Practical and Scalable Installation of Neglected S(VI) Functionality with Applications to the Enantiospecific Synthesis of Pharmaceuticals

Zachary P. Shultz,1 Thomas Scattolin,1 Lukasz Wojtas,2 Justin M. Lopchuk1,2,3*

1Drug Discovery Department, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL 33612, USA.
2Department of Chemistry, University of South Florida, Tampa, FL 33620, USA
3Department of Oncologic Sciences, College of Medicine, University of South Florida, Tampa, FL 33612, USA.

ABSTRACT: Sulfoximines and related sulfonimidoyl groups have been largely ignored for decades until their value was demonstrated in biological settings. The realization of their importance has ushered in a new wave of discovery and pharmaceutical applications. In attempts to remove the "neglected" description of the lesser-known S(VI) groups, a practical and modular approach for α-substituted heterocycles bearing sulfonimidoyl functional groups was developed. A variety of sulfoximines containing diverse functionality and complexity were rapidly introduced in discovery settings and found their way into many drug discovery programs and greater than 70 FDA approved drugs. More recently, the exploration of historically neglected sulfonimidoyl S(VI) functional groups, containing S=N and S-N bond(s), has provided novel clinical candidates for a variety of indications as well as important agrochemicals (Figure 1).3

INTRODUCTION

The ability of sulfur to adopt a range of oxidation states (II-VI) with defined molecular geometries has led to many advancements in the discovery sciences. From materials to medicines, sulfur-containing functional groups are pervasive across disciplines. The more common S(VI) functional groups, such as sulfones and sulfonamides, have attracted the most attention – finding their way into many drug discovery programs and greater than 70 FDA approved drugs. More recently, the exploration of historically neglected sulfonimidoyl S(VI) functional groups, containing S=N and S-N bond(s), has provided novel clinical candidates for a variety of indications as well as important agrochemicals (Figure 1).3

Sulfoximines, the mono-aza S=N variants of sulfones (found in 1-5), have recently been accepted in medicinal chemistry as viable bioisosteres for carboxylic acids, alcohols and sulfones (Figure 1B).3,4,5 Additionally, sulfonimidamides can serve as bioisosteres for amines, sulfones and sulfonamides.3,6 The unique H-bond donor and acceptor properties of the sulfonimidoyl groups allow them to mimic a wide range of other functionality while commonly providing other advantages, such as a chiral environment and increases in aqueous solubility.3,6,7 Recent enthusiasm over the physiochemical properties of sulfoximines (and other sulfonimidoyl groups)3,6 has led to an exponential increase in their use to improve pharmacokinetic (PK) and pharmacodynamic (PD) properties during lead optimization studies.3,6-8

Figure 1. (A) Biologically active heterocycles containing α-substituted sulfonimidoyl functional groups. (B) Structural and physiochemical features of sulfoximides. (C) Different disconnections to install sulfonimidoyl functional groups.
A specific example of this was demonstrated by AstraZeneca during the discovery and subsequent development of their ATR inhibitor, ceralasertib (I). Among the final optimization stage of preclinical development, a sulfone was replaced for a sulfoxime. The resulting introduction of a sulfoxime led to an increased aqueous solubility while maintaining potency, which allowed for the advancement of I to the clinic where it is currently undergoing multiple phase II clinical trials. Other discovery programs at Bayer, Pfizer, Genentech, Hoffman-La Roche, Novartis, Nestlé Skin Health, and Corteva Agriscience, have been actively researching neglected S(VI) functional groups with respect to methods for their installation and incorporation into lead scaffolds.

Furthermore, the novelty of sulfinimidoyl groups, with their inherent stereochemical and additional spatial vectors capable of modifications, provides ample opportunities for new intellectual property (IP) development. An increase in patent applications and issuances within the last ten years is a growing testament to the untapped potential of sulfoximes (2,074 total patents since their first report in 1953, 1,536 of those coming in the last decade), sulfinimidamides (140 total patents since their first report in 1967, 121 of those coming in the last decade), sulfonimidines (33 total patents since their first report in 1967, 18 of those coming in the last decade) and related functional groups. Pioneering work by Bolm, Bull, Johnston, Luecking, Maruoka, Sharpless, Willis and others for the creation and modifications of S(VI) functionality has given rise to new possibilities in the field. However, despite the increase in methods to access neglected sulfinimidoyl-containing compounds, there has been relatively little advancement toward the modular installation of these groups to pharmaceutical scaffolds.

Owing to the growing attention of higher order sulfur-based functional groups as bioisosteres and PK modulators in the pharmaceutical sciences, the unmet need for their incorporation into medicinally relevant structures with an emphasis on asymmetric control must be addressed. Traditional methods to introduce α-substituted sulfinimidoyl units relies on S-C bond disconnection (a) (Figure 1C) involving a laborious 4-6 step synthetic sequence from carboxylic acids or esters. Limitations of disconnection (a) include the lengthy step count, challenging asymmetric control at the stereogenic S-center and the difficulty of late-stage modifications at sulfur – the last of which explains the high prevalence of methyl substituted sulfoximines and sulfonimidines. Other methods for the synthesis of α-arylated sulfoximines rely on exotic transition metal-catalyzed systems and conditions accompanied by limited scope with respect to both sulfoximines and aryl coupling partners – especially with regards to heterocycles.

To address the aforementioned limitations and provide a modular approach to aid in discovery efforts, a straightforward solution was sought that can be applied to readily available pharmaceutically relevant heterocyclic building blocks. Disconnection (b) (Figure 1C) outlines an S-Ar approach for the installation of α-substituted sulfinimidoyl functionality to widely available electrophilic heterocycles. This alternative disconnection will provide discovery chemists with a multifunctional method for the introduction of highly oxidized neglected sulfur moieties of varying complexity in a single step. The utilization of enantipure sulfinimidoyl nucleophiles grants an enantiospecific entry into α-heteroarylated products that will transform the targeted synthesis process, relieving the pressure of relying on chiral separation techniques and loss of material.

**DEVELOPMENT AND SCOPE**

The requisite sulfoximines were accessible from the direct oxidation/amination of sulfoxides or sulfoxides via Bull’s sulfoxime synthesis, followed by N-H protection (Figure 2A). Although the modern method developed by Willis for the synthesis of sulfonimidines could be used to access dimethyl sulfonimidine, the direct imination of dimethyl sulfoxide with t-BuOCl and NH₃ was chosen for this application. orthogonally protected sulfonimidamide was made available from a 4 step procedure starting from disulfide. Chiral alkyl sulfoximines can be made readily available.

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<th>NPG</th>
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Figure 2. (A) Synthetic routes to access S(VI) nucleophiles. (B) Optimization of sulfinimidoyl S-Ar conditions with heterocycles. All reactions were performed on 0.25 mmol scale. Isolated yields. 4,6-Dichloro-2-(methylthio)pyrimidine was used. 2-Fluoropyridine was used. THF was used with NaHMDS. Dioxane was used with NaH and 15-crown-5 ether.
available via Maruoka’s S-alkylation strategy from N-Piv protected sulfonamide 22. Enantiopure t-Bu methyl sulfoximine 23 provides a chiral bifunctional sulfoximine linchpin, which will be highlighted in the synthetic applications below. To maintain the practical nature of an S_{Ar} approach, we sought a general, operationally simple and scalable procedure that could be carried with minimal manipulations.

A variety of bases and reaction conditions were screened (see Supplementary Information for full reaction screen) with respect to the S(VI) nucleophile 24 and electrophilic heterocycles 11 (Figure 2B, entries 1-6). Two different procedures, cryogenic (NaHMDS, -78 °C, entries 1-4) and thermal (NaH/15-crown-5, 50-80 °C, entry 6), were found to be compatible with a wide range of electrophilic heterocycles. Both methods were designed for ease of use by premixing the nucleophile and electrophile followed by the addition of base. Due to the increased acidity of the α-H in the S_{Ar} product 25 relative to the S(VI) nucleophile 24, at least 2 equivalents of base (entry 2) are required for i° and 2° nucleophiles (1.1-1.5 equivalent for 3°) to obtain full conversions and high yields (up to 99%). Thermal conditions were employed for less electron-deficient heterocycles (entry 6), such as pyridines, that were unable to undergo the S_{Ar} reaction at room temperature (heating the reaction mixtures with NaHMDS lead to decomposition and side product formation). In nearly all cases, a 1:1 stoichiometry of nucleophile and electrophile provides good to excellent yields under the optimized reaction conditions.

With two procedures in hand that provide reactivity with electron-deficient and (relatively) more electron-rich heterocycles, the S(VI) nucleophile scope was investigated (Table 1). Symmetrical pyrimidine 26 was chosen to be the model heterocyclic electrophile due to its electronic nature as well as a practical scaffold for further synthetic manipulations. Various protecting groups including hydrolytically cleavable groups (N-Bz, 28; N-COP-tol, 29), commonly used tosyl group (N-Ts, 30) and silyl groups (N-TBS, 32; N-TMS, 35) were compatible to provide good to excellent yields (Table 1). When an N-TMS protecting group is employed, silyl group cleavage is observed under the work-up conditions to provide free sulfoximine 36 (N-H) in 77% yield, allowing for the introduction and protection of a sulfoximine unit to heterocycles in a single step. N-Cyan (N-CN, 37) sulfoximines, a commonly used imino N-substituent,36 undergo the S_{Ar} smoothly in high yields (86%).

A myriad of N-Bz protected sulfoximines were screened to provide a wide nucleophile scope as seen in Table 1. Sulfonimidoyl S_{Ar} is not limited to the previously mentioned primary sulfoximines. Both secondary (39, 47) and tertiary dimethyl sulfoximine (41) examples resulted in the desired S_{Ar} product in high yields. Cyclic α-substituted nucleophiles, such as cyclopropy1 (41, 42), cyclobutyl (43) oxetane (44) and azetidine (45) provided sterically congested heterocyclic sulfoximines with increased molecular complexity in a single step. Chiral sulfoximines (48-51) were investigated and determined to undergo an enantiospecific S_{Ar} reaction with pyrimidine 26 on gram-scale and in high yields (75-90%). The utility of this transformation is two-fold: 1) introduction of an asymmetric sulfoximine unit without erosion of enantiopurity (as determined by chiral HPLC, see Supplementary Information) and 2) capability of further modifications at sulfur upon t-Bu cleavage, providing a platform for late-stage diversifications.

Arene-substituted sulfoximines containing electron donating and withdrawing groups were well tolerated (52-54). As expected, the presence of other acidic functionality (O–H or N–H) and enolizable groups (MeCO-R) were not compatible. Protection of these reactive groups, such as acetonide 55, provides access to masked carbonyl groups that can be later manipulated. Heterocycle-containing sulfoximines including pyridyl substituents (56, 57), a saccharin analog (58), and benzothiazine oxide (59) can be appended to other heterocyclic moieties in good yields (65-82%). In the cases of 58 and 59, method B was required due to the poor solubility of the nucleophiles at low temperatures. Cyclic aliphatic sulfoximine 60 and those containing heteroatoms (61, 62) were also compatible and gave diastereomeric mixtures (ca. 4:1 to 1:1) in good yields (62-78%).

With an established sulfoximine scope, we turned our attention to neglected sulfonimidamides and sulfonimidines to determine their compatibility under our optimized S_{Ar} conditions. Orthogonally-protected sulfonimidamide 63 proved to be a suitable nucleophile that give the desired S_{Ar} product in 82% yield – the first example of the direct installation this functional group to a heterocycle. The bis N-Bz protected sulfonimidine 64 was also a suitable nucleophile using both method A (65% yield) and method B (92% yield). Classical oxidized sulfur groups, such as sulfonamides, sulfones and sulfoxides afforded the expected S_{Ar} products in 77-99% yields (65-69). The six different gram-scale examples found in Table 1 demonstrate the scalability of the method without a diminishment in yield.

Next, the electrophilic scope with regards to common place heterocyclic scaffolds in drug discovery was investigated. Three different sulfoximines were used to interrogate electrophilic reactivity, each with a different protecting group that proved critical (Table 2). For most electron deficient systems (e.g. triazenes and pyrimidines), a benzyol (N-Bz) protecting group sufficed. For less reactive substrates, benzoyl transfer to the sulfoximine α-carbon was observed. To eliminate protecting group transfer, more robust PGs, such as pivaloyl (N-Piv) and tosyl (N-Ts), were used. The use of both methods A and B allowed for an extensive electrophilic scope that delivered a large variety of sulfoximine-containing heterocycles.

Electron-deficient ring systems known to readily undergo S_{Ar} chemistry were first examined. Substituted 1,3,5-triazine (72) served as an excellent substrate along with pyrimidines that were substituted with electron donating groups (78, 79). When 2,4,6-trichloropyrimidine was used as an electrophile, a mixture of regioisomers (12, 73,74) was observed. Regioselective nucleophilic substitution on pyrimidine ring systems was achieved by a leaving group (LG) switch from chloro to SO_{2}Me to provide C-2 selective S_{Ar} products 74 and 75 in high yields (93% and 89%).
Trifunctional 4,6-dichloro-2-iodopyrimidine provided C-4 selective displacement of a chloro over iodo leaving group to give 78 and 79 as the major products on gram-scale. The utility of both SAr products, 78 and 79, will be further demonstrated in the forthcoming synthetic applications. Other 2-substituted pyrimidines decorated with naphthyl (80) and azaindole (81) substituents resulted in the desired SAr products in high yields (79-89%). The diazine scope is not limited to pyrimidines; 2-chloropyrazine also served as a suitable electrophile in good yield (82, 71%).

Commercial and readily available pyridines were thoroughly explored. Initial attempts at affecting the sulfonimidoyl SAr with 2-fluoropyridine under both cryogenic and thermal conditions using N-Bz protected sulfoximine nucleophiles proved unfruitful, due to Bz transfer to the sulfoximine starting material. To our delight, switching the PG to N-Ts made 83 accessible in 81% yield. An electron-deficient pyridine bearing a t-Bu ester (CO₂t-Bu) at the 3-position provided 84 in 72% yield. Trifluoromethyl-substituted pyridines proved troublesome under the optimized reaction conditions, reflective by a 22% isolated yield of 85. However, other halogenated pyridines underwent the SAr smoothly to afford an array of highly useful pyridine products (86-93). Preferential displacement of fluoro over chloro was demonstrated with 2-chloro-4-fluoropyridine granting site-selective 4-substitution product 87.

When 2,4,6-trichloropyridine was used, C-2 selectivity was observed in a modest, but still serviceable, 6.61:1 ratio of 88 (isolated r.r.). Site selectivity can be reversed by the replacement of chloro with –SO₂Me at the 4-position, where 89 was obtained in high yield (79%) as the sole regioisomer. It should be noted that when SO₂Me is used as a LG in the less reactive pyridine series, dimerization of the electrophile via SAr with the sulfone is observed as a side-product (not observed with pyrimidines). Conversely, 2,4,6-trifluoropyridine was less selective for the 2-position (1.91 r.r.) to give 90 and 91 in 50% and 27% yields respectively. In the case where iodide could act as a LG, demonstrated by 2,6-dichloro-4-iodopyridine, a 91% regioselectivity was observed favoring substitution at the 2-position to provide 92. In addition, 2-chloro-3-iodopyridine was subjected to method B to give 3-iodo pyridyl sulfoximine 93 (44% yield) capable of further functionalization. The polyhalopyridine substrates examined provide unique opportunities for downstream modifications, via further SAr and/or cross-coupling chemistry, which may serve as important intermediates for future discovery efforts.

Table 1. Nucleophile scope containing sulfoximines and other S(VI) and S(IV) nucleophiles. All reactions were performed on 0.25 mmol scale unless otherwise stated. *Method A was used. †Method B was used.
Table 2. Electrophile scope containing commonly used heterocyclic pharmacophores and electrophilic arenes. All reactions were performed on 0.25 mmol scale unless otherwise stated. *Method A was used. **Method B was used.
Although this work focuses on providing a straightforward and robust method for the installation of methylene-linked sulfonimidoyl functional groups to pharmaceutically relevant heterocycles, a brief exploration of arene compatibility was warranted to understand the full scope of sulfonimidoyl S_{Ar} chemistry. As expected, hexafluorobenzene was reactive under cryogenic S_{Ar} conditions (105, 89% yield) while 1,3,5-trifluorobenzene was not — more forceful thermal conditions were required (106, 77% yield). Interestingly, and in contrast to the pyridine example 85, 2- and 4- fluorotrifluorobenzene underwent an S_{Ar} with method B to provide 107 and 109. To our surprise, and with modifications to the general procedure, fluoro-nitrobenzenes were able to serve as electrophiles to give sulfoximines 109 and 110 (for full reaction details and modifications see Supplementary Information). Based on a short arene screen, the scope of this transition metal-free method for the installation of methylene functionality is not limited to activated heterocycles but is also suitable for numerous electron-deficient arene substrates.

**SYNTHETIC APPLICATIONS**

Current synthetic strategies to access \( \alpha \)-substituted sulfoximines, and other neglected S(VI) groups, are typically arduous. Nucleophilic substitutions at activated benzylic positions by alkyl thiolates followed by oxidation to the desired sulfoximine are the most common routes, as demonstrated in the synthesis of BAY125152 (5, Figure 3A, right).\(^4\) The recent disclosure of S-alkylations of sulfimides with benzylic halides developed by Maruoka can circumvent the oxidation steps (1-2 steps), while providing enantiopure sulfoximine products.\(^3\) In order to apply an S-alkylation strategy to access sulfoximines, the requisite benzylic halides (Br or I) are required via 2-3 step functionalizations of carboxylic acids or esters and is mainly limited to primary halides. An alternative S_{Ar} strategy provides increased modularity and a large selection of electrophilic partners while maintaining enantiospecificity.

Bayer relied on the traditional approach, a thiolation/oxidation sequence (4 steps), to access the sulfoximine used in the synthesis of BAY125152. Their route resulted in a racemic mixture that was separated by preparative chiral HPLC in order to access the desired enantiomer. A more modular approach utilizing a stereospecific sulfoximine installation would expedite the target synthesis and aid in future analog discovery. Sulfonimidoyl S_{Ar} was employed in the development of a concise synthesis of BAY125152 that is amenable for target and medicinal chemistry applications.

Beginning with commercially available 2-chloro-4-fluoropyridine (114) and our chiral bifunctional sulfoximine (R)-23, S_{Ar} method B gave enantiomerically pure pyridyl sulfoximine 101 in high yield (87%, Figure 3B). The two-step procedure for S-alkylation developed by Maruoka was employed to install the desired methyl (Me) sulfoximine. A previously reported method for the Buchwald-Hartwig coupling of 2-aminopyridine 115\(^5\) was adopted allowing coupling to 2-chloropyridyl sulfoximine 101. Deprotection of the \( \text{N-Piv} \) with NaOH furnished BAY125152 in 78% yield over two steps from 116. With the new sulfonimidoyl disconnection, the desired target was made accessible in 5 steps and 50% overall yield of the desired enantiomer from known starting materials — a more than five-fold increase in overall yield of BAY125152.

Other drug discovery programs have a vested interest in evaluating the sulfoximine moiety as shown by the antibacterial candidate 4 developed by Zoetis (Figure 4).\(^6\) The pyridyl sulfoximine moiety 117 used in the synthesis of 4 was accessed in the traditional manner starting from benzylic alcohol 118. Bayer’s macrocyclic CDK9 inhibitor 2, structurally related to BAY125152 (5), shares a similar protected pyridyl sulfoximine building block 120.\(^4\) Both sulfoximine building blocks (117 and 120) were prepared as racemic mixtures in a 5 step sequence from either 118 or 121.\(^4\) By utilizing the S_{Ar} approach, both pyridyl sulfoximines can be readily made as single enantiomers.

For the synthesis of Zoetis’ pyridyl sulfoximine, commercially available 5-bromo-2-fluoropyridine (114) and chiral sulfoximine (R)-23 underwent a smooth S_{Ar} using method A (102, 86% yield). The two-step S-functionalization sequence provided methyl pyridyl sulfoximine 123 in 70% yield. Deprotection of the pivaloyl group under basic hydrolysis conditions gave the desired free sulfoximine 117 in 53% overall yield as a single enantiomer. A reported Suzuki coupling of the requisite boronic ester with rac-117 provides access to 4.\(^4\) The improved route increased the overall yield of Zoetis’ chiral sulfoximine intermediate from 5% to 53% overall yield and decreased the step count while providing a diversifiable intermediate for analog development (N-Piv sulfonamide after t-Bu cleavage).

Bayer’s macrocyclic CDK9 inhibitor 2 was made accessible from (rac)-2,6-dichloropyridyl sulfoximine 120 where the protecting group was Cbz or Boc — introduced from the imination step.\(^5\) A pivaloyl protected 2,6-dichloropyridyl
The medicinal chemistry team at AstraZeneca (AZ) had to revamp the medicinal chemistry route that was disclosed in 2018 (Scheme 3A, top left). At this stage, an alkylation at the benzylic position was made accessible on gram scale (Scheme 3A, bottom left). The newly developed process route to the AZ's process route, which was addressed the issue of installing a sulfoximine building block for Bayer's macrocycle CDK9 inhibitor aids in targeting four distinct sites and advanced intermediates that were separated by column chromatography or iterative recrystallizations. In order to overcome the cumbersome purifications and to increase overall yield of the desired diastereomer, AZ's process team subsequently (Scheme 3A, top right) utilized an enantioselective enzymatic oxidation to introduce the chirality at sulfur (as a sulfone) that was later iminated to give the desired sulfoximine functionality. One of the major drawbacks with their 13 step process synthesis was the installation of the sulfoximine building block for Bayer's macrocycle CDK9 inhibitor. This expedient 3 step synthesis of the chiral enantiopure protected sulfoximine, syntheses of pyridyl sulfoximine units and boronic ester core of azaindole pyrimidine were subjected to sulfonimidoyl S McNally chemistry. The two steps coupling between pyrimidine and boronic ester oriented, gram scale synthesis of dichinal chemistry was improved via sulfonimidoyl S McNally chemistry route with a higher yielding route. During the development of our sulfinamidyl S McNally method, AZ's process team disclosed an improved route (Scheme 3A, middle left) and an attempt at a photocatalyzed flow approach via a Minisci reaction (Scheme 3A, middle right). The newly developed process route to the AZ's process route (Scheme 3A, middle left) addressed the issue of installing a sulfoximine building block for Bayer's macrocycle CDK9 inhibitor. The newly developed process route to (A) was chosen as the second step (see Figure 4). The newly developed process route to (B) began with a Suzuki coupling between pyrimidine and boronic ester core of azaindole pyrimidine. Gratifyingly provided the congested pyrimidine and pyrimidine core. To deliver the azaindole pyrimidine desired diastereomer, AZ's process team described the core structure of ceralasertib (1) from enantiopure t-butylic cyclopropyl sulfoximine and pyrimidine. Concurrently, an alternative medicinal chemistry-oriented synthesis of 1 was developed (Scheme 3A, bottom right) to provide multiple points of diversity that would aid in analog development for related scaffolds of 1.

The target-oriented, gram-scale synthesis of 1 (Scheme 3B) began with a Suzuki coupling between pyrimidine and boronic ester to deliver the azaindole pyrimidine core. Utilizing method A, sulfoximine and pyrimidine gratifyingly provided the congested pyrimidine core of 1 in a single step on multi-gram scale (104, 79% yield, >3 g prepared in a single flask). A one-pot t-butylic cleavage/S McNally sequence with morpholine gave rise to protected sulfonamide in 88% yield. The desired methyl sulfonamide arose from an S-alkylation with methyl iodide to afford 139. Lastly, bis-deprotection of N-Piv and N-Bn was realized after extensive reaction screening. A two-step optimized deprotection via acid hydrolysis of N-Piv followed by oxidative N-Bn cleavage resulted in 1 (>1 g) with an 87% yield over two steps and one final purification.

Conversely, the diversity-oriented synthetic route highlights four distinct sites and advanced intermediates that can be exploited for analog development. Enantiopure t-Bu pyrimidyl sulfoximine 78 was made accessible on gram scale from trifunctional pyrimidine in 86% yield using method A. At this stage, an alkylation at the benzylic position, a second S McNally on the pyrimidine or a cross-coupling are all options. Functionalization of the benzylic position was chosen as the second step (see Scheme S7 in SI for alternative routes) via alkylation with 1,2-dibromoethane to give 79 in good yield (72%).

Figure 4. (A) Synthetic route analysis of antibacterial 4 and CDK9 inhibitor 2. (B) Synthesis of pyridyl sulfoximine units via sulfinamidyl S McNally.

sulfoximine should serve the same purpose and is expected to be compatible with the subsequent chemistry for the synthesis of macrocycle 2. To prepare the appropriately protected sulfoximine, pyridyl sulfone and chiral sulfoximine (R)-23 were subjected to S McNally method A giving enantiopure t-butylic sulfoximine 103. The two step S-alkylation sequence resulted in the desired methyl pyridyl sulfoximine intermediate 124 in 50% overall yield in 3 steps from readily available starting materials. The overall yield was improved from 11% to 50% while decreasing the step count by two. This expedient 3 step synthesis of the chiral sulfoximine building block for Bayer’s macrocycle CDK9 inhibitor aids in targeted synthetic efforts while providing another platform for analog development.

One of the most noteworthy developments pertaining to the use of sulfinamidyl functional groups in medicinal chemistry is the development of the AstraZeneca’s ATR inhibitor ceralasertib (1). In order to provide sufficient quantities of 1 for evaluation in clinical trials, the process chemistry team at AstraZeneca (AZ) had to revamp the medicinal chemistry route that was disclosed in 2018 (Scheme 3A, top left). Owing to the traditional method of α-substituted sulfoximine installation, the medicinal chemistry group produced 1 (and analogs) as mixtures of diastereomers that were separated by column chromatography or iterative recrystallizations. In order to overcome the cumbersome purifications and to increase overall yield of the desired diastereomer, AZ’s process team subsequently (Scheme 3A, top right) utilized an enantioselective enzymatic oxidation to introduce the chirality at sulfur (as a sulfoxide) that was later iminated to give the desired sulfoximine functionality. One of the major drawbacks with their 13 step process synthesis was the installation of the sulfoximine building block for Bayer’s macrocycle CDK9 inhibitor. This expedient 3 step synthesis of the chiral enantiopure protected sulfoximine, syntheses of pyridyl sulfoximine units and boronic ester core of azaindole pyrimidine were subjected to sulfonimidoyl S McNally chemistry route with a higher yielding route.

During the development of our sulfinamidyl S McNally method, AZ’s process team disclosed an improved route (Scheme 3A, middle left) and an attempt at a photocatalyzed flow approach via a Minisci reaction (Scheme 3A, middle right). The newly developed process route to the AZ’s process route (Scheme 3A, middle left) addressed the issue of installing a sulfoximine building block for Bayer’s macrocycle CDK9 inhibitor. The newly developed process route to (A) was chosen as the second step (see Figure 4). The newly developed process route to (B) began with a Suzuki coupling between pyrimidine and boronic ester oriented, gram scale synthesis of dichinal chemistry was improved via sulfonimidoyl S McNally chemistry route with a higher yielding route. During the development of our sulfinamidyl S McNally method, AZ’s process team disclosed an improved route (Scheme 3A, middle left) and an attempt at a photocatalyzed flow approach via a Minisci reaction (Scheme 3A, middle right). The newly developed process route to the AZ’s process route (Scheme 3A, middle left) addressed the issue of installing a sulfoximine building block for Bayer’s macrocycle CDK9 inhibitor. The newly developed process route to (A) was chosen as the second step (see Figure 4). The newly developed process route to (B) began with a Suzuki coupling between pyrimidine and boronic ester oriented, gram scale synthesis of dichinal chemistry was improved via sulfonimidoyl S McNally chemistry route with a higher yielding route.
Figure 5. (A) Various routes towards ceralasertib (1) by AstraZeneca along with two sulfonimidoyl S$_2$Ar routes. (B) Target-oriented gram-scale enantiospecific synthesis of 1. (C) Medicinal chemistry route to 1 via sulfonimidoyl S$_2$Ar outlining points of diversity.
A second SnAr was achieved with morpholine 126 with good regiocontrol (ca. 91%) and high yield (92%) at low reaction temperatures – providing advanced intermediate 141 and leaving two diversification sites remaining.

The two step S-alkylation sequence using 2-iodopyrimidine 141 could be employed at this point, leaving the last diversification site at the 2-position of the pyrimidine capable of eastern region analog development (see SI). However, we decided to push the boundaries of the t-butyl sulfoximine to determine if it were stable under typical cross-coupling conditions. To our delight, 141 underwent a Suzuki coupling with boronic ester 136 to give fully protected t-Bu sulfoximine 142 in 83% yield. An S-alkylation sequence provided methyl sulfoximine 143 that was subsequently deprotected to give ceralasertib 1, fully demonstrating the feasibility of the diversity-oriented route. The disclosed improvements made to incorporate congested sulfoximine moieties provides an alternative approach to 1 and related scaffolds. By utilizing the SnAr approach with trifunctional pyrimidine 135, the points of diversity were increased by two, the overall yield increased by 20%, and the step count decreased by two.

CONCLUSION

A modular approach for the installation of sulfonimidoyl motifs via SnAr chemistry has been extensively examined and its utility demonstrated, culminating with 80 examples and 4 synthetic applications. The diversity displayed with both nucleophile and electrophile scopes exemplifies the far-reaching implications of the developed method. We fully anticipate that the method described herein will be adopted by discovery chemists interested in the unique physiochemical properties of sulfonimidoyl functional groups, with an emphasis on pharmacologically relevant heterocycles. By removing synthetic barriers for the introduction and late-stage modifications, neglected S(VI) functionality can be incorporated into more discovery campaigns and hopefully become as commonly used as their related sulfone and sulfonamide counterparts. While developing the sulfonimidoyl SnAr method, we noted the remaining limitations in accessing enantiotpure sulfoximines and sulfonimidamides. Currently, investigations into further solutions for the asymmetric introduction of sulfoximines and sulfonimidamides is ongoing in our laboratory and will be reported on in due course.

ASSOCIATED CONTENT

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

General information, experimental details, graphical procedures, and analytical data (1H, 13C, 19F NMR, MS, chiral HPLC) for all new compounds (PDF)

X-ray crystallographic data are available free of charge from the Cambridge Crystallographic Database Centre (CCDC 2087123 (48), CCDC 2087211 (103), CCDC 2087124 (107), CCDC 2087122 (133) (CIF))

AUTHOR INFORMATION

Corresponding Author
* Justin M. Lopchuk
Email: justin.lopchuk@moffitt.org.

Notes
The authors declare no competing interests.

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