

# Enantioselective, Lewis Base-Catalyzed, Intermolecular Sulfenoamination of Alkenes

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**S** Supporting Information

**ABSTRACT:** A method for the catalytic, enantioselective, intermolecular, 1,2-sulfenoamination of alkenes is described. Functionalization is achieved through the intermediacy of an enantioenriched, configurationally stable thiiranium ion generated by Lewis base activation of a readily available sulfur electrophile. A diverse set of anilines and benzylamines react with different styrenes to afford products in good yield and stereoselectivity. Downstream manipulation of the products is facilitated by deprotonation of the amines to enable carbon–sulfur bond cleavage.

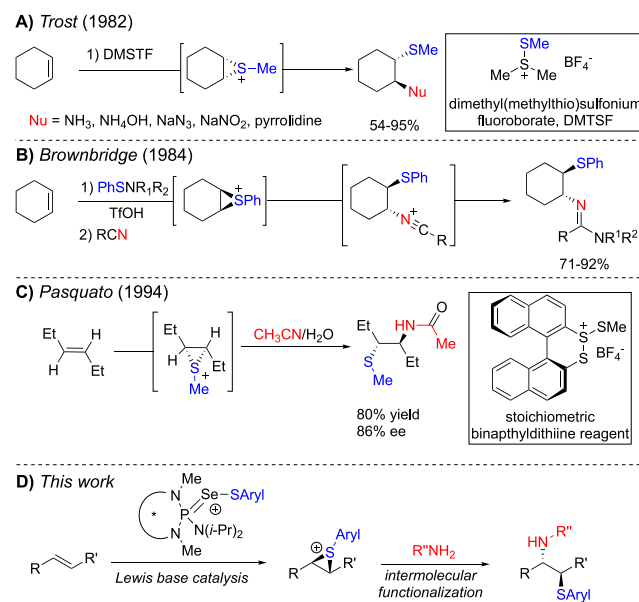
The transformation of simple alkenes into chiral, non-racemic, vicinally functionalized building blocks serves as an important strategy for the production of value added chemicals. In the past 30 years, numerous approaches to alkene difunctionalization such as epoxidation, dihydroxylation, aminohydroxylation and halofunctionalization have been reported.<sup>1–5</sup> On the other hand, the sulfenofunctionalization of alkenes proceeding through racemic thiiranium ion intermediates has been known since the early 1960s, but enantioselective variants are significantly less developed. Despite their high reactivity, thiiranium ions are configurationally stable at low temperature and readily intercepted stereospecifically with various nucleophiles to afford *anti*-sulfenofunctionalized products.<sup>6</sup>

As part of an ongoing program on the enantioselective functionalization of alkenes, we have exploited the activation of group 16 Lewis acids by Lewis bases to access seleno- and sulfenofunctionalized products.<sup>7</sup> Association of a Lewis basic selenophosphoramidate catalyst **5** and group 16 Lewis acid **4** (“Sulfenylating Agent”) results in a highly electrophilic donor–acceptor complex.<sup>8</sup> This complex is intercepted by an unactivated alkene to form an enantioenriched, configurationally stable thiiranium ion which subsequently undergoes stereospecific nucleophilic opening. A number of nucleophiles including alcohols, phenols, amines, anilines, arenes and alkenes serve effectively in intramolecular processes.<sup>9–13</sup> In addition, a recent report from these laboratories demonstrated the sulfenocyclization of polyenes enabled by the use of hexafluoroisopropyl alcohol (HFIP) as the solvent.<sup>14</sup> The utility of protic solvents has since been further applied to the carbosulfenylation of alkenylboronates.<sup>15</sup> Although intramolecular functionalization has proven successful, previous attempts to achieve intermolecular functionalization with similar nucleophiles have met with limited success largely

owing to the use of a strong acid (MsOH) which leads to decomposition of starting material. We reasoned the use of HFIP, which obviates the need for strong acids, could enable successful intermolecular sulfenofunctionalization.

The intermolecular functionalization of thiiranium ions, pioneered in 1982 by Trost, involves formation of a racemic thiiranium ion (generated from dimethyl(methylthio)sulfonium tetrafluoroborate (DMSTF)), which then undergoes invertive opening (Scheme 1A).<sup>16</sup> A variety of nitrogen-based nucleophiles afford the sulfenoamination products including amines, azide, and nitrite nucleophiles to provide the amino, azido, and nitro sulfides, respectively. Brownbridge subsequently reported the treatment of alkenes with phenylsulfenamides in dichloromethane to access 1,2-aminothiols in moderate yields and, when in the presence of acetonitrile, the corresponding amidines were formed (Scheme 1B).<sup>17</sup> In the intervening years a number of methods have been disclosed to access racemic 1,2-aminothiols including trifluoromethylthioamination of alkenes catalyzed by diaryl selenides reported by Zhao et al. and a highly efficient electrochemical oxy- and aminosulfenylation of alkenes by Yuan et al.<sup>18,19</sup>

## Scheme 1. Intermolecular Sulfenoamination by Interception of Thiiranium Ions



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Indeed, strategies to access enantiomerically enriched 1,2-amino thiols have largely relied on the desymmetrization of aziridines.<sup>20</sup> In contrast, the formation and functionalization of enantioenriched thiiranium ions has been significantly less explored. In 1994 Rayner reported the synthesis of benzoxazines by the intramolecular capture of thiiranium ions generated from enantiomerically enriched sulfenyl sulfonium salts.<sup>21</sup> Although the products are obtained in acceptable yield, enantioinduction was poor, ostensibly from substrate-mediated background reaction. In the same year, Pasquato et al. disclosed the first enantioselective intermolecular sulfenoamination achieved through an enantioenriched thiiranium ion intermediate (Scheme 1C).<sup>22</sup> A stoichiometric quantity of a chiral dinaphtho[2,1-c:1',2'-e][1,2]dithiin sulfenylating agent produces enantioenriched thiiranium ions which undergo capture with acetonitrile in a Ritter-type process to provide the corresponding sulfeno acetamides in good yield and enantioselectivity. Herein, we report a catalytic, enantioselective, intermolecular sulfenoamination of alkenes enabled by the stereospecific capture of enantioenriched thiiranium ions.

Orienting experiments (Table 1) initially employed HFIP (0.5 M), (*E*)-2-methylstyrene **1a**, sulfenylating agent **4**<sup>8b</sup> (1.0 equiv), catalyst (*S*)-**5** (0.1 equiv) or tetrahydrothiophene (THT, 0.1 equiv) and *p*-toluenesulfonamide (TsNH<sub>2</sub>, 1.0 equiv) as the nucleophile. Unfortunately, only the oxysulfenylated product **3** corresponding to solvent incorporation was observed (entry 1). The same result was observed when the comparatively less nucleophilic nonfluoro-*tert*-butyl alcohol (9F-*t*-BuOH) was employed (entry 2). The use of mixed solvent systems (dichloromethane/HFIP, dichloro-

methane/9F-*t*-BuOH and toluene/9F-*t*-BuOH) failed to provide the desired products, resulting in the generation of undesired side products (entries 3–5). At this point it was deemed prudent to survey several amines that could intercept the thiiranium ion more readily than HFIP. Nucleophiles such as *tert*-butyl carbamate and 2-aminobenzothiazole again afforded the oxysulfenylated product (entries 6 and 7). Gratifyingly, *p*-anisidine was identified as an effective nucleophile and no solvent incorporation was observed (entry 8).

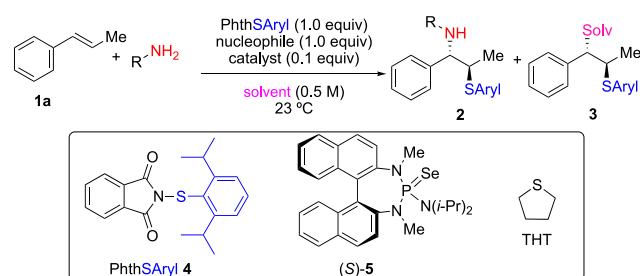
Reaction conditions were further refined through the use of Design of Experiment software.<sup>23</sup> Four reaction factors were examined in this protocol: overall concentration, equivalents of both sulfenylating agent and *p*-anisidine, as well as catalyst loading. A total of 25 experiments were conducted and the results were analyzed by <sup>1</sup>H NMR spectroscopy and a response surface was generated. A slight excess of sulfenylating agent (1.2 equiv) and *p*-anisidine (1.6 equiv) were required because sulfenylation of the *p*-anisidine to form the corresponding thiohydroxylamine was identified as a parasitic pathway. Additionally, high concentration was key to minimize the formation of any oxysulfenylated product. Lastly, reactions run for 24 h at ambient temperature maintain high yields with catalyst loading as low as 5 mol %.

Under the optimized conditions, a number of anilines containing both electron rich and electron withdrawing functional groups were evaluated (Table 2). 4-Haloanilines were competent, affording the corresponding aminofunctionalized products **2a–2c** as single diastereomers in good yield and 98:2 enantiomeric ratio. Absolute configuration was confirmed by single crystal X-ray diffraction<sup>24</sup> of **2c** and corresponds to the selectivity models previously described.<sup>8</sup> 2-Iodoaniline was incorporated in good yield and high enantioselectivity was maintained. Electron-rich anilines were also incorporated giving products **2e** and **2f** in good yield. Owing to the mild conditions afforded by HFIP, acid-labile protecting groups are compatible as demonstrated by synthesis of pivalate **2g** in 84% yield and carbamate **2h** in 83% yield. Of note is the ability of electron deficient anilines to outcompete the formation of oxysulfenylated product. 4-Aminoacetophenone and benzocaine were cleanly incorporated to afford products **2i** and **2j** respectively in good yield. 4-Aminophenylboronic acid pinacol ester provided the desired product **2k** in 82% yield and thereby provides an additional functional group for subsequent cross coupling reactions. 2-Aminopyridine was also competent affording **2l** in good yield and selectivity.

The method was extended to a number of benzylic amine nucleophiles. Benzylamine was incorporated efficiently as was 2-methylbenzylamine to give the corresponding products **2m** and **2n** in 70% and 75% yield respectively with no appreciable loss in enantioselectivity. Benzylamines containing the inductively withdrawing and resonance withdrawing trifluoromethyl and 4-cyano substituents reacted efficiently to give **2p** and **2q**. 2-Furfurylmethylamine was smoothly incorporated in 75% yield and 98:2 e.r. Incorporation of aliphatic amines was largely unsuccessful owing to their increased Brønsted basicity (leading to protonation under these conditions) resulting in the formation of the oxysulfenylation product exclusively.

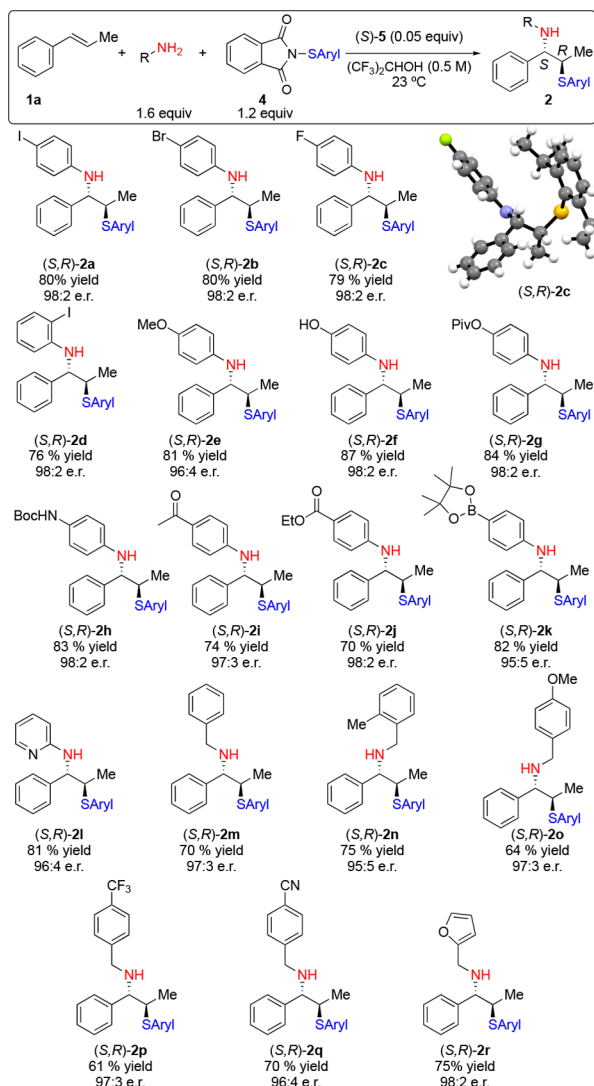
With respect to the olefin scope (Table 3), styrene, which had previously given poor results in the presence of strong acid, was readily functionalized in 80% yield and 96:4 e.r. Additionally, products **7b** and **7c** arising from 2-fluorostyrene and 2-methylstyrene respectively were obtained in synthetically

Table 1. Reaction Optimization



entry	nucleophile	Lewis base	solvent	2	3
1	TsNH <sub>2</sub>	( <i>S</i> )- <b>5</b>	HFIP	0%	76% <sup>a</sup>
2	TsNH <sub>2</sub>	( <i>S</i> )- <b>5</b>	9F- <i>t</i> -BuOH	0%	67% <sup>a</sup>
3	TsNH <sub>2</sub>	( <i>S</i> )- <b>5</b>	HFIP/ CH <sub>2</sub> Cl <sub>2</sub>	0%	0% <sup>b</sup>
4	TsNH <sub>2</sub>	THT	9F- <i>t</i> -BuOH/ CH <sub>2</sub> Cl <sub>2</sub>	0%	0% <sup>b</sup>
5	TsNH <sub>2</sub>	THT	9F- <i>t</i> -BuOH/ toluene	0%	0% <sup>b</sup>
6		THT	HFIP	0%	81% <sup>c</sup>
7		THT	HFIP	0%	79% <sup>c</sup>
8		( <i>S</i> )- <b>5</b>	HFIP	73% <sup>a</sup>	0%

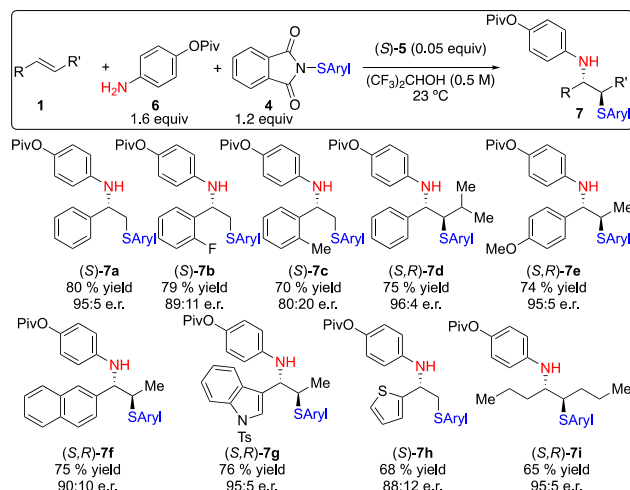
<sup>a</sup>Yield of isolated products. <sup>b</sup>Starting material remaining and side products were formed. <sup>c</sup>Yield obtained by <sup>1</sup>H NMR analysis against an internal standard.

Table 2. Aniline and Benzyl Amine Scope<sup>a,b,c</sup>

<sup>a</sup>All reactions performed on a 1.00 mmol scale. <sup>b</sup>Yield of isolated, analytically pure product. <sup>c</sup>Enantiomeric ratio determined by CSP-HPLC (high performance liquid chromatography) or CSP SFC analysis.

useful yields however, both suffered from slight degradation in selectivity. 3-Methylbutenylbenzene reacted to afford 7d in good yield and selectivity. Attempts to functionalize  $\alpha$ -methylstyrene afforded the desired sulfenofunctionalized product, however in racemic form. This outcome likely arises from the intermediacy of a stabilized, open carbocation rather than by stereospecific ring opening of a thiiranium ion. Similarly, anethole is also capable of efficient cation stabilization which might result in a mixture of diastereomers. Gratifyingly, anethole was competent in the reaction providing the desired product 7e in 74% yield and 95:5 e.r. Difunctionalized products containing extended aromatic systems (7f), e.g., *N*-tosyl substituted indole (7g), heterocycles (7h) and aliphatic alkenes (7i), were all produced in good yield and good to excellent selectivity.

A major objective of this project was the subsequent derivatization of the sulfenofunctionalized products. Although the increased steric bulk of the 2,6-diisopropylsulfenylating agent 4 affords superior enantioselectivities, this same property

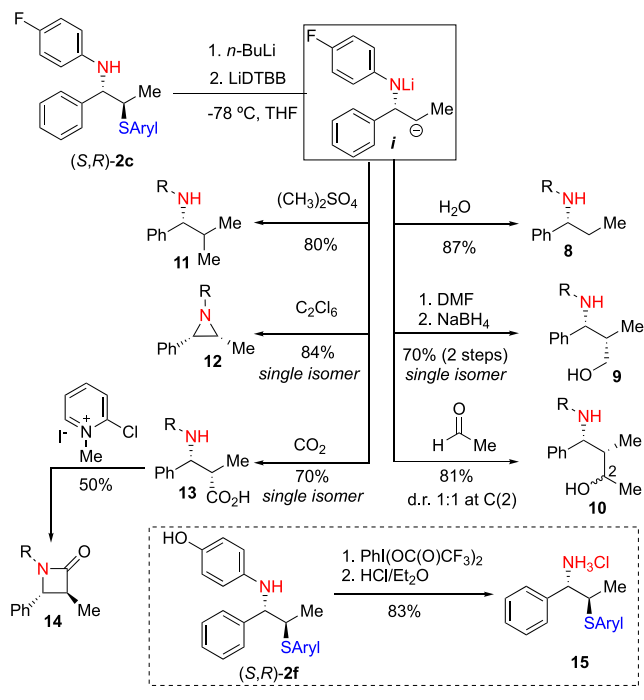
Table 3. Olefin Scope<sup>a,b,c</sup>

<sup>a</sup>All reactions performed on a 1.00 mmol scale. <sup>b</sup>Yield of isolated, analytically pure product. <sup>c</sup>Enantiomeric ratio determined by CSP-HPLC or CSP SFC analysis.

reduces reactivity and complicates subsequent functionalization. Initial attempts to affect C–S cleavage employed a variety of reducing agents that simply returned starting material even under forcing conditions. Treatment with lithium naphthalenide successfully affected C–S cleavage but resulted in spontaneous decomposition of the anion through  $\beta$ -elimination. To address this limitation, we were inspired by a report from Yus and co-workers, which describes the generation of stable  $\beta$ -amido alkylolithium species through a two-step, one-pot protocol by preforming the lithium amide, which serves to prevent  $\beta$ -elimination.<sup>25</sup> This strategy has also been employed in the derivatization of  $\beta$ -oxyanionic alkylolithium reagents,<sup>26–31</sup> however, to the best of our knowledge, no subsequent reports using this strategy in the derivatization of  $\beta$ -amido alkylolithiums have been disclosed.

By preforming the lithium amide (by deprotonation with *n*-BuLi) prior to treatment with lithium 4,4'-di-*tert*-butylbiphenylide (LiDTBB), the  $\beta$ -amido alkylolithium adduct *i* was successfully converted into a number of functionalized derivatives (Scheme 2). The desulfurized product 8 was formed in 87% yield by quenching the dianion with water whereas the 1,3-amino alcohol 9 was formed as a single diastereomer through capture with dimethylformamide and subsequent reduction with no loss in enantiomeric purity. Reaction of *i* with acetaldehyde proceeded in good yield to provide 10 as a mixture of C(2) diastereomers whereas treatment with dimethyl sulfate afforded the C-methylated product 11 in 84% yield. Aziridine 12 was accessed via the intermediate *syn*-2-chlorolithiophenyl amide (by reaction with hexachloroethane) and subsequent invertive displacement. Finally, carbon dioxide was captured to afford the *syn*-amino acid 13, which was next cyclized to the  $\beta$ -lactam 14 after treatment with Mukaiyama's reagent.<sup>32</sup> The relative configurations of these adducts were established by comparison to literature values.<sup>33,34</sup> Attempts to form the corresponding piperidine and azepine through capture of 1,3-dibromopropane and 1,4-dibromobutane were unsuccessful as numerous byproducts were observed while exhaustive allylation proceeded in poor yield and afforded the bis-allylated product in 55:45 d.r. Lastly, 15, derived from 4-aminophenol, was cleanly

## Scheme 2. Product Manipulations



transformed to the primary amine through PIFA-mediated oxidation and subsequent hydrolysis.

From previous mechanistic investigations, a catalytic cycle is proposed in Figure 1. Activation of sulfenylating agent **4** by protonation with HFIP facilitates sulfur transfer to selenophosphoramidate catalyst **5** to form cationic species **ii**. Subsequent transfer of the sulfenyl group to the alkene results in enantioselective thiiranium ion formation (species **iii**). Stereospecific, intermolecular nucleophilic capture and subsequent deprotonation affords the vicinally functionalized product and regenerates the catalyst.

In conclusion, an enantioselective, Lewis base-catalyzed, intermolecular sulfenoamination has been described. By

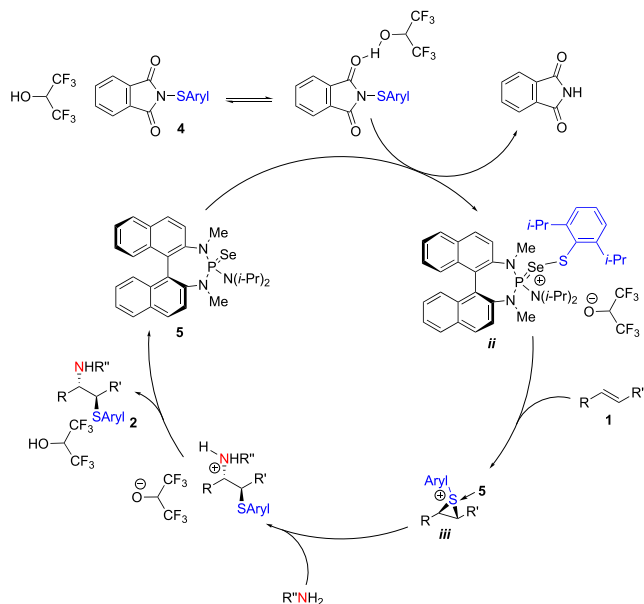


Figure 1. Proposed catalytic cycle.

employing HFIP as the solvent, both anilines and benzylic amines were employed as competent nucleophiles. The corresponding 1,2-sulfenoaminated products were obtained in good yields and excellent selectivities. A number of derivatives were accessed in high diastereoselectivity through a  $\beta$ -amido organolithium intermediate.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b07019.

Experimental Procedures, characterization data for all new compounds along with copies of spectra and chromatograms (PDF)

Data for 2c (CIF)

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### Notes

The authors declare no competing financial interest.

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