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Catalytic Regio- and Stereoselective Alkene Sulfenoamination for 1,4-Benzothiazine Synthesis

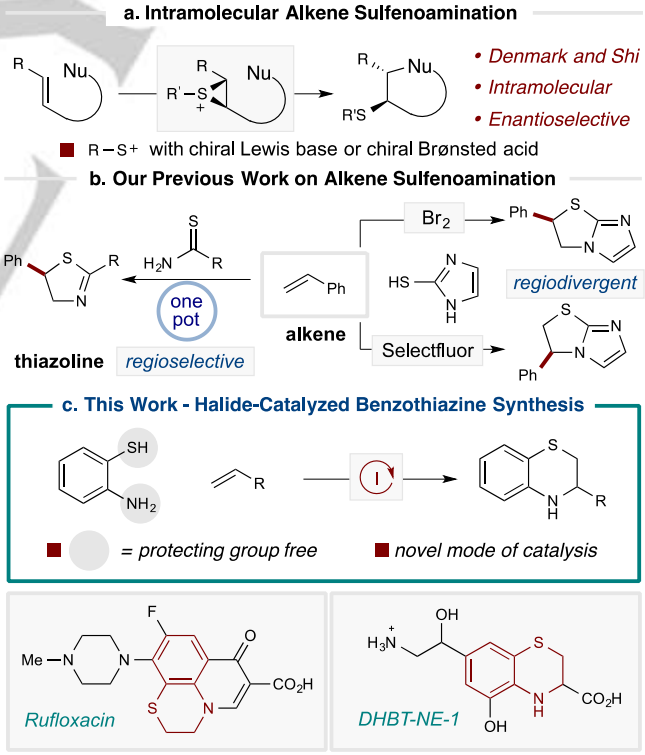
Nur-E Alom, Navdeep Kaur, Fan Wu, Shannon Jasmine Saluga, and Wei Li*[a]

Abstract: An alkene sulfenoamination reaction with 2-aminothiophenol is developed via iodide catalysis. This reaction renders access to useful 1,4-benzothiazines with good functional group compatibility including both electron-donating and electron-withdrawing substituents. The reaction is proposed to proceed through a polarity inversion of the thiol functionality. Our mechanistic studies reveal that both thiiranium and thiyl radical pathways are plausible and that the disulfide reagent can also function as viable substrate in this reaction.

Alkene difunctionalization is an exceptional strategy for the rapid assembly of molecular complexity with the simultaneous installation of two functional groups across a C=C π bond.[1] Of these, alkene sulfenoamination is a difficult process to accomplish yet highly useful to access a number of sulfur (S)- and nitrogen (N)-containing molecules.[2] A major contributing cause to this quandary is that the thiophilic nature of many metal catalysts often precludes the use of transition metal catalysis for alkene thioaminations.[3] Typically, either the sulfur or nitrogen functionality needs to be masked as an electrophile for olefin activation.[4] Subsequent nucleophilic attack from the other heteroatom can afford the vicinal thioamine product. In this regard, the Denmark and Shi groups have developed distinct and elegant strategies to enable intramolecular and enantioselective alkene sulfenoaminations.[5] Alternative intermolecular coupling processes offering a complementary and modular entry to a range of S- and N-heterocycles, however, remain to be exceptionally challenging and rare.[6] In particular, intermolecular coupling protocols utilizing unfunctionalized sulfur and nitrogen coupling partners are highly desirable due to the ease for further synthetic elaborations.[7]

S- and N-containing heterocycles such as 1,4-benzothiazines, are common motifs in pharmaceuticals and agrochemicals, possess a wide range of bioactivities.[8] For example, Rufloxacin is a second-generation fluroquinolone often prescribed to treat bacterial infection.[9] DHBT-NE-1 has been known to be relevant in neurodegenerative disease.[10] To access this class of heterocycle, multistep procedures involving α-halo carbonyls, dielectrophilic precursors, or synthetic elaborations based on existing core structures, have been developed.[11] However, these methods are often limited to specialized starting materials and/or tedious protecting group manipulations. Realization of an effective coupling protocol from unadorned 2-aminothiophenols and alkenes will significantly expedite the synthetic access to 1,4-benzothiazines for timely biological studies.

As part of our program to access bioactive heterocycles from simple chemical feedstock,[12] we are interested in the utilization of alkenes as building blocks for 1,4-benzothiazine synthesis. Based on our previous studies, we observed that a halogen source such as Selectfluor could activate a thiol to an electrophilic sulfur source, capable of engaging the alkene in thiiranium formation, and ensuing nitrogen addition to afford the desired product (Scheme 1b).[13] On the contrary, the use of bromine afforded a complementary regioisomer proceeding via a 1,2-dibromoalkane intermediate. More importantly here, we questioned whether an in situ generated catalytic halogen source would suffice for such a thiol polarity inversion.[14] Herein, we demonstrate an iodide-catalyzed alkene sulfenoamination to produce 1,4-benzothiazines, in a straightforward manner, from alkenes and 2-aminothiophenols.



Scheme 1. Alkene Sulfenoamination Background.

With these ideas in mind, we began our study with α-methylstyrene **1** and 2-aminothiophenol **2** as our standard substrates. Our initial conditions focused on the use of an iodide source and an oxidant. Gratifyingly, the combination of sodium iodide (NaI) as the catalyst, potassium persulfate ($K_2S_2O_8$) as

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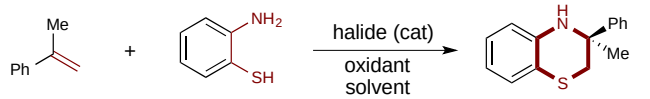
the terminal oxidant, and dichloroethane (DCE) as the solvent at 80 °C afforded the desired 1,4-benzothiazine product in 10% yield (Table 1, entry 1). Examination of solvents and various oxidants revealed that acetonitrile (MeCN) and $K_2S_2O_8$ were the optimal choices (Table 1, entries 2-6). The identity of the iodide catalyst had marginal effect on the reaction yields (Table 1, entries 7-9). Lowering the temperature to 50 °C, however, led to a decrease in reaction yield (Table 1, entry 10). Furthermore, control reactions without oxidant completely inhibited the reaction while the absence of the iodide catalyst still afforded the product, albeit at a significantly lower yield of 12% (Table 1, entries 11 and 12). Based on these optimization studies, we chose entry 7 as our optimal conditions for substrate scope studies.

Table 1. Reaction Optimization.[a]



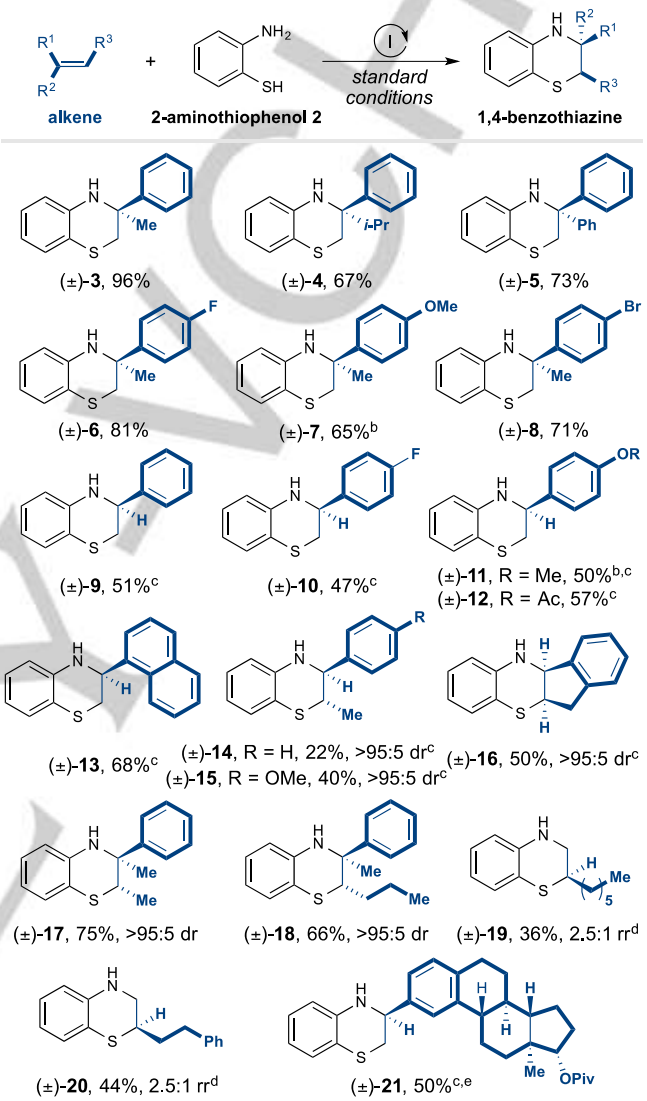
alkene 1 **2-aminothiophenol 2** **(±)-1,4-benzothiazine**

entry	halide catalyst (%)	oxidant (%)	solvent	yield (%)[b]
1	NaI (10)	$K_2S_2O_8$ (100)	DCE	10
2	NaI (10)	$K_2S_2O_8$ (100)	DMF	29
3	NaI (10)	$K_2S_2O_8$ (100)	MeCN	65
4	NaI (10)	$Na_2S_2O_8$ (100)	MeCN	36
5	NaI (10)	oxone (100)	MeCN	60
6[c]	NaI (10)	$K_2S_2O_8$ (100)	MeCN	78
7[d]	NaI (10)	$K_2S_2O_8$ (100)	MeCN	98(96)
8[d]	LiI (10)	$K_2S_2O_8$ (100)	MeCN	95
9[d]	KI (10)	$K_2S_2O_8$ (100)	MeCN	94
10[d,e]	NaI (10)	$K_2S_2O_8$ (100)	MeCN	74
11[d]	-	$K_2S_2O_8$ (100)	MeCN	12
12[d]	NaI (10)	-	MeCN	0

[a]Reaction conditions: alkene **1** (0.25 mmol), 2-aminothiophenol **2** (0.375 mmol), oxidant (0.25 mmol), iodide catalyst (10 mol%), solvent (4 mL), 80 ºC, 16 h. [b]Yields were determined by crude ^{1}H NMR using 1,3-benzodioxole as the internal standard. Yield shown in parenthesis was isolated yield. [c]alkene (0.375 mmol). [d]alkene (0.625 mmol). [e]50 ºC.

With the optimal conditions in hand, we evaluated a range of alkene substrates. A number of 1,1-disubstituted styrene derivatives participated in the reaction with excellent yields (Table 2, products **3**-**8**).[15] In these cases, highly steric congested carbon centers were established with great yields. Cross-coupling ready functional groups such as -bromo, -fluoro, and -methoxy were tolerated. Similarly, mono-substituted styrene derivatives worked effectively to afford the desired products (Table 2, products **9**-**13**). In addition, exceptional diastereoselectivities were observed for both *trans*- and *cis*-1,2-disubstituted styrene (Table 2, products **14**-**16**). Interestingly, tri-substituted alkenes also proceeded in this reaction to generate highly steric congested 1,4-benzothiazine products with excellent yields and diastereoselectivities (Table 2, products **17** and **18**). Furthermore, mono-substituted aliphatic olefins could afford the desired product with modest regioselectivity (Table 2, products 1**9** and **20**). Notably, a steroid derived alkene resulted in the product formation with a reasonable 50% yield and excellent regioselectivity (Table 2, product **21**).

Table 2. Alkene substrate scope.[a]

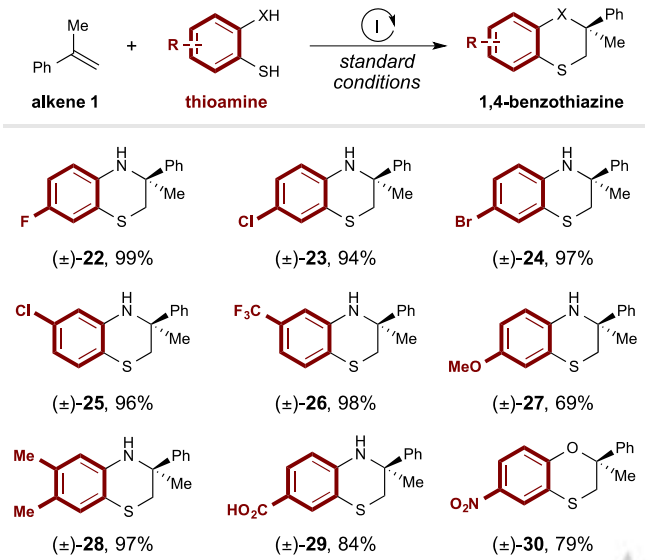


[a]Standard reaction conditions. [b]benzoyl peroxide was used as the oxidant. [c]NaI (20 mol%). [d]NaI (20 mol%), 36 h. [e]the product was isolated as an indistinguishable mixture of diastereomers.

Next, we wanted to examine the extent of functional group tolerance of the 2-aminobenzenethiol substrates. In this regard, we evaluated a range of 2-aminothiophenol possessing a variety of halogen functional groups. Specifically, versatile bromo-, chloro-, and fluoro-functionalities all worked with excellent efficiency under the standard reaction protocol (Table 3, products **22**-**25**). In addition, the pharmaceutically relevant trifluoromethyl substituted substrate could also afford the 1,4-benzothiazine product (Table 3, products **26**). Regardless of the electronic nature of the substitution on the 2-aminothiophenol, the reaction proceeded with high yields with methoxy-, alkyl-, and carboxyl-functional groups (Table 3, products **27**-**29**). In the case of product **29**, unprotected carboxylic acid could be

tolerated in this reaction to deliver the desired product in great yield. Furthermore, we could also synthesize 1,4-benzooxathiine **30** when a 2-mercaptophenol was used as the substrate (Table 3, product **30**). Finally, these substrates all uniformly afforded a single regioisomeric product in good yields and compatible to a wide range of functional groups.

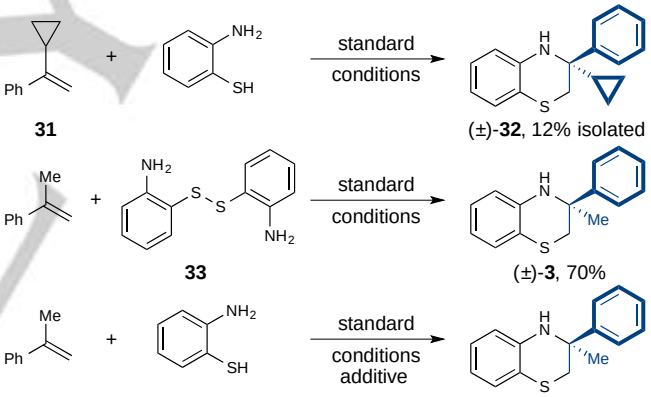
Table 3. Thioamine substrate scope.[a]



[a]Standard reaction conditions.

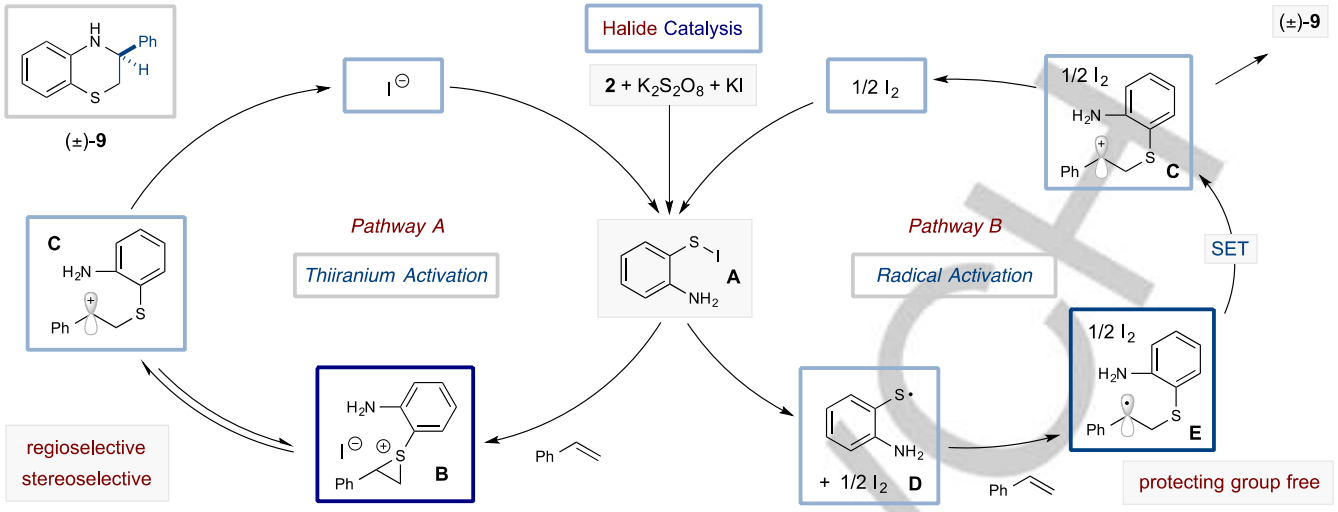
To gain an understanding of the reaction mechanism, we first evaluated the regiochemical features for this reaction. For the styrene-derived substrates, the nitrogen was uniformly added to the benzylic position whereas the sulfur was attached to the homobenzylic carbon. This regiochemical outcome was distinct from our previously developed alkene sulfenoamination based on halogenation protocols, in which the more nucleophilic sulfur was usually added to the benzylic position.[12][a] For aliphatic alkenes, the regioselectivity was lower and favored the nitrogen atom adding to the terminal position and the sulfur atom attached to the internal position. With this consideration in mind, we hypothesize that two potential mechanistic pathways can be operative here. Based on the control reactions, we reason that the 2-aminothiophenol can react with the oxidant and the iodide catalyst to generate the sulfur-based electrophile **A** (Scheme 2). From this intermediate, pathway A involves the direct electrophilic attack on the alkene to form the thiiranium ion **B**.[16] The thiiranium ion can be in equilibrium with the open carboncation **C**, which can then react with the tethered nitrogen nucleophile to produce the final heterocyclic product.[17] For the aliphatic alkenes, when the thiiranium is generated, the ring opening to the carbocation is likely slow. Lewis base addition by the iodide can occur to open the thiiranium ring at the less sterically hindered terminal position, followed by intramolecular displacement to afford the corresponding major regioisomer. Alternatively, pathway B from intermediate **A** involves homolysis to generate the thiyl radical **D**. Radical addition to the alkene then affords the radical intermediate **E**. Single electron transfer (SET) from the oxidant potassium persulfate produces the carbocation intermediate **C**, followed by intramolecular cyclization to afford the final product and regenerate the catalyst.

To support our mechanistic claim, we conducted several additional reactions (Scheme 3). First, we installed a radical clock on the alkene **31**. Under the standard conditions, we isolated 12% yield of the cyclopropyl ring intact product **32**, suggesting an ionic pathway was operative.[18] However, we also observed a complex mixture of ring opening adducts from product isolation. Second, we used the disulfide **33** as the thioamine structure in the reaction, and observed a comparable 70% yield. This result indicates that the active catalytic halogen source is capable of cleaving the S–S bond to form the sulfur electrophile **A**. Our control experiments demonstrated that in the absence of the oxidant, the iodide salt could also promote disulfide **33** for product formation to a certain extent (12%). In the absence of NaI, less than 2% product was observed. Third, we introduced a radical scavenger such as TEMPO in this reaction. With 1 equivalent of TEMPO, we did not see complete inhibition of the reaction. Instead, a decreased yield of 65% was observed. As the addition TEMPO increased, the yield decreased further. These data, collectively, suggest that both pathway A and B were likely to be operative here.



Scheme 3. Mechanistic experiments.

In summary, we have disclosed a novel and practical alkene sulfenoamination reaction using 2-aminothiophenols via iodide catalysis. A range of 1,4-benzothiazines is produced with good functional group compatibility and excellent regioselectivity and stereoselectivity. The substituent electronic nature of the 2-aminothiophenol has minimal effect on the reaction efficiency. Furthermore, we demonstrated that disulfide reagents are also viable substrates. Finally, mechanistic experiments indicate that both thiiranium activation and radical activation are operative in this reaction.



Scheme 2. Potential Reaction Mechanisms.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkene sulfenoamination • iodide catalysis • S- and N-heterocycles • 1,4-benzothiazine • thiiranium

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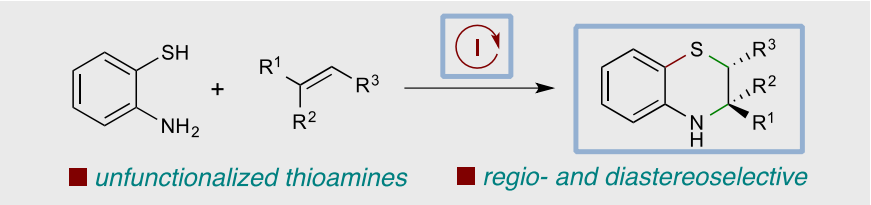

A novel catalytic strategy is introduced to couple alkenes and unfunctionalized thioamines for the synthesis of useful heterocycles. This catalytic protocol tolerates a wide range of substrates with great regioselectivty and diastereoselectivity.

*Nur-E Alom, Navdeep Kaur, Fan Wu, Shannon Jasmine Saluga, and Wei Li**

Page No. – Page No.

Catalytic Regio- and Stereoselective Alkene Sulfenoamination for 1,4-Benzothiazine Synthesis