A modular photoredox route towards sulfoximines

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Abstract: We report a modular photoredox strategy for the synthesis of aryl vinyl sulfoximines from sulfinamides and vinyl halides starting materials. This strategy demonstrates a difunctionalization of sulfinamides to sulfoximine products with excellent configurational retention and stereoselective trans alkenes. Under mild redox conditions, we propose the generation of a nitrogen centered radical that is resonance stabilized by a sulfur radical partner, increasing overall radical lifetime. This strategy we disclose is thus well suited for vinyl halide radical capture, leading to sulfoximine products. This process also entails broad modularity about the alkene, arene, and acyl protecting group, providing synthetic chemists multiple functional handles allowing for further exploration into the physicochemical properties that have shown promise in recent studies.

Introduction: Since their discovery in 1949, sulfoximines have remained broadly underexplored despite the pharmacological and synthetic promise they exhibit.[1] To date, the presence of sulfur in FDA approved drugs is quite abundant. In particular, sulfonamides constitute 25% of sulfur-containing drugs (Figure 1a);[2] however, exchanging sulfonamides for sulfoximines have demonstrated enhancements in various pharmacokinetic properties.[1,2] These properties have made sulfoximines a compelling topic for recent research. However, no drug molecules on the market contain a sulfoximine scaffold despite its similarities to numerous groups. This discrepancy is particularly concerning considering the recent data collected that indicate sulfoximines as competitive moieties over traditional chemical classes.[3] In the last few years of drug design, sulfoximines have demonstrated improved lipophilicity, 3D control, and functional handle opportunities compared to the more conventional alternatives (Figure 1b).[4] This has led to sulfoximines being identified as suitable bioisosteres for functional groups such as sulfones, sulfonamides, carboxylic acids, alcohols, ketones, and amines, among others (Figure 1c).[3,4]

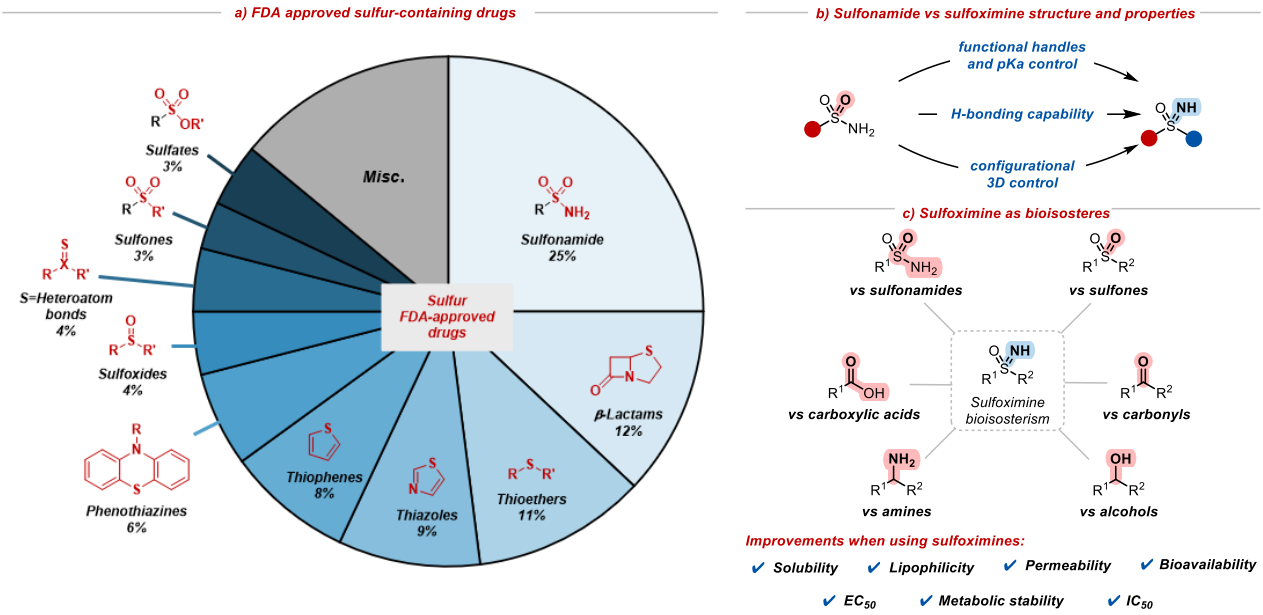
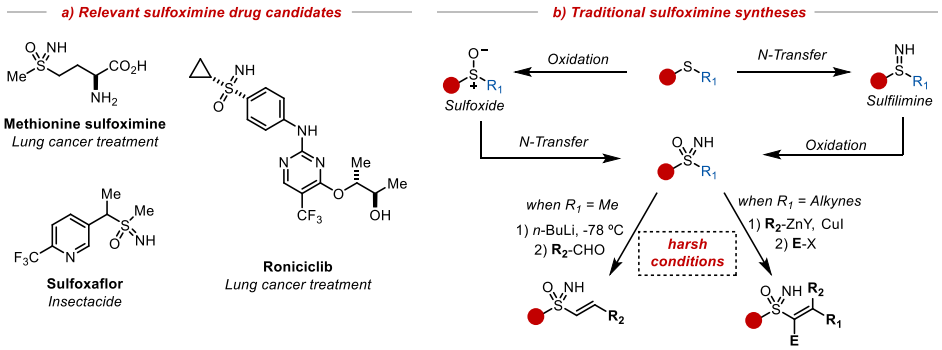


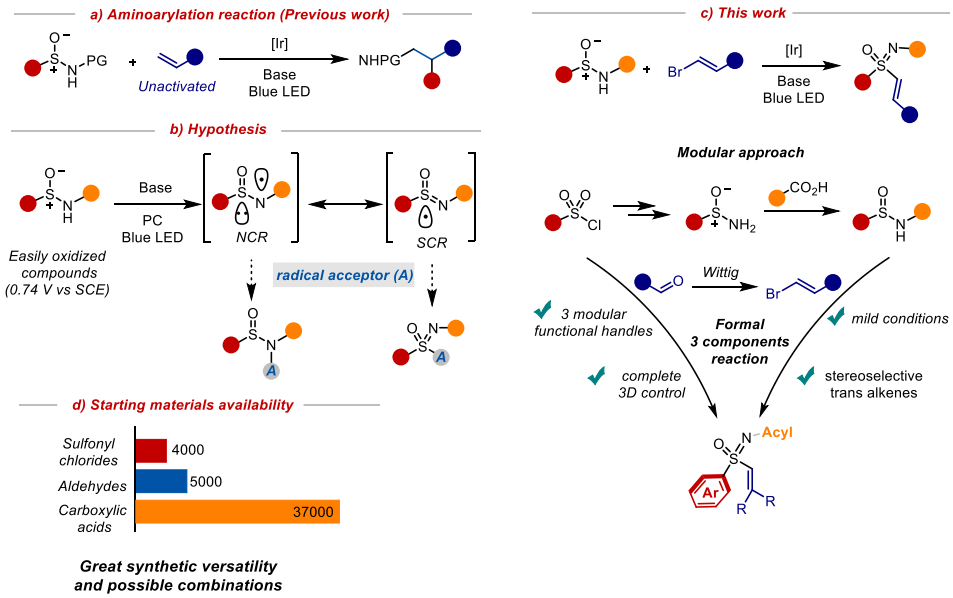
Figure 1. a) FDA approved sulfur-containing drugs; b) Sulfonamide and sulfoximine structure and properties; c) sulfoximine bioisosterism.

The rationale behind the lack of incorporation of this novel functional group is attributed to the difficulty in synthesizing the sulfoximine scaffold.[5] Therefore, only a few drug candidates are currently under evaluation (Scheme 1a).[3] Classical approaches to access sulfoximines typically employ harsh conditions involving a two-step oxidative or nitrogen transfer process (Scheme 1b).[5] Other methods take advantage of metal catalysts, especially rhodium species,[6] and supra-stoichiometric loading of (diacetoxyiodo)benzene.[7] In recent years, copper catalysis,[8] and Grignard strategies have also been employed to access the sulfoximine core,[9] representing the most modern approaches. Specifically, *vinyl* sulfoximines have only shown to be synthesized via hydroxyalkylation-elimination sequence of metalated sulfoximines,[10] the carbometalation of alkynyl sulfoximines,[11] and Horner-Wadsworht-Emmons approaches using (arylsulfonimidoyl)phosphonates and aldehydes.[12] Most of these strategies require pre-functionalized starting materials and have a limited functional group tolerance. Moreover, the photocatalytic synthesis of these compounds has not been reported to date.



Scheme 1: a) Relevant sulfoximine drug candidates under evaluation; b) traditional sulfoximine syntheses.

In our previous work, we designed a general methodology for the aminoarylation reaction of unactivated alkenes using sulfinamides as precursors for nitrogen-centered radicals (NCRs) (Scheme 2a).[13] In that work, the NCR was trapped by the unactivated alkene, leading to the Smiles-Truce rearrangements. We had hypothesized divergent reactivity can be achieved when alternative radical acceptors are employed (Scheme 2b). In practice when using vinyl bromides only sulfoximines were observed (Scheme 2c). This was particularly encouraging considering the redox potentials for sulfinamides (0.77 V vs SCE) entail mild conditions. This approach enables the design of a modular process that can be conceptually viewed as a formal three-component reaction. Of those modular pieces, acyl aryl sulfinamides, and vinyl bromides can be obtained from the corresponding carboxylic acids, sulfonyl chlorides, and aldehydes respectively. The ubiquitous nature of the starting materials has lent this methodology to be extremely versatile offering chemists diverse control of three functional handles (Scheme 2d).[14] The nature of this mechanism is currently believed to be a radical process wherein a nitrogen radical is resonance stabilized by a sulfur radical, thus extending the radical lifetime.[15] The details of the mechanism are still under investigation, however, work conducted thus far has led us to believe we can develop conditions to favor and capture this postulated sulfur-centered radical (SCR) for identification and subsequent reactivity.

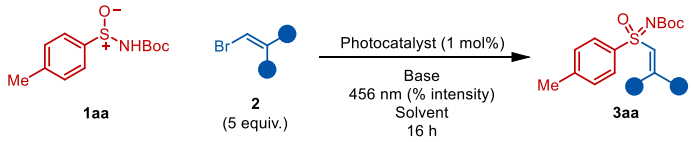


Scheme 2: a) Divergent reactivity observed when unactivated alkenes were used as coupling partners; b) hyphothesis and SCR reactivity; c) This work; d) Starting materials availability.

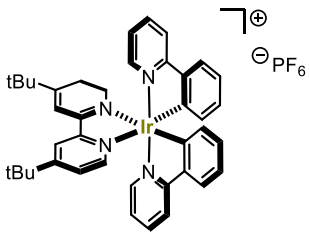
Results and discussion: Inspired by our prior research on the aminoarylation reaction involving unactivated alkenes and the use of sulfinamides as precursors for NCRs (Scheme 2a),[13] we

envisioned synthesizing enamines by employing alkenes bearing leaving groups (Scheme 2c). We hypothesized the generation of a NCR that would perform an addition reaction with a vinyl halide followed by a rapid elimination to the enamine. To validate our hypothesis, we exposed the *N*-Boc *para*-tolyl sulfinamide to our previous optimized aminoarylation conditions in the presence of 1-bromoprop-1-ene as a mixture of *cis:trans* isomers. Surprisingly, instead of the enamine, the C-S coupling sulfoximine product *trans*-**3aa** was generated in 35% yield as the single isomer. In light of these findings, we made the decision to refine the synthesis of sulfoximines, due to the significance of these compounds in medicinal chemistry.

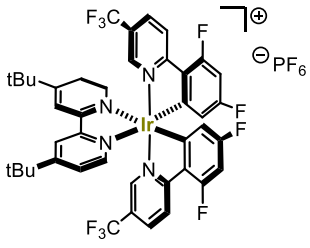
Optimization



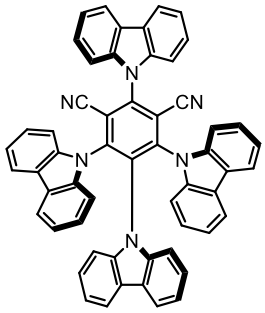
Entry	R = H/Ph	Photocatalyst	Base (equiv.)	Solvent	% Light Intensity	Yield (%)[a]
1	H	Ir-1	K_2CO_3 (4.0)	1:5 DCE/H_2O	100	54
2	H	Ir-1	K^{t}OBu (4.0)	1:5 DCE/H_2O	100	29
3	H	Ir-1	Quinuclidine (4.0)	1:5 DCE/H_2O	100	6
4	H	Ir-2	K_2CO_3 (4.0)	1:5 DCE/H_2O	100	13
5	H	4-CzIPN	K_2CO_3 (4.0)	1:5 DCE/H_2O	100	12
6	H	----	K_2CO_3 (4.0)	1:5 DCE/H_2O	100	<5
7	H	Ir-1	K_2CO_3 (4.0)	0.16 M, DCE	100	8
8	H	Ir-1	K_2CO_3 (4.0)	0.16 M, H_2O	100	43
9	H	Ir-1	K_2CO_3 (4.0)	1:6 DCE/H_2O	75	65
10	Ph	Ir-1	K_2CO_3 (4.0)	1:6 DCE/H_2O	75	71



Ir-1
[Ir(ppy)$_2$(dtbbpy)](PF$_6$)



Ir-2
[Ir(dF[CF$_3$]ppy)$_2$(dtbbpy)](PF$_6$)

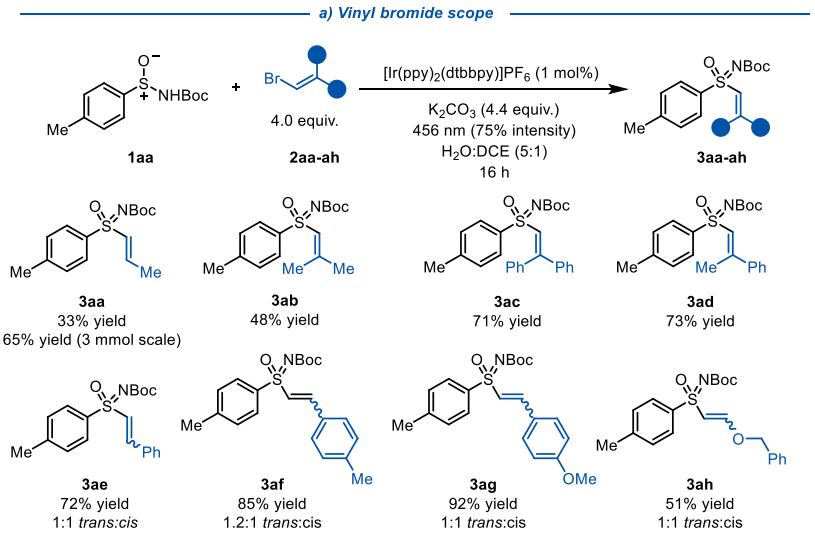


4CzIPN

Table 1: Reaction optimization. [a] Assay yields were determined by ^{1}H-NMR integration relative to 1.0 equiv. of 1,3 dibromopropene as an internal standard.

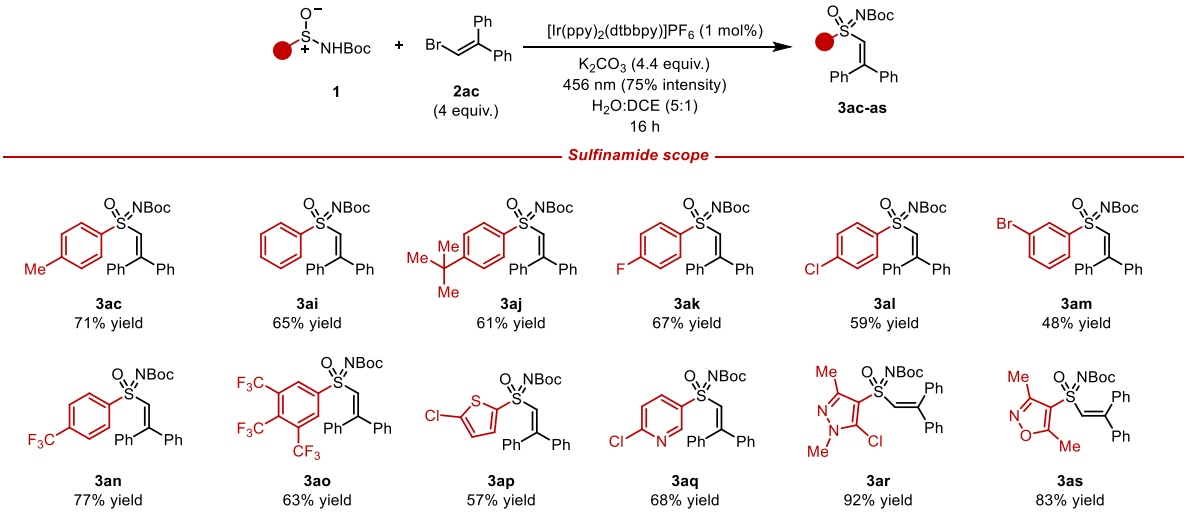
We began optimization with N-Boc para-tolyl sulfinamide (**1aa**) and 1-bromoprop-1-ene as the model coupling partners (Table 1). Our initial studies were concerned with identifying a suitable loading of base. We identified potassium carbonate as providing the greatest yields of **3aa**. Organic and inorganic bases were tested in entries 1-3, however only diminished yields were observed. Due to the best results being obtained with potassium carbonate, it was hypothesized that water was necessary to solubilize the base. As expected, when the reaction was run with no water the reaction saw a steep decrease in yield, entry 7. Interestingly, when DCE was omitted and only water was used, the reaction still proceeded and produced a significant yield, albeit decreased from the optimized conditions. We also studied the effects of the photocatalyst. Photocatalysts **Ir-2** and **4CzIPN** in entries 4 and 5 both had well established redox potentials within the range of the sulfinamide anionic intermediate we had postulated to be making in situ. However, these photocatalysts proved ineffective demonstrating how the milder photocatalyst **Ir-1** significantly improves the reaction. Finally, we had hypothesized the addition of the NCR into a vinyl halide, thus generating an alkyl radical intermediate. In an attempt to lower the energy barrier to access this intermediate, we exchanged 1-bromoprop-1-ene for the diphenly derivative in entry 10. This resulted in a significant increase in yield and is further suggestive of the existence of a benzylic radical.

We then studied the variability of the reaction with respect to the vinyl bromide using **1aa** as the model substrate. Initially, we examined both aliphatic and aromatic vinyl bromides, as well as more highly substituted compounds, to determine if increasing substitution in the alkene moiety led to higher yields of the desired sulfoximine (Scheme 3). We hypothesized that the use of 4.0 equivalents of the vinyl bromide would lead to more favorable interactions given the relative radical lifetimes. However, when non-volatile vinyl bromides were employed, recovery of the unreacted alkene was obtainable with column chromatography giving good mass balance between product and starting materials. Aliphatic vinyl bromides **2aa,ab** yielded the corresponding sulfoximine in moderate yield, and crude reaction mixtures typically did not contain left over unreactive vinyl bromides due to the low boiling point of these compounds. Furthermore, only *trans*-**3aa** isomer was obtained. Subsequently, we upscaled the reaction to a 3 mmol scale using a 25 mL round-bottom flask, resulting in an increased isolated yield of 65% for **3aa**. We hypothesized that the reduced headspace in the round-bottom flask, as compared to the 0.1 mmol scale reactions conducted in a 1-dram vial, facilitated improved contact between the volatile vinyl bromide and the reaction medium. On the other hand, biaryl vinyl bromides improved conversion into sulfoximines (**3ac-ag**) with excellent isolated yields. Notably, there was an increase in the yield when electron-rich vinyl bromides were utilized (**3af-ag**). When a racemic mix of *cis/trans* vinyl bromides were employed, only the trans isomer was obtained in cases **3aa,ad**. However, when electron-rich styryl-type vinyl bromides were used, both *cis* and *trans* isomers of **3ae,af,ag** were recovered with a near 1:1 ratio. We hypothesized about a contra-thermodynamic photoisomerization of these styrenyl compounds since it is well understood and explored in the literature; however in the presence of sulfoximines, has not been addressed to the best of our knowledge.[16]



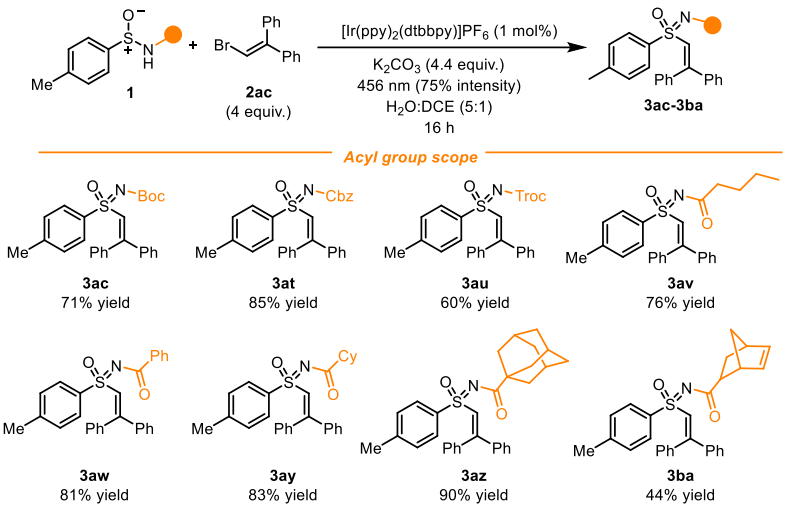
Scheme 3. a) Vinyl bromide scope.

We then explore the scope of the reaction with respect to the sulfinamide (Scheme 4). We evaluated the effect different aryl groups had on the yield of the corresponding sulfoximines (**3ac-as**). Minor variations in yield were observed across a series of electronically distinct sulfinamides (**3ac-ao**), with isolated yields ranging from 48% to 77%. Heteroarenes containing chloride atoms in their structure were also effective, yielding sulfoximines **3ap,aq,ar** in moderate to good isolated yields. Given the medicinal chemistry promise of sulfoximines and the crucial role of nitrogenous heterocycles in drug development,[17] our efforts have been concentrated on synthesizing sulfoximines derived from 5-chloro-1,3-dimethyl pyrazole (**3ar**) and 3,5-dimethyl isoxazole (**3as**). Remarkably, in these cases, it was possible to isolate the corresponding sulfoximines with high yields (92 and 83%, respectively).



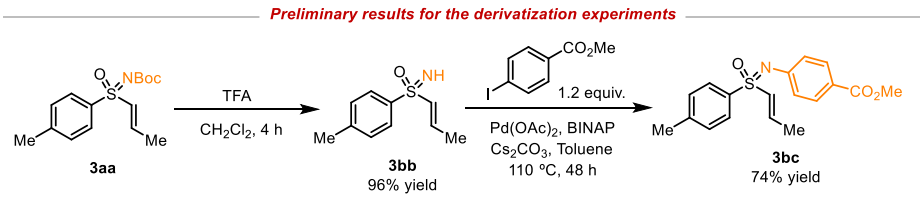
Scheme 4. Sulfinamide scope.

To enhance the synthetic versatility of this approach, we explored various substitution patterns on the nitrogen atom of the sulfinamide (Scheme 5). In addition to Boc, we also considered other protecting groups such as Cbz-, or Troc-, which enabled us to obtain the respective sulfoximines in high isolated yields (85 and 60% respectively). These carbamates can be cleaved under distinct conditions, so this methodology provides the user with control over the choice of protecting groups. Subsequently, we explored the possibility of introducing other acyl groups on the nitrogen atom that were not solely protective groups. By testing both aliphatic (**3av,ay**) and aromatic (**3aw**) acyl groups, the reaction consistently produced the desired sulfoximines in high yields. The reaction is suitable for incorporating bulky substituents in this region of the molecule, resulting in the formation of sulfoximine **3az** in high yield (90%). Finally, due to the advantages of using 3-dimensional sp^3-rich structures in drug discovery and medicinal chemistry,[18] instead of flat-sp^2 structures, we employed this methodology in the synthesis of the sulfoximine derived from norbornene **3ba**, resulting in its synthesis in a moderate yield, obtaining it as the single endo isomer. These results pave the way for the incorporation of various functionalizations in this region of the molecule.



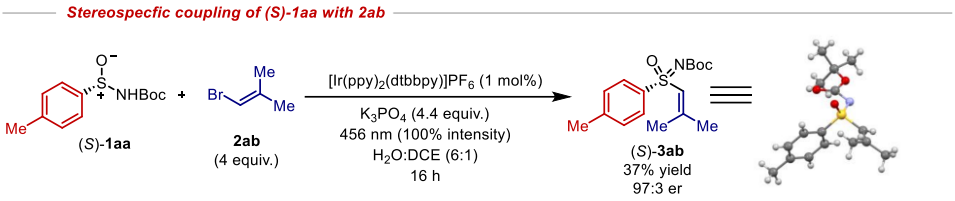
Scheme 5. Nitrogen acyl group scope.

To emphasize the utility of vinyl sulfoximines, we conducted several derivatization experiments. Initially, we deprotected N-Boc sulfoximine **3aa** using trifluoroacetic acid (TFA) to yield N-H sulfoximine **3bb**. This allowed us to facilitate various reactions at this site (Scheme 6). After obtaining the deprotected sulfoximine **3bb**, we conducted a Buchwald-Hartwig arylation reaction, resulting in the formation of sulfoximine **3bc** with a yield of 74%.[19] We are currently exploring additional reactions to further enhance the synthetic versatility of the vinyl sulfoximines obtained.



Scheme 6. Preliminary derivatization experiments of sulfoximine **3aa.**

Finally, considering the potential for sulfoximines to exhibit chiral conformations, we devised an asymmetric approach. To assess this chiral variant, (*S*)-**1aa** was utilized as a model substrate with 1-bromo-2-methylprop-1-ene as the coupling partner. Under the preliminary reaction conditions, it was possible to isolate sulfoximine (*S*)-**3ab** with a 97:3 enantiomeric ratio, confirming the enantio retention of the reaction (Scheme 7). The absolute configuration of (*S*)-**3ab** was determined through X-ray diffraction. Work to demonstrate the asymmetric capabilities of this reaction is currently underway.



Scheme 7. Stereospecific coupling of sulfoximine *(S)*-**1aa** with vinyl bromide **2ab**.

Conclusion: We have introduced a general and straightforward methodology for obtaining sulfoximines under mild reaction conditions by forming a novel C-S bond using vinyl bromides and sulfinamides as starting materials. This method enables the production of highly substituted sulfoximines, providing flexibility in introducing various substitution patterns throughout the molecule. We also highlight the enantioselective aspect of this reaction, which opens up possibilities for synthesizing chiral sulfoximines.

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The authors declare no competing financial interests.

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References

[1] H. R. Bentley, E. E. McDermott, J. Pace, J. K. Whitehead, T. Moran, *Nature*, **1950**, *165,* 150-151.
[2] K. A. Scott, J. T. Njardarson, *Top. Curr. Chem.* **2018**, *5*, 376.
[3] U. Lücking, *Chem. Eur. J.* **2022**, *28*, e202201993.
[4] Y. Han, K. Xing, J. Zhang, T. Tong, Y. Shi, H. Cao, H. Yu, Y. Zhang, D. Liu, L. Zhao, *Eur. J. Med. Chem.* **2021**, *209*, 112885.
[5] M. A. Andresini, A. Tota, L. Degennaro, J. A. Bull, R. Luisi, *Chem. Eur. J.* **2021**, *27*, 17293-17321.
[6] a) T. Siu, A. K. Yudin, *Org. Lett*. **2002**, *4*, 1839-1842; b) J. L. Jat, M. P. Paudyal, H. Gao,Q.-L. Xu, M. Yousufuddin, D. Devarajan, D. H. Ess, L. Kürtis, J. R. Falck, *Science*, **2014**, *343*, 61-65.
[7] a) A. Tota, M. Zenzola, S. J. Chawner, S. St John-Campbell, C. Carlucci, G.Romanazzi, L. Degennaro, J. A. Bull, R. Luisi, *Chem.Commun*. **2017**, *53*, 348-351; b) K. M. Foote, J. W. M. Nissink, T. McGuire, P. Turner, S. Guichard, J. W. T. Yates, A. Lau, K. Blades, D. Heathcote, R. Odedra, et al., J*. Med.Chem*. **2018**, *61*, 9889-990; c) M. A. Graham, H. Askey, A. D. Campbell, L. Chan, K. G. Cooper, Z. Cui, A. Dalgleish, D. Dave, G. Ensor, M. R. Galan Espinosa, et al.,*Org. Process Res. Dev*. **2021**, *25*, 43-56.
[8] a) Y. Aota, T. Kano, K. Maruoka, *J. Am. Chem. Soc*. **2019**, *141*,19263-19268; b) Y. Aota, T. Kano, K. Maruoka, *Angew. Chem. Int. Ed*. **2019**, *58*, 17661-17665; c) X. Zou, H. Wang, B. Gao, *Org. Lett.* **2023**, doi.org/10.1021/acs.orglett.3c02970.
[9] a) P. M. Matos, W. Lewis, J. C. Moore, R. A.Stockman, *Org.Lett*. **2018**, *20*, 3674-36; b) P. M. Matos, W. Lewis, S. P. Argent, J. C. Moore, R. A. Stockman, *Org.Lett*. **2020**,**22**, 2776-278.
[10] D. Craig, N. J. Geach, *Synlett*, **1993**, *7*, 481-482.
[11] G. Sklute, C. Bolm, I. Marek, *Org. Lett*. **2007**, *9*, 1259-162.
[12] a) M. J. McGrath, C. Bolm, Beilstein *J. Org. Chem*. **2007**, *3*, 33; b) P. K. Chinthakindi, G. C. Nandi, T. Govender, H. G. Kruger, T. Naicker, P. I. Arvidsson, *Synlett*, **2016**, 27, 1423-1427.
[13] E. Noten, C. Ng, R. Wolesensky, C. Stephenson, *ChemRxiv*, **2022**, 10.26434/chemrxiv-2022-28crb.

[14] Enamine has at its disposal 4000 sulfonyl chlorides, 5000 aldehydes, and 37000 carboxylic acids (October 2023).
[15] a) R. G. Hicks, *Org. Biomol. Chem.* **2007**, *5*, 1321-1338; b) D. Leifert, A. Studer, *Angew. Chem. Int. Ed.* **2020**, *59*, 73-108.
[16] T. Neveselý, M. Wienhold, J. J. Molloy, R. Gilmour, *Chem. Rev.* **2022**, *122*, 2650-2694.
[17] E. Vitaku, D. T. Smith, J. T- Njardason, *J. Med. Chem.* **2014**, *57*, 10257-10274.
[18] F. Lovering; J. Bikker, C. Humblet, *J. Med. Chem*. **2009**, *52*, 6752-6756.
[19] C. Bolm, J. P. Hildebrand, *Tetrahedron Lett.* ***1998****, 39, 5731-5734.*