A General Method for the Asymmetric Synthesis of N-H Sulfoximines via C-S Bond Formation

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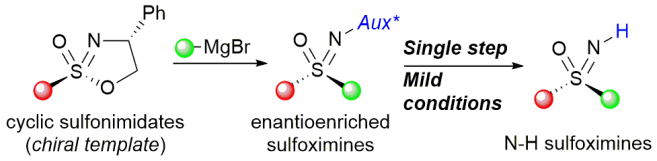
Supporting Information Placeholder

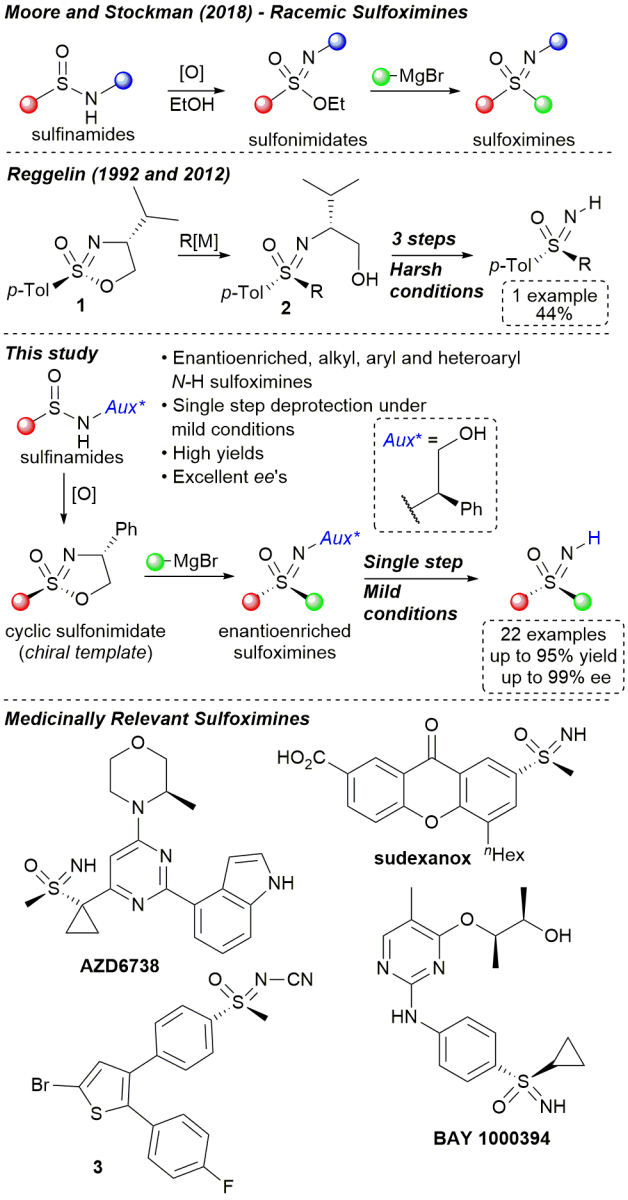


ABSTRACT: A versatile method for the synthesis of enantioenriched N-H sulfoximines is reported. The approach stems from the organomagnesium-mediated ring opening of novel cyclic sulfonimidate templates. The reactions proceed in high yield and with excellent stereofidelity with alkyl, aryl and heteroaryl Grignard reagents. The chiral auxillary is readily removed from the resultant sulfoximines via an unusual oxidative debenzylation protocol that utilises molecular oxygen as the terminal oxidant. This provides a general strategy for the synthesis of highly enantioenriched N-H sulfoximines.

In the last few years, chiral sulfur-(VI) derivatives have received a considerable influx of attention in the medicinal and synthetic chemistry communities.[1–4] This renaissance has largely been driven by observations that the once neglected sulfoximine functionality can imbue favourable properties to a candidate drug substance. Examples include the ATR inhibitor AZD 6738,[5,6] the anti-asthmatic Sudexanox,[7] the cyclin-dependent kinase inhibitor BAY 1000394[8] and the COX inhibitor **3**.[9] When compared to their more commonly employed achiral analogues (e.g. sulfones and sulfonamides), sulfoximines can offer improved solubility and polarity, whilst providing an additional chiral point of diversity. Unsurprisingly, the stereochemistry at the sulfur atom has been shown to be an important factor in the bioactivity of many chiral sulfoximine compounds.[10] For example, considerable differences are observed between the sulfur epimers of each of the aforementioned medicinally relevant sulfoximines (Figure 1).

Whilst metal- and organo-catalysed methods for the kinetic resolution of racemic sulfoximines have recently been developed,[11–13] there is still a scarcity of synthetic methods that provide direct access to enantioenriched sulfoximines. This is due, in part, to the fact that the majority of methods for sulfoximine synthesis[14–16] stem from the oxidation or imination of lower oxi-

Figure 1. From top to bottom: Our previous study on the racemic synthesis of sulfoximines via C-S bond formation; seminal work by Reggelin and co-workers; this study; examples of medicinally relevant sulfoximines.



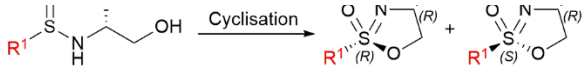
dation state sulfur derivatives[17–27] and only a few of these methods are enantioselective. Consequently, many methodologies require enantiopure sulfur(IV) derivatives as substrates, such as sulfoxides. These are most commonly obtained in their non-racemic form using a chiral templating strategy[28] such as the classical procedure developed by Anderson that utilises menthol derived sulfinic esters.[29,30]

For the above reasons, alternative methods for sulfoximine synthesis are in high demand. In recent years, methodologies centred on C-S bond forming reactions have been gaining traction as an alternative strategy. For example, an unusual asymmetric approach to sulfoximine synthesis was reported this year that proceeds via the nucleophilic, *S*-functionalisation of sterically encumbered sulfinamides.[31] A complimentary strategy utilises the electrophilic nature of certain sulfur(VI) derivatives. In 2018, as part of our own studies into the synthesis of sulfur(VI) compounds,[32–39] we reported an approach to sulfoximine synthesis that capitalises on the reaction of sulfonimidates with organomagnesium reagents (Scheme 1).[39] In the same year, Sharpless and co-workers reported that sulfonimidoyl fluorides can also serve as useful synthetic intermediates in this context.[40] Whilst these are each effective methods, they are limited to the generation of racemic sulfoximines. To address this challenge, we sought to develop a procedure where the same mode of reactivity could be utilised in a chiral templating strategy - comparable to that used for sulfoxide synthesis. To this end, we were inspired by pioneering reports from Reggelin and co-workers concerning the cyclic sulfonimidate **1**, which upon reaction with a small range of organometallic reagents, was shown to yield non-racemic sulfoximines bearing an *N*-valinyl moiety (Figure 1).[41] The main limitation to this approach is that removal of the *N*-valinyl moiety requires an inconvenient 3-step deprotection sequence.[42] Namely, *O*-mesylation, bromination and finally C-N bond cleavage with zinc and molecular iodine. Furthermore, this deprotection sequence was only demonstrated on a single example. Consequently, the method has not seen wide-spread adoption as a general method for the synthesis of sulfoximines. We reasoned however, that if this limitation could be overcome, a general method could be developed for the synthesis of enantioenriched N-H sulfoximines. Since a number of methods exist for the functionalisation of these derivatives via alkylation, arylation, acylation and sulfonylation,[43–54] N-H sulfoximines are a versatile and sought-after synthetic intermediate for the synthesis of numerous sulfoximine derivatives.

We report here the synthesis of new chiral cyclic sulfonimidate scaffolds that are readily prepared from (*R*)-phenyl glycinol. These species serve as excellent chiral templates for the synthesis of enantioenriched sulfoximines via their reaction with organomagnesium reagents. A salient feature of this approach is that the chiral auxiliary can be readily removed from the resultant sulfoximines in a single step via an unusual oxidative debenzylation strategy that preserves the chirality on the sulfur atom. This approach provides access to N-H sulfoximines in excellent yield and enantiomeric excess.

Our synthetic route to the cyclic sulfonimidates **7a**-**9a** and **7b**-**9b** centres on the intramolecular oxidative alkoxylation of the corresponding sulfinamides **4a**-**6a** and **4b**-**6b**, which are themselves readily available from the coupling of sulfinyl chlorides and phenyl glycinol (*see supporting information*). In our racemic study,[39] the hypervalent iodine derived oxidant PhIO was employed for

Table 1. Optimisation of conditions for the synthesis of the cyclic sulfonimidates **7a**-**9a** and **7b**-**9b**. All reactions were performed at -78 °C in THF unless otherwise stated. Yields are for isolated material, obtained following column chromatography. [a]This reaction was performed at 25 °C in acetonitrile.



4a(R_S); **4b**(S_S) (R = Ph) **7a**(R_S) (R = Ph) **7b**(S_S) (R = Ph)
5a(R_S); **5b**(S_S) (R = Me) **8a**(R_S) (R = Me) **8b**(S_S) (R = Me)
6a(R_S); **6b**(S_S) (R = ^{t}Bu) **9a**(R_S) (R = ^{t}Bu) **9b**(S_S) (R = ^{t}Bu)

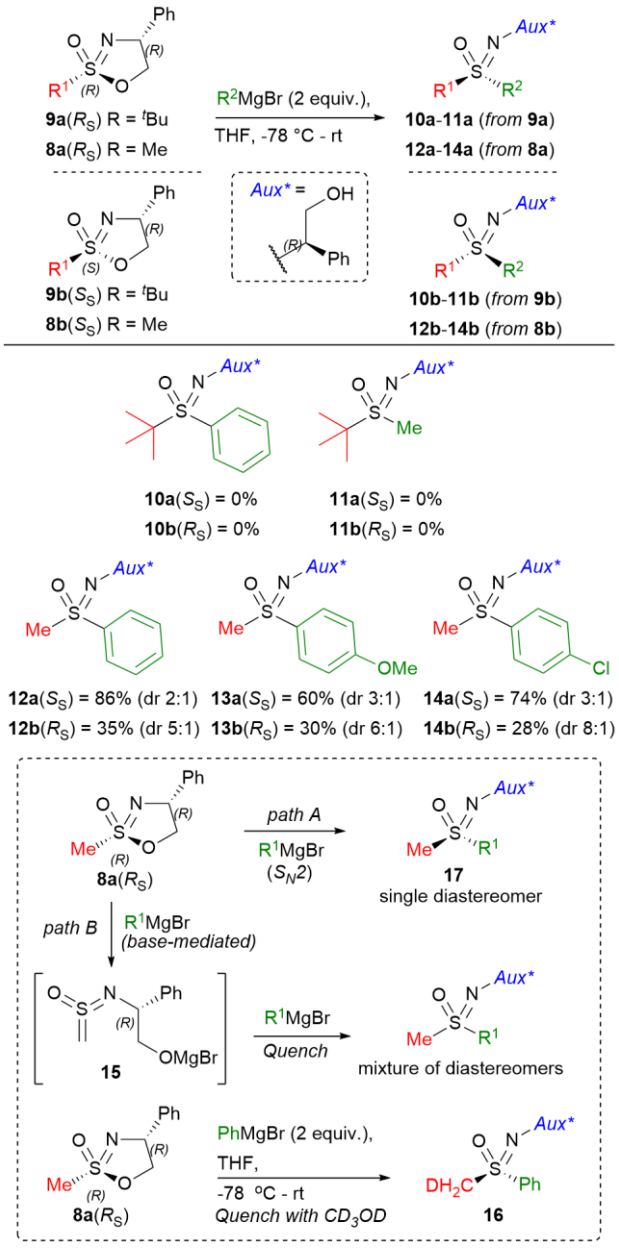
entry	R =	substrate	[O]	result (yield)
1[a]	Ph	**4a**	PhIO	**7a**:**7b** = 1:1
2	Ph	**4a**	NCS	**7a**
3	Ph	**4a**	^{t}BuOCl	**7a**
4	Ph	**4a**+**4b** (1:1)	NCS	**7a**:**7b** = 1:1 (86%)
5	Me	**5a**+**5b** (1:1)	NCS	**8a**:**8b** = 1:1 (79%)
6	^{t}Bu	**6a**+**6b** (1:1)	NCS	**9a**:**9b** = 1:1 (60%)
7	Ph	**4a**+**4b** (1:1)	^{t}BuOCl	**7a**:**7b** = 1:1 (92%)
8	Me	**5a**+**5b** (1:1)	^{t}BuOCl	**8a**:**8b** = 1:1 (94%)
9	^{t}Bu	**6a**+**6b** (1:1)	^{t}BuOCl	**9a**:**9b** = 1:1 (80%)

sulfonimidate synthesis.[55–57] Whilst this is an efficient procedure, it has previously been reported that the sulfur stereochemistry is scrambled under these conditions.[55] This was corroborated in our own studies; when the sulfinamide **4a** was employed as a single diastereoisomer, oxidation with PhIO yielded the cyclic sulfonimidates **7a** and **7b** as a 1:1 mixture of diastereomers (Table 1, Entry 1).

This obstacle was overcome by using *N*-chlorosuccinamide (NCS) or *tert*-butyl hypochlorite (^{t}BuOCl) as oxidants. The sulfur stereochemistry was preserved when these reagents were employed and the sulfonimidate **7a** was obtained as a single diastereomer in each case (Table 1, Entries 2-3). For the purposes of this study, we targeted both sulfonimidate diastereomers. Accordingly, we adopted a procedure where the sulfinamides were employed as a (1:1) mixture of diastereomers (Table 1, Entries 4-9). In the case of the phenyl, methyl and tert-butyl derivatives, the highest yields were obtained using ^{t}BuOCl and the sulfonimidate diastereomers were found to be readily separable by standard column chromatography in each case (Table 1, Entries 7-9). With six cyclic sulfonimidates templates in hand (**7a**-**9a** and **7b**-**9b**), we proceeded to investigate the proposed organomagnesium-mediated ring opening to enantioenriched sulfoximines.

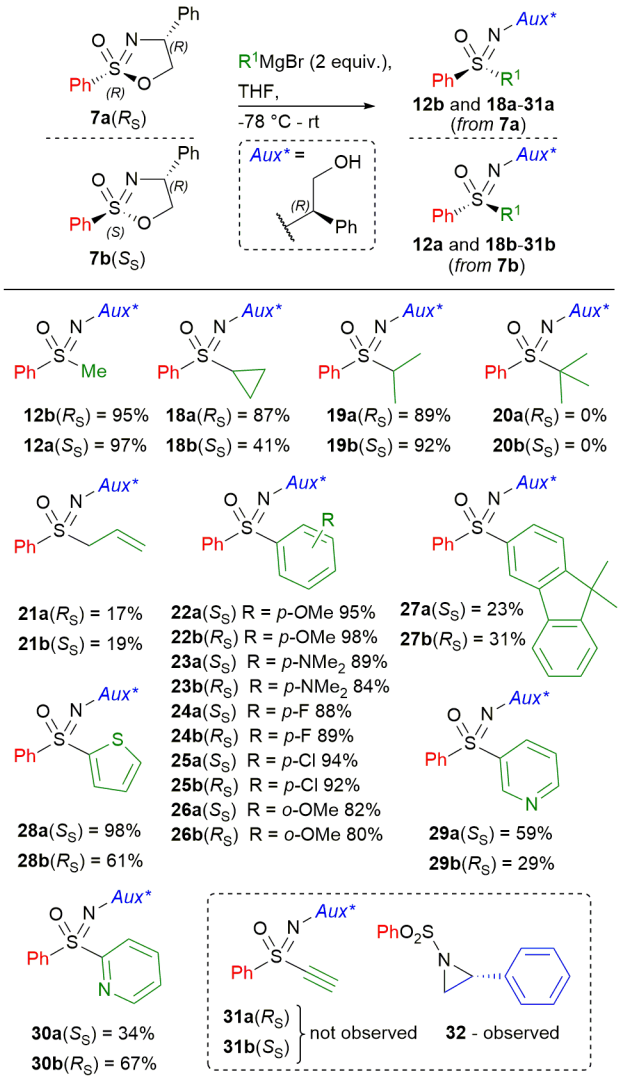
The *S*-*tert*-butyl sulfonimidates **9a** and **9b** were found to be unproductive as intermediates for sulfoximine synthesis (Scheme 1). In the case of each diastereomer, only recovered starting material was obtained upon treatment with phenyl or methyl magnesium bromide. It should be noted that this is consistent with our previous report that acyclic *S*-*tert*-butyl sulfonimidates are unreactive towards Grignard reagents.[39] In contrast, the *S*-methyl derivatives **8a** and **8b** each reacted smoothly with both electron-rich and –poor aryl magnesium bromides. Each of the targeted sulfoximines were obtained with this approach but we

Scheme 1. Evaluation of S-Me and S-^{t}Bu cyclic sulfonimidates as precursors for sulfoximine synthesis (Top). Plausible mechanism for the observed stereodegradation in the synthesis of the S-Me sulfoximines (Bottom).



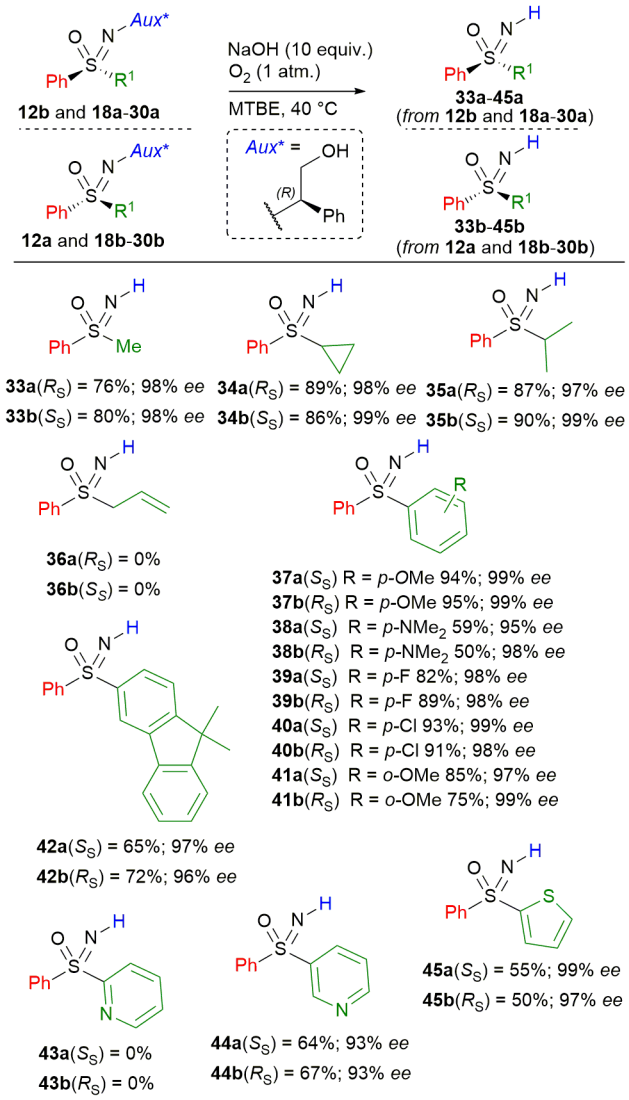
were disappointed to observe that the products were isolated as a mixture of diastereomers in each case (Scheme 1). It was postulated that the observed stereo-degradation at the sulfur centre

Scheme 2. Substrate scope for the formation of the enantioenriched sulfoximines from the sulfonimidates **7a** and **7b.**



could be due to a competitive base-mediated ring opening, followed by nucleophilic addition to the resultant methylene derivative **15** (Scheme 1). The observed formation of the deuterated derivative **16** upon quenching of the reaction mixture with CD_3OD is consistent with this hypothesis. Moreover, when the *S*-phenyl sulfonimidates **7a** and **7b** were employed - which lack an acidic proton alpha to the sulfur – we were delighted to observe that the products were obtained as a single diastereomer in each case (Scheme 2). As expected, the reaction proceeds with inversion of the sulfur stereochemistry, as confirmed by X-ray crystallography (see *supporting information*). Initially, alkyl substituted Grignard reagents were investigated. Pleasingly, in the case of each diastereomer (**7a** and **7b**), the reaction proceeded well with methyl, cyclopropyl and isopropyl magnesium bromide, yielding the targeted sulfoximines as a single diastereomer in each case. A limit to the steric tolerance was found when *tert*-butyl magnesium bromide was employed; in these cases, the reaction failed to proceed and only recovered starting material was obtained. When allyl magnesium bromide was used, the sulfoximines **21a** and **21b** were obtained, albeit in moderate yields (17% and 19%, respectively). Aryl organomagnesium reagents were particularly well tolerated and a number of *S*-phenyl

Scheme 3. Oxidative debenzylation to yield enantioenriched N-H sulfoximines.



sulfoximines were produced containing a range of electron-donating and -withdrawing substituents (10 examples). The reactions proceeded well with each diastereomer (**7a** and **7b**), yielding the targeted sulfoximines **22-26a** and **22-26b** in 80-98% yield. The unusual fluorene derivatives **27a** and **27b** could also be accessed with this method. Next, heteroaryl organometallics were trailed. Pleasingly, thienyl (**28a** and **28b**), 3-pyridyl (**29a** and **29b**) and 2-pyridyl (**30a** and **30b**) sulfoximines could each be obtained with this approach. Again, forming as a single diastereomer in each case. Interestingly, when ethynyl magnesium bromide was employed, the targeted sulfoximines **31a** and **31b** were not observed. Instead, the aziridine **32** was obtained, presumably via bromide-mediated ring-opening followed by intramolecular displacement.

Finally, we investigated conditions for removal of the chiral auxiliary to yield enantioenriched N-H sulfoximines (Scheme 3). In Reggelin's report, the analogous *N*-deprotection required a rather low yielding three-step procedure (Figure 1).[42] Improving upon this would be essential for the development of a general and synthetically tractable procedure. We were somewhat surprised to observe that the *N*-benzylic functionality appeared to be completely robust under a range of hydrogenative debenzylation conditions (*see supporting information*). To combat this issue, we were drawn to a report from Escolano and co-workers, where a rather unusual oxidative debenzylation procedure was utilised for the removal of the same functionality from lactam derivatives.[58] This method employs molecular oxygen as oxidant under basic conditions in an ethereal solvent (MTBE). We were delighted to observe that under these conditions, the N-H sulfoximines were obtained in good to excellent yields (Scheme 3). Of the 26 sulfoximines that were trialled, the only examples where the deprotection reaction failed to occur were the *S*-allyl sulfoximines **21a** and **21b**, (which yielded a complex mixture of degradation products) and the 2-pyridyl derivatives **30a** and **30b** (from which only recovered starting material could be obtained). In all other cases, the targeted N-H sulfoximines were obtained in good to excellent yield with this method. Crucially, the sulfur chirality is retained under these conditions and in each case, the products were obtained in excellent enantiomeric excess (93-99% *ee*).

This work constitutes a general and versatile method for the synthesis of enantioenriched N-H sulfoximines via C-S bond formation, allowing a modular approach to chiral sulfoximine synthesis. The strategy utilises cyclic sulfonimidates as chiral templates, which are readily prepared in two steps from the simple and cheap amino acid derivative (*R*)-phenyl glycinol. The method provides access to either enantiomer of the desired sulfoximines in excellent yields and stereoselectivities through reaction of the appropriate template with a wide range of Grignard reagents. Removal of the auxiliary was shown to be facile in a single step using cheap and environmentally benign reagents.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthetic Procedures and compound characterization (PDF); X-ray crystallography data (PDF).

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Notes

The authors declare no competing financial interests.

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