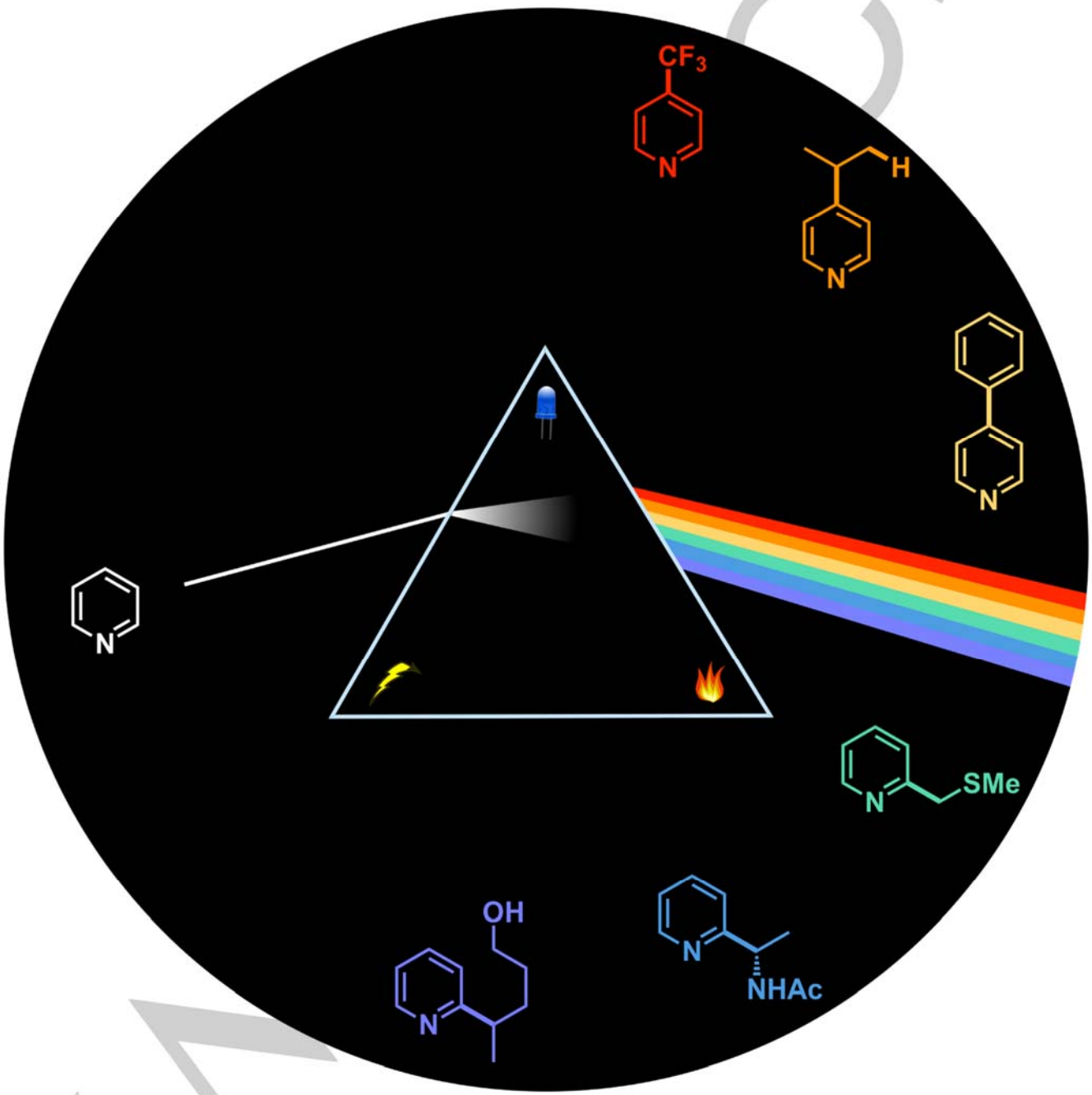
Recent Advances in Minisci-Type Reactions

Rupert S. J. Proctor and Robert J. Phipps*



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Abstract: Reactions that involve the addition of carbon-centered radicals to basic heteroarenes, followed by formal hydrogen atom loss, have become widely known as Minisci-type reactions. First developed into a useful synthetic tool in the late 1960s by Minisci, this reaction type has been in constant use over the last half century by chemists seeking to functionalize heterocycles in a rapid and direct manner, avoiding the need for *de novo* heterocycle synthesis. Whilst the originally developed protocols for radical generation remain in active use today, they have been joined in recent years by a new array of radical generation strategies that allow use of a wider variety of radical precursors that often operate under milder and more benign conditions. The recent surge of interest in new transformations based on free radical reactivity has meant that numerous choices are now available to a synthetic chemist looking to utilize a Minisci-type reaction. Radical-generation methods based on photoredox catalysis and electrochemistry have joined approaches which utilize thermal cleavage or the *in situ* generation of reactive radical precursors. This review will cover the remarkably large body of literature that has appeared on this topic over the last decade in an attempt to provide guidance to the synthetic chemist, as well as a perspective on both the challenges that have been overcome and those that still remain. As well as the logical classification of advances based on the nature of the radical precursor, with which most advances have been concerned, recent advances in control of various selectivity aspects associated with Minisci-type reactions will also be discussed.

1. Introduction

Over the past several decades, there has been intensive effort from synthetic chemists to develop methods able to directly and selectively transform C-H bonds in molecules. The plethora of reactions that have been developed have certainly gone some way towards changing the way a chemist approaches retrosynthetic analysis. Whilst many of the recent developments in this area have employed reactive transition metal complexes to form versatile organometallic intermediates, it is important to remember that the formal functionalization of C-H bonds by the action of reactive free radicals is a parallel approach that has a long and illustrious history in organic chemistry.[1] For example, the abstraction of a hydrogen atom by reactive radicals is one way in which C-H bonds can be directly cleaved in a homolytical manner in aliphatic systems.[2] Whilst this pathway is much more challenging in unsaturated systems, alternative and favorable pathways exist whereby a reactive radical can initially react with a π-system, following which the C-H bond in question may be cleaved either homolytically or heterolytically.[3,4] Fundamental reactivity patterns such as these have been well established for many years and radical chemistry has undergone sustained and continuous study. However, the last decade has witnessed a dramatic increase in attention on the development of new radical processes.[4] This has partly been due to the synthetic community's embracing of photoredox catalysis,[5–10] but wider exploration of radical transformations has advanced outside this rapidly expanding field.[11–13]

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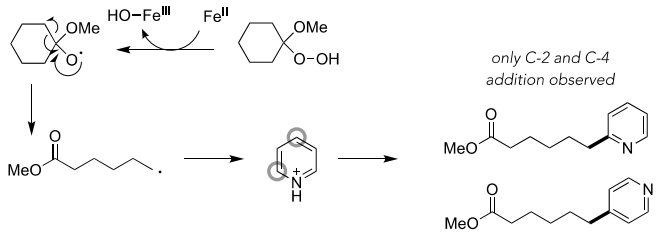
It is in this context that we will herein examine recent progress in a specific application of radical reactivity that has been established now for at least half a century but has seen particular advancement over the last decade. The addition of radicals to electron deficient heteroarenes was first investigated in detail in the 1960s by Lynch and several other groups.[14,15] Lynch's work led to the key observation that mixtures of isomers obtained in phenylation of pyridine could be biased towards C-2 if the reaction was carried out in acetic acid, which they attributed to preferable radical addition to a more reactive pyridinium intermediate.[16] A pioneering report from Minisci and co-workers in 1968 demonstrated that under strongly acidic conditions several alkyl radicals, generated *in situ* via radical rearrangements, added to the 2- and 4- positions of pyridine and quinoline in high yield, with no C-3 product observed (Scheme 1).[17]



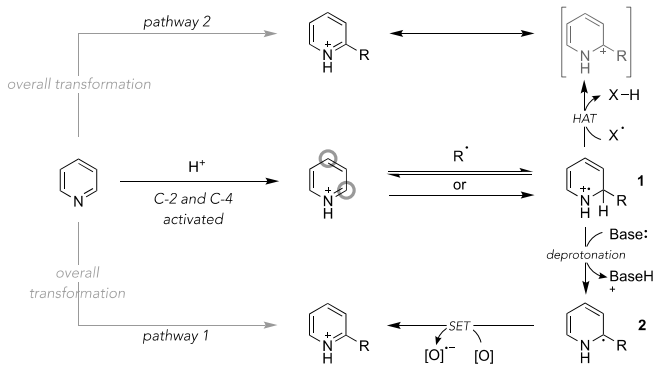
Scheme 1. C_2 and C_4-selective alkylation of protonated pyridine through C-C fragmentation, as reported by Minisci and co-workers in 1968.

A report involving alkyl radical generation through decomposition of structurally diverse peroxides followed from the same authors in 1970.[18] Shortly after, in 1971, they reported what is now the defining protocol for what is sometimes referred to simply as 'the Minisci reaction', wherein an alkyl carboxylic acid undergoes oxidative decarboxylation using a combination of silver catalysis and peroxydisulfate (see section 2.1 for further details).[19] In this paper, they demonstrated the reaction to be effective on both pyridines and quinolines, two of the most commonly occurring basic heteroarenes.[20] Molecules incorporating basic heteroarenes are diverse and continue to pervade many different areas of medicinal chemistry in particular. For example, the heteroaromatic ring count of marketed oral drugs has increased decade upon decade since the 1960s. A study by GlaxoSmithKline found that, come the 2010s, successful drug candidates comprise an average of 0.38 to 0.69 heteroaryl rings per molecule, correspondent to an 80% rise.[21] This prevalence in pharmaceutically-relevant scaffolds makes Minisci-type chemistry highly useful for medicinal chemistry and as such it has been constantly used throughout the years, as emphasized in a 2011 review from Duncton.[20] In particular, the specificity of the reaction for basic heteroarenes contrasts with the challenges that these substrates often present to transition metal catalyzed reactions due to their natural ability to act as ligands and interrupt delicate catalytic cycles. The Duncton review also succinctly emphasized the limitations of Minisci chemistry, which included the propensity for obtaining mixtures of regioisomers, the often-moderate chemical yields and the resulting challenge of purification in light of these two factors. In a drug discovery context, these limitations are often outweighed by the rapid access that the chemistry provides to pharmaceutically desirable scaffolds. Furthermore, in an early-stage drug discovery program, low yields of target compounds separable on an automated purification system are not a serious issue considering the time saved and the low amounts required. But it is likely that these drawbacks of the classic protocols have limited the wider uptake of Minisci-type chemistry within the synthetic community as well as in process chemistry applications.

Minisci and co-workers authored important reviews on the earlier developments of the reaction in 1973,[22] 1989[23] and 1990.[24] Following a review by Harrowven and co-workers in 2004,[25] the topic has been reviewed subsequently by Duncton in 2011, from a medicinal chemistry perspective,[20] and by Opatz and co-workers in 2014, who also discussed radical additions to iminium ions alongside.[26] The reader is directed to the earlier reviews for coverage of advances prior to 2009. In this review, we will detail the significant advances that have been made over the past ten years. In order to concentrate on the most synthetically general, we will only cover intermolecular transformations. Whilst the majority of these advances concern new approaches for radical generation, we will also present advances which address various aspects of reaction selectivity, particularly the challenge of regioselectivity. For the purposes of this review, we will use the phrase 'Minisci-type reaction' to refer broadly to processes that involve *the addition of a carbon-centered radical to a basic heteroarene, followed by formal hydrogen atom loss, in an overall substitution reaction.*

In general terms, the overall mechanism followed in most Minisci-type reactions involves an initial step wherein a typically nucleophilic carbon-centered radical adds to a basic heteroarene (Scheme 2). Acid is commonly used as a stoichiometric additive as *protonation* of the basic heteroarene lowers the energy of its LUMO and facilitates this radical addition. The resulting LUMO coefficients at C-2 and C-4 of substrates such as pyridine and quinoline are often very similar, which accounts of the mixtures of regioisomers typically obtained if one position is not blocked. The 2014 review by Opatz and co-workers contains an excellent discussion of the theoretical background to Minisci-type reactions in terms of frontier orbital theory.[26] Depending on the nature of the substrate and radical, the *radical addition* may or may not be reversible.[27] In the resulting radical cation **1**, the *α*-proton is rendered acidic and one possible pathway (*pathway 1)* involves this proton being lost in a *deprotonation* step, resulting in neutral radical **2**.[27] An alternative pathway open to unprotonated heteroarenes reverses the order of these steps, with aromaticity-driven oxidation of the *N*-centered radical adduct proposed to precede deprotonation. Oxidation of this radical results in rearomatization of the heteroarene, possessing a newly formed C-C bond in place of a former C-H bond. Another possibility (*pathway 2)* is that the hydrogen atom transfer (*HAT*) could occur from the radical cation intermediate. In this scenario the pyridine would be rearomatized in a single HAT step. The specific pathway followed in any given case could depend on a number of factors including the substrate, oxidant and reaction conditions. Whilst these basic mechanistic pathways lie at the heart of most Minisci-type reactions, the overall mechanism for any individual

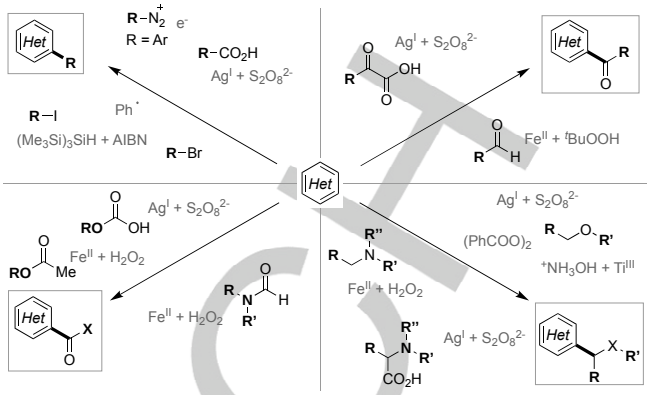
transformation is typically rather more complicated due to the need for the mechanism of radical generation to be integrated with the underlying Minisci-type addition mechanism.



Scheme 2. General overview of common mechanistic pathways in Minisci-type reactions.

The aforementioned issue of regioselectivity arguably remains of the of outstanding challenges in Minisci chemistry. Certain substrates, such as pyridines and quinolines are inherently C2/C4 selective but controlling selectivity between these two most activated positions is often very challenging; mixtures of isomers often result as well as byproducts arising from multiple additions. To complicate matters, ring substituents can in some cases override natural regioselectivity.[28] Over the years, studies by Minisci and others have identified a number of factors that can influence the balance between C2 and C4 selectivity in radical additions to pyridine in particular, which include the nature of the radical, solvent polarity and the Brønsted acid used for activation.[27] A recent detailed analysis of regioselectivity in Minisci-type chemistry on a range of different heteroarenes was carried out by O'Hara, Blackmond and Baran (discussed in section 5) highlights the continuing need for methods able to exercise control over this aspect.[29] To this end, we have tried to emphasize in the text of this review examples in which high regioselectivity is reported for substrates which more often give mixtures, with the caveat that rationalization of the origin of selectivity is often challenging. Section 8 details a recent method from our own laboratories in which catalyst control has been successfully applied to control both regioselectivity and enantioselectivity in the addition of certain radicals to quinolines.

In scheme 3 we summarize a number of important methods for radical generation that have been developed by Minisci and others since the late 1960s, in order for the reader to place the later developments reviewed herein in proper context (Scheme 3).



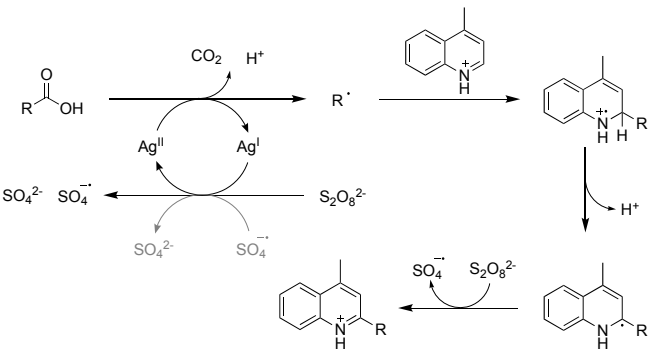
Scheme 3. A non-exhaustive selection of established methods for radical generation in Minisci-type reactions.

The sections of the review will be based on advances in the use of each type of radical precursor and a final section will concern advances in control of stereochemistry in Minisci-type reactions. At the beginning of each section, a summary of the key relevant classical methods for each approach to radical generation method will be given with the accompanying primary references.

2. Advances in Radical Generation *via* Decarboxylation

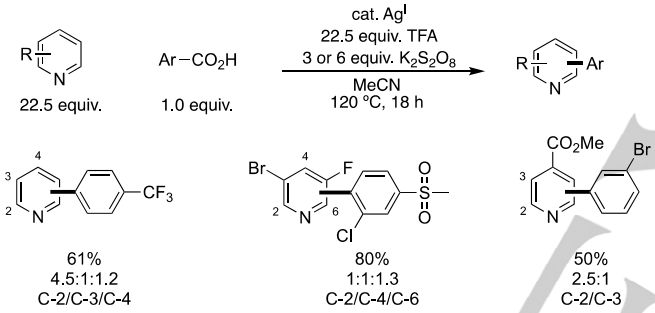
2.1 Direct decarboxylation of carboxylic acids

The archetypical Minisci-type alkylation procedure originally reported by Minisci and co-workers involved radical generation through decarboxylation of alkylcarboxylic acids,[19] the proposed mechanism for which is shown in Scheme 4.[30] Using a simple system of acid, persulfate as oxidant and a silver catalyst, this strategy is very attractive due to the wide availability and pervasiveness of the carboxylate moiety in organic compounds. Given that this original procedure had limitations in reaction scope,[31] the fact that low yields were often observed from primary alkyl radical fragments and that no aryl radical formation was possible, the motivation for further refinement of this powerful approach for radical generation is clear.



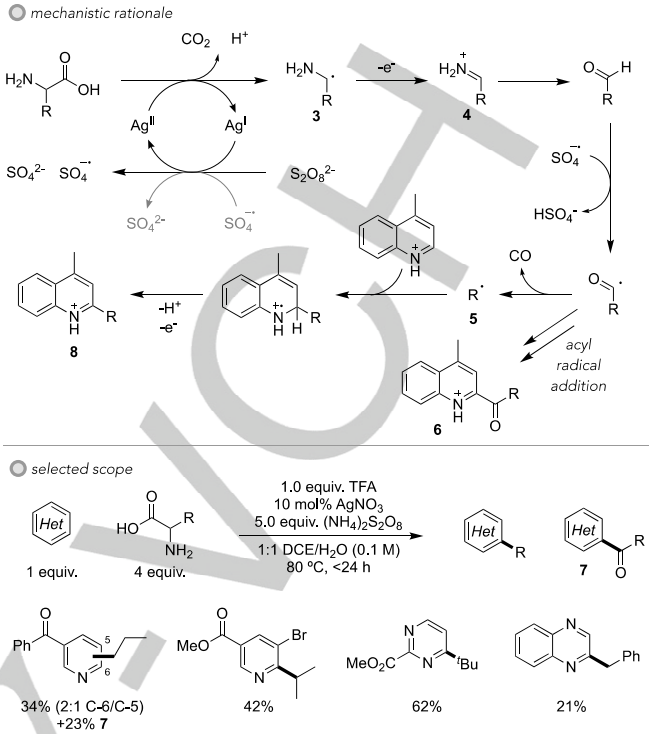
Scheme 4. Proposed mechanism of the classical Minisci protocol for generation of alkyl radicals from alkyl carboxylic acids using silver catalysis.

A number of advances in the last decade have been made involving radical generation from carboxylic acids and derivatives thereof. Su and co-workers in early 2015 showed that aryl carboxylic acids are amenable to silver catalysis for the arylation of pyridines, a reaction that had not been achieved thus far under the original Minisci conditions (Scheme 5).[32] Their investigation built on earlier findings related to silver-catalyzed decarboxylative cross-coupling reactions. High temperatures were required to induce the carboxyl radical to undergo decarboxylation, and a large excess of heteroarene and trifluoroacetic acid (TFA) was necessary to promote radical addition. Although low regioselectivity is observed in most cases, there is a slight preference for the 2-position on simple pyridine. They show that the procedure is effective on electron-deficient arenes as well as pyridines and notably an *ortho*-substituent on the aryl carboxylic acid is not mandatory to allow decarboxylation, as it sometimes is in other related methods.



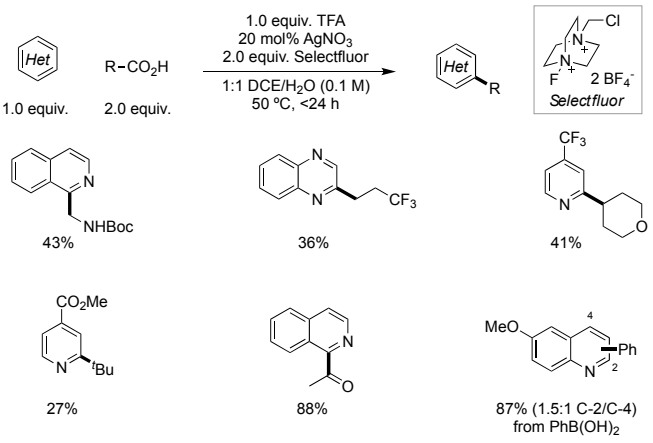
Scheme 5. Arylation of pyridines through silver catalysis and persulfate oxidant.

In 2016, Mai and Baxter showed that unprotected amino acids are effective pro-radicals for a Minisci-type reaction under the standard silver-persulfate system (Scheme 6).[33] Their approach exploits Strecker degradation,[34] through the oxidation of α-aminoalkyl radical **3** and hydrolysis of the generated iminium ion **4**. This generates aldehydes that can undergo HAT and decarbonylation with extrusion of CO to furnish the desired alkyl radical fragment **5**. The radical scope is relatively narrow, with mostly simple primary, secondary and tertiary alkyl fragments coupling to varying degrees of success. Because of their relatively low stability compared to acyl radicals, primary, and in some cases secondary, radicals undergo incomplete decarbonylation, giving the ketone byproduct **6** (**7**) in addition to the desired alkylation product **8**. The heteroarene scope encompasses a variety of 6-membered rings, with pyridine substrates appearing to require an electron-withdrawing substituent for successful reaction.



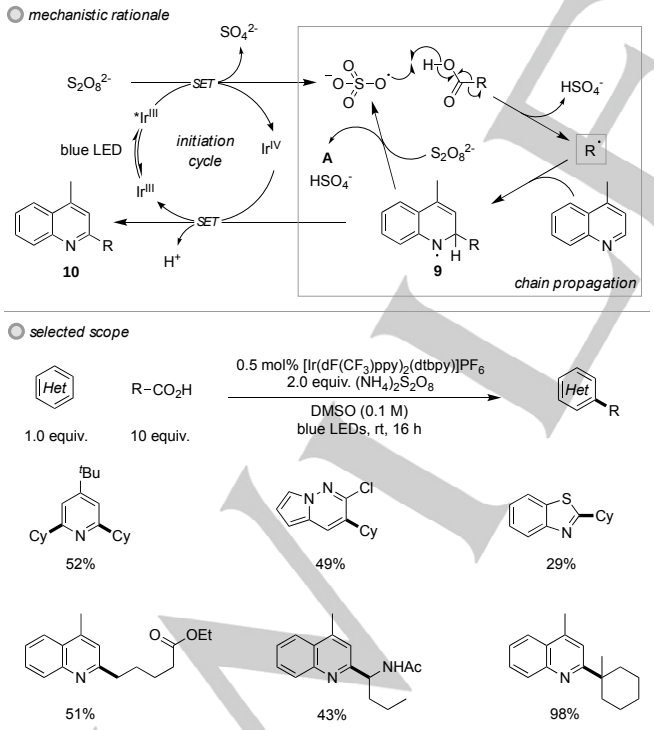
Scheme 6. Unprotected amino acids as precursors to alkyl radicals following decarboxylation, oxidation and hydrolysis.

A year later, the same group reported another silver-catalyzed Minisci-type reaction of carboxylic acid-derived alkyl radicals using Selectfluor as the oxidant (Scheme 7).[35] As in the group's previous amino acid generation method, it works on a variety of 6-membered heteroarenes. The alkyl fragments that add successfully cover a range of stabilities and functionality, allowing acylation and aminoalkylation. An important aspect of this advance is that it has generality that can extend to Baran's "borono-Minisci"[36] (see Section 4), allowing the smooth arylation of a number of heteroarenes using aryl boronic acids (see example, scheme 7).



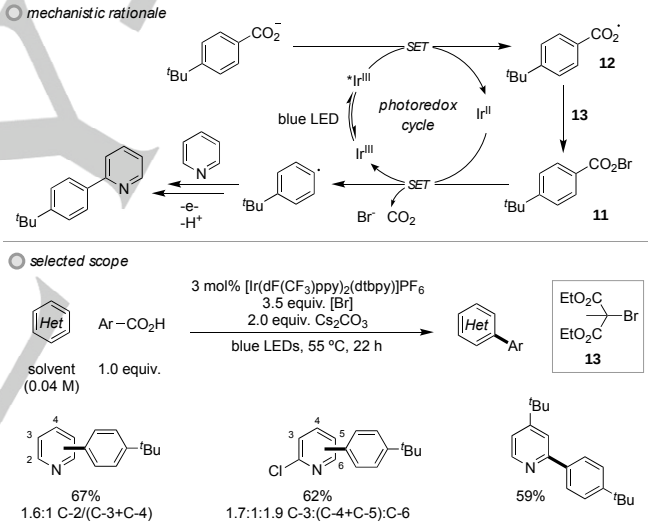
Scheme 7. Decarboxylative Minisci-type reaction using Selectfluor as oxidant. Additional example from $PhB(OH)_2$ also shown.

Also in 2017, Glorius and co-workers communicated a visible-light mediated decarboxylative Minisci-type alkylation reaction using photoredox catalysis (Scheme 8).[37] Although many photoredox-catalyzed decarboxylations propose the decarboxylation to proceed *via* single electron oxidation of the carboxylate by the photocatalyst, Glorius proposes that this mechanism proceeds via a radical chain/HAT process (see *mechanistic rationale*), based on quantum yield measurements. The reaction is initiated through photocatalyst excitation and reduction of a persulfate anion, the resultant radical anion of which abstracts a hydrogen atom from the carboxylic acid group. Following decarboxylation and addition of the resultant radical to the neutral heteroarene, persulfate oxidizes radical adduct **9**, forming the final product **10** and generating another sulfate radical anion for propagation. The scope is broad with respect to both coupling partners and a range of heteroarenes of both 5- and 6-membered structure can be effectively alkylated, the only disadvantage being that 10 equivalents of carboxylic acid were required. Primary, secondary and tertiary radical fragments are successfully employed, along with those derived from protected amino acids. Yang, Xia and co-workers later published a related protocol for incorporation of masked formyl groups into heteroarenes.[38] Notably in this latter case no photoredox catalyst was required, only irradiation with visible light.



Scheme 8. Decarboxylative Minisci-type reaction using photoredox catalysis.

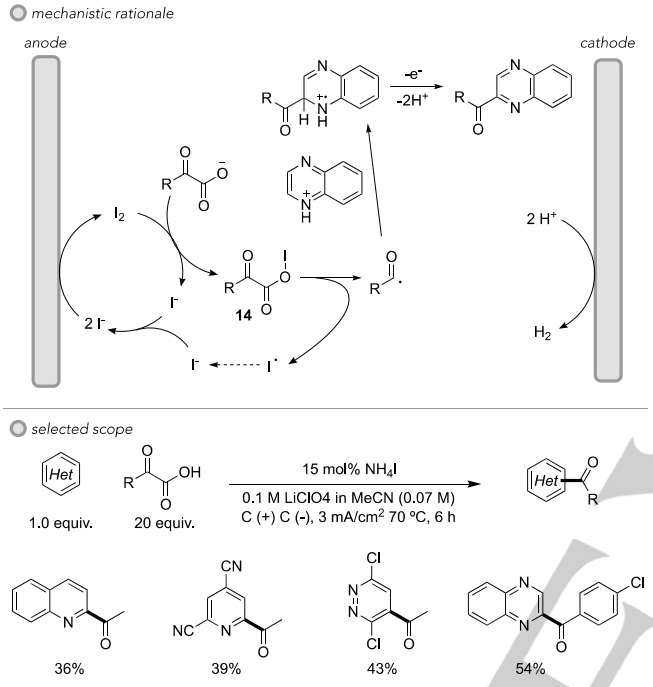
The same year, Glorius reported a method for Minisci-type reaction of aryl radicals from arylcarboxylic acids (Scheme 9).[39] Direct decarboxylation of arylcarboxyl radicals is challenging at low temperatures and these reactive intermediates are prone to alternative pathways such as HAT and arene addition. As such, they sought an alternative strategy and hypothesized that if they could transform the carboxylic acid group into a benzoyl hypobromite **11**, this may undergo single electron reduction with a suitable photocatalyst, facilitating decarboxylation. The proposed mechanism involves initial oxidation of the arylcarboxylate by the excited photocatalyst, with the resultant radical **12** being trapped by the brominating agent **13**. The hypobromite formed can then undergo photocatalytic reduction and supposedly more facile decarboxylation to furnish an aryl radical that can undergo Minisci-type reaction amongst other transformations. The focus of the scope was addition to unactivated arenes but featured three examples of addition to pyridines, included in Scheme 8, which resulted in mixtures of regioisomers in substrates with mulitple activated positions available.



Scheme 9. Decarboxylative addition of aryl radicals proceeding via the corresponding benzoyl hypobromites.

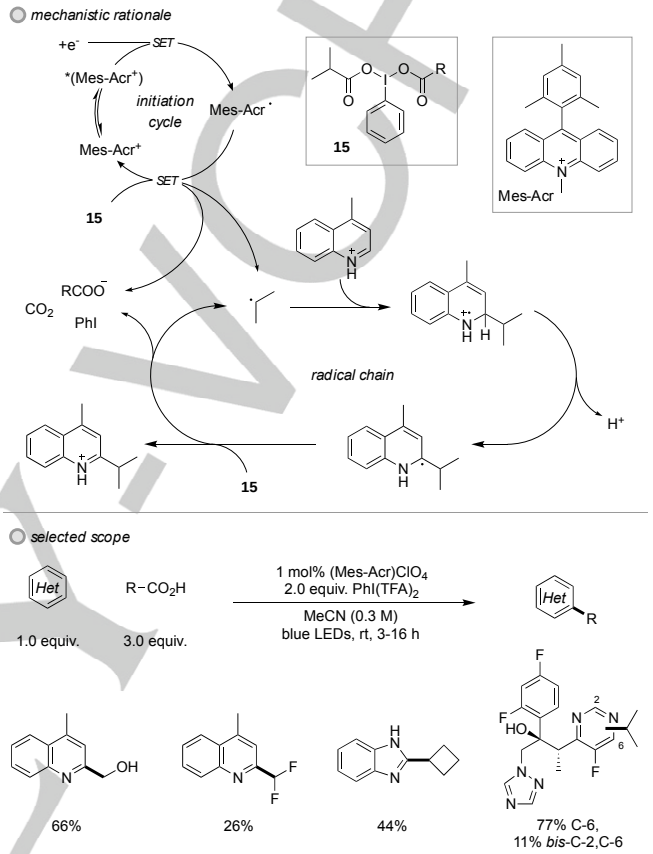
As Baran and Blackmond and co-workers had demonstrated previously using sulfinate salts (see section 5),[40] it is not only using thermal and photochemical methods that Minisci-type reactions can be mediated. In 2017, Zeng and co-workers adapted electrochemical techniques to perform Minisci-type reactions with α-keto acids, showing that it can be an effective technique for the acylation of heteroarenes which avoids the use of transition metals and strong oxidants (Scheme 10).[41] In an approach with similarities to that used by Glorius, the authors propose that radical generation occurs through homolysis of an acyl hypoiodite **14**,[42] formed from a carboxylate anion and electrochemically generated molecular iodine. Several different 6-membered heteroarenes can be effectively acylated in moderate

yield and benzoyl radicals can be employed in addition. Interestingly, for one particular substrate they also observed differences in regioselectivity with their protocol when compared with classical Minisci conditions, employing silver salts and strong oxidants. Wencel-Delord and co-workers would later show that a similar transformation is possible through direct decarboxylation promoted by visible light. They provide evidence that this could proceed via electron donor-acceptor interactions and provide three possible mechanistic scenarios in which this could feasibly occur.[43]



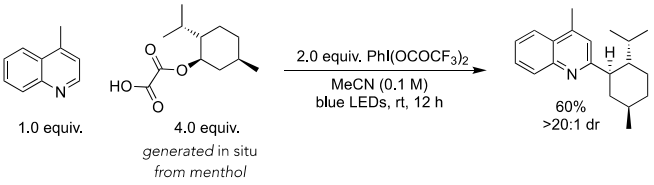
Scheme 10. Minisci reaction via electrochemical decarboxylation of α-keto acids

In 2018, Genovino, Frenette and co-workers demonstrated that a similar, reductive decarboxylation of *in situ*-generated phenyliodine (III) diacetate (PIDA) analogues could be an effective method for generating radical nucleophiles for Minisci-type reactions (Scheme 11).[44] The technique employs the Fukuzumi organic photoredox catalyst Mes-Acr (9-mesityl-10-methyl acridinium),[45] to initiate what is proposed to be a chain reaction (see *mechanistic rationale*). The excited Mes-Acr catalyst accepts an electron from an unidentified donor and is then able to reduce hypervalent iodine compound **15,** generated through ligand exchange between the carboxylic acid and the trifluoroacetyl group on PIFA, to initiate the reaction. After fragmentation and decarboxylation of the carboxyl radical, radical addition to the heteroarene occurs. Subsequent deprotonation and rearomatizing oxidation ensues, reducing the phenyliodine (III) dicarboxylate to propagate the cycle. With good functional group tolerance and a wide variety of primary, secondary and tertiary alkyl radical fragments undergoing successful Minisci-type reaction to a range of 5- and 6-membered heteroarenes, this reaction is a powerful method for heteroarene diversification. It benefits strongly from the ability to use an unmodified carboxylic acid as a reagent. Landais and co-workers recently also showed that iodine (III) reagents can allow carbamoylation of heteroarenes using oxamic acids under photoredox conditions.[46]



Scheme 11. Minisci-type alkylation from carboxylic acids using hypervalent iodine reagents together with a Mes-Acr photocatalyst

Several months later, Yang, Zhang and co-workers showed that a similar method was effective in the absence of photocatalyst, through a proposed visible light-promoted homolysis of a phenyliodine (III) dicarboxylate,[47] in a similar manner to a prior approach by Antonchick (see section 3.1). [48,49] In addition to the carboxylic acid precursors, they make a nice advance in terms of generation method by utilizing oxalates, which are generated *in situ* by treatment of the alcohol by oxalyl chloride. An example of the latter transformation is shown in Scheme 12.



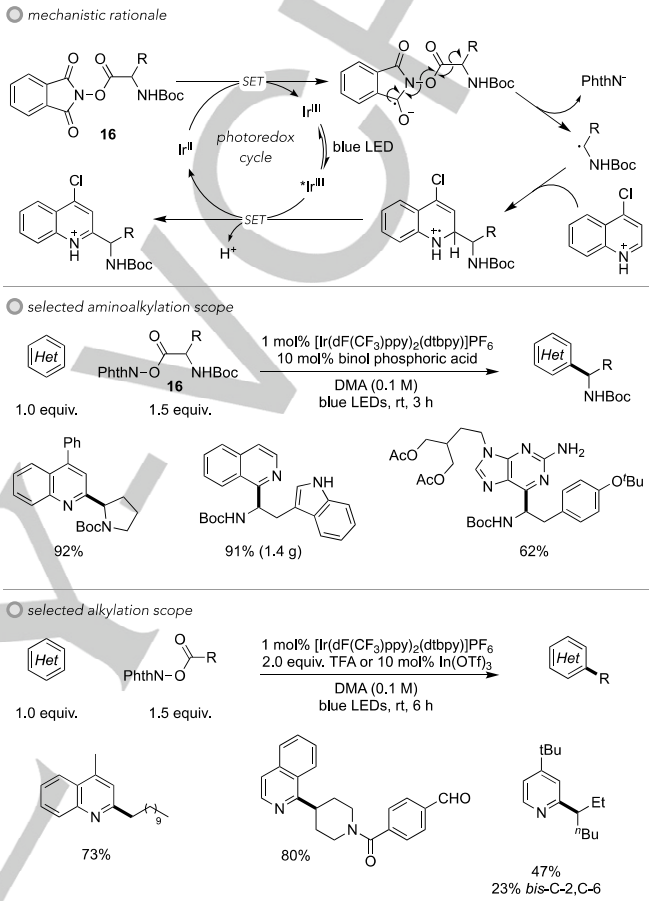
Scheme 12. Decarboxylative alkylation using in situ formed oxalates as radical precursor.

Most recently, Lee and co-workers published a protocol in which only ammonium persulfate is used, without need for any irradiation or a metal catalyst.[50] A range of primary, secondary and tertiary carboxylic acid-derived radicals can be added to an impressive variety of basic heteroarenes, as well as 1,4-quinones. Whilst advantageous to use carboxylic acids as radical precursors, large excesses (typically 10 equiv.) were used, which could be a limitation in some circumstances. The authors point out that use of DMSO as a solvent appears crucial to allow the reaction without any added catalyst, such as the silver catalyst that would be used in the classical Minisci protocol. They propose that the DMSO plays a key role in allowing the persulfate decomposition under mild conditions (40 °C). Jouffroy and Kong soon after developed a persulfate-promoted method that uses only one equivalent of oxamic acid under photocatalytic conditions.[51]

2.2 Decarboxylation of activated carboxylic acids

Direct decarboxylation of carboxylate salts represents a direct and economical method for the direct formation of alkyl radicals from readily available carboxylic acids, particularly in redox-neutral couplings to electrophiles.[52] However, in a Minisci-type reaction this approach necessitates an external oxidant to be employed due to the formally oxidative nature of the transformation. *N*-acyloxypthalimides are both surrogates of carboxylic acids as well as being oxidants, hence are 'redox active' and often referred to as 'Redox Active Esters' (RAEs). Originally developed for the purpose of alkyl radical generation by Okada, Okamoto and Oda,[53] these compounds have become popular tools for synthetic organic chemists in recent years, in part due to numerous interesting applications by the Baran group,[54] following earlier influential reports by Overman.[55–57]

The first uses of *N*-acyloxyphthalimides for performing Minisci-type reactions were disclosed in two reports from Cheng, Shang and Fu in 2017 (Scheme 13).[58,59] In the first, they used a photoredox catalysis approach for the aminoalkylation of heteroarenes using RAEs derived from *N*-protected amino acids. In their proposed mechanism, fragmentation of the RAE **16** is triggered by SET from a reduced Ir^{II} photocatalyst. After decarboxylation, the resultant carbon-centered radical undergoes Minisci-type addition to the heteroarene. The photoexcited $*Ir^{III}$ is proposed to act as oxidant in the final step of the Minisci mechanism. The *aminoalkylation* scope is very broad - a wide variety of amino acid–derived RAEs were compatible for addition to a broad range of basic heteroarenes. They were also able to demonstrate that RAEs derived from dipeptides and tripeptides were also highly effective as radical precursors for addition to isoquinolines. In the second report from the same authors, they demonstrated a similar scope but for alkyl carboxylic acid-derived RAEs (see Scheme 13, *alkylation scope*). Primary, secondary and tertiary radicals were smoothly added, tolerating olefins, alkyl bromides, heteroatoms and aldehydes. A notable aspect of both reactions is that they can be performed using sub-stoichiometric amounts of either Brønsted acid (optimal for the aminoalkylation) or Lewis acid (optimal for the alkylation). The authors note that catalytic use of a relatively weak acid allows the survival of acid-sensitive amine protecting groups, such as *tert*-butyloxycarbonyl (Boc).[60]



Scheme 13. Radical generation from the photocatalyzed reduction of *N*-acyloxyphthalimides for both aminoalkylation and alkylation of heteroarenes

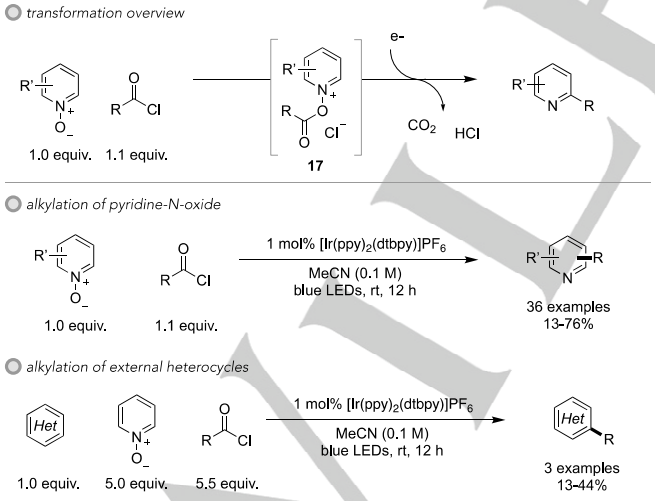
In 2018, Sherwood and co-workers also reported Minisci-type addition using RAE-derived alkyl radicals.[61] Their report has a very extensive heteroarene scope, incorporating a number of examples of late-stage functionalization. Their procedure also has the practical advantage of using redox-active esters that are generated *in situ* using DIC and DMAP. They also use the organic dye 4CzIPN as photoredox catalyst, for a transition metal-free approach which avoids the use of the expensive iridium photocatalyst.[62,63]

Very shortly after, Opatz and co-workers reported a Minisci protocol using RAEs with the difference here they are able to use commercially available $Ru(bpy)_3Cl_2$, which is somewhat cheaper than the typical iridium photocatalysts.[64] Interestingly, a light-dark cycle experiment suggest that a radical chain process is in operation in their procedure.

Alkyl carboxylic acid-derived peresters and diacylperoxides can also be utillized as redox-activate radical precursors. Bao and

co-workers recently exploited these reagents for the alkylation of several classes of azoles including as benzothiazoles and benzoxazoles, wherein the alkyl group from the perester or diacylperoxide is transferred.[65]

In an effort to make redox-neutral Minisci-type additions more atom-economical, Stephenson and co-workers have developed a procedure that they describe as a 'fragment-coupling approach' (Scheme 14).[66] Here, an acyl chloride reacts with a pyridine-*N*-oxide to generate *N*-acyloxypyridinium salt **17** *in situ*. These complexes are capable of undergoing reductive decarboxylation after single electron reduction from a photoredox catalyst, in analogy to *N*-acyloxyphthalimides, to generate alkyl radical fragments. These can then undergo Minisci-type reaction to another molecule of the functionalized pyridine-*N*-oxide. This is an ingenious advance, since most redox auxiliaries go to waste as byproducts, whereas here they are an integral coupling partner. In a related trifluoromethylation reaction they had previously developed, Stephenson and co-workers explore deeper into the mechanistic detail.[67] The *N*-acyloxypyridinium salt receives an electron from a reducing Ir species and undergoes decarboxylative radical fragmentation with the resultant radical undergoing Minisci-type reaction to either protonated pyridine, after HCl has started to be produced, or pyridine *N*-oxide. Numerous substituted pyridines and quinolines can be functionalized through this method, although the transformation is limited to less electron-deficient heteroarenes, due to the lower nucleophilicity of the corresponding *N*-oxides. However, this challenge can be addressed by relegating the role of the *N*-oxypyridine to solely that of redox auxiliary (see alkylation of pyridine *N*-oxide). The *N*-acyloxypyridinium salts are formed in a five-fold excess compared to the more electron-deficient heteroarene being functionalized, allowing modest to good yields of the desired Minisci product (lower scheme).



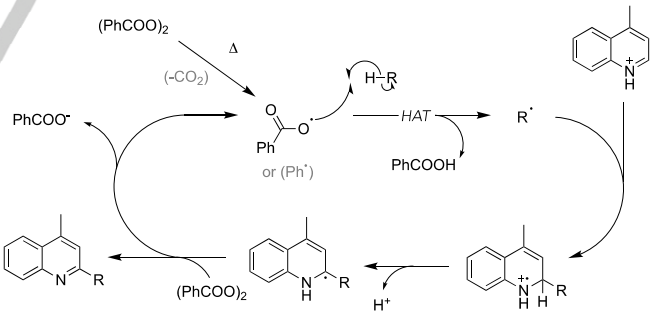
Scheme 14. Net redox-neutral method for Minisci reactions, starting from heterocyclic *N*-oxides.

3. Advances in Radical Generation *via* Hydrogen Atom Abstraction

In general, direct transformations of C-H bonds are highly desirable, particularly with regard to atom economy and synthesis of starting materials. It follows therefore, that if two C-H bonds could be formally converted a new C-C bond, this would be a highly desirable process. Due to their nature, such transformations have been sometimes referred to as "dehydrogenative cross-couplings" or "cross-dehydrogenative couplings" (CDCs) and have become a research goal across a variety of sub-fields in organic chemistry in recent years.[68] Minisci-type reactions provide a valuable opportunity to perform this type of coupling if the radical nucleophile can be generated from abstraction of a hydrogen atom (HAT, hydrogen atom transfer). In general, HAT most commonly occurs from sp^3 hybridized carbons (heteroarene alkylation) or from acyl sp^2 hybridized carbons (heteroarene acylation) and advances in these areas will be covered in the following two subsections.

3.1 Hydrogen Atom Abstraction at sp^3 Hybridized Carbon

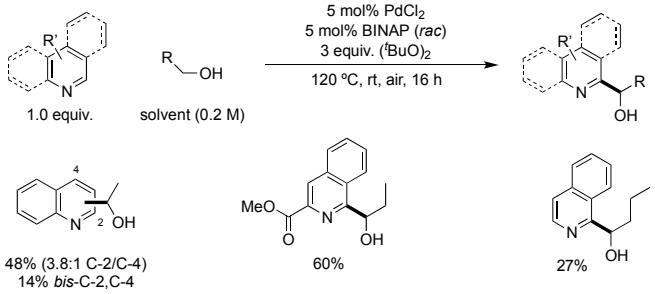
In 1970, Minisci and co-workers first demonstrated that a range of ethers and alcohols could be coupled with various basic heteroarenes either by heating with peroxydisulfate or under ambient conditions with an iron/peroxide combination.[18] It was thought that the radical species generated by cleavage of the peroxide acted as a means of abstracting hydrogen atoms from the α-positions of the ethers, and alcohols, the resultant stabilized radicals were then able to undergo a Minisci-type reaction (Scheme 15). This approach, subsequently further developed by Minisci,[69] has spawned many developments and improvements, particularly over the last five years. The achievement of general and tolerant dehydrogenative cross-couplings between pro-radicals and heteroarenes remains an attractive goal for those developing Minisci-type reactions.



Scheme 15. Proposed mechanism of the coupling of solvents possessing abstractable hydrogen atoms (THF, Methanol) with quinolines.

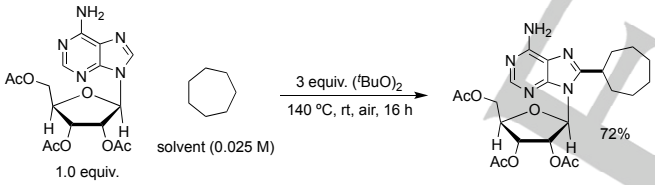
The first advance in recent years was reported by Li and co-workers who in 2011 developed an addition of alcohols to quinolines and related heterocycles that used dicumylperoxide (DCP) as oxidant with a palladium catalyst and no added Brønsted acid (Scheme 16).[70] Although it is advantageous that no Brønsted acid was required, it did require temperatures of 120 °C, presumably to enable thermal peroxide cleavage. Interestingly, the optimal yield was obtained if catalytic BINAP was used as

ligand. Replacing $PdCl_2$ with catalytic Lewis acids such as $Sc(OTf)_3$ and $FeCl_3$ was detrimental. Replacing the 5 mol% palladium catalyst with 10 mol% HCl gave only a much-reduced yield, suggesting it is not simply HCl release from the metal catalyst that is responsible.



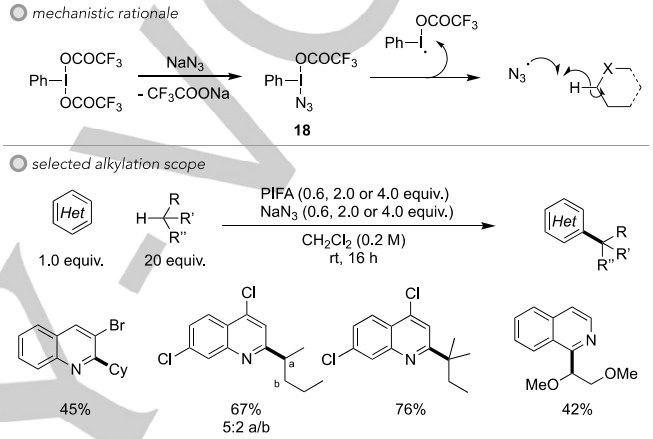
Scheme 16. Thermally induced Minisci addition of alcohols to heteroarenes employing palladium catalysis rather than a Brønsted acid additive.

The following year, Qu and Guo reported a similar procedure that used di-*tert*-butyl peroxide to abstract unactivated C-H bonds from cycloalkanes, with subsequent Minisci-type reactivity of the resultant radical (Scheme 17).[71] The cleavage of the peroxide was thermally initiated at high temperature. Their scope placed a particular emphasis on cycloalkylation of purine bases and complementary C-N coupling of anilines was achievable by including a copper catalyst.



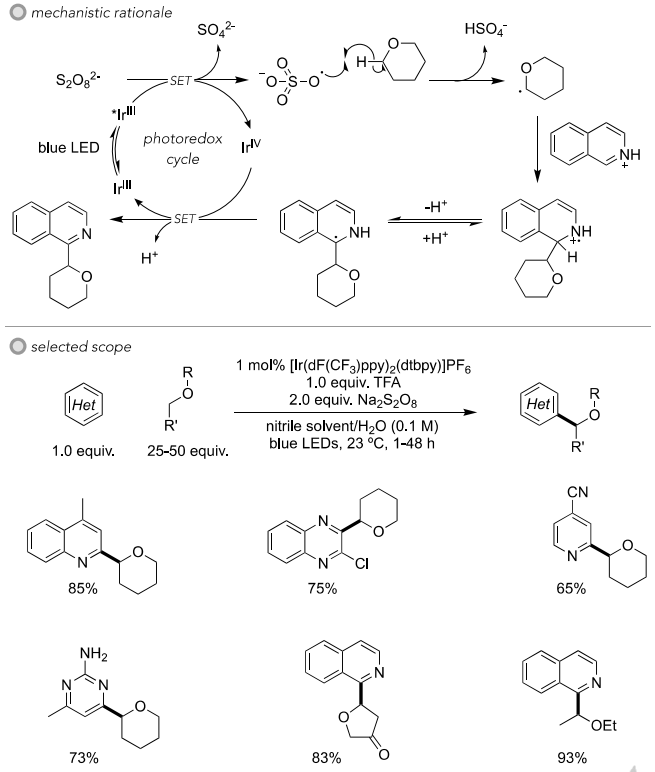
Scheme 17. Thermally induced Minisci addition of cycloheptane to a purine derivative by C-H abstraction with dialkyl peroxide-derived radicals.

In 2013, Burgmann and Antonchick reported Minisci-type alkylation using a combination of sodium azide and the hypervalent iodine reagent [bis(trifluoroacetoxy)iodo]benzene (PIFA) (Scheme 18).[48] They proposed that PIFA undergoes ligand exchange with azide to produce intermediate **18**, which is liable to homolytic cleavage of the I-N bond to form an azide radical. It is this azide radical that is thought to perform hydrogen atom abstraction from an unactivated alkane C-H bond or α-C-H of an ether, generating a carbon-centered radical that undergoes a Minisci-type reaction. The ability to functionalize unactivated aliphatic C-H bonds is an important challenge, and Antonchick's procedure shows a powerful and general method for the coupling of such precursors with heteroarenes.[72] It is able to be carried out at room temperature, which is in stark contrast to the prior procedures that require thermal peroxide cleavage. The procedure has a good heteroarene scope but is a little more limited in the radical scope. Secondary and tertiary radicals are successful coupling components and a number of ethers are shown to be compatible with the reaction conditions. The Antonchick group later reported that the same protocol could be used for HAT from aldehydes in a Minisci-type acylation of heteroarenes (see section 5.2). Interestingly, the alkylation and acylation procedures give complementary regioselectivity in certain cases. For example, an acetyl radical is incorporated into the 4-position of 3-bromoquinoline, whereas a cyclohexyl group is incorporated into the 2-position. The source of this divergence is not clear: it could be potentially related to the differing radical nucleophilicity or differing solvent polarity.



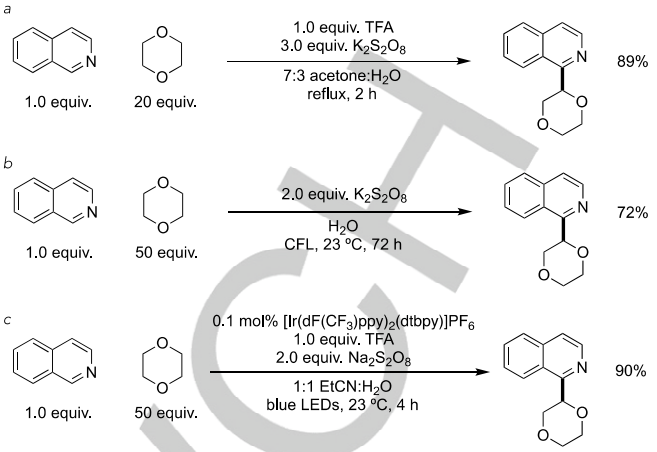
Scheme 18. Alkylation of heteroarenes using radicals generated through hydrogen atom abstraction from alkanes and ethers, with HAT performed by azide radicals.

In 2015, Jin and MacMillan reported that persulfate anions could be reductively decomposed by single electron transfer from a photoredox catalyst (Scheme 19, see *mechanistic rationale*).[73] They utilized the resultant sulfate radical anion to perform hydrogen atom abstraction from ethers in analogy to Minisci's original method.[69] The heterocycle scope is extensive, going beyond simple quinolines to more varied 6-membered heteroarenes. A range of ethers can be successfully employed as radical precursors in the reaction (see *selected scope*). From a practical point of view, the photoredox conditions obviate the need to heat the reaction, enabling room temperature reactivity although a disadvantage is the large excesses of the ether that are used. This is notable as one of the early examples of the application of photoredox catalysis to radical generation in Minisci chemistry.



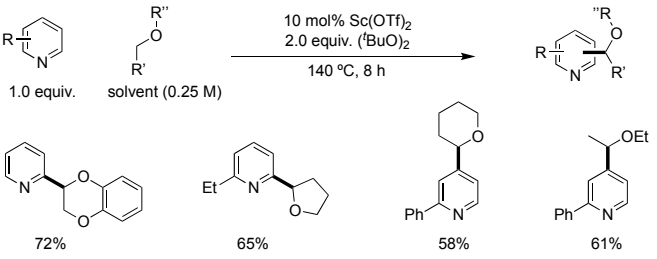
Scheme 19. Addition of various ethers to heteroarenes using photoredox catalysis with persulfate oxidants

Later in 2015, persulfate was used as oxidant in two related Minisci protocols. Barriault and co-workers forego the photoredox catalyst and instead reflux the reaction in order to cleave the peroxide (Scheme 20a).[74] Shah and co-workers use a compact fluorescent lamp (CFL) in the absence of a photocatalyst (Scheme 20b) to obtain similar products to the above-mentioned MacMillan report (Scheme 20c).[75] The authors propose that this proceeds via an electron-donor-acceptor (EDA) complex to account for the lack of requirement for a photocatalyst. Whilst this is surprising, the optimization table in the MacMillan report did show 4% yield without photocatalyst so it is not inconceivable that the change of the solvent in the Shah report could render the EDA proposal viable. A related addition of ethers using thermal cleavage of benzoyl peroxide was also reported by Togo and coworkers.[76]



Scheme 20. Various protocols for addition of ethers to heteroarenes utilising persulfates as oxidants.

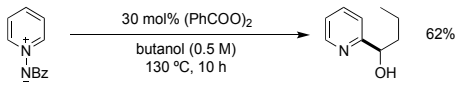
A further coupling of ethers with heteroarenes was reported in 2015 by the group of Huang.[77] Thermal decomposition of a dialkylperoxide allowed HAT from ethers. Optimized conditions employ 10 mol% $Sc(OTf)_2$, without which no product was obtained, making it a rare example of a Minisci-type reaction promoted by a sub-stoichiometric amount of acid and also where the acid is of a Lewis type, rather than Brønsted (Scheme 21). A practical disadvantage is the use of the ether coupling partner as solvent. As reported, the transformation exhibits remarkably high regioselectivity on pyridines: when the substituent in the 2-position is alkyl or a hydrogen, the reaction is 6-selective. However, with 2-phenylpyridine is the substrate, 4-selectivity is observed. The authors state that they are not able to isolate either alternative regioisomers or double addition product in their reactions.



Scheme 21. Coupling of ethers with heteroarenes using catalytic scandium triflate and thermal peroxide cleavage.

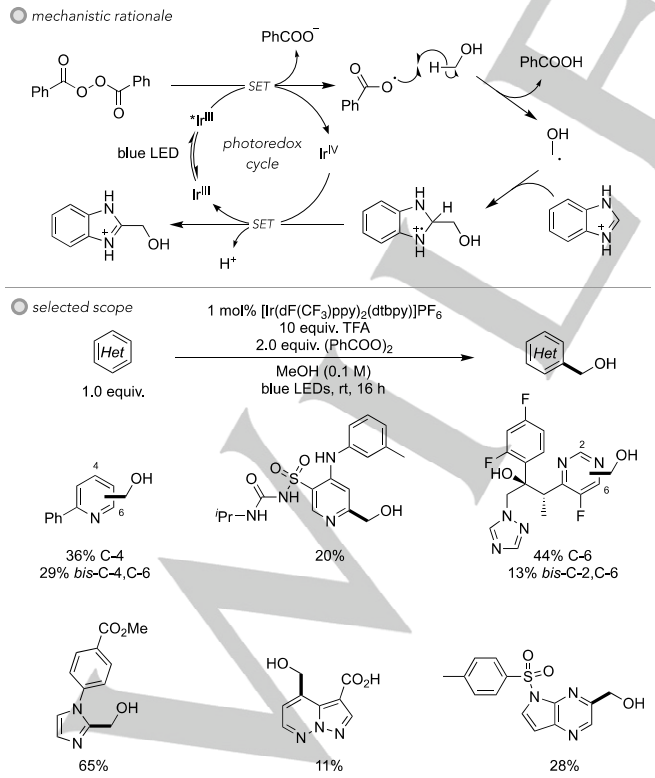
The same year, Wang and co-workers demonstrated that benzoyl peroxide could be used as an initiator in the alkylation of *N*-iminopyridinium ylides (see Scheme 22 for a representative example).[78] It is proposed that a by-product of the N-N bond cleavage is able to abstract a hydrogen atom from the alkane, ether or alcohol to propagate the reaction, hence why only 30 mol% of peroxide is required. Interestingly, the reaction exhibits excellent regioselectivity for the 2-position. Cai and co-workers

later reported a method for cycloalkylation and benzylation of azoles with di-tert-butyl peroxide, utilizing thermal homolysis.[79]



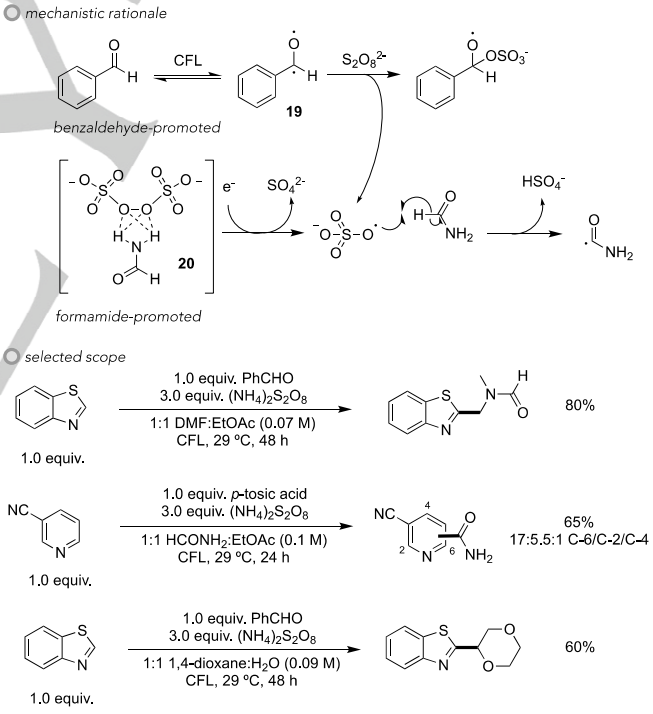
Scheme 22. Thermal coupling of an N-iminopyridinium ylide with butanol.

In 2016, DiRocco, Krska and co-workers at Merck demonstrated the use of a methanol-peracid system to hydroxymethylate heteroarenes.[80] Like MacMillan's report with persulfates, the work uses the photoredox catalyst $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ to reductively cleave the oxidant, which then abstracts an α-hydrogen from methanol and the resultant α-hydroxymethyl radical undergoes addition to heteroarenes (Scheme 23). Although hydroxymethylation of heteroarenes had previously been reported by Minisci many years ago,[81] this method is far milder, expanding the scope and allowing more oxidation-sensitive functionality to be tolerated in the transformation. The reaction displays excellent functional group tolerance and the scope places a great emphasis on complex scaffolds of biological importance. A variety of ring sizes and classes could be successfully hydroxymethylated in low to good yields. Overall it constitutes a powerful method for the late-stage functionalization of pharmaceutically important structures. The following year, a related hydroxymethylation strategy was reported by Togo for substituted pyridines and quinolines that relied on the thermolysis of persufate anions.[82]



Scheme 23. Hydroxymethylation of a variety of heterocycles using peracid and photoredox catalysis.

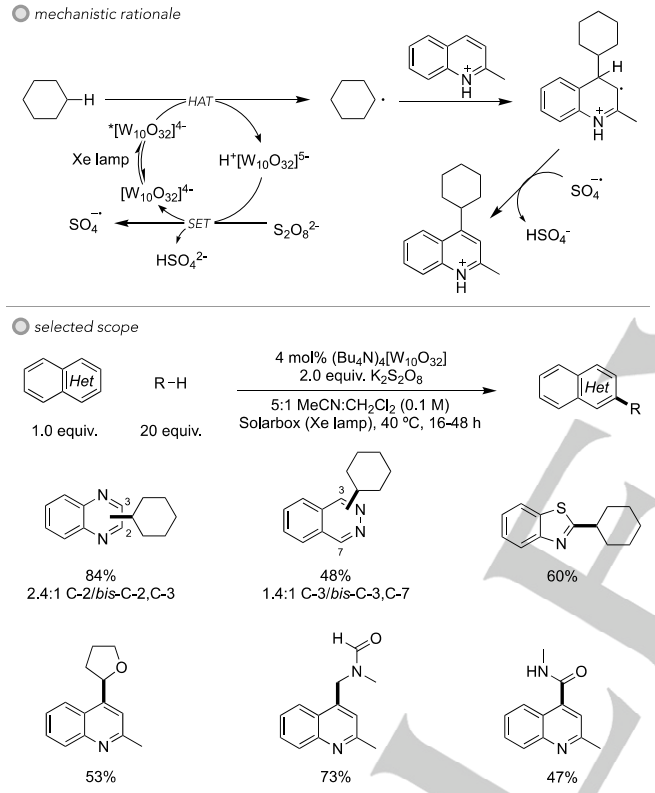
In 2016, Ji and co-workers showed that a benzaldehyde-mediated photochemical strategy could allow the CDC of stabilized C-H bonds and basic heteroarenes (Scheme 24).[83] This work is notable for its demonstration of hydrogen atom transfer from an amine α-C-H bond. It is also effective on the formyl C-H bonds of formamide as well as ether α-C-H bonds. The mechanism proposed for the transformation is complex. Depending on the promoter present in the reaction system (formamide or benzaldehyde), it is proposed that decomposition of the persulfate occurs through complexation to photoexcited triplet-state benzaldehyde **19** (benzaldehyde-promoted) or through an H-bonding complexation to the $-NH_2$ moiety of a formamide molecule **20** (formamide promoted). Although mechanistically complicated, it is synthetically practical and provides a versatile method for the installation of a variety of groups onto a number of classes of heteroarene. The transformation works smoothly across a range of 5- and 6-membered rings.



Scheme 24. Use of benzaldehyde as a promoter in a visible light promoted Minisci-type reaction using sp^2 and sp^3 nucleophiles

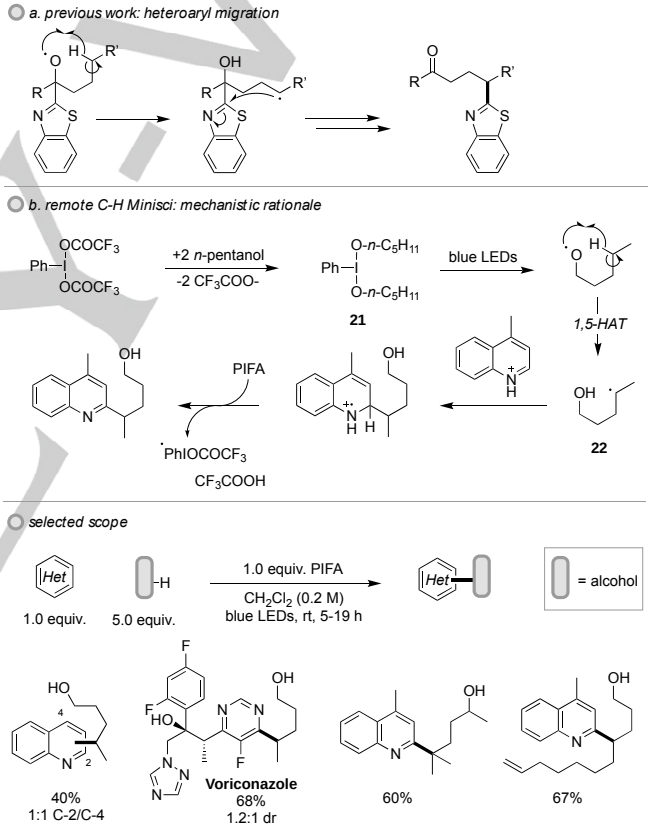
Hydrogen atom transfer from both activated and unactivated C-H bonds was used in a Minisci-type reaction through dual photoredox/HAT catalysis by Ravelli, Ryu and co-workers in 2017 (Scheme 25).[84] The C-H abstraction is believed to be performed by a decatungstate photocatalyst, which has the capability to act as both an SET catalyst and an HAT catalyst.[85] Interestingly, the

authors use a 'solar simulator' to emulate sunlight, which effectively promotes the reaction, this compatibility being one of the advantages of the decatungstate photocatalyst. The demonstrated heteroarene scope is moderate, only showing bicyclic systems (although multiple substitution patterns and benzothiazole are successful substrates) undergoing effective alkylation. It is in the radical scope and operation of this reaction that it is strongest. Showing decatungstate to be a versatile HAT catalyst, unactivated alkyl, activated α-heteroatomic and formyl hydrogen atoms are shown to undergo successful abstraction and subsequent Minisci-type reaction. The authors do note that in the case of activated C-H bonds, sulfate radical anion could be performing C-H abstraction as an alternative pathway, as in previous work. [73–75,86]



Scheme 25. Use of a decatungstate photocatalyst with a 'solar simulator' to perform C-H abstraction/Minisci addition.

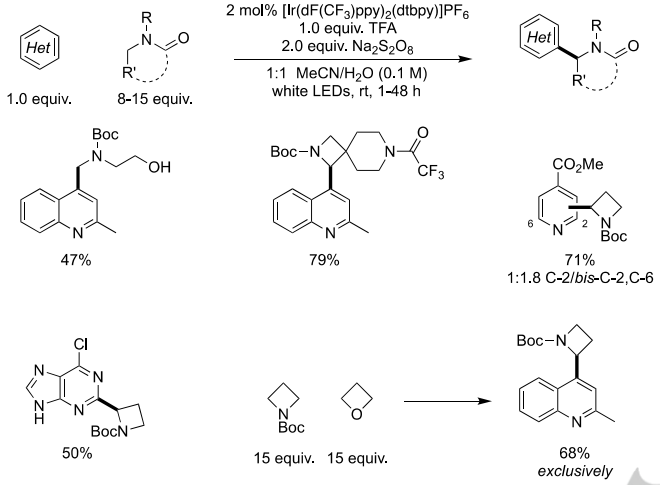
Chen, Liu and co-workers previously showed that hypervalent iodine reagents were useful for activating boronic acids for Minisci-type reactions.[87] In 2018, Zhu and coworkers showed that similar reagents can also activate alcohols to form alkoxyl radicals, which can in turn activate remote aliphatic C-H bonds through HAT for the alkylation of heteroarenes.[88] In previous work by the same authors, formation of an alkoxyl radical enables the migration of a heteroaryl group along a long-chain alcohol (Scheme 26a).[89] Zhu and co-workers realized that this approach may be applied to intermolecular Minisci reactions where the radical nucleophile is generated at a remote alkyl position (Scheme 26b). The mechanism is proposed to operate *via* homolysis of hypervalent iodine compound **21**, generated *in situ*, wherein the alcohol substrate has become a ligand on the I(III) center. The resultant alkoxyl radical undergoes 1,5-hydrogen atom transfer to abstract a cleave a distal C-H bond, generating remote alkyl radical **22** that can undergo a Minisci-type reaction with a heterocycle that is protonated by the trifluoroacetic acid released as a consequence of the initial ligand exchange. Although the heteroarene scope is limited to 6-membered rings, within this category the tolerance is broad. Quinoline gives a statistical mixture of regioisomers but complex substrate voriconazole is modified as a single regioisomer. The reaction can deliver and couple a 1º, 2º or 3º radical and leaves an olefin on the alkyl chain untouched (*selected scope*). Overall, the transformation demonstrates an elegant strategy to perform a remote radical functionalization and employ it subsequently in Minisci chemistry.



Scheme 26. Use of hypervalent iodine reagents with alcohols to perform remote C-H bond cleavage prior to Minisci reaction

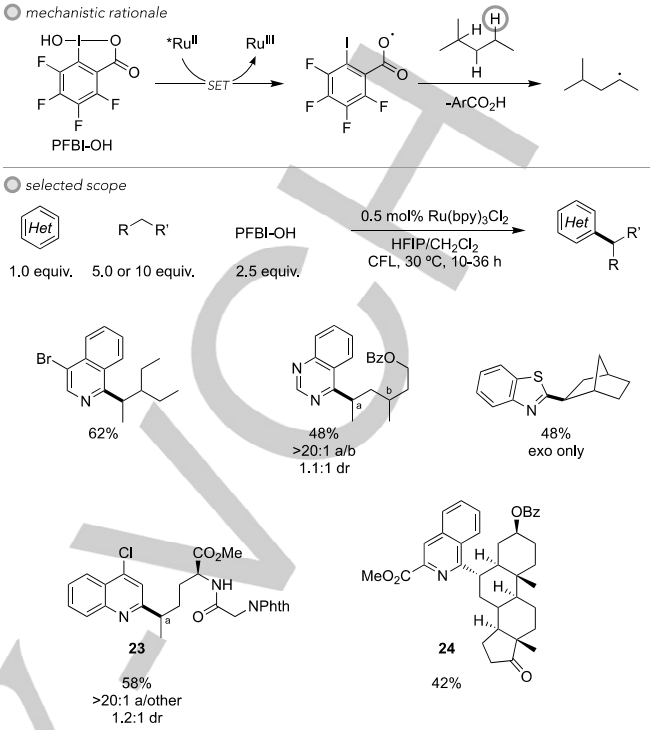
In 2018, Wang and co-workers showed that *tert*-butyl peracetate is a viable reagent for C-H abstraction from protected secondary amines, as well as other hydrogen atom donors, for a photoredox-catalysed Minisci-type reaction.[90] Almost simultaneously, Berthelot and co-workers published a similar protocol that uses persulfate anion (Scheme 27).[91] A notable aspect of this transformation is its high chemoselectivity for HAT adjacent to carbamate-protected amines, even in the presence

of ethers. In the presence of either an alcohol group or a trifluoroacetylamine substituent, a Boc-protected α-amino radical is selectively heteroarylated. Both primary and secondary radical fragments can successfully undergo addition to a range of 6-membered heteroarenes. In a direct competition experiment, *N*-Boc azetidine outcompetes oxetane for heteroarylation. A similar procedure was adopted by Grainger, Johnson and co-workers in their high throughput reactivity mapping for fragment-based drug discovery.[92]



Scheme 27. Photoredox catalysis with persulfate oxidant for HAT adjacent to protected-amines.

Most recently, He and Chen developed a method for the highly selective abstraction of methylene C-H bonds for Minisci-type reactions (Scheme 28).[93] Upon proposed reduction by excited Ru^{II}, hypervalent iodine reagent PFBI-OH loses hydroxide and forms a highly electrophilic carboxyl radical, capable of abstracting aliphatic C-H bonds. The high methylene selectivity is thought to be aided by an ortho-fluorine substituent on the aryl ring, perhaps affecting conformation in the C-H abstraction transition state. The scope is very broad and the reaction displays such high selectivity for methylene positions that amino acid derivative **23** and steroid derivative **24** are formed by reaction of only one aliphatic C-H bond.

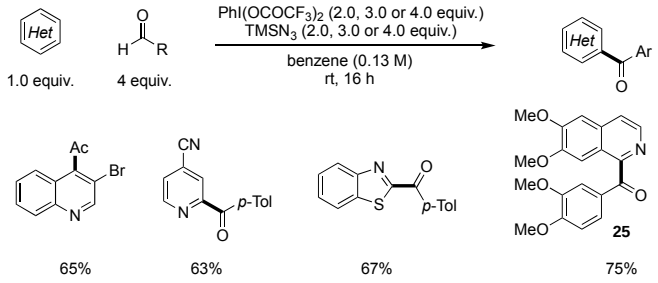


Scheme 28. Minisci-type alkylation via highly selective HAT from methylene groups.

3.2 Hydrogen Atom Abstraction at sp^2 Hybridized Carbon

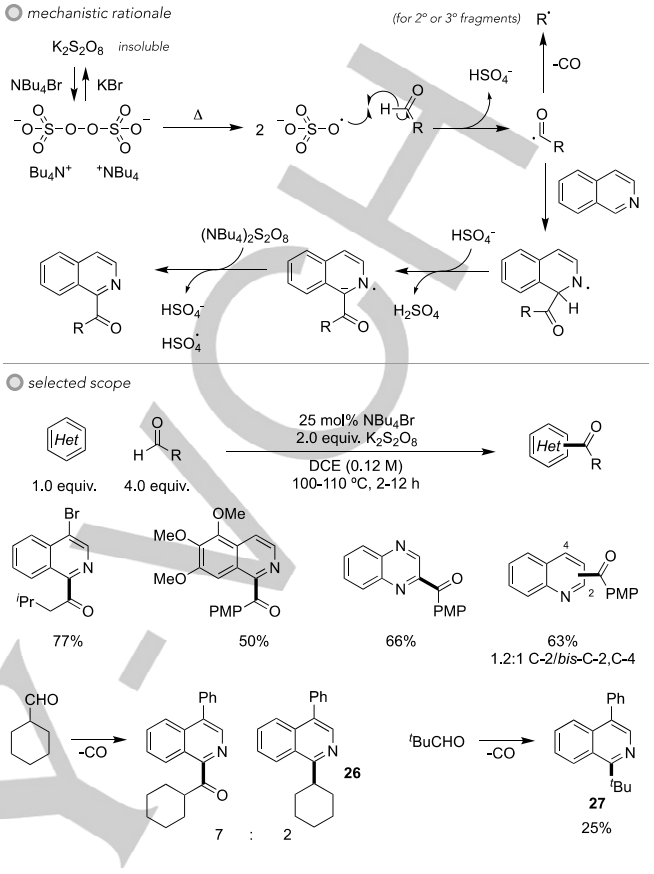
As early as 1969, Minisci and co-workers demonstrated that acyl radicals for Minisci-type reactions could be generated through HAT from aldehydes using peroxides in the presence of iron.[94,95] In numerous following papers over the years, this method was extensively refined and explored.[23,24]

In 2013 Matcha and Antonchick reported the direct acylation of heteroarenes using a combination of the hypervalent iodine reagent PIFA and azide anion to generate azide radicals, which are able to perform the desired HAT from the aldehyde functional group (Scheme 29).[49] This process uses conditions very similar to the aforementioned alkylation procedure from the same authors (see Scheme 18) but in this case $TMSN_3$ is preferred as the azide source. Please see section 5.1 for mechanistic discussion. The acylation procedure has a good scope of both heteroarenes and acyl radicals. Demonstrating clear utility, the transformation was directly applied to the rapid assembly of a number of natural and pharmaceutically interesting alkaloids, such as papaveraldine, **25**.



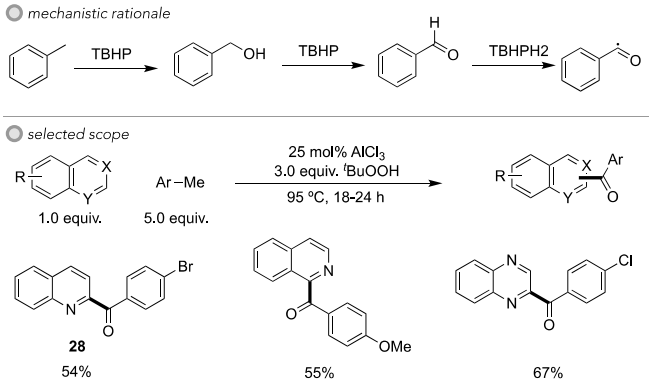
Scheme 29. Acylation of heteroarenes using radicals generated through hydrogen atom abstraction from aldehydes.

A year later, Prabhu and co-workers reported their own procedure for Minisci-type acylation of heteroarenes (Scheme 30).[86] Like Antonchick's, it relies on hydrogen atom abstraction from an aldehyde C-H bond, but utilizes a persulfate salt as oxidant.[96] This is not all that unusual in Minisci-type reactions, since persulfate anions were the oxidant of choice for the original silver-promoted decarboxylation procedure and other additions have since relied on the abstraction of α-hydrogens.[19,22,81,97] However, in the case of this transformation, the thermal decomposition products of the persulfate are proposed to perform hydrogen atom abstractions from the aldehyde proton, generating an acyl radical able to undergo Minisci-type reaction. Tetrabutylammonium bromide is included in the reaction system, having been found to give significantly increased yields. In Prabhu's proposed operative mechanism, this additive is thought to act as a solid-solution phase transfer reagent, to bring the persulfate anion into the reaction medium. Whilst the majority of the substrate scope is demonstrated on isoquinolines, products are formed successfully from other scaffolds too. A range of acyl radicals can be added although competitive decarbonylation can occur if the resultant radical is stabilized (secondary or tertiary), like cyclohexyl (**26**) or *tert*-butyl (**27**). This overoxidation was later observed by the same group in a similar acylation procedure they developed using *tert*-butyl hydrogen peroxide with *N*-chloro succinimide as initiator.[98] In 2014, Xie, Zeng and co-workers reported a related protocol that could operate thermally or photochemically, but was demonstrated on phenanthradine only.[99]



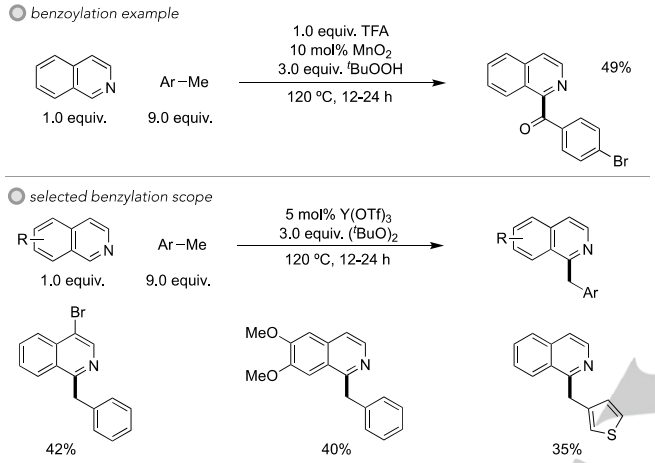
Scheme 30. Minisci-type acylation of heteroarenes via thermal decomposition of peroxides.

In 2015, Patel and co-workers reported an approach to benzoylation of heteroarenes that proceeds via hydrogen atom abstraction from aldehydes that are formed *in situ* by oxidation of toluene derivatives (Scheme 31).[100] Although the scope is moderate, with simply substituted quinoline, isoquinoline and quinoxaline scaffolds being functionalized, the transformation has a desirably modularity. As with the work of Huang, a notable aspect about the transformation is the full regioselectivity the reaction displays for the 2-position of quinoline (**28**).



Scheme 31. Benzoylation of heteroarenes starting from toluene derivatives by twofold oxidation and then HAT from the aldehyde.

Several months later, Liu and co-workers reported a very similar reaction using MnO_2, TFA and TBHP (Scheme 32, *benzoylation example*).[101] Interestingly, they observed that by changing the conditions, a *benzylation* could be performed by switching to di-*tert*-butyl peroxide, replacing TFA with the Lewis acidic $Y(OTf)_3$ and omitting manganese dioxide (see *benzylation scope*). Although the reaction is only reported on isoquinolines, this second transformation constitutes a rare example of a Minisci-type reaction involving tolyl radicals.



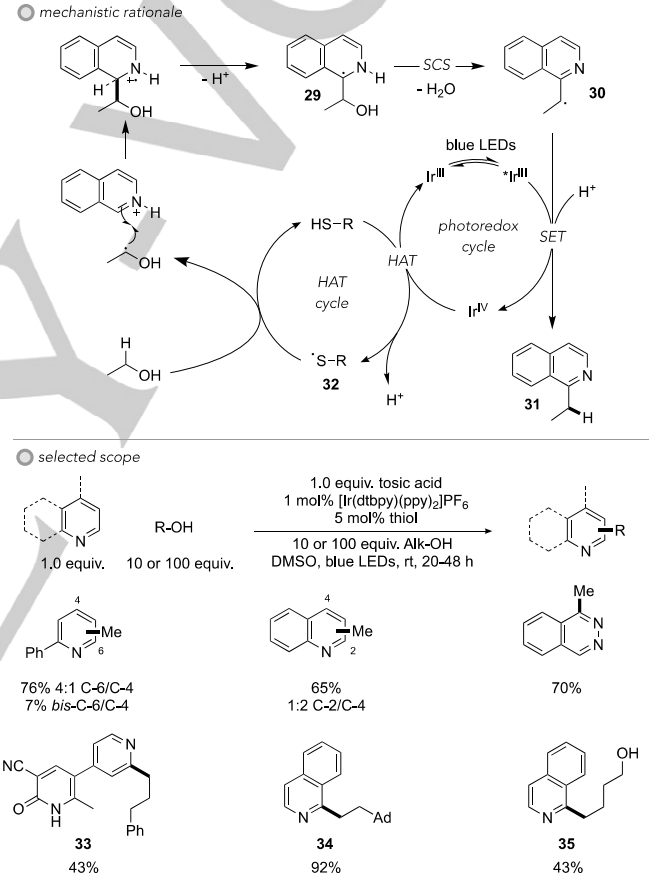
Scheme 32. Benzoylation and benzylation of isoquinoliones.

In 2015, several groups reported decarbonylative Minisci-type alkylations proceeding *via* initial HAT from aldehydes. Paul and Guin were able to identify conditions whereby the acyl radical evidently decarbonylates before adding to the heteroarene, using 1 atm. of O_2 as the oxidant.[102] The authors observed that the selectivity for alkylation over competitive acylation was very much reduced with linear aldehydes, correlating with the alkyl radical stability. Very good selectivities for the desired alkyation could be achieved with aldehydes that would produce tertiary and secondary alkyl radicals on decarbonylation and this was demonstrated on a variety of heteroarenes. Yang and co-workers reported a related procedure which used di-*tert*-butyl peroxide as oxidant.[103] In their process they observed similarly that branched aldehydes gave higher yields of desired alkylation product than linear ones and mechanistic studies supported the underlying Minisci-type mechanism.

Additionally, Han and co-workers reported a CDC of formamides and pyridines using a silver/peroxodisulfate system in 2016.[104]

3.3 Hydrogen Atom Abstraction followed by Spin-Centere-Shift Dehydration

Due to its being a feedstock chemical, methanol's employment as a surrogate for a methyl radical, through a formal C-O functionalization, is a very attractive prospect. In 2015, MacMillan and co-workers reported an elegant procedure for the alkylation of basic heteroarenes using primary alcohols as the alkylating agent (Scheme 33). The system relies on dual photoredox and hydrogen atom transfer (HAT) catalytic systems and exploits a spin-center shift (SCS) elimination event from key radical intermediate **29** (see *mechanistic rationale*). After addition of the α-hydroxyalkyl radical to the heteroarene and subsequent deprotonation, **29** undergoes an SCS elimination of water. With this, the radical migrates from the C2-carbon to the benzylic position, resulting in intermediate **30**. This is then reduced and protonated, furnishing the final product **31**.

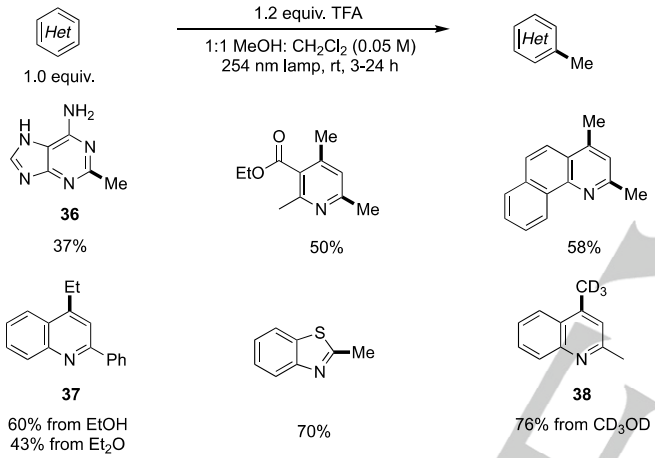


Scheme 33. Alcohols as Minisci-type alkylating agents *via* thiol catalysis.

The required α-hydroxyalkyl radical is generated through thiol hydrogen atom transfer (HAT) catalysis, previously developed in the MacMillan group. A thiyl radical (**32**), generated by reductive quenching of an Ir^{II} species, abstracts a hydrogen atom from the α-position of the alcohol, which is used in large excess. Although endergonic (BDE's), this transformation is feasible through the low energy transition state created due to polarity matching. A wide range of heterocycles and primary alcohols can be combined, demonstrating an elegant method for the alkylation of heteroarenes. Where there is regioselectivity

choice, the reaction does exhibit mild preferences. When there is no regioselectivity choice, other heterocycles, such as the pharmaceutical milrinone (**33)**, can be smoothly alkylated. Neither secondary alcohols, nor those with steric bulk close to the alcohol group can be tolerated. However, an adamantyl group is tolerated further down the chain (**34**). Tetrahydrofurans can also be employed, resulting in products bearing pendant alcohol groups after SCS ring opening (**35**).

Two years later, Li and co-workers demonstrated a similar transformation with a more streamlined reaction system.[105] Using ultraviolet radiation, α-hydroxyalkyl radicals can be generated from alcohols (Scheme 34). The precise mechanism of this reaction is not clear and a variety of pathways are proposed, ranging from direct homolysis of dichloromethane to electron donor-acceptor (EDA) complexation between the alcohol and other reaction components.



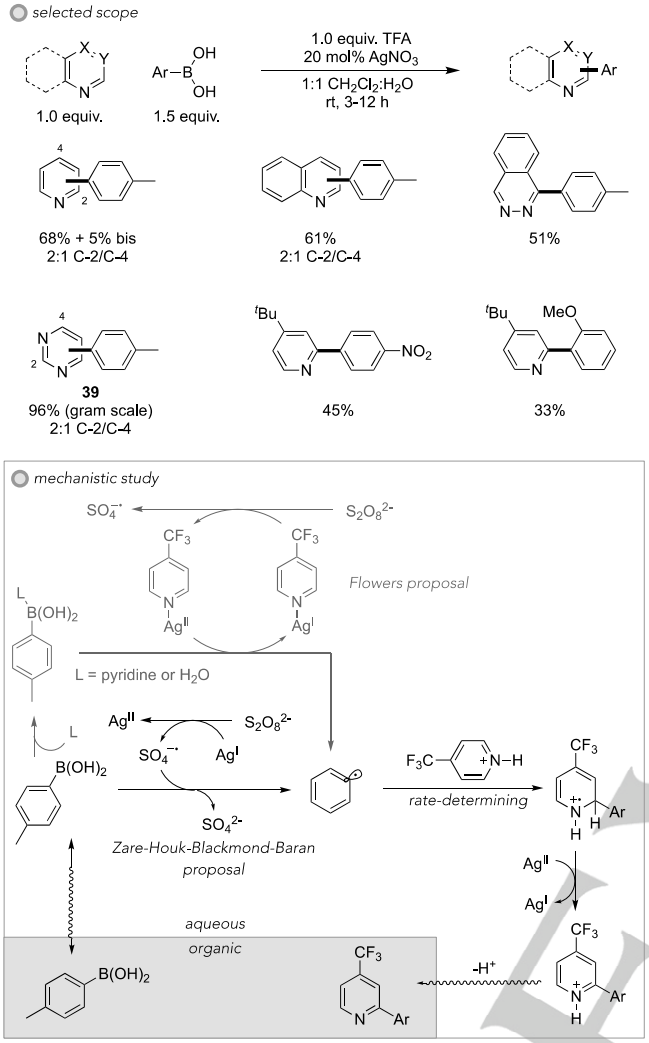
Scheme 34. Photochemical alkylation of heteroarenes.

Both 5- and 6-membered rings can be functionalized and nitrogen-rich scaffolds, such as the nucleobase adenine, can be methylated effectively (**36**). Methylation is primarily described, although two examples of ethylation are given: from ethanol and from diethyl ether (**37**). In addition, trideuteromethylation is demonstrated effectively (**38**). In many cases, where there is choice of regioisomers, double alkylation is observed. Although the reaction requires no photocatalyst or thiol catalyst, it suffers from the practical drawback of requiring ultraviolet light.

4. Advances in Radical Generation from Boron Compounds

The Minisci-type addition of aryl radicals to heteroarenes would constitute a powerful method for the construction of poly(hetero)aromatic building blocks. Early pioneering work in the 1960s from Lynch and others had involved the decomposition of arenediazonium compounds to produce aryl radicals (see section 1).[16] Minisci and co-workers had subsequently used the thermal cleavage of aroylperoxides to achieve the same ends.[28] Yet neither of these methods was able to produce good yields of product from readily available precursors, severely hindering uptake of this approach more broadly, despite the obvious potential. One might contemplate whether Minisci's original decarboxylative protocol for alkylation could be extended to aryl carboxylic acids, but this goal remained elusive for many years.

In 2010, Baran and co-workers reported a powerful strategy that addressed this challenge, in which ubiquitous aryl boronic acids are used as aryl radical precursors (Scheme 35). They anticipated that carbon-boron bond cleavage may be amenable to silver catalysis, in analogy to the carbon-carbon bond cleavage of alkylcarboxylic acids in the classic Minisci protocol. They discovered that, in a biphasic CH_2Cl_2/H_2O solvent system, limiting amounts of basic heteroarenes could be successfully arylated by employing a system of silver nitrate catalyst, potassium persulfate oxidant and TFA. The reaction was effective across a range of unsaturated heterocycles, such as pyridines, quinolines, isoquinolines, pyridazines and pyrazines. Pyrimidine was arylated in 96% yield in an open flask on a 1.0 g scale (**39**), although in a number of other cases yields were more moderate. Proceeding in an open flask at room temperature in a biphasic mixture of water and dichloromethane, the transformation benefits from operational simplicity. A mechanistic hypothesis was advanced in the original report in which persulfate is reduced by the silver catalyst. The sulfate radical anion then reacts with the boronic acid to form an aryl radical through an unknown mechanism.

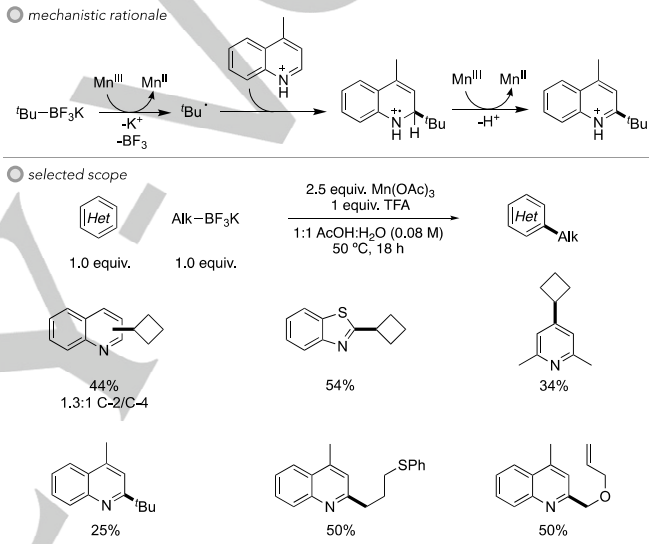


Scheme 35. Borono-Minisci reaction and subsequent mechanistic studies.

The mechanism was investigated in more detail in two subsequent studies, although the precise details of the roles of the various redox species are contentious. In 2013, Patel and Flowers carried out a detailed study which concluded that the pyridine substrate complexes Ag^{I} in an equilibrium.[106] This complex then reduces persulfate and the resulting pyridine-Ag^{II} complex then acts as a single electron oxidant to fragment the boronic acid to form an aryl radical (Figure 35, mechanistic study, *Flowers proposal*). They propose that either water or pyridine interacts with the boronic acid, rendering it susceptible to the oxidation.

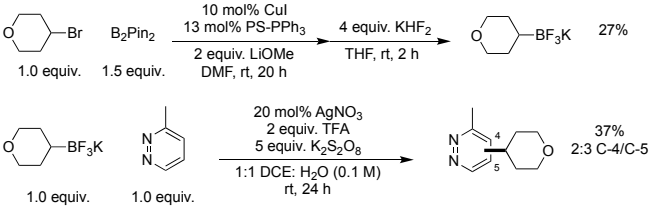
Two years later, Zare, Houk, Blackmond, Baran and co-workers published their own detailed study which involved kinetics, KIE experiments, DFT and MS elements.[107] They did not favor as important a role for a pyridine-Ag complex, with experiments suggesting that this dissociates under the reaction conditions and is therefore not requisite for effective reaction. Ultimately, their results support Baran's initial proposal that a sulfate radical anion combines with the boronic acid, or derivative thereof, to form an activated complex that is then susceptible to C-B bond cleavage (see Figure 35, mechanistic study, *Zare-Houk-Blackmond-Baran proposal*).

A year after Baran's original communication, Molander and co-workers reported a method for the alkylation of heteroaryl compounds using potassium alkyltrifluoroborate salts together with a manganese oxidant (Scheme 36).[108] In analogy to Baran's proposal, the boron precursor is proposed to be oxidized by manganese, subsequently cleaving its carbon-boron bond homolytically to release the alkyl radical. Exhibiting good scope, the alkylation can be performed on quinolines, pyridines and 5-membered rings. The reaction shows tolerance to a range of radicals, including 1º, 2º and 3º alkyl radicals and those possessing heteroatoms and unsaturation.



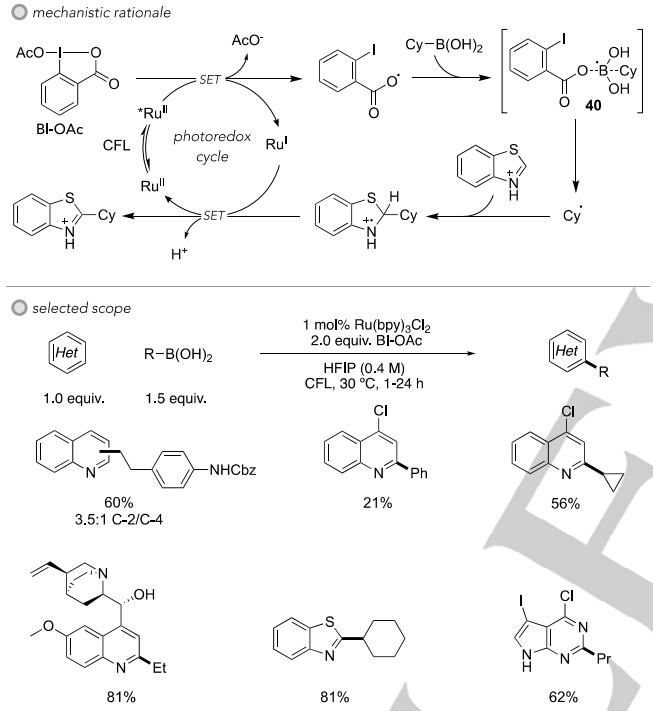
Scheme 36. Manganese-promoted heteroarylationg of trifluoroborate salts.

The same group later developed a copper-catalyzed Miyaura-type borylation of alkyl halides and the subsequent Minisci-type coupling of those products under silver/persulfate conditions. This rendered the reaction catalytic in transition metal, contrasting with the 2.5 equivalents of $Mn(OAc)_3$ that were used in the previous protocol (Scheme 37).[109] The scope is mainly demonstrative and limited to secondary radical fragments.



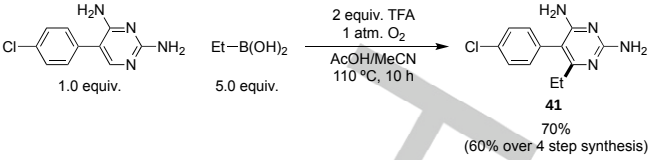
Scheme 37. Combined synthesis and Minisci reaction of organotrifluoroborate salts.

In 2016, Chen, Liu and coworkers showed that through photoredox catalysis, boronic acids could also be employed as precursors for alkyl (as well as aryl) radicals in a Minisci-type addition (Scheme 38). The reaction uses hypervalent iodine-based benziodoxole-derived oxidant BI-OAc, as opposed to the more common persulfate oxidants. Nevertheless, in a similar way to that proposed by Baran, they propose that an oxygen-centered radical from reductive decomposition of the oxidant combines with the boronic acid, followed by C-B homolysis of this activated intermediate **40** to give the radical nucleophile. A compact fluorescent lamp serves to excite the photocatalyst $Ru(bpy)_3Cl_2$, which mediates the required electron transfers. The procedure can support 1º and 2º alkyl radicals, as well as aryl radicals and a variety of heteroatom-containing substrates, both on the radical and on the heteroarene.



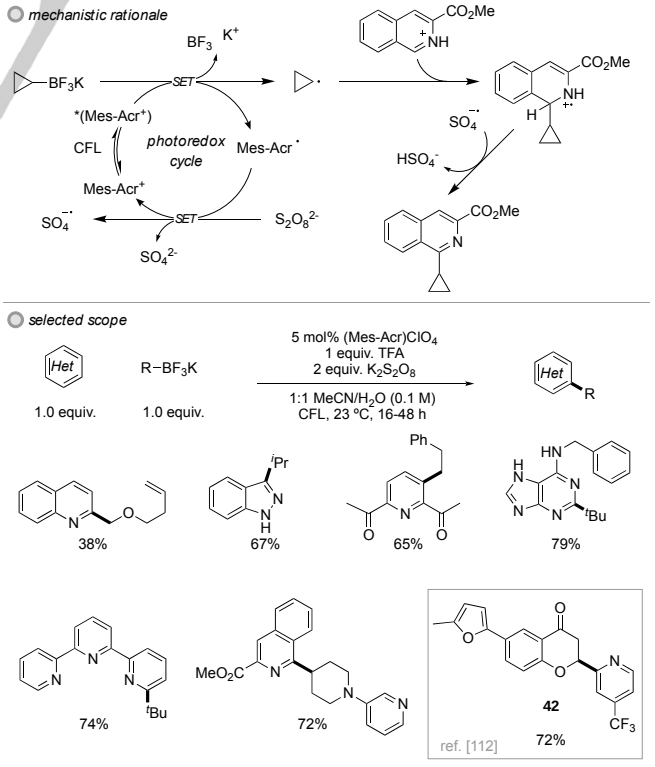
Scheme 38. Photocatalytic Minisci-type functionalization through hypervalent iodine-promoted decomposition of boronic acids.

A year later, the group of Liu showed that a Minisci-type reaction can be conducted from alkylboronic acid precursors using simple conditions.[110] The transformation is catalyst-free, operating under thermal conditions in an oxygen atmosphere. The authors propose a mechanistic pathway through a chain reaction *via* the known autooxidation of organoboron compounds.[111] They applied their method to the synthesis of pharmaceutical compounds, including the antimalarial pyrimethamine (**41**) (Scheme 39). Relatively environmentally benign, cheap and quite atom-economic, this procedure is practically rather attractive.



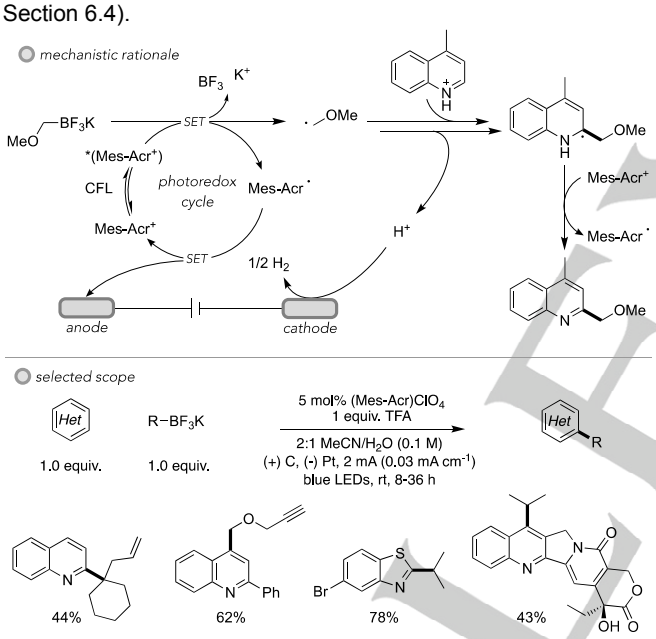
Scheme 39. Application of oxygen-promoted borono-Minisci to pharmaceutical synthesis.

Molander and co-workers later applied a photoredox catalysis approach to utilize trifluoroborate salts for Minisci chemistry (Scheme 40). This method built on their previous use of silver, replacing this with Fukuzumi's organic dye Mes-Acr in low loadings to mediate the electron transfers under CFL irradiation. Direct oxidation of the trifluoroborate by the excited $Mes\text{-}Acr^+$ is proposed to initiate the cycle, with all subsequent oxidations performed by persulfate and decomposition products thereof. The diversity of functionality tolerated on substrate and radical precursor is impressive, operating successfully with 1º, 2º and 3º stabilized and unstabilized radicals on heterocycles of 5- and 6-membered ring construction in the presence of alkenes, alcohols, amines and possibly competing heterocycles. The use of an organic photocatalyst could be advantageous compared with competing methods to form the same products which rely on the use of precious metals and the reaction scope would likely be more restricted if using harsher classical Minisci conditions. In addition, Matsui and Molander more recently published a separate communication dedicated to 2-heteroaryl chromanone products that would be difficult to synthesize otherwise (for example see Scheme 40, **42**).[112]



Scheme 40. Photocatalytic Minisci-type functionalization through the direct oxidation of trifluoroborate salts.

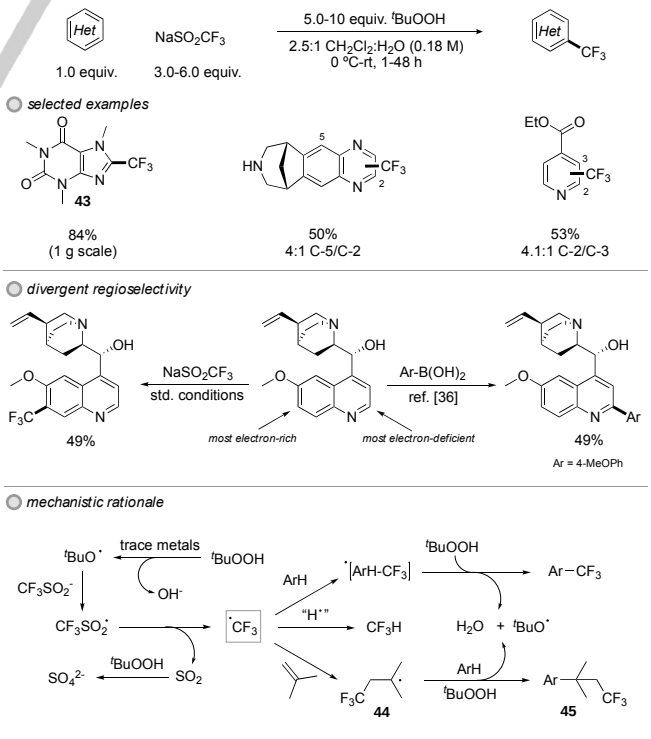
In early 2019, Xu and co-workers reported a Minisci-type addition of organotrifluoroborates to heteroarenes which builds on Molander's but uses electrochemistry in place of a terminal oxidant.[113] According to their hypothesis, the photoredox cycle should be used to generate the radical whilst electrochemical oxidation serves in place of the chemical oxidant that would typically be required in such a transformation. The proposed mechanism is analogous to that proposed by Molander but now the electrochemical cell takes the place of the peroxydisulfate oxidant (Scheme 41, *mechanistic rationale*). The ground state photocatalyst is presumed to act as the single electron oxidant to rearomatize the product, rather than the anode, on the basis of reduction potentials. The authors found that both light and electricity were necessary to get useful yields of product and a good scope of heterocycles and organotrifluoroborate salts was reported (Scheme 41, *selected scope*). An example of a 1,4-dihydropyridine as an alkyl radical source was also shown (see Section 6.4).



Scheme 41. Chemical oxidant-free Minisci-type alkyaltion through photocatalytic oxidation of trifluoroborate salts in an electrochemical cell.

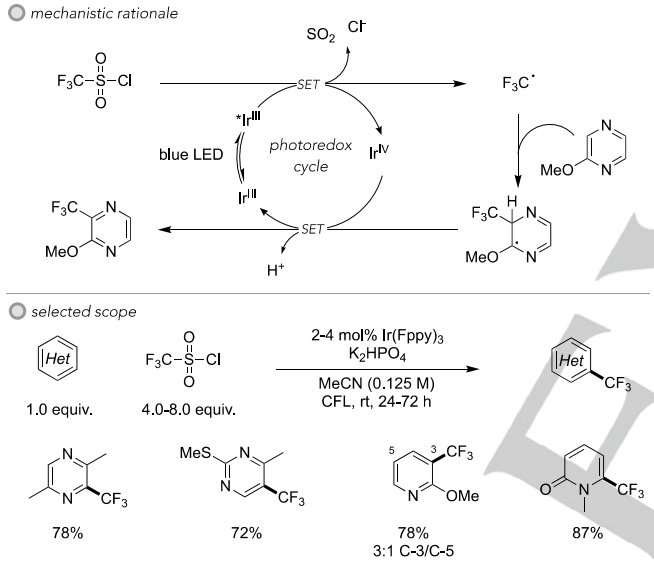
5. Advances in Radical Generation from Sulfur Compounds

Building upon their success with boronic acids for arylation (see section 4), the Baran group in 2011 disclosed a method for radical trifluoromethylation of heteroarenes (Scheme 42).[114] After evaluation of a number of trifluoromethylation reagents under various reaction conditions, the authors discovered that sodium trifluoromethanesulfinate (Langlois reagent)[115] in combination with *tert*-butylhydroperoxide (TBHP) was effective for the trifluoromethylation of a wide range of heteroarenes (Scheme 42, *selected examples*). This includes a number of electron-deficient heteroarenes which would be typical substrates for Minisci-type chemistry. Remarkably, the reaction is also compatible with more electron rich heterocycles such as indoles and pyrroles, which are not what we might consider to be substrates amenable to conventional 'Minisci-type' chemistry. The authors rationalized that the electrophilic nature of the trifluoromethyl radical makes it compatible with both electron deficient and rich heteroarenes, including on a 1 gram-scale with caffeine (**43**). In many cases regioselectivity is determined by the location of the most electron-rich arene position and they compellingly demonstrated this by comparing the regioselectivity of trifluoromethylation with that of arylation, using their previously developed method (see section 4). In these cases, the arylation proceeded to the most electron-deficient position (as would be predicted for a nucleophilic radical) whilst the trifluoromethylation occurred at the most electron-rich (Scheme 42, *divergent regioselectivity*). The less acidic conditions of this procedure may also improve the heteroarene's reactivity towards highly electrophilic trifluoromethyl radicals. The authors propose a mechanism that is initiated by a trace metal impurity that reduces the peroxide to generate an oxygen centered radical, which oxidizes the trifluoromethanesulfinate anion. This then forms the trifluoromethyl radical on extrusion of SO_2. Following radical addition, the chain is propagated by the peroxide-induced rearomatization of the heterocycle (Scheme 42, *mechanistic rationale*). Side products can result from trapping of the trifluoromethyl radical by isobutene (**44**), followed by Minisci type addition of this carbon-centered radical (**45**). Studies showed that the optimized biphasic system was important to gain useful yields although significant excesses of the two reagents had to be employed due to the formation of several byproducts arising from HAT as well as the aforementioned addition to isobutene.



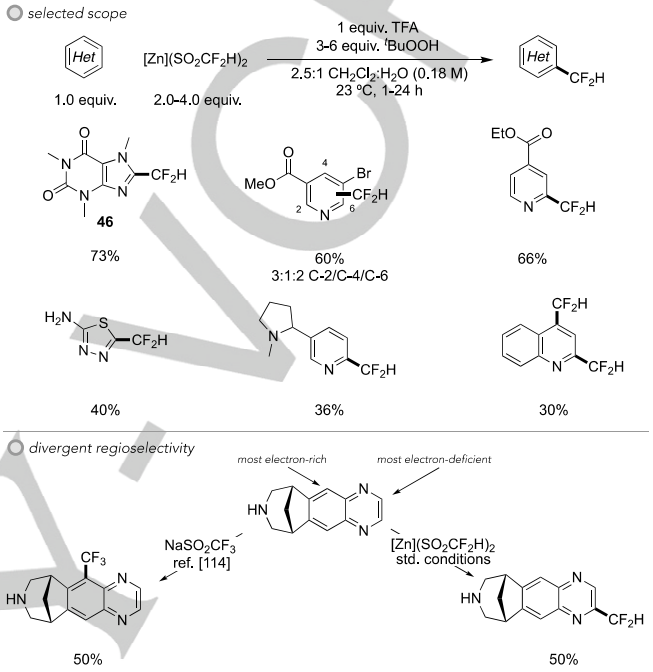
Scheme 42. Trifluoromethylation of heteroarenes using sodium trifluoromethanesulfinate (Langlois reagent), together with *tert*butylhydroperoxide.

Also in 2011, the MacMillan group reported the trifluoromethylation of a range of arenes and heteroarenes using photoredox catalysis and triflyl chloride as a CF_3 radical source (Scheme 43).[116] Here, the excited Ir(dFppy)$_3$ photocatalyst acts as a single electron reductant to reduce the triflyl chloride, extruding SO_2 and Cl-, leaving the CF_3 radical to add to the electron-deficient heteroarene. As in the Baran work, electron-rich and electron-deficient heterocycles were compatible and the MacMillan protocol also allowed for the use of electron rich arenes in addition to heteroarenes. In this work also, the regioselectivity outcome is determined by the position of highest electron density on the substrate, presumably due to the aforementioned electrophilicity of the trifluoromethyl radical.



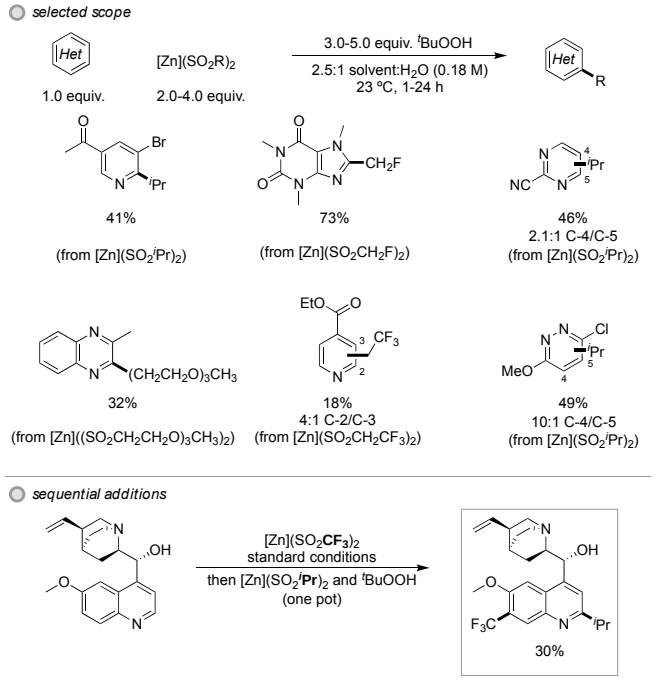
Scheme 43. Trifluoromethylation of heteroarenes using triflyl chloride together with photoredox catalysis

Following the success that they enjoyed using Langlois reagent for trifluoromethylation, Baran and co-workers in 2012 investigated use of sodium sulfinate salts with the target of achieving difluoromethylation. However, they found that the analogous difluoro analogue of Langlois reagent could not be synthesized. This led them to turn to alternative metal counterions in place of sodium and they observed that zinc difluoromethanesulfinate (DFMS) could successfully difluoromethylate caffeine in 73% isolated yield (Scheme 44, **46**).[117] As before, TBHP is used as an oxidant in a biphasic system, but now trifluoroacetic acid is used as an additive to improve rate and conversions. A variety of heteroarenes reacted successfully, the scope including numerous electron-deficient heteroarenes and also several electron rich ones that also bear an electron-withdrawing group. In contrast to their trifluoromethylation reaction, regioselectivity was always determined by the most electron-deficient position on the heteroarene, in line with classical Minisci-type chemistry (Scheme 44, *divergent regioselectivity*). This likely reflects the predominantly nucleophilic character of the difluoromethyl radical,[118] although the authors did demonstrate the strong effect that solvent can have on this regioselectivity outcome.



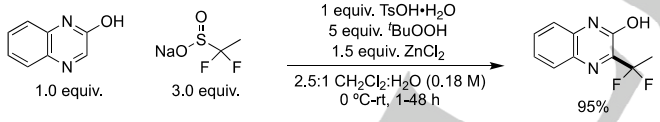
Scheme 44. Difluoromethylation of heteroarenes using zinc difluoromethanesulfinate (DFMS) together with peroxide.

In 2012, Baran and co-workers explored this idea further and demonstrated that zinc sulfinate salts are very capable and general precursors for a broad range of alkyl radicals in Minisci-type reactions and show higher reactivity than the corresponding sodium salts.[119] In this showcase study a 'toolkit' of six zinc sulfinate salts was presented, which encompassed transfer of CF_3, CF_2H, CH_2CF_3, CH_2F, $CH(CH_3)_2$ and $(CH_2CH_2O)CH_3$ (Scheme 45). These six were demonstrated on eight diverse heteroarenes and were also shown to be applicable in a sequential manner for molecules that possess one site that is 'electrophilic' and one that is 'nucleophilic', as long as the correctly matching radical partner is utilized (Scheme 45, *sequential additions*).



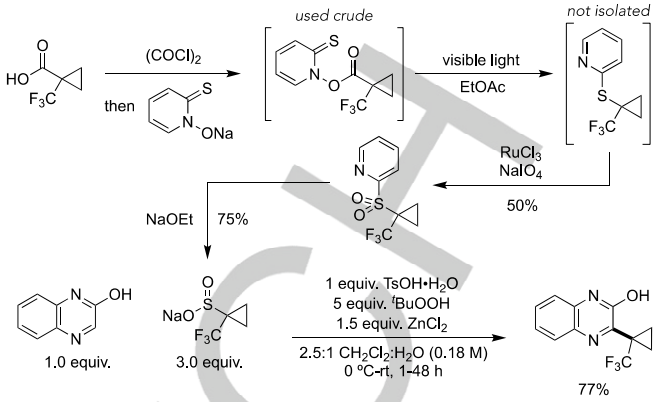
Scheme 45. Application of a 'toolkit' of zinc sulfinate salts to alkylate a variety of basic heteroarenes.

Since these reports, the Baran group have demonstrated a number of impressive applications of sodium sulfinate salts for heteroarene functionalization. In 2013 they reported the transfer of difluoroethyl groups using sodium difluoroethylsulfinate (DFES-Na), an example of which is shown in Scheme 46.[120] In this work, the presence of a Lewis acid was found to be required for good yields, with stoichiometric zinc chloride being used together with TsOH, again in a biphasic system.



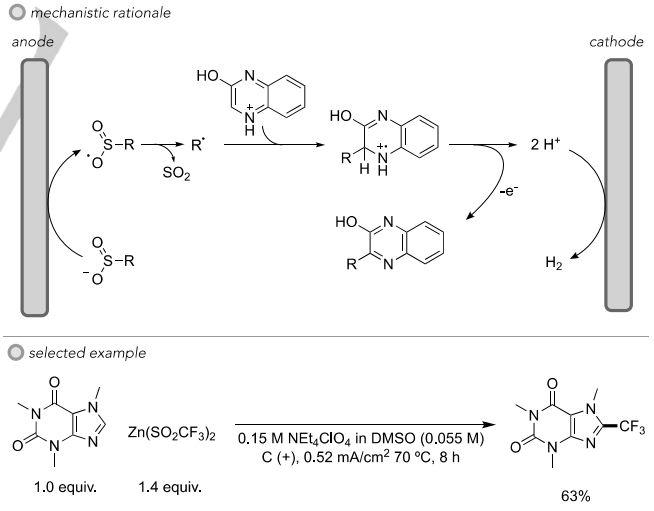
Scheme 46. Selected example of difluoroethylation using DFES-Na.

The following year Baran and co-workers reported a simple and convenient synthetic approach to alkyl sodium sulfinate salts from carboxylic acids (Scheme 47).[121] They developed a panel of ten new sulfinate reagents that would likely be useful for medicinal chemistry applications and this also included a reagent for trifluoromethylcyclopropanation.



Scheme 47. Synthesis of alkyl sodium sulfinate salts from carboxylic acids and subsequent trifluoromethylcyclopropanation.

Being an attractive prospect in terms of minimizing catalyst and reagent costs, electrochemistry has is becoming a research focus in mainstream organic chemistry in recent years.[13,122] In 2014, Baran and Blackmond and co-workers demonstrated that zinc sulfinate salts are effective for trifluoromethylation, difluoromethylation and trifluoroethylation under electrochemical initiation, rather than employing peroxides (Scheme 48).[40] This approach allowed the use of a much smaller excess of zinc sulfinate reagent than in their previous protocol and was enabled by understanding gleaned from careful monitoring of the reaction progress; appropriate control of the rate of radical formation could then be accomplished allowing good product yields.

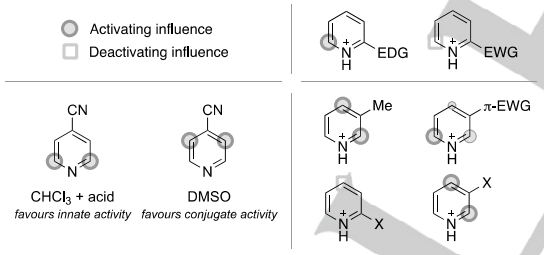


Scheme 48. Electrochemical trifluoromethylation of heteroarenes with zinc sulfinate salts.

Recognizing the long standing challenge of control of regioselectivity in Minisci-type reactions, in 2013, O'Hara, Blackmond and Baran published a detailed study which aimed to delineate the key reaction variables that control and influence the site of radical addition to a variety of electron-deficient

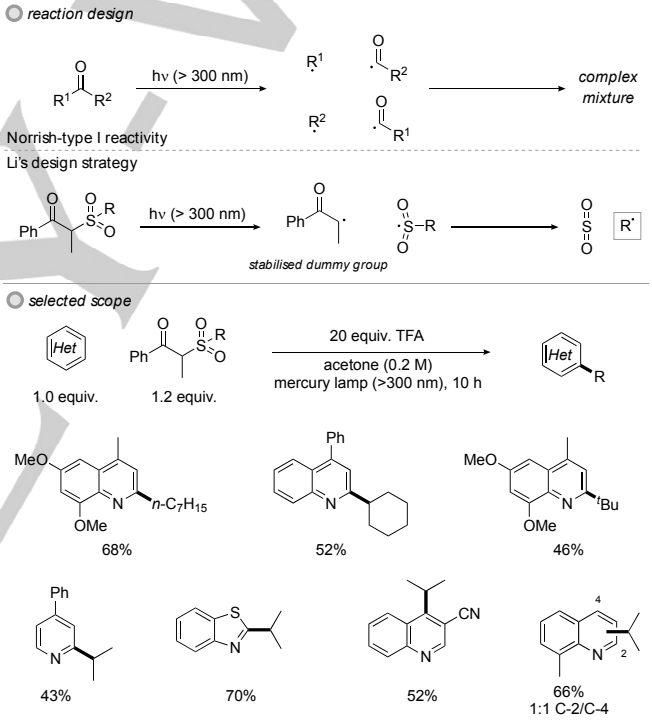
heteroarenes.[29] They noted that there was extensive literature precedent for a number of variables being important, including acidic additives, solvent, substituents on the heteroarene and the electronic nature of the incoming radical. However, there was not a clear picture of how to take these factors into account to give a systematic and instructive method for predicting and understanding the regioselectivity of Minisci-type reactions. In their detailed analysis, the authors used trifluoromethyl- and isopropyl-derived zinc sulfinates under varying conditions to probe a matrix of reaction aspects: electronic nature of the radical, substituents on the heteroarene and reaction medium, including presence or absence of acid. Their investigation introduces a sharper interpretation of previous literature reports and formulates guidelines for designing and predicting the regioselectivity outcome of a given, or desired, transformation.

They summarize that regiocontrol can either be driven by the "innate reactivity" of the heterocycle or the "conjugate reactivity" of its substituents. With innate reactivity (promoted by acid and lower polarity solvents), the regioselectivity of the radical nucleophile addition will be governed by the basic nitrogen, adding either *ortho* or *para* to it. With conjugate reactivity (promoted by polar solvents), the selectivity is controlled by a π-acceptor with a substitution pattern at odds with that of the basic nitrogen. In the case where conjugate reactivity dominates, regiochemistry favors *ortho* or *para* to the electron-withdrawing group. Additional substituents can then either augment or divert the overall reactivity and regiochemistry of the reaction. Figure 49 shows a summary of some of their conclusions in this regard, notably the effect on regiocontrol of substituents on a pyridine substrate. This careful study also includes detailed studies on diazines, complex substrates and the unique behavior of the electrophilic CF_3 radical.



Scheme 49. Examples from O'Hara, Baran and Blackmond's study of factors that affect regioselectivity in Minisci-type reactions.

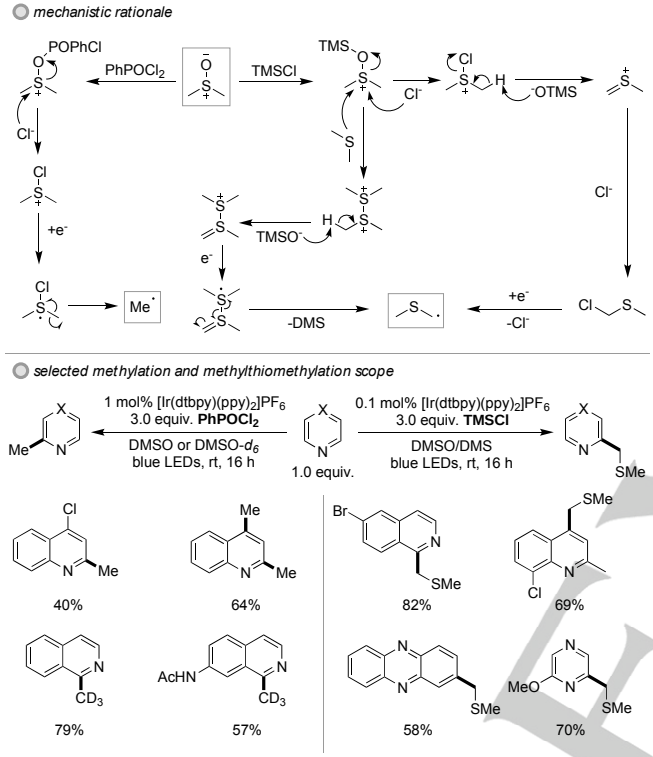
Metal sulfinates are not the only sulfur-based radical precursors that have been employed in Minisci-type reactions. In 2017, Li and co-workers demonstrated the generation of a range of radicals, including alkyl radicals, from α-methyl-α-sulfone phenyl methyl ketones (Scheme 50).[123] Not only did they employ the alkyl radicals in Minisci-type reactions to electron-deficient heteroarenes, but also demonstrated that electrophilic trifluoromethyl radicals could be produced for reaction with electron-rich arenes. Their design strategy was based around Norrish type I reactivity, wherein ultraviolet radiation induces homolysis of a ketone into two radical fragments. One of these is an acyl radical which can undergo decarbonylation to produce an alkyl radical (Scheme 50, *reaction design*).[124] In an intramolecular context, this can be a useful transformation but is difficult to harness in a productive intermolecular manner due to a number of reactive radicals being formed. The authors reasoned that a controlled decomposition of sulfones with a sacrificial group on one side which generates a low-reactivity radical, could be a strategy to obtain the desired reactive radical fragment R· after extrusion of SO_2 (Scheme 50, *design strategy*). This is an attractive strategy for Minisci-type reactions as it is redox neutral, avoiding both external oxidant and photoredox catalysts, although the drawback is that UV light is required to generate the alkyl radicals. While the range of alkyl radicals generated is limited in terms of functionality, the Minisci-type alkylation procedure is amenable to primary, secondary and tertiary hydrocarbon radical fragments and is applicable to a range of basic heteroarenes (Scheme 50, *selected scope*).



Scheme 50. Minisci-type alkylation by UV-light induced decomposition of α-methyl-α-sulfone phenyl methyl ketones.

In 2018, Glorius and co-workers introduced protocols that allow for the visible-light-promoted methylation and methylthiomethylation of heteroarenes, both of which use DMSO as the alkylating source.[125] The authors speculated that it may be possible to generate radicals from activated DMSO reagents by single electron reduction, employing photoredox catalysis. They discovered that depending on the reagent used to activate DMSO, divergent reactivity of the analogous activated intermediates could be obtained. Phenylphosphonic dichloride produced a methyl radical to furnish the methylated heteroarene, while trimethylsilyl chloride (with dimethyl sulfide co-solvent to

enhance yield) resulted in a methylthiomethyl radical to generate the methylthiomethylated heteroarene (Scheme 51, *mechanistic rationale*). Each transformation is viable on a range of 6-membered heteroarenes with moderate to very good yields (Scheme 51, *selected scope*). Usefully, the methylation reaction can be performed in deuterated DMSO, allowing trideuteromethylation of heteroarenes. This procedure represents a very convenient procedure for the installation of a methyl group with radical species derived from the simplest building blocks.

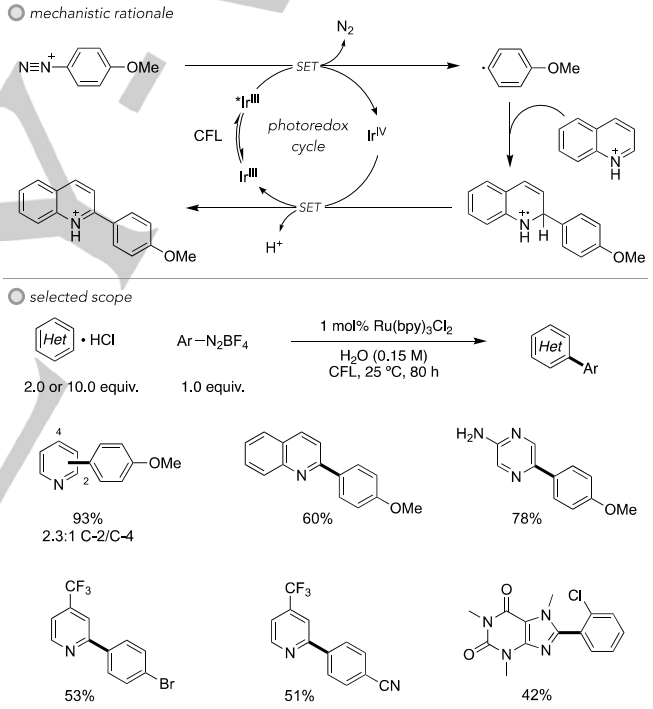


Scheme 51. Methylation and methylthiomethylation of heteroarenes using activated DMSO reagents and photoredox catalysis, switchable depending on the activating agent used.

6. Miscellaneous Advances in Radical Generation

6.1 Radicals from Diazonium Salts

Arenediazonium salts were utilized as phenyl radical precursors in some of the earliest studies on radical addition to heteroarenes and found early utility in the Gomberg-Bachmann reaction for biaryl synthesis.[16] However, until recently they have not been used extensively in Minisci-type reactions due to typically low yields and formation of byproducts. In 2014, Xue and co-workers reported a procedure that used them in combination with photoredox catalysis to achieve practically useful Minisci additions (Scheme 52).[126] In addition, this constitutes one of the earliest examples of the application of photoredox catalysis to a Minisci-type reaction. Due to the oxidative nature of diazonium salts, the reaction is net redox-neutral and utilizes $Ru(bpy)_3Cl_2$ as a photoredox catalyst under aqueous conditions. The HCl salts of the heteroarenes are used as substrates and the scope is broad, with a range of heterocycles arylated. Although pyridine gives a mixture of regioisomers under Xue's conditions, interestingly quinoline is arylated exclusively at the 2-position. More exotic heterocycles are also smoothly arylated, including aminopyrazine and caffeine, based on a 5-membered ring. The aryl group installed can comprise a variety of electron-rich and electron-poor functionality and the author demonstrated a 'one-pot' process in which the diazonium salt can be formed *in situ* and then telescoped into the Minisci reaction. Mechanistic studies supported the mechanism shown whereby the excited photocatalyst reduces the diazonium, triggering aryl radical formation. The oxidized photocatalyst then acts as single electron oxidant at the end of the cycle to rearomatize the heteroarene (Scheme 52, *mechanistic rationale*).



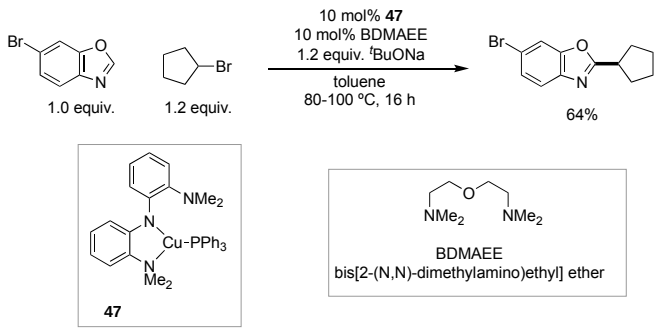
Scheme 52. Minisci-type arylation using diazonium salts as radical precursors together with photoredox catalysis.

6.2 Radicals from Alkyl Halides

As long ago as 1978, Minisci and co-workers demonstrated that alkyl radicals could be generated from alkyl iodides by decomposition of aroylperoxides or arenediazonium salts.[28,127] This proceeds *via* generation of high energy aryl radicals which abstract iodine from the alkyl iodide. Both of these methods possess disadvantages involving either intermediate formation of reactive aroyloxyl radicals which may cause undesired reactions (in the case of peroxides) or being susceptible to radical attack

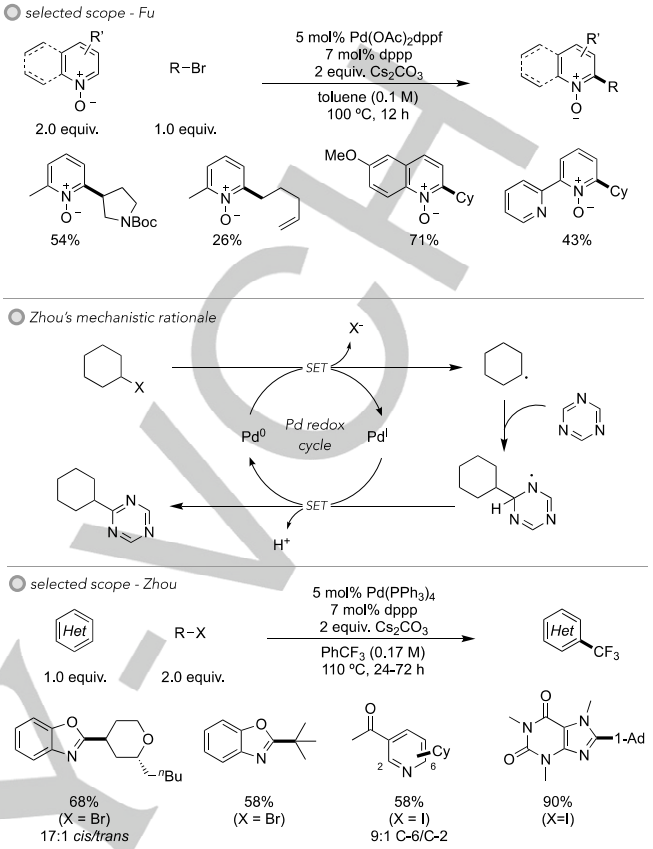
themselves (in the case of diazoniums). They subsequently developed a process wherein methyl radicals are initially generated to perform the iodine abstraction, which addressed some of these limitations.[128] Nevertheless, the common availability of alkyl halides means that further effort has gone into developing methods for their use as radical precursors.

An alkylation of benzoxazoles with secondary alkyl halides, catalyzed by copper complex **47**, was reported in 2012 by the group of Hu (Scheme 53).[129] The reaction proceeded under basic conditions at high temperature, furnishing a number of benzoxazoles with secondary radical fragments coupled to the 2-position. Preliminary mechanistic experiments suggested that a radical mechanism was in operation.



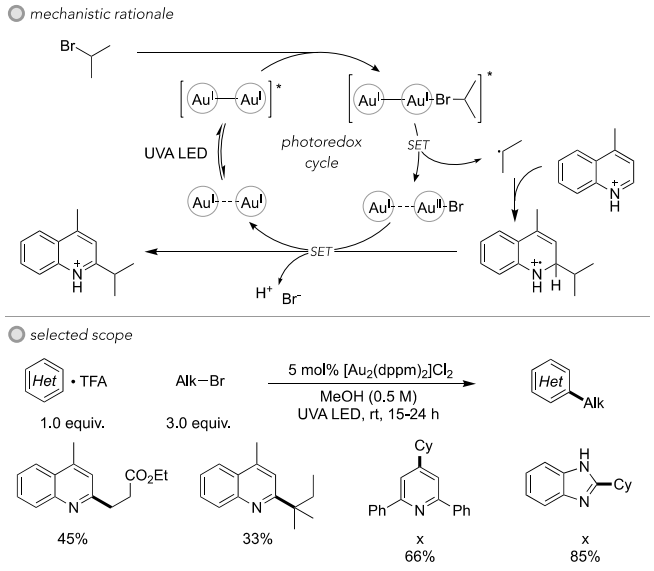
Scheme 53. Copper-catalysed alkylation of benzoxazoles.

Following this work, in 2013, Fu and co-workers developed an intriguing palladium-catalyzed coupling of alkyl bromides with pyridine *N*-oxides at the C2 position.[130] Phosphine ligands and stoichiometric base were used in conditions fairly typical of Pd-catalyzed C-H activation reactions. However, several key experiments pointed to a likely mechanism proceeding *via* alkyl radical intermediates in a manner akin to Minisci-type reactivity (Scheme 54, *selected scope – Fu*). This was followed in 2014 by a report from Zhou and co-workers which expanded this to include a broader variety of basic heteroarenes.[131] Furthermore, under these conditions, pyridines could be used without forming the *N*-oxide, as long as they possessed an electron-withdrawing group. Electron rich heterocycles were also compatible if possessing an electron withdrawing group (Scheme 54, *selected scope – Zhou*). The presence of radical intermediates was supported by trapping of the alkyl radicals with TEMPO and DFT calculations supported a radical addition pathway. Their proposed catalytic cycle involves SET from Pd(0) to the alkyl halide, generating the alkyl radical. Following radical addition, the Pd(I) complex oxidizes the radical intermediate to return the Pd(0) catalyst (Scheme 54, *Zhou's mechanistic rationale*).



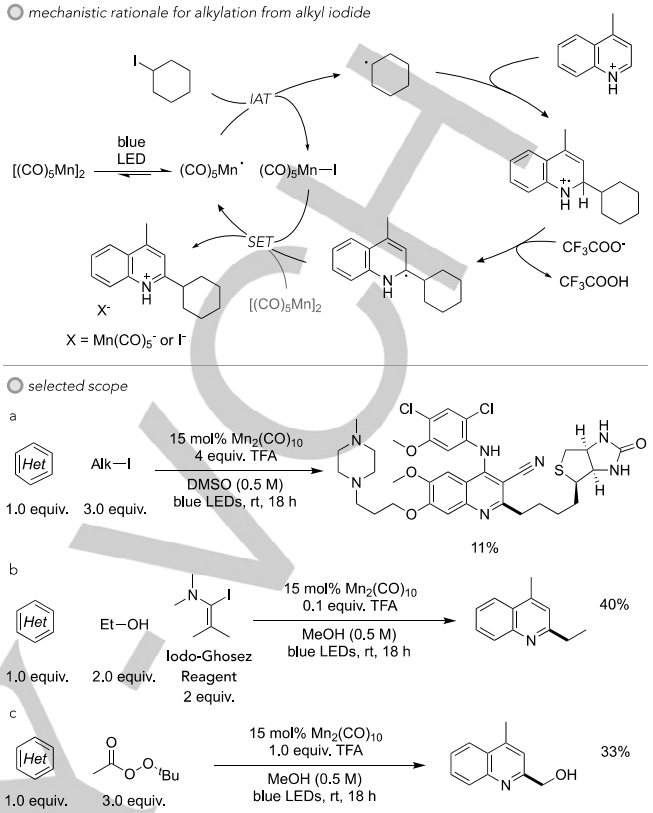
Scheme 54. Pd-catalyzed radical generation from alkyl halides.

In 2016, McCallum and Barriault reported a combination of gold catalysis and photoredox catalysis to generate alkyl radicals from alkyl bromides, for the purposes of Minisci-type reactions.[132] Based on the precedent that photoexcited $[Au_2(dppm)_2]Cl_2$ is able to reduce alkyl bromides through inner sphere photoinduced single electron transfer (Scheme 55, *mechanistic rationale*),[133] they imagined that this might fit well into a Minisci-type mechanism in a redox-neutral manner. As such, they found that combining the TFA salt of 4-methylquinoline with alkyl bromides and $[Au_2(dppm)_2]Cl_2$ with irradiation from 365 nm LEDs gave excellent yields of the desired alkylation products. This was also effective on pyridines as well as other basic heterocycles (Scheme 55, *selected scope)*. They were additionally able to demonstrate efficient and selective three-component reactions, which will be discussed further in Section 7. Finally, the absolute rate constant of primary radical addition to 4-methylquinoline was determined. Although an elegant method for the SET reduction of alkyl bromides for Minisci chemistry, it does suffer from the practical disadvantage of requiring ultraviolet light.



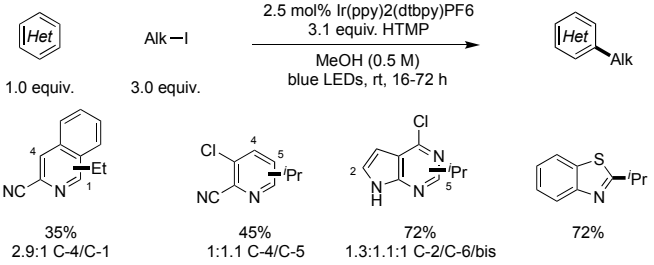
Scheme 55. Use of gold catalysis for the generation of alkyl radicals from alkyl bromides.

In 2017, Frenette, Fadeyi and co-workers reported the use of visible-light-initiated manganese catalysis to enable Minisci-type alkylation from alkyl iodides.[134] The hypothesis was that the weak Mn-Mn bond of $Mn_2(CO)_{10}$ would undergo homolysis upon exposure to visible light, generating a metal radical that could abstract an iodine atom (IAT, iodine atom transfer) from the alkyl iodide (Scheme 56, *mechanistic rationale*). This was found to work very smoothly upon exposure to blue LED light with 4-methylquinoline being alkylated in good yield at room temperature, avoiding the need for precious metal catalysts. Primary, secondary and tertiary alkyl radicals were all accessible with this method and the scope of heterocycles was broad, including examples of late-stage functionalization (Scheme 56, *selected scope a)*. Other radical precursors were shown to be amenable to the manganese catalysis by altering the conditions. It was found that alkylation was possible by the use of an alcohol precursor and iodo-Ghosez's reagent, which converts the alcohol to an alkyl iodide, as additive *(selected scope b)*. Additionally, they showed that hydroxymethylation can be achieved from the methanol solvent using *tert*-butyl peracetate, demonstrating the manganese complex's versatility as a more general photocatalyst *(selected scope c)*.[80] Mechanistic studies utilizing laser flash photolysis allowed observation of $^{\bullet}Mn(CO)_5$, the signal of which decayed more rapidly upon addition of an alkyl iodide, providing support for their mechanistic hypothesis. DFT calculations support the catalytic cycle shown below, which could proceed as a chain.



Scheme 56. Alkylation of heteroarenes using $Mn_2(CO)_{10}$ catalysis under visible light with alkyl iodides.

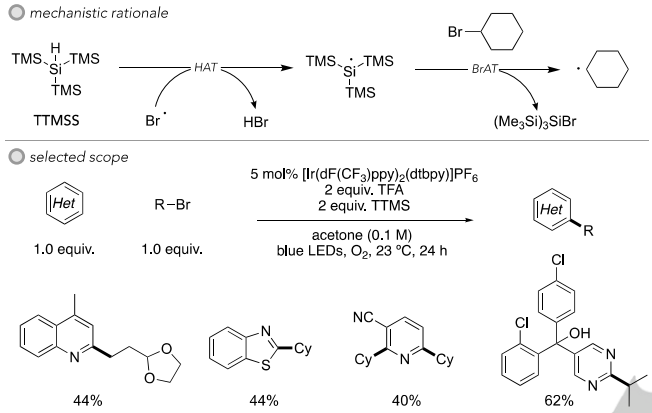
Nuhant and co-workers recently demonstrated the Minisci-type reaction of radical fragments derived from alkyl iodides through iridium photoredox catalysis (Scheme 57).[135] The reaction proceeds using 2,2,6,6-tetramethylpiperidine (HTMP) as a base and sacrificial cycle-initiating reductant. The scope is broad with respect to heteroarenes, and a variety of primary, secondary and tertiary fragments can be coupled. Regioselectivity receives particular attention in the study, with the researchers noting synergistic and antagonistic effects of conjugate and innate reactivity.



Scheme 57. Photocatalytic alkylation of heteroarenes using alkyl iodides.

Wang and co-workers in late 2018 demonstrated that bromine atom transfer using silicon radicals is a productive

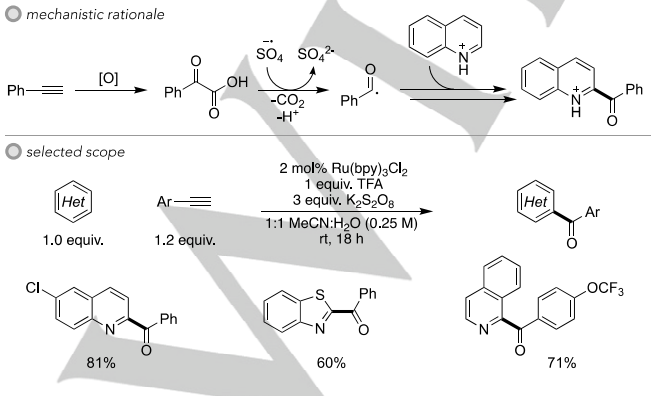
system for Minisci-type alkylation.[136] In their mechanistic hypothesis, bromide anions are oxidized by an excited iridium photocatalyst, and these subsequently abstract a hydrogen atom from the tris(trimethylsilyl)silane (TTMSS) shown to generate [$(Me_3Si)_3Si^{\bullet}$]. This silyl radical then abstracts a bromine atom to generate the nucleophilic alkyl radical which undergoes addition (Scheme 58, *mechanistic rationale*). The scope is tolerant of primary, secondary, tertiary and benzylic radicals and a wide variety of heterocycles and works on alkyl iodides as well as bromides (Scheme 58, *selected scope*). Considering the use of molecular oxygen to turn over the reaction, this procedure is an attractive method for alkylating heteroarenes.



Scheme 58. Alkylation of heteroarenes *via* halogen atom abstraction by a silicon-based radical.

6.3 Radicals from Alkynes

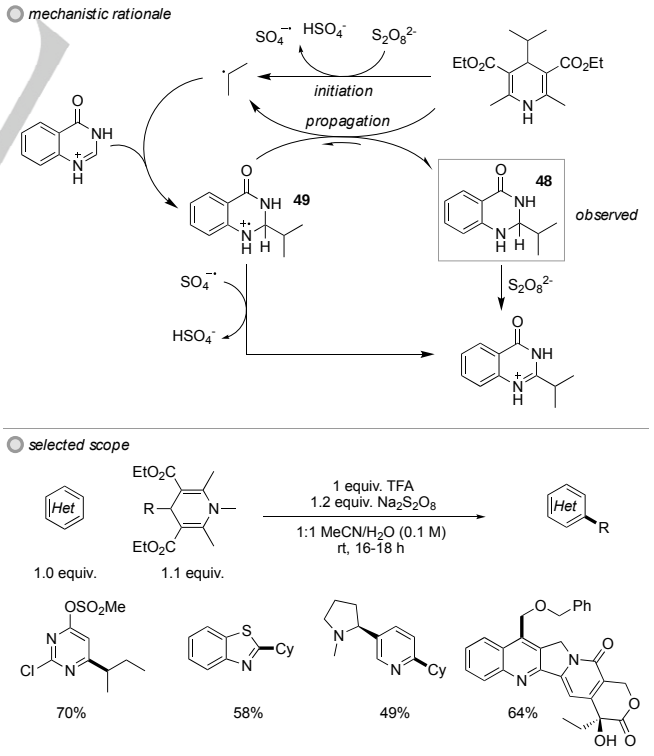
An interesting report from Shah and co-workers demonstrated that in terminal arylacetylenes, the alkyne can be oxidatively cleaved under the Minisci reaction conditions to form an *α*-ketoacid.[137] This *α*-ketoacid is then decarboxylated in the precedented manner following HAT from a sulfate radical anion to ultimately form the acyl radical which adds to the heteroarenes (Scheme 59, *mechanistic rationale*). The reaction is effective on quinoline and a number of related heteroarenes, as long as an arylacetylene is used as partner (*selected scope*).



Scheme 59. *In situ* cleavage of alkynes to form α-ketoacids which decarboxylate, enabling heteroarene acylation.

6.4 Radicals from Dihydropyridines

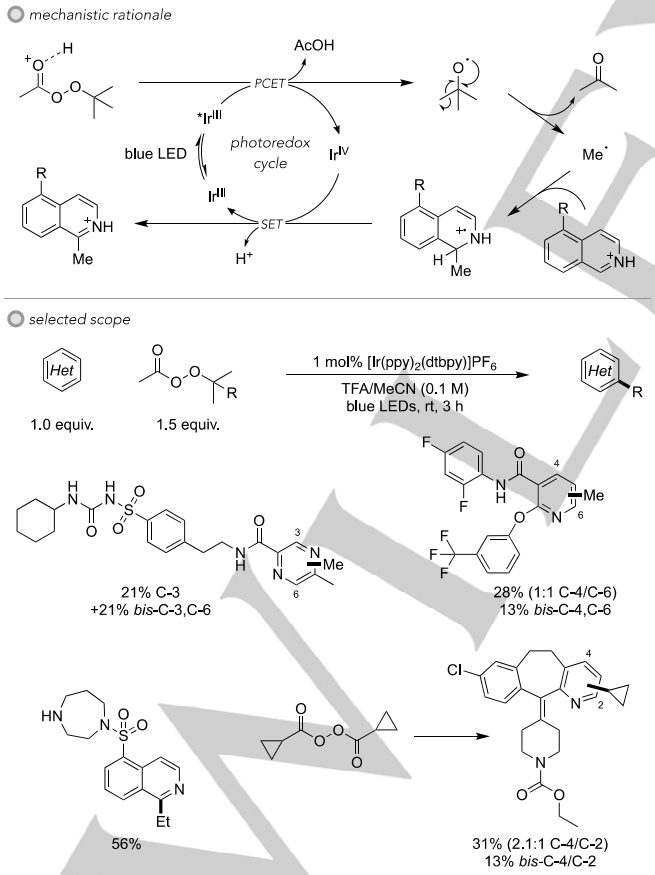
In 2017, Molander and co-workers demonstrated that single electron oxidation of 4-alkyl-1,4-dihydropyridines results in homolytic cleavage to form alkyl radicals that can add to heteroarenes.[138] They noted that aldehydes are convenient precursors to alkyl radicals however existing decarbonylative protocols are prone to give mixtures resulting from incomplete decarbonylation and that typically high temperatures are required to favor alkylation (see Section 3.2). They envisaged that 1,4-dihydropyridines, which are synthesized in one step from aldehydes, could act as masked aldehydes for mild and selective alkyl radical generation. The mechanism was envisaged to proceed *via* SET oxidation of the 1,4-dihydropyridine, which forms the desired alkyl radical (Scheme 60, *mechanistic rationale*). They found that using sodium persulfate as oxidant and stoichiometric TFA, the Minisci-type reaction proceeded in very high yield at room temperature. Detection of intermediate **48** suggested that a chain mechanism was operative, in which radical cation **49** can act to oxidize the dihydropyridine. Secondary alkyl radicals form the major part of the scope but primary alkyl radicals could also be formed with the aid of heteroatom stabilization (*selected scope*). They also demonstrated that this is effective in a number of late-stage functionalizations of natural products and pharmaceuticals. They also showed that *p*-quinones are viable radical acceptors, in addition to heteroarenes.



Scheme 60. Generation of alkyl radicals for Minisci reactions from 1,4-dihydropyridines.

6.5 Radicals from C-C fragmentation

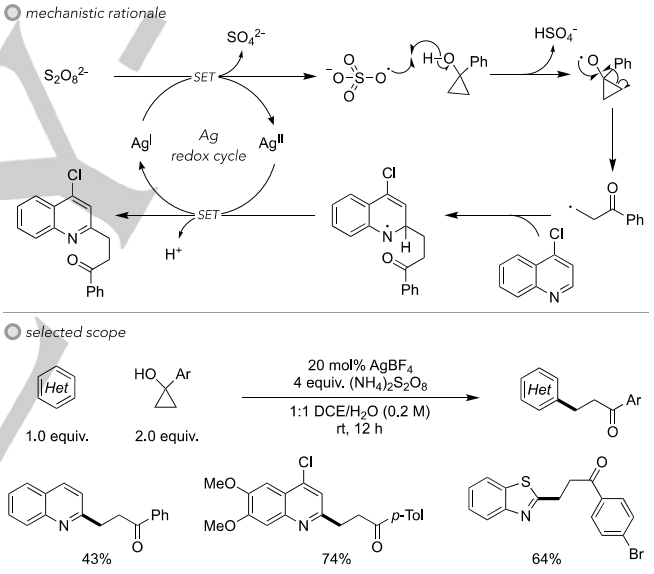
In 2014, DiRocco and co-workers demonstrated a method for late-stage alkylation of heteroarene-containing pharmaceuticals using photoredox catalysis and C-C bond cleavage from a peroxide.[139] Their approach exploits the reductive decomposition of alkyl peroxides and peracids through proton-coupled electron transfer (PCET) and subsequent homolysis and β-scission of tertiary alkoxyl radical fragments (Scheme 61, *mechanistic rationale*). An excited iridium photocatalyst reduces the peracid, followed by fragmentation and β-scission to reveal an alkyl radical, which can undergo addition to a protonated heteroarenes. The Ir^{IV} complex then rearomatizes the arene following deprotonation of the radical cation adduct. Yields are low to moderate but the complexity of the derivatives and difficult alternative syntheses mark them as highly attractive products. The "magic methyl" effect denotes the ability of a small alkyl substituent, in particular a methyl group, to profoundly modulate the biological and physical properties.[140] Given the streamlined approach of late-stage functionalization, methods for the installation of small alkyl groups into complex scaffolds is therefore a desirable prospect.



Scheme 61. Late-stage alkylation of pharmaceuticals *via* peroxide fragmentation and β-scission.

The following year, Li, Wu and co-workers demonstrated a method for the methylation of heteroaryl *N*-oxides in a similar fashion through the β-scission of dicumyl peroxide fragments.[141] Cai and co-workers would also go on to exploit this same β-scission for azole functionalization under thermal conditions in 2017.[79]

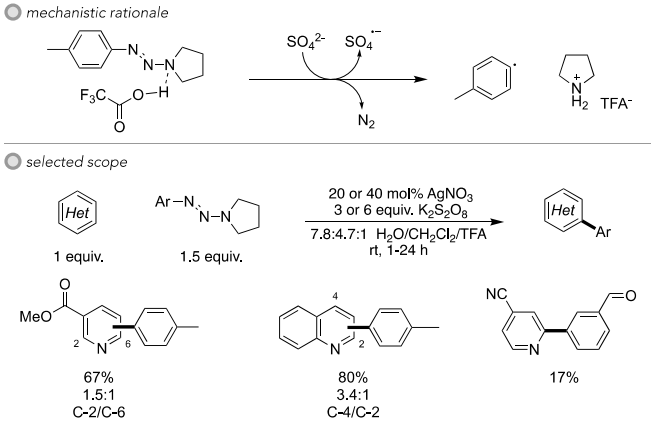
As mentioned in the introductions, Minisci reported in 1968 the fragmentation of cyclohexane derivatives to form primary alkyl radicals for addition to heteroarenes through β-scission.[17] Li and co-workers recently exploited this mechanistic strategy in their Minisci-type reaction of cycloalkanol-derived alkyl radicals (Scheme 62).[142] They propose that a sulfate radical anion abstracts the alcohol hydrogen from the cycloalkanol, generating an alkoxyl radical capable of fragmenting to form a primary carbon-centered radical which can then undergo Minisci-type addition to a thiazole or quinoline.



Scheme 62. C-C fragmentation of cycloalkanol radicals for Minisci-type reaction.

6.6 Radicals from Triazenes

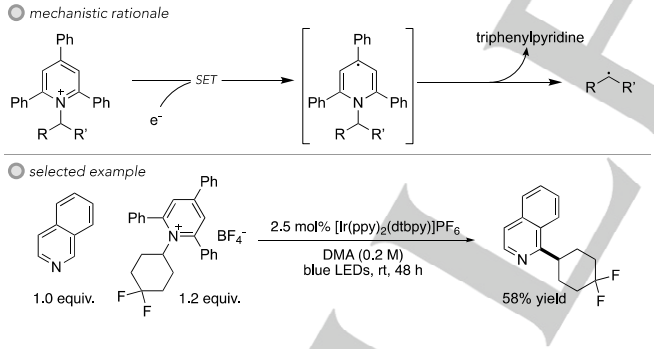
As well as diazonium salts, triazenes have recently been shown to be successful pro-radicals for Minisci-type arylation.[143] Radical generation is proposed to proceed through reduction of the triazene, by a sulfate dianion, after protonation by TFA (Scheme 63, *mechanistic rationale*). A variety of bi- and monocyclic rings can be functionalized and the reaction is relatively tolerant to electronic variation in the aryl radical (*selected scope*). Compared with the earlier work from Baran, which operates under similar conditions, the requirement to presynthesize the triazine is a disadvantage.



Scheme 63. Arylation of heteroarenes through reductive decomposition of triazenes.

6.7 Radicals from Alkylpyridinium Salts

Given the ready availability of alkyl amines, cleavage of C-N bonds in alkyl amine-derivatives represents an attractive option for the generation of carbon-centered radical fragments. Glorius and co-workers recently communicated a Minisci-type protocol that uses such an approach (Scheme 64).[144] In their procedure, the authors propose that bench-stable alkylpyridinium (Katritzky) salts,[145] synthesized in one step from primary amines, are able to receive an electron from a reducing photocatalyst. The resultant radical then undergoes aromaticity-driven fragmentation to furnish a carbon-centered radical capable of undergoing Minisci-type addition.

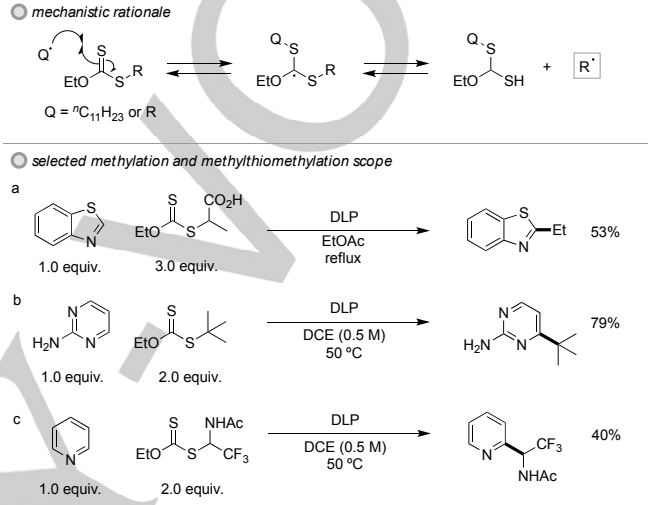


Scheme 64. A deaminative Minisci-type reaction.

The scope for basic heteroarenes focuses on isoquinolines and appears to be limited to secondary radical fragments, however they also demonstrate that amino ester-derived precursors can used with electron-rich heteroarenes due to the more electrophilic nature of those resultant radicals. Although the salts require synthesis, the ability to cleave C-N bonds to generate the alkyl radical opens up new possibilities for future disconnection strategies in Minisci reactions.

6.8 Radicals from Xanthates

The decomposition of xanthates by radical initiation was first used for heteroarylation of carbon radicals by Minisci in 1992, when he and co-workers reported the cyclohexylation of a variety of heteroarenes.[146] In recent years, this methodology has been expanded by Zard to include primary (Scheme 65a),[147] tertiary (Scheme 65b)[148] and α,α-trifluoromethylaminyl (Scheme 65c)[149] radicals.



Scheme 65. Xanthates as radical precursors for Minisci-type reactions.

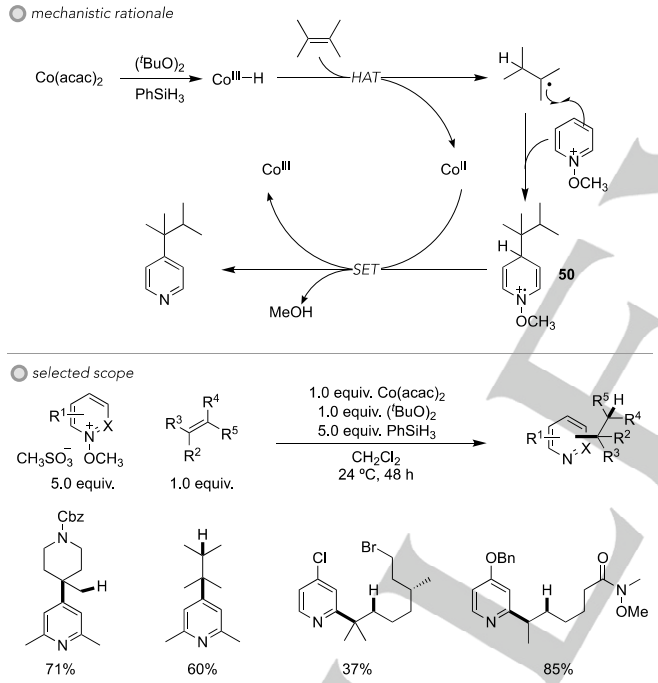
It is proposed that dilauroyl peroxide (DLP) undergoes thermal decomposition forming alkyl radicals capable of adding to the xanthate and triggering reversible release of the radical, which can then add to the heteroarene. Although an interesting radical precursor is used, this methodology suffers from the need to add the DLP portionwise.

7. Advances in Multicomponent Minisci-Type Reactions Using Alkenes

The success of a typical Minisci-type reaction relies on the ability of the initially of the generated radical to react selectively with the heteroarene partner before interacting with any other reaction component. That said, carefully orchestrated multi-component couplings based on Minisci chemistry could provide efficient methods for rapidly building up molecular complexity. Minisci demonstrated as long ago as 1978 that alkenes could be oxidized in the presence of a nucleophile, initially water, enabling the resulting radical to add to heteroarenes in a three-component coupling reaction.[150,151] There have been a number of recent advances which build on this fundamental approach and constitute powerful methods for heteroarene diversification.

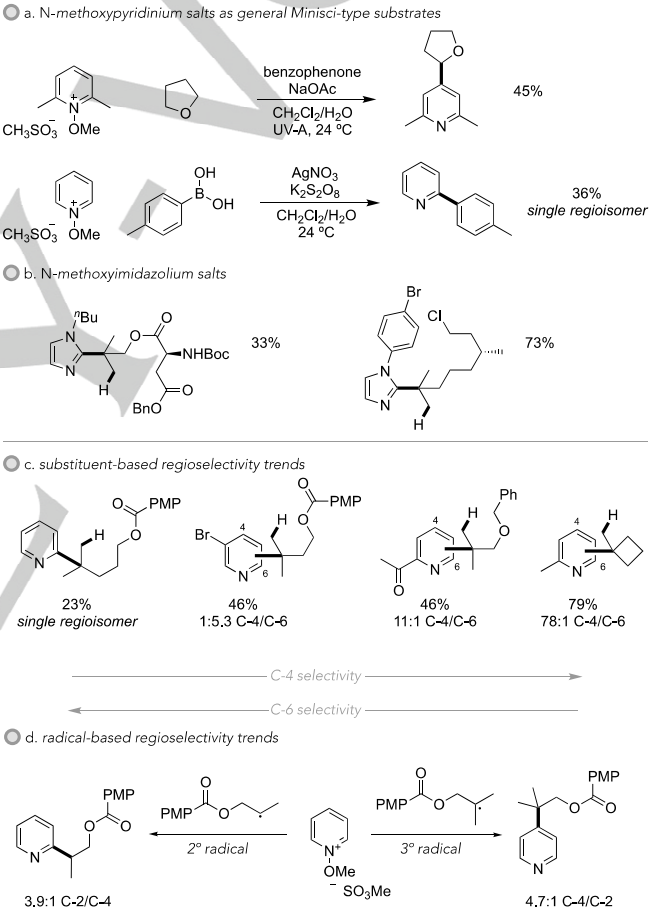
Herzon and co-workers first demonstrated in 2016 that hydropyridylation of unactivated alkenes could be achieved

through cobalt catalysis and Minisci-type reactivity (Scheme 66).[152] A cobalt (III) hydride complex is proposed to be generated *in situ* (see *mechanistic rationale*) which can transfer a hydrogen atom to a highly substituted alkene, with addition selectivity driven by resultant radical stability. The secondary or tertiary radical fragment can then undergo addition to an *N*-methoxypyridinium salt, followed by single electron reduction of resultant adduct **50** and elimination of methanol to furnish the product. This latter part of the mechanism is a significant divergence from most Minisci-type reactions, which typically proceed *via* deprotonation/oxidation after radical addition, rather than in a reduction/elimination fashion. The peroxidation of the heteroarene which allows this may hold potential for the advancement of radical generation for redox-neutral Minisci-type additions. The reaction scope exhibits very good functional group tolerance. A variety of substitution patterns are permissible in the alkene, as long as the HAT from the metal hydride produces a secondary radical fragment. Some of the functional groups tolerated by the reaction include heteroatoms, alkyl halides, pyridyl halides and a Weinreb–Nahm intermediate.[153]



Scheme 66. Hydropyridylation of alkenes through reductive Minisci-type reaction (bold bond indicates the new bond formed in the reaction).

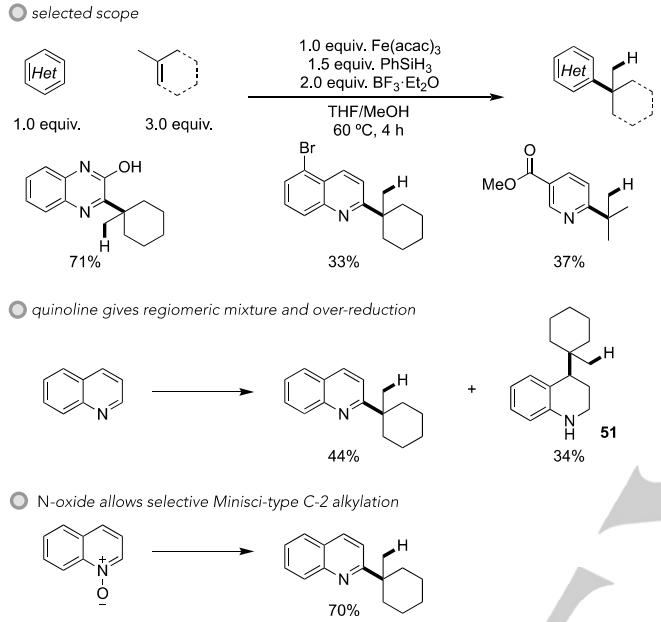
The Herzon group elaborated on their approach in a subsequent full article, in which they significantly expanded the substrate scope to encompass a variety of heteroarenes beyond pyridine, including *N*-methoxypyridazinium, imidazolium, quinolinium, and isoquinolinium salts (Scheme 67a). [154] They also further demonstrated the versatility of their *N*-methoxypyridinium substrates through established Minisci-type protocols such as dehydrogenative coupling with tetrahydrofuran and the Borono-Minisci addition. *N*-methoxyimidazolium salts are additionally successful substrates (Scheme 67b). They also investigate the effect of substituents and radical character on regioselectivity trends for their salts (Scheme 67c). Interestingly, complementary site selectivities were observed between addition of secondary and tertiary radicals to pyridinium salts: harder secondary radicals prefer C-2 addition to some degree, although selectivities were typically modest, whilst tertiary radicals favor C-4 addition with high selectivity (Scheme 67d). The authors rationalized that, presuming radical addition is irreversible, electrostatic interactions favor C-2 addition by secondary radicals and C-4 alkylation by tertiary radicals with higher SOMO energies can be accounted for by invoking frontier orbital interactions. A detailed survey of regioselectivities on substituted pyridines was included.



Scheme 67. Further application of *N*-methoxyheteroaryl substrates to other Minisci-type reactions (bold bonds indicate the new bond formed).

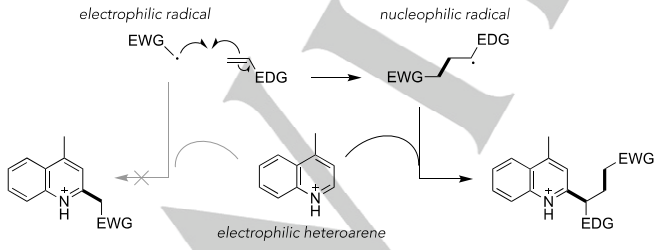
Shortly after, Baran and co-workers described a general iron-promoted olefin-olefin cross coupling technique, the scope of which they extended to Minisci-type reactivity through alkene hydrofunctionalization.[155] In this work, Brønsted acid activation was ineffective but they found that the heterocyclic *N*-oxides could be activated effectively by $BF_3{\cdot}Et_2O$ for reactivity to be obtained. Quinoline-, pyridine- and quinoxaline-derived *N*-oxides furnished

products of tertiary radical addition at C-2. An intriguing finding was the product mixture obtained when simple quinoline was used as substrate: both C-2-functionalized Minisci-type product and over-reduced C-4-functionalized hydroquinoline **51** (scheme 68). When the *N*-oxide substrate was used instead, only the C-2-functionalized Minisci-type product is formed. Liu and co-workers later communicated another iron-promoted reductive hydroheteroarylation, proceeding from the unactivated heteroarenes.[156]



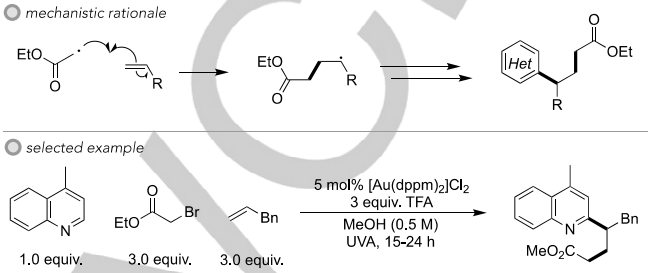
Scheme 68. *N*-oxide allows enhanced chemo- and regiocontrol in iron-promoted hydroheteroarylation.

As alluded to in Section 6.2, in McCallum and Barriault's gold-catalyzed Minisci-type reaction, they also trap radicals with olefins to give open-shell intermediates capable of undergoing addition to heteroarenes.[132] This fundamental reactivity was also reported by Minisci in 2004, exploiting the concept of polarity matching to allow perfluoroalkylation of heteroarenes (Scheme 69) .[157]



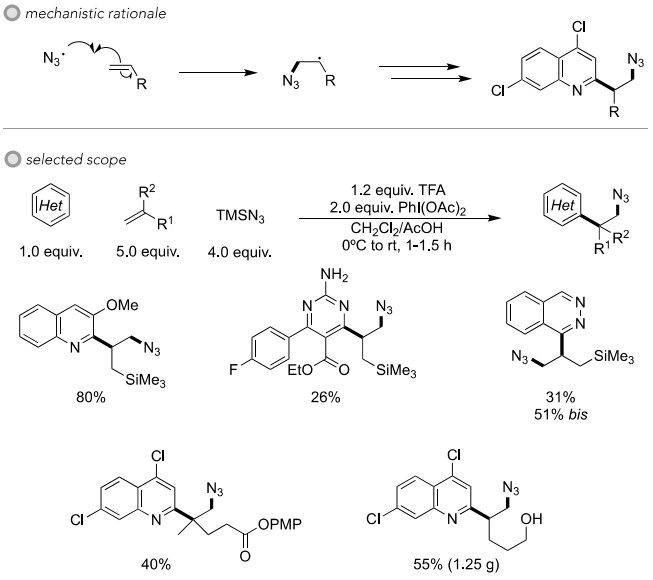
Scheme 69. Overview of polarity matching of nucleophilic and electrophilic radicals to achieve desired three component-coupling.

In a nice demonstration of such polarity matching between the electronics of both the initial radical and that resulting from radical-alkene combination, McCallum and Barriault were able to achieve highly selective Minisci-type three component reaction. By utilizing *α*-bromoesters in the presence of acceptor alkenes, a modest scope of this three-component coupling was obtained, with the methyl ester product obtained after presumable transesterification (Scheme 70).



Scheme 70. Multicomponent coupling of α-carbonyl radicals, alkenes and heteroarenes.

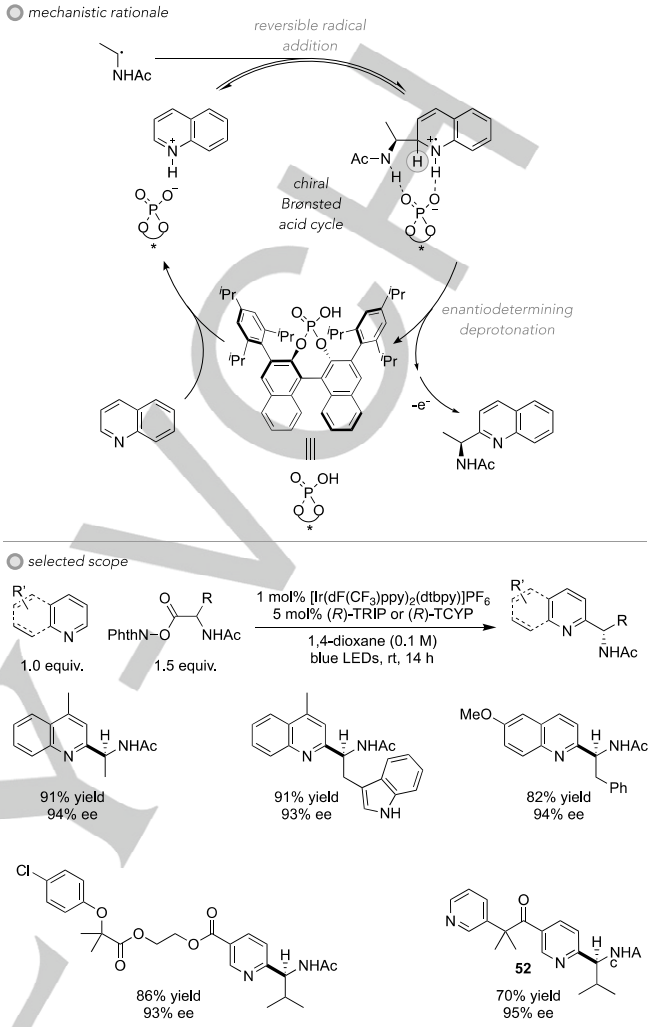
Liu and co-workers then went on to advance the capacity of this approach in an azidoheteroarylation of alkenes (Scheme 71).[158] The reaction exploits polarity matching between azido radicals and electron-rich olefins. As with Antonchick's C-H abstraction technique, azido radicals are formed *in situ* from $TMSN_3$ and PIDA (see Section 3.1). Rather than using the azide radical to perform HAT, in this work the azide radical reacts with an electron-rich alkene, the product of which engages in Minisci-type reaction (Scheme 71, *mechanistic rationale*). The transformation works well on a broad range of heterocycles with very quick reaction time and on gram scale. A variety of alkene substituents can be tolerated as long as they are electron-rich or electron-neutral.



Scheme 71. Azidoheteroarylation of alkenes enabled by polarity matching.

8. Advances in Control of Stereochemistry

Methods to directly functionalize C-H bonds whilst also generating stereocenters in an enantioselective manner are highly desirable due to the complexity that is rapidly generated.[159] Although many of the methods discussed herein are able to form stereocenteres through the addition of prochiral radicals, controlling absolute stereochemistry at such centers has been a long-standing challenge. In 2018, Phipps and co-workers reported the use of chiral Brønsted acid catalysis to induce asymmetry in the addition of prochiral, acyl-protected α-aminoalkyl radicals to basic heteroarenes (Scheme 72).[160] As in the prior reports from Shang and Fu (see Section 2.2), *N*-acyloxyphthalimides were utilized as convenient radical precursors in combination with a photoredox catalyst to mediate reduction of the RAE and oxidation in the final step of the Minisci cycle (photoredox mechanism not shown here). The authors hypothesized that if the incoming prochiral radical possessed a hydrogen bond donor then it may be possible to orchestrate multiple non-covalent interactions between a chiral phosphoric acid catalyst, protonated substrate and radical nucleophile either in the transition state of the addition or in subsequent diastereomeric intermediates. Based on observation of a significant primary KIE in an intermolecular competition experiment, they proposed that reversible radical addition occurs, followed by product- and enantio-determining deprotonation.[161]

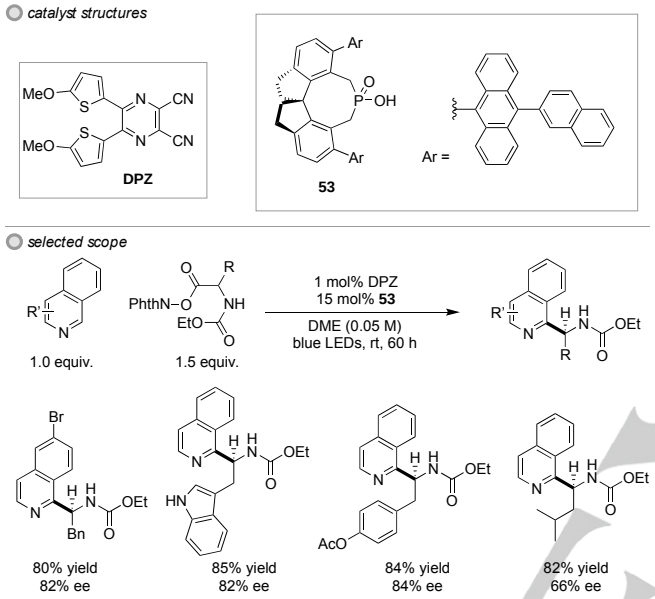


Scheme 72. Enantioselective addition of aminoalkyl radicals to quinolines and pyridines using TRIP phosphoric acids and photoredox catalysis

Many α-aminoalkyl radicals, derived simply from commercially available *N*-acetyl protected amino acids, can undergo the asymmetric Minisci-type reaction. Excellent enantioselectivity is observed with R groups as small as methyl and as large as a methylene-linked indole. The reaction can be performed successfully on a variety of quinoline-derived scaffolds. The authors discovered that very high regioselectivity for the C-2 position was observed on quinolines bearing no C-4 substituent, which is rare in most Minisci protocols. Control experiments showed that the extended catalyst structure was crucial for both enantio- and regioselectivity. A range of substituents of varying electronics can be incorporated into the benzo-portion of the heterocycle substrates and pyridine-portion can tolerate both aryl and aryloxyl substituents. With a change in catalyst from TRIP to TCYP,[162] electron-deficient pyridines can also be made amenable to the asymmetric reaction with high enantioselectivities. Additionally, several examples of late-stage functionalization of pharmaceuticals were demonstrated, such as

Metyrapone which was functionalized exclusively at one site of a possible six in high ee and good yield (**52**).

Later in 2018, Jiang and co-workers demonstrated an enantioselective Minisci-type reaction of isoquinolines.[163] Using a similar approach involving RAEs as radical precursors, they employ a chiral SPINOL-derived phosphoric acid **53** to give high enantioselectivities in additions to isoquinolines, substrates that had given low ee in the catalyst system used by Phipps and co-workers (Scheme 73). Advantageously, they were able to use the organic dye DPZ as a photocatalyst rather than iridium complexes.



Scheme 73. Enantioselective radical addition to isoquinolines using SPINOL-derived phosphoric acids and photoredox catalysis.

9. Summary and Outlook

As is evident from the quantity and diversity of material presented in this review article, a great deal of progress has been made over the past ten years in Minisci-type reactions. The fact that the basic heterocyclic substrates most suited to this reactivity type are those amongst the most widely used in medicinal chemistry research means that further development and refinement of Minisci-type reactions will always be in demand. This includes methods which can utilize readily available precursors, operate under milder conditions, exert greater control of selectivity and avoid the use of precious metals.

A renewed appreciation of the power and versatility of free radical chemistry has been instrumental in spurring new developments in Minisci chemistry. Innovative and efficient ways to generate the required radicals have been a constant driver. Photoredox catalysis has undoubtedly been an enabling approach which has led to numerous Minisci protocols in the past five years. Electrochemistry is sure to provide further breakthroughs in the near future, given the surge of interest within the synthetic community. As more and more synthetic chemists become accustomed to working with and exploiting free radicals in their methodology development, it seems unlikely that the pace of progress in Minisci chemistry will slow. Indeed, Minisci-type reactions have become something of a testbed for the latest developments in free radical chemistry, which goes some way to explaining the dramatic rise in advances over the past decade. For this reason, the practicing chemist might question if so many diverse methods are needed for the generation of such often-similar radical fragments, particularly since the original conditions developed by Francesco Minisci in the early '70s were so effective. It is true that there are many situations where those original conditions would be perfectly suitable and more elaborate reaction protocols may not be necessary. But we posit that all of this academic attention is inevitably of benefit to end users of Minisci chemistry as some proportion of these advances will turn out to be of long-term practical utility. Perhaps some of the advances will stand the test of time and may supersede the original protocol, potentially for reasons of sustainability (avoiding previous metal catalysts), functional group compatibility (eg. in late-stage functionalization) or control of selectivity (regio- or enantioselectivity).

Whilst the application of catalysis in Minisci-type reactions has typically focused on the radical generation aspect of the mechanism, it is likely that catalysis will play a leading role in efforts to modulate various selectivity aspects, which occur in later stages of the mechanism. The fact that catalytic amount of Lewis and Brønsted acids have been employed in a number of studies hints at the potential here, in contrast to classical conditions typically used stoichiometric strong acid. Indeed, the last year has seen the development of the first enantioselective processes, which employ chiral Brønsted acid catalysis.

We hope that this review will serve readers in two capacities: firstly, as a useful reference guide to a synthetic chemist wishing to forge C-C bonds to basic heterocycles; but secondly as an illustration of some of the most exciting new developments in synthetic chemistry of the past decade, played out in the context of a single reaction type of great significance to a number of applications, most notably in pharmaceutical chemistry research.

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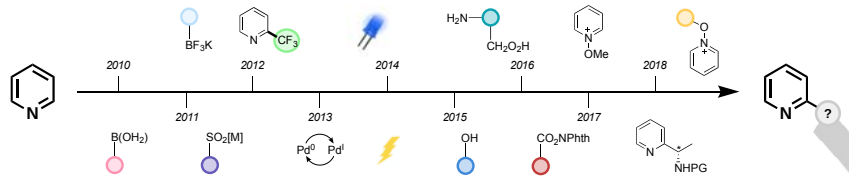

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Page No. – Page No.

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