

Recent Advances in the Synthesis of Piperazines: Focus on C–H Functionalization

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Abstract: Piperazine ranks as the third most common nitrogen heterocycle in drug discovery, and is the key component of several blockbuster drugs such as *Imatinib* (also marketed as *Gleevec*) or *Sildenafil*, sold as *Viagra*. Despite its wide use in medicinal chemistry, the structural diversity of piperazines is limited, with about 80% of piperazine-containing drugs containing substituents only at the nitrogen positions. Recently major advances have been made in the C–H functionalization of the carbon atoms of the piperazine ring. Herein, we present an overview of the recent synthetic methods to afford functionalized piperazines with a focus on C–H functionalization.

Keywords: piperazines; N-heterocycles; C–H functionalization; photoredox; heterocyclic chemistry; six-membered heterocycles; nitrogen heterocycles; drug discovery; medicinal chemistry

1. Introduction

Beyond doubt, nitrogen heterocycles constitute the most important structural motifs in medicinal chemistry and pharmaceuticals, making up for more than 75% of FDA approved drugs [1]. Among nitrogen heterocycles, piperazine ranks as the third most common nitrogen heterocycle in drug discovery, which is prevalent in diverse pharmacological agents with anxiolytic, antiviral, cardioprotective, anticancer and antidepressant properties, and the key component of several blockbuster drugs such as *Imatinib* (also marketed as *Gleevec*) or *Sildenafil*, sold as *Viagra* (Figure 1) [1,2]. Structurally, piperazine is characterized by the 1,4-relationship of the two nitrogen atoms that comprise the six-membered ring. These two heteroatoms improve the pharmacological and pharmacokinetic profiles of drug candidates containing piperazines since the nitrogen atom sites serve as hydrogen bond donor/acceptor, thus tuning the interactions with receptors as well as increasing water solubility and bioavailability [3,4]. It is worthwhile to point out that the presence of the additional nitrogen permits for adjusting a 3D geometry at the distal position of the six-membered ring, which is not easily available with morpholines or piperidines as the closest six-membered ring heterocyclic analogues of piperazines. In this context, the effect of the piperazine ring on bioactive compounds and drugs under the pharmacophore approach should also be mentioned. As such, it comes as no surprise that piperazine has been positioned as the privileged structure in drug design of a plethora of biologically active compounds [3].

Principally, piperazine derivatives are known for their broad therapeutic spectrum, including antidepressant, antihelmintic, anticonvulsant, antihypertensive, antibacterial, antifungal, antipsychotic, anti-inflammatory, antimalarial, anticancer or for the treatment of HIV [1–5]. In these cases, the biological properties of piperazines are ascribed to the presence of the additional nitrogen atom at the 4-position. However, only approximately 20% of piperazines currently utilized in medicinal chemistry research feature additional substituents on the carbon atoms of the piperazine ring [1,2,5]. Indeed, compared to the well-established substitution patterns at the N1-nitrogen, the lack of structural diversity

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at the carbon atoms hinders applications in medicinal chemistry and demonstrates the clear need for the development of new, efficient and selective methods to access carbon functionalization of the piperazine ring [6–8].

While traditional approaches used to introduce diverse substituents at the carbon atoms of piperazines are generally lengthy and limited by the availability of starting materials [4–6], recently major advances have been made in C–H functionalization of the carbon atoms of the piperazine ring. These approaches provide new attractive avenues for the synthesis of defined substitution patterns of piperazines and expand the growing portfolio of piperazine toolbox for broad applications in medicinal chemistry research. It is worthwhile to point out that the methods applied for the C–H functionalization of other heterocycles such as pyrrolidines or piperidines typically cannot be used for functionalization of piperazines due to the existence of the second nitrogen atom in piperazines, which results in the side reactions or inhibits the reactivity of the catalytic system [5]. In this review, we present an overview of the recent synthetic methods to afford carbon functionalized piperazines with a focus on C–H functionalization. We hope that the review will encourage future research on selective C–H functionalization of piperazine ring by a range of interested chemists.

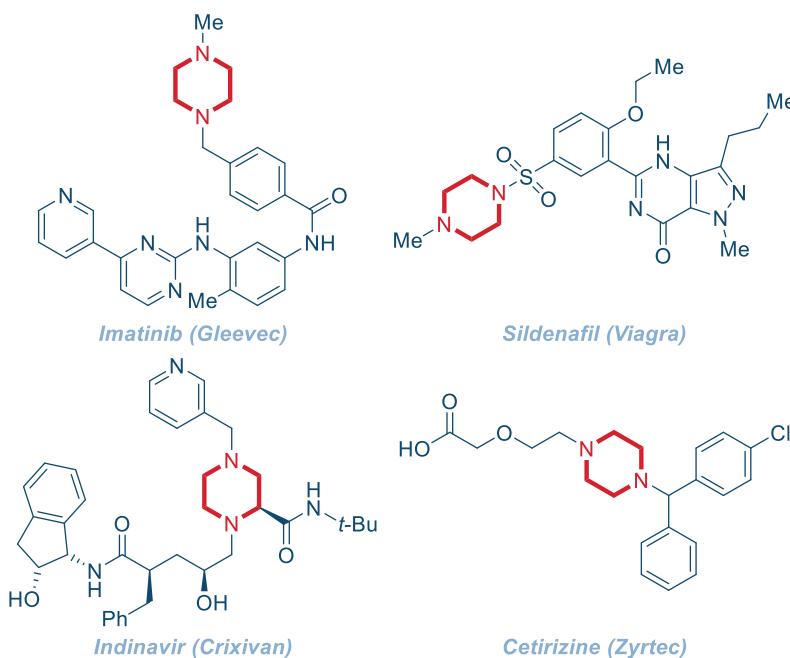


Figure 1. Blockbuster drugs that incorporate the piperazine ring.

2. Discussion

2.1. Photoredox C–H Arylation and C–H Vinylation

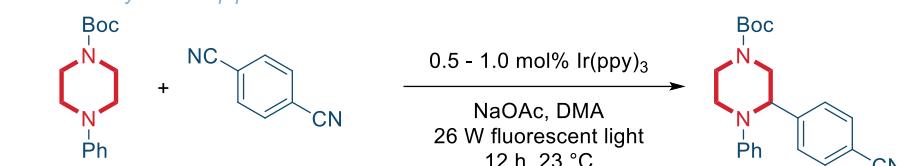
Over the past few years, the interest in visible-light photoredox catalysis has risen dramatically as a mild and green alternative to classical methods [9–11]. The most common catalysts include transition metal complexes of iridium and ruthenium, and organic dyes. The fundamental principle relies on the conversion of visible light energy into chemical energy generating highly reactive intermediates in a controlled fashion, which can be exploited for C–H functionalization of heterocycles [9–11].

In 2011, MacMillan and co-workers reported one of the earliest examples of photoredox catalysis for the synthesis of C–H functionalized piperazines (Scheme 1A) [12]. The photoredox-catalyzed C–H arylation of piperazines with 1,4-dicyanobenzene was discovered using high throughput technology, in which a pool of substrates was exposed to a series of photoredox catalysts. During optimization, commercially available $\text{Ir}(\text{ppy})_3$ gave the best results and found to be a suitable photocatalyst. Mechanistic studies showed that

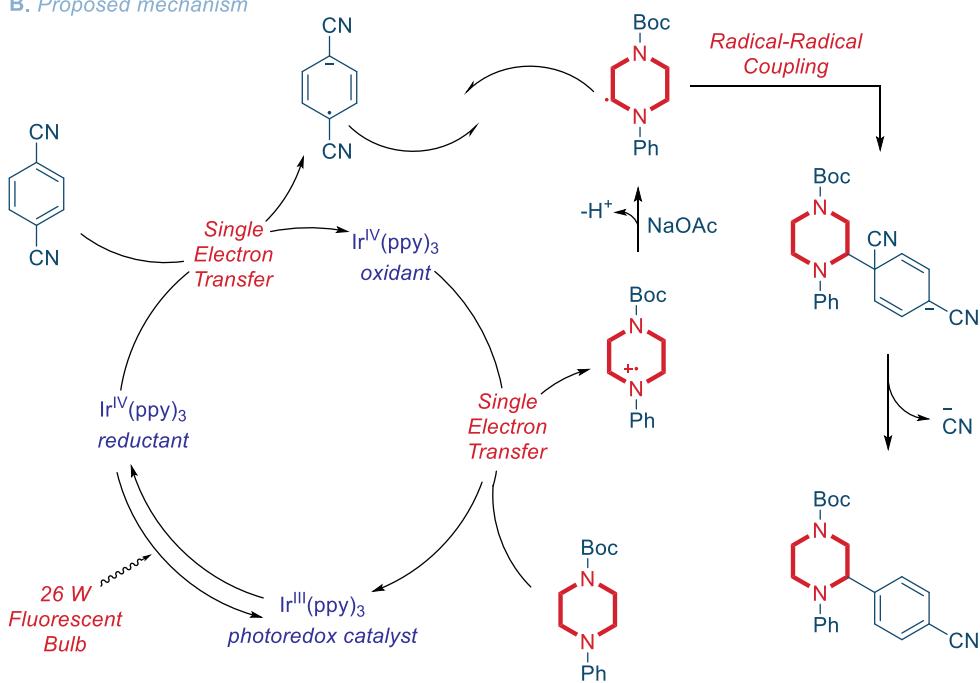
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this process proceeds via single-electron transfer. The authors proposed a mechanism involving the following steps (Scheme 1B): (1) upon excitation from the light source $\text{Ir}^{\text{III}}(\text{ppy})_3$ becomes a powerful reductant; (2) in the presence of 1,4-dicyanobenzene, $\text{Ir}^{\text{III}}(\text{ppy})_3$ donates an electron forming the arene radical anion; (3) the resultant $\text{Ir}^{\text{IV}}(\text{ppy})_3$, a strong oxidant, undergoes a single electron transfer with piperazine generating an amino radical cation of the N-Ph (vs. N-Boc) nitrogen and regenerating $\text{Ir}^{\text{III}}(\text{ppy})_3$; (4) the piperazine C–H bond adjacent to the nitrogen atom undergoes deprotonation upon treatment with NaOAc to afford α -amino radical; (5) a coupling between the arene radical anion and the α -amino radical generates the α -functionalized piperazine ring; (6) rearomatization occurs by elimination of the cyano group. This synthetic method provides a powerful entry to directly couple N-Boc piperazines with 1,4-dicyanobenzenes to produce the corresponding α -aryl-substituted piperazines.

A. α -C–H arylation of piperazines



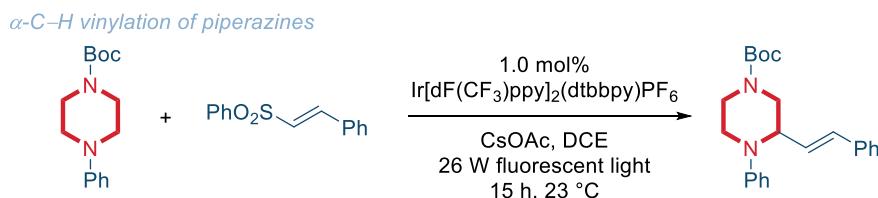
B. Proposed mechanism



Scheme 1. Photoredox C–H Arylation of Piperazines.

To expand the utility of this methodology, MacMillan and co-workers set to explore the application of this protocol to the direct C–H vinylation of piperazines (Scheme 2A) [13]. Vinyl sulfones were identified as the alkene coupling partners of choice for this reaction due to their electron deficient properties that facilitate the radical addition and promote β -elimination. Although the proposed vinylation reaction proved to work under the previously developed conditions, efficiency of this protocol was further improved by changing the catalyst system to $\text{Ir}^{\text{III}}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6/\text{CsOAc}/\text{DCE}$ to provide the product with high *E*-selectivity. Using the identified reaction conditions (*E*)-(2-(phenylsulfonyl)vinyl)benzene was combined with the N1-Ph/N2-Boc piperazine to afford the corresponding product with an *E*:*Z* ratio of 94:6. Mechanistically, the authors proposed that C–H vinylation proceeded through a similar radical coupling pathway as C–H arylation (Scheme 2B).

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Scheme 2. Photoredox C–H Vinylation of Piperazines.

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Based on their earlier work, MacMillan and co-workers reported the successful α -C–H heteroarylation of piperazines via a homolytic substitution pathway (Scheme 3A) [14]. In the previous protocols, functionalization was achieved using electron deficient benzonitriles or vinyl sulfones as coupling partners. Mechanistically, this first reaction proceeded via a single electron transfer and radical–radical coupling, which generated an anion driving the reaction to completion. However, such transformation could be achieved by an alternative mechanism that would obviate the radical anion pathway. During optimization of the α -heteroarylation reaction, $\text{Ir}^{\text{III}}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ was found suitable as a photocatalyst to oxidize the piperazine N-Ph atom via a single electron transfer. Mechanistically, the resulting amine radical cation is then deprotonated at the α -position of the nitrogen atom to give α -aminyl radical (Scheme 3B). The intermediate is then coupled to a heteroarene through homolytic aromatic substitution. This intermediate undergoes reduction with $\text{Ir}^{\text{II}}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ via single electron transfer and the loss of chloride to afford the C–H heteroarylated product (Scheme 3B). This new mechanism permitted to utilize a range of heteroarenes to achieve the direct α -C–H heteroarylation of piperazines.

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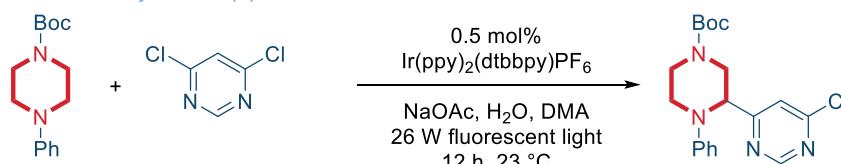
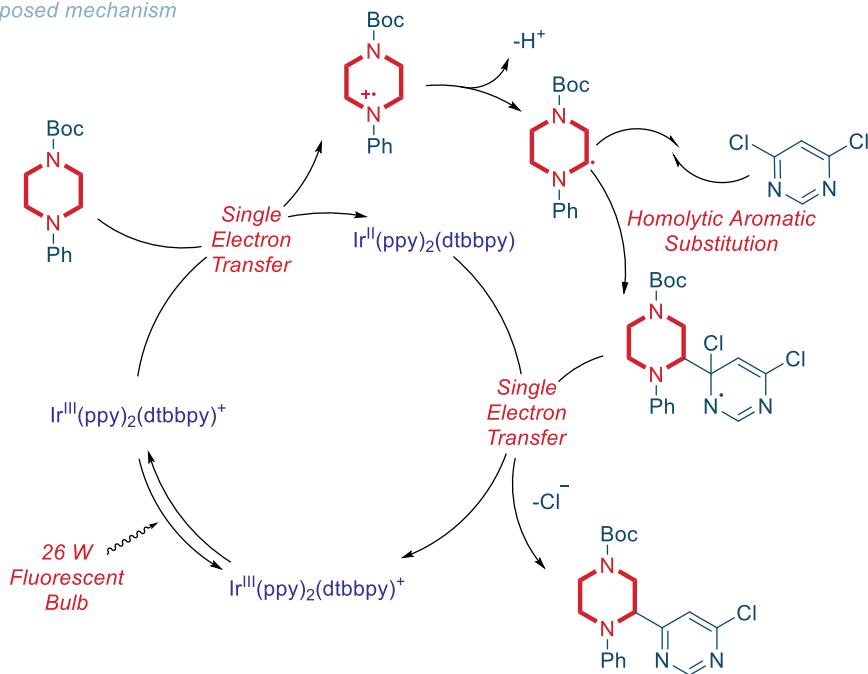
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A. α -C–H heteroarylation of piperazines**B. Proposed mechanism****Scheme 3.** Photoredox C–H Heteroarylation of Piperazines.

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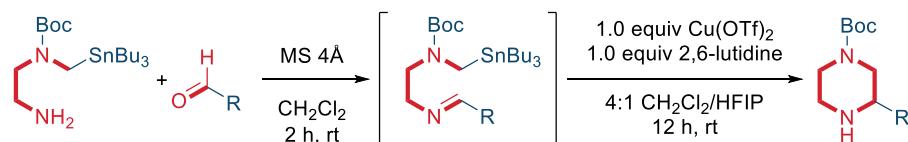
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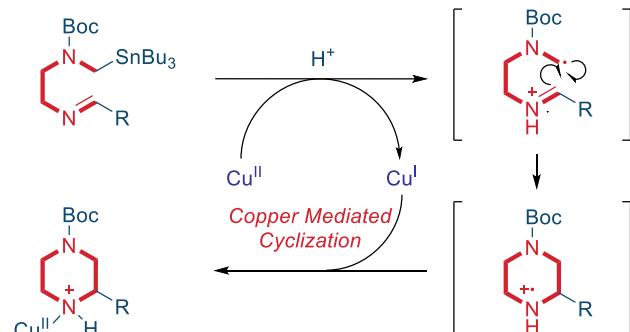
2.2. SnAP Reagents

In an alternative mechanistic approach to a formal C–H functionalization of piperazines during their *de novo* synthesis, Bode and co-workers developed SnAP (stannyl amine protocol) chemistry as a convergent method for the synthesis of piperazines from aldehydes (Scheme 4A) [15–20]. This strategy relies on a facile radical generation from the stannane reagent to achieve the combined cyclization/C–C bond addition to imines [15,16]. The tin-substituted starting materials are readily synthesized from the corresponding diamines and tributyl(iodomethyl)stannane [15,16]. Mechanistically, the reaction is initiated by a copper-mediated oxidation of the C–Sn bond to form a heteroatom-stabilized α -amino radical, which then undergoes cyclization with the intermediate imine (Scheme 4B) [16–17]. This methodology delivers access to diverse piperazines with the functionalization at the carbon atom by a streamlined condensation of aldehydes and the SnAP reagent to generate the imines, which are cyclized with stoichiometric amounts of copper at mild room temperature conditions.

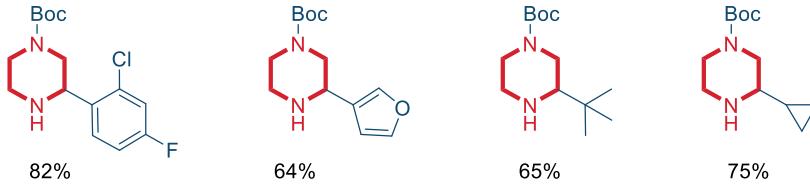
A. Piperazine synthesis with SnAP reagents



B. Proposed mechanism



C. Representative substitution patterns



Scheme 4. Synthesis of C–H Functionalized Piperazines with SnAP Reagents.

This SnAP chemistry developed by Bode and co-workers offers several major advantages in terms of ease of execution, functional group tolerance, and mild reaction conditions; however, the stoichiometric use of copper decreases the efficiency of the reaction and limits its potential large-scale applications on industrial level [15–17]. Thus, research led by Bode and co-workers identified the conditions at which the synthesis of piperazines proceeds under catalytic amounts of copper by changing the solvent from 4:1 CH_2Cl_2 /HFIP to 4:1 HFIP/CH₃CN (Scheme 5) [18]. Importantly, this improved procedure permitted to expand the substrate scope in the synthesis of piperazines to engage previously inaccessible heterocyclic aldehydes for the functionalization at the C2 position, thus leading to a facile synthesis of α -heteroarylated piperazines.

Another area of improvement in the SnAP method for the synthesis of piperazines was to address the use of potentially toxic tin reagents and the complex workups to

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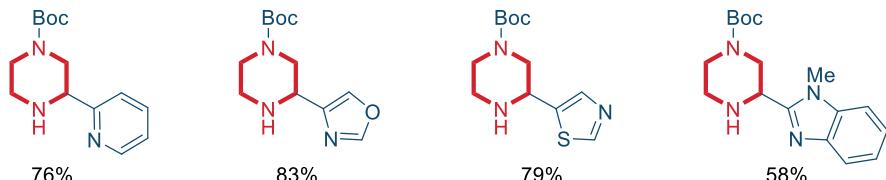
remove copper salts. To circumvent these problems, Bode's group introduced silicon amine protocol (SLAP) under photocatalytic conditions (Scheme 6) [19]. In this method, silicon was selected as a surrogate for tin in a radical-based process. Upon subjecting to the previous reaction conditions, SLAP reagents showed no cyclization; however, further studies revealed that $\text{Ir}^{\text{III}}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ as a promoter under blue light irradiation resulted in efficient cyclization to piperazine products. It is noteworthy from a practical point of view that copper was effectively replaced by a photoredox catalyst. Although full conversion was not observed when the *N*-Boc SLAP reagent was used, the corresponding *N*-Ph and *N*-Bn reagents afforded the piperazine products in high yields. This SLAP protocol provides an attractive alternative to SnAP chemistry, showing high functional group tolerance, practical reaction conditions and the absence of tin and copper by-products.

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A. Catalytic piperazine synthesis with SnAP reagents



B. New substitution patterns



Scheme 5. Catalytic Synthesis of C–H Functionalized Piperazines with SnAP Reagents.

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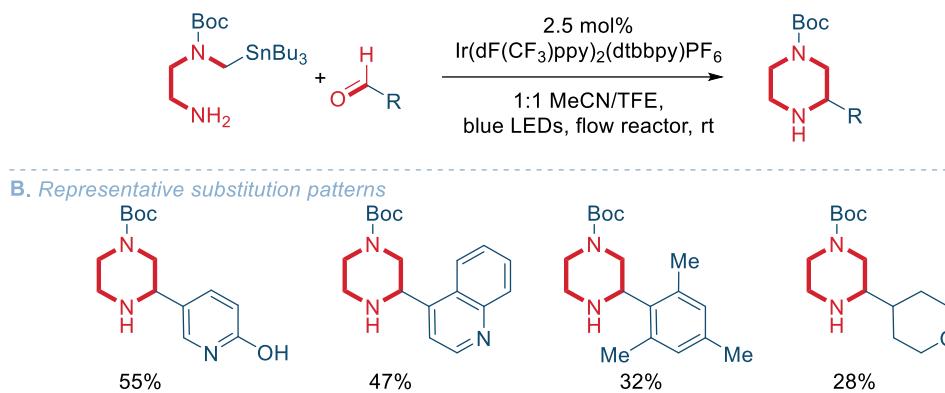
Photocatalytic piperazine synthesis with SLAP reagents



Scheme 6. Photoredox Synthesis of C–H Functionalized Piperazines with SLAP Reagents.

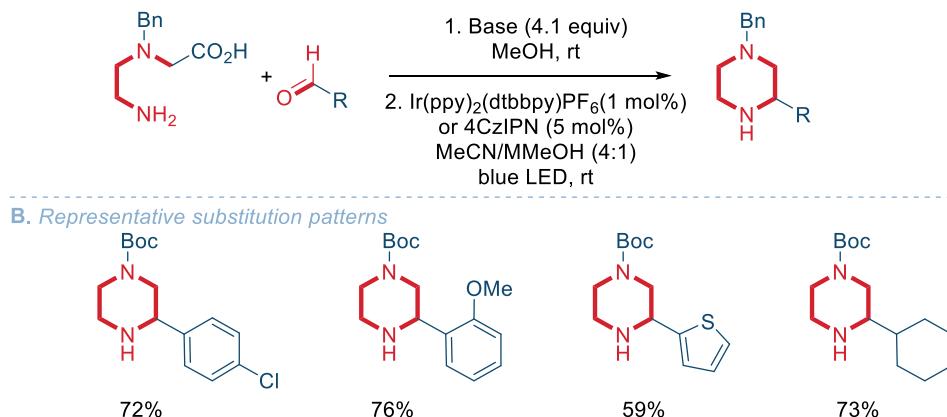
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While SnAP and SLAP chemistry have become widely available for the synthesis of piperazines, including commercial availability of the reagents [20,21], incompatibility with select substrate combinations and toxicity of tin still limited applications of these methods. To address this problem, Bode and co-workers reported the use of photoredox catalysis under continuous flow conditions (Scheme 7) [22]. In contrast to the previously described SnAP methodology, this approach made use of a single photoredox catalyst replacing the combination of copper and amine ligands which resulted in a simplified reaction workup. Notably, unlike SLAP chemistry, which also uses a single catalyst, this flow method also allows access to synthetically easily modifiable *N*-Boc C-2 functionalized piperazines. Perhaps most important is the operational mode of reaction under continuous-flow conditions, which facilitates reaction scale-up and offers simplified operational conditions. Thus, although tin reagents are still used, the continuous flow set-up makes this approach scalable and efficient, while safety concerns are at least minimized by limiting contact with the reagents.

A. Photocatalytic piperazine synthesis with SnAP reagents

Scheme 7. Photoredox Synthesis of C–H Functionalized Piperazines with SnAP Reagents in Flow.

In line with the photoredox catalysis for the synthesis of C2-functionalized piperazines, Bigot and co-workers developed a photoredox CLAP protocol (Carboxylic Acid Protocol) (Scheme 8) [23]. This method is based on a decarboxylative cyclization between a variety of aldehydes and amino-acid-derived diamine to access diverse C2-substituted piperazines. Parallel to Bode’s work, this new annulation process used an iridium-based photoredox catalyst to generate α -aminyl radical that cyclizes with the intermediate imine. Interestingly, organic photocatalyst, carbazolyl dicyanobenzene (4CzIPN), also showed high efficiency. In this case, although batch conditions were not directly transposable to flow conditions due to the presence of a precipitate, replacement of KOH with a soluble base, DBU, allowed for this synthesis to be conducted in flow. In contrast to previous reactions, this method offers a green approach for the synthesis of piperazines by the use of a purely organic photoredox catalyst to promote the radical generation [10, 24–28]. Successful transition of this method from batch to continuous flow conditions offers another advantage over other methods. Moreover, substrates derived from toxic reagents such as tin are avoided by using amino-acid-derived radical precursors through decarboxylation, thus further improving the sustainability of the reaction.

A. Photocatalytic piperazine synthesis with CLAP reagents

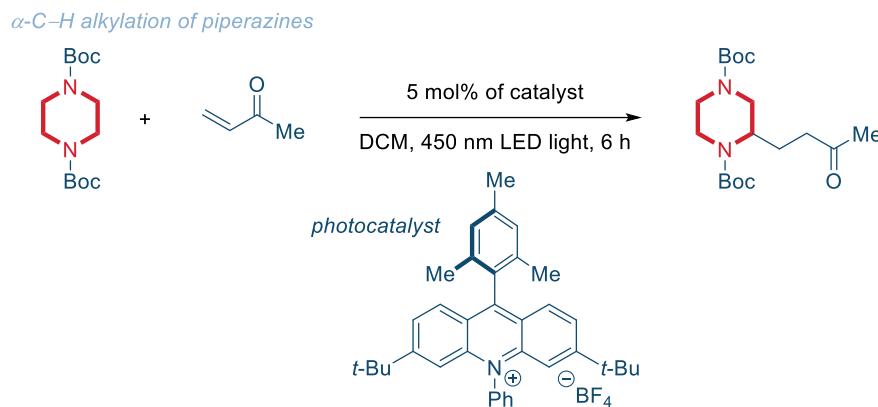
Scheme 8. Photoredox Synthesis of C–H Functionalized Piperazines with CLAP Reagents.

2.3. Organic Photoredox C–H Alkylation

Photoredox catalysis introduces sustainable and greener methods for chemical synthesis; however, due to the potential toxicity and cost associated with transition-metal-

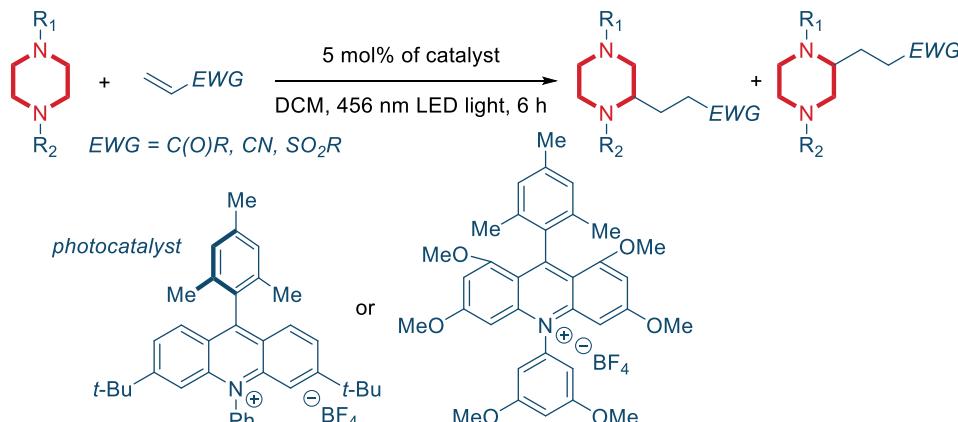
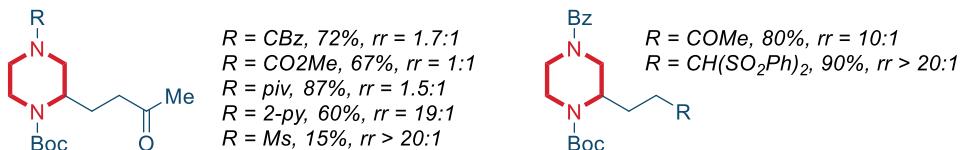
catalysts, recent research has been directed towards the use and development of organic photocatalysts [10, 24–28]. Organic photocatalysts offer significantly more sustainability as they can be synthesized from renewable organic materials.

In this context, work by Nicewicz and co-workers has been focused on establishing alternative organic photocatalysts with comparable performance to that of transition-metal photoredox catalysts [29]. Recently, they reported substituted acridinium salts as organic photocatalysts for the C–H alkylation of carbamate protected piperazines (Scheme 9) [30]. This reaction proceeds via coupling of α -carbamyl radicals with α,β -unsaturated carbonyl compounds and is compatible with *N,N*-bis-Boc-piperazine, which allows to chemoselectively produce a single α -C–H alkylation product in good yield.



Scheme 9. Organic Photoredox C–H Alkylation of Piperazines.

Inspired by this finding, Nicewicz and co-workers further developed a mild and site-selective approach to C–H functionalization of piperazines from its unsubstituted precursors and Michael acceptors using acridinium photocatalysts (Scheme 10A) [31]. This method relies on the electronic differentiation between the two nitrogen atoms of the piperazine core (Scheme 10B). For each of the nitrogen atoms, DFT natural population analysis was performed to determine the relative electron density and predict the ease of formation of the corresponding radical cation. This model successfully predicted the major product, wherein the nitrogen atom that showed the most significant change in electron density between the neutral and radical cation intermediate underwent the alpha-alkylation process. This sustainable and cost-efficient method offers synthetic opportunity for late-stage modifications of the piperazine core using Michael acceptors as alkylating reagents.

A. α -C–H alkylation of piperazines**B. Representative regioselectivity patterns****Scheme 10.** N1 or N2-Guided Organic Photoredox C–H Alkylation of Piperazines.

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2.4. Direct C–H Lithiation

Another successful approach to C–H functionalization of piperazines involves direct C–H lithiation of *N*-Boc-protected piperazines [32]. O’Brien and co-workers reported the synthesis of enantiopure piperazines by asymmetric lithiation–substitution of α -methylbenzyl piperazines (Scheme 11) [33]. This method utilizes *s*-BuLi/(-)-sparteine or (+)-sparteine surrogate to produce an α -methylbenzyl functionalized *N*-Boc piperazines via asymmetric lithiation. The enantioselectivity was governed by the distal substituent and the electrophile. The method provides access to α -functionalized piperazines with typically good levels of diastereocontrol. The utility of the method was highlighted in the asymmetric synthesis of *Indinavir* intermediate.

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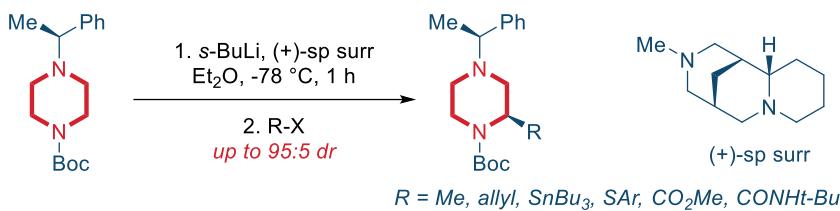
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 α -C–H lithiation of *N*-Boc piperazines $R = Me, allyl, SnBu_3, SAr, CO_2Me, CONHt-Bu$

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Scheme 11. Direct Diastereoselective α -C–H Lithiation of *N*-Boc Piperazines.

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Subsequently, O’Brien and co-workers reported a unified general procedure for the C–H functionalization of *N*-Boc-protected piperazines via direct lithiation/addition [34]. *In situ* IR monitoring revealed that diamine-free lithiation of *N*-Boc-*N*-benzyl is feasible, allowing trapping with a range of alkyl and acyl electrophiles (not shown). Furthermore, O’Brien and coworkers reported a protocol for the direct lithiation of *N*-Boc piperazines at temperatures higher than $-78\text{ }^\circ\text{C}$ (Scheme 12) [35]. Thus, asymmetric lithiation was successfully carried out at $-50\text{ }^\circ\text{C}$ for 3 min, affording the α -acyl substituted product in high enantioselectivity. This method could potentially address some of the limitations of special reaction set-up required for direct lithiation methodologies of piperazine ring that need low cryogenic temperatures at $-78\text{ }^\circ\text{C}$.

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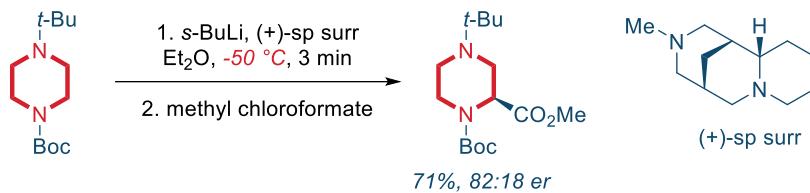
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α-C–H lithiation of N-Boc piperazines**Scheme 12.** Direct α -C–H Lithiation of N-Boc Piperazines at Higher Temperatures.**3. Conclusions**

As the recent studies indicate, there is a pressing need for further structural exploration of carbon functionalized piperazines. As presented in this review, recent developments have a significant potential to address the issue of the lack of practical and direct methodologies to perform direct C–H functionalizations of the piperazine core. In particular, photocatalytic strategies have allowed the rational and strategic design of powerful synthetic methods including direct arylation, vinylation, heteroarylation, alkylation, SLAP, SnAP, and CLAP protocols. Recent developments in industry, such as the introduction of microreactors that allow automation of photoredox reactions, along with the synthetic potential offered by photochemical strategies are especially promising. Moreover, based on the sustainability concept of photoredox catalysis, organic photocatalysts have been developed offering greener and more cost-efficient synthetic alternatives. Another alternative involves direct α -lithiation of N-Boc piperazines, a reaction that is particularly suitable for introducing C2-acyl substitution of piperazines. More generally, the recent C–H functionalization methods of the piperazine ring should be compared and contrasted with pioneering examples of CH-piperazine functionalization, including Rh, Ta and Cu catalysis [36–38]. The reader is further encouraged to consult additional reviews on the topic of the synthesis and application of piperazines [39–41].

While significant progress has been achieved, several challenges remain to be addressed. Photoredox reactions suffer from long reaction times which thwarts their scalability due to the need for a well-lit surface-to-volume ratio. Flow reactors provide promising solutions for such problem; however, the reactions are often not readily transferable from batch to flow processes. Furthermore, the extensive use of metals presents another limitation in the future progress of photoredox catalysis. Organic dyes are one potential solution to this issue; nonetheless, the synthetic accessibility of diverse organic photocatalysts prevents their more widespread use. Likewise, cryogenic temperatures are a limiting factor of direct lithiation methods; however, promising studies indicating the feasibility of lithiation at temperatures above -80 °C have already been reported. Nevertheless, recent advances in the direct C–H functionalization of piperazines provide great synthetic opportunities for the introduction of the much-needed structural variety at the carbon atoms of the piperazine core.

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References

1. Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274.
2. Brunton, L.; Chabner, B.; Knollman, B. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*; MacGraw-Hill: New York, 2010.
3. Elliott, S. Current awareness of piperazines: pharmacology and toxicology. *Drug. Test. Anal.* **2011**, *3*, 430–438.
4. Shaquiquzzaman, M.; Verma, G.; Marella, A.; Akhter, M.; Akhtar, W.; Khan, M. F.; Tasneem, S.; Alam, M. M. Piperazine scaffold: A remarkable tool in generation of diverse pharmacological agents. *Eur. J. Med. Chem.* **2015**, *102*, 487–529.
5. Rathi, A. K.; Syed, R.; Shin, H. S.; Patel, R. V. Piperazine derivatives for therapeutic use: a patent review (2010–present). *Expert. Opin. Ther. Pat.* **2016**, *7*, 777–797.

6. Zhang, R. H.; Guo, H. Y.; Deng, H.; Li, J.; Quanb, Z. S. Piperazine skeleton in the structural modification of natural products: a review. *J. Enzyme Inhib. Med. Chem.* **2021**, *36*, 1165–1197. 311
312

7. Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic Synthesis Provides Opportunities to Transform Drug Discovery. *Nat. Chem.* **2018**, *10*, 383–394. 313
314

8. Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krksa, S. W. The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016**, *45*, 546–576. 315
316

9. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363. 317
318

10. Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075–10166. 319

11. McAtee, R. C.; McClain, E. J.; Stephenson, C. R. J. Illuminating Photoredox Catalysis. *Trends Chem.* **2019**, *1*, 111–125. 320

12. McNally, A.; Prier, C. K.; MacMillan, D. W. C. Discovery of an α -amino C–H arylation reaction using the strategy of accelerated serendipity. *Science* **2011**, *334*, 1114–1117. 321
322

13. Noble, A.; MacMillan, D. W. C. Photoredox α -Vinylation of α -Amino Acids and N-Aryl Amines. *J. Am. Chem. Soc.* **2014**, *136*, 11602–11605. 323

14. Prier, C. K.; MacMillan, D. W. C. Amine α -heteroarylation via photoredox catalysis: a homolytic aromatic substitution pathway. *Chem. Sci.* **2014**, *5*, 4173–4178. 324
325

15. Vo, C.-V. T.; Mikutis, G.; Bode, J. W. SnAP reagents for the transformation of aldehydes into substituted thiomorpholines—an alternative to cross-coupling with saturated heterocycles. *Angew. Chem. Int. Ed.* **2013**, *52*, 1705–1708. 326
327

16. Vo, C.-V. T.; Luescher, M. U.; Bode, J. W. SnAP reagents for the one-step synthesis of medium-ring saturated N-heterocycles from aldehydes. *Nat. Chem.* **2014**, *6*, 310–314. 328
329

17. Luescher, M. U.; Vo, C.-V. T.; Bode, J. W. SnAP reagents for the synthesis of piperazines and morpholines. *Org. Lett.* **2014**, *16*, 1236–1239. 330

18. Luescher, M. U.; Bode, J. W. Catalytic Synthesis of N-Unprotected Piperazines, Morpholines, and Thiomorpholines from Aldehydes and SnAP Reagents. *Angew. Chem. Int. Ed.* **2015**, *54*, 10884–10888. 331
332

19. Hsieh, S.-Y.; Bode, J. W. Silicon Amine Reagents for the Photocatalytic Synthesis of Piperazines from Aldehydes and Ketones. *Org. Lett.* **2016**, *18*, 2098–2101. 333
334

20. Jindakun, C.; Hsieh, S.-Y.; Bode, J. W. Iridium-catalyzed Synthesis of Saturated N-Heterocycles from Aldehydes and SnAP Reagents with Continuous Flow Photochemistry. *Org. Lett.* **2018**, *20*, 2071–2075. 335
336

21. SnAP Reagents <https://www.sigmaaldrich.com/US/en/technical-documents/protocol/chemistry-and-synthesis/reaction-design-and-optimization/snap-reagents> (accessed Aug 25, 2021). 337
338

22. SLAP reagents for piperazine synthesis <https://www.sigmaaldrich.com/US/en/technical-documents/protocol/chemistry-and-synthesis/reaction-design-and-optimization/slap-reagents> (accessed Aug 25, 2021). 339
340

23. Gueret, R.; Pelinski, L.; Bousquet, T.; Sauthier, M.; Ferey, V.; Bigot, A. Visible-Light-Driven Carboxylic Amine Protocol (CLAP) for the Synthesis of 2-Substituted Piperazines under Batch and Flow Conditions. *Org. Lett.* **2020**, *22*, 5157–5162. 341
342

24. Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. Site-selective arene C–H amination via photoredox catalysis. *Science* **2015**, *349*, 1326–1330. 343
344

25. Majek, M.; Jacobi von Wangenheim, A. Mechanistic Perspectives on Organic Photoredox Catalysis for Aromatic Substitutions. *Acc. Chem. Res.* **2016**, *49*, 2316–2327. 345
346

26. Crisenza, G. E. M.; Melchiorre, P. Chemistry glows green with photoredox catalysis. *Nat. Commun.* **2020**, *11*, 803. 347

27. Bobo, M. V.; Kuchta, J. J., III; Vannucci, A. K. Recent advancements in the development of molecular organic photocatalysts. *Org. Biomol. Chem.* **2021**, *19*, 4816–4834. 348
349

28. Reischauer, S.; Pieber, B. Emerging concepts in photocatalytic organic synthesis. *iScience* **2021**, *24*, 102209. 350

29. Joshi-Pangu, A.; Lévesque, F.; Roth, H. G.; Oliver, S. F.; Campeau, L.-C.; Nicewicz, D.; DiRocco, D. A. Acridinium-Based Photocatalysts: A Sustainable Option in Photoredox Catalysis. *J. Org. Chem.* **2016**, *81*, 7244–7249. 351
352

30. McManus, J. B.; Onuska, N. P. R.; Nicewicz, D. A. Generation and Alkylation of α -Carbamyl Radicals via Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 9056–9060. 353
354

31. McManus, J. B.; Onuska, N. P. R.; Jeffreys, M. S.; Goodwin, N. C.; Nicewicz, D. A. Site-Selective C–H Alkylation of Piperazine Substrates via Organic Photoredox Catalysis. *Org. Lett.* **2020**, *22*, 679–683. 355
356

32. Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A. Asymmetric Deprotonation of N-Boc Piperidine: React IR Monitoring and Mechanistic Aspects. *J. Am. Chem. Soc.* **2010**, *132*, 7260–7261. 357
358

33. Firth, J. D.; O'Brien, P.; Ferris, L. Synthesis of Enantiopure Piperazines via Asymmetric Lithiation-Trapping of N-Boc Piperazines: Unexpected Role of the Electrophile and Distal N-Substituent. *J. Am. Chem. Soc.* **2016**, *138*, 651–659. 359
360

34. Firth, J. D.; O'Brien, P.; Ferris, L. General Procedures for the Lithiation/Trapping of N-Boc Piperazines. *J. Org. Chem.* **2017**, *82*, 7023–7031. 361

35. Gelardi, G.; Barker, G.; O'Brien, P.; Blakemore, D. C. Asymmetric Lithiation Trapping of N-Boc Heterocycles at Temperatures above -78 °C. *Org. Lett.* **2013**, *15*, 5424–5427. 362
363

36. Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. Rhodium-Catalyzed Reaction of N-(2-Pyridinyl)piperazines with CO and Ethylene. A Novel Carbonylation at a C–H Bond in the Piperazine Ring. *Organometallics* **1997**, *16*, 3615–3622. 364
365

37. Payne, P. R.; Garcia, P.; Eisenberger, P.; Yim, J. C.-H.; Schafer, L. L. Tantalum Catalyzed Hydroaminoalkylation for the Synthesis of α - and β -Substituted N-Heterocycles. *Org. Lett.* **2013**, *15*, 2182–2185. 366
367

38. Genovino, J.; Lütz, S.; Sames, D.; Touré, B. B. Complementation of Biotransformations with Chemical C–H Oxidation: Copper-Catalyzed Oxidation of Tertiary Amines in Complex Pharmaceuticals. *J. Am. Chem. Soc.* **2013**, *135*, 12346–12352. 368
369

39. Gettys, K. E.; Ye, Z.; Dai, M. Recent Advances in Piperazine Synthesis. *Synthesis* **2017**, *49*, 2589–2604. 370

40. Magriotis, P. A. Recent progress toward the asymmetric synthesis of carbon-substituted piperazine pharmacophores and oxidative related heterocycles. *RSC Med. Chem.* **2020**, *11*, 745–759. 371
372

41. Sharma, A.; Wakode, S.; Fayaz, F.; Khasimbi, S.; Pottoo, F. H.; Kaur, A. An Overview of Piperazine Scaffold as Promising Nucleus for Different Therapeutic Targets. *Curr. Pharm. Design* **2020**, *26*, 4373–4385. 373
374