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A conjugate Lewis base-Brønsted acid catalyst for the sulfenylation of nitrogen containing heterocycles under mild conditions

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Catalysts that contain a thiourea tethered to a carboxylic acid were found to affect the sulfenylation of indoles and other *N*-heterocycles on the hour time scale at room temperature. The mild nature of these conditions allowed for the incorporation of diverse functionalities into more complex heterocycles.

Aryl sulfides are common functionalities and synthetic intermediates in drug discovery and material science (Figure 1a). For instance, the kinase inhibitor axitinib is a recent example of an FDA approved diaryl sulfide, a diaryl sulfide is a late stage intermediate in the synthesis of omeprazole, and the industrial polymer polyphenylene sulfide (PPS) has found numerous industrial applications as high performance thermo-plastics. Because of these and other examples, the formation of C-S bonds has received significant attention, with metal catalyzed cross-couplings comprising the majority of examples.[1,2] The direct formation of C-S bonds from unfunctionalized starting materials has also received recent attention with examples of both metal catalyzed C-H[3–5] functionalization and aromatic sulfenylation that proceed via electrophilic aromatic substitution (S_EAr).

Historically, aromatic sulfenylation via S_EAr is achieved using *in situ* generated sulfenyl halides,[6,7] however these approaches often result in a mixture of sulfenylated and halogenated products. Kita[8] has shown that activation of quinone *O,S*-acetals by TMS triflate results in a robust sulfenylation system, albeit with limited substrate scope with respect to the substitution on sulfur. Recent examples have shown that sulfenylation of indoles and pyrroles can be achieved at elevated temperatures via the *in situ* formation of sulfenyl halides by activation of *N*-sulfenyl imides (phthalimides or succinimides) with hard halide sources (Figure 1b).[9–11] Lewis acids have also been demonstrated to activate *N*-sulfenyl imides towards aromatic sulfenylation.[12–16] It has also been shown that *ortho*-thioquinones, generated from the corresponding *N*-sulfenyl imides with mild base, are suitable electrophilic sulfenylation reagents for S_EAr.[17] Most recently it[18,19] has been shown that super-stoichiometric amounts of TFA (5-20 equivalents) can mediate sulfenylation of electron rich arenes by *N*-thiosuccinimides at room temperature. While these examples represent useful new chemistries, they suffer from various issues including a lack of chemoselectivity and a reliance on elevated temperatures or harsh conditions that likely preclude them from being applied in more complex settings such as on natural products or peptides.

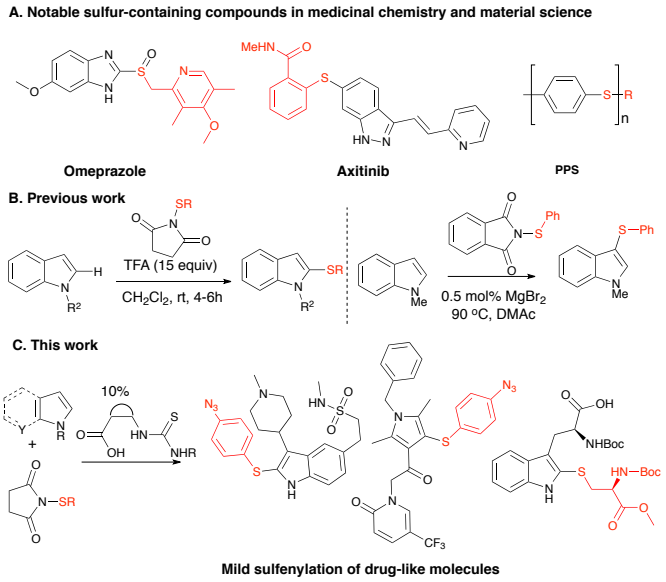

Figure 1 a) Representative examples of sulfur-containing compounds in drug discovery and material science. b) Recent examples of sulfenylations. c) Mild sulfenylations mediated by catalysts reported within.

We have recently demonstrated that Lewis bases such as triphenylphosphine sulfide are effective catalysts for the halogenation of aromatics with *N*-halosuccinimides.[20,21] With this work in mind we set out to determine if Lewis base

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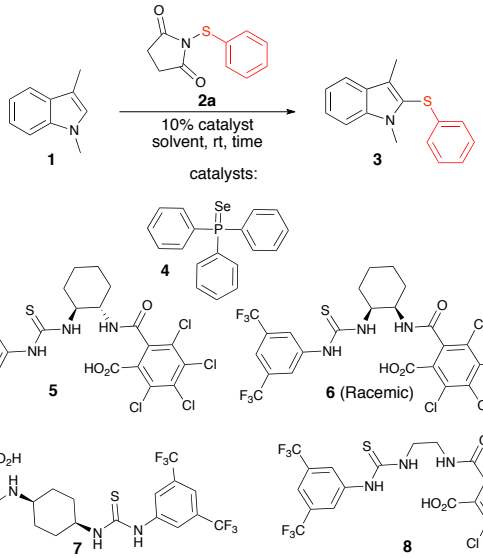
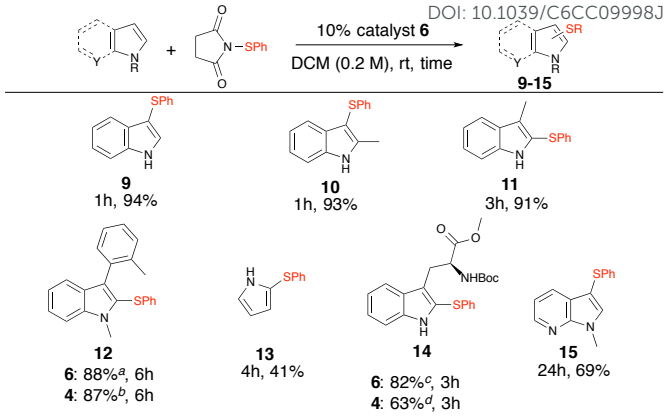


Entry	Catalyst	Additive	Solvent	Time	Yield
1 [a,b]	None	None	$CDCl_3$	2 Hours	0
2 [a,b]	None	1 eq. TFA	$CDCl_3$	2 Hours	0
3 [a,b]	4	None	$CDCl_3$	2 Hours	0
4 [a,b]	4	1 eq. TFA	$CDCl_3$	5 Min.	99
5 [a,b]	5	None	$CDCl_3$	2 Hours	34
6 [a,b]	6	None	$CDCl_3$	2 Hours	81
7 [a,b]	6	None	CD_2Cl_2	30 Min.	80
8 [a,b]	6	1 eq. TFA	$CDCl_3$	5 Min.	99
9 [a,b]	6	1 eq. TFA	CD_2Cl_2	5 Min.	99
10 [a,b]	7	None	$CDCl_3$	2 Hours	70
11 [a,b]	8	None	$CDCl_3$	2 Hours	3
12 [c,d]	6	None	H_2O	1 Hour	69

Table 1 Reactions were performed at room temperature by the addition of .03 mmol of **1**, 0.003 mmol of catalyst, and 600 µL of solvent into an NMR tube, followed by the addition of 0.033 mmol of **2a**. [a]Solvents were run through a short column of basic alumina prior to reaction. [b]Percent conversions by ^{1}H NMR represent an average of three trials using tetramethylsilane as internal standard. [c]30% MeOH in DI water was used 0.2M to **1**. [d]Obtained as an isolated yield as an average of two trials on a 0.043mmol scale to **1**.

catalysis could also mediate aromatic sulfenylation. We initially studied the sulfenylation of indole **1** with *N*-thiophenylsuccinimide (**2a**), observing no reaction in the presence or absence of one equivalent TFA (Table 1, entries 1,2). While Lewis bases proved ineffective in the absence of TFA (*i.e.* Table 1, entry 3), we found that the combination of 10% triphenylphosphine selenide **4** and 1 equivalent of TFA (Table 1, entry 4) resulted in rapid conversion to **3** on the minute time scale. This synergy between Brønsted acid and Lewis base has previously been observed by Denmark[22–24] in the context of olefin sulfenylation.

As our overarching goal was to make aromatic sulfenylation applicable to more complex molecules, particularly those with with acid sensitive functionalities, we were concerned by the use of stoichiometric strong acid in entry 4. Because of this, we set out to determine if we could exploit the observed acid-base synergy in the context of a single catalyst. We quickly found that catalyst **5** which was



Scheme 1. Reactions were performed at room temperature by the addition of 1 equivalent of substrate, 0.1 equivalent of catalyst, 1.1 equivalent of reagent at a concentration of 0.2M. Isolated yields represent an average of two trials. [a]1 equivalent of TFA was added. [b]0.1 equivalent of **4** with 1 equivalent of TFA was used. [c]0.5 equivalents of TFA was added. [d]0.1 equivalent of **4** with 0.5 equivalent of TFA was used.

previously developed by Seidel[25] and possesses a thiourea (a known Lewis base)[26,27] tethered to a tetra-chlorinated carboxylic acid was able to catalyse sulfenylation in the absence of added TFA (Table 1, entry 5), albeit on a prolonged time scale compared to that of entry 4.

We next evaluated the effect of changing the orientation of the thiourea and Brønsted acid relative to each other, finding racemic catalyst **6**, which is based on a *cis*-1,2-cyclohexyldiamine scaffold, to be a more effective catalyst than **5** (Table 1, Entry 6). A noticeable jump in reaction rate was observed when running this reaction in dichloromethane (Table 1, Entry 7), allowing this chemistry to be complete in under an hour. While our goal was to avoid the use of strong acid, it is worth noting that the combination of one equivalent TFA and 10% **of 6** in (Table 1, entries 8, 9) resulted in full conversion to product in minutes. **6** Also mediated this chemistry in water/methanol mixtures (Table 1, Entry 12), suggesting this chemistry may be applicable to challenges in more complex biological settings including the sulfenylation of peptides, proteins, and polar natural products.

The increased activity of **6** led us to evaluate other catalysts with different relative orientations and distances between the carboxylic acid and thiourea (Table 1, Entries 10, 11). Catalyst **7**, where the thiourea and carboxylic acid are linked via a *cis*-1,4-cyclohexyldiamine scaffold, proved only slightly less efficient than **6**. On the other hand, catalyst **8,** where the catalyst moieties are tethered by a more flexible ethylene diamine linker, did not mediate significant sulfenylation. This data suggests that the relative orientation of the thiourea and carboxylic acid is a key factor for catalysis.

We next sought to determine the substrate scope of this chemistry (Scheme 1). For indole, we observed clean sulfenylation at the more electron rich C-3 position, recovering 94% of **9**. This is complementary to Cossy's sulfenylation conditions[19] which result in C-2 sulfenylation, due to an acid mediated rearrangement of C-3 sulfenylated product.

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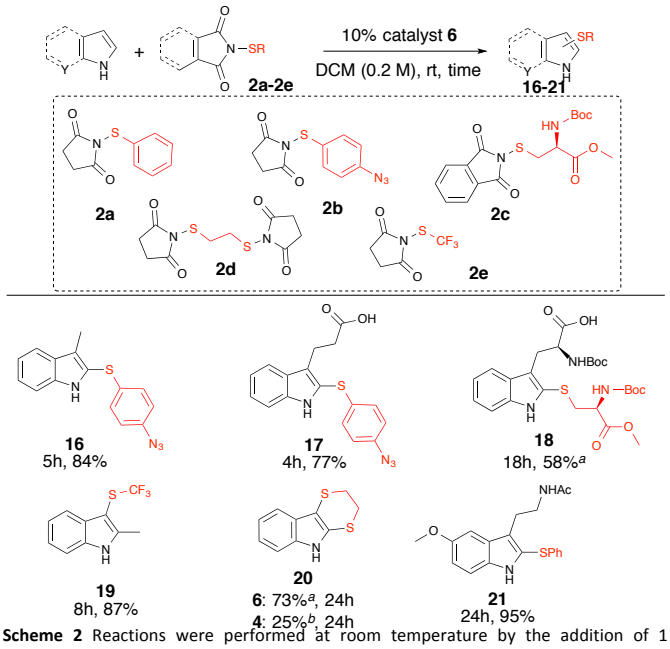
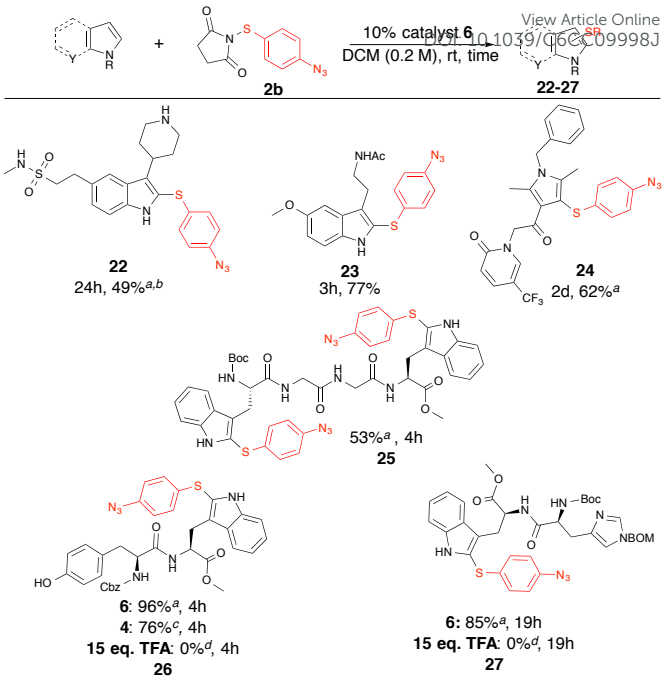


Scheme 2 Reactions were performed at room temperature by the addition of 1 equivalent of substrate, 0.1 equivalent of catalyst, 1.1 equivalent of reagent at a concentration of 0.2M. Isolated yields represent an average of two trials. [a]1 equivalent of TFA was added. [b]0.1 equivalent of **4** with 1 equivalent of TFA was used.



Scheme 3 Sulfenylation of biologically relevant molecules using 2b. Reactions were performed at room temperature by the addition of 1 equivalent of substrate, 0.1 equivalent of catalyst, and 1.1 equivalent of reagent at a concentration of 0.2M in substrate**.** Isolated yields represent an average of two trials. [a]1 equivalent of TFA was added. [b]A 9:1 mixture of DCM/MeOH was used as the solvent. [c]0.1 equivalent of **4** with 1 equivalent of TFA was used. [d]No catalyst, 15 equivalents of TFA at a concentration of 0.5M in substrate with 1 equivalent of reagent.

Several C-3 and C-2 substituted indoles also proceeded smoothly to give **10**, **11**, and **12** in good yields. Pyrrole was also amenable to this chemistry to give **13,** however at lower yields due to the formation of multiple constitutional isomers. *tert*-Butoxy carbonyl (boc) protected tryptophan also sulfenylated rapidly to yield 82% of **14** with no observed deprotection.. Finally, azaindoles, which are markedly less electronically activated than indoles, sulfenylated to give **15** in good yield, notably very little azaindole sulfenylation was observed under TFA conditions, perhaps due to protonation of the 7-nitrogen.

It should be noted that conversion to **12** and **14** required some added TFA in addition to 10% **6** to ensure the reaction proceeded on a timely manner. For these cases the conditions in table 1, entry 4 (**4**, 1 equivalent TFA) proved comparable (for **12)** or noticeably less efficient (for **14**).

Next, we determined the scope of sulfenylating reagents **2a-2e** that could be employed. Several *N*-thiosuccinimides or *N*-thiophthalimides were synthesized according to literature procedures for similar reagents (see SI for details). We first looked at azide containing *N*-thiosuccinimide **2b**, which proved an effective sulfenylation reagent with catalyst **6**, yielding **16** and **17** in good yields. The ability to facilely incorporate azides onto *N*-heterocycles should find utility in chemical biology, as azides are a common tool that allow for the incorporation of diverse moieties through the Huisgen cycloaddition. Cysteine derived **2c** was also amenable to this chemistry, with **6** effecting the sulfenylation of Boc-Trp-OH with **2C** to give **18** in good yield with no observed deprotection.

We were also able to achieve trifluoromethyl thiolation[28] in excellent yields (**19**) on the hour time scale. The ability to easily install the S-CF_3 group using **6** may find use in a medicinal chemistry setting as the S-CF_3 group is commonly employed to modulate the lipophilicity of drug candidates.[29] Bis-*N*-thiosuccinimides **2d** was also synthesized, allowing for the synthesis of new heterocycles such as **20** in which the C-3 and C-2 are bridged. As before, in some cases the addition of 1 equivalent of TFA was necessary for the reaction to progress in a timely manner. This is observed especially when using *N*-thioalkyl imides, which proved to be less electrophilic reagents. Notably in some of these instances (*i.e* **20**) the conditions in Table 1, entry 4 proved to be less efficient.

We next evaluated known biologically active small molecules and FDA approved drugs. In addition to leading to new analogs, the addition of an azide using **2b** would represent an efficient way to insert a linker to obtain chimeric molecules such as PROTACs[30] or affinity labelled analogs to determine the molecular targets of a bioactive.[31] We first looked at Naratriptan[32] an FDA approved treatment for migraines, finding conversion to **22** in moderate isolated yield with **2b** in a mixture 9:1 DCM/MeOH. Melatonin (**23**) was quickly converted in good yield, to the expected sulfenylated product with reagent **2b**. We were also able to sulfenylate biologically active pyrrole **24**[33] in good yield, albeit a longer reaction time was needed. Finally, we evaluated peptides as substrates, observing clean conversion of Boc-Trp-Gly-Gly-Trp-OMe to doubly sulfenylated peptide **25** with **2b**. We were also able to cleanly sulfenylate Z-Tyr-Trp-OMe and Boc-His(*N*-Bom*)*-Trp-Ome at tryptophan using **6** to give functionalized peptide **26** and **27** in high yields. This highlights the mildness and specificity of our sulfenylation conditions as these peptides

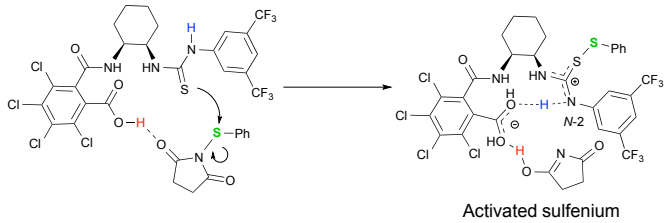


Figure 2. A proposed mechanism for the catalytic activation of *N*-thiosuccinimides by conjugate Lewis Base-Brønsted acid catalysis.

possess both acid labile protecting groups and other electron rich aromatic side chains. Indeed evaluating the sulfenylation of these peptides using 15 equivalents of TFA resulted in a mixture of isomers and deprotected products (see SI).

We have hypothesized that this catalytic sulfenylation operates through a mechanism in which the carboxylic acid activates the *N*-thiosuccinimide via protonation and the thiourea acts as a Lewis base and forms a thiouronium adduct (figure 2A) that functions as a more electrophilic sulfenium source.. While thioureas are also known to function as Brønsted acids, the Lewis basic hypothesis is supported by the data in Table 1, entry 4, in which both a Lewis base and a Brønsted acid was needed to affect sulfenylation.

We also turned to preliminary DFT studies (B3LYP/6-31G(d)) to better understand the observed differences in reactivity between catalysts **5** and **6** (Figure S1).. In less reactive **5** these studies predicted the complete deprotonation of N-2 (proton in blue,) resulting in a neutral intermediate. On the other hand, in catalyst **6** the N-2 hydrogen largely remains on N-2, and participates in a hydrogen-bonding network with the carboxylate and succinimide. This leads to a larger degree of thiouronim character in the **6**-sulfenium adduct, as evidenced by the increased predicted partial positive charge at the catalyst sulfur in **6** (+0.201 in **6** vs +0.138 in **5**, see SI), which would be expected to translate to a more electrophilic sulfenium.[34] This study also provides an explanation for the accelerating effects of TFA as the catalyst would remain fully protonated resulting in greater thiouronim character.

One possible explanation for why N-2 participates in H-bonding with succinimide in catalyst **6** but not in **5** is that in catalyst **6** the catalytic moieties are separated (one is axial), resulting in an open cleft that allows the succinimide to come in close contact with the carboxylate (predicted through space O-O bond distance of 2.57 Å). In catalyst **5** each moiety is equatorial and there is no such cleft, resulting in a steric interaction forcing the succinimide away from the carboxylate, lessening any H-bonding (O-O bond distance of 3.98 Å).

In summary we have developed a mild catalytic system to sulfenylate electron rich heterocycles including peptides and biologically relevant small molecules. The mildness of this chemistry coupled with the versatility of the groups that can be incorporated via sulfur is expected to render this chemistry broadly useful, particularly in chemical biology.

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