Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 3211−3214

pubs.acs.org/OrgLett

Lewis Base/Bronsted Acid Dual-Catalytic C−H Sulfenylation of Aromatics

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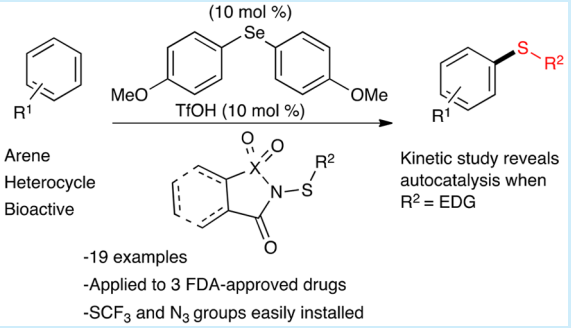
Supporting Information

ABSTRACT: A Lewis base/Bronsted acid catalyzed aromatic sulfenylation is reported. These studies demonstrated that the incorporation of electron-rich sulfenyl groups proceeded in the absence of a Lewis base, with kinetic studies indicating an autocatalytic mechanism. The incorporation of electron-poor sulfenyl groups demonstrated little autocatalysis necessitating the use of a Lewis base. This method proved amenable to diverse arenes and heterocycles and was effective in the context of the late-stage functionalization of biologically active small molecules.



Aryl and alkyl sulfides are common motifs in drug discovery[1−3] and have seen use in polymer[4] and synthetic chemistry.[5−7] As such, the formation and transformation of carbon sulfur (C−S) bonds have recently received significant attention.[8,9] Typically, the introduction of aryl or alkyl sulfides has been achieved through cross-couplings via metal catalysis.[10−12] However, more recently, aromatic (C−H) sulfenylation has been achieved via electrophilic aromatic substitution (S_EAr). Aromatic sulfenylation via S_EAr was originally achieved via sulfenyl halide intermediates generated in situ; however, these methods can often result in a mixture of halogenated and sulfenylated products.[13,14] More recently, several groups have found sulfenyl halides can be generated in situ from *N*-thiosuccinimides using $MgBr_2$; however, these methods can suffer from a reliance on elevated temperatures and often only work on the most electron-rich aromatics such as indoles.[15−18] In a recent advance, aromatic sulfenylation of arenes was achieved by employing superstoichiometric quantities of trifluoroacetic acid (tfa) to activate *N*-thiosuccinimides; however, the harshness of these conditions can limit the substrate scope to electron-rich arenes that are free of acid-sensitive groups (Figure 1A).[19]

Recently, we disclosed a bifunctional catalyst consisting of a Lewis basic thiourea conjugated to a Bronsted acid that was able to effect the sulfenylation of aromatics under mild conditions;[20] however, the scope of the reaction was limited to electron-rich *aza*-heterocycles. Based on mechanistic studies from that work we hypothesized that sulfide and selenide ethers, which have been used as catalysts for the sulfenofunctionalization of alkenes,[21−25] might prove to be a more efficient catalyst, as there would be no mechanism to stabilize the putative Lewis base/sulfenium adducts. The destabilized adducts would be expected to be more electrophilic and thus perhaps more amenable to less electron-rich aromatics.

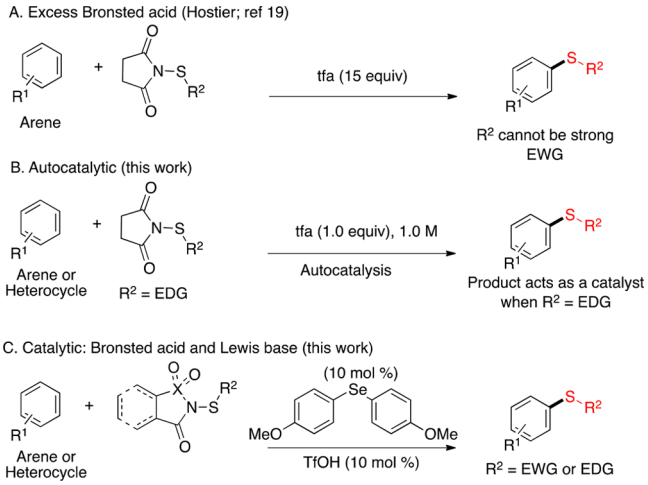


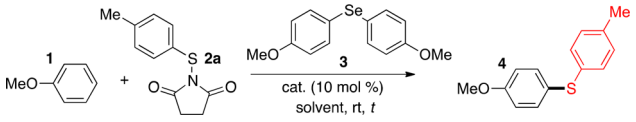
Figure 1. (A) Excess Bronsted acid sulfenylation of arenes. (B) Autocatalytic profile of sulfenylation. (C) Catalytic: Bronsted acid and Lewis base sulfenylation.

We began our studies by evaluating different Lewis bases in the absence or presence of different acids for the sulfenylation of anisole (**1**) with reagent **2a** which possessed a methyl group that could be used as a handle to monitor the reaction conversion by ^{1}H NMR. We observed no reaction in the absence of catalyst (Table 1, entry 1), with 1 equiv of tfa (Table 1, entry 2), in the presence of triphenylphosphine selenide with 1 equiv of tfa (Table 1, entry 3),[20] or in the presence of diarylselenide **3** in the absence of tfa (Table 1 entry 4). Conversely, when catalyst **3** was

Received: April 4, 2018
Published: May 15, 2018

DOI: 10.1021/acs.orglett.8b01066
Org. Lett. 2018, 20, 3211−3214

Table 1. Optimization of Reaction Conditions



entry	catalyst	additive	molarity (M)	time	yield (%)
1	none	none	0.2	6 h	0
2	none	1 equiv of tfa	0.2	6 h	0
3	$SePPh_3$	1 equiv of tfa	0.2	6 h	0
4	3	none	0.2	6 h	0
5	3	1 equiv of tfa	0.2	6 h	82
6	3	1 equiv of tfa	0.5	1 h	83
7	3	1 equiv of tfa	1.0	10 min	88
8	3	10 mol % TfOH	1.0	10 min	89[b]
9	none	10 mol % TfOH	1.0	10 min	90[b]
10	none	1 equiv of tfa	1.0	10 min	1
11	none	1 equiv of tfa	1.0	3 h	85
12	4	1 equiv of tfa	1.0	1 h	95

[a]Percent conversion by NMR represents an average of three trials using tms as an internal standard. Reactions were performed on 0.12, 0.3, or 0.6 mmol scale of **1** in 0.6 mL of $CDCl_3$; please see SI for more details. [b]Isolated yield using $CHCl_3$ as solvent.

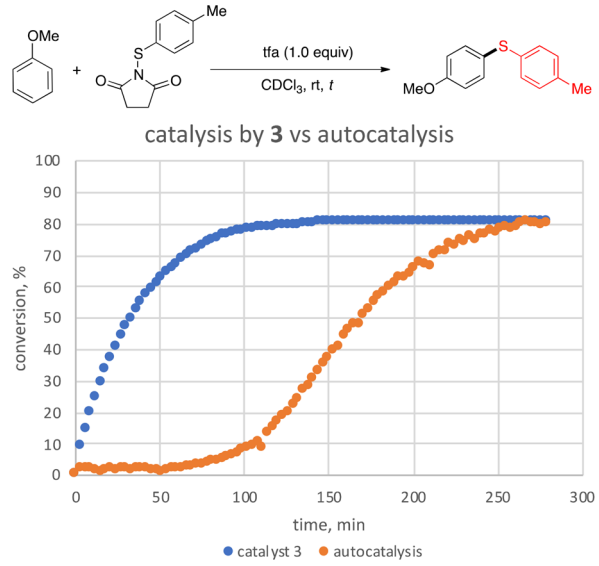
combined with 1 equiv of tfa, we observed good conversion to **4** at 6 h (Table 1, entry 5).

This could be improved by increasing the reaction concentration up to 1.0 M (Table 1, entry 7) to give nearly complete conversions on the minute time scale. Next, we sought to determine the effect of the strength of the acid additive, finding the combination of **3** with catalytic triflic acid also resulted in near-complete conversion in 10 min (Table 1, entry 8). Surprisingly, 10 mol % triflic acid, in the absence of a Lewis base, also effected sulfenylation on a similar time scale. This led us to take a closer look at the reactions employing 1 equiv of tfa without **3** at 1.0 M, wherein we observed no conversion to **4** at 10 min (Table 1, entry 10); however, near-complete conversion at 1.0 M concentration took place after 3 h (Table 1 entry 11). This led us to investigate the role of the product **4** in the reaction. When 10 mol % **4** is added as a catalyst (Table 1, entry 12), the reaction is notably faster than with no catalyst, yielding a conversion of 95% after 1 h. Taken together these data suggest that while selenide ethers are more efficient catalysts, the resulting product sulfide, which is itself a Lewis base, can also catalyze the reactions; thus the reactions occurring in the absence of **3** are likely proceeding autocatalytically.

To probe the potential for autocatalysis we performed preliminary kinetics experiments in which the reaction was monitored at 3 min increments by ^{1}H NMR with 1 equiv of tfa in the absence or presence (Scheme 1) of catalyst **3**. As we suspected, the reaction without **3** displayed a considerable lag time before the rate increased, indicative of autocatalysis. Conversely, the reaction with 10 mol % **3** displayed no lag time and was complete significantly sooner. While we were unable to obtain kinetics using triflic acid due to the short reaction time not being amenable to NMR kinetics, we feel that it is probable that autocatalysis is also a factor in this case.

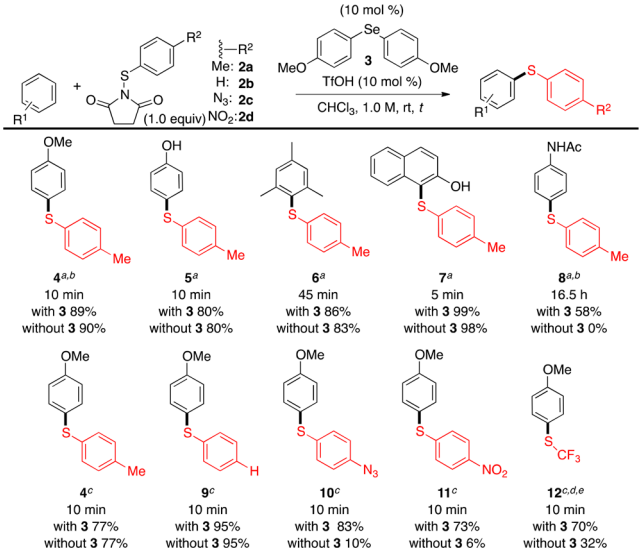
Next, we sought to evaluate the sulfenylation of different aromatics using reagent **2a** in both the presence and absence of **3** (Scheme 2). Anisole (**1**), phenol, mesitylene, and 2-naphthol were all sulfenylated cleanly on the minute time scale using 10 mol % triflic acid, with the conversion being nearly indistinguishable with or without **3**. On the other hand,

Scheme 1. NMR Study Comparing Kinetic Profiles[a]



[a]Catalyst **3** kinetics were obtained using conditions from Table 1 entry 10. Autocatalysis kinetics were obtained using conditions from Table 1 entry 6.

Scheme 2. Comparison of Several Aromatic Substrate Classes with Catalyst 3 and without Catalyst 3



[a]Isolated yield. [b]1.2 equiv sulfenylation reagent. [c]Conversions determined by ^{1}H NMR (see SI for details). [d]0.25 equiv of TfOH. [e]**2e** was used.

acetanilide, which is less electron-rich than the other evaluated substrates,[26] did display a dependence on catalyst, as the corresponding product **8** was only observed in the presence of Lewis base catalyst **3**.

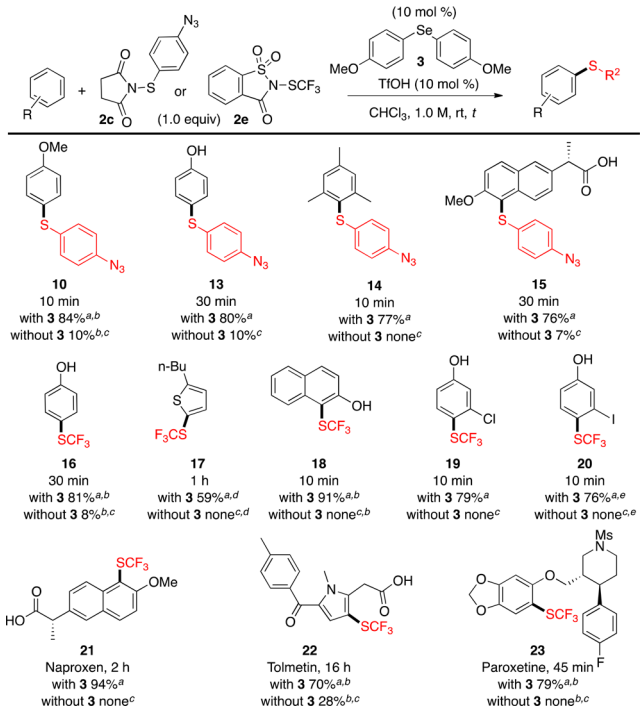
We next set out to investigate the electronic effect of the substitution off of the sulfur in the sulfenylation reagent. We accomplished this by evaluating the sulfenylation of **1** by ^{1}H NMR with sulfenylation reagents of varying electronic properties. Electron-rich reagents (**2a** and **2b**) showed no difference in conversion to products (**4** or **9**) with or without **3**. When more electron-poor sulfenylation reagents (**2c**, **2d**, and **2e**) were used we observed a significant increase in conversion with **3**. For

DOI: 10.1021/acs.orglett.8b01066
Org. Lett. 2018, 20, 3211−3214

example, when **2c** is used we observe 83% sulfenylation to **10** in the presence of 10 mol % **3**, however, only 10% conversion at the same time point without **3**. Similarly, with **2d** we observe 73% conversion to **11** with **3** and only 6% without **3**, and with **2e** we observe 70% conversion with catalyst and 32% without. These results can be justified, as the products that possess electron-withdrawing groups (**10**, **11**, **12**) will have attenuated the Lewis basicity leading to lessened autocatalysis.

We next sought to define the substrate scope of the selenide ether catalyzed sulfenylation reaction employing electron-poor *N*-thiosuccinimide reagents **2c** and **2e** (Scheme 3). Reagent **2c**

Scheme 3. Substrate Scope of Trifluoromethylthiolation



[a]Isolated yield. [b]1.2 equiv of **2c** or **2e**. [c]Conversions determined by ^{1}H NMR (see SI for details). [d]1.05 equiv of **2e**. [e]Toluene was used as solvent.

was chosen, as the azido group possesses a wide range of applications, particularly those related to bioorthoganol conjugation chemistry.[27] Reagent **2e** was chosen, as the SCF_3 group is becoming increasingly employed by medicinal chemists to modulate the lipophilicity and bioavailability of lead compounds, and as such the late-stage introduction of the SCF_3 group has become a sought-after strategy in synthetic chemistry.[28−30]

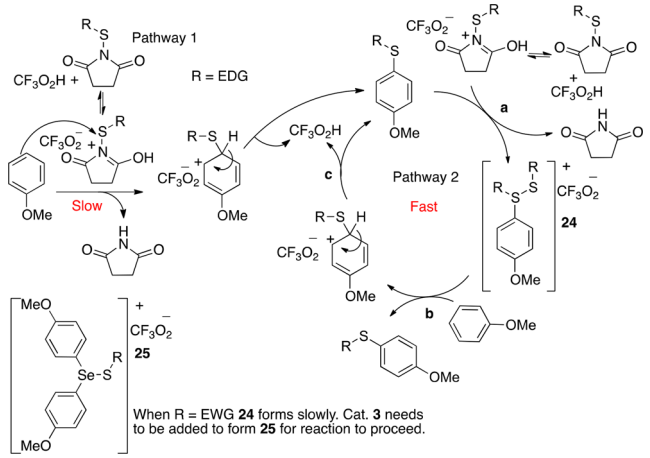
The trends from Scheme 2 proved to hold quite well across several different classes of aromatics, as we observed a significant increase in conversion when catalyst **3** was employed for each substrate evaluated. For example, in the absence of catalyst, less than 10% conversion was observed using **2c** for the sulfenylation of **1**, phenol, mesitylene, or the venerable NSAID naproxen. Conversely, the addition of 10 mol % **3** allowed for the isolation of the corresponding sulfides **10**, **13**, **14**, and **15** in yields ranging from 76% to 84% in <1 h.

The incorporation of the SCF_3 group using **2e** displayed a similar, if not more marked, trend. Phenol derivative **16** was isolated in 81% yield when 10 mol % **3** was employed and only 8% without **3**. Trifluoromethylthiolated thiophene **17** was isolated in 59% with 10 mol % **3** while we observed no conversion without **3**. Similarly, naphthol **18** and phenol derivatives **19** and **20** were isolated in 91%, 79%, and 76% yields, respectively with **3**, while each showed no conversion without **3**. Naproxen derivative **21** was also cleanly trifluoromethylthiolated in 94% yield with **3** while showing no conversion without **3**. Tolemetin another FDA-approved NSAID drug commonly used to treat pain from arthritis was functionalized in 70% yield in the presence of **3**; however, it displayed a larger background reaction in the absence of **3** (28%).

Overall, we found this chemistry to be amenable to a wide range functional groups including phenols, carboxylic acids, heterocycles, and protected amines. Free amines, however, presented a problem, as we would often isolate *N*-sulfenylated products.

This can be overcome by protecting the amine as we did with the FDA-approved selective serotonin reuptake inhibitor (SSRI) paroxetine, wherein we found mesylated paroxetine cleanly sulfenylated allowing for the isolation of **23**, in 79% yield with 10 mol % **3**, while we observed no conversion in the absence of **3**. In general, the substrates that reacted significantly in the absence of the Lewis base were more electron-rich, and thus more innately reactive. Despite this, the fact that the resultant products (i.e., **12**, **22**) would be more Lewis basic and thus possess the potential for greater autocatalysis should not be overlooked. The mechanistic proposal in Scheme 4 summarizes our findings in this letter. The

Scheme 4. Autocatalytic Mechanistic Proposal



first pathway presented, pathway 1, is an acid-mediated mechanism where product formation happens slowly representing the lag period in the kinetic profile in Scheme 1. When enough product has formed a second pathway, pathway 2, that involves a Lewis base, autocatalysis drives the reaction to completion represented by the dramatic increase of rate later on in the reaction. When the formed product is less electron-rich, it will possess attenuated Lewis basicity and thus lessened autocatalysis, which can be overcome by the addition of a sufficiently Lewis basic catalyst such as **3**.

In conclusion, we have studied the C−H sulfenylation of arenes via S_EAr. We found that the combination of a selenide ether with either 1.0 equiv of tfa or 10 mol % TfOH resulted in rapid and robust conversions across several different arene classes, including several known bioactive compounds. When the product sulfide had electron-rich substitutions, the reaction did not require a Lewis base catalyst, as the reaction could proceed via an autocatalytic pathway. Conversely, electron-poor sulfides

DOI: 10.1021/acs.orglett.8b01066
Org. Lett. 2018, 20, 3211−3214

were reliant on the presence of a Lewis base catalyst. These results are significant for two reasons. First, they represent a mild and efficient route for the addition of diverse sulfur containing functionalities into arenes. Second, the potential for autocatalysis can have implications when developing regio- or enantioselective sulfenylation, an area that has recently received significant attention.[21−25]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01066.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Primary support for this project came from the National Science Foundation (Che-1664565). E.A. is thankful for support from the SDSU LSAMP National Science Foundation (HRD-1302873). We would like to thank Professor Byron Purse (SDSU) for insightful discussions, Professor Erica Forsberg and Brijinder Soni for help obtaining HRMS, and Dr. Bennett Addison (SDSU) for technical support regarding NMR.

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