Sulfenylnitrene-Mediated Nitrogen-Atom Insertion into Pyrroles, Indoles, and Imidazoles

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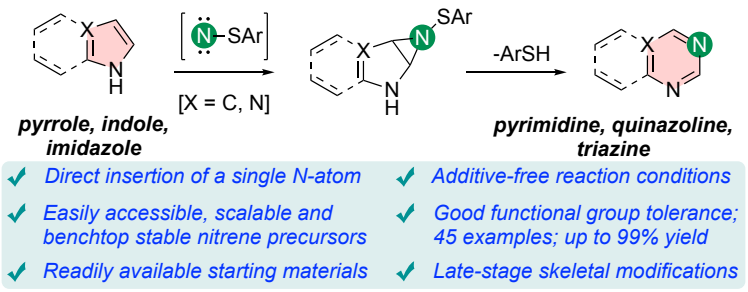
Abstract: In this study, we harness the distinct reactivity of sulfenylnitrenes, which insert a single nitrogen atom to transform readily available pyrroles, indoles, and imidazoles into synthetically challenging pyrimidines, quinazolines, and triazines, respectively. Our additive-free method for skeletal editing employs easily accessible, benchtop-stable sulfenylnitrene precursors as a source of a single nitrogen atom. This chemical approach is compatible with free pyrroles, indoles, and imidazoles with diverse functional groups, including oxidation-sensitive functionalities like phenol and thioether. Additionally, this approach facilitates the selective incorporation of a single nitrogen atom into various natural products, amino acids, and pharmaceuticals. Furthermore, we have conducted mechanistic studies and explored regioselectivity outcomes through DFT calculations.



Introduction

Since the inception of scaffold hopping, a term coined by Schneider and colleagues in 1999,[1] several methods have been developed to alter the biological and pharmacological properties of molecules through seemingly simple modifications to their molecular structures.[2] Among them, skeletal editing has taken center stage as it modifies the molecular frameworks by adding or removing atoms.[3] In the late-stage functionalization of scaffolds, notable progress has been achieved through the editing of carbon, nitrogen, or oxygen atoms within a skeleton.[3-4] This process enhances the chemical diversity in existing libraries, allowing exploration of the vast uncharted regions of chemical space in drug discovery.[5]

The inclusion of nitrogen atoms in organic compounds holds pivotal significance in medicinal chemistry and drug development.[6] For example, pyrroles, indoles, and imidazoles are prevalent in nitrogen-containing heterocycles, and direct incorporation of a single nitrogen atom into these structures offers a straightforward route to synthetically challenging heterocycles (quinazoline, pyrimidine, or triazine) without altering the substitution pattern. Therefore, incorporation of a single nitrogen atom could revolutionize late-stage diversification by adding the key pharmacophores in drug discovery libraries.[2a]

The strategy of *N*-atom insertion into an aromatic compound goes back to 1964 when ammonium chloride was used as a source of a single nitrogen atom in the presence of oxidizing agents[7] (**Figure 1a**). Despite significant advances in direct *N*-atom addition,[8] most methods rely on nitrene intermediates that requires harsh reaction conditions for their generation, involving heavy metals[8g] or excessive use of potent oxidizing agents[8f, 9] constraining their synthetic applicability. Additionally, some methods require the protection of free nitrogen in substrates like indoles, necessitating a separate pre-functionalization step.[8i] Moreover, direct insertion of nitrogen atoms into pyrroles and imidazoles remains underexplored, with only a limited number of reports.[8j, 10]

Motivated by the potential of nitrenes bearing a leaving group to incorporate a single nitrogen atom, we aimed to uncover a mild protocol that does not depend on oxidizing agents. Our investigation led us to sulfenylnitrenes, which possess a thio-functionality, known for its leaving group capabilities.[11]

Interestingly, despite their discovery in 1967,[12] these nitrenes have not been extensively explored.[8e, 13] Following a comprehensive literature survey, we identified precursors (**SNP-1** and **SNP-2**) capable of generating sulfenylnitrenes over a broad temperature range (**Figure 1b**). These thermal precursors have been significantly underutilized, except for a few reports of aziridination. [13b, c]

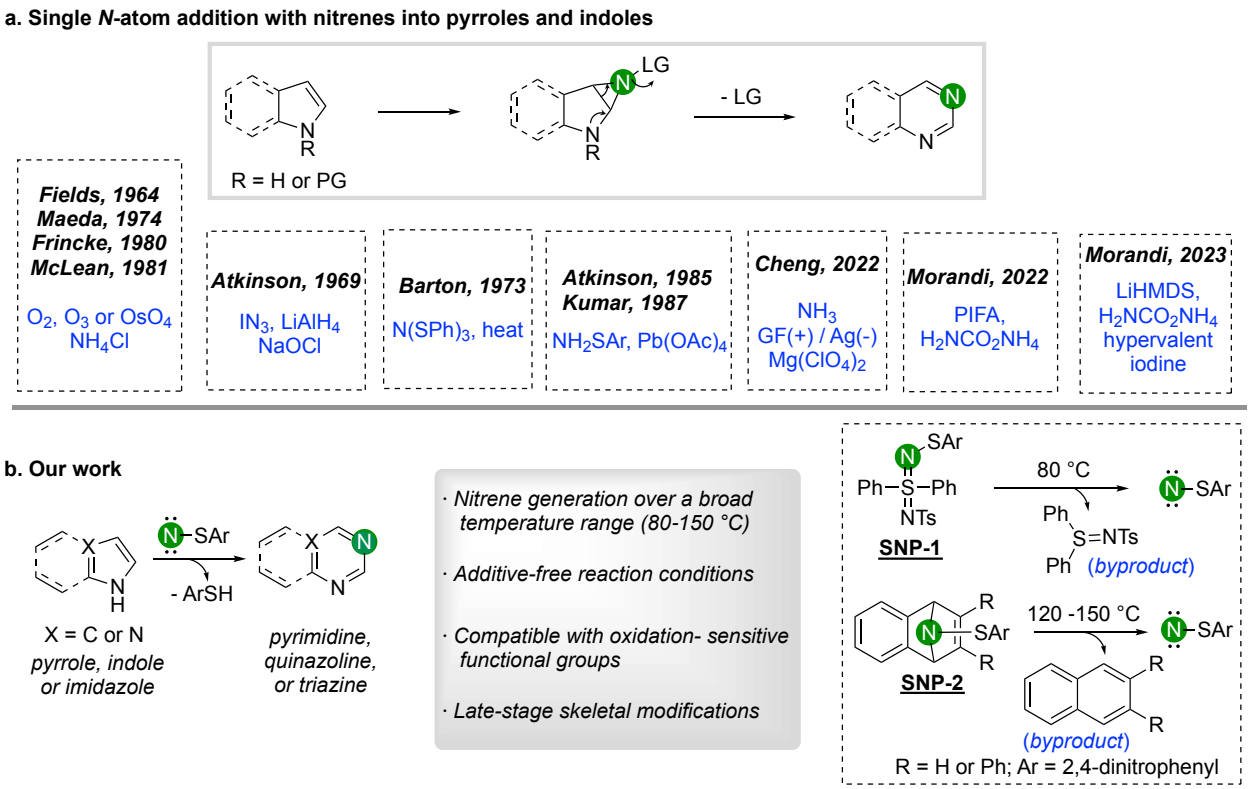


Figure 1: Nitrene strategies for single *N*-atom insertion.

Building upon the literature precedents, we hypothesize that the aziridine intermediate, featuring an inbuilt thio-moiety as a leaving group, will facilitate the ring expansion and enable the selective incorporation of a single nitrogen atom. Additionally, the S–N bond length in sulfenylnitrene is approximately 1.51 Å, indicating the double bond character between sulfur and nitrogen.[13b] This implies that the reactivity of sulfenylnitrenes can be easily tuned for a variety of synthetic transformations.

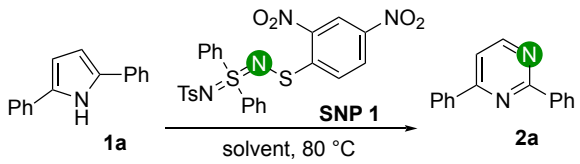
To insert a single nitrogen atom into pyrroles, indoles, and imidazoles, we envision utilizing benchtop stable precursors of sulfenylnitrenes, **SNP-1** and **SNP-2**, which allow the generation of these nitrenes under additive-free conditions over a broad temperature range (80–150 ºC) as described in the Figure 1b.

Our optimization studies commence by employing a symmetric 2,5-diphenyl pyrrole **1a** as our model substrate (**Figure 2a**), using two equivalents of **SNP-1**. Acetonitrile was selected as a solvent with **SNP-1** as described in the literature for the aziridination.[13b] To our delight, the reaction resulted in the formation of the corresponding pyrimidine **2a** in 77% yield (entry 1). Changing the reaction solvent to dichloromethane or toluene did not lead to a significant improvement in reaction yields (entries 2, 3). To increase the reaction yield further, we screened chlorobenzene as a solvent, which was utilized by Atkinson and coworkers for aziridination with **SNP-2b**.[13e] Gratifyingly, the reaction led to a nearly quantitative formation of the corresponding pyrimidine **2a** (99%) (entry 4). We also employed industrially preferred solvents, including esters and alcohols. To our delight, the reaction worked in both types of solvents with moderate yields (entries 5–8). Finally, we also screened 1 and 1.5 equivalents of **SNP-1** precursors. However, a slightly lower yield was obtained along with the unreacted pyrrole (entries 9, 10).

Moving forward, we investigated the reactivity of various **SNP-2** precursors in the *N*-addition reaction with pyrrole **1a** (**Figure 2b**). Three distinct nitrene precursors were synthesized and reacted with pyrrole **1a**. **SNP-2a** demonstrated a moderate yield (75%) at 100°C[13c] when chlorobenzene was used as the reaction solvent (entry 1). In contrast, both **SNP-2b** and **SNP-2c** exhibited comparable reactivity with pyrrole **1a**, yielding the desired pyrimidine **2a** in nearly quantitative yield, with chlorobenzene as the solvent (entries 2, 3). Notably, the decomposition temperature of **SNP-2b** and **SNP-2c** were determined to be 120°C and 150°C respectively. Other aromatic solvents such as toluene and xylene provided a slightly lower yield (entries 4, 5). However, the industrially preferred solvents (esters and alcohols), provided a moderate yield of the desired pyrimidine **2a** (entries 5, 6, 7).

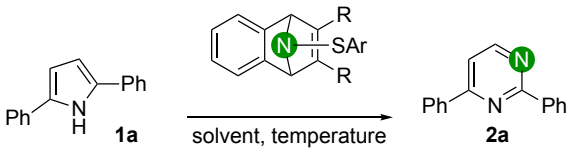
We selected **SNP-2b** as the optimal nitrene precursor due to the generation of naphthalene as a byproduct, facilitating the purification process as it can be easily removed from the reaction mixture under reduced pressure. Additionally, **SNP-2b** can be easily synthesized at a large scale (~10–20g) in three simple steps (see the SI page S6 for additional details).

a. ***Optimization with SNP 1***



Entry	Solvent	Yield[a]
1.	acetonitrile	77%
2.	dichloroethane	75%
3.	toluene	80%
4.	**chlorobenzene**	**99%**
5.	ethyl acetate	73%
6.	*t*-butanol	48%
7.	isoproponal	40%
8.	ethanol	45%
9.[b]	chlorobenzene	68%
10.[c]	chlorobenzene	82%

b. ***Optimization with SNP 2***



R = H, Ar = 4-nitrophenyl, **SNP 2a**
R = H, Ar = 2,4-dinitrophenyl, **SNP 2b**
R = Ph, Ar = 2,4-dinitrophenyl, **SNP 3c**

Entry	SNP	Solvent	Temperature	Yield[a]
1.	SNP 2a	chlorobenzene	100 °C	70%
2.	**SNP 2b**	**chlorobenzene**	**120 °C**	**99%**
3.	**SNP 2c**	**chlorobenzene**	**150 °C**	**99%**
4.	SNP 2b	toluene	120 °C	81%
5.	SNP 2b	xylene	120 °C	92%
6.	SNP 2b	*n*-butanol	120 °C	50%
7.	SNP 2b	*n*-butyl acetate	120 °C	50%

Figure 2: Optimization of the *N*-addition reaction. Reactions were carried out on a 0.1−0.3 mmol scale in a sealed vial. [a]Yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]1 equiv. of **SNP-1** was used. [c]1.5 equiv. of **SNP-1** was used.

With these optimized conditions, we investigated the scope and regioselectivity of pyrroles (**Figure 3**). Notably, the *N*-addition exhibited a preference for electron-donating substituents over electron-withdrawing ones. For instance, a pyrrole featuring an aryl group at the 3-position and various electron-withdrawing substituents at the 4-position consistently produced the corresponding pyrimidine in good to excellent yields favoring *N*-addition to the aryl side (**2b**–**2f**). We were pleased to observe that a highly oxidation-sensitive thioether functional group smoothly underwent the expansion reaction with a satisfactory yield (**2g**). Next, various 3-substituted pyrroles were subjected to the reaction conditions, and the *N*-addition predominantly occurred from the most substituted pyrrole side. Interestingly, phenyl ring bearing electron -donating and -withdrawing groups at the 3-position of pyrrole did not affect the regioselectivity outcome (**Figure 3**, **2h**–**2l**). As anticipated, 3-naphthyl-pyrrole also produced the corresponding pyrimidine in high yield (90%) with 1:5 regioselectivity (**2m**). Notably, the *di*- and *tri*-substituted pyrroles provided a single regio-isomer, favoring the most substituted side (**2n**, **2o**). Pyrrole featuring an 8-membered carbocycle also furnished the corresponding pyrimidine in a high yield (**2p**).

Pyrroles having electron-withdrawing esters provided a lower regioselectivity favoring the electron-rich side (**2q**, **2r**).

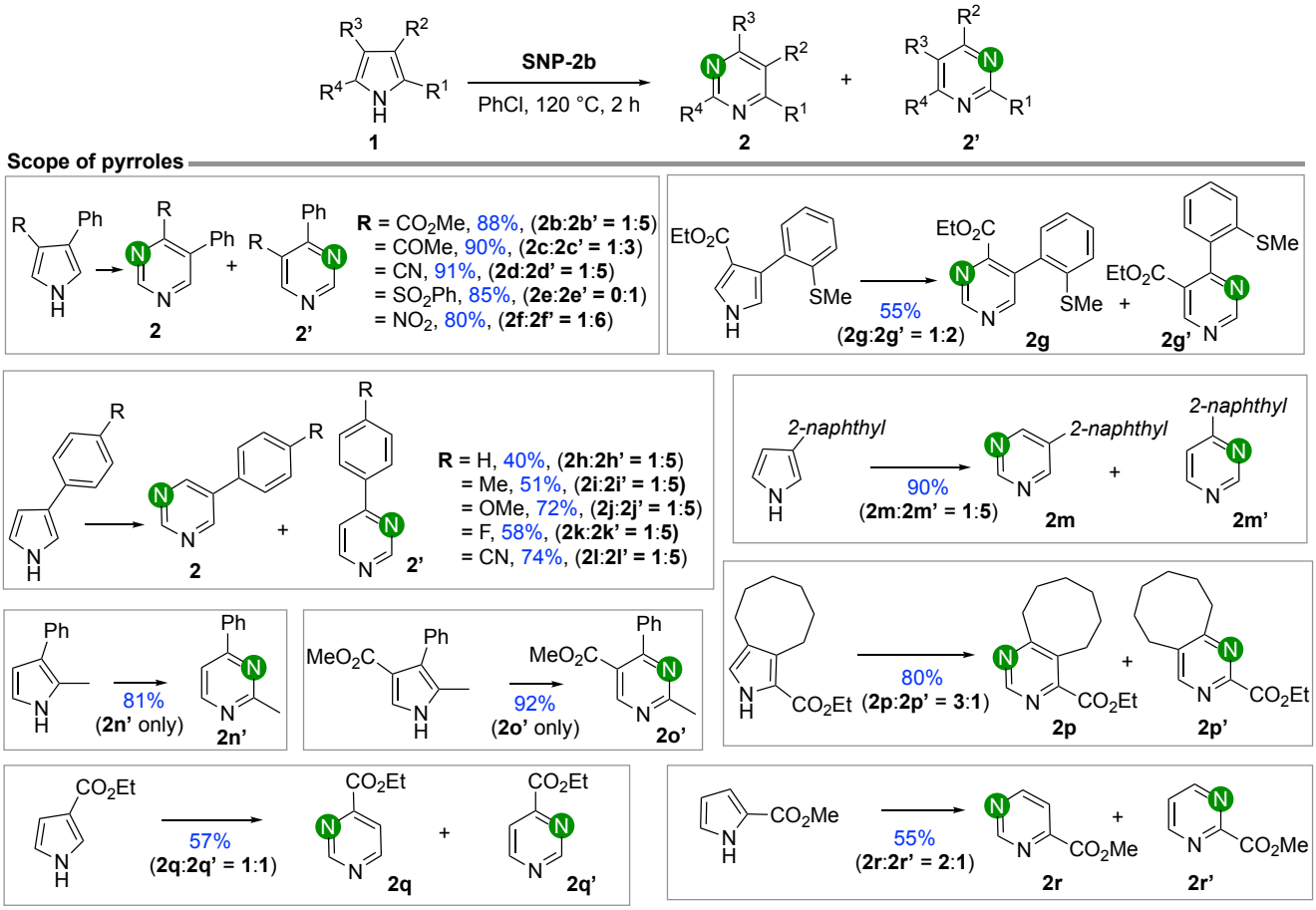


Figure 3: Scope and selectivity of pyrroles. Conditions: **1** (1 equiv.), **SNP-2b** (2 equiv.), chlorobenzene (0.1 M), 120 °C, 2 h. Reactions were carried out on 0.1−0.3 mmol scale. Yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

To further expand its utility, we applied this methodology to complex bioactive pyrroles (**Figure 4**). Gratifyingly, a pyrrole containing benzyl-protected α-methyl glucopyranoside was well tolerated, preserving the stereoselectivity at the sensitive anomeric acetal functionality (**2s**). Likewise, a trimethoxy-phenyl substituted pyrrole, recognized as an antitumor agent,[14] underwent successful conversion into the corresponding pyrimidine (**2t**) with a high yield. The reaction also proved effective with fenpiclonil, an agricultural phenylpyrrole fungicide,[15] yielding the expansion product in a good yield (**2u**). Additionally, elopiprazole, an antipsychotic drug,[16] demonstrated compatibility with the reaction, providing a

synthetically useful yield of 72%, with only one regio-isomer obtained (**2v'**). Finally, fludioxonil, a fungicide used for seed treatment,[17] underwent a successful transformation to the corresponding pyrimidine (**2w**).

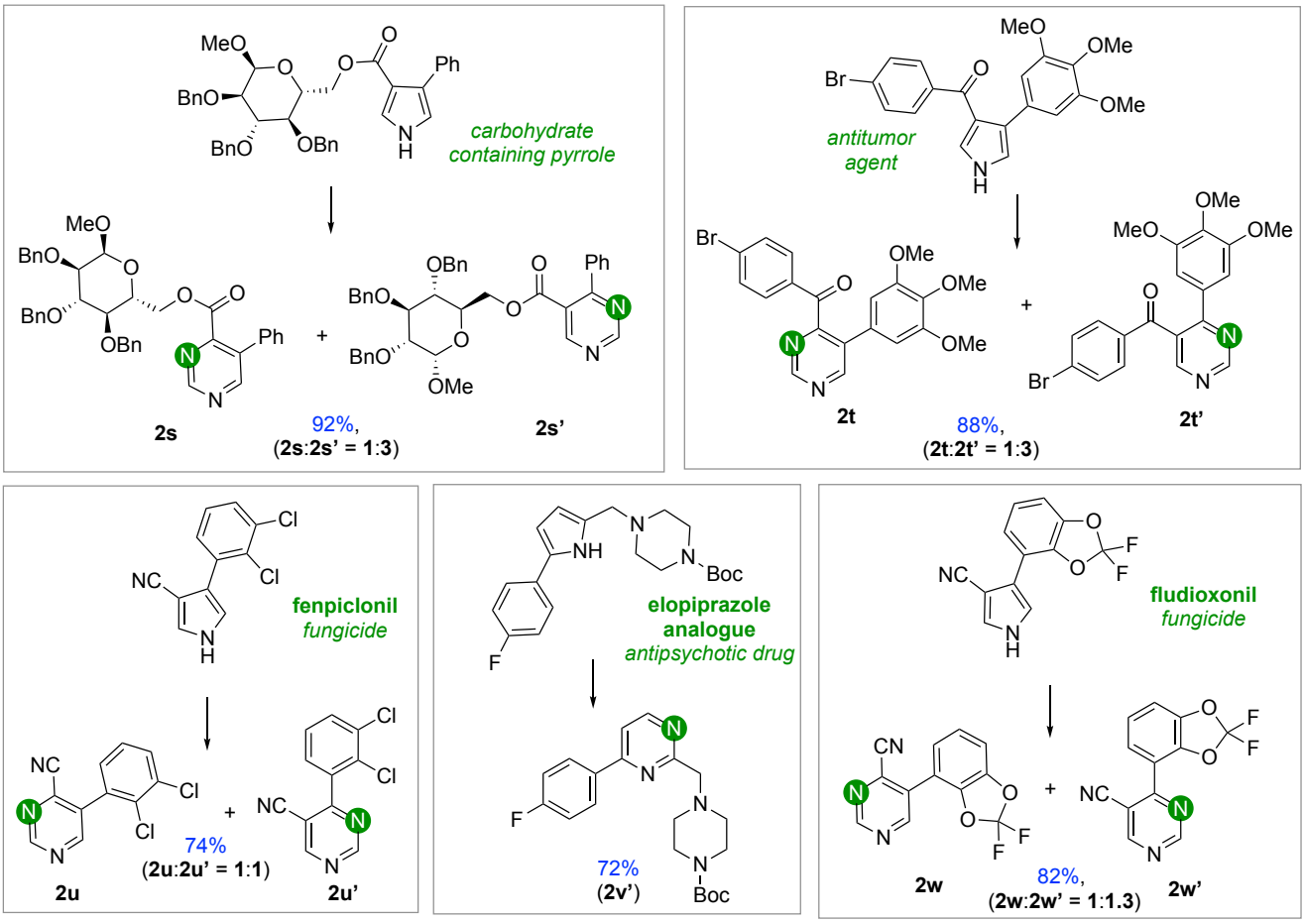


Figure 4: Application to complex pyrroles. Conditions: **pyrrole** (1 equiv.), **SNP-2b** (2 equiv.), chlorobenzene (0.1 M), 120 °C, 2 h. Reactions were carried out on 0.1−0.3 mmol scale. Yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

Having showcased the synthetic capabilities of this approach, we aimed to understand the regioselectivity of nitrogen insertion into asymmetric pyrroles. 3-phenylpyrrole was chosen as a substrate for computational studies. To validate our mechanistic hypothesis (see the SI page S39 for details), density functional theory (DFT) calculations as implemented in the software package *QChem*[18] were performed using the B3LYP functional at the 6-31G(d) level of theory in vacuo, shown in **Figure 5**.

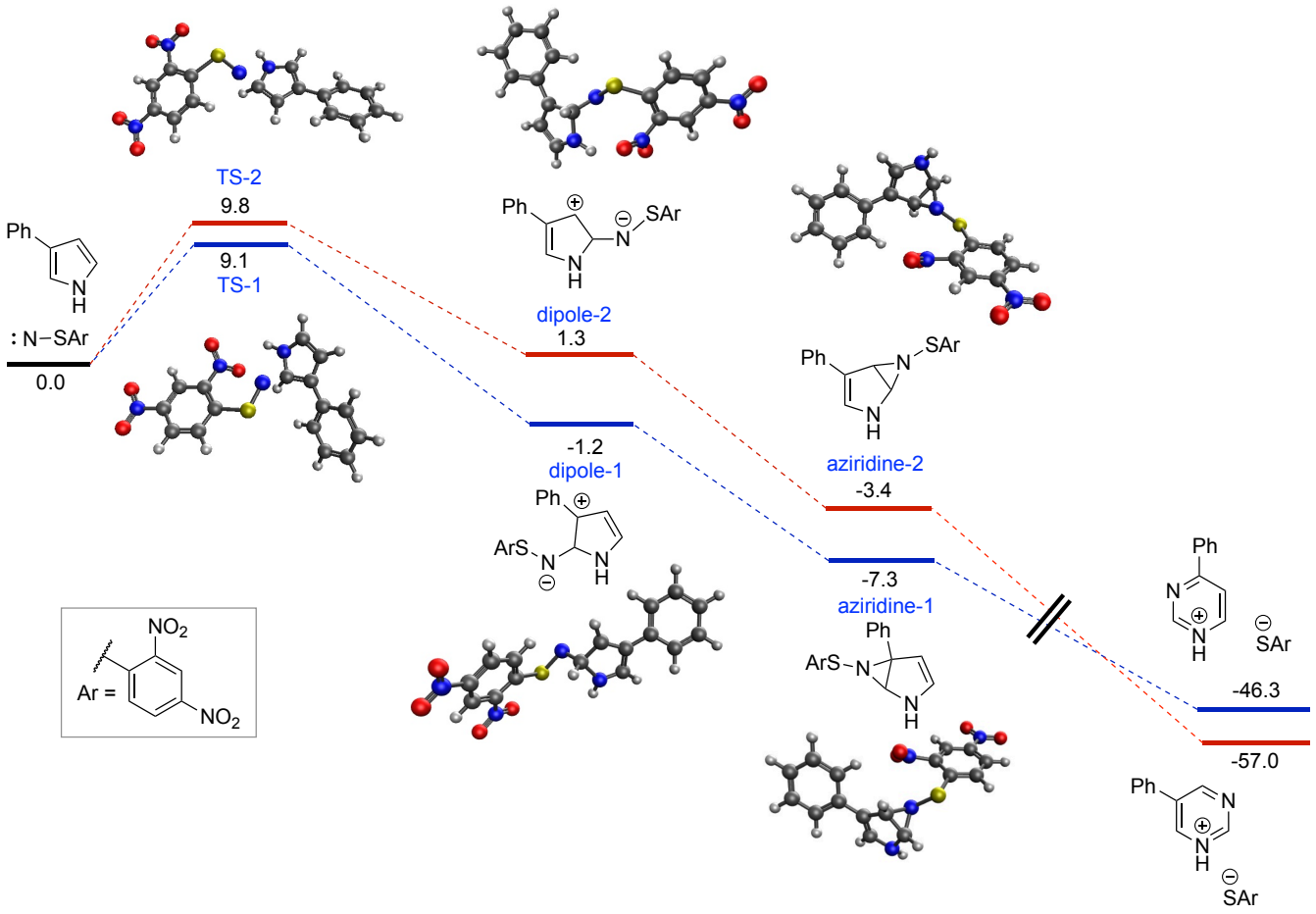


Figure 5: Computational Calculations: Free energy profile for reaction of 3-Phenylpyrrole with sulfenylnitrene. Energies are in kcal/mol; atomic colors: C = gray, O = red, N = blue, S = yellow, H = light gray.

These calculations revealed that the nitrene is likely to exist exclusively as a singlet. Transition states were confirmed by Hessian analysis and characterized by a single, physically relevant imaginary vibrational frequency. Likewise, intermediates were characterized by zero imaginary vibrational frequencies with a gradient also equal to zero. Relaxed potential energy surface (PES) scans were performed to search for the minimum energy pathway (MEP) which revealed a single asymmetric transition state, followed by a series of barrierless steps to shelf-like intermediates resulting in a waterfall pathway.[19] From a qualitative molecular orbital point of view, it is reasonable for this process to occur asymmetrically, as the filled sp^2 and empty p* orbitals on the nitrene are orthogonal to one another, while the relevant π and π* orbitals of pyrrole are parallel to one another. To maximize orbital overlap, it is

more facile for this transformation to occur in two steps. The height of this single transition state barrier explains the observed regioselectivity of this process. Again, from a qualitative perspective, it is reasonable to assume that a dipolar process would favor the substituted side of the pyrrole due to stabilization from the aromatic ring.

Furthermore, we harnessed the potential of sulfenylnitrene to add a single *N*-atom to the indole, an important motif in numerous bioactive molecules[20] (**Figure 6**). Contrary to the literature reports, where indole *N*-protection was necessary for the *N*-addition, our methodology did not require any protection.[8i]

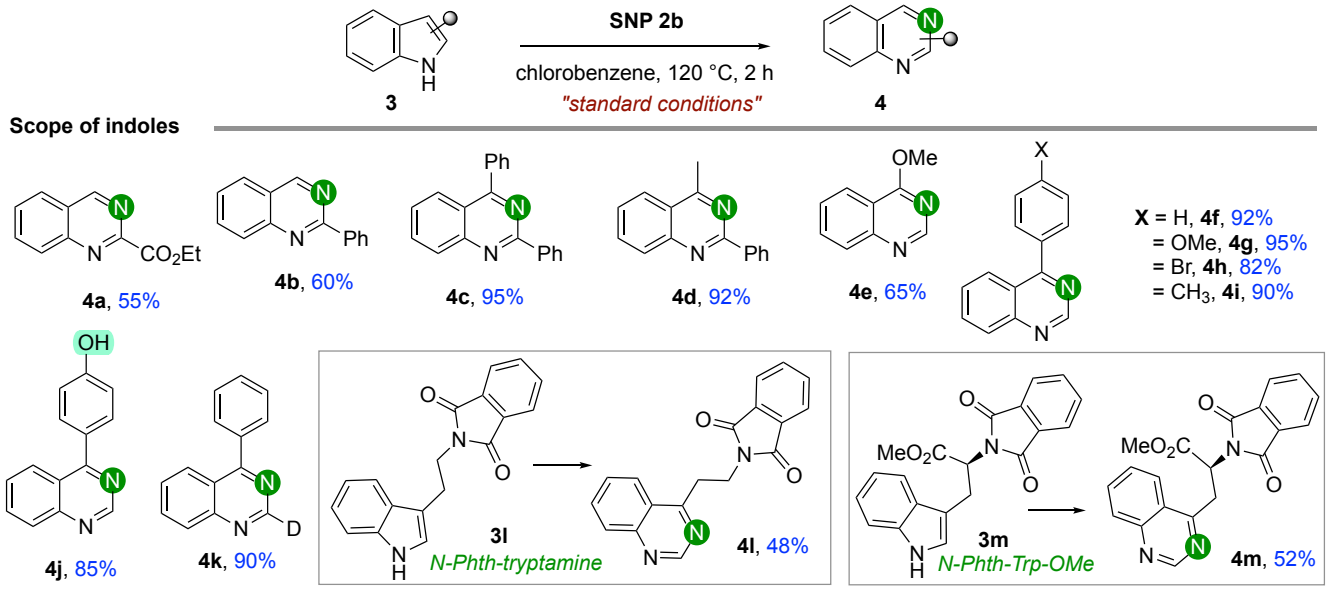


Figure 6: Application to indoles, Conditions: **3** (1 equiv.), **SNP-2b** (2 equiv.), chlorobenzene (0.1 M), 120 °C, 2 h. Isolated yields, 0.1−0.3 mmol scale. Yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

This methodology accommodated various indoles, bearing electron-donating and -withdrawing groups, and provided the corresponding quinazolines in good to high yields (**4a**–**4i**). Remarkably, the method exhibited compatibility with oxidation-sensitive functionalities, such as phenol (**4j**), which was not compatible with the existing methods as they require potent oxidizing agents. For further understanding of the reaction mechanism, we also attempted the reaction with a 2-deuterium substituted indole. As expected, no loss of deuterium was observed in the product (**4k**), supporting the mechanistic

hypothesis described in the SI (page S39). Subsequently, we employed the method on naturally occurring amino acids and their metabolites. Phthalimide-protected tryptamine and tryptophan were converted into the respective quinazoline products (**4l**, **4m**), providing access to previously underexplored unnatural amino acids and their derivatives.[21]

We further demonstrate the potential of this method for synthesizing medicinally relevant compounds, such as an anti-cancer agent erlotinib and gefitinib.[22] To access their analogues, a substituted indole bearing a thioether functionality **3o** was transformed into quinazoline **4o** (**Figure 7a**).

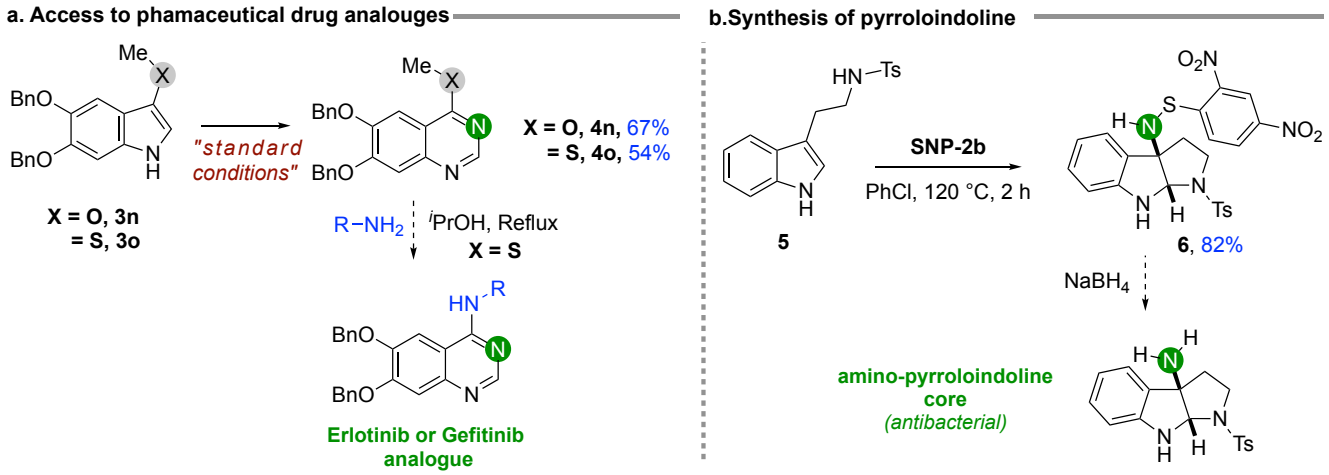


Figure 7: Access to pharmaceutical drug analogues and complex pyrroloindoline. Conditions: **3n** or **3o** or **5** (1 equiv.), **SNP-2b** (2 equiv.), chlorobenzene (0.1 M), 120 °C, 2 h. Isolated yields, 0.1−0.3 mmol scale. Yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

The subsequent treatment of quinazoline **4o** with amines, would provide erlotinib or Gefitinib analogues as described in the literature.[23] We also envisioned applying these sulfenylnitrenes to access bioactive pyrroloindolines.[24] As anticipated, the tosyl-protected tryptamine **5** provided the corresponding pyrroloindoline **6** as a single diastereomer with a high yield (**Figure 7b**). Notably, aziridine opening was preferred over the ring expansion, which took place from the same side of the aliphatic chain at the 3-position of tryptamine, resulting in the exclusive *cis*-selectivity (see SI page S54 for additional details). The reduction of the N–S bond with sodium borohydride would provide the free amine, an amino-pyrroloindoline core, which is of particular interest due to their potent antibacterial properties.[9, 25]

Following the successful implementation of *N*-insertion into pyrroles and indoles, we also extended its application to imidazoles (**Figure 8**). We were pleased to observe that various aryl-substituted imidazoles smoothly converted into the corresponding 1,3,5-triazenes with high yields (**8a**–**8e**). Notably, lophine, a chemiluminescent molecule known for its prolonged luminescence,[26] readily underwent expansion with a yield of 91% (**8f**). Finally, the phthalimide-protected naturally occurring amino acid L-histidine (**7g**) was successfully transformed into the corresponding triazine core structure (**8g**).

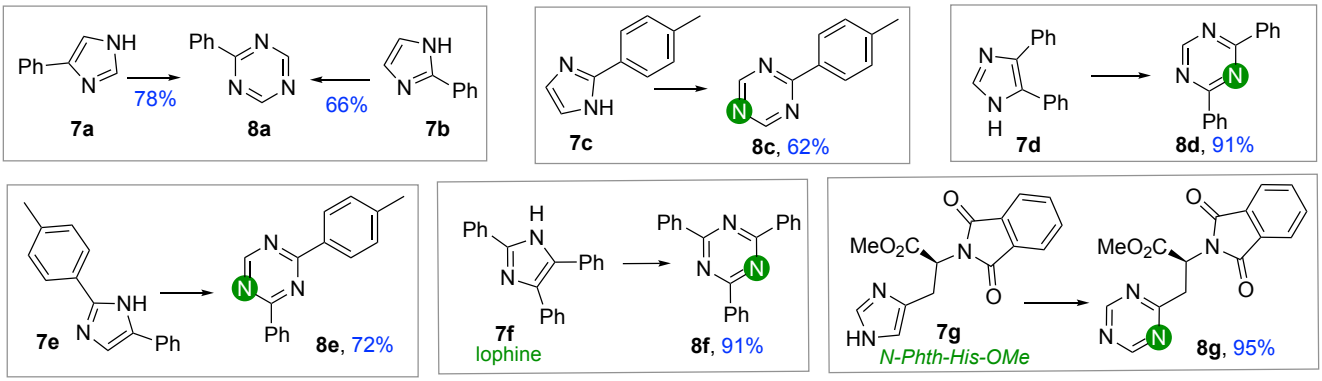


Figure 8: Application to imidazoles. Conditions: **7** (1 equiv.), **SNP-2** (2 equiv.), chlorobenzene (0.1 M), 120 °C, 2 h. Isolated yields, 0.1−0.3 mmol scale. Yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

CONCLUSION

In summary, we have demonstrated the utilization of sulfenylnitrenes for the selective insertion of a single nitrogen atom into the skeleton of pyrroles, indoles, and imidazoles. DFT calculations provide insights into pyrrole regioselectivity, where the reaction proceeds via an aziridine intermediate favoring the electron-rich side to provide the major regio-isomer. This methodology tolerates a variety of functional groups, including oxidation-sensitive phenols and thioethers, which were previously found incompatible with known *N*-addition methods. The synthetic utility of this approach has been demonstrated through the late-stage functionalization of natural products, amino acids, and pharmaceuticals. These unique sulfenylnitrenes hold great promise for scaffold hopping, and their applications to various transformations are currently under investigations in our laboratory.

Associated Content

Supporting Information

The supporting information experimental procedures, NMR spectroscopic, and analytical data for all compounds (PDF).

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Notes

The authors declare no competing financial interests.

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