Advancements in Visible-Light-Enabled Radical C(sp)^2–H Alkylation of (Hetero)arenes

Alexandra C. Sun
Rory C. McAtee
Edward J. McClain
Corey R. J. Stephenson*

Willard Henry Dow Laboratory, Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, MI 48109, USA
crjsteph@umich.edu

Published as part of the 50 Years SYNTHESIS – Golden Anniversary Issue

Abstract The Minisci reaction, which encompasses the radical C–H alkylation of heteroarenes, has undergone revolutionary development in recent years. The application of photoredox catalysis to alkyl radical generation has given rise to a multitude of methods that feature enhanced functional group tolerance, generality, and operational simplicity. The intent of this short review is to bring readers up to date on this rapidly expanding field. Specifically, we will highlight key examples of visible-light-driven Minisci alkylation strategies that represent key advancements in this area of research. The scope and limitations of these transformations will be discussed, with a focus on examining the underlying pathways for alkyl radical generation. Our goal is to make this short review a stepping stone for further synthetic research development.

Key words Minisci reaction, photoredox catalysis, visible light, radical alkylation, late-stage functionalization, heteroarenes

1 Introduction

Nitrogen-containing heterocycles constitute the backbone of natural products, medicinally valuable small molecules, and agrochemicals (Scheme 1A). Methodologies for the direct C–H alkylation and perfluoroalkylation of N-heteroarenes enable both the late-stage modification of clinical leads and rapid diversification of drug-like libraries. These strategies allow for expedient access to unexplored chemical space and circumvent conventional de novo chemical syntheses. Notably, the medicinal chemistry community has placed growing interest on late-stage functionalization technologies, as they allow for rapid modulation of drug metabolism and pharmacokinetic profiles of lead compounds. Thus, synthetic approaches that are not dependent on strong oxidants/reductants, high reaction temperatures, or pre-functionalized substrates are of high-value to both academic and industrial sectors.

The addition of open-shell alkyl and perfluoroalkyl radical intermediates to heteroarenes is referred to as the Minisci reaction (Scheme 1B). Minisci’s original protocol relied on free radical formation from carboxylic acids via formation of their corresponding silver salts, followed by oxidative decarboxylation upon treatment with a persulfate oxidizing agent. Addition of an alkyl radical intermediate onto a protonated heteroarene, followed by rearomatization, yields the desired alkylated heterocyclic product (Scheme 1C). Based on Studer and Curran’s mechanistic studies, rearomatization is proposed to occur via deprotonation and sequential single electron oxidation of the functionalized heteroarene upon radical addition. Since Minisci’s seminal contributions, this reactive paradigm for the alkylation of (hetero)arenes has been a stalwart foundation for modern drug discovery and development. Furthermore, renewed interest in the mild and operationally simple generation of radical intermediates has spurred rapid evolution in the area of (hetero)arene alkylation.

In part, the driving inertia for this interest has been the emergence of visible-light-mediated photoredox catalysis, which facilitates exceptionally mild single-electron-transfer (SET) events with organic substrates. Importantly, the pharmaceutical industry has recognized the transformative impact of photoredox catalysis, as it has far-reaching implications in harnessing sustainable energy sources, reducing waste streams, and avoiding hazardous and/or toxic
reagents classically employed for carbon-centered radical formation (e.g., Bu3SnH, BEt3/O2). Given that state-of-the-art photochemical methods are already employed in drug development (e.g., elbasvir20 and artemisinin21), we anticipate that the photoredox radical (perfluoro)alkylation of (hetero)arenes will be an invaluable synthetic technology for years to come.

In light of the importance of such transformations, we have decided to summarize recently reported methods for visible-light-enabled radical C(sp2)–H alkylations and perfluoroalkylations of medicinally relevant (hetero)arenes. The sections to follow are organized based on radical precursor reagents. When appropriate, the discussions will aim to highlight the unique selectivity outcomes dictated by the electronic properties of alkyl and perfluoroalkyl radicals. This short review is not intended to be comprehensive and is aimed at emphasizing novel photoredox catalysis techniques for the radical alkylation of (hetero)arenes, which we anticipate will have an enduring impact in academic and industrial settings.

2 Alkyl Carboxylic Acids and Carboxylic Acid Derivatives

Alkyl carboxylic acids are versatile feedstock chemicals that are ubiquitous throughout nature and have been widely used as chemical building blocks.12,21 Owing to their low cost, stability, minimal toxicity, and commercial availability, alkyl carboxylic acids have been widely utilized across a variety of synthetic transformations and represent preeminent building blocks for combinatorial chemistry (e.g., amide bond formation). In recent years, the radical decarboxylation of aliphatic carboxylic acids and their activated derivatives has emerged as a powerful strategy for the Minisci functionalization of bioactive organic molecules.

A broad selection of methods have been developed to promote the decarboxylation of alkyl carboxylic acid derivatives through a reductive pathway. In the context of photoredox catalysis, the formation of alkyl radicals via a reductive pathway would enable a net redox neutral catalytic cycle, thereby eliminating the need for a terminal oxidant. At the same time, a reductive alkylation strategy has the
potential to expand upon the scope of alkyllating reagents, allowing access to compounds with significantly higher oxidation potentials.\textsuperscript{24} Pioneering studies on the reductive de-carboxylation generation of alkyl radicals were conducted by Barton and co-workers in the 1960s.\textsuperscript{22} Barton and co-workers utilized N-hydroxypyridine-2-thione in the reductive activation of carboxylic acids for applications such as carbonyl reduction and reductive halogenation.\textsuperscript{25,26} In 1991, Oda, Okada, and co-workers disclosed the use of N-(acyl-oxo)phthalimides (NAP) as redox auxiliaries to enable the decarboxylative generation of alkyl radicals upon single electron reductive fragmentation ($E_{1/2} = -1.26$ to $-1.39$ V vs. SCE), using visible-light-mediated photoredox catalysis.\textsuperscript{27}

Since 2017, NAP esters have been employed in several visible-light-driven Minisci alkylation protocols to promote reductive alkyl radical generation.\textsuperscript{28–32} Notably, Phipps and co-workers have reported an enantioselective variant of the Minisci reaction (Scheme 2) that utilizes a combination of asymmetric Brønsted acid catalysis and photoredox catalysis.\textsuperscript{30} The use of a chiral phosphoric acid catalyst provides both stereo- and regiocontrol in the direct addition of prochiral α-amino alkyl radicals to the 2-position of a variety of pyridine and quinoline-based substrates. This strategy elegantly facilitates the synthesis of enantioenriched α-heterocyclic amines through an efficient late-stage functionalization approach. Jiang and co-workers have also designed an alternative, organocatalytic approach for constructing α-isouquinoline-substituted secondary amines in an enantioselective manner.\textsuperscript{31} Nonetheless, the use of NAP esters for photoredox Minisci alkylations typically necessitates a separate isolation step following ester formation, resulting in an overall two-step procedure. In 2018, Sherwood and co-workers at Bristol-Meyers Squibb developed an operationally simple, one-pot protocol for the \textit{in situ} generation of NAP esters, which obviates the need for isolating the pre-functionalized alkyl partner and facilitates the rapid generation of analogous libraries.\textsuperscript{32}

In 2015, the Stephenson group developed a novel strategy for the visible-light-driven trifluoromethylation of electron-rich (hetero)arenes (Scheme 3), by using pyridine N-oxide to induce reductive radical generation from trifluoroacetic anhydride (TFAA).\textsuperscript{24} With respect to considerations including safety, material availability, and reagent price (TFAA $35 per kg at 1,000 kg), trifluoroacetic acid (TFA) and its derivatives represent highly attractive sources of CF$_3$. Given the prohibitively high oxidation potential of the TFA anion ($F_3CCO_2Na E^{\text{red}}_{1/2 > +2.4}$ V vs. SCE), the authors were able to promote a mild reductive decarboxylation of a TFAA/pyridine N-oxide adduct ($E^{\text{red}}_{1/2 = -1.10}$ V vs. SCE) to access the trifluoroacetyl radical within the electrophilic window of [Ru(bpy)$_3$Cl$_2$]. Notably, following reductive cleavage of the weak N–O bond and CO$_2$ extrusion, the generation of pyridine as a byproduct resolves the need for an exogenous base. Furthermore, TFAA and pyridine N-oxide are used in equal stoichiometry with respect to the substrate, and this reagent combination is sufficiently inexpensive for large-scale operations (pyridine N-oxide $40–$70 per kg at 1,000 kg). The authors have demonstrated the efficacy of this design in the C–H trifluoromethylation of a number of electron-rich heterocyclic and aromatic substrates, including medicinally important MIDA boronates. Through a collaboration with Eli Lilly, the trifluoromethylation of a Boc-protected pyrrole substrate was carried out on a 1.2 kg scale in a continuous flow system, which produced the trifluoromethylated product in 50% yield at production rates of 87.2 mmol per hour (approx. 0.5 kg per day).\textsuperscript{33}

The Stephenson group has further expanded upon this methodology to achieve the radical perfluoroalkylation of a variety of electron-rich (hetero)arene substrates.\textsuperscript{33} In particular, they have designed a radical chlorodifluoromethylation strategy that provides a valuable synthetic entryway to accessing electron-rich difluoromethylated (hetero)arenes.\textsuperscript{34} Moreover, chlorodifluoromethylation, followed by hydrogenolysis, of 6-methoxyquinoline was demonstrated to furnish the 7-difluoromethylated product. This electronically mismatched product is otherwise inaccessible via the nucleophilic difluoromethyl radical, which is selective for the electrophilic 2- and 4-positions of the quinoline core. An orthogonal, fragment coupling approach (Scheme 3) has been developed by the Stephenson group for the addition of electron-rich (fluoro)alkyl radicals onto electron-deficient heteroarenes.\textsuperscript{35} Notably, this fragment coupling
The dual role of the heterocyclic N-oxide minimizes chemical waste production, since the yields. By using pyridine to undergo successful alkylation in modest to good yields from pyridine, quinoline, and azaindole cores were reported pharmaceutically important heterocyclic groups, and a norbornene bicyclic scaffold. A variety of motifs such as tertiary azetidines, fluorinated cyclopropyl groups, and various alkyl radical intermediates from methyl, ethyl, and cyclopropyl radical intermediates from bench-stable and inexpensive alkyl peracetates. The methodology was shown to be amenable to the late-stage alkylation of an array of complex medicinal and agrochemical agents bearing both 6- and 5-membered heterocyclic scaffolds. Most importantly, the transformation proceeded smoothly in the presence of functionalities such as basic amines, alcohols, amides, and esters, without the need for protecting groups. With respect to methyl radical generation, the authors propose a mechanistic pathway involving the activation of tert-butyl hydroperoxide through a reductive proton-coupled electron transfer (PCET) process. The resulting α-peroxy radical subsequently undergoes homolytic O–O bond cleavage to afford acetic acid and a tert-butoxy radical species. The authors hypothesize that methyl radical formation arises from β-scission of the tert-butoxy radical, thereby producing acetone as a byproduct.

In 2014, the MacMillan group reported the first use of alkyl peracetates in the arylation of α-amino acids.37 In 2017, Glorius and co-workers disclosed a Minisci alkylation strategy that enables access to alkyl radical intermediates through the oxidative decarboxylation of carboxylic acids.18 Sodium persulfate is used as an external oxidant to mediate...
alkyl radical formation, as well as facilitate photocatalyst turnover. The authors propose that the generation of desired alkyl radicals occurs through a hydrogen-atom transfer (HAT) event between a reduced sulfate radical anion species and a carboxylic acid precursor, resulting in oxidative decarboxylation. This reaction manifold enables the expedient functionalization of heterocyclic scaffolds, including pyridine, quinoline, and quinazoline cores. A range of primary, secondary, and tertiary alkyl radicals could be accessed from their corresponding alkylcarboxylic acid and amino acid precursors. In 2018, Genovino, Frenette, and co-workers disclosed a separate visible-light-driven Minisci alkylation protocol using hypervalent iodine reagents and organophotocatalysis to facilitate alkyl radical generation from carboxylic acids.29

3 Alkylboronic Acids

Since 2000, aryl/alkylboron reagents have been identified to serve as radical precursors for C–C bond forming processes via oxidative C–B bond cleavage.40–47 In 2016, Chen, Liu, and co-workers disclosed the Minisci C–H alkylation of N-heteroarenes with primary and secondary alkylboronic acids using the photocatalyst Ru(bpy)₃Cl₂ and acetoxybenziodoxole (BI-OAc) as a sacrificial oxidant (Scheme 5).48 Diversely substituted primary and secondary boronic acids (e.g., alkyl bromide,aryl iodide, ester, amide, carboxylic acid, terminal alkene, and benzyl chloride) were well tolerated. Pyridines, pyrimidines, and a purine riboside substrate were all efficiently functionalized. It should be noted that more electron-rich heteroarenes, including benzoazole and benzimidazole, could also be successfully alkylated. The authors propose that the reaction is initiated by a single-electron reduction from the photoexcited Ru(II)* to acetoxybenziodoxole, providing an oxygen-centered radical intermediate. This radical species is then proposed to react with the alkylboronic acid reagent to form the desired alkyl radical via a radical ‘ate’ transition state. DFT calculations support that this is a facile and highly exothermic process at room temperature.

4 Potassium Alkyl- and Alkoxymethyltrifluoroborates

Potassium organotrifluoroborates are considerably more attractive radical precursors than their corresponding boronic acids, given their lack of an empty p-orbital, which increases their overall stability and robustness toward harsh reaction conditions.49 In 2011–2013, Molander and co-workers reported the first use of potassium alkyl- and alkoxymethyltrifluoroborates as radical precursors in the direct C–H alkylation of (hetero)arenes employing manganese(III) acetate as an oxidant in the presence of trifluoroacetic acid.50,51 Under the optimized reaction conditions, the authors were able to functionalize several nitrogen-containing heterocycles all in good to excellent yields.

In 2017, Molander and co-workers reported an impressive advance from their earlier manganese(III) acetate mediated Minisci chemistry by showcasing that alkyltrifluoroborates (many of which are commercially available) can be activated by an inexpensive, sustainable organophotocatalyst (Scheme 6).52 Following reaction optimization, the authors found the utility of a mesitylacridinium photocatalyst (MesAcr), potassium persulfate (as a sacrificial oxidant), and trifluoroacetic acid to be the optimal reagent combination for the C–H functionalization of heteroarenes. Under these reaction conditions, medicinally important cores including quinolines, isooquinolines, indazoles, pyridines, and quinazolinones, could all be functionalized with an impressive scope of primary, secondary, and tertiary alkyltrifluoroborates in good to excellent yields. As expected, electron-rich cores such as benzimidazole, were unreactive toward these Minisci alkylation conditions. These conditions proved tolerant of a diverse array of functional groups including aryl halides, unprotected amines, thiocarbamates, and amidines. Notably, quinine, which features a free alcohol, terminal alkene, and a tertiary amine (which has a known pro-
5 Alkyl Halides

Alkyl halides are among the most widely used materials in organic chemistry. However, their application as radical precursors has been hindered because of the harsh conditions required for radical generation, such as the use of highly toxic trialkyltin hydrides.53 The advent of modern photocatalytic oxidation (Scheme 6).54 This report represented a significant milestone, as it was the first Minisci alkylation that was promoted by photoredox catalysis. The authors’ proposed mechanism involved generation of a Ru(I) species through reductive quenching of the excited state photocatalyst. This Ru(I) species could then reduce malonyl bromides to produce a carbon-centered radical; subsequent trapping of the radical intermediate by electron-rich indoles and pyrroles afforded the functionalized products. Following this initial report, the Stephenson group extended this methodology to access intermolecular C–H alkylations (Scheme 7A),55 as well as the intermolecular construction of quaternary centers.56

![Scheme 6 Organophotocatalytic Minisci alkylation using alkyltrifluoroborate radical precursors](image)

Two reports in 2018 have highlighted the continued expansion of Minisci protocols featuring dehalogenative radical generation. First, a group at Vertex Pharmaceuticals demonstrated the ability to predictably access C3- and C5-functionalized products by performing the Minisci reaction under basic conditions.57 This report featured the reductive dehalogenation of unactivated alkyl iodides and demonstrated the ability to predictably access C3- and C5-functionalized products by performing the Minisci reaction under basic conditions. Additionally, the Wang group reported a separate Minisci alkylation protocol which utilizes a halogen atom abstraction event to promote radical generation.58 This work was enabled through the adaptation of conditions concurrently reported by the Stephenson59 and MacMillan60 groups for visible-light-mediated bromide atom abstraction from alkyl and aryl bromides, facilitated by a tris(trimethylsilyl)silane rad-
the Barriault group proposed a mechanistic pathway in- 
lecular radical additions in 2016. In this more recent study, 
cation of unactivated alkyl bromides to the alkylation of 
described the use of gold photoredox catalysis for the appli- 
gen atom abstraction events. In 2015, the Barriault group 
strate through inner-sphere electron transfer or direct halo- 
non-canonical photocatalysts that engage the halide sub- 
generation has also been demonstrated to be driven by 
ner-sphere electron transfer to furnish the alkyl radical spe- 
cies (Scheme 9).64 The development of these methods has 
provided mild conditions for accessing primary alkyl radic- 
fragments. In 2017, a group from Pfizer reported the use of 
manganese decacarbonyl (Mn2CO10) for the alkylation of 
heteroarenes utilizing simple alkyl iodides as substrates.65 
The authors proposed that the Mn2CO10 catalyst undergoes 
Mn–Mn bond homolysis upon irradiated with blue light. 
The resultant (CO)5Mn• radical species can then abstract an 
iodine atom from the alkyl iodide reagent to enable alkyl 
radical generation.

![Scheme 8](image)

**Scheme 8** Photoredox trifluoromethylation of unactivated (hetero)arenes

In the aforementioned examples, catalysis is promoted 
by engaging the photosensitizer in outer-sphere electron 
transfer events. At the same time, dehalogenative radical 
generation has also been demonstrated to be driven by 
non-canonical photocatalysts that engage the halide sub- 
strate through inner-sphere electron transfer or direct halog- 
atom abstraction events. In 2015, the Barriault group 
described the use of gold photoredox catalysis for the appli- 
cation of unactivated alkyl bromides to the alkylation of N- 
heteroarenes through an intramolecular cyclization 
(Scheme 9).53 This methodology was extended to intermo- 
olecular radical additions in 2016. In this more recent study, 
the Barriault group proposed a mechanistic pathway in-
volving an excited state epxiclex that could undergo an in- 
nner-sphere electron transfer to furnish the alkyl radical spe- 
cies (Scheme 9).64 The development of these methods has 

![Scheme 9](image)

**Scheme 9** Dehalogenative alkylation using gold photoredox catalysis

### 6 Alcohols and Ethers

The late-stage incorporation of oxygenated functional- 
ity into complex molecules can have a significant impact on 
the physical properties (e.g., solubility) of a compound. For 
drug discovery, the optimization of these properties for a 
lead compound is vital to the development of clinical candi- 
dates.66 Thus, the development of methods for the installa- 
tion of simple oxygenated fragments, such as those derived 
from alcohols and ethers, is an important point of develop- 
ment for the Minisci reaction.

The application of alcohols in the visible-light-driven 
Minisci alkylation of heteroarenes was first reported in 
2015 by the MacMillan group (Scheme 10).67 The authors
proposed that the methylation of heteroarenes could be achieved through the initial addition of a carbon-centered hydroxymethyl radical onto a heteroarene substrate. The hydroxymethyl group could then be converted into the desired methyl fragment through a spin-center shift induced by the concomitant loss of water. The subsequent benzylic radical species was proposed to be reduced and protonated to furnish the final methylated product. Importantly, the proposed hydroxymethyl radical intermediate in this report was generated through C–H abstraction of methanol with a thiol co-catalyst. This method provided a general manifold for accessing Minisci reactivity, as a variety of alcohols, pyridines, quinolines, and isoquinolines were amenable to these alkylation conditions. Following this report, in 2016, DiRocco and co-workers utilized a radical relay reaction to promote the visible-light-mediated hydroxymethylation of heteroarenes with methanol. This reaction was proposed to proceed through the generation of a phenyl radical species from the Ir(III)-catalyzed reductive decomposition of benzoyl peroxide. The phenyl radical intermediate then undergoes hydrogen atom abstraction from methanol, thereby generating the active hydroxymethyl radical species, which could be trapped by a variety of heteroarenes. This hydroxymethylation protocol allows for the late-stage functionalization of an array of pharmaphores. While the above two examples utilize iridium photocatalysts to promote reactivity, Minisci reactions featuring alkyl alcohol reagents have also been reported in the absence of photocatalysts. In 2017, the groups of Li and Barriault independently reported the application of near UV irradiation to promote the methylation of heteroarenes.

In 2014, the MacMillan group reported the first application of ethers in conjunction with photoredox catalysis for Minisci reactivity. The developed method utilized persulfate salts as both an oxidant and C–H abstraction reagent. From a mechanistic standpoint, oxidative quenching of the photocatalyst by the persulfate salt generates an equivalent of sulfate radical anion, which readily abstracts a hydrogen atom from the ethereal substrate. This seminal report demonstrates the impact of photoredox catalysis on broadening the scope of Minisci reaction protocols, as both cyclic and acyclic ethers could be innovatively used as radical alkylating reagents under mild conditions. In 2017, the Ryu group described the use of a polyoxometalate photocatalyst tetrabutylammonium decatungstate (TBADT) for a visible-light-driven Minisci alkylation reaction. In its excited state, the TBADT photocatalyst enabled the selective, oxidative generation of radical intermediates through the direct abstraction of electron-rich hydrogen atoms present across ether, alkane, and amide substrates. It is noteworthy that Minisci reactions enabled by the C–H abstraction of saturated molecules are not limited to oxygenated substrates, as this mechanistic paradigm has also been reported with the employment of protected amines and alkanes.

7 Conclusion

As exemplified in this short review, the utility of photoredox catalysis for the Minisci alkylation reaction provides synthetic chemists with a myriad of opportunities to utilize inexpensive, commercially abundant alkylating reagents (e.g., carboxylic acids, alcohols, alkyltrifluoroborates, alkyl halides, etc.) for the direct, C–H alkylation of heteroarenes. Notably, visible-light-driven Minisci alkylation reactions have been demonstrated to proceed under mild reaction conditions and are tolerant of a variety of complex functionalities. In particular, these strategies have been shown to hold significant value for late-stage functionalization efforts in drug discovery. The continued development of photoredox Minisci alkylation reactions that are amenable to a broader scope of complex heterocyclic compounds, while providing improved regioselectivity, is vital to enhancing the synthetic utility and impact of this transformation. Furthermore, demonstrating the scalability of ph-
toredox Minisci alkylation protocols (e.g., using continuous flow systems) may offer valuable opportunities for bridging drug discovery efforts with process development needs.

Funding Information

The authors acknowledge the financial support for this work from the NIH (R01-GM127774) and the University of Michigan. This work is supported by an NSF Graduate Research Fellowship for A.C.S. The authors acknowledge the financial support for this work from the National Institute of General Medical Sciences (R01-GM127774) and National Science Foundation (DGE 1256260). (grant DGE 1256260).