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Catalytic, Enantioselective, Intramolecular Carbosulfenylation of Olefins. Mechanistic Aspects: A Remarkable Case of Negative Catalysis

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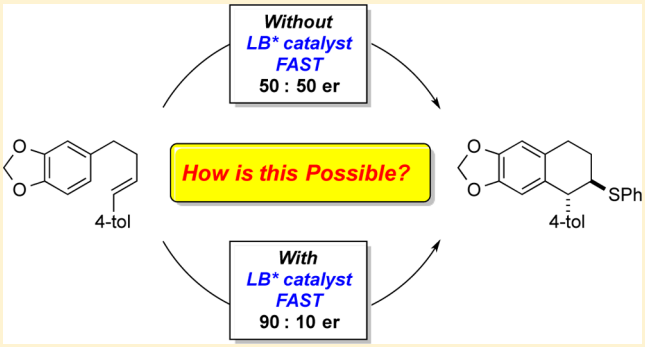
Supporting Information

ABSTRACT: In the course of developing an enantioselective, Lewis base/Brønsted acid co-catalyzed carbosulfenylation of alkenes, a seemingly impossible conundrum arose: How could a catalyst inhibit a stoichiometric reaction? Despite the observation of very good enantioselectivities, the rate of the uncatalyzed reaction (i.e., no Lewis base) was found to be comparable to or slightly faster than that of the catalyzed process. A combination of detailed kinetic and spectroscopic studies revealed that the answer is not the direct involvement of the Lewis base catalyst, but rather the secondary consequences of its conversion to the catalytically active sulfenylating agent. Generation of the chiral sulfenylating species is accompanied by the formation of equimolar amounts of sulfonate ion and phthalimide which serve to buffer the remaining Brønsted acid and thus inhibit the racemic background reaction. Thus, the actual background reaction operative under catalytic conditions is not well mimicked by simply removing the catalyst.



INTRODUCTION AND BACKGROUND

1. Brønsted Acid–Lewis Base Co-catalytic Carbosulfenylation of Alkenes. Recently published studies from these laboratories detail the optimization and development of a catalytic, enantioselective carbosulfenylation of alkenes using electron-rich arenes as the nucleophilic partner (Scheme 1).[1] In the course of optimization of this process, it was discovered that the enantioselectivity was not reliably reproduced from orienting experiments (0.2 mmol) to descriptive scale (1.0 mmol). Consideration of the experimental variables that could be responsible led to detailed reevaluation of the role of the Brønsted acid co-catalyst, methanesulfonic acid (MsOH). Foregoing studies in these laboratories on the related heterofunctionalization of alkenes revealed the need for a Brønsted acid co-catalyst to enable Lewis base activation of both Group 16 and Group 17 electrophiles.[2] However, in none of these previous studies was the Brønsted acid dependence found to be problematic and, in general, a full equivalent with respect to the substrate could be employed without affecting reproducibility. For the carbosulfenylation, empirical optimization outlined in the preceding studies[1] led to the use of 0.75 equiv of ethanesulfonic acid ($EtSO_3H$) for all preparative experiments. Satisfactory rates and reproducible enantioselectivities were found.

Despite the successful deployment of these conditions for the method, it was nonetheless of significant interest to elucidate the basis for the heightened sensitivity of this particular sulfenofunctionalization toward the Brønsted acid. In addition, as part of our general program in Lewis base activation of Lewis acids, we were interested in a more fundamental understanding of the role of all reaction components and the mechanistic underpinnings of this type of catalysis.

2. Objectives of This Study. The goal of this study was to provide a detailed understanding of the mechanism of catalysis of carbosulfenylation using the combination of chiral Lewis base (*S*)-**1** and Brønsted acids MsOH and $EtSO_3H$ with **2** and substrate **3** (Scheme 1). To gain insight into this process, a number of different spectroscopic and kinetic studies were carried out to provide answers to the following questions: (1) What are the rates of the catalyzed and uncatalyzed reactions promoted by varying amounts of MsOH and $EtSO_3H$? (2) What is the protonation state of the sulfenylating agent under catalytic conditions with MsOH and $EtSO_3H$? (3) What is the resting state of (*S*)-**1** under catalytic conditions? (4) What is the structure of the catalytically active species? (5) What is the protonation state of the catalyst in the absence of sulfenylating agent **2**? The answers to these questions are provided below and together provide a refined picture of the mechanism of catalysis and a striking illustration of how seemingly contradictory results can be understood in the light of thorough mechanistic analysis.

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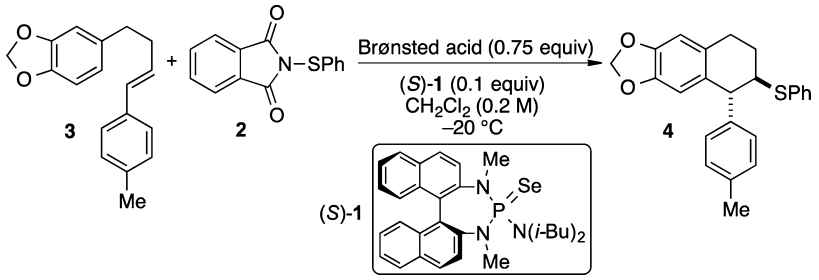
Scheme 1



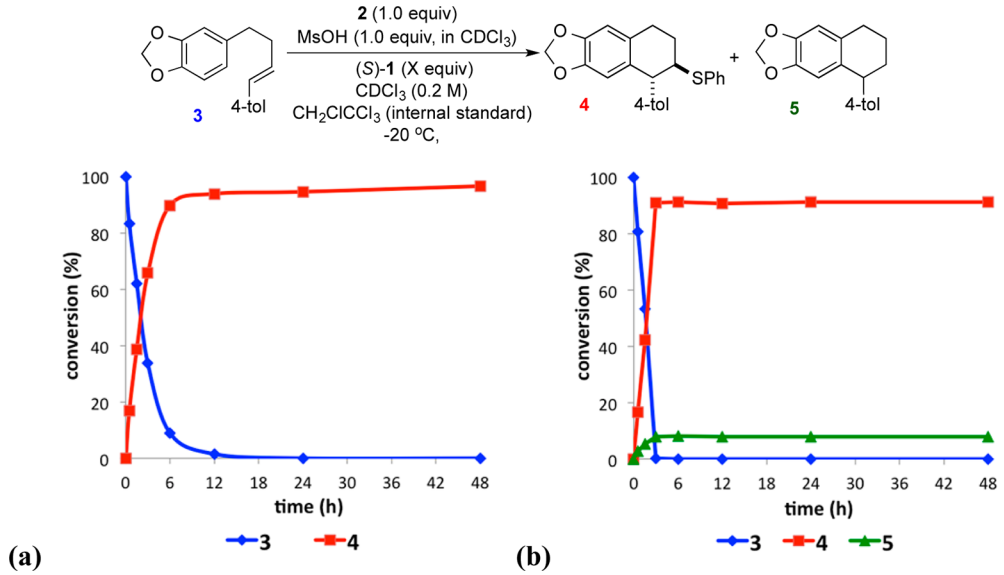


Figure 1. Reactions with MsOH (1.0 equiv). (a) Rate profile for catalyzed cyclization with 0.1 equiv of (*S*)-**1**. (b) Rate profile for uncatalyzed cyclization.

RESULTS

1. Rates of Catalyzed and Uncatalyzed Reactions. To establish the rates of the Lewis base catalyzed cyclization and the uncatalyzed cyclization in the presence of both Brønsted acids, MsOH and $EtSO_3H$, NMR kinetic analysis with an internal standard was performed at −20 °C for the reaction of alkene **3** to produce **4**. Reactions were carried out at 0.2 M concentrations.[3]

1.1. Observations on the Purity of Alkylsulfonic Acids. As part of the optimization experiments designed to elucidate the origin of the variable enantioselectivity, the purity (i.e., hydration level) of the sulfonic acids was investigated. The hydration level of the highly hygroscopic alkylsulfonic acids could be specified by integration of the OH signal in the ^1H NMR spectra in $CDCl_3$. It was found that the hydration level significantly influenced the rate and enantioselectivity of the cyclization such that high hydration levels (e.g., 20 mol % water) led to slower, but more selective reactions. Accordingly, to vouchsafe the quality of the sulfonic acid for reproducibility, both MsOH and $EtSO_3H$ were rigorously dried by established procedures (see Supporting Information), and the hydration levels were checked by ^1H NMR integration on a regular basis. All of the experiments described below were performed with MsOH and $EtSO_3H$ of specified purity.

1.2. Reaction Rates at 0.2 M. The time course for the catalyzed reaction with MsOH at the preparative reaction concentration (Figure 1a) reveals clean and high-yielding conversion of **3** to **4**, reaching completion in 12 h.[4] Surprisingly, the uncatalyzed reaction is significantly faster than the catalyzed process and follows apparent zeroth-order kinetic behavior. Curiously, the formation of **4** was accompanied by formation of **5**, the product of proton-initiated cyclization (ca. 15%). Thus, the competitive production of racemic **4** at a rate comparable to that of the catalyzed process clearly reveals the problems associated with irreproducible enantioselectivity in the presence of MsOH.

The time courses for the corresponding reactions in the presence of $EtSO_3H$ are similar to those in the presence of MsOH. The catalyzed cyclizations at various loadings of $EtSO_3H$ (Figure 2a) display normal first-order kinetic behavior, but in this case, the initial rates of the reaction at all loadings of $EtSO_3H$ are similar. Interestingly, the enantiomeric composition of **4** eroded only slightly at higher loadings of $EtSO_3H$.[5]

The uncatalyzed reactions of **3** in the presence of varying amounts of $EtSO_3H$ (Figure 2b,c) mimic the results obtained with MsOH. Interestingly, with 1.00 equiv of $EtSO_3H$, the rate of formation of **4** was comparable to that in the presence of (*S*)-**1** and again displayed zeroth-order kinetic behavior. Here again, **5**, the product of proton-initiated cyclization, was formed in minor amounts.

Four critical insights were gained from the low-temperature NMR kinetic studies: (1) Both MsOH and $EtSO_3H$ are competent Brønsted acids for both the catalyzed and the uncatalyzed sulfenocarbocyclizations. (2) Proton-initiated cyclization to form **5** was observed in the absence of catalyst (*S*)-**1** but not in its presence. (3) Overall first-order kinetic

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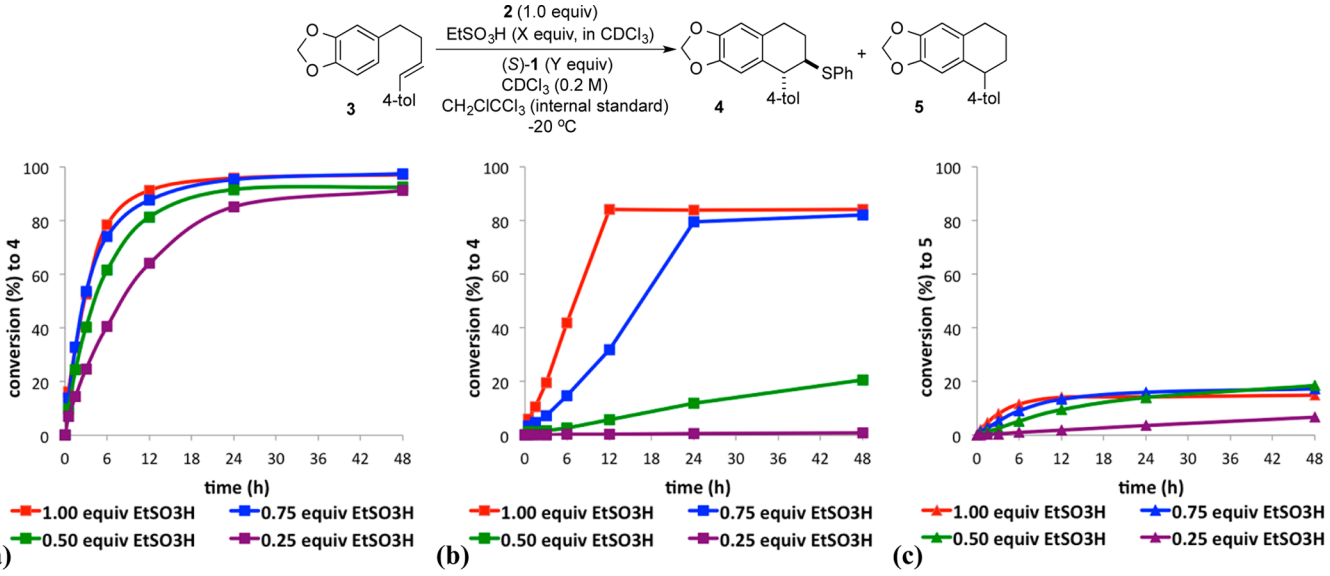
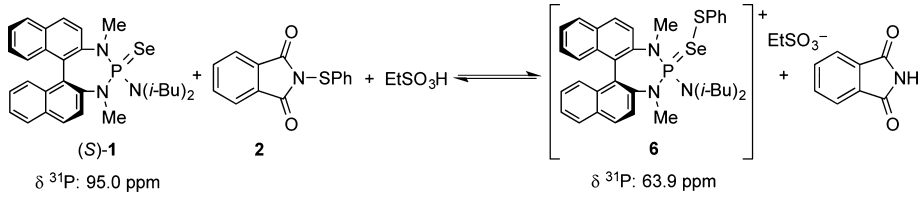


Figure 2. Reactions with $EtSO_3H$ (X equiv). (a) Rate profile for catalyzed cyclization with 0.1 equiv of (*S*)-**1**. (b) Rate profile for formation of **4** in the uncatalyzed cyclization. (c) Rate profile for formation of **5** in the uncatalyzed cyclization.

Table 1. Determination of Equilibrium for Formation of 6 at 8.3 μM in (*S*)-1



reagents (equiv)			^{31}P NMR (δ, ppm)	
i-Bu cat.	PhthSPh	$EtSO_3H$	at −20 °C	at −50 °C
1.0	10.0	0.0	95.0	
1.0	10.0	1.0	94.9 (br)	95.2 (br)
1.0	10.0	2.5	94.3 (br), 64.7 (br)	95.4 (br), 63.9 (br) (ratio = 1.00:0.91)
1.0	10.0	5.0	63.7 (br)	64.0
1.0	10.0	7.5	63.7	64.0
1.0	10.0	10.0	63.6	63.9

behavior was observed under catalysis by (*S*)-**1**. (4) Overall zeroth-order kinetic behavior was observed for the formation of **4** in the absence of (*S*)-**1**.[3]

In addition to these important insights, the kinetic analysis also raises interesting questions: (1) How is it possible to obtain enantiomerically enriched **4** if the background, uncatalyzed, racemic reaction is comparable to ($EtSO_3H$) or faster than (MsOH) the reaction catalyzed by chiral Lewis base (*S*)-**1**? (2) How can the formation of **5** in the background reaction be reconciled with its absence in the catalyzed reactions? Answers to these questions require a better understanding of what actually constitutes the background reaction and will be addressed in the following sections.

2. Catalyst Resting State and Titration Studies. *2.1. Identifying and Quantifying the Catalytically Active Species.* Foregoing studies with (*S*)-**1** established that the catalytically active sulfenylating agent is formed by sulfenyl group transfer from **2** to the selenophosphoramide mediated by a Brønsted acid. In view of the unusual dependence of the rate of catalyzed sulfenocarbocyclization on acid loading (Figure 2a), it was of interest to establish the magnitude of the pre-equilibrium formation of that species. Thus, low-temperature NMR experiments were undertaken under catalytic conditions without substrate (**2**/(*S*)-**1**, 10.0:1.0) with varying amounts of $EtSO_3H$ at −20 °C (8.3 μM in (*S*)-**1**). At this temperature, the exchange between (*S*)-**1** and **6** was too fast to allow accurate integration, so the experiments were repeated at −50 °C (Table 1).[6] Under these conditions, both species could be detected simultaneously, and this revealed that the catalyst becomes saturated as **6** somewhere between 2.5 and 5.0 equiv of $EtSO_3H$

Table 2. Determination of Equilibrium for Formation of 6 at 25 μM in (*S*)-1

reagents (equiv)			ratio of ^{31}P NMR signals at 95 and 64 ppm (−57 °C)
i-Bu cat.	PhthSPh	$EtSO_3H$	
1.0	10.0	1.0	3.12:1.00
1.0	10.0	2.5	1.00:1.86
1.0	10.0	3.0	1.00:4.07
1.0	10.0	3.5	1.00:24.88
1.0	10.0	4.0	1.00:54.49

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Method 1: Solvent-separated ion pair

Catalyst (5 μmol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 μL $CDCl_3$, -50 °C) ^{31}P NMR 95 ppm : 64 ppm ratio: 1.00 : 0.91

Catalyst	Phth−SPh	$EtSO_3H$	⇌	[catalyst−SPh]$^+$	[$EtSO_3$]$^-$	PhthH
8.3 μM	83.3 μM	20.8 M		0 μM	0 μM	0 μM
8.3 - X μM	83.3 - X	20.8 - X μM		X μM	X μM	X μM

(8.3 - X) : X = 1.00 : 0.91

X = 3.97

$$K_{eq} = \frac{X^3}{(8.3 - X)(83.3 - X)(20.8 - X)} = 1.08 \times 10^{-2}$$

Catalyst (15 μmol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 μL $CDCl_3$, -57 °C) ^{31}P NMR 95 ppm : 64 ppm ratio: 1.00 : 1.86

Catalyst	Phth−SPh	$EtSO_3H$	⇌	[catalyst−SPh]$^+$	[$EtSO_3$]$^-$	PhthH
25 μM	250 μM	62.5 μM		0 μM	0 μM	0 μM
25 - X μM	250 - X μM	62.5 - X μM		X μM	X μM	X μM

(25 - X) : X = 1.00 : 1.86

X = 16.3

$$K_{eq} = \frac{X^3}{(25 - X)(250 - X)(62.5 - X)} = 4.55 \times 10^{-2}$$

Figure 3. Calculation of K_{eq} for **6** assuming solvent-separated ion pair structure.

Method 2: Intimate ion pair

Catalyst (5 μmol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 μL $CDCl_3$, -50 °C) ^{31}P NMR 95 ppm : 64 ppm ratio 1.00 : 0.91

Catalyst	Phth−SPh	$EtSO_3H$	⇌	[catalyst−SPh]$^+$ [$EtSO_3$]$^-$	PhthH
8.3 μM	83.3 μM	20.8 μM		0 μM	0 μM
8.3 - X μM	83.3 - X	20.8 - X μM		X μM	X μM

(8.3 - X) : X = 1.00 : 0.91

X = 3.97

$$K_{eq} = \frac{X^2}{(8.3 - X)(83.3 - X)(20.8 - X)} = 2.73 \times 10^{-3}$$

Catalyst (15 μmol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 μL $CDCl_3$, -57 °C) ^{31}P NMR 95 ppm : 64 ppm ratio 1.00 : 1.86

Catalyst	Phth−SPh	$EtSO_3H$	⇌	[catalyst−SPh]$^+$ [$EtSO_3$]$^-$	PhthH
25 μM	250 μM	62.5 μM		0 μM	0 μM
25 - X μM	250 - X μM	62.5 - X μM		X μM	X μM

(25 - X) : X = 1.00 : 1.86

X = 16.3

$$K_{eq} = \frac{X^2}{(25 - X)(250 - X)(62.5 - X)} = 2.80 \times 10^{-3}$$

Figure 4. Calculation of K_{eq} for **6** assuming intimate ion pair structure.

(with respect to (*S*)-**1**). Repeating the titration experiments at −57 °C and at higher concentration (25 μM in (*S*)-**1**) allowed a more accurate determination of the saturation point (Table 2). Thus, approximately 4.0 equiv of $EtSO_3H$ was needed to convert ca. 98% of (*S*)-**1** into **6**, whereas with 2.5 equiv of $EtSO_3H$ only 65% of (*S*)-**1** was converted.

2.2. Calculation of Equilibrium Constants (K_{eq}). Equilibrium constants were calculated for the two preceding experiments both at the 2.5 equiv data points. Calculations were carried out assuming that the catalytically active species **6** exists either as a solvent-separated ion pair (Figure 3) or as an intimate ion pair (Figure 4). Solving the equations at two concentrations for the tight ion pair afforded the same equilibrium constant, whereas solving for the solvent-separated ion pair did not. Thus, it can be safely (and logically) concluded that **6** is a tight ion pair in dichloromethane under the reaction conditions.

*2.3. Protonation State of Phenylsulfenophthalimide (**2**) and the Catalyst ((S)-**1**).* To gain insight into the curious behavior of noncatalyzed cyclizations, the protonation states of (*S*)-**1** and **2** were determined by VT-NMR experiments. The exchange rate between **2** and **2**·$H^+RSO_3^-$ was sufficiently rapid at −20 °C (125 MHz ^{13}C) to allow observation of a sharp singlet for the carbonyl groups that shifted from 167.8 ppm (no RSO_3H) to 168.9 ppm (10.0−15.0 equiv of RSO_3H, Figure 5a).

These data were fitted to a curve with nonlinear regression (single-site total binding model). Extrapolation of the curve for MsOH gave 169.2 ppm as the chemical shift of **2**·$H^+RSO_3^-$, whereas doing the same for $EtSO_3H$ gave 169.0 ppm. These extrapolated values lead to a single, apparent K_{eq} = 3.63 M^{-1} for MsOH and K_{eq} = 2.05 M^{-1} for $EtSO_3H$ (K_d = 0.276 ± 0.018 M for MsOH and K_d = 0.488 ± 0.049 M for $EtSO_3H$). As expected, the K_{eq} value for MsOH is larger than that for $EtSO_3H$, because the ability of MsOH to protonate **2** is greater than that of $EtSO_3H$. By using the average of the extrapolated

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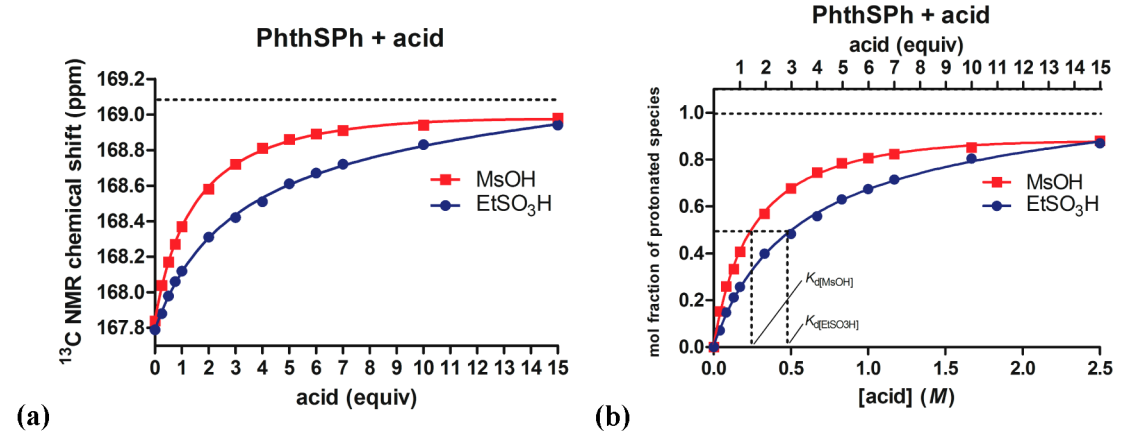

Figure 5. Titration curves for protonation of **2** with MsOH and $EtSO_3H$.

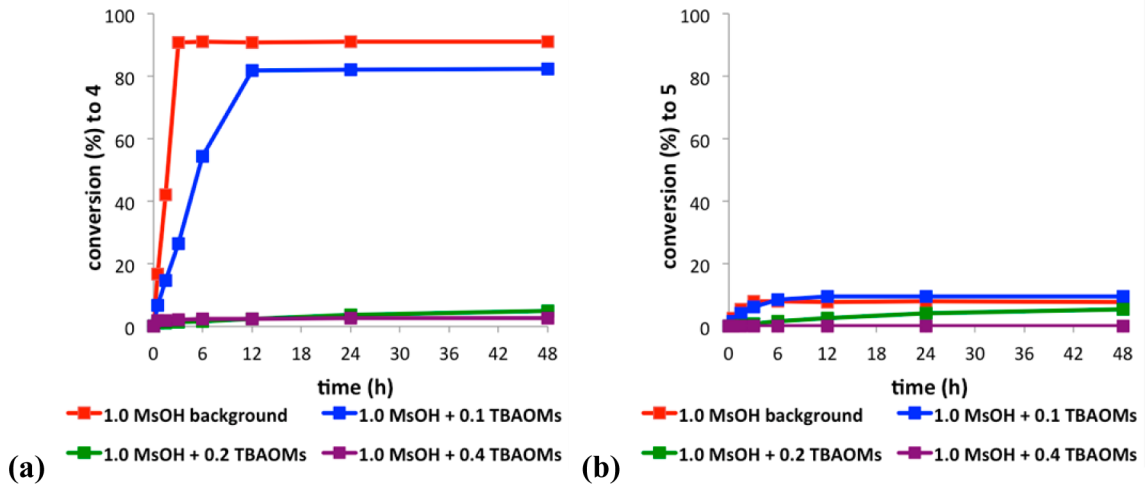

Figure 6. Reactions with MsOH (1.0 equiv) and $Bu_4N^+OMs^-$. (a) Rate profile for formation of **4** in the uncatalyzed cyclization. (b) Rate profile for formation of **5** in the uncatalyzed cyclization.

chemical shifts of **2**·$H^+RSO_3^-$, the mole fraction of **2**·$H^+RSO_3^-$ present at various loadings of acid could be calculated (Figure 5b); at 1.00 equiv of acid, **2**·$H^+RSO_3^-$ is present at 41 mol % with MsOH and 26 mol % with $EtSO_3H$. These numbers represent a significant amount of an active, achiral sulfenylating agent that is responsible for the background reaction. However, given the high enantioselectivities observed, the actual amount of **2**·$H^+RSO_3^-$ must be significantly less, the reason for which is addressed below.

The protonation of catalyst (*S*)-**1** was examined briefly. Addition of 1.0 equiv of $EtSO_3H$ to a 0.1 mM solution of (*S*)-**1** in $CHCl_3$ had no effect on the ^{31}P NMR chemical shift, indicating a negligible degree of protonation.

3. Effect of the Presence of Sulfonate Anion on the Rate of the Uncatalyzed Reaction. The realization that (1) formation of catalytically active species **6** is quantitative under the catalytic reaction conditions, (2) sulfenylating agent **2** is partially protonated under these conditions, and (3) both of these species carry sulfonate counterions led to the recognition that the action of the remaining Brønsted acid could be attenuated by the buffering effect of the sulfonate. Thus, a modified version of the background reaction was formulated in which the amounts of **6** and protonated **2** formed under catalytic conditions were mimicked by adding varying amounts of tetrabutylammonium mesylate ($Bu_4N^+OMs^-$) (Figure 6).

The results were striking: whereas 0.1 equiv of $Bu_4N^+OMs^-$ slows the formation of **4** (but not **5**), 0.2 equiv of $Bu_4N^+OMs^-$ was able to almost completely shut down the formation of **4** and **5** in the presence of 1.0 equiv of MsOH. This observation implies that the *actual* background reaction operating under catalytic conditions is *not* accurately represented by simply omitting the catalyst. Moreover, reconsideration of the components present under catalytic conditions reveals that the actual amount of MsOH available is only 0.9 equiv and that 0.1 equiv of phthalimide is also present, both as a consequence of the formation of **6**. Figure 7a shows the rate profile for the uncatalyzed reaction with 0.9 equiv of MsOH and 0.1 equiv of $Bu_4N^+OMs^-$; Figure 7b shows the rate for the same uncatalyzed reaction but with also 0.1 equiv of phthalimide. Here again, suppression of the formation of **4** is striking, illustrating that both methanesulfonate and phthalimide are serving as buffers to attenuate the acidity of MsOH in the medium. Figure 7c shows the superposition of all of these experiments.

It is now easy to see how a catalyzed reaction (black line) can be slower than the corresponding uncatalyzed reaction (red line) and still give rise to high enantioselectivities. One must consider the circumstances under which the uncatalyzed reaction is proceeding under the conditions of the catalyzed

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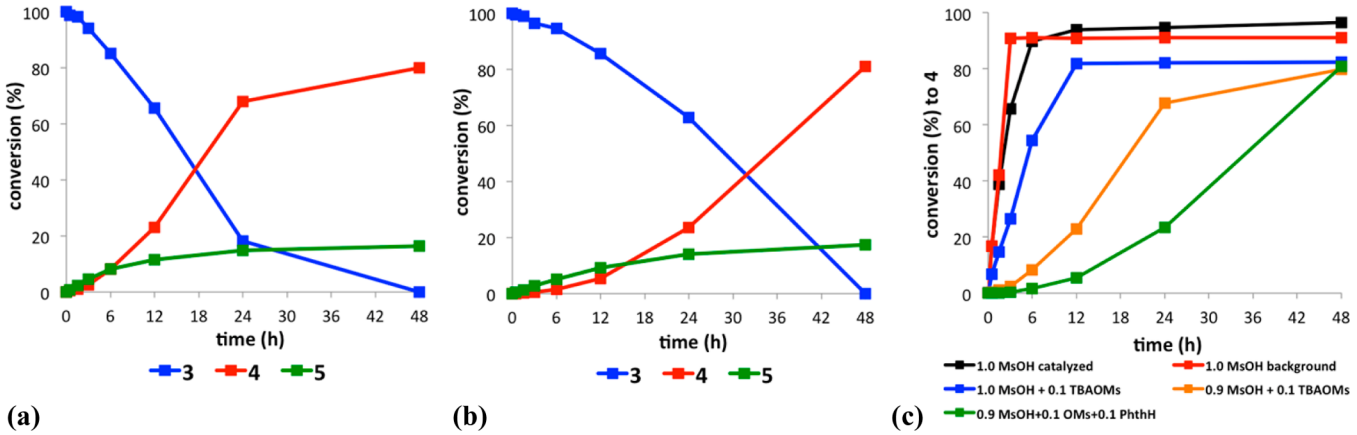

Figure 7. (a) Rate profile for the uncatalyzed reaction with 0.9 equiv of MsOH and 0.1 equiv of $Bu_4N^+OMs^-$. (b) Rate profile for the uncatalyzed reaction with 0.9 equiv of MsOH, 0.1 equiv of $Bu_4N^+OMs^-$, and 0.1 equiv of phthalimide. (c) Superposition of all reactions with MsOH; only formation of **4** is depicted.

process. Simply removing the catalyst is not sufficient to accurately mimic those conditions.

The true background formation of **4** under "catalytic conditions" was significantly slower than assumed on the basis of the results shown in Figure 7c. In the time required for complete consumption of **3** under catalytic conditions, only 8.6% of **4** is produced in the background reaction. Obviously, this amount would be considerably less in the catalyzed reaction because the concentration of **3** would be decreasing faster (and the amount of phthalimide would be increasing faster) as a result of the productive enantioselective pathway. However, the formation of byproduct **5**, which is not observed in any of the catalytic reactions, suggests that this experiment is still not perfectly mimicking the actual catalytic reaction conditions.

DISCUSSION

1. Role of the Brønsted Acid. The irreproducibility of the catalytic sulfenocarbocyclizations upon scale-up for descriptive purposes revealed a dramatic sensitivity to the Brønsted acid that was not seen in the preceding studies on sulfenoetherification reactions.[2a] Systematic reinvestigation of the effects of Brønsted acid loading on the rate and selectivity of the reactions, the formation of the catalytically active sulfenylating agent, and the protonation equilibria for **2** was highly informative and revealed a dramatic sensitivity of the reaction behavior to the stoichiometry of the acid and also overall concentration.

1.1. Comparison of Methane- and Ethanesulfonic Acids. The Brønsted acidity of sulfonic acids has been the subject of intense study for many years.[7] Alkylsulfonic acids are classified as "moderately strong acids", with pK_a's between +2 and −2, and as such are amenable to a variety of acidity determinations. In water, methanesulfonic acid has pK_a = −1.92, whereas that of ethanesulfonic acid is −1.68. Similarly small differences have been found in DMSO and acetonitrile. The slightly weaker acidity of $EtSO_3H$ has been manifested in all of the experiments described above: both catalyzed and uncatalyzed cyclizations of **3** proceed more slowly with $EtSO_3H$ than with MsOH.[8] The preparative advantage of $EtSO_3H$ that was used for all descriptive cyclizations arises from the slightly larger difference in the catalyzed and uncatalyzed reactions at lower loadings and also the lower melting point that allowed cold delivery of the acid.

1.2. Effect of Brønsted Acid on the Rate and Enantioselectivity of the Sulfenocarbocyclization. The use of MsOH (1.0 equiv) in the catalytic sulfenocarbocyclization led to a rapid consumption of the alkene, leveling off at 98.5% conversion at 12 h to afford **4** with a 75:25 er (Figure 1a). In the absence of catalyst (*S*)-**1**, the reaction profile showed zeroth-order decay, leveling off at >99% conversion at 3 h.[9] Under these conditions, the product composition was ca. 91% **4** and 8% **5**.

The use of $EtSO_3H$ in varying stoichiometries led to very similar reaction profiles albeit at overall lower rates compared to MsOH. The sulfenocarbocyclization of **3** proceeded with normal first-order kinetics to afford **4** with highly reproducible and higher enantioselectivities (ca. 92.5:7.5 er) (Figure 2a). With 1.0 equiv of $EtSO_3H$ the rates of the catalyzed and uncatalyzed reactions are comparable, leveling off at 98.6% conversion of **3** at 24 h with (*S*)-**1** and 99.3% conversion at 12 h without (*S*)-**1**. Here again, the uncatalyzed reaction is competitive at 1.00 and 0.75 equiv of $EtSO_3H$ (Figure 2b).[10] The reason for the difference between MsOH and $EtSO_3H$ will be discussed below in the section on protonation equilibria with **2**.

1.3. Effect of Brønsted Acid on the Resting State of the Catalyst. The unusual similarity of the rate profiles for the catalyzed sulfenocarbocyclization in the presence of various amounts of $EtSO_3H$ (Figure 2a) stimulated an investigation into the effect of the Brønsted acid on the conversion of catalyst (*S*)-**1** into the catalytically active sulfenylating agent **6**. Low-temperature ^{31}P NMR titration experiments revealed that catalyst (*S*)-**1** becomes saturated as **6** with ca. 4.0 equiv of $EtSO_3H$ and 10.0 equiv of **2** with respect to (*S*)-**1** (i.e., 0.40 equiv with respect to **2** and substrate **3** under catalytic conditions). Thus, the similarity of rates for 1.00, 0.75, and 0.50 equiv of $EtSO_3H$ and the lower rate for 0.25 equiv can be readily understood from the amount of active sulfenylating agent **6** present. Above 0.4 equiv of $EtSO_3H$, the catalyst is saturated, and thus the rate has reached a maximum.

An additional insight into the nature of the active sulfenylating agent was secured by taking advantage of the fact that the equilibrium formation of **6** was measured at two different concentrations (Figures 3 and 4). The K_{eq} was calculated at both concentrations (using data from 2.5 equiv of $EtSO_3H$) assuming that **6** was either a solvent-separated ion pair (Figure 3, Method 1) or an intimate ion pair (Figure 4,

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Method 2). Interestingly, the solution for the two concentrations using Method 1 produced two different K_{eq}'s, whereas the solution using Method 2 gave nearly identical K_{eq}'s. From these data, we assume that the catalytically active species is an intimate ion pair in dichloromethane.

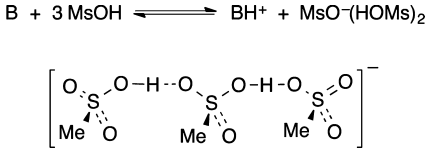
1.4. Protonation Equilibria for N-Phenylsulfenylphthalimide. Sulfenylating agent **2** was shown to be significantly protonated under standard reaction conditions (0.2 M, 1.00 equiv of RSO_3H). The high rate of the uncatalyzed reaction (in the absence of (*S*)-**1**) can be ascribed to the reactivity and concentration of **2**·$H^+RSO_3^-$. The greater *difference* in the rates of the catalyzed and uncatalyzed reactions for $EtSO_3H$ compared to MsOH can be understood from the differing consequences of their acidities. The rates of the catalyzed reactions are very similar because these reactions are governed by the concentration of the active sulfenylating agent **6**, which reaches its (saturated) maximum in the presence of both acids at 1.00 equiv loading. However, the weaker proton-donating strength of $EtSO_3H$ compared to MsOH, as illustrated in the measured K_{eq}'s of protonation of **2**, has a greater rate-attenuating effect on the uncatalyzed reaction, thus leading to a larger "split" in the catalyzed/uncatalyzed rates, which leads to a better-behaved system for enantioselectivity.

The dramatic drop in the rate of the uncatalyzed reaction upon the addition of *n*-$Bu_4N^+OMs^-$ and phthalimide together with the attendant decrease in the amount of MsOH implies that the concentration of **2**·$H^+RSO_3^-$ must be substantially lower under the condition of the catalytic reaction for reasons described below.

2. Role of Sulfonate Ions in the Uncatalyzed Cyclization: The Structure of Ion Pairs. The counterintuitive observation that the cyclization of **3** in the absence of catalyst ("racemic background reaction") proceeded with a rate comparable to that of the catalyzed cyclization of **3** (which afforded high enantioselectivity) demanded a reevaluation of the *actual* racemic background reaction that may intervene under catalytic conditions. As shown in Figures 6 and 7, sulfonate ions and phthalimide (necessary consequences of the formation of the catalytically active species **6**) were effective inhibitors of the racemic background reaction. The results shown in Figure 7c were most informative. With as little as 0.1 equiv of *n*-$Bu_4N^+OMs^-$, 0.1 equiv of phthalimide, and 0.9 equiv of MsOH (the actual stoichiometries with respect to **3** at the beginning of the catalyzed reaction), the cyclization is extremely slow, reaching less than 10% conversion in the same time that the catalytic reaction would be complete. *Thus, the apparent contradiction seen in Figures 1 and 2 is, in reality, a consequence of the incorrect assumption that the racemic background reaction is accurately represented by simply leaving out the catalyst.*

A possible explanation for the inhibition of the racemic background reaction under catalytic conditions may be found in the buffering effect of the sulfonate ion. The strong buffering effect of sulfonate ions on the acidity of sulfonic acids has in fact been studied in nonaqueous media, but not in chlorinated solvents. The self-association of acids with their conjugate bases, known as the "homoconjugation reaction", has been studied for sulfonic acids in dipolar aprotic solvents.[11a] In the conductometric titration of MsOH in benzonitrile (with Et_3N), a large maximum is observed at one-third of the equivalence point. Such maxima are characteristic of the formation of triple ions[11b] according to the formula shown in Scheme 2. The maximum at one-third equivalence for MsOH is much larger

Scheme 2



than that for $PhSO_3H$ or TsOH because of its weaker acidity and corresponding greater basicity of MsO^-, thus leading to a higher concentration of the triple ion. In the cyclization reactions, the base (B) is *N*-phenylthiophthalimide (**2**). With 1.00 equiv of $EtSO_3H$, **2** is ca. 25% protonated, leading to a significant concentration of the triple ion which sequesters two additional molecules of $EtSO_3H$.

An important issue that could well impact the understanding of this phenomenon is the actual structure of the ion pairs involved in the various stages of the reaction. Although the structure of the catalytically active species **6** could be established as an intimate ion pair in $CHCl_3$, the structures of **2**·$H^+RSO_3^-$ and protonated phthalimide could not be established. Clearly, the buffering power (i.e., homoconjugation strength) will depend on the structure of the ion such that the more solvent-separated the ions, the greater their ability to bind to their conjugate acids.[12]

3. Mechanistic Rationale and Catalytic Cycles. The formation of (racemic) **4** at a rate greater than that of the catalyzed reaction provided a compelling explanation for the variability of the enantioselectivities in preparative reactions, but also presented a conundrum: how can a catalytic reaction outcompete a faster stoichiometric reaction and produce enantiomerically enriched products?

The answer to this question has been found in a deeper understanding of the stoichiometry for generation of the catalytically active sulfenylating agent **6** and in the buffering effect of sulfonate ions and phthalimide formed under catalytic conditions. These phenomena result in the simultaneous operation of two catalytic cycles illustrated in Scheme 3. Initiation of both cycles begins with the pre-equilibrium protonation of **2** to form species ***i***. Under catalytic conditions (i.e., with 0.1 equiv of (*S*)-**1**) the catalyst is saturated as the kinetically active sulfenylating agent **6** with as little as 0.4 equiv of $EtSO_3H$ (with respect to **2**). Once **6** is stoichiometrically generated, the catalytic cycle has no further need for $EtSO_3H$ (as was seen in the similarity of rates in Figure 2a). Any additional acid would be deleterious in promoting the uncatalyzed pathway, but the presence of MsO^- from both ***i*** and **6** serves to neutralize the excess acid and inhibit the racemic background reaction. First-order kinetic behavior requires that the formation of episulfonium ion ***iv*** be the rate-determining step which is followed by rapid cyclization and rearomatization.

The striking behavior of this catalytic system bears some resemblance to the inhibition of the asymmetric catalytic pathway in the Povarov reaction elegantly analyzed by Jacobsen.[13] In that study a similar observation was made regarding the suppression of a Brønsted acid catalyzed racemic background reaction that they ascribed to "negative catalysis".[14] The high association constant of the chiral urea for the protonated imine resulted in the removal of the Brønsted acid from the reaction. In our system, this behavior is reflected in the formation of species **6**. However, Jacobsen et al. employed only half as much Brønsted acid as catalyst loading, whereas in

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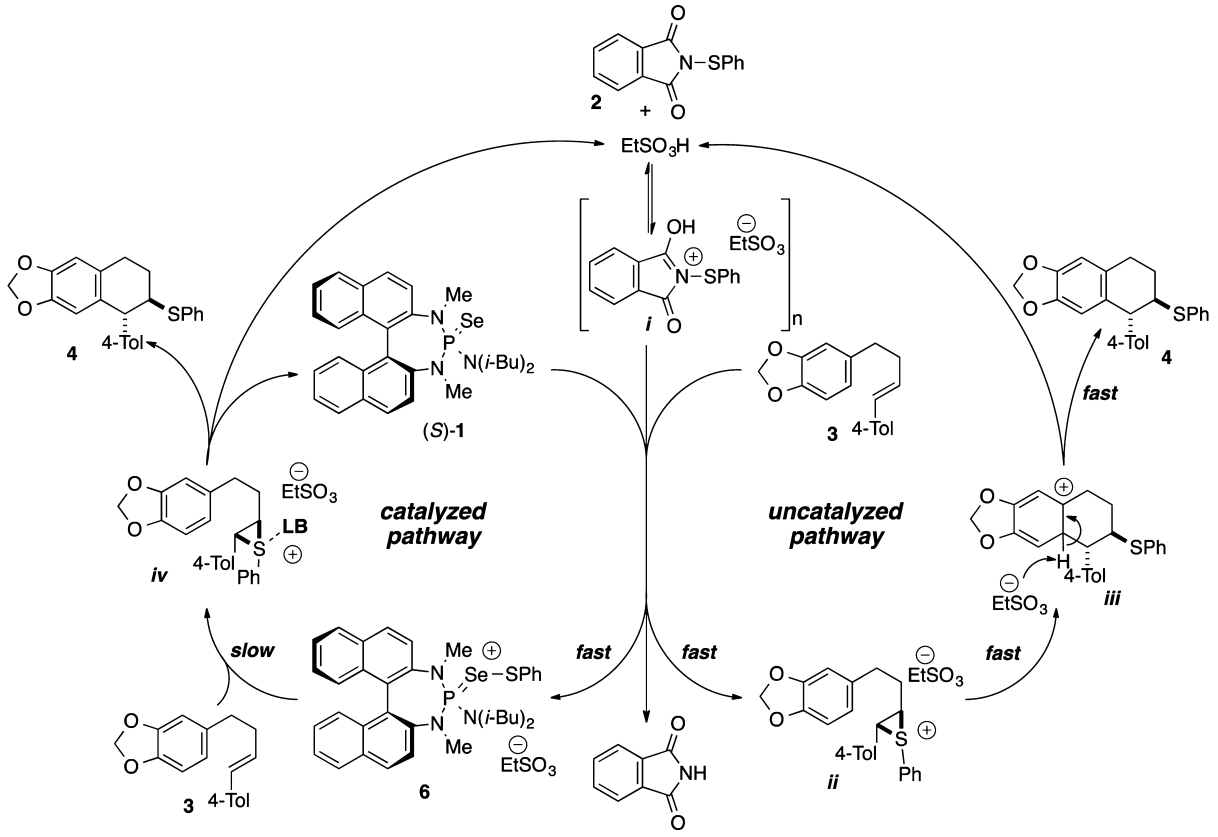
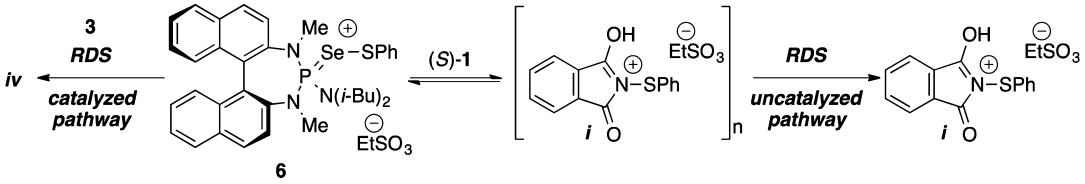
Scheme 3



Scheme 4



our system the Brønsted acid is deployed in stoichiometric quantities with respect to substrate. Thus, consuming 0.1 equiv of $EtSO_3H$ in the formation of **6** is insufficient to explain the inhibition of the background reaction. Instead, we have identified the crucial role of the conjugate base $EtSO_3^-$ in sequestering the excess Brønsted acid through the homoconjugation reaction, which forms triple ions, as well as the buffering effect of the phthalimide generated from **2**.

Although not directly relevant to the focus of this study, the curious zeroth-order dependence for the formation of **4** in the absence of (*S*)-**1** warrants comment (Figures 1b and 2b). This unusual behavior implies that the rate of cyclization depends only on the Brønsted acid, whose concentration does not change over the course of the reaction (Scheme 3). This unique dependence would obtain if the cyclization becomes rate determining in the absence of the Lewis base catalyst. In this scenario, the resting state is the species ***ii***, whose concentration is set by the amount of Brønsted acid employed. Since this step is an intramolecular reaction, it will exhibit zeroth-order kinetic dependence on **2** and **3**. The subsequent rearomatization step from ***iii*** should be very fast. This hypothesis posits that intermediate ***ii*** should be observable under the reaction conditions. However, NMR analysis of the uncatalyzed reactions revealed a consistently high mass balance (>98%) consisting of only **2**, **3**, and **4**.

An alternative explanation for zeroth-order behavior would be a rate-determining step outside of the catalytic cycle. If the protonated sulfenylating agent ***i*** existed in an aggregated state (perhaps intermolecularly hydrogen bonded) which had to dissociate to form a catalytically competent agent, and all downstream reactions were faster than dissociation, overall zeroth-order behavior would be observed (Scheme 4). The amount of reactive monomer would be dependent on the amount of ***i***, which is dependent only on the amount of Brønsted acid. In the presence of (*S*)-**1**, either the monomer is rapidly intercepted to form **6** or the catalyst is capable of reacting with the aggregate in a rapid pre-equilibrium which (as was established above) is acid dependent.[15]

■ CONCLUSION

Detailed kinetic and spectroscopic analysis of the enantioselective Lewis base/Brønsted acid co-catalyzed carbosulfenylation reaction has revealed a number of interesting features that explain previously observed, contradictory behavior. The unusual observation that the rate of the catalyzed reaction is similar to that of the uncatalyzed process, yet still affords high

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enantioselectivity, is now understood. The actual background reaction operating under catalytic conditions is not accurately mimicked by simply leaving out the catalyst. In the presence of the Lewis base catalyst, the active sulfenylating agent **6** is formed quantitatively. Two byproducts of this step conspire to inhibit the Brønsted acid catalyzed pathway, namely, equimolar amounts of a sulfonate and phthalimide. The sulfonate forms triple ions with the remaining sulfonic acid, thus sequestering twice its molar concentration, and the phthalimide serves as a buffer to neutralize additional amounts of the acid. The consequences of these observations on other Brønsted acid catalyzed reactions are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

All kinetic and spectroscopic data, along with preparation and characterization of **5**. 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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(3) A parallel set of experiments run at 0.1 M concentration displayed dramatically different behavior than those run at 0.2 M. For example, with MsOH (1.0 equiv), the catalyzed reaction showed an induction period of ca. 6 h before the rapid onset of reaction, approximating an autocatalytic process. Moreover, with $EtSO_3H$, the uncatalyzed reaction afforded only **5**, the product of proton-initiated cyclization. These results, while intriguing and potentially informative, did not represent the preparative-scale reactions and as such were not further investigated or analyzed. See Supporting Information for details.

(4) The enantiomeric ratio (er) for **4** in this run using purified MsOH was only 75:25.

(5) Enantiomeric ratios: 1.00 equiv, 86.9:13.1; 0.75 equiv, 90.2:9.8; 0.50 equiv, 92.6:7.4; 0.25 equiv, 92.9:7.1.

(6) It is recognized that the equilibria measured at −50 and −57 °C may not be exactly the same as the equilibrium at the reaction temperature (−20 °C); however, the temperature difference is not large.

(7) For reviews, see: (a) King, J. F. In *The chemistry of sulphonic acids, esters and their derivatives*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1991; Chapt. 6. (b) Furukawa, N.; Fujihara, H. In *The chemistry of sulphonic acids, esters and their derivatives*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1991; Chapt. 7.

(8) Only at 0.1 M concentration were the differences more pronounced. $EtSO_3H$ did not promote the formation of **4** in the uncatalyzed reaction but afforded only **5** in a process that exhibited zeroth-order kinetic behavior. See Supporting Information for details.

(9) The different overall reaction order makes comparison of the relative rates difficult. Under these conditions the times to 50% conversions are calculated to be 2.0 h for the catalyzed reaction and 1.67 h for the uncatalyzed reaction.

(10) The initial rates of the catalyzed reactions are actually greater than those of the uncatalyzed runs at comparable $EtSO_3H$ loadings, but the differences in overall reaction order make comparisons difficult. For example, the time to 50% conversion using 1.0 equiv of $EtSO_3H$ is calculated to be 2.4 h for the catalyzed reaction and 7.1 h for the uncatalyzed reaction.

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(15) An intriguing consequence of this interpretation is that this system may be operating analogously to the negative catalysis observed by Jacobsen. If the amount of reactive monomer is small relative to the amount of catalyst, then the interception of this highly reactive species to form the less reactive, but chiral **6** could also explain these observations. Studies on the colligative properties of ***i*** are underway.