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Synthetic Methods

Enantioselective Synthesis of Sulfinamidines via Asymmetric Nitrogen Transfer from N–H Oxaziridines to Sulfenamides

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Abstract: Sulfinamidines are promising aza-S^{IV} chiral building blocks in asymmetric synthesis and drug discovery. However, no report has documented their enantioselective synthesis. Here we present an enantioselective synthesis of sulfinamidines via electrophilic amination of sulfenamides using an enantiopure N–H oxaziridine. The resulting enantiomerically enriched primary sulfinamidines are configurationally stable at 90 °C in solution and show remarkable stability against organic acids and bases under non-aqueous conditions. We also demonstrate a one-pot, three-component, enantioselective synthesis of sulfinamides using N–H oxaziridine reagents.

In contrast to the demonstrated utility of sulfinamides (e.g., Ellman's sulfinamide[1]), applications of their aza-analogs sulfinamidines have been hardly explored.[2] Because this neglect likely stems from the lack of effective preparative methods for sulfinamidines, many efforts have recently been dedicated to devising practical syntheses of these aza-S^{IV} structures, including cycloaddition[3] or ene[4] reactions of sulfurdiimides, the addition of organometallic nucleophiles to sulfurdiimides,[5] and imidation[6] or oxidative amination[7] of sulfenamides. Despite these advancements, the enantioselective synthesis of sulfinamidines remains elusive, even though it is crucial to explore the potential applications of these sulfur motifs in synthetic and medicinal chemistry.

In this paper, we now report an enantioselective synthesis of sulfinamidines based on electrophilic amination of sulfenamides using an enantiopure N–H oxaziridine. The enantioenriched primary sulfinamidines show remarkable configurational and chemical stabilities towards acids and bases in non-aqueous solution. Additionally, we demonstrate a one-pot, three-component, enantioselective synthesis of primary sulfinamidines with a related enantiopure N–H oxaziridine reagent.

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N–H oxaziridines are effective nitrogen transfer agents that react with carbon, nitrogen, oxygen, and sulfur nucleophiles.[8] In the early 2000s, Page and co-workers developed enantiopure N–H oxaziridines **1** and **2** and demonstrated asymmetric nitrogen transfer to nitrile enolates (Figure 1).[9] Notably, these sterically hindered N–H oxaziridines are amenable to long-term storage and readily prepared from commercially available, inexpensive (+)-camphor and (−)-fenchone, respectively.[10] More recently, Kürti and co-workers employed **1**, **2**, and other stable N–H oxaziridines **3** and **4** for electrophilic amination of organometallic reagents.[11] The Kürti group also achieved catalytic enantioselective aziridine synthesis with in situ generated N–H oxaziridines embedded in a camphor skeleton.[12] In another relevant study disclosed in 2003, Armstrong and co-workers showed enantioselective nitrogen transfer reactions from N-carbamoyl oxaziridines to sulfides, albeit their attempts resulted in low stereoselectivity.[13] Inspired by these key precedents, our approach for enantioselective sulfinamidine synthesis was based on asymmetric nitrogen transfer from N–H oxaziridines to sulfenamides.

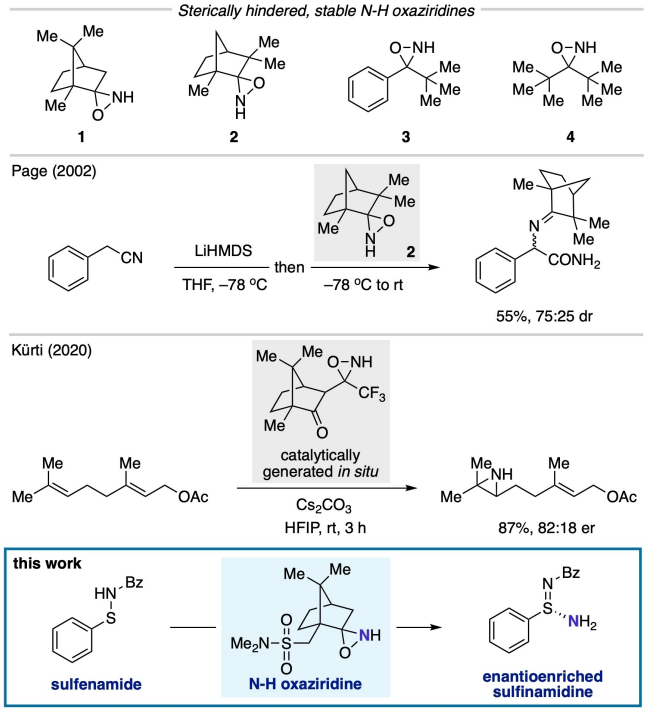
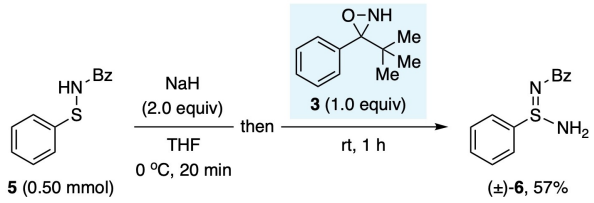


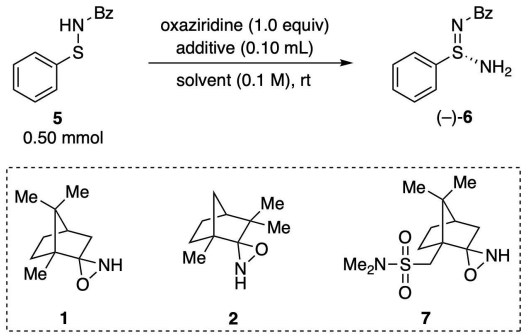
Figure 1. Enantioselective electrophilic amination using N–H oxaziridines.

Our investigation started with the racemic synthesis of sulfinamidines from sulfenamides. We chose sulfenamides substituted with an electron-withdrawing group on nitrogen because these compounds can be easily accessed from thiols[14] or aryl iodides[15] and have been frequently employed as substrates for accessing aza-S^{IV} functionalities.[7,16] We found that stable, readily prepared N–H oxaziridine **3**[17] is an effective nitrogen atom transfer agent; when N–Bz sulfenamide substrate **5** was deprotonated with NaH and treated with reagent **3**, we observed the formation of primary sulfinamidine (±)-**6** (Scheme 1). This operationally simple protocol yielded a range of sulfinamidines diverse in S- and N-substituents; sulfenamides equipped with aryl, heteroaryl, and alkyl groups on sulfur were transformed into sulfinamidines, while the benzyloxycarbonyl (Cbz) and pivaloyl (Piv) groups proved to be other viable N-substituents (for scope of racemic sulfinamidines, see Supporting Information).



Scheme 1. Synthesis of primary sulfinamidine (±)-**6** using racemic oxaziridine **3**.

Table 1: Optimization of reaction conditions for enantioselective sulfinamidine synthesis.[a]



Entry	Oxaziridine	Additive	Solvent	Time	Yield	er
1	**1**	NaH[b]	THF	1 h	64%	rac
2	**1**	–	THF	24 h	–	–
3	**2**	–	THF	24 h	–	–
4	**7**	–	THF	12 h	44%	71:29
5	**7**	–	toluene	12 h	49%	80:20
6[c]	**7**	–	toluene	48 h	22%	79:21
7	**7**	NEt_3	toluene	12 h	51%	rac
8	**7**	AcOH	toluene	12 h	44%	95:5
9[d]	**7**	AcOH	toluene	12 h	46%	96:4
10	**7**[e]	AcOH	toluene	12 h	84%	96:4

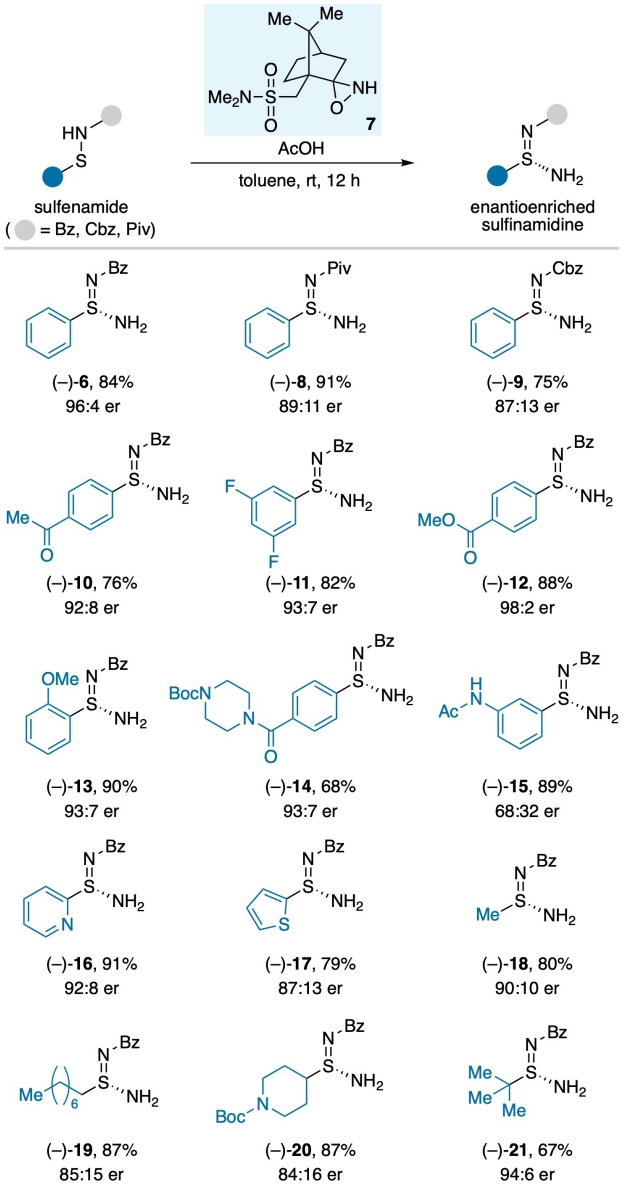
[a] Reactions were performed on 0.50 mmol scale in 5.0 mL of solvent under a N_2 atmosphere. Isolated yields are shown. The enantiomeric ratios were determined by chiral HPLC. [b] NaH (1.5 equiv) was used. [c] Performed at −45 °C. [d] Performed on 3.0 mmol scale. [e] Oxaziridine **7** (2.0 equiv).

Having confirmed the nitrogen transfer reactivity of **3** to sulfenamides, we next sought to devise an enantioselective synthesis of sulfinamidines using enantiopure N–H oxaziridines. Using sulfenamide **5** as our model substrate, we screened reaction conditions for asymmetric nitrogen atom transfer reaction (Table 1). When a reaction of **5** with reagent **1** was performed in the presence of NaH, the sulfinamidine product was produced in racemic form (entry 1). For both reagents **1** and **2**, no reaction proceeded in the absence of NaH (entries 2 and 3). Fortunately, we identified N–H oxaziridine **7**, which was prepared from inexpensive (+)-10-camphorsulfonyl chloride, as a superior reagent for our purpose; the nitrogen transfer proceeded without deprotonation of **5** and gave sulfinamidine (−)-**6** with moderate enantioselectivity (entry 4). While we found toluene to be an optimal solvent, decreasing the reaction temperature did not improve the enantioselectivity (entries 5 and 6). Upon further optimization, we found a dramatic effect of additives; while triethylamine completely shut down asymmetric induction, acetic acid significantly improved the enantioselectivity of our model reaction (entries 7 and 8). This protocol was equally successful on 3.0 mmol scale to deliver sulfinamidine (−)-**6** with high enantioselectivity (entry 9). Upon purification of (−)-**6** in this large-scale experiment, we isolated the unreacted starting material **5** in 52% yield, whereas oxaziridine **7** was almost fully consumed during the reaction. We ascribed these observations to the decomposition of **7** under the reaction conditions, leading to the formation of (−)-**6** in moderate yields. To support this hypothesis, when the reaction was performed using 2.0 equivalents of **7**, the yield of (−)-**6** was improved to 84% without loss of enantioselectivity (entry 10). Importantly, we recovered the ketone byproduct in 96% yield, which can be reused to prepare **7**. The absolute configuration (*S*)-(−)-**6** was assigned by X-ray diffraction of a single crystal.[18]

After an optimization campaign, we next evaluated the scope of the transformation (Table 2). We first examined N-substituents, including the Bz, Piv, and Cbz groups, and synthesized sulfinamidines (−)-**6**, (−)-**8**, and (−)-**9**, respectively. Among these, N–Bz product (−)-**6** was obtained with the highest enantioselectivity; we thus focused on N–Bz sulfenamides as substrates to study the enantioselectivity of our protocol with varied S-substituents. Pleasingly, a variety of aryl sulfenamides underwent the enantioselective nitrogen transfer reaction to deliver sulfinamidines (−)-**10**–(−)-**15**. These results demonstrate the compatibility of various functionalities in our protocol, including ketone, ester, and a complex heterocycle, whereas secondary amide is detrimental to enantioselectivity. Heteroaryl and alkyl sulfenamides were also competent substrates to afford enantioenriched sulfinamidines (−)-**16**–(−)-**21**.

The preparation of highly enantioenriched sulfinamidines allowed us to investigate their configurational stability, hitherto unavailable information for any sulfinamidines.[2] When a 0.05 M solution of (−)-**6** in toluene or 1,4-dioxane was heated at 90 °C for 5 h, no loss of enantiopurity was

Table 2: Scope of enantioselective synthesis of sulfinamidines using oxaziridine **7**.[a]

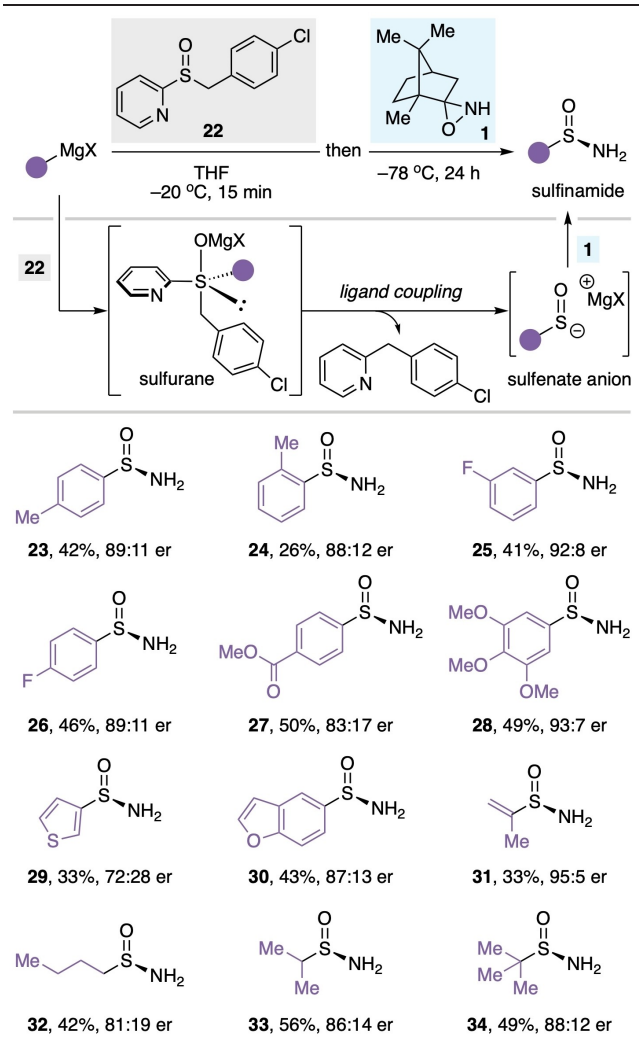


[a] Typical conditions: sulfenamide (0.50 mmol, 1.0 equiv), **7** (2.0 equiv), AcOH (3.5 equiv), toluene, rt, 12 h. Isolated yields are shown. The enantiomeric ratios were determined by chiral HPLC.

confirmed by chiral HPLC analysis, suggesting that primary sulfinamidines are configurationally stable under thermal conditions. Sulfinamidine (–)-**6** was also stable in the presence of organic acids (TFA or MsOH) or bases (NEt_3 or DBU) in toluene at room temperature, and no racemization or decomposition was observed after 24 h. On the other hand, (–)-**6** was labile under aqueous acidic or basic conditions; for instance, the complete decomposition of (–)-**6** was observed upon exposure to a 1.0 M HCl solution in a mixture of H_2O and 1,4-dioxane (1:1) over 3 h.

Encouraged by the success in asymmetric sulfinamidine synthesis, we explored the enantioselective synthesis of sulfinamides using N–H oxaziridine reagents. We have recently developed sulfoxide **22** as an easily prepared, bench-stable sulfur monoxide equivalent that reacts with various Grignard reagents (RMgX).[19] The resulting sulfenate anions (RSO^-) can be trapped with electrophilic aminating agents to deliver sulfinamides. Optimization of reaction conditions based on this one-pot, three-component coupling protocol revealed that nitrogen atom transfer from oxaziridine **1** at –78 °C proved to be optimal (see Supporting Information). Under the optimized conditions, we synthesized a broad range of primary sulfinamides (**23**–**34**) with moderate to high enantioselectivity where oxaziridine **1** reacted with sulfenate anions in situ generated from sulfoxide **22** and Grignard reagents (Table 3). It is worth mentioning that this is the first demonstration of enantioselective sulfinamide synthesis via sulfenate anion chemistry.[20]

Table 3: One-pot, three-component, enantioselective access to sulfinamides.[a]



[a] Typical conditions: sulfoxide **22** (1.1 equiv), Grignard reagent (1.1 equiv), THF, –20 °C, 15 min; oxaziridine **1** (0.75 mmol, 1.0 equiv), –78 °C, 24 h. Isolated yields are shown. The enantiomeric ratios were determined by chiral HPLC.

In summary, we have shown that nitrogen atom transfer from a stable, enantiopure N–H oxaziridine offers an enantioselective access to sulfinamidines. Enantiomerically enriched primary sulfinamidines are configurationally stable at 90 °C in solution and exhibit excellent chemical and configurational stability in the presence of organic acids or bases under non-aqueous conditions. Enantiopure N–H oxaziridines can also be used for a one-pot, three-component assembly of enantioenriched primary sulfinamides via sulfenate anions in situ produced from a sulfoxide reagent (–S(O)– building block) and Grignard reagents. The method for the enantioselective preparation of sulfinamidines and sulfinamides reported herein will allow for explorations of these S^{IV} motifs as chiral building blocks to create new catalysts, ligands, and reagents for asymmetric synthesis and as sulfur pharmacophores to develop new drugs. Furthermore, this work will inspire the further development of sulfinamidine and sulfinamide syntheses, including catalytic enantioselective methods.[21–23]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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