

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

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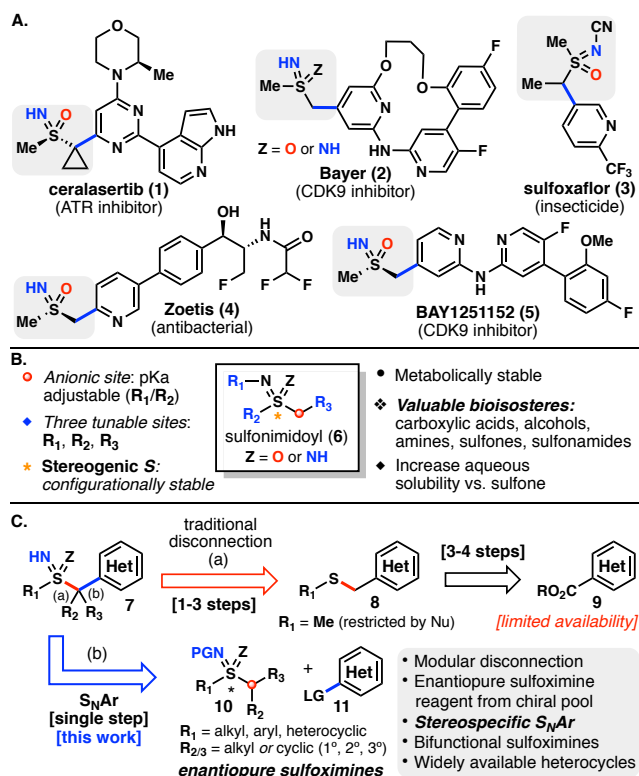
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**ABSTRACT:** Sulfoximines and related sulfonimidoyl groups have been largely ignored for decades until their value was demonstrated in biological settings. The realization of their importance has ushered in a new wave of discovery and pharmaceutical applications. In attempts to remove the “neglected” description of the lesser-known S(VI) groups, a practical and modular approach for  $\alpha$ -substituted heterocycles bearing sulfonimidoyl functional groups was developed. A variety of sulfoximines containing diverse functionality and complexity were rapidly introduced in an enantiospecific fashion with good to excellent yields. Pharmaceutically important heterocyclic scaffolds were shown to undergo the facile nucleophilic substitution, while sulfoximines, sulfonimidamides and sulfondiimines were all demonstrated to be compatible nucleophiles. The utility and practicality of the method was exhibited in target- and diversity-oriented syntheses of four sulfoximine-containing pharmaceuticals including ceralasertib, an ATR inhibitor currently in clinical trials. The introduction of underexplored sulfur functionality to common heterocyclic pharmacophores provides a practical platform for rapid analog development that is expected to aid future efforts in the discovery sciences.

## 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.<sup>1</sup> 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.<sup>2</sup> 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).<sup>3</sup>

Sulfoximines, the mono-aza S=N variants of sulfones (found in 1–5),<sup>4</sup> have recently been accepted in medicinal chemistry as viable bioisosteres for carboxylic acids, alcohols and sulfones (Figure 1B).<sup>3a,5</sup> Additionally, sulfonimidamides can serve as bioisosteres for amines, sulfones and sulfonamides.<sup>3d,6</sup> 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.<sup>3d,7</sup> Recent enthusiasm over the physicochemical properties of sulfoximines (and other sulfonimidoyl groups)<sup>3f</sup> has led to an exponential increase in their use to improve pharmacokinetic (PK) and pharmacodynamic (PD) properties during lead optimization studies.<sup>3a–c,8</sup>



**Figure 1.** (A) Biologically active heterocycles containing  $\alpha$ -substituted sulfonimidoyl functional groups. (B) Structural and physicochemical features of sulfonimidoyls. (C) Different disconnections to install sulfonimidoyl functional groups.

A specific example of this was demonstrated by Astra-Zeneca during the discovery and subsequent development of their ATR inhibitor, ceralasertib (**1**).<sup>4a</sup> Amid the final optimization stage of preclinical development, a sulfone was replaced for a sulfoximine. The resulting introduction of a sulfoximine led to an increased aqueous solubility while maintaining potency, which allowed for the advancement of **1** to the clinic where it is currently undergoing multiple phase II clinical trials.<sup>9</sup> Other discovery programs at Bayer,<sup>4b-c, f, 10</sup> Pfizer,<sup>11</sup> Genentech,<sup>12</sup> Hoffman-La Roche,<sup>13</sup> Novartis,<sup>14</sup> Nestlé Skin Health<sup>15</sup> and Corteva Agriscience,<sup>16</sup> 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 sulfonimidoyl 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 sulfoximines (2,074 total patents since their first report in 1953, 1,536 of those coming in the last decade)<sup>17</sup>, sulfonimidamides (140 total patents since their first report in 1967, 121 of those coming in the last decade)<sup>18</sup>, sulfondiimines (33 total patents since their first report in 1967, 18 of those coming in the last decade)<sup>19</sup> and related functional groups. Pioneering work by Bolm,<sup>20</sup> Bull,<sup>21</sup> Johnston,<sup>22</sup> Luecking,<sup>23</sup> Maruoka,<sup>24</sup> Sharpless,<sup>25</sup> Willis<sup>26</sup> and others for the creation and modifications of S(VI) functionality has given rise to new possibilities in the field.<sup>27</sup> However, despite the increase in methods to access neglected sulfonimidoyl-containing compounds, there has been relatively little advancement toward the modular installation of these groups to pharmaceutical scaffolds.

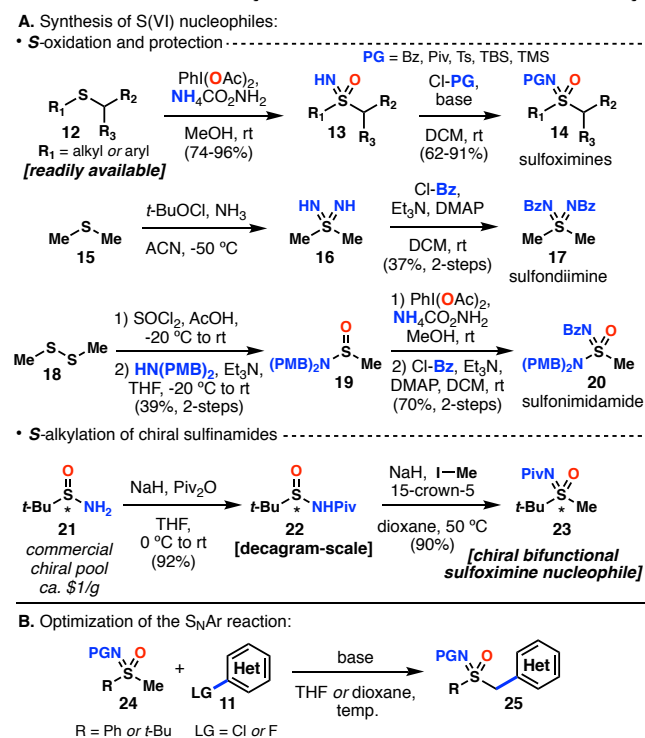
Owing to the growing attention of higher order sulfur-based functional groups as bioisosteres and PK modulators in the pharmaceutical sciences, the unmet need for their incorporation into medicinally relevant structures with an emphasis on asymmetric control must be addressed. Traditional methods to introduce  $\alpha$ -substituted sulfonimidoyl units relies on S-C bond disconnection (a) (Figure 1C) involving a laborious 4-6 step synthetic sequence from carboxylic acids or esters.<sup>4a-c, e-f</sup> 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 sulfondiimines. Other methods for the synthesis of  $\alpha$ -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.<sup>23a, 28</sup>

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<sub>N</sub>Ar approach for the installation of  $\alpha$ -substituted sulfonimidoyl 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 enantiopure sulfonimidoyl nucleophiles grants an enantiospecific entry into  $\alpha$ -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/imation of sulfides or sulfoxides via Bull's sulfoximine synthesis,<sup>21c</sup> followed by N-H protection (Figure 2A). Although the modern method developed by Willis for the synthesis of sulfondiimines could be used to access dimethyl sulfondiimine **16**,<sup>26b</sup> the direct imination of dimethyl sulfide with *t*-BuOCl and NH<sub>3</sub> was chosen for this application.<sup>29</sup> Orthogonally protected sulfonimidamide **20** was made available from a 4 step procedure starting from disulfide **18**. Chiral alkyl sulfoximines can be made readily



Entry	NPG	Het	Base (eq.)	temperature	% yield <sup>a</sup>
1	NBz	pyrimidine <sup>b</sup>	NaHMDS (1.1)	-78 °C to rt	55%
2	NBz	pyrimidine <sup>b</sup>	NaHMDS (2.2)	-78 °C to rt	91%
3	NBz	pyridine <sup>c</sup>	NaHMDS (2.2)	-78 °C to rt	0%
4	NTs	pyridine <sup>c</sup>	NaHMDS (2.2)	-78 °C to rt	32%
5	NTs	pyridine <sup>c</sup>	NaH (2.2), 15-crown-5	rt	0%
6	NTs	pyridine <sup>c</sup>	NaH (2.2), 15-crown-5	rt to 80°C	81%

**Figure 2.** (A) Synthetic routes to access S(VI) nucleophiles. (B) Optimization of sulfonimidoyl S<sub>N</sub>Ar conditions with heterocycles. All reactions were performed on 0.25 mmol scale. <sup>a</sup>Isolated yields. <sup>b</sup>4,6-Dichloro-2-(methylthio)pyrimidine was used. <sup>c</sup>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 sulfinamide **22**.<sup>24a</sup> 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  $S_NAr$  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  $\alpha$ -H in the  $S_NAr$  product **25** relative to the *S*(VI) nucleophile **24**, at least 2 equivalents of base (entry 2) are required for 1° 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  $S_NAr$  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 manipulation. 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 deprotection of a sulfoximine unit to heterocycles in a single step. *N*-Cyano (*N*-CN, **37**) sulfoximines, a commonly used imino *N*-substituent,<sup>30</sup> undergo the  $S_NAr$  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. Sulfonylimidoyl  $S_NAr$  is not limited to the previously mentioned primary sulfoximines. Both secondary (**39**, **47**) and tertiary dimethyl sulfoximine (**41**) examples resulted in the desired  $S_NAr$  product in high yields. Cyclic  $\alpha$ -substituted nucleophiles, such as cyclopropyl (**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  $S_NAr$  reaction with pyrimidine **26** on gram-scale and in high yields (75-90%). The utility of this transformation is two-

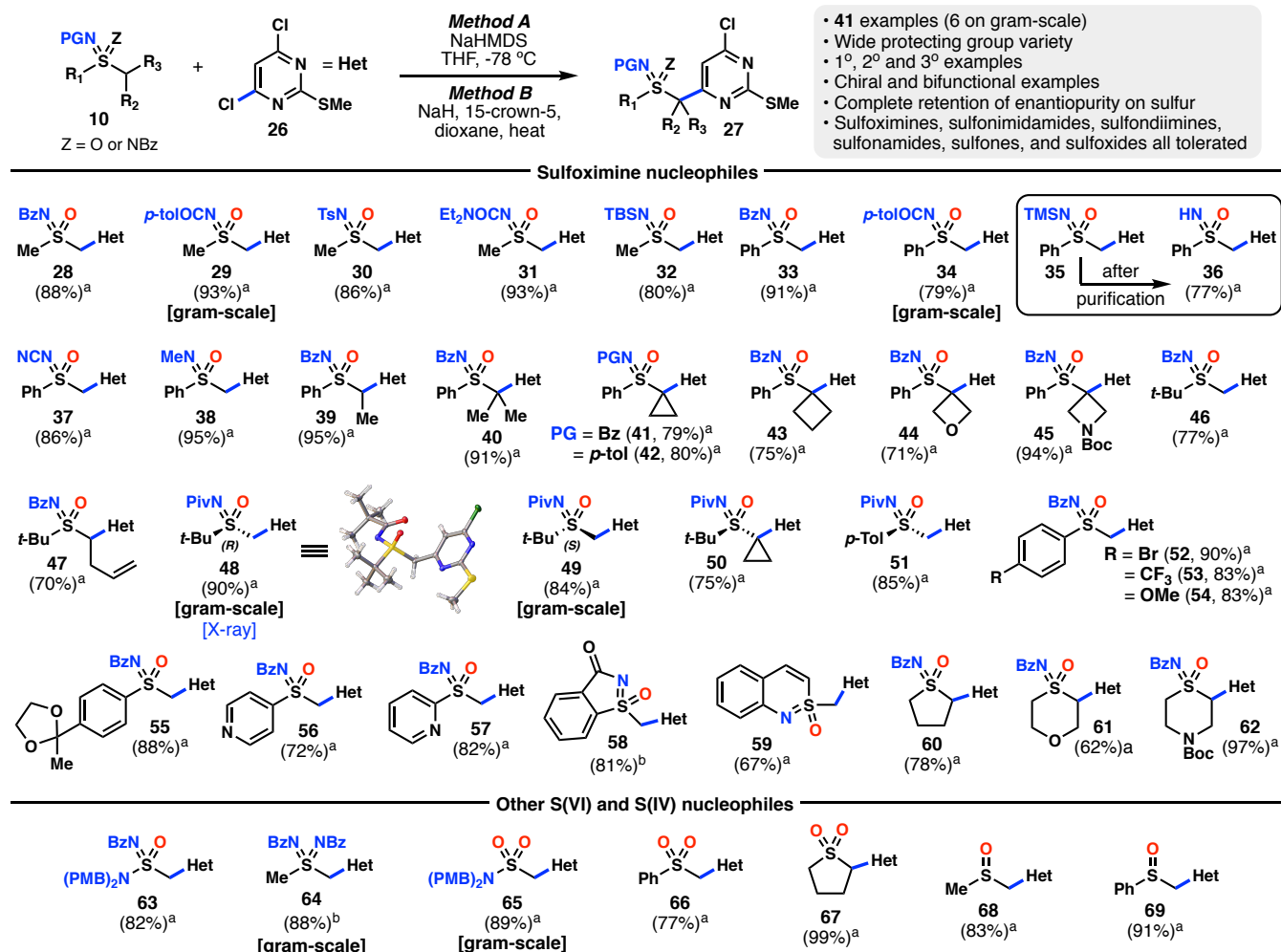
fold: 1) introduction of an asymmetric sulfoximine unit without erosion of enantiopurity (as determined by chiral HPLC, see Supplementary Information) and 2) capability of further modifications at sulfur upon *t*-Bu cleavage, providing a platform for late-stage diversifications.

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 sulfondiimines to determine their compatibility under our optimized  $S_NAr$  conditions. Orthogonally-protected sulfonimidamide **63** proved to be a suitable nucleophile that give the desired  $S_NAr$  product in 82% yield – the first example of the direct installation this functional group to a heterocycle. The bis *N*-Bz protected sulfondiimine **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  $S_NAr$  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. triazines and pyrimidines), a benzoyl (*N*-Bz) protecting group sufficed. For less reactive substrates, benzoyl transfer to the sulfoximine  $\alpha$ -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 electrophile scope that delivered a large variety of sulfoximine-containing heterocycles.

Electron-deficient ring systems known to readily undergo  $S_NAr$  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 (1:2, **73:74**) was observed. Regioselective nucleophilic substitution on pyrimidine ring systems was achieved by a leaving group (LG) switch from chloro to SO<sub>2</sub>Me to provide C-2 selective  $S_NAr$  products **74** and **75** in high yields (93% and 89%).



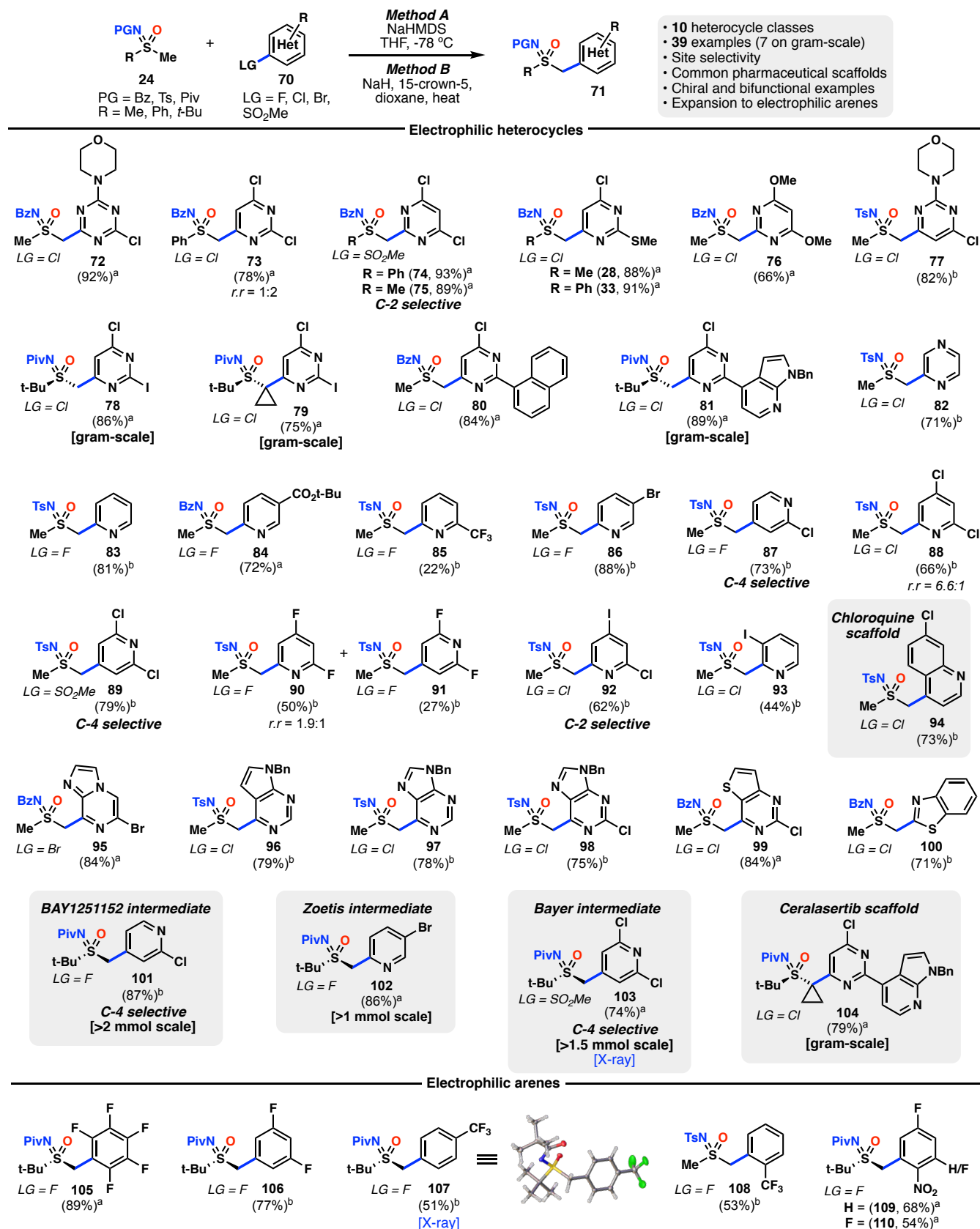
**Table 1.** Nucleophile scope containing sulfoximines and other S(VI) and S(IV) nucleophiles. All reactions were performed on 0.25 mmol scale unless otherwise stated. <sup>a</sup>Method A was used. <sup>b</sup>Method B was used.

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 S<sub>N</sub>Ar 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 S<sub>N</sub>Ar 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 S<sub>N</sub>Ar with 2-fluoropyridine under both cryogenic and thermal conditions using *N*-Bz protected sulfoximines 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 (CO<sub>2</sub>*t*-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 S<sub>N</sub>Ar 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, 6.6:1 ratio of **88** (isolated r.r.). Site selectivity can be reversed by the replacement of chloro with –SO<sub>2</sub>Me at the 4-position, where **89** was obtained in high yield (79%) as the sole regioisomer. It should be noted that when SO<sub>2</sub>Me is used as a LG in the less reactive pyridine series, dimerization of the electrophile via S<sub>N</sub>Ar 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 (1.9:1 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 19:1 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 S<sub>N</sub>Ar and/or cross-coupling chemistry, which may serve as important intermediates for future discovery efforts.



**Table 2.** Electrophile scope containing commonly used heterocyclic pharmacophores and electrophilic arenes. All reactions were performed on 0.25 mmol scale unless otherwise stated. <sup>a</sup>Method A was used. <sup>b</sup>Method B was used.

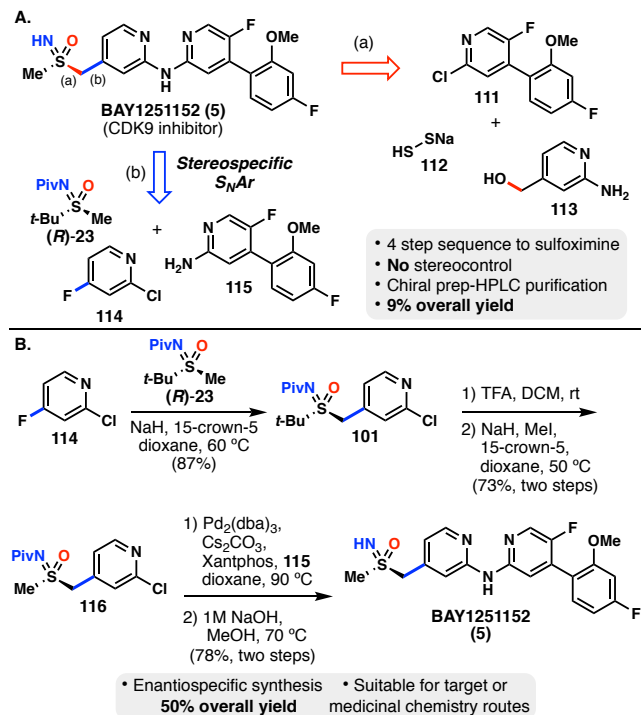
Although this work focuses on providing a straightforward and robust method for the installation of methylene-linked sulfonimidoyl functional groups to pharmaceutically relevant heterocycles, a brief exploration of arene compatibility was warranted to understand the full scope of sulfonimidoyl  $S_NAr$  chemistry. As expected, hexafluorobenzene was reactive under cryogenic  $S_NAr$  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  $S_NAr$  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 S(VI) 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 BAY1251152 (**5**, Figure 3A, right).<sup>4f</sup> The recent disclosure of *S*-alkylations of sulfinamides with benzylic halides developed by Maruoka can circumvent the oxidation steps (1-2 steps), while providing enantiopure sulfoximine products.<sup>24a</sup> 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  $S_NAr$  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 BAY1251152. Their route resulted in a racemic mixture that was separated by preparative chiral HPLC in order to access the desired target. A more modular approach utilizing a stereospecific sulfoximine installation would expedite the target synthesis and aid in future analog discovery. Sulfonimidoyl  $S_NAr$  was employed in the development of a concise synthesis of BAY1251152 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**,  $S_NAr$  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**<sup>4f</sup> was adopted allowing coupling to 2-chloropyridyl sulfoximine **101**. Deprotection of the *N*-Piv with NaOH furnished BAY1251152 in 78% yield over two steps from **101**. With the new sulfonimidoyl disconnection, the desired target was made accessible in 5



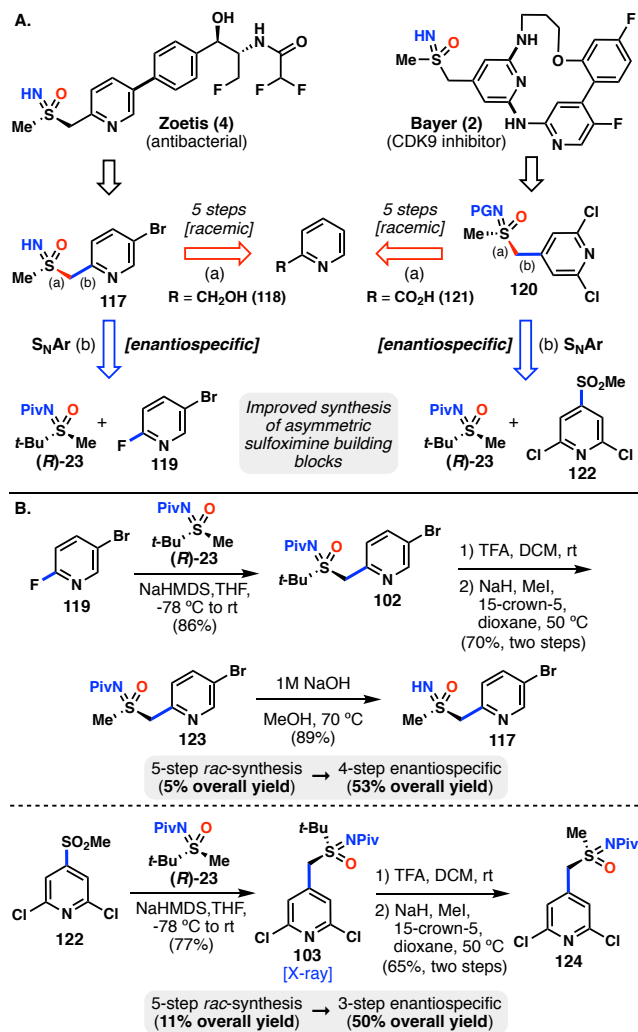
**Figure 3.** (A) Synthetic route analysis of BAY1251152. (B) Synthesis of BAY1251152 via sulfonimidoyl  $S_NAr$  approach.

steps and 50% overall yield of the desired enantiomer from known starting materials – a more than five-fold increase in overall yield of BAY1251152.

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).<sup>4e</sup> 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 BAY1251152 (**5**), shares a similar protected pyridyl sulfoximine building block **120**.<sup>4b</sup> Both sulfoximine building blocks (**117** and **120**) were prepared as racemic mixtures in a 5 step sequence from either **118** or **121**.<sup>4e,b</sup> By utilizing the  $S_NAr$  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  $S_NAr$  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**.<sup>4e</sup> 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 sulfinamide 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.<sup>4b</sup> A pivaloyl protected 2,6-dichloropyridyl



**Figure 4.** (A) Synthetic route analysis of antibacterial **4** and CDK9 inhibitor **2**. (B) Synthesis of pyridyl sulfoximine units via sulfonimidoyl  $S_NAr$ .

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 **122** and chiral sulfoximine (**R**)-**23** were subjected to  $S_NAr$  method A giving enantiopure *t*-Bu 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 sulfonimidoyl 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).<sup>4a</sup> Owing to the traditional method of  $\alpha$ -substituted sulfoximine installation, the medicinal chemistry

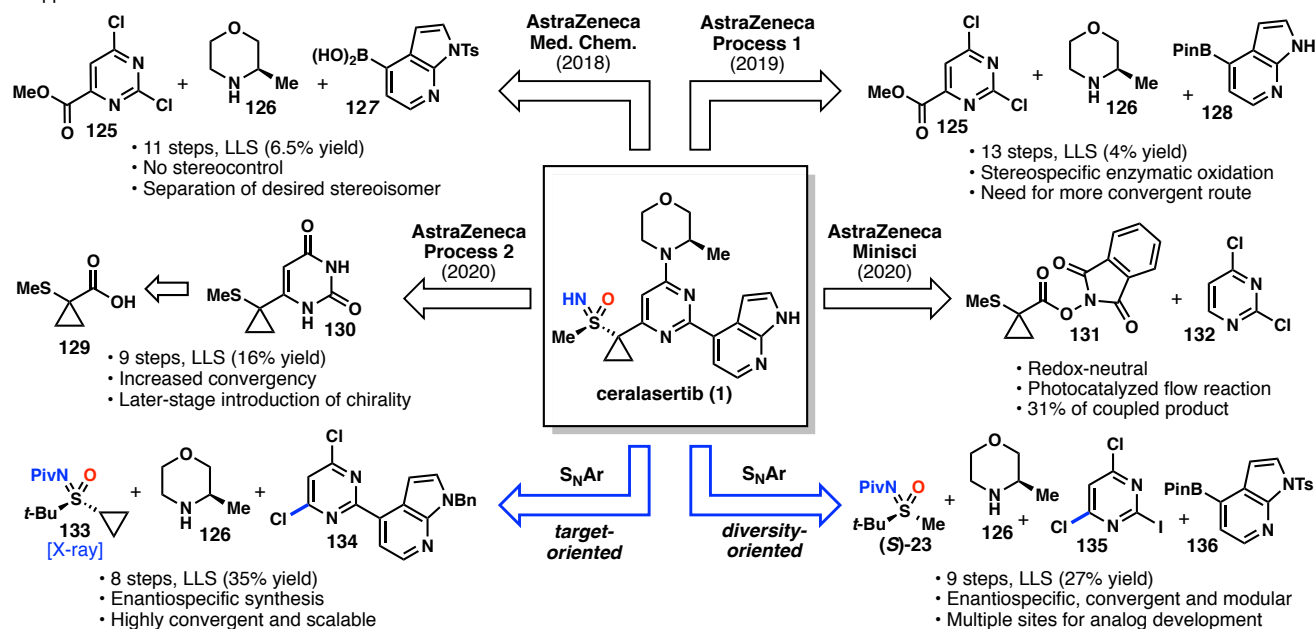
group produced **1** (and analogs) as mixtures of diastereomers that were separated by column chromatography or iterative recrystallizations. In order to overcome the cumbersome purifications and to increase overall yield of the desired diastereomer, AZ's process team subsequently (Scheme 3A, top right) utilized an enantioselective enzymatic oxidation to introduce the chirality at sulfur (as a sulfoxide) that was later iminated to give the desired sulfoximine functionality.<sup>32</sup> One of the major drawbacks with their 13 step process synthesis was the installation of the cyclopropyl group in **1**. As the AZ process team described: "The manufacture of AZD6738 remains a challenge for the future of this medicine, due to the difficult nature of installing the dense functionality around the pyrimidine core. Longer term it would be beneficial to have a more convergent approach with a higher yielding route".<sup>32</sup>

During the development of our sulfonimidoyl  $S_NAr$  method, AZ's process team disclosed an improved route (Scheme 3A, middle left)<sup>33</sup> and an attempt at a photocatalyzed flow approach via a Minisci reaction (Scheme 3A, middle right)<sup>34</sup>. The newly developed process route to **1** (Scheme 3A, middle left) addressed the issue of installing a cyclopropyl methyl sulfide moiety from **129** and **130** in a single step, while still relying on an enantioselective enzymatic oxidation. To address the remaining drawbacks of the AZ's process route, we developed an enantiospecific convergent approach utilizing our  $S_NAr$  method to generate the core structure of ceralasertib (**1**) from enantiopure *t*-butyl cyclopropyl sulfoximine **133** and pyrimidine **134** (Scheme 3A, bottom left). 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**.

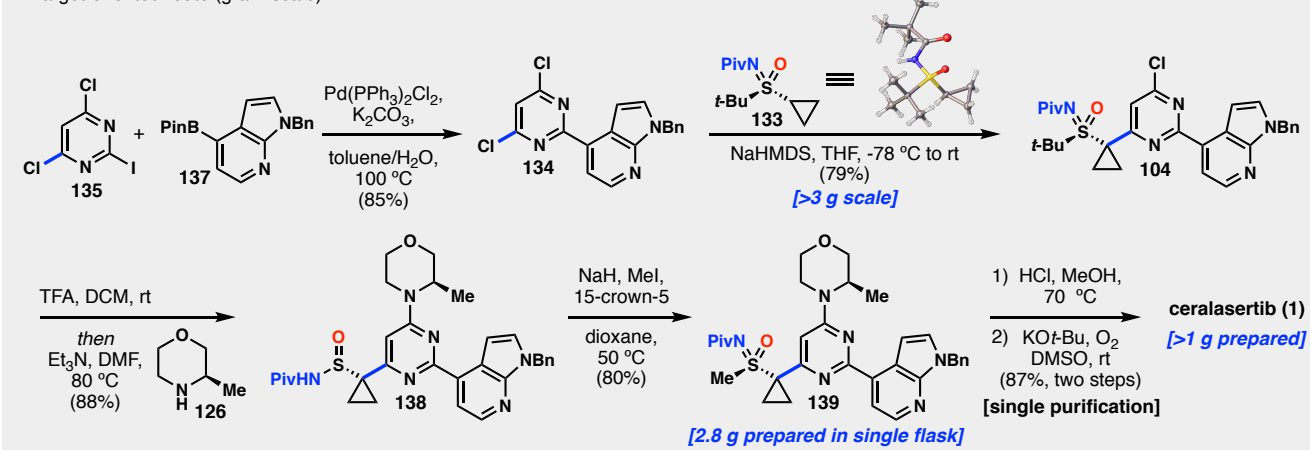
The target-oriented, gram-scale synthesis of **1** (Scheme 3B) began with a Suzuki coupling between pyrimidine **135** and boronic ester **137** to deliver the azaindole pyrimidine core **134**. Utilizing method A, sulfoximine **133** and pyrimidine **134** gratifyingly provided the congested pyrimidine 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*-butyl cleavage/ $S_NAr$  sequence with morpholine **126** gave rise to protected sulfinamide **138** in 88% yield. The desired methyl sulfoximine 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 **135** in 86% yield using method A. At this stage, an alkylation at the benzylic position, a second  $S_NAr$  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 (**140**) to give **79** in good yield (72%).

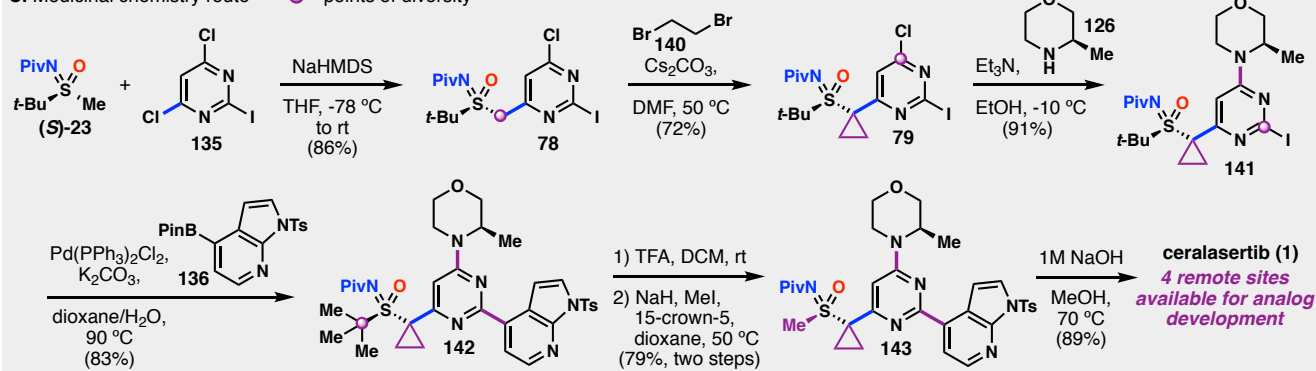
**A. Approaches to ceralasertib**



**B. Target-oriented route (gram-scale)**



**C. Medicinal chemistry route** ○ = points of diversity



**Figure 5.** (A) Various routes towards ceralasertib (**1**) by AstraZeneca along with two sulfonimidoyl  $\text{S}_{\text{N}}\text{Ar}$  routes. (B) Target-oriented gram-scale enantiospecific synthesis of **1**. (C) Medicinal chemistry route to **1** via sulfonimidoyl  $\text{S}_{\text{N}}\text{Ar}$  outlining points of diversity.



A second  $S_NAr$  was achieved with morpholine **126** with good regiocontrol (ca. 9:1) and high yield (91%) 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  $S_NAr$  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  $S_NAr$  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 pharmaceutically 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  $S_NAr$  method, we noted the remaining limitations in accessing enantiopure 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 ( $^1H$ ,  $^{13}C$ ,  $^{19}F$  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 2087121 (**103**), CCDC 2087124 (**107**), CCDC 2087122 (**133**) (CIF))

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### Notes

The authors declare no competing interests.

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