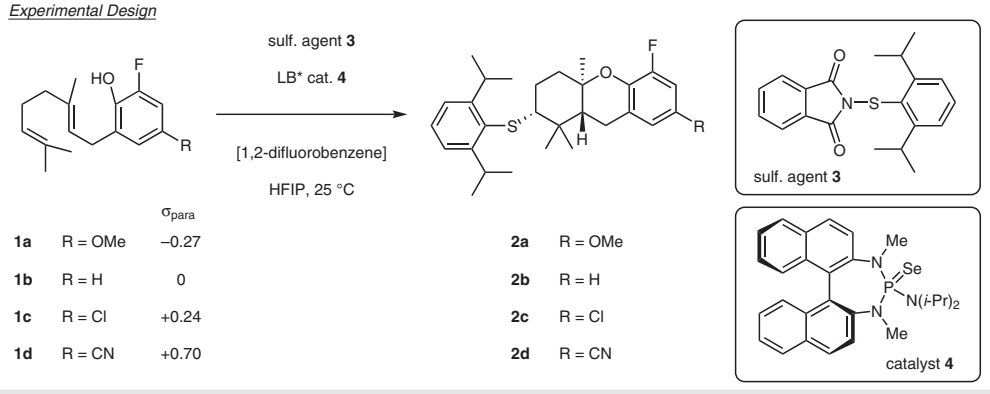
ion is opened by nucleophilic attack, generating *anti*-functionalized products. In the present case, the generation of the thiiranium ion serves as the initiating event for a cationic polyene cascade cyclization that is ultimately terminated by the pendent phenol nucleophile with formation of the tricyclic product **2**.



Scheme 2 Proposed catalytic cycle

In previous mechanistic studies on Lewis base-catalyzed, intramolecular oxysulfenylation,[12] with dichloromethane (DCM) as the solvent, the following kinetic profile was observed. First, the reaction is first order in both catalyst and olefin, and zeroth order in the sulfenylating agent. Secondly, it has a positive fractional order in mesic acid. These data are consistent with a mechanism in which sulfenyl-group transfer from the donor–acceptor complex ***i*** to the olefin is the turnover-limiting step. Although this mechanism is generally presumed to be operative, there was reasonable suspicion that this might not be the case in the aforementioned polyene cyclization for two reasons. First, the reaction solvent is HFIP rather than DCM. This polar, protic solvent can participate in hydrogen-bonding and fluorophobic interactions with all of the reaction components, which might affect the kinetic profile. Secondly, the nature of the thiiranium-ion opening step is quite different from that in previous systems because the transfer of electron density is propagated over the entire molecule as part of a cationic cascade process. Over forty years ago, Johnson observed a pronounced dependence of the rate of acid-mediated cyclization of epoxypolyenes on the electronic properties of the terminal arene nucleophile.[14] Specifically, faster reaction rates were observed for electron-rich arenes than for electron-deficient ones ($\rho < 0$), even though these motifs were located far from the site of cascade initiation, in which case the electronic perturbation would be transmitted through the alkene double bonds. It was hypothesized that a similar phenomenon might be operating in the present system (i.e. the rate-determining step has switched from thiiranium generation to thiiranium opening), in which case a rate dependence on the electronic character of the terminal nucleophile would be expected.

To test this hypothesis, the following experiments were carried out (Scheme 3). A series of *ortho*-geranylated phenols **1a–d** bearing electronically diverse *para*-substituents were subjected to the standard reaction conditions. Additionally, all substrates were *ortho*-fluorinated, so that reaction conversion could be monitored in real time by ^{19}F NMR spectroscopy. A routine solvent-suppression protocol was employed to decrease the intensity of the HFIP ^{19}F resonance ($\delta = -77.9$ ppm), which permitted accurate integration of the ^{19}F resonances corresponding to **1** and **2**



Scheme 3 Substrates employed for kinetic studies of the sulfenocyclization reaction

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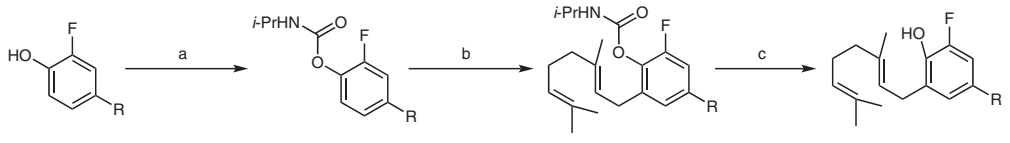
(δ = –143.0 to –141.0 ppm). Comparison of the reaction rates across the series would provide valuable insight into the turnover-limiting step.

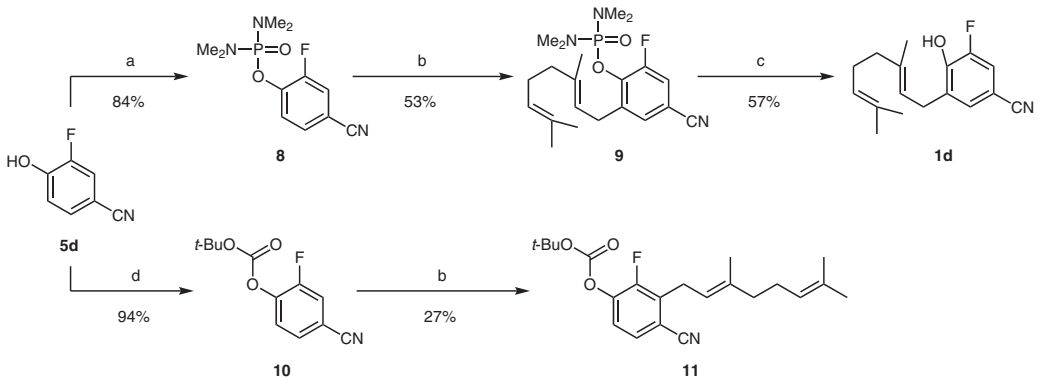
Synthesis of the geranylated fluorophenols proved to be a formidable challenge. Initially, it was envisioned that **1a–d** might be obtained in one step from commercially available fluorophenols **5** by using previously developed conditions for C-selective phenol alkylation.[15] Unfortunately, in the case of *ortho*-fluorinated phenols, this alkylation protocol afforded complex product mixtures and low yields of **1**. Additionally, chromatographic separation of pure **1** from the various reaction byproducts proved difficult. Alternative strategies were explored for the clean, selective alkylation of **5** (Scheme 4). Kauch and Hoppe previously developed a protocol for *ortho*-lithiation of *ortho*-fluorophenols that employs an *N*-isopropyl carbamate as a directing group.[16,17] The aryllithium can be trapped by diverse electrophiles in high yields. Although allylic halides were not included in the demonstrated scope, this route appeared to be promising for installation of a geranyl side chain. Preparation of carbamates **6a–d** from the corresponding phenols was trivial. Directed lithiation of the *N*-silylated carbamate generated in situ and subsequent trapping with geranyl bromide afforded the desired alkylation products **7a–c** in modest but synthetically useful yields. Most importantly, the isolated products were isomerically pure. Finally, the carbamate was readily hydrolyzed under basic aqueous conditions to afford phenols **1a–c**.[18]

This synthetic sequence was unfortunately not appropriate for the preparation of **1d**, as the nitrile was susceptible to nucleophilic addition of butyllithium during the directed lithiation step. In the interest of retaining the same general synthetic strategy, the substitution of lithium bases with less-nucleophilic magnesium amide bases was investigated (Scheme 5). Knochel has reported efficient methods for directed *ortho*-magnesiation of electron-deficient arenes, including those bearing fluorine atoms and nitrile groups. First, the directing group ability of *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate[19] was investigated with both monobasic and dibasic magnesium tetramethylpiperidide reagents. Treatment of **8** with dibasic $(tmp)_2Mg{\cdot}2LiCl$ complex, followed by transmetalation and trapping with geranyl bromide, resulted in a dialkylated arene as the only isolable product. Encouragingly, the nitrile was untouched



5a	R = OMe	**6a**	78%	**7a**	39%	**1a**	87%
5b	R = H	**6b**	78%	**7b**	40%	**1b**	88%
5c	R = Cl	**6c**	82%	**7c**	17%	**1c**	84%
5d	R = CN	**6d**	71%	**7d**	–	**1d**	–

Scheme 4 Synthesis of geranylated fluorophenols. *Reaction conditions*: (a) *i*-PrNCO (1.1 equiv), DMAP (0.05 equiv), THF, 60 °C; (b) TMEDA (1.1 equiv), TMSOTf (1.05 equiv), Et_2O, 25 °C, then TMEDA (2.0 equiv), *n*-BuLi (2.0 equiv), –78 °C, then geranyl bromide (1.25 equiv), –78 °C; (c) aq NaOH (2.5 equiv), EtOH, 25 °C. All values are isolated yields after recrystallization (**6**), chromatography (**7**), or distillation (**1**).



Scheme 5 Synthesis of nitrile **1d**. *Reaction conditions*: (a) $ClP(O)(NMe_2)_2$ (1.2 equiv), Et_3N (1.2 equiv), DMAP (0.1 equiv), THF, 25 °C; (b) tmpMgCl·LiCl (1.1 equiv), THF, 0 °C, then $ZnCl_2$ (1.2 equiv), THF, –40 °C, then CuCN·2LiCl (0.5 equiv), geranyl bromide (1.5 equiv), THF, –40 °C to 25 °C; (c) HCO_2H–EtOH–H_2O (1:9:1) (0.9 M), MW, 140 °C; (d) Boc_2O (1.5 equiv), Et_3N (2.2 equiv), DMAP (0.05 equiv), DCM, 25 °C.

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under these reaction conditions. To prevent overmetalation, the monobasic (tmp)MgCl·LiCl complex was substituted for the dibasic reagent. Gratifyingly, this led to the formation of the desired *ortho*-alkylation product **9** in good yield. The phosphorodiamidate moiety is crucial for directing magnesiation to the desired position. When compound **10** was treated with (tmp)MgCl·LiCl under identical conditions, magnesiation occurred at the most acidic position, leading to the undesired isomer **11**, even though *tert*-butyl carbonate is known to be an effective directing group for magnesium amides in other aromatic systems.[20] Removal of the directing group was accomplished by microwave-assisted acidic hydrolysis to afford phenol **1d**.

With all of the desired substrates **1a–d** in hand, the kinetics experiments outlined in Scheme 3 were carried out. To obtain the order in each reaction component, the loadings of catalyst (*S*)-**4**, sulfenylating agent **3**, and substrate **1** were varied from run to run, and the data were processed according to the variable time normalization analysis (VTNA) method described by Burés.[21–23] The VTNA semiquantitative data treatment permits the user to extract more information from fewer experiments, compared with classical methods, at the cost of slightly diminished accuracy (e.g. the treatment can easily differentiate between reaction orders of 2.0, 1.0, and 0.5, but not, perhaps, between 1.1, 1.0, and 0.9). As an example, for the conversion of **1c** into **2c**, the time-normalized rate plots from four different experiments (run at variable concentrations of each reactant, Exp1 through Exp4) only overlaid when the exponent terms within the time integral are equal to 0.5, 0.5 and 1.0 (Figure 1). Nearly identical behavior was likewise observed for all other substrates **1** (Table 1).

The results of these experiments were quite surprising; a drastically different kinetic profile as compared with earlier kinetic studies performed in this laboratory for related systems[12] was seen. For the sulfenocyclization of **1** to **2**, the reaction was observed to be first order in catalyst (*S*)-**4** and fractional order in both the substrate **1** (~0.5 order) and the sulfenylating agent **3** (also ~0.5 order). Similar fractional orders were obtained for all substrates, regardless of the electronic nature of the phenol (Table 1; see also the Supplementary Information). A catalyst order of 1.0 is consistent with sulfenyl-group transfer (thiiranium ion formation) as the rate-determining step, and is also consistent with previous mechanistic studies. The fractional orders observed for both **1** and **3** were unexpected, and are more difficult to explain. In particular, the presence of any nonzero order for sulfenylating agent **3** is puzzling, because the catalyst (*S*)-**4** is presumed to be saturated at all times (i.e., donor–acceptor complex ***i*** is presumed to be the resting state of the catalyst prior to the rate-determining step). The results indicate that, at least for the present system, the concentration of **3** *does* influence the rate of reaction, although the nature and origin of this influence remains unclear and is a topic of active study. The observation of a fractional order for substrate **1** was also surprising, as an order of 1.0 is expected for a rate-determining step that involves sulfenyl-group transfer between complex ***i*** and one molecule of **1**. Interestingly, similar fractional orders were obtained in the arene-terminated cyclization of the nonphenolic substrate **12a** to **13a** (first order in (*S*)-**4**, 0.7 order in **3**, and 0.5 order in **12a**) (Scheme 6). This observation rules out the possibility that

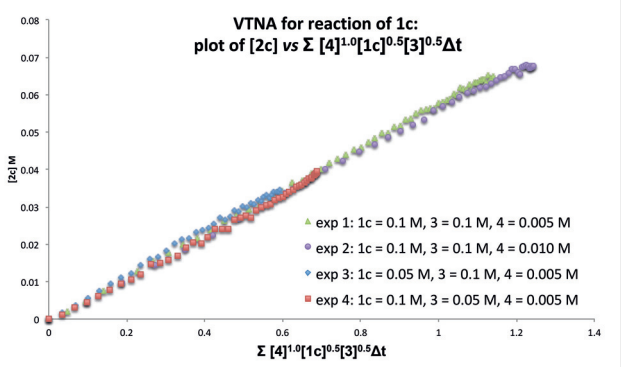
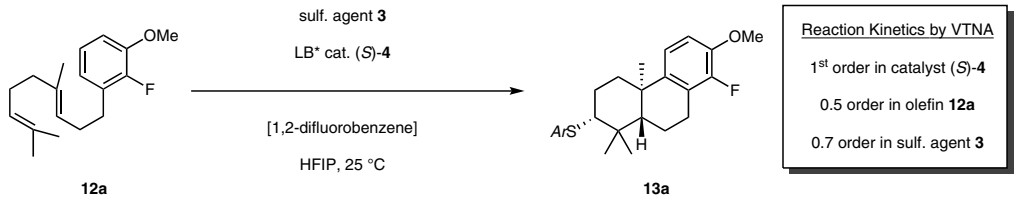


Figure 1 VTNA kinetic analysis of the sulfenocyclization reaction of **1c** in HFIP by analysis of four different experiments (exp 1 through exp 4). Values in the graph legend denote concentrations in molarity units.

Table 1 Results of VTNA Kinetic Analyses for the Reaction of Substrates **1a–d**

Substrate	Rate equation	k_{obs}
1a (R = OMe)	k_{obs}[(*S*)-**4**]^{1}[**1a**]$^{0.6}$[**3**]$^{0.5}$	0.062 ± 0.004
1b (R = H)	k_{obs}[(*S*)-**4**]^{1}[**1a**]$^{0.5}$[**3**]$^{0.4}$	0.051 ± 0.003
1c (R = Cl)	k_{obs}[(*S*)-**4**]^{1}[**1a**]$^{0.5}$[**3**]$^{0.5}$	0.055 ± 0.001
1d (R = CN)	k_{obs}[(*S*)-**4**]^{1}[**1a**]$^{0.5}$[**3**]$^{0.6}$	0.075 ± 0.001



Scheme 6 VTNA kinetic analysis of the sulfenylation reaction of **12a** in HFIP

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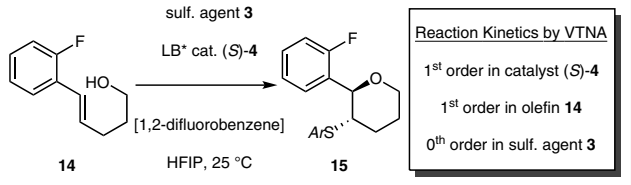
the fractional order in **1** might arise because of the necessity for dissociation from a phenolic hydrogen-bonded dimer.[24]

To ascertain whether this intriguing kinetic profile is an innate property of the polyene sulfenocyclization reaction or whether it is caused by carrying out the reaction in HFIP, the previously studied oxysulfenylation reaction[12] was performed in HFIP (Scheme 7). The results of this experiment (first order in catalyst **4**, first order in alkene **14**, and zeroth order in sulfenylating agent **3**) matched those obtained previously when the reaction was carried out in CH_2Cl_2 with mesic acid. This outcome suggests that the polyene sulfenocyclization indeed displays a unique kinetic behavior, which clearly warrants further and more-detailed investigation.[25]



Scheme 7 VTNA kinetic analysis of the sulfenylation reaction of **14** in HFIP

As to the relative rates of reaction of **1a** through **1d**, the value of k_{obs} seemed immune to changes in the electronic properties of the terminating phenol. From a qualitative assessment of the raw concentration–time data (Figure 2), one might conclude that the reaction of electron-deficient **1d** (R = CN) is marginally slower compared with those of **1a–c**. These differences are quite small, however, especially when compared with the over sixfold rate difference between electron-rich and electron-deficient substrates originally reported by Johnson.[14] Furthermore, qualitatively, the rate of C-capture (substrate **12a**) appears essentially identical to the rate of O-capture (substrates **1a–d**). However, it is important to note that a Hammett plot of the rate data from Johnson's study indicates two distinct mechanistic regimes. For the electronically deficient terminating arenes, the rate was strongly influenced by the electronic character of the substrate ($\rho = -1.4$), whereas for electron-rich terminating arenes, this dependence was much weaker ($\rho = -0.2$). This implies a potential change in the rate-determining step from capture (for electron-deficient terminators) to initiation (for electron-rich terminators). In the present case, one cannot exclude the possibility that all of the phenols **1a–d** are sufficiently electron-rich for all four cyclizations to operate in the latter mechanistic regime. Alternatively, one also cannot exclude the possibility that **1a–d** are too similar (i.e. the *para*-substituent exerts little influence on the overall electronic character compared with the other three substituents, which are preserved across the series), which would result in similar rates of reaction in either mechanistic regime. However, the fact that a comparable reaction rate was measured for **12a** containing a markedly less-nucleophilic terminator strongly suggests that the rate-determining step is *not* the nucleophilic capture of a thiiranium ion, consistent with previous mechanistic proposals.

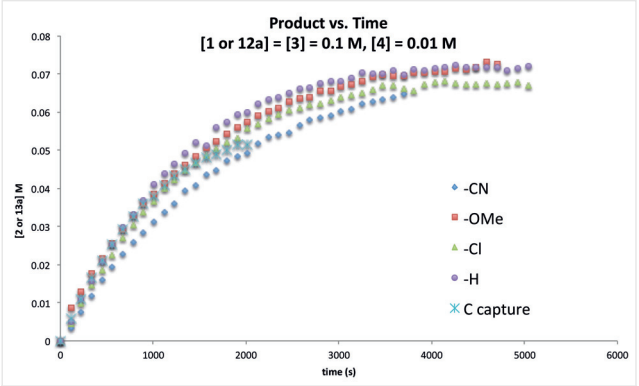


Figure 2 Reaction progression for the sulfenocyclization of **1a–d** and **12a**

To summarize, the kinetic behavior of Lewis base-catalyzed polyene sulfenocyclization reactions in HFIP[26] demonstrates the following salient features: (1) the reaction rate shows a fractional-order (~0.5) concentration dependence on both reactants and a first-order concentration dependence on the catalyst, (2) this kinetic profile is unique to the polyene substrate and is observed for both carbon- and oxygen nucleophiles, and (3) the reaction rate is essentially invariant across the substituted phenols tested. The fractional orders indicate a more complex mechanism than previously postulated (Scheme 2). One possibility includes a preequilibrium substrate–aggregate dissociation step. Another possibility is a mechanistic sequence in which both the reactants are involved in elementary steps that promote the reaction as well as in separate elementary steps that inhibit the overall transformation. Although the kinetic and mechanistic picture is clearly incomplete, these experiments represent an important and necessary step in understanding Lewis base-catalyzed transformations, and might provide further insight into optimization of sulfenocyclizations to include more-diverse polyene substrates. A satisfactory explanation that justifies the unusual kinetic profile remains elusive and is the subject of ongoing mechanistic studies.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690111.

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(18) An additional phenol **1e** (R = Me) was prepared from **5e** (R = Me) in an analogous fashion. Unfortunately, it was discovered that the ^{19}F NMR resonances of **1e** and product **2e** overlapped when HFIP was used as the reaction solvent. As a result, rate data could not be obtained for this substrate by using this experimental setup.
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(24) An additional homogeranylarene substrate **12b** (see Supplementary Information) was prepared, but did not convert cleanly into **13b** under the standard reaction conditions, indicating that the arene of **12b** is a poor nucleophile compared with **12a**. This disparity is rationalized by the large difference between the σ_{meta} (+0.12) and σ_{para} (–0.27) Hammett constants for the methoxy group.
(25) In addition to nucleophilic ring-opening reactions at carbon, thiiranium ions are also susceptible to nucleophilic attack at sulfur. The relative rates of these reactions are dependent on the substitution patterns of the thiiranium ion; see: Lucchini, V.; Modena, G.; Pasi, M.; Pasquato, L. *J. Org. Chem.* **1997**, *62*, 7018; It is noted that differences in reactivity probably exist between thiiranium ions resulting from the trisubstituted alkene **1** (or **12**) and the disubstituted alkene **14**, although it is unclear how these differences would impact the overall mechanistic picture.
(26) **Hexahydroxanthenes 2a–d; General Procedure**
A 50-mL round-bottomed flask equipped with a stirrer bar was charged with sulfenylating agent **3** (1.01 mmol, 1.01 equiv), HFIP (10 mL), and substrate **1** (1.0 mmol). Catalyst (*S*)-**4** (0.01 mmol, 0.01 equiv) was added and the mixture was stirred at 25 °C for 12 h. Some white precipitates and/or a color change were typically observed at longer reaction times. Upon completion of the reaction [TLC; hexanes–CH_2Cl_2 (80:20)], the mixture was diluted with CH_2Cl_2 (5 mL) and volatile components were removed by rotary evaporation (30 °C, 15 mm Hg). The crude product was purified by chromatography [silica gel, hexanes–CH_2Cl_2 (gradient elution)] to give a white solid. The product was triturated in boiling MeOH or EtOH (~1.5 mL) and the mother liquor was decanted to afford **2** in >99% purity (quantitative ^1H NMR analysis).
(2*R*,4a*R*,9a*R*)-2-[(2,6-Diisopropylphenyl)thio]-5-fluoro-7-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (2a)
White solid; yield: 355.5 mg (75%); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.7 Hz, 1 H), 7.18 [d, *J* = 7.7 Hz, 2 H, HC(19)], 6.52 [dd, *J* = 12.3, 2.7 Hz, 1 H, HC(11)], 6.41 [br s, 1 H, HC(9)], 3.96 (hept, *J* = 6.7 Hz, 2 H), 3.73 (s, 3 H), 2.77 (dd, *J* = 16.7, 5.3 Hz, 1 H), 2.75–2.70 (m, 1 H), 2.69 (dd, *J* = 12.1, 3.9 Hz, 1 H), 1.97 (dt, *J* = 12.7, 2.9 Hz, 1 H), 1.76 (dd, *J* = 12.6, 5.3 Hz, 1 H), 1.74–1.64 (m, 1 H), 1.61 (dq, *J* = 14.0, 3.7 Hz, 1 H), 1.48 (td, *J* = 13.3, 3.6 Hz, 1 H), 1.41 (s, 3 H), 1.26 (d, *J* = 6.8 Hz, 6 H), 1.23 (s, 3 H), 1.20 (d, *J* = 6.9 Hz, 6 H), 1.08 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.1, 152.5 (d, J_{C-F} = 10.0 Hz), 152.0 (d, J_{C-F} = 244.4 Hz), 135.3 (d, J_{C-F} = 11.4 Hz), 130.3, 129.2, 124.9 (d, J_{C-F} = 3.2 Hz), 123.9, 109.0 (d, J_{C-F} = 3.0 Hz), 101.3 (d, J_{C-F} = 21.8 Hz), 77.0, 60.9, 55.9, 49.6, 39.9, 38.7, 31.5, 28.9, 26.7, 25.0, 24.1, 23.9 (d, J_{C-F} = 2.7 Hz), 19.7, 16.6.

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