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Review

Nitrogen-Centered Radicals in Functionalization of sp^2 Systems: Generation, Reactivity, and Applications in Synthesis

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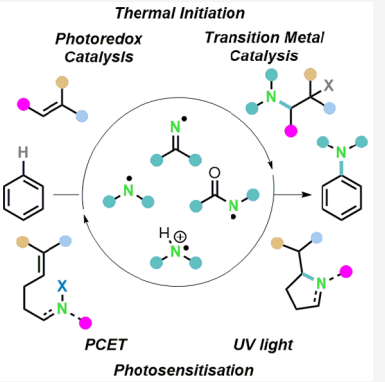
ABSTRACT: The chemistry of nitrogen-centered radicals (NCRs) has plentiful applications in organic synthesis, and they continue to expand as our understanding of these reactive species increases. The utility of these reactive intermediates is demonstrated in the recent advances in C−H amination and the (di)amination of alkenes. Synthesis of previously challenging structures can be achieved by efficient functionalization of sp^2 moieties without prefunctionalization, allowing for faster and more streamlined synthesis. This Review addresses the generation, reactivity, and application of NCRs, including, but not limited to, iminyl, aminyl, amidyl, and aminium species. Contributions from early discovery up to the most recent examples have been highlighted, covering radical initiation, thermolysis, photolysis, and, more recently, photoredox catalysis. Radical-mediated intermolecular amination of (hetero)arenes can occur with a variety of complex amine precursors, generating aniline derivatives, an important class of structures for drug discovery and development. Functionalization of olefins is achievable in high anti-Markovnikov regioselectivity and allows access to difunctionalized structures when the intermediate carbon radicals are trapped. Additionally, the reactivity of NCRs can be harnessed for the rapid construction of N-heterocycles such as pyrrolidines, phenanthridines, quinoxalines, and quinazolinones.



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1. INTRODUCTION

1.1. The Importance of Nitrogen

The ubiquity of nitrogen in agrochemicals, drug molecules, and synthetic materials highlights the significance of incorporating the moiety into organic compounds. The input of nitrogen atoms into medicinal compounds bears a high impact on a compound's physiological parameters, such as hydrogen-bonding interactions and polarity. As a result, the atom is prevalent in drug molecules,[1] as the fine-tuning of physicochemical properties is a crucial factor in the development of a successful drug molecule.[2] Thus, transformations to incorporate nitrogen are a powerful part of the synthetic chemist's toolbox.

1.2. Radicals in Organic Chemistry

The chemistry of radicals has progressed rapidly in recent years. Understanding the inherent reactivity of the species has led to a greater appreciation of their use in synthesis.[3−5] Radical reactions are a valuable tool for chemists and allow access to synthetic pathways which have previously been considered to be highly challenging or unfeasible. In a retrosynthetic sense, conventional methods of disconnecting bonds have relied on the polar-bond approach. Although this chemistry is extremely valuable and well-understood, a radical approach can expose exciting new retrosynthetic disconnections. A one-electron strategy can reveal previously unexplored disconnections and minimize the need for functional group interconversions and protecting groups.[6,7]

1.3. Radical-Mediated Amination with Nitrogen-Centered Radicals

Traditional methods of C−N bond formations include the well-established Pd-catalyzed Buchwald−Hartwig amination,[8] Cu-catalyzed Ullmann coupling,[9] and the Chan−Lam reaction,[10,11] all of which have extensive application in traditional settings. The use of C−N cross-coupling methods in medicinal chemistry accounts for approximately 23% of reported reactions in recent publications, demonstrating the omnipresent nature of the transformation.[12] Furthermore, functionalized amide and lactam products are ubiquitous in active pharmaceutical ingredients (APIs).[12,13] However, elevated temperatures and pre-functionalized coupling partners are needed for the success of these strategies. A recently evolved approach to amination is the application of selective C−H functionalization, where no prefunctionalized handles are needed. Thus, a large proportion of the respective reactants is incorporated into the final product, rendering the overall process more atom-efficient, while minimizing undesired waste production.

1.4. Scope of this Review

This Review aims to cover both inter- and intramolecular radical-mediated amination, amidation, and imination, particularly focusing on the evolution of N-centered radicals (NCRs) for the synthesis of aniline derivatives and N-heterocycles. An introductory section is included, outlining the main types of NCRs, their generation, and their reported reactivities. We hope this provides an accessible tool for organic chemists who may be unfamiliar with aspects of NCRs. The first half of the Review is focused on older literature which largely employed thermal or ultraviolet (UV) light irradiation of N−X, N−N, N−O, and N−S bonds, and to a lesser extent, N−C bonds. Use of hypervalent iodine reagents for the generation of NCRs and the construction of heterocycles via tandem radical cyclization reactions has also been specified. The Review then moves to address transition-metal redox catalysis, where metal-complexed NCRs have emerged as reactive intermediates for the amination of (hetero)arenes and diaminations of olefins. The second half of the Review spans the emergence of photocatalysis in relation to NCRs. Here, we delve into preliminary, high-impact, and conceptually interesting publications relating to photoredox and photosensitization methods for the amination of (hetero)arenes and olefins. This is split into two main classes, oxidative and reductive quenching, which include recent efforts in proton-coupled electron transfer (PCET) reactions. Other excellent reviews have focused on reporting more recent transformations.[14−23] A number of relevant reviews have surfaced since submitting this Review that the authors would like to highlight.[24−26]

1.5. Types of N-Centered Radicals

NCRs offer diverse possibilities in the context of amination; the "type" of radical determines the inherent reactivity imposed on the intended coupling partners, both intra- and intermolecularly. The nature of NCRs has been defined and can be categorized into four main types, shown in Figure 1.[18,27]

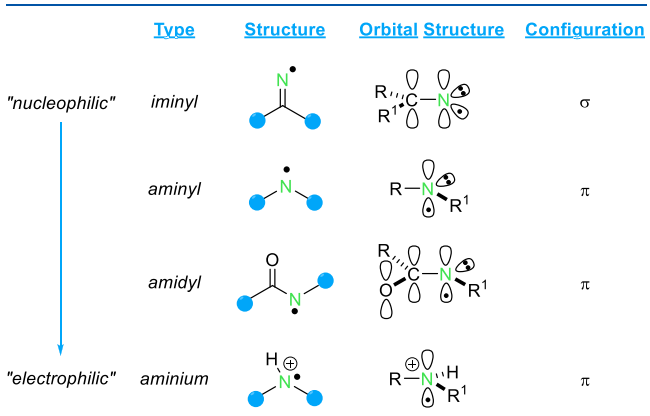

Figure 1. Four main types of N-centered radicals and the structure/orbital configuration of each.

Each type of radical has its own unique reactivity which can be interpreted or rationalized by the orbital structure and configuration. In general terms, they can be classed as "nucleophilic" or "electrophilic" in nature; these can be used as loose terms when rationalizing their reactivity with reaction partners. Stability of these radicals can be determined on a case-by-case basis and is largely dependent on the substituents and choice of solvent.[28−30]

Iminyl radicals are classed as σ-type radicals, as the single electron resides in an sp^2-hybridized orbital, and they possess a planar structure.[31−33] Iminyl radicals are considered to be nucleophilic and have a similar philicity to carbon-centered radicals.[34] Aminyl radicals are considered to be weakly

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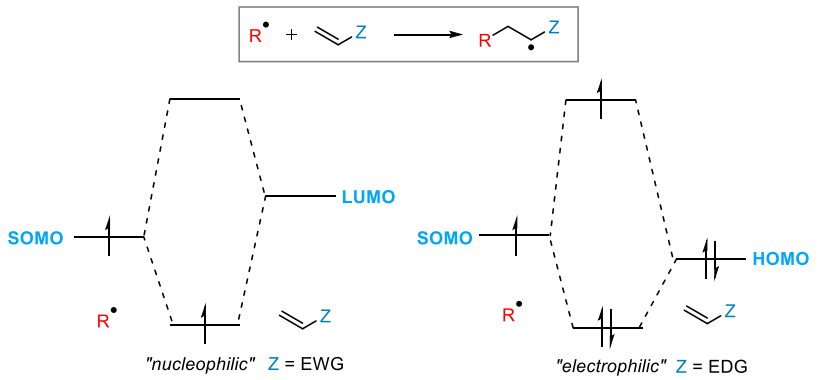

Figure 2. Orbital interaction diagrams between the singly occupied molecular orbital (SOMO) of the radical and either the lowest unoccupied molecular orbital (LUMO) or the highest occupied molecular orbital (HOMO) of the alkene acceptor. EWG = electron-withdrawing group, EDG = electron-donating group.

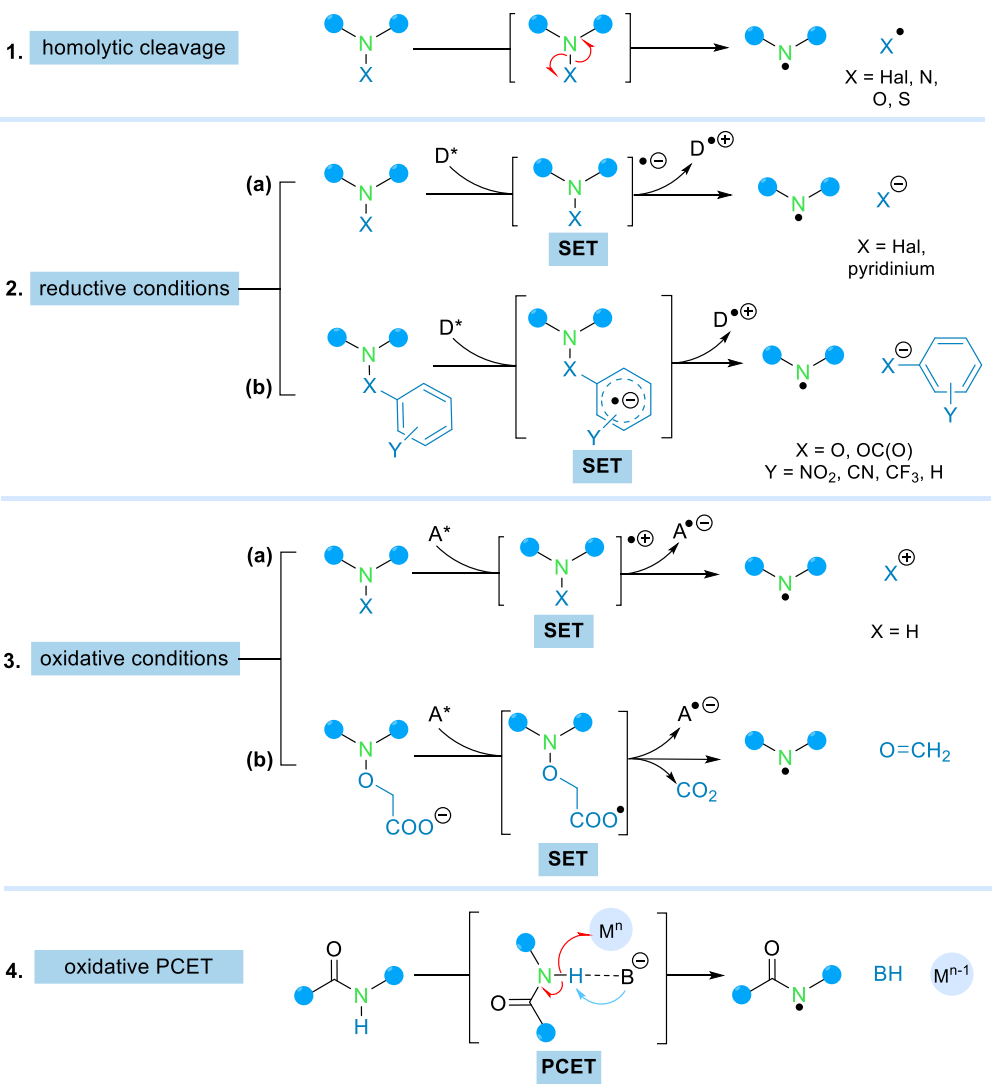

Figure 3. General methods to generate NCRs. D = donor, A = acceptor.

nucleophilic; however, they are least commonly utilized of the four due to their preference for H-atom abstraction and reversible addition to olefins.[35−37] It is known that aminyl radicals can be activated by Lewis acids, although it has been noted that this imposed a high steric barrier in the transition state for synthetic transformations.[38] Amidyl and aminium radicals both possess a π-type configuration as the unpaired electron resides in a p-orbital, perpendicular to the R groups.[39,40] Aminium radicals are considered to be the most electrophilic species of the four, due to the radical cation. These four classes of NCRs cover the majority of reports detailing radical-mediated amination, although NCRs also extend to other types, such as

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sulfonamidyl and hydrazonyl radicals,[27] which are also exemplified in this Review.

1.5.1. A Quick Note on Radical Philicity. Philicity of radicals is an important concept and strongly influences the selectivity and reactivity of the species. Using the radical addition to alkenes as an example, when the polar effects on the frontier orbitals are taken into account, predictions of which alkenes are best matched to the incoming radical can be made (Figure 2).[41,42]

Radicals that are "polarity matched" favor a successful reaction outcome—a nucleophilic radical will favor addition to an electron-poor species, and an electrophilic radical will seek to react with an electron-rich species. The energy of the SOMO is heavily influenced by electronegativity and thus is a useful indicator of philicity.[42] Computational and experimental studies have been effective in defining philicity of radicals and have been regularly documented in the literature.[43−45] The recent review by Welin and co-workers[46] delves into the selectivity of radicals by assessing their philicity. An easy-to-follow, but in-depth guide has been coupled with recent literature examples to demonstrate the importance of this parameter when designing radical reactions.

1.5.2. Generation of NCRs. Methods of generating NCRs can be divided into four main categories: (1) homolytic cleavage, (2) reductive conditions, (3) oxidative conditions, and (4) oxidative proton-coupled electron transfer (PCET) (Figure 3).[18,47]

1. Homolytic cleavage of an N−X bond generates two radical products, which is often induced by exposure to UV light.
2. Reductive conditions require single-electron transfer (SET) to the nitrogen species, which can occur in the following ways:
   a. SET from a donor to the N−X σ^*-orbital, which gives rise to a radical anion and results in cleavage.
   b. SET from a donor to a π^*-acceptor orbital, which gives rise to a radical anion and subsequent fragmentation.

   The former conditions (2a) generally use a redox-active metal [e.g., Fe, Ti(III)Cl_3] in non-catalytic amounts.[48] The latter (2b), have become extensively documented in recent years, aligned with the rise in photoredox catalysis. This has permitted milder conditions to be employed, thus protecting the integrity of substrates.
3. Oxidative conditions require SET to an acceptor species and can occur in the following ways:
   a. SET to an acceptor from the HOMO of the precursor gives rise to a radical cation intermediate and results in cleavage.
   b. SET to an acceptor from an oxidizable group (external to the key NCR moiety) gives rise to a fragmentation event and cleavage of the N−X bond.

   The former (3a) has traditionally used stoichiometric oxidants (e.g., *tert*-butyl hypochlorite[49] and hypervalent iodine reagents); however, recent developments in photocatalysis have allowed the application of milder conditions. The latter (3b) is a strategy pioneered by Forrester[50] and Zard,[51] which commonly involves a decarboxylative cascade mechanism to generate the NCR counterpart.
4. Oxidative PCET consists of a catalytic concerted homolytic bond activation. The blue arrow represents a proton transfer, while the red arrows represent electron transfer to a metal catalyst, in a concerted step. Although the concept of PCET has been extensively documented, primarily in biological systems,[52] the generation of amidyl radicals via oxidative PCET was pioneered by the Knowles group.[53,54] Catalytic amounts of base and oxidant can be used to selectivity activate amide N−H bonds over weaker X−H bonds, achieved through the formation of a hydrogen-bonding complex.[55]

1.5.3. General Reactivities of NCRs. Depending on the type of radical, general reactivities can vary, resulting in a diverse set of possible chemical transformations (Figure 4). Knowledge

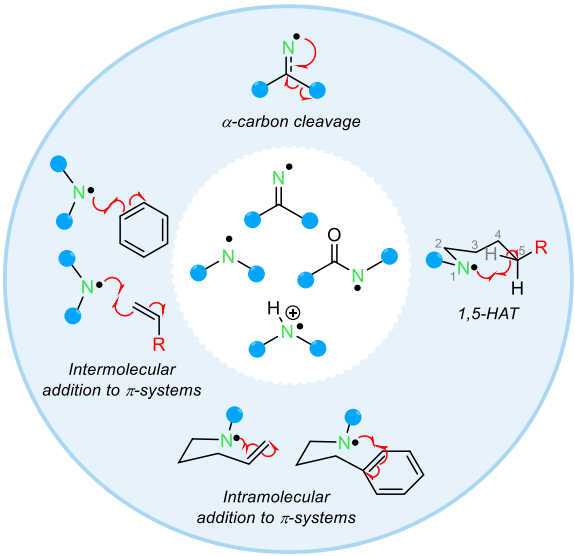

Figure 4. General reactivities of NCRs.

of the favored reactivities of each radical can predict selectivity in a chemical reaction, a significant advantage when designing syntheses. It has been noted that increased electrophilic character of NCRs directly correlates with increased reactivity.[27]

The general reactivities displayed in Figure 4 offer a plethora of synthetic utility and are discussed in more detail below:

1. The fragmentation of an α-carbon commonly involves the β-scission of an iminyl radical to a nitrile derivative, first demonstrated by Zard and co-workers.[56] The β-scission of an aminium radical was also observed by Minisci and Galli.[57] The pivotal focus of this Review is upon C−H amination and related reactions with NCRs, as well as their addition to alkenes; thus, this cascade-type process is not a point of discussion. For further examples, we direct the reader to the review in ref 58.
2. 1,5-Hydrogen-atom transfer (HAT) occurs in radical systems via a 6-membered cyclic transition state, due to favorable alignments in the transition state.[59] It is a powerful transformation when building complexity into synthetic molecules, specifically at the δ-position, the site of C-centered radical formation.
3. Intramolecular addition to π-systems offers a route to the generation of heterocycles and lactam products (formed by cyclization of amidyl radicals) without the need for

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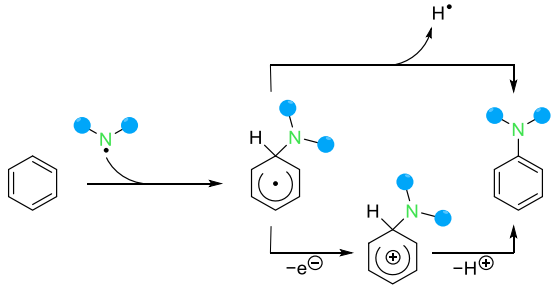
functionalized motifs. Radicals commonly undergo 5-*exo*-trig cyclization, following the Beckwith−Houk model.[60,61] It is known that certain substituents on the π-systems can affect the stability of the transition state, thus promoting a 6-*endo*-trig cyclization process.[60] Radical addition to arenes occurs by homolytic aromatic substitution (HAS) (Scheme 1).[62−64] Addition of a

Scheme 1. General Mechanism for Homolytic Aromatic Substitution



radical to the π-system generates a delocalized radical. Either loss of a hydrogen atom or rapid single-electron oxidation to a cationic σ-complex and loss of a proton affords the C−H functionalized product. Alternatively, a base-promoted version of HAS (i.e., BHAS) can occur where the electron is the catalyst.[65,66] This can be a useful way to rapidly synthesize complex heterocycles.

4. Intermolecular addition to π-systems is a powerful method of incorporating an amine functional group into organic molecules, without the need for prefunctionalization. These transformations usually proceed via a HAS mechanism (Scheme 1). Late-stage functionalization is amenable to this approach and highly applicable to the development of novel medicines.

The substituents on the NCR species can influence selectivity by the presence of either electron-poor or electron-rich groups. The "philicity" of radicals dominates the characteristic reactivity of the NCR. This was demonstrated in a study of rate constants for the cyclization of different NCRs, measured by laser flash photolysis (Figure 5).[67]

A known characteristic of radical additions to unsaturated systems is their ability to achieve anti-Markovnikov selectivity (cf. the peroxide effect).[68,69] This selectivity is also consistently observed for the additions of electrophilic NCRs to alkenes, which are exemplified in this Review.[70] The cyclization of aminyl radicals is rather slow, in comparison to their protonated forms, although aminyl radicals that are complexed with Lewis acid catalysts cyclize more rapidly.[71,72] Amidyl radicals are the most reactive species in cyclization reactions, particularly toward the acyl side chain vs the N-substituent side chain. A clear trend is observed in the switch of reactivity, with a diminished rate for "nucleophilic" species. A recent review by Walton documented similar rate constants for the 5-*exo*-cyclization of aminyl and iminyl radicals, measured by electron paramagnetic resonance (EPR).[34] Attempted measurement of the rate of a 6-membered cyclization resulted in a 1,5-HAT translocation rather than cyclization.[67]

2. CATALYST-FREE GENERATION OF NITROGEN-CENTERED RADICALS

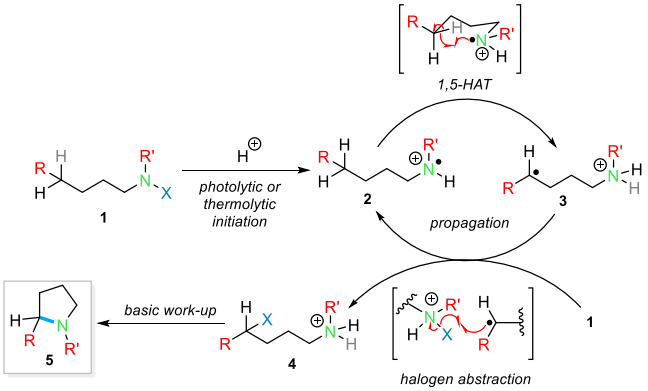
2.1. NCRs Derived from Nitrogen−Halogen Bonds

2.1.1. The Hofmann−Löffler−Freytag Reaction.

Although this reaction does not functionalize sp^2 centers, it provides inspiration for a number of the reactions that are covered later in the Review, and so it is briefly mentioned here as background. The evolution of this transformation is not covered by this Review.

The first uses of NCRs in organic synthesis were pioneered by Hofmann[73] (1883) and Löffler and Freytag[74−76] (1909). The process was named the Hofmann−Löffler−Freytag (HLF) reaction, and mechanistic studies by Wawzonek and Thelan[77−79] supported the radical chain mechanism shown in Scheme 2, which was further iterated by Corey[80] in 1960.

Scheme 2. General Mechanism for the Hofmann−Löffler−Freytag (HLF) Reaction, an Intramolecular C−H Amination



After protonation of N-halogenated amine **1** with a strong acid, homolytic cleavage under photolytic or thermal conditions occurs. The highly electrophilic, cationic, aminium radical **2** induces an intramolecular 1,5-HAT from the δ-carbon. Transfer of the H-atom gives rise to the alkyl radical **3**, and subsequent halogenation of the δ-carbon yields **4**. Basic workup conditions afford the cyclic amine **5** via displacement of the halide. Selectivity for the δ-carbon can be rationalized by the 6-membered cyclic transition state that arises from the H-atom

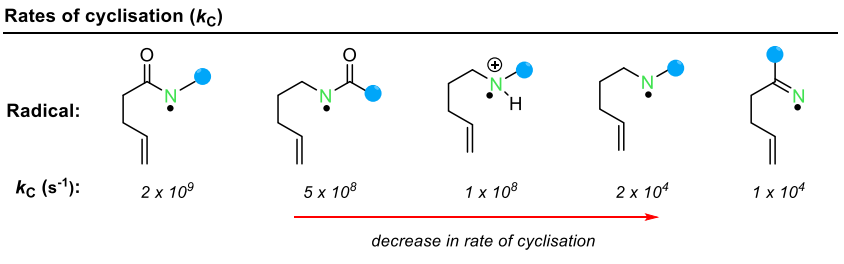


Figure 5. Comparison of rate constants associated with the rate of cyclization.[67]

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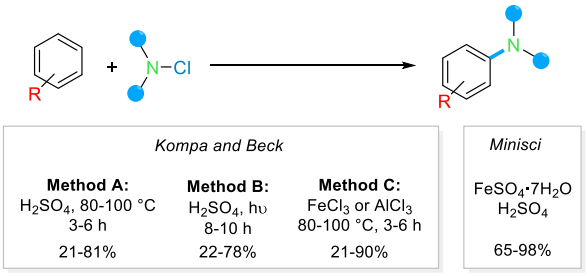
abstraction, giving rise to the 1,5-HAT term. Ferrous salts and potassium persulfate have also been shown to promote the HLF reaction, as demonstrated by Corey.[80]

2.1.2. Radical-Mediated Amination via NCRs Derived from Nitrogen−Halogen Bonds. Early contributions to intermolecular examples of C−H amination of *N*-chloroalkylamines were pioneered by Kompa and Beck[81] and Minisci[82] (Scheme 3). Kompa and Beck focused their efforts on thermal,

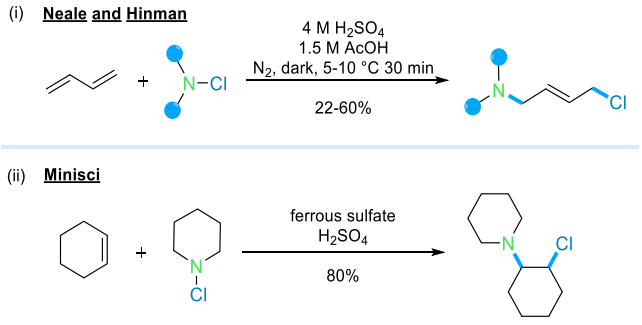
Scheme 3. Reaction Conditions for the Initial Iterations of Intermolecular C−H Amination of Aromatics with *N*-Chloroamines



photochemical, and Lewis acid-catalyzed systems. Minisci reported the use of ferrous sulfate to provide a redox system for the amination of electron-rich aromatics. A review was published containing the extensive work by Minisci on the range of amenable substrates, varying in electron density and substitution patterns.[83]

In 1963, Neale and Hinman reported the intermolecular addition of aminium radicals to butadiene [Scheme 4, (i)].[84,85]

Scheme 4. Intermolecular Amination of Olefins with Aminium Radicals Generated from *N*-Chloroamines[a]

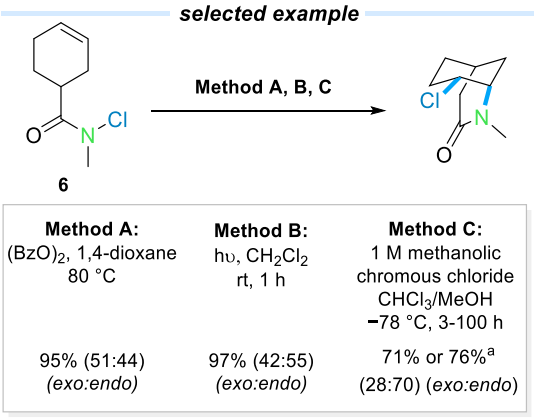


[a]The colored bonds in (ii) define the formation of new bonds only and do not define the stereochemistry.

N-chloroamines in highly acidic media reacted spontaneously with butadiene, yielding 1,4-chloroamination products. Further development of the protocol was instigated by Minisci, who applied the ferrous redox system to intermolecular olefins [Scheme 4, (ii)].[86] A review published by Minisci described the application of redox systems and *N*-chloroamines to the intermolecular and intramolecular amination of olefins.[87]

Olefinic *N*-chloroamides (**6**) were investigated by Lessard and co-workers, who presented three different methods to achieve cyclization (Scheme 5). Their publications detailed the use of photochemical or peroxide initiation[88] and chromium chloride[89] reagents to trigger a radical chain process. The *N*-chloroamides (**6**) were synthesized from reacting their

Scheme 5. Methods Presented by Lessard et al.[88,89] for the Cyclization of *N*-Chloroamides[a]



[a]A buffered solution of NaOCl was used to synthesise the N-chloro precursor.

corresponding amides with NaOCl. In the selected example, excellent yields were obtained with all methods (Scheme 5).

In 1985, Skell et al. investigated the reactivity of imidyl radicals (e.g., **7**) generated from a variety of *N*-haloimides. Rates and selectivities of *N*-haloimide derivatives (**8**−**10**) were examined in four different reactivities: ring-opening, H-abstraction, and their additions to olefins and arenes (Scheme 6).[90−92]

N-Bromosuccinimide (**8**, NBS) and *N*-chlorosuccinimide (NCS) were found to reversibly ring-open to the corresponding isocyanate radical **11**. When NBS was present, faster trapping of radical **11** by conversion of **8** to **7** occurred, resulting in the formation of the ring-opened product **12**. In the case of NCS, abstraction of chlorine atom with **11** was slow; consequently, less ring-opened product **12** was observed, and the radical **7** was intercepted by other radical pathways, such as addition to alkenes. Use of *N*-bromophthalimide (**9**) and *N*-bromo-3,3-dimethylglutarimide (**10**) significantly decreased the formation of the ring-opened product.[93,94] Studies were carried out on the selectivities of the H-atom abstraction capabilities of imidyl radicals furnishing imide products (e.g., **13**). The radicals generated were shown to have similar reactivity to chlorine or hydroxyl radicals. For alkene additions to give intermediate **14**, rates were found to be most rapid when electron-rich alkenes were employed, indicating the electrophilic nature of the imidyl radicals generated. The carbon radical generated after the addition acted as a chain carrier, abstracting a halogen from the *N*-haloimide to afford 1,2-disubstituted alkanes **15**. The rate of addition to arenes to give **16** was found to be significantly lower than that of imidyl addition to alkenes.

In 2001, Oshima presented a radical [3+2] annulation with *N*-allyl-*N*-chlorotosylamides **17** and functionalized alkenes **18** to afford functionalized pyrrolidines **19** [Scheme 7, (i)].[95] Reaction of **20** with a strong base and NCS generates the NCR precursor **17**. Initiation with triethylborane (Et_3B) in the presence of a trace of oxygen affords the sulfonamidyl radical **21**. Intermolecular radical addition to an olefin induces a [3+2] cyclization, resulting in the carbon radical intermediate **22**. Halogen atom transfer furnishes several nitrogen-containing heterocycle derivatives in good to excellent yields (**19a**−**19d**). It was found that the rate of addition and cyclization outcompeted any allylic H-atom abstraction. In 2003, the Oshima group reported a one-pot protocol utilizing *N*,*N*-dichlorobenzenesul-

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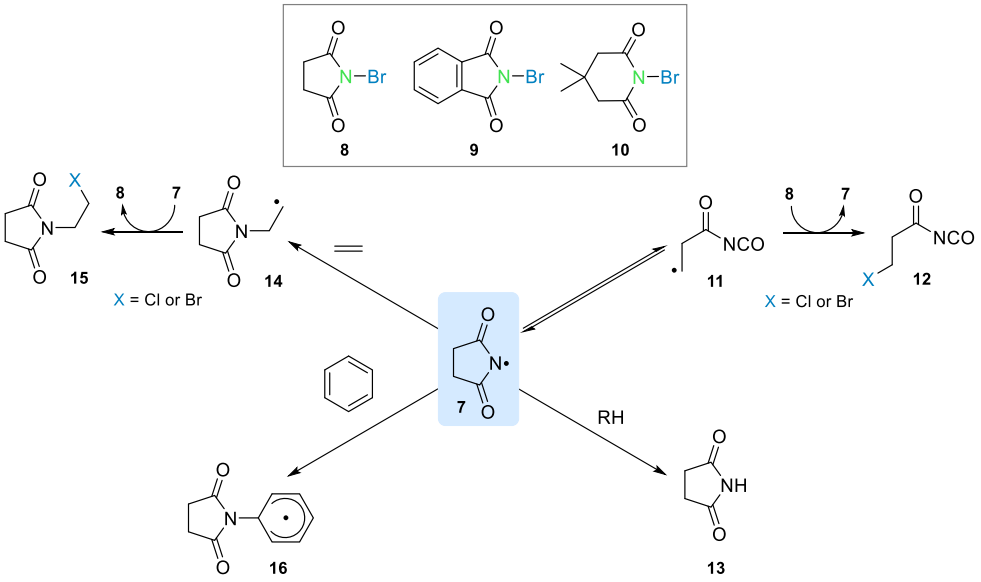
Scheme 6. Reactivities of Imidyl Radicals Investigated by Skell et al.[90−92]



fonamide (**23**), which acted as a nitrogen diradical equivalent [Scheme 7, (ii)]. Utilizing the reaction conditions, intermolecular addition to a 1,3-diene afforded **24**, and subsequent radical annulation with styrene led to pyrrolidine **25**.[96]

In 2014, Luo and Cheng proposed a procedure with a novel precursor, *N*-bromosaccharin (NBSA, **26**), to deliver the imidated products **27** (Scheme 8).[97] A lower bond dissociation energy of NBSA was calculated, which allowed facile homolytic cleavage of the weak N−Br bond, generating NCR **28**.

Exposing NBSA (**26**) to visible light induced the facile homolysis of the N−Br bond to NCR **28**. Addition to the (hetero)arene gave **29**, which underwent addition/elimination or oxidation/re-aromatization to the desired product (Scheme 8). Alkylarenes and haloarenes were tested, giving products **27a**−**27d**, and furnished the regioisomers in good yields with generally favored *para* selectivity. Imidation of a 1,4-disubstituted arene resulted in good regioselectivity in the product **27e**; however, the steric bulk of the *t*Bu group did not completely prevent *ortho* substitution occurring (10% of regioisomer, position *b*, observed). Boc-protected indoles were selectively imidated at the C3-position, and the products were isolated in excellent yields (**27f**−**27h**). Other electron-rich heterocycles were imidated at the C3-position to give products **27i** and **27j** in lower isolated yields. A density functional theory (DFT) study rationalized the observed regioselectivity of NBSA as an imidation agent.

Further research using NBSA to imidate olefins was reported by Luo and Cheng.[98] NBSA or *N*-chlorosaccharin (NCSA, **30**) was used as precursor to the radical species **31**. Subsequent imidation and halogenation of olefins afforded **32** (Scheme 9).

Despite efforts to optimize the reaction, the formation of the haloetherfication product **33** could not be avoided. The authors see this as a sequential addition of bromine radical and succinimidyl radicals to alkenes; however, the mechanism is likely to be more complex. Excellent isolated yields were obtained for products derived from styrene derivatives (**32a**−**32c**, **33a**−**33c**) and from aliphatic alkenes (**32d**, **33d**), although low selectivity between the imidation and etherification products was observed. Examples using NCSA (9 examples, 79−91%) included the successful reaction with ethylene (**32e**, **33e**), which was performed on a gram scale. Further functionalizations of **32a** and **33a** were demonstrated; adding DBU promoted an elimination and furnished **34** in moderate yield. Acetophenone (**35**, 21%) was also isolated as a minor product, derived from the bromoetherification product **33a**.

A recent development by Marsden and co-workers utilized an *in situ* generation of N−Cl substrates **36** to achieve a homogeneous amination protocol. In the presence of UV light, homolytic cleavage generated an aminium radical which cyclized to produce 1,2,3,4-tetrahydroquinoline derivatives **37** (Scheme 10).[99]

Products containing N-substituents (**37a**−**37c**) and α-substituents (**37d**−**37f**) were isolated in good to moderate yields under the reaction conditions. Functional groups in the *para* position on the arene substrates were explored; products containing halide (**37g**, **37h**), boron pinacolate (**37i**), and trifluoromethyl (**37j**) gave lower yields than previous examples. Regioselectivity issues were observed on products derived from *meta*-substituted arenes (**37k**); however, moderate yields were obtained. Other examples demonstrated amination of angular or linear fused or bridged substrates to afford polycyclic systems. A one-pot chlorination with NCS, followed by irradiation with UV light to yield the aminated product (**37a**, 60%) was also described. The electrophilic nature of the NCR was established with competition experiments detailing the preference of reactivity toward more electron-rich arenes. An interesting reactivity was observed when 2,6-disubstituted arenes were subjected to the reaction conditions. The chloro substrate (**36a**) underwent radical substitution at the *ortho* position to furnish **37l** as a trisubstituted arene. The 2,6-dimethylphenyl substrate **36b** unexpectedly formed **37m** in a 1,2-methyl migration, arising from the cationic Wheland intermediate formed. Both examples (**37l**, **37m**) serve as possible examples for further development. This methodology was later examined in a continuous-flow system which had significant advantages in large-scale synthesis over batch-scale processes.[100]

2.2. N-Centered Radicals Derived from Nitrogen−Nitrogen Bonds

In early years, the photolyses of *N*-nitroamines (**38**),[36] *N*-nitrosamines[101−103] (**39**), and *N*-nitrosamides[104,105] (**40**) were

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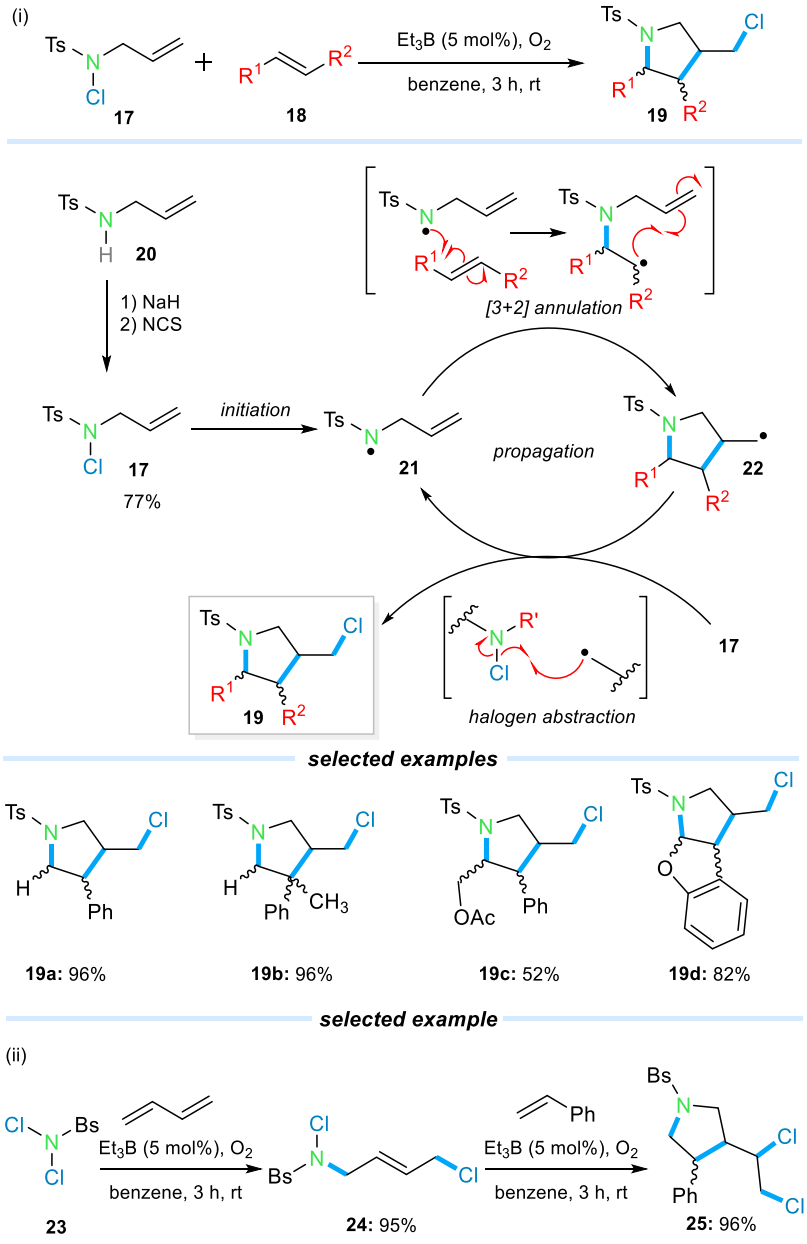
Scheme 7. [3+2] Annulation of N-Centered Radicals to Synthesize Functionalized Pyrrolidines



documented (Figure 6). The generation of these N−N derivatives is analogous to Barton nitrite esters.[102] A key difference in the reactivity of NCRs vs alkoxyl radicals is that the former favor the addition to π-systems, while the latter preferentially perform a 1,5-HAT. Difference in the reactivities can be rationalized by addressing the philicity of the radicals.

Under conditions that are both photolytic and acidic, precursors **38** and **39** can generate aminium radicals and the corresponding NO_2 or NO radical, respectively. The presence of the acyl group on precursor **40** facilitates the photolytic cleavage of the N−N bond to yield an amidyl and NO radical; however, the instability of *N*-nitrosamides in reactions precludes their viability in synthetic use.[105] Investigation into the toxicity of these precursors revealed them to be carcinogenic, and therefore these reagents are no longer considered as viable precursors for the generation of NCRs.[106]

Initiation with azobisisobutyronitrile (AIBN, **41**) and tributyltin hydride for the generation of NCRs has been documented by the teams of Zard[98,99] (**42**, **43**) and Meyer[107] (**44**) (Scheme 11). Both methods exploit the cleavage of the weak N−N bond in a radical fragmentation mechanism, which affords cyclic imine derivatives **45**, **46**, and **47** via an iminyl radical of general formula **48**.

In Zard's methodology, a tributyltin radical (**49**) adds to the thiocarbonyl group, generating the intermediate **50** [Scheme 11, (i)]. β-Scission of **50** yields the iminyl radical **48**, which cyclizes to afford derivatives **45** and **46** in respectable yields (8 examples, 65−92%).[108] The methodology was applied to synthesizing lactams via amidyl NCRs in good yields (2 examples, 74−88%). Zard successfully employed these carbodithioate derivatives (cf. **43**) in the total synthesis of natural products (±)-γ-lycorane[109] and (±)-fortucine.[110] Meyer synthesized the *N*-benzotriazolylimine precursor (**44**), which fragmented to an iminyl radical under tin-mediated conditions; a tributyltin radical (**49**) attacks the triazole moiety, initiating a cascade fragmentation [Scheme

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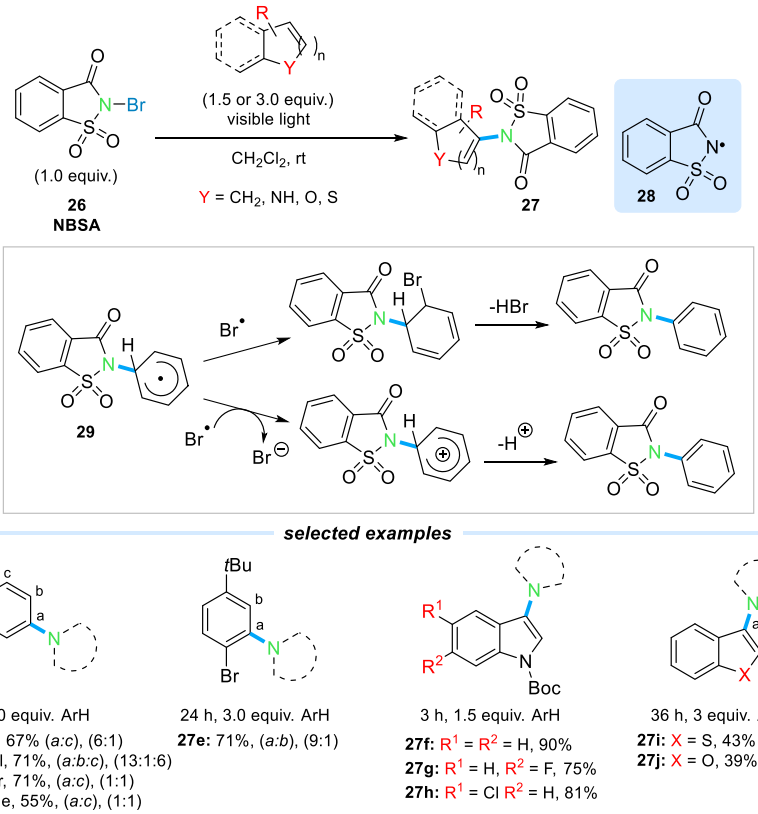
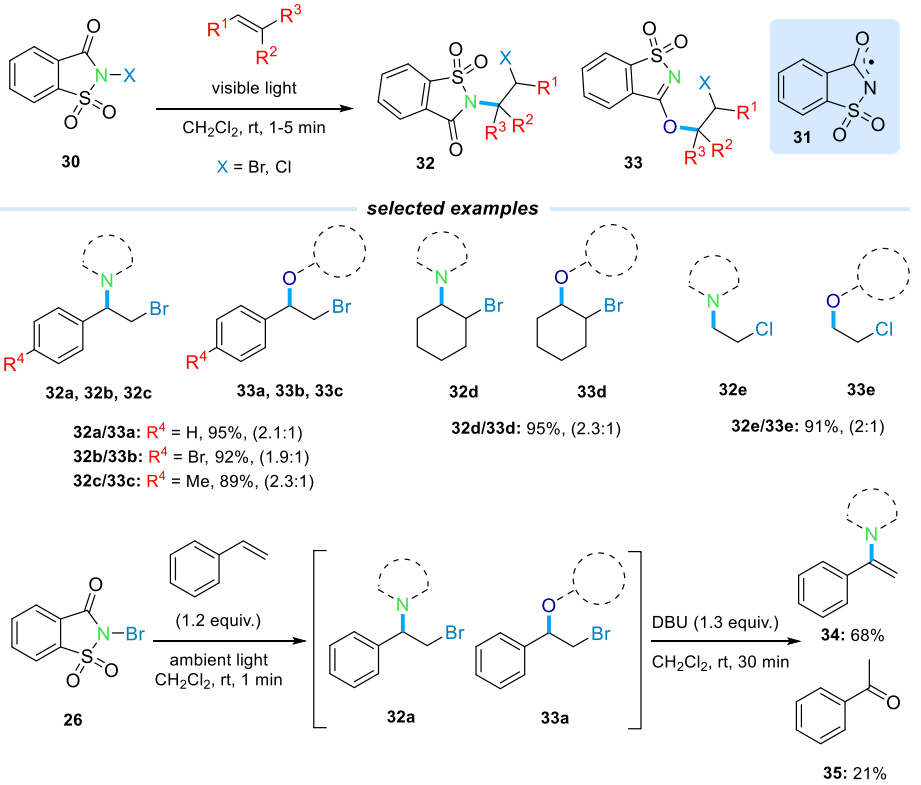
Scheme 8. C−H Imidation of (Hetero)arenes with *N*-Bromosaccharin and Visible Light



Scheme 9. *N*-Bromosaccharin and *N*-Chlorosaccharin as Precursors for the Imidation and Haloetherfication of Olefins



11, (ii)]. Very good yields were reported for this transformation (e.g., **47**) on selected substrates (6 examples, 61−89%).[107]

Thermal decomposition of tetrazenes **51** has been proposed to yield aminium radicals[111−113] under acidic conditions and neutral aminyl radicals[114,115] in dilute acid conditions (Scheme

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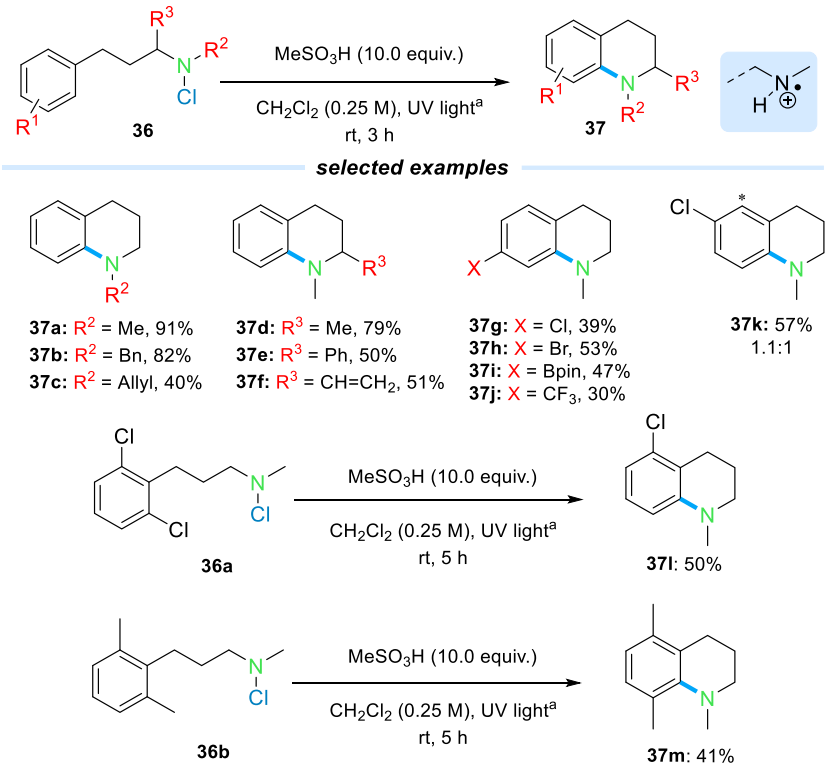
Scheme 10. Intramolecular Amination of Arenes to Yield 1,2,3,4-Tetrahydroquinoline Derivatives



[a]A 125 W high-pressure Hg lamp was used. The C−N bond in the major isomer is shown; the minor isomer is formed at the site marked with the asterisk.

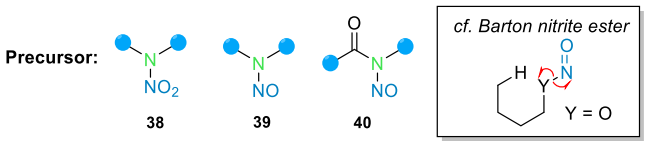


Figure 6. N−N precursors to NCRs: *N*-nitroamine (**38**), *N*-nitrosamine (**39**), and *N*-nitrosamide (**40**).

12). For the latter, the primary product of these precursors results in the bimolecular coupling of the aminyl radicals, to form hydrazines. Aminium radicals generated from tetramethyl-2-tetrazine were shown to undergo addition to olefins under photolytic conditions.[37] Although reports demonstrated the synthetic ability of these precursors, safety concerns over the explosive nature of tetrazenes precludes the synthetic use of these intermediates.[116]

More recently, Li et al. reported the use of *N*-acyltriazenes as precursors to amidyl NCRs under tin-free and initiator-free conditions (Scheme 13).[117] *N,N′*-Diphenyl-*N*-(5-methyl-4-hexenoyl)triazene (**52**) was synthesized in a one-step procedure from aniline, benzenediazonium tetrafluoroborate, and 5-methylhex-4-enoyl chloride.[118]

Substrate **52** was found to be thermally stable when refluxed in benzene; however, direct photolysis with a 125 W high-pressure mercury lamp at room temperature resulted in a complex mixture of products. Reflux in toluene generated amidyl radical **53**, which afforded the desired cyclized products **54** in moderate to good yields (20−78%). A major byproduct resulted from the subsequent carbon radical **55**, reacting further with the phenyl group present on the nitrogen to yield tricyclic lactam derivatives **56**. This observation was more prominent when terminal substitution was present on the alkene bond.

In 1980, McNab observed a novel reaction involving NCRs.[119] Pyrolysis of 1,5-diaryl-1,2,5-triazapentadiene derivatives (**57a**, **57b**) generated iminyl radicals (**58a**, **58b**) which underwent cyclization (Scheme 14). Investigation into the mechanism exhibited the interconversion between a spirodienyl radical via *ipso* attack (**59**) and a classical *ortho* attack (**60a**, **60b**), resulting in isomeric quinoxalines (**61a**, **61b**).

Under pyrolysis conditions, regioisomers **57a** and **57b** were each expected to lead exclusively to the corresponding quinoxaline, **61a** and **61b**, respectively. However, selective generation of iminyl **58a** or **58b** resulted in both quinoxaline isomers being formed (**61a**, **61b**). Rationalization of this observation led to the suspected formation of spirocyclohexadienyl radical **59**. Control experiments varying the radical leaving group showed no change in the ratio of isomers. Further reports were published by McNab and co-workers investigating the thermolysis of polyazapentadienes and their cyclization onto arenes via spirodienyl radical intermediates.[120−123]

Generation of NCRs from azide precursors has been widely reported using tin-initiated conditions. Kim and co-workers reported intramolecular addition to carbonyl compounds **62** to afford lactams **63**, using *N*-stannylaminyl radicals.[124] It was envisaged that the unfavorable addition of the NCR to a carbonyl substrate could be offset with a subsequent favorable *β*-fragmentation of the alkoxyl radical, to yield the corresponding lactams **63** [Scheme 15, (i)].

The reaction of an alkyl azide (**62a**) with a tin radical generated the *N*-stannylaminyl radical **64**, with loss of N_2. Intramolecular addition to the carbonyl resulted in the alkoxyl radical **65**, which rapidly underwent *β*-fragmentation to afford

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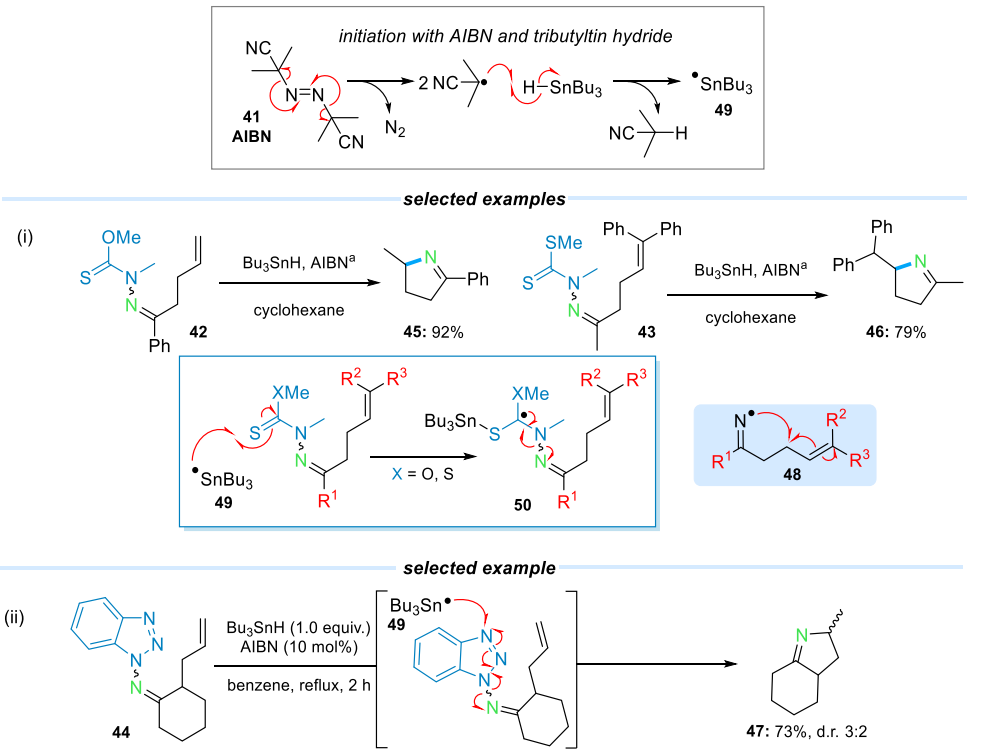
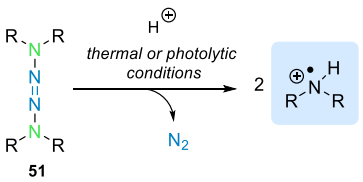
Scheme 11. Types of Azobisisobutyronitrile- and Tributyltin-Mediated N−N Bond Cleavage



[a]Slowly added over 4 h.

Scheme 12. Generation of Aminium Radicals from Tetrazene Precursors

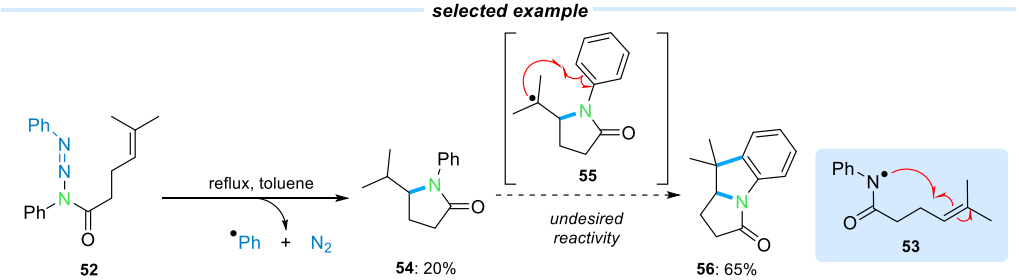


the carbon radical **66**. Subsequent H-atom abstraction from tributyltin hydride yielded the lactam product **63a** in excellent yield. Interestingly, the Kim group went on to demonstrate the use of alkyl azides as radical acceptors, rather than the *N*-stannylaminyl radical acting in a nucleophilic fashion [Scheme 15, (ii)].[125] The publication detailed the cyclization of aliphatic C-centered radicals onto alkyl azides **67** to synthesize N-heterocycles **68**. This procedure was the inspiration for the novel total syntheses of alkaloids (±)-aspidospermidine[126−128] and (±)-vindoline,[129] via a tandem radical cyclization using aryl iodides. Some important works from Kim et al. included their investigation into the unusual reactivity of the "aminyl" radicals.[130,131] Computational studies revealed that *N*-stannylaminyl radicals have a higher SOMO energy and higher electron density at the nitrogen atom. This explains the increased nucleophilicity of *N*-stannylaminyl radicals when compared to aminyl radicals.

In 1999, Benati and co-workers revealed a radical rearrangement to amides with α-azido-β-keto esters **69** via *N*-stannylaminyl radicals (Scheme 16).[132,133]

Thermal reaction of **69** with tributyltin radicals results in the loss of N_2 gas and the formation of *N*-stannylaminyl radical **70**. A 3-*exo* cyclization from the *N*-stannylaminyl radical to the ketone moiety then occurs, furnishing the alkoxyl radical **71**. A β-scission of the alkoxyl radical re-forms the ketone, and ring-opening of the aziridine generates the carbon radical **72**. A final H-atom abstraction gives the corresponding amide or lactam derivative **73**. A number of acyclic (75−80%) and cyclic (15%−81%) amides were synthesized in moderate to excellent yields under the reaction conditions. In general, larger cyclic systems gave lower yields than 5/6-membered systems. Azide **69a** was

Scheme 13. Thermal Decomposition of Triazenes for the Generation of Amidyl N-Centered Radicals



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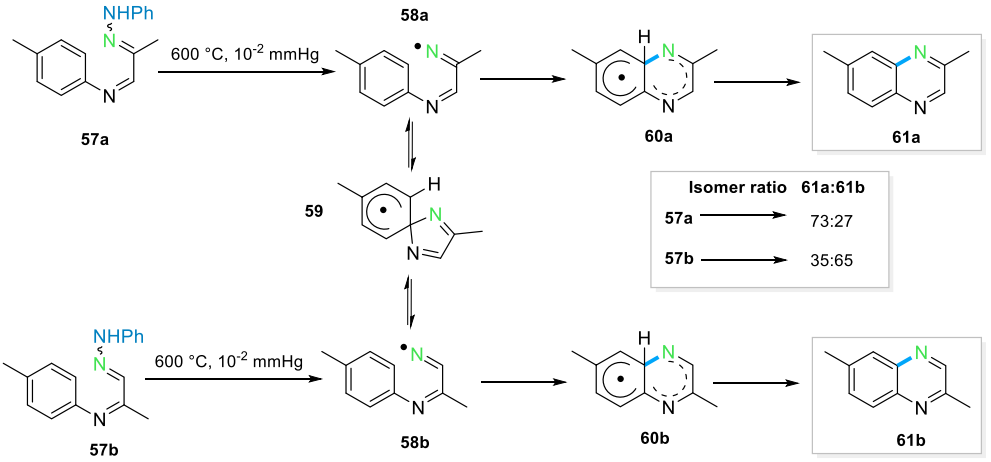
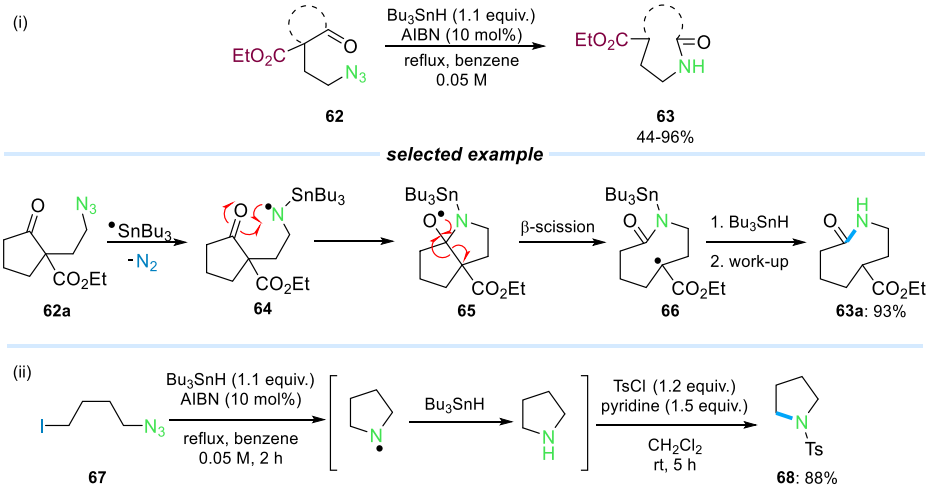
Scheme 14. Generation of Iminyl Radicals via Pyrolysis of Hydrazine Imines[a]

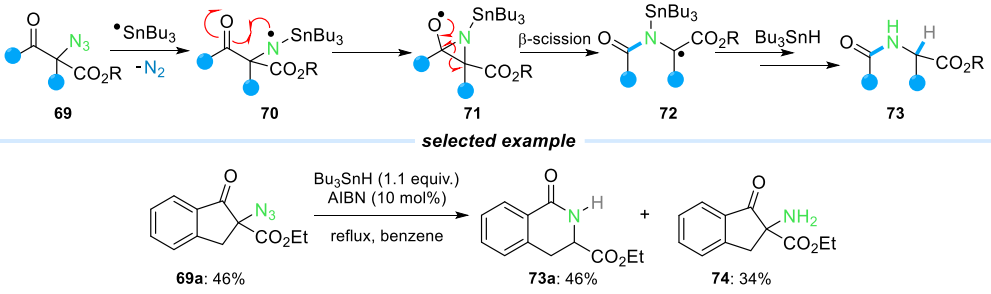


[a]10^{-2} mmHg = 1 mbar.

Scheme 15. Alkyl Azides as N-Centered Radical Precursors Reported by the Kim Group: (i) Addition of *N*-Stannylaminyl Radicals to Carbonyls, Performing a Ring Expansion to Access Lactams, and (ii) Radical Cyclization of Alkyl Azides for the Synthesis of N-Heterocycles



Scheme 16. Tin-Mediated Rearrangement of Azides to Lactams and Amines via *N*-Stannylaminyl Radicals



subjected to the reaction conditions and yielded the lactam **73a**. A major byproduct that was observed arose from reduction of the azide to the free amine **74**. In some instances, the deazidated keto-ester was observed as a byproduct. Further reactivities of azides under tin-mediated conditions were investigated by Benati and co-workers who reported the cyclization of aminyl radicals onto nitriles[134] and cyclization to triazoline derivatives.[135] It was also noted that cyclization of azides onto nitriles could be accessed by an indium-mediated pathway, an alternative to using tin.[136] A more recent contribution was published by Spagnolo et al. in 2009, documenting the use of azides as NCR precursors in intra- and intermolecular processes.[137]

Studer et al. developed a strategy for hydroamination by exploiting an N-amidated Hantzsch ester (**75**) in an elegant synthesis, based on polarity reversal catalysis (Scheme 17).[138,139] Aminations of olefins were regioselective (anti-Markovnikov) and gave Boc-protected amine products **76**.

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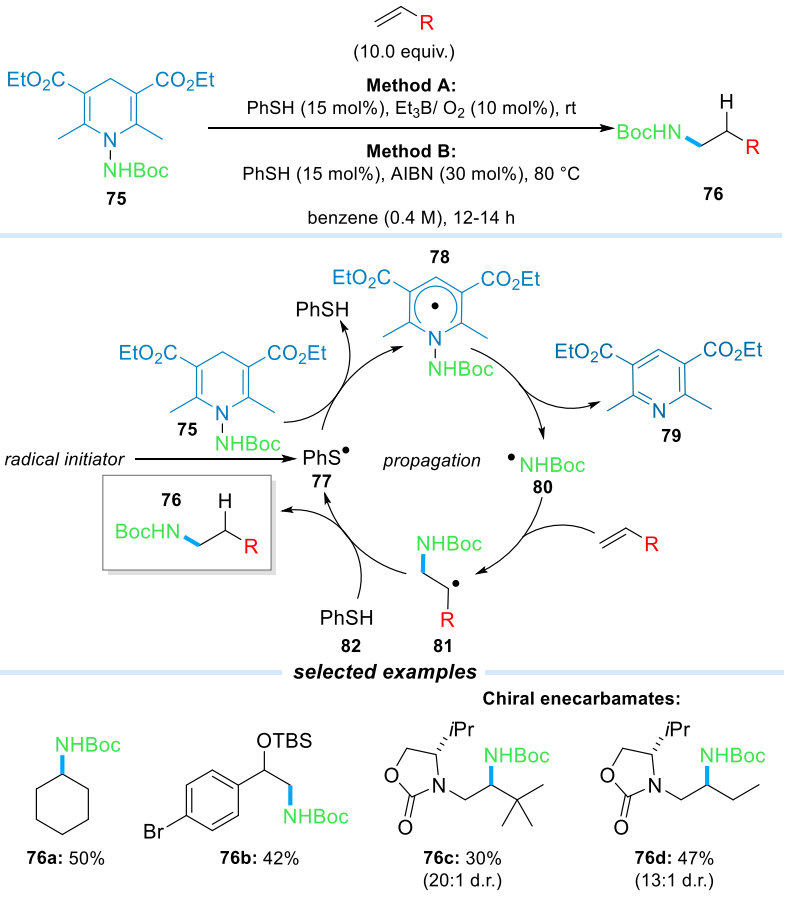
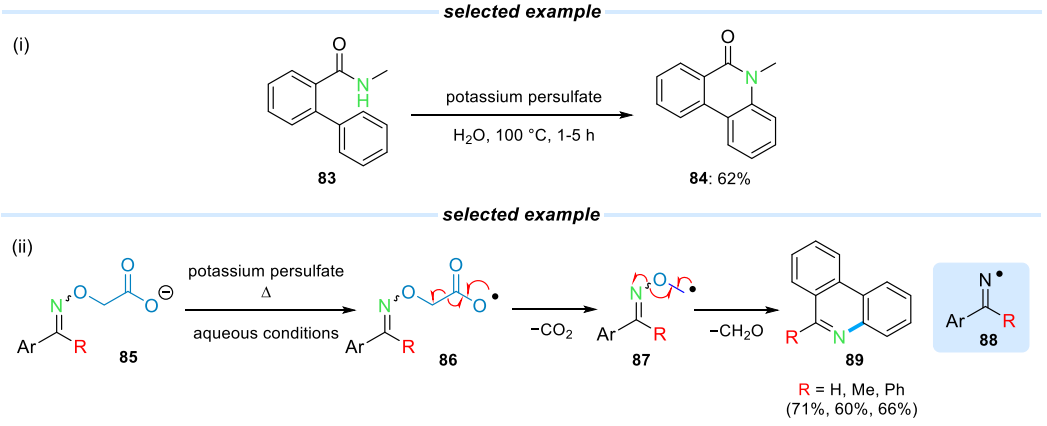
Scheme 17. N-Amidated Hantzsch Esters as Precursors to N-Centered Radicals in Polarity Reversal Catalysis



Scheme 18. Use of Potassium Persulfate as an Oxidant for the Generation of N-Centered Radicals: (i) Oxidative Generation of Amidyl Radicals and (ii) Oxidative Decarboxylative Fragmentation to Generate Iminyl Radicals



Initiation generates the thiyl radical species **77**, which can abstract a hydrogen atom from the Hantzsch ester **75** to yield the radical intermediate **78**, in a polarity-matched system. The rapid re-aromatization of intermediate **78** acts as a driving force for the reaction, cleaving the weak N−N bond to form the pyridine byproduct **79** and NCR **80**. Addition of **80** to an olefin yields the carbon radical **81**, and subsequent hydrogen abstraction from the thiol H-atom donor **82** affords the amidated product **76**. The substrates reported gave low to moderate yields (33−62%); however, unactivated olefins were amidated (**76a**), and a high regioselectivity for the anti-Markovnikov product was observed (**76b**). Selected chiral enecarbamates, derived from Evans oxazolidinones, were reacted and gave adequate yields with high diastereoselectivity (**76c**, **76d**). Comparatively, higher selectivities were observed for *tert*-butyl substituents (20:1 d.r.) than for less sterically demanding ethyl substituents (13:1 d.r.). More recently in 2021, the Wang group developed a similar hydroamidation protocol utilizing organic photoredox catalysis with Hantzsch ester **75**.[140] Anti-Markovnikov selectivity was achieved with various unactivated alkenes and amidyl radical precursors.

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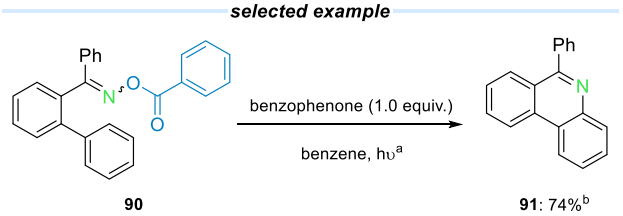
2.3. NCRs Derived from Nitrogen−Oxygen Bonds

Pioneering work by Forrester et al. in 1972 reported the use of potassium persulfate as an oxidant in the reactions of biphenyl-2-carboxamide derivatives **83** [Scheme 18, (i)].[141] The amidyl radicals generated underwent cyclization onto phenyl groups furnishing phenanthridones **84**. This methodology was later adapted to the decarboxylative fragmentation of oximinoacetic acid derivatives **85**, which formed iminyl radicals [Scheme 18, (ii)].[50,142,143]

Addition of a persulfate as a strong oxidizing agent and heat initiated the decarboxylation (**86**) of the carboxylate **85**, to form the radical species **87**. An entropic driving force resulted in further fragmentation of **87** to generate the iminyl radical **88** and formaldehyde as a byproduct. Effective amination of selected substrates afforded the relevant phenanthridines **89** in good yields (60−71%).

Following on from the oxidative method by Forrester,[50,142,143] Tokumaru et al. reported a photochemical approach to iminyl radicals.[144,145] *O*-Aroyloxime **90** was subjected to photoirradiation and underwent homolysis to the NCR, which was found to occur more rapidly in the presence of benzophenone. Intramolecular homolytic aromatic substitution of the iminyl radical onto the nearby phenyl ring furnished phenanthridine **91** (Scheme 19).

Scheme 19. Synthesis of Iminyl Radicals from Photoirradiation of *O*-Aroyloxime



[a]Pyrex immersion well with a 400 W mercury lamp. [b]Measured by vapor-phase chromatography.

Early contributions by Newcomb in 1985 introduced *N*-hydroxypyridine-2-thione carbamates (PTOC) (**92**) as precursors to NCRs (Scheme 20) via a radical fragmentation pathway.[146−151] These precursors were analogous to the well-documented Barton esters (**93**), used for the generation of carbon radicals via a decarboxylative mechanism.[152] Derivatives of **92** were synthesized by reaction of phosgene and the respective amine with base to form the carbamoyl chloride; addition of the *N*-hydroxypyridine-2-thione sodium salt yielded the desired PTOC. Examples of their reactivities as precursors to aminyl and aminium radicals are shown in Scheme 20, respectively featuring H-atom abstraction (**96**) and 5-*exo* cyclization (**97**).[148,149] Further synthetic applications include intermolecular additions[150] and functionalization of carbon radical intermediates.[151] Innate instability of the PTOC carbamate on primary amine systems resulted in the discovery of an alternative NCR precursor, thioxothiazolyloxycarbonyl (TTOC) carbamates **94**.[153] Synthesis of these intermediates was analogous to the previously mentioned PTOC precursors. A weaker efficiency in radical propagation was observed with a TTOC carbamate, resulting in a slightly diminished yield of **98** (70%). In 1991, Newcomb and co-workers expanded this methodology to amidyl radicals using *N*-hydroxypyridine-2-thione imidate esters[154] **95** and reported excellent yields for the corresponding lactams **99**.

The observations made by Newcomb and co-workers strongly correlated to the reactivities associated with each class of NCR.[35,155,156] The experimental results regarding aminyl radicals showed that hydrogen abstraction was the preferred reactivity. Conversely, electrophilic amidyl and aminium radicals are known to favor the addition to olefins, which is reflected by the obtained products.

In 1991, Zard and co-workers adapted the methodology reported by Forrester (Scheme 18).[50] Use of a Barton-type decarboxylative method resulted in the generation of iminyl radicals (Scheme 21).[51,157,158]

Precursor **100** was easily prepared from a direct condensation with the corresponding ketone and carboxymethoxylamine in excellent yield (85%, 3:1 isomer ratio). Radiation with a tungsten lamp stimulates fragmentation of **101**; by loss of CO_2 and formaldehyde, iminyl radical **102** is generated. Subsequent cyclization and intermolecular addition to methyl acrylate occurs, yielding a carbon radical intermediate. The final step of the radical chain process furnishes **103**, which contains a pyridinethiyl handle.

Zard and co-workers continued to develop accessible methods to generate NCRs. Oxime esters were investigated as precursors to iminyl radicals (Scheme 22).[159] It was proposed that the weak N−O bond and fragmentation cascade compensated for the slow addition of the tributylstannyl radical to the carbonyl group. This methodology was further demonstrated in the generation of amidyl and carbamyl radicals (Scheme 22).[160,161]

Reaction of the corresponding carbonyl with hydroxylamine hydrochloride, followed by the addition of benzoyl chloride afforded the desired oxime benzoate derivatives (**104**, **105**). Subjection to the reaction conditions with tributylstannane and AIBN gave the desired pyrrolenines (**45**, **106**) in good to excellent yields. Example **105** contained a phosphonate ester which was synthesized by the Arbuzov reaction and gave the desired cyclized product (**106**) without undergoing β-scission to the corresponding nitrile. Adaptation to the amide derivative (**107**) produced the corresponding bicyclic lactam (**108**). For the *O*-benzoyl-*N*-hydroxyurethane example (**109**), a decreased efficiency was observed for the carbamyl radical; however, **110** was still obtained in 20% yield. Zard and co-workers elegantly synthesized natural products (±)-13-deoxyserratine[162] and (±)-aspidospermidine[163] via amidyl radicals generated from the benzoyl precursors (cf. **107**).

Extensive work on the synthesis of dihydropyrrole derivatives was carried out by Narasaka and co-workers.[164−167] Initial investigations used *O*-2,4-dinitrophenyloxime (**111**) as the NCR precursor [Scheme 23, (i)].[164] The iminyl radical (**112**) cyclized to the pyrrolenine derivative (**113**). Extension of this work led to the development of *O*-(*p*-cyanophenyl)oximes (**114**) as NCR precursors. Cyclization of γ,δ-unsaturated ketone oximes to pyrrolenines (**115**) was reported [Scheme 23, (ii)].[165,166]

It was found that the reaction conditions employing 1,4-dimethoxynaphthalene (DMN, **116**) likely proceed through an electron-transfer process, although energy transfer was not ruled out. Furthermore, running the reaction in acetonitrile-d^3 revealed that the solvent could act as a H-atom donor, in the absence of 1,4-cyclohexadiene (CHD) (42%). The proposed mechanism proceeded via electron transfer to the NCR precursor, which resulted in N−O bond cleavage. The iminyl

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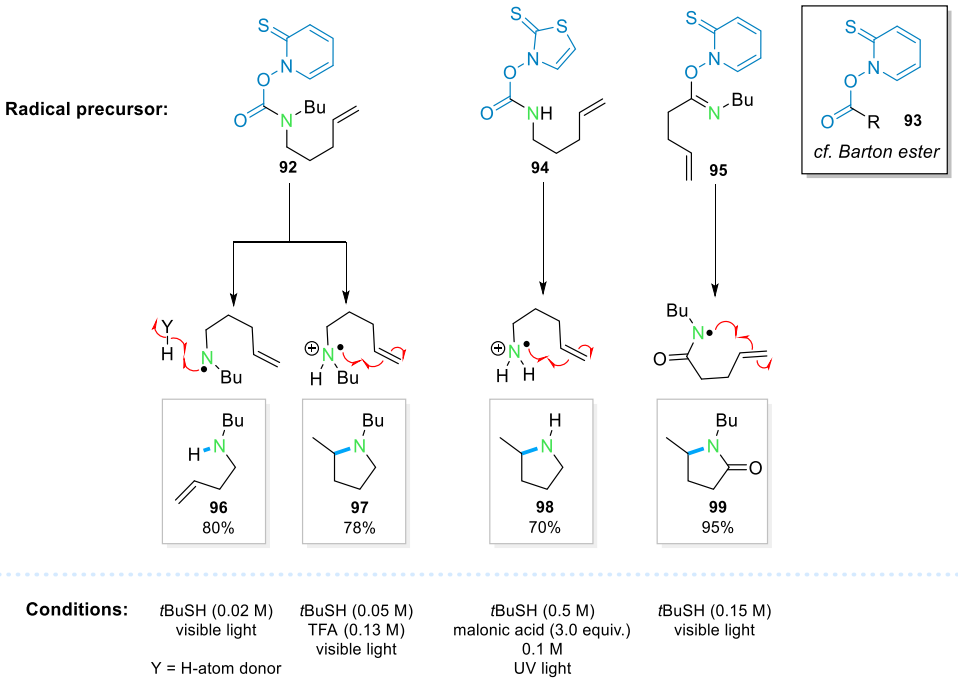
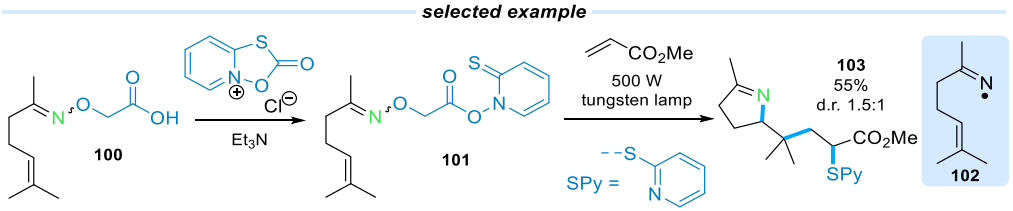
Scheme 20. *N*-Hydroxypyridine-2-thione Carbamates and Thioxothiazolyloxycarbonyl Carbamates as Precursors to N-Centered Radicals[a]

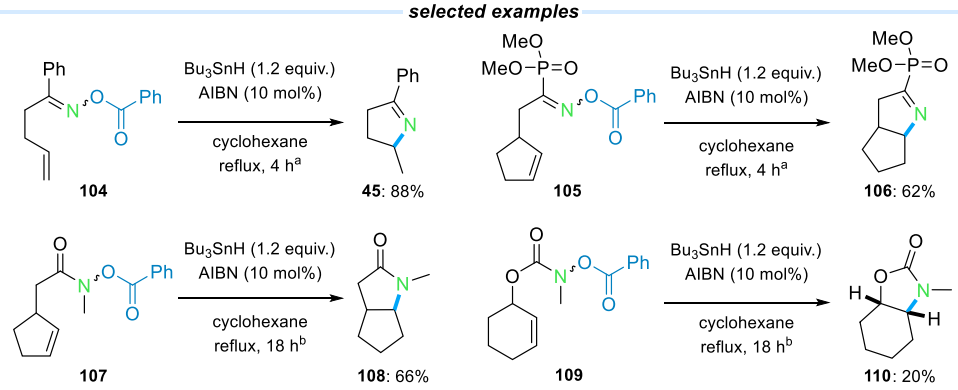


[a]Reactions carried out in benzene at 25 °C.

Scheme 21. Mild Decarboxylative Conditions to Generate Iminyl Radicals



Scheme 22. Use of Oxime Benzoates as Precursors to Iminyl, Amidyl, and Carbamyl Radicals



[a]Slow addition of tributylstannane (in cyclohexane) over 4 h. [b]Slow addition of tributylstannane and AIBN (in toluene:cyclohexane, 1:1) over 6 h, refluxed for a further 12 h, and a further 0.6 equiv of tributylstannane was added, if necessary.

radical cyclized to generate the corresponding carbon radical, which underwent H-atom abstraction from CHD. The scope of the reaction included the synthesis of pyrrolenine derivatives (**115**, 8 examples, 13−78%). A further advance from the Narasaka group revealed that *O*-acetyloximes and *O*-methyloximes (**117**) were amenable to N−O bond homolysis to generate iminyl radicals [Scheme 23, (iii)].[167] Cyclizations of conjugated oximes, α-keto esters, and α,β-unsaturated ketones were demonstrated (**45**, 7 examples, 12−79%). Alkyl oximes were believed to undergo electron transfer, while conjugated oxime derivatives underwent cyclization via energy transfer.

In 1999, Zard and co-workers continued their efforts in the discovery of N−O bond derivatives for the generation of iminyl radicals. The group focused on the use of ketoxime esters[168]

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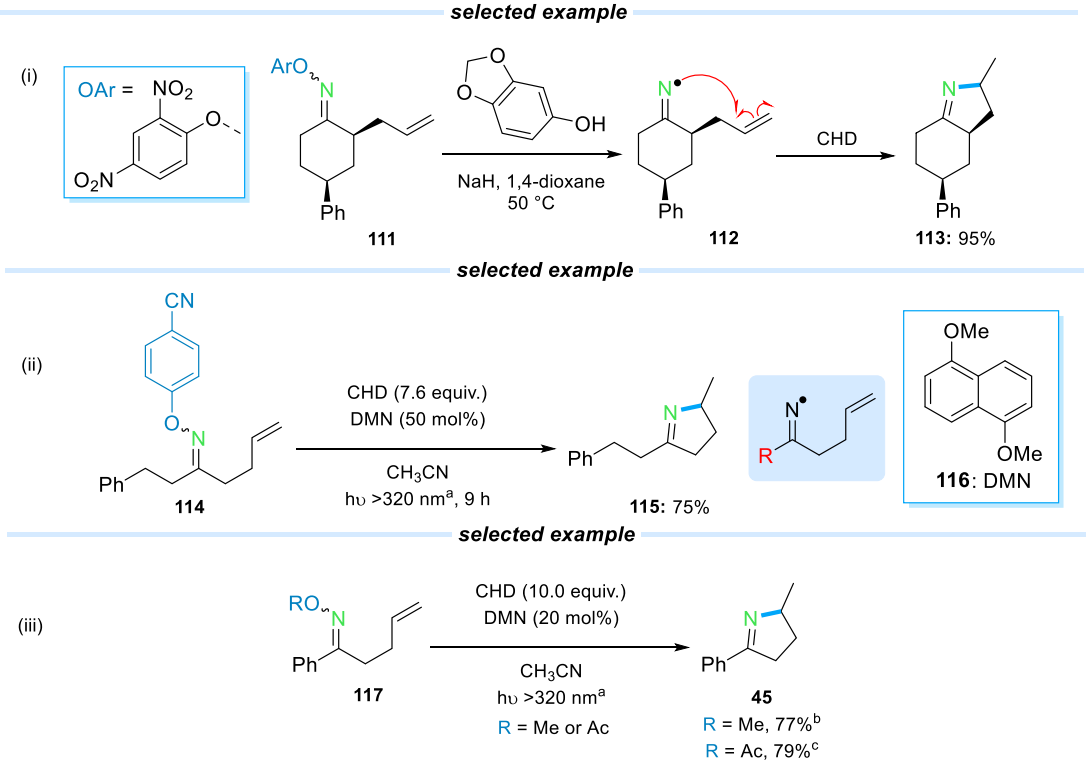
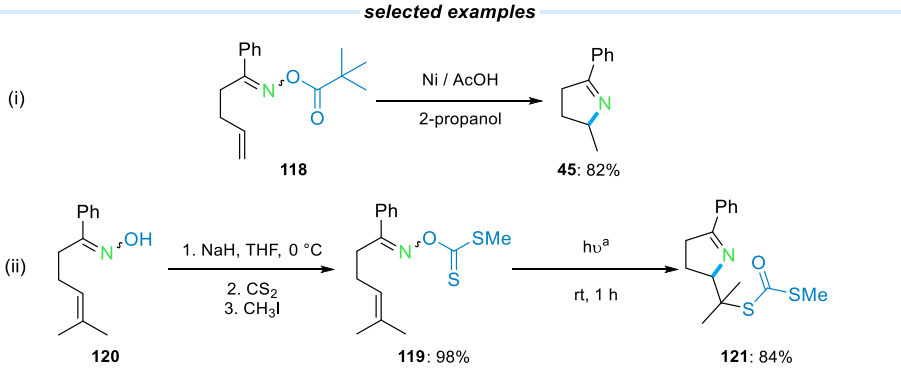
Scheme 23. *O*-2,4-Dinitrophenyloximes, *O*-(*p*-Cyanophenyl)oximes, and *O*-Acetyloximes as Precursors to Iminyl Radicals



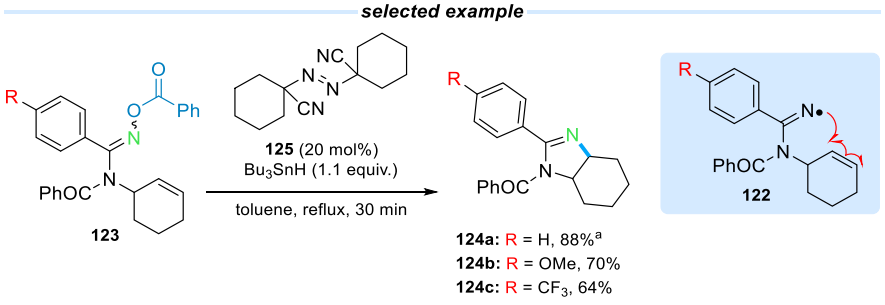
[a]500 W mercury−xenon lamp. [b]Reaction time = 30 min. [c]Reaction time = 3 h.

Scheme 24. Use of Ketoxime Esters and Xanthates as Precursors to Iminyl Radicals for the Synthesis of Pyrrolenine Derivatives



[a]250 W Osram Xenophot HLX lamp used, under an atmosphere of argon.

Scheme 25. Synthesis of Imidazolines from Amidinyl Radical Precursors



[a]Yield obtained by simple mixing of reagents. No slow addition of tributylstannane was required.

(**118**) and ketoxime xanthates[169] (**119**) as precursors to NCRs (Scheme 24).

Preliminary studies were published on the 5-*exo*-cyclization of iminyl radicals generated from pivalate precursors [Scheme 24,

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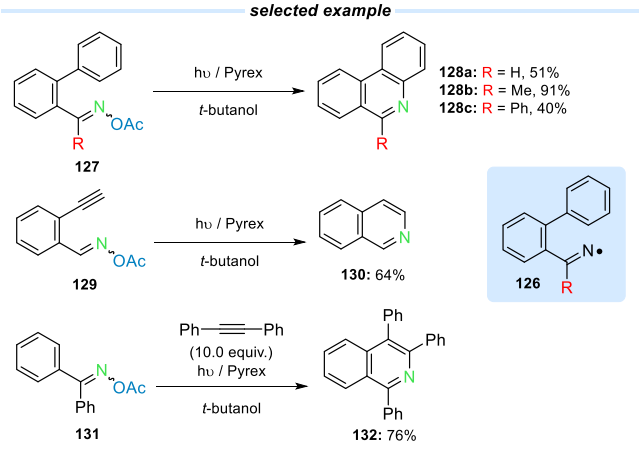
(i)]. The combination of nickel powder and acetic acid, under reflux conditions, constituted a mild reducing agent and was previously established in the synthesis of γ-lactams.[170] SET to the ketoxime ester (**118**) generated the iminyl radical and the corresponding carboxylate anion. 2-Propanol as the solvent acted as a H-atom donor in the reaction, furnishing the desired pyrrolenine (**45**) in excellent yield. Iterations using oxime acetates were examined; however, these were not as efficient as the pivalate derivatives. A further study was published on the use of *O*-(*S*-methyl xanthates) (**119**) as precursors to iminyl radicals [Scheme 24, (ii)], synthesized from the corresponding oximes (**120**). Promising results were obtained when photochemical conditions were employed, triggering the chain reaction mechanism. A range of precursors were prepared which cyclized to give the desired heterocycles (**121**) (7 examples, 72−88%).

In 2003, Zard and co-workers reported the synthesis of imidazolines via amidinyl radicals (**122**).[171] Oxime benzoate precursors (**123**) were synthesized and subsequently cyclized under radical initiation conditions to furnish imidazolines (**124**) (Scheme 25). It was also demonstrated that oxidation of the imidazolines resulted in the corresponding imidazoles.

Using 1,1′-azobis(cyanocyclohexane) (ACHN, **125**) as the radical initiator, imidazolines (**124a−124c**) were synthesized with electron-rich and electron-poor phenyl substituents. The paper described 12 examples including bicyclic and spirocyclic imidazolines and those featuring a quaternary center.

In 2006, Alonso et al. described the generation of iminyl radicals (**126**) from *O*-acyloximes (**127**), which cyclized to the corresponding phenanthridines (**128a−128c**) (Scheme 26).[172]

Scheme 26. Photochemical Generation of Iminyl Radicals from *O*-Acyloximes for the Synthesis of Heterocycles

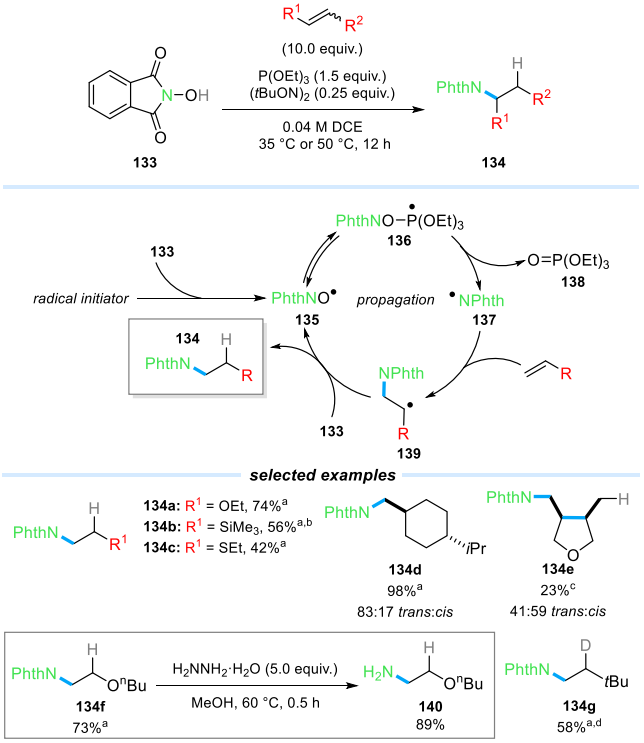


Development of the protocol using a terminal alkyne (**129**) to capture the iminyl radical furnished the isoquinoline (**130**) in good yield. Further iterations revealed that reacting precursor **131** intermolecularly with an alkyne resulted in cyclization, providing the isoquinoline derivative **132** in 76% yield.

A more recent example of a hydroxylamine-derived precursor was reported by Schmidt in 2018.[173] Exploitation of the economical and available reagent *N*-hydroxyphthalimide (NHPI, **133**) enabled access to anti-Markovnikov hydroimidation products (**134**) via phthalimidyl radicals (Scheme 27).

The mechanism is believed to proceed via thermal initiation with fragmentation of *tert*-butyl hyponitrite and the resulting radicals generating the oxygen-centered radical **135** by HAT.

Scheme 27. Hydroimidation of Unactivated and Functionalized Alkenes with Hydroxylamine Precursor, *N*-Hydroxyphthalimide



[a]The reaction was run at 50 °C. [b]Dilauroyl peroxide (1 equiv) was used as the initiator, and the reaction was heated to 110 °C. [c]Dilauroyl peroxide (0.20 equiv) was used as the initiator, and the reaction was heated to 110 °C. [d]0.10 equiv of $(t\text{BuON})_2$ was used with deuterated NHPI (1.0 equiv). PhthN = phthalimide.

Reversible radical addition to the triethyl phosphite results in a β-scission from **136** to NCR **137** and the triethyl phosphate byproduct (**138**). Anti-Markovnikov addition to an alkene gives **139**, and sequential propagation with another molecular of NHPI affords the desired product (**134**) and restarts the radical chain process (**135**). Initial explorations of functionalized alkenes were fruitful, giving the hydroimidated products (**134a−134c**) in good to moderate yields. Aliphatic examples (**134d**) were demonstrated which included cyclic alkenes. Diallyl ether was imidated, and the resulting C-centered radical rapidly underwent 5-*exo* cyclization and H-atom abstraction to yield **134e**, although a lower yield was obtained. Deprotection of **134f** was achieved with hydrazine and gave the desired primary amine (**140**) in excellent yield. Lastly, use of deuterium-labeled NHPI yielded the deuterimidated product (**134g**), which aligned with the suggested radical chain mechanism.

A 2021 report by the Studer group detailed a procedure for the radical aminoboration of unactivated alkenes (Scheme 28).[174] This work follows on from their previously published transition metal-free method for 1,2-carboboration of unactivated alkenes.[175] The *O*-2,4-dinitrophenyl precursor (**141**) was selected due to its ease of engaging in SET reduction for the generation of amidyl radicals.[18,176,177]

Formation of an electron−donor−acceptor (EDA) complex was proposed and supported by UV−vis studies, revealing a bathochromic shift was present when **141** was treated with $B_2(OH)_4$ in dimethylacetamide (DMAc). Generation of the amidyl radical (**143**) results in cyclization to the C-centered

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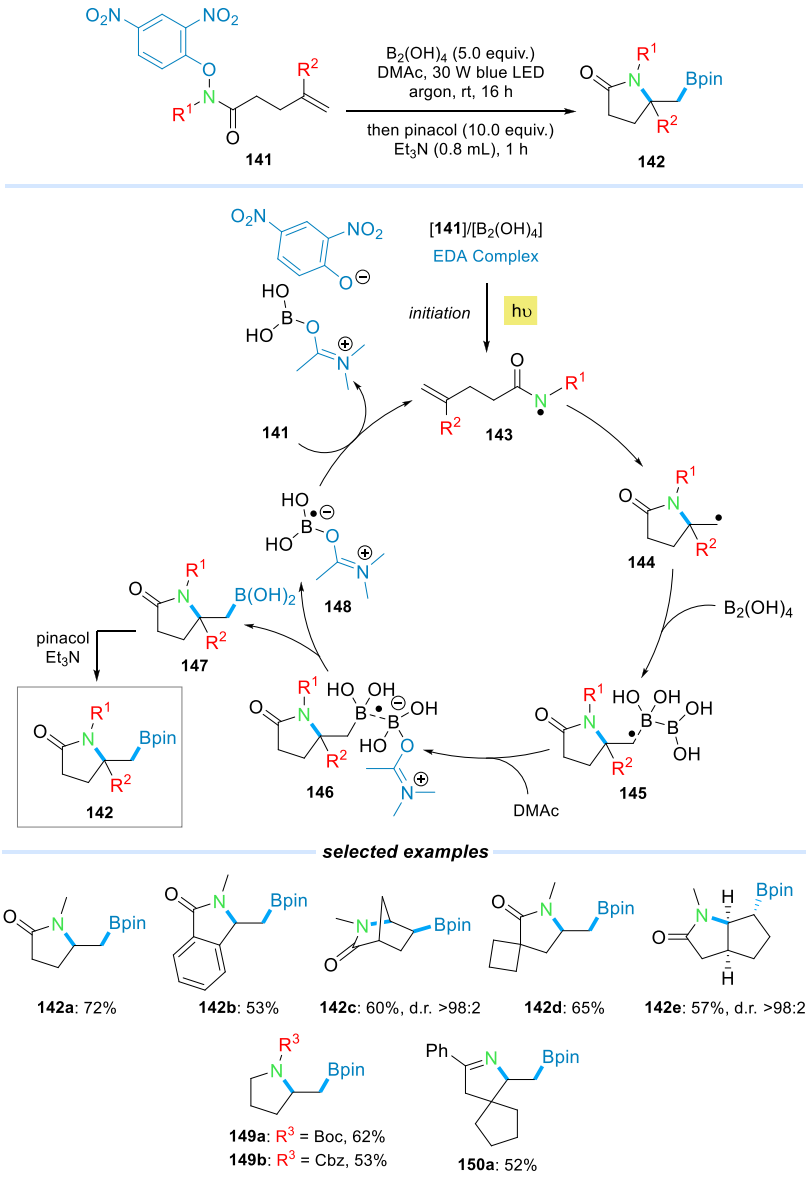
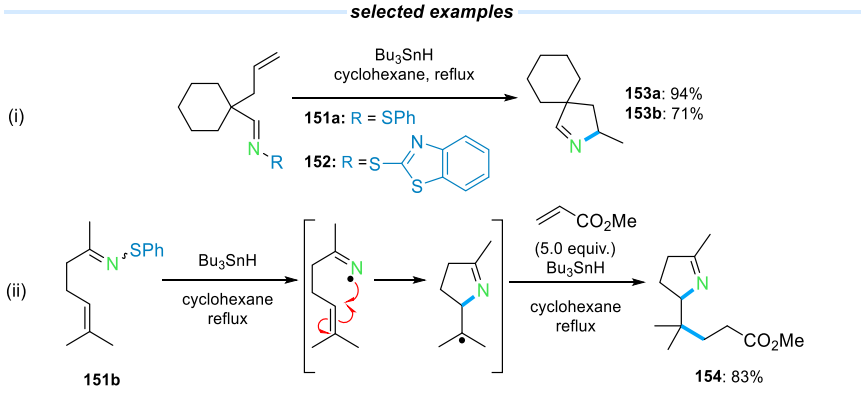
Scheme 28. Radical-Mediated Aminoboration of Unactivated Alkenes



Scheme 29. *S*-Phenylsulfenimines and 2-Benzothiolyl-sulfenamide Derivatives as Precursors to Iminyl Radicals



radical **144**. The alkyl radical (**144**) then reacts with the diboron reagent to give adduct **145**, which then interacts with an equivalent of the solvent, DMAc, giving **146**. Fragmentation of the B−B bond affords the desired boronic acid (**147**), which is subsequently converted to the boron pinacolate (**142**). The resulting radical anion from **146**, depicted as **148**, is then able to propagate the radical chain with starting material **141**. The group synthesized a number of 5-membered lactam products

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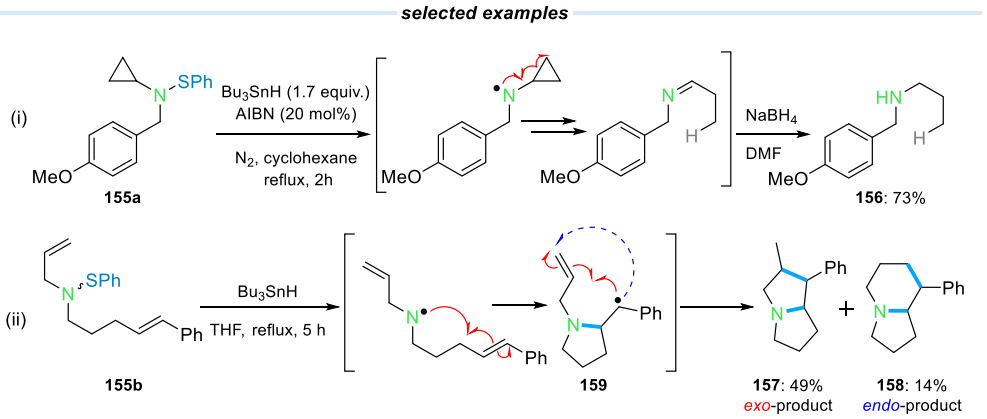
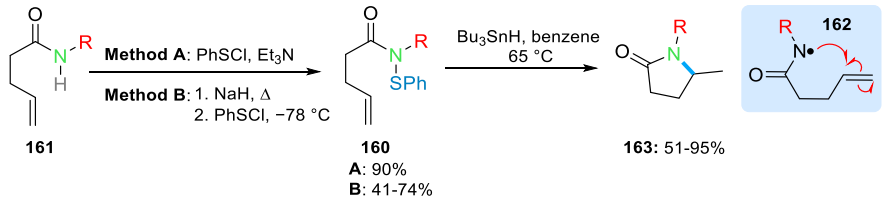
Scheme 30. Use of Sulfenamide Precursors for the Generation of Aminyl Radicals[a]



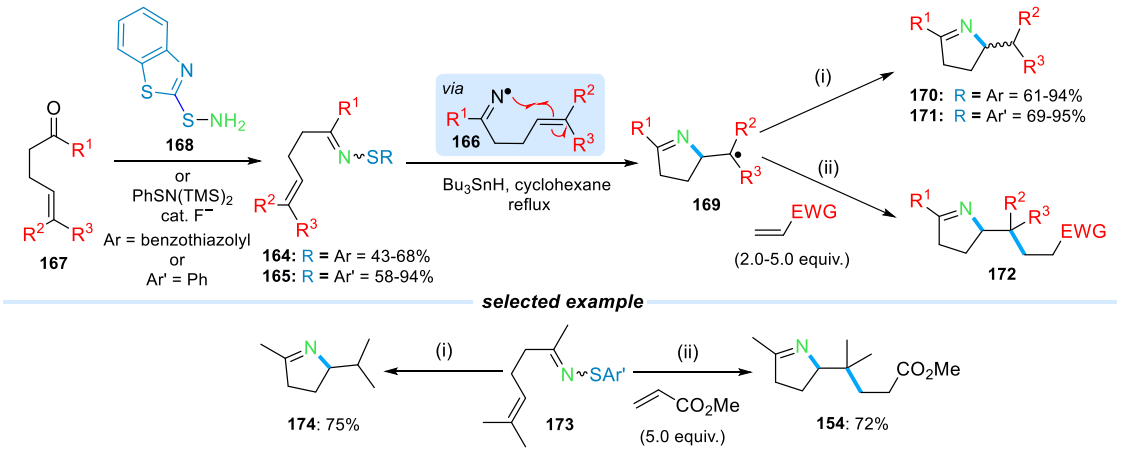
[a]The blue arrow is indicative of the reactivity to give the endo product.

Scheme 31. *N*-(Phenylthio)amides as Precursors to Amidyl Radicals under Tin-Initiated Conditions[a]



[a]R = saturated or unsaturated alkyl chain.

Scheme 32. Generation of Iminyl Radicals from Sulfenylimine Precursors



(**142a**−**142e**), including isoindolinones (**142b**) and bridged (**142c**), spirocyclic (**142d**), and bicyclic (**142e**) derivatives. Exploration of *N*-aryloxyamine precursors yielded the corresponding pyrrolidine derivatives (**149a**, **149b**), while extension to *O*-aryloximes gave pyrrolenines (**150a**).

2.4. NCRs Derived from Nitrogen−Sulfur Bonds

In 1990, Zard and co-workers presented sulfenylimine derivatives (**151**, **152**) as precursors to iminyl radicals. Initiation with tributylstannane prompted N−S homolysis, followed by cyclization to the corresponding pyrrolenine derivatives (**153a**, **153b**) [Scheme 29, (i)].[178] Later that year, an extension of the protocol was published with sulfenylimines (**151b**). After the cyclization, the corresponding carbon radical was trapped with an external olefin acceptor to provide the addition product (**154**) [Scheme 29, (ii)].[158,179]

The *S*-phenyl sulfenylimines (**151a**, **151b**) were easily prepared by a method published by Morimoto.[180] The 2-benzothiolyl-sulfenamide derivatives (**152**) were prepared from 2-mercaptobenzothiazole, ammonia, and sodium hypochlorite.[181] Excellent yields were obtained, and further bicyclic and spirocyclic examples were presented. Further cyclization−addition products (e.g., **154**) were exemplified with methyl acrylate, acrylonitrile, and methylene di-*tert*-butyl malonate as the electron-poor olefin acceptors.

With cyclopropylsulfenamides (**155a**), it was predicted by Bowman that upon the formation of an aminyl radical, a ring-opening would occur [Scheme 30, (i)].[182] It was found that the aminyl radicals were largely unreactive to cyclization, and the reaction furnished the alkylamine products (**156**). However, a communication was later released which detailed that aminyl radicals were prone to cyclization with activated alkenes from

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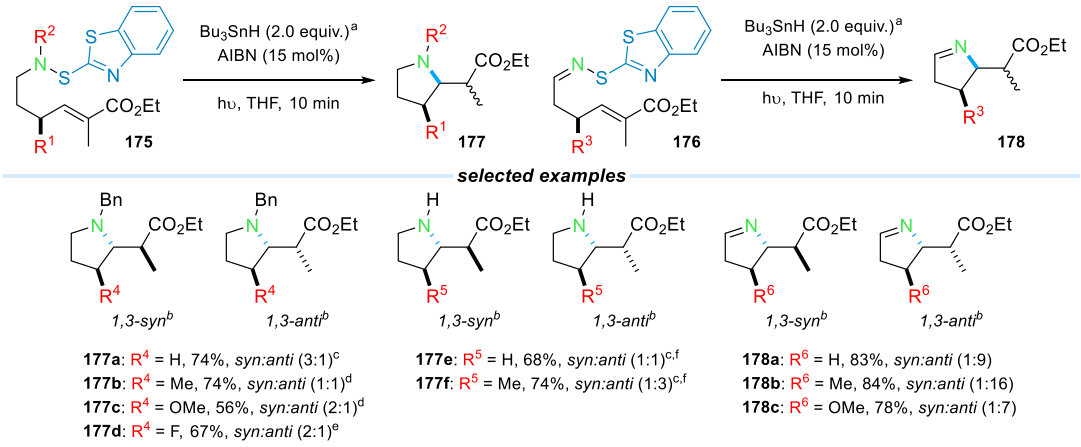
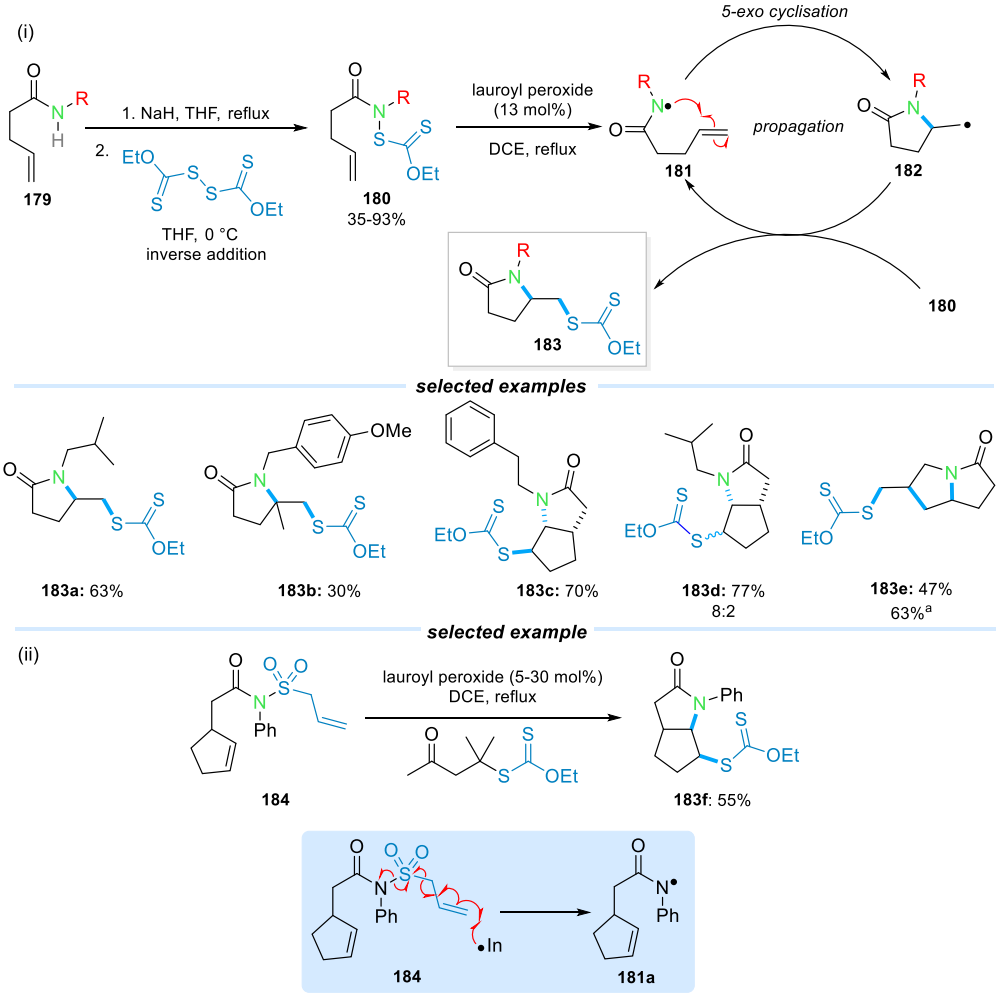
Scheme 33. Cyclization of Aminyl and Iminyl Radicals Generated from *N*-Benzothiazolylsulfanylbenzylamine Precursors



[a]Slow addition of Bu_3SnH over 3 h via syringe pump, followed by 10 min irradiation of *hν* (solar lamp 275 W). [b]*Trans*-diastereomer shown as the major product, relative to the R-group and the newly formed N−C bond (1,2-*syn*). The *cis*-diastereomer is not shown. [c]Reaction carried out at −23 °C. [d]Only *trans*-cyclized (20:1) product was obtained. [e]Ratio of *trans*-cyclized:*cis*-cyclized = 4:1. [f]The crude mixture was treated with BnBr and Et_3N in CH_3CN, and the ratio was determined on the benzylated products.

Scheme 34. Use of *N*-(*O*-Ethyl thiocarbonylsulfanyl)amide as a Precursor to Amidyl Radicals in a Tin-Free Reaction



[a]In chlorobenzene with 7.5 mol% of cumyl peroxide. In = initiator.

precursors like **155b** [Scheme 30, (ii)].[183] A 5-*exo* cyclization afforded the desired pyrrolizidine (**157**); however, the formation of the 6-*endo* cyclization product (**158**) was also observed. Aminyl radical addition to alkenes is known to be reversible,[148,183,184] and this was indicated by the formation of **158**. The stability of the benzylic radical (**159**) resulted in some

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thermodynamic control of the cyclization step. Further publications by Bowman and co-workers detailed the reactivity of aminyl radicals in cyclization reactions.[184−186]

Extension of the previously described methodology was reported by Esker and Newcomb in 1993. Formation of amidyl radicals was achieved with *N*-(phenylthio)amides (**160**) (Scheme 31).[187]

Amides (**161**) are converted into *N*-(phenylthio)amides (**160**) in a single step in good yields. Initiation with tributyltin hydride affords amidyl radical **162**. Cyclization of **162** yields a carbon radical which can abstract a hydrogen atom from the tin hydride to yield cyclic lactams **163**.

Additional studies on the use of sulfenylimines (**164**, **165**) as precursors to iminyl radicals (**166**) were performed by Zard and co-workers (Scheme 32).[188] The publication presented additional examples and findings to their earlier publication.[178,179]

Sulfenylimines (**164**, **165**) were accessed by a direct condensation reaction with the appropriate aldehyde or ketone substrate (**167**), in reasonable yields, as a mixture of isomers. The N−S linker (**164**) was easily synthesized from 2-mercaptobenzothiazole, ammonia, and sodium hypochlorite.[181] Iminyl radical (**166**) resulted upon subjection of **164** or **165** to reflux conditions, followed by cyclization to give the carbon radical **169**. HAT afforded cyclic imines **170** and **171** as a mixture of isomers in good yields [Scheme 32, pathway (i)]. The alternative pathway resulted in the nucleophilic carbon radical **169** being intercepted with an electrophilic olefin to afford **172** [Scheme 32, pathway (ii)]. The selected example **173**, could undergo either pathway; (i) cyclization to furnish **174** or (ii) addition of the corresponding carbon radical **169** to methyl acrylate to yield **154**. A further publication detailed the use of analogous precursors of cyclobutyliminyl radicals to undergo *β*-scission and ring-opening to the corresponding nitrile product. However, this reactivity of iminyl radicals will not be discussed in further detail.[56,189]

In 2001, Landry described the cyclization of aminyl and iminyl radicals using an *N*-benzothiazolylsulfanylbenzylamine precursor (**175**, **176**) (Scheme 33).[190]

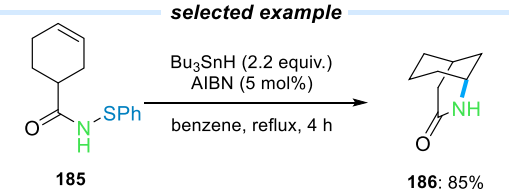
Pyrrolidines bearing an *N*-benzyl moiety were prepared, including those containing ether or fluorine substituents (**177a**−**177d**). Emphasis was placed on achieving 1,3-*syn* selectivity by increasing the bulk on the R^2 substituent (**175**). A high 1,2-*trans* selectivity was observed with respect to the newly formed N−C bond and the alkyl R^4 substituent; however, only a modest 1,3-*syn*:1,3-*anti* ratio was achieved. It was suggested that 1,3-strain in the transition state contributed to the observed relative stereochemistry. The publication also detailed the investigation into the cyclization to the 6-membered heterocycle, which featured an additional CH_2 unit compared to precursor **175**. However, the desired product was not formed. To attain *anti*-selectivity, pyrrolidines **177e** and **177f** were synthesized, although only moderate relative selectivities were achieved. The pyrrolenine series (**178a**−**178c**) promoted an *anti* diastereoselectivity which was attributed to the absence of an N-substituent.

More recently, Zard and co-workers have developed a tin-free approach to amidyl radicals, adapting the previous methodology of Newcomb and Esker[187] [Scheme 34, (i)].[191]

The corresponding amides (**179**) furnished the required dithiocarbonyl precursors (**180**) in good yields. Thermal initiation by lauroyl peroxide induces cleavage of the xanthate group on **180** to afford amidyl radical **181**. A facile 5-*exo*-cyclization then occurs to yield the carbon radical **182**. The propagation of the radical chain by reaction of radical **182** with precursor **180**, forms product **183**, a cyclic lactam with a xanthate handle. The xanthate moiety can be used for further functionalization. A range of monocyclic (**183a**, **183b**) and bicyclic products (**183c**, **183d**) including pyrrolidines (**183e**) were synthesized via a selective 5-*exo* intramolecular thioamidation. The substrates demonstrated were aliphatic, unfunctionalized molecules with exceptions of the electron-rich N-substituent *para*-methoxybenzyl (PMB) motif (**183b**). Structures with newly implemented quaternary centers were synthesized with a diminished yield; however, bicyclic products displayed good tolerance to the reaction conditions (**183c**, **183d**). Further development of this protocol in 2004 revealed a novel *N*-allylsulfonimide precursor (**184**), which generated amidyl radicals in a tin-free NCR cyclization to lactam derivatives (**183f**) [Scheme 34, (ii)].[192] Radical addition (by the initiator, in this case) results in the release of SO_2 and generation of the amidyl radical (**181a**), which then participates in a radical chain mechanism, analogous to the one shown in Scheme 34 (i).

In 2005, Lessard et al. reported the first examples of intramolecular addition to olefins with primary amidyl radicals (Scheme 35).[193] The *N*-(phenylthio)amide precursors (**185**)

Scheme 35. Generation of Primary Amidyl Radicals from *N*-(Phenylthio)amides



185 **186**: 85%

were easily accessed from a 2-step synthesis from the corresponding carboxylic acids. Conversion to the acid chloride and subsequent treatment with ammonia yielded the primary amide. Reaction with phenylsulfenyl chloride afforded the precursors (60−84%). Under radical initiation conditions, a 5-*exo*-trig cyclization occurred to the desired lactam (**186**) (4 examples, 63−85%).

2.5. NCRs Derived from Nitrogen−Carbon Bonds

NCRs derived from cleavage of a nitrogen−carbon *σ*-bond are not precedented in the literature due to the high bond energy associated with the N−C bond. Consequently, the majority of chemistry surrounding NCRs is focused on the attainable bond-breaking nature of N−(heteroatom) bonds. The selected few examples that involve the homolytic cleavage of N−C bonds generally rely on a fragmentation mechanism to facilitate the generation of NCRs.

Exploitation of strained aziridines as synthetic precursors to NCRs was introduced by Murphy et al., which furnished functionalized pyrrolidine derivatives (Scheme 36).[194,195] A radical mechanism permitted a selective formation of aminyl radicals via a fragmentation mechanism and selective C−N cleavage, mechanistically concordant with Barton's protocol for radical epoxide ring-opening.[196]

Allylic alcohol (**187**) was converted to aziridine derivative **188** (R^2 = quinazolinone or phthalimide), followed by the synthesis of a thiocarbonylimidazolide intermediate (**189**). Quinazolinone derivatives were subjected to tin-mediated conditions; a Lewis acid ($MgBr_2$) facilitated the reaction to

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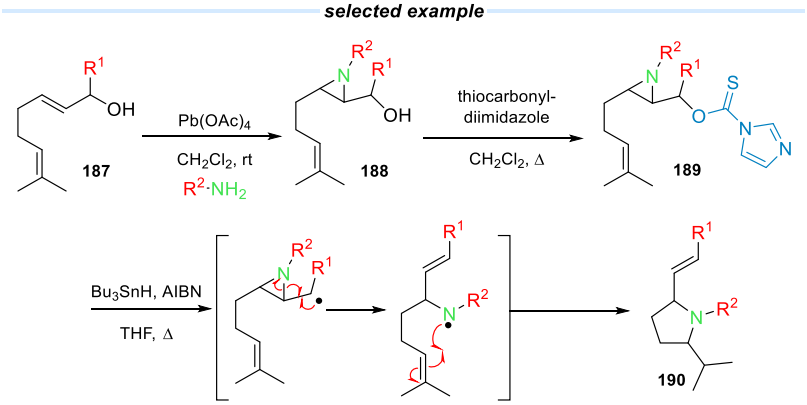
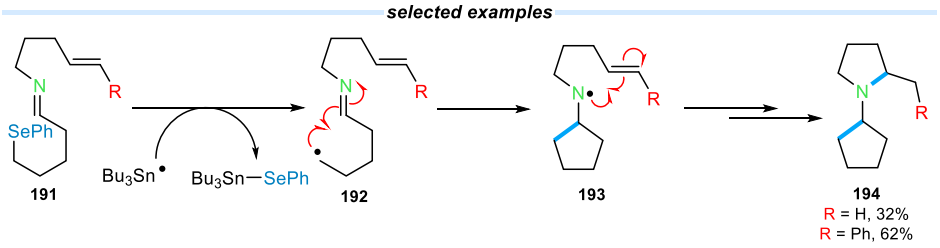
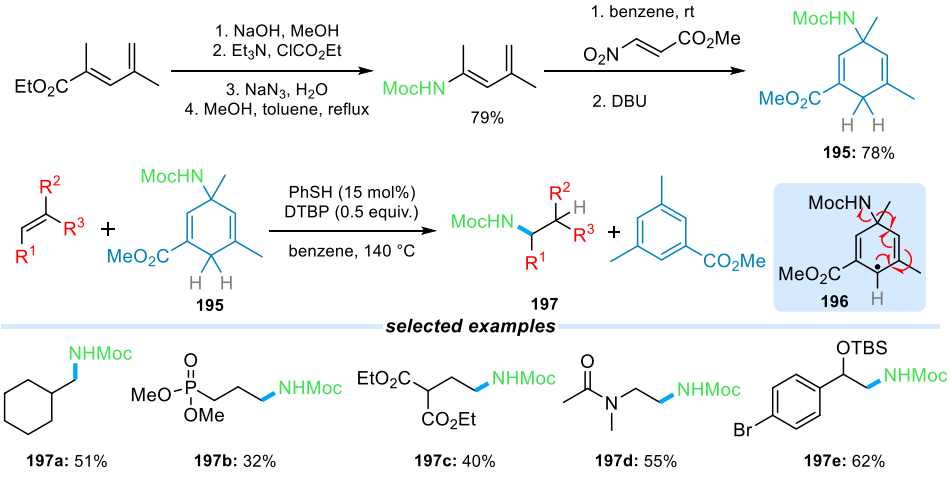
Scheme 36. Tin-Mediated β-Cleavage of Aziridines to Generate Aminyl Radicals to Afford Pyrrolidine Derivatives



Scheme 37. Tandem Radical Cyclization to Cleave a N−C Bond to Generate an Aminyl Radical for the Synthesis of Cyclic Amines



Scheme 38. Cleavage of N−C Bonds to Generate N-Centered Radicals for Hydroamination[a]



[a]Moc = methoxycarbonyl.

furnish the required pyrrolidines (**190**) in good yields, as 1:1 mixture of isomers [R^1 = H (70%), R^1 = *n*-Bu (83%)]. Addition of protic acid was found to cause decomposition and impede the desired product formation.

A number of studies displaying the reactivities of these motifs have since been reported to generate corresponding allylic amine or pyrrolidine derivatives. Use of samarium(II) iodide,[197] triethylborane,[198,199] and Zn(Cu)/sonochemical[200] systems has been documented to induce β-cleavage of aziridines to generate NCRs. Mechanistic insights were revealed by Schwan and Refvik,[201] detailing the effect of substitution of bulkier aromatic groups onto the aziridine, which resulted in a switch in selectivity to C−C homolytic bond cleavage. Further DFT studies investigating aziridine derivatives ring-opening and cyclizing to pyrrolizidines and indolizidines were reported by Speybroeck and co-workers.[202]

Bowman and co-workers demonstrated a tandem radical cyclization, involving aminyl radicals (Scheme 37).[203] The selenium group on substrate **191** underwent S_H2 with a tributyltin radical, generating carbon radical **192**. Cyclization onto the imine afforded the subsequent aminyl radical **193**, which cyclized to afford pyrrolidines (**194**) in moderate yields. Spirocyclic amine derivatives were also prepared in a further publication.[204]

More recently, Studer and co-workers facilitated a fragmentation mechanism to induce homolytic cleavage of a N−C bond, which furnished amidyl radicals (Scheme 38).[205,206] The generation of the active NCR is conceptually similar to the

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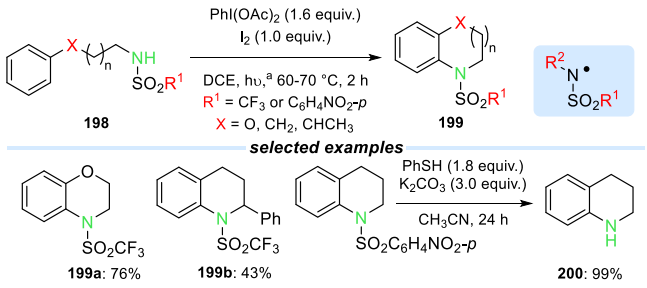
fragmentation mechanism described in Scheme 17, and the driving force of achieving full aromatization is exploited.

Precursor **195** was accessed by a multistep synthesis, described in Scheme 38. Under the reaction conditions, a radical initiator, di-*tert*-butyl peroxide (DTBP), abstracts a hydrogen atom from **195** to generate radical intermediate **196**. A cascade reaction occurs to create the NCR, driven by achieving full aromatization of the precursor. The NCR can subsequently add to olefins in a selective anti-Markovnikov fashion to give **197**. Amidation of unactivated and functionalized aliphatic substrates containing phosphonate esters, esters, and amides was demonstrated (**197a**−**197d**). Selected *β*-substituted styrene derivatives containing functionalities such as primary alcohols, silyl-protected alcohols, and aryl bromides (**197e**) were also included. It was noted that electron-poor olefins were not hydroamidated with this procedure. A general trend was observed with computational studies; deployment of an acyl protecting group on the nitrogen with a substituted cyclohexadienyl derivative lowered the activation barrier to elimination of the corresponding NCR.

3. USE OF HYPERVALENT IODINE REAGENTS FOR THE GENERATION OF N-CENTERED RADICALS

Hypervalent iodine complexes as reagents for the generation of NCRs were documented by Togo in 1998.[207] Investigations with sulfonamide precursors (**198**) and phenyliodine(III) diacetate (PIDA) as a reagent yielded 1,2,3,4-tetrahydroquinoline derivatives (**199**) with a sulfonamide protecting group (Scheme 39).

Scheme 39. Cyclization with N-Centered Radicals Generated by the Use of Hypervalent Iodine Species



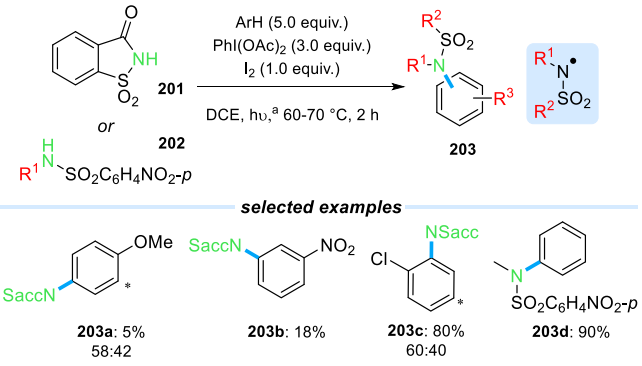
[a]500 W tungsten lamp used.

The proposed mechanism suggested the iodination of the sulfonamide; the N−I bond was homolytically cleaved by the light source. The *N*-amidosulfonyl radical imidated aromatics intramolecularly (**199a**, **199b**), and an instance of deprotection of the sulfonamide group was exemplified (**200**). Intermolecular examples utilized saccharin (**201**) or *N*-alkylsulfonamides (**202**) as sulfonamidation agents (Scheme 40).

The arenes were in large excess and used as a solvent for the reaction. When highly electron-rich or electron-poor substrates were employed, products were obtained in poorer yields (**203a**, **203b**) compared to other imidated products (**203c**). Imidation with other *N*-alkylsulfonamide derivatives proved fruitful (**203d**); however, it was reported that any increase in alkyl steric bulk on the imidation agent decreased the desired product formation.

Later in 2000, the Togo group refined the generation of iodinated 3,4-dihydro-2,1-benzothiazine 2,2-dioxide derivatives from sulfonamides **204** (Scheme 41). The choice of solvent

Scheme 40. Intermolecular Amination of Aromatics with N-Centered Radicals Generated by Hypervalent Iodine Species



[a]500 W tungsten lamp was used. The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

affected the major product of the amination (**205** or **206**). It was found that DCE promoted a regioselective iodination of the aromatic ring, a synthetically useful handle for further functionalization.[208]

Due to the disadvantages around the use of UV light, Muñiz et al. developed a methodology combining sulfonamides (**207**) and visible light to produce 3,4-dihydro-2,1-benzothiazine 2,2-dioxide derivatives (**208**) with a hypervalent iodine species (Scheme 42).[209]

Biaryl substrates with varied electron density at the *para* position were converted to the products in excellent yields (**208a**−**208f**). Examples with an unsymmetrical substitution pattern produced regioisomers (**208g**). Alkyl derivatives (**208h**, **208i**) were also examined. The scope was expanded to tethered diarylsilanes, which proceeded to form a 7-membered ring (**209a**, **209b**). Subsequent removal of the diarylsilanes revealed a protected aniline motif (**210a**, **210b**). Removal of the nitrogen protecting group then afforded the aniline derivatives in excellent yields (**211a**, **211b**).

The use of *ortho*-iodoxybenzoic acid (IBX, **212**) as a SET oxidant has been reported for the generation of NCRs (Scheme 43). Nicolaou et al. published detailed reports on the use of IBX with anilides (**213**) where amidyl radicals underwent 5-*exo*-trig cyclization to form heterocycles (**214**).[210−212] A number of functionalized and complex heterocycles were synthesized, which contributed to seminal work in natural product synthesis. Studer and Janza adopted this methodology, which generated alkoxyamidyl radicals from acetylated alkoxyamines (**215**) that could perform a stereoselective 5-*exo* or 6-*exo* cyclization to form isoxazolidines or [1,2]oxazinanes (**216**). Suitable reduction with samarium diiodide furnished 1,3- or 1,4-amido alcohols (**217**).[213]

In 2012, Zhu et al. reported a transition metal-free approach to the synthesis of benzimidazoles (Scheme 44). Use of *N*-arylbenzamidine substrates (**218**) with PIDA promoted the C−H imination of arenes, furnishing benzimidazole derivatives (**219**).[214]

Alkyl and halide functionalities at the *para* position on the arene moiety were well tolerated, with the relevant substrates cyclizing in excellent yields (**219a**−**219c**). Derivatization of the 2-position in the substrates with alkyl substituents did not significantly affect the isolated yields, regardless of steric bulk (**219d**−**219f**). For *meta*-substituted examples (**219g**), a mixture of regioisomers was isolated with a slight preference for

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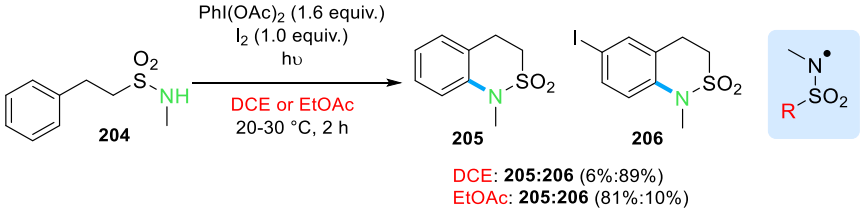
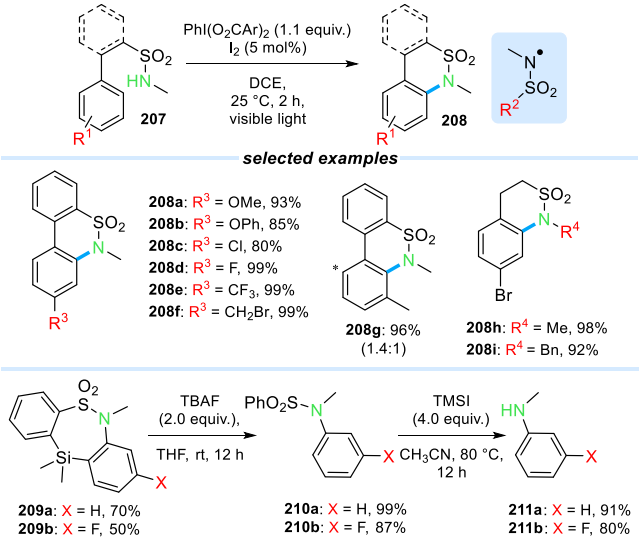
Scheme 41. Synthesis of 3,4-Dihydro-2,1-benzothiazine 2,2-Dioxide Derivatives and the Effect of Solvent Change on the Major Product

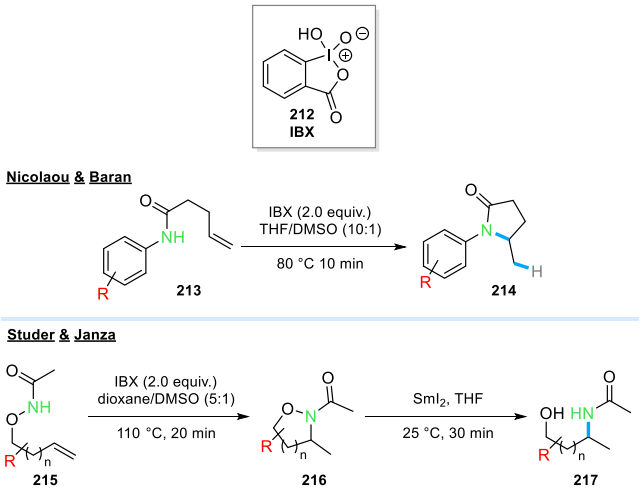


Scheme 42. Intramolecular Arene Amination Facilitated by Hypervalent Iodine to Form Cyclic Sulfonamides[a]



[a]The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

Scheme 43. Examples of *ortho*-Iodoxybenzoic Acid-Mediated Generation of N-Centered Radicals



imination *para* to the halide group. Cyclization gave the tricyclic amidine **219h** in an excellent yield.

4. INDIRECT GENERATION OF IMINYL RADICALS FROM NITRILES IN CASCADE RADICAL SYNTHESIS FOR HOMOLYTIC AROMATIC SUBSTITUTION

In 1995, Nanni and co-workers published a report detailing the radical cascade synthesis of cyclopenta-fused quinoxalines (**220**) (Scheme 45).[215] The work was inspired by protocols reported by Curran et al.,[216,217] who utilized isonitriles and alkynes in a novel [4+1] radical annulation in a strategy toward (±)-camptothecin.

The resulting radical from AIBN initiation (**221**) adds to phenylacetylene to furnish the vinyl radical **222**. Addition to an isonitrile affords the imidoyl radical **223**, which subsequently adds into the nitrile derived from the AIBN initiator, generating the iminyl radical **224**. Cyclization to the 6-membered ring resulted in the formation of quinoxaline **220**.

In 1997, Zanardi and Nanni presented a procedure for the [3+2] radical annulation using tetrafluoroborates (**225**) and aryl isothiocyanates (**226**), which afforded benzothienoquinoxalines (**227**) (Scheme 46).[218]

The reaction proceeds through a radical cascade, beginning with generation of the aryl radical from the diazonium tetrafluoroborate (**225**). Attack of the aryl radical onto the sulfur in the isothiocyanate (**226**) results in an α-(arylthio)-imidoyl radical (**228**). Cyclization onto the nitrile afforded an iminyl radical (**229**), which underwent cyclization onto the arene moiety furnishing **227** in 80% yield. Other benzothienoquinoxalines (14 examples, 34−80%) were prepared containing varied arene substituents such as nitro groups, halides, and methyl ethers. Further investigations on radical annulations were documented by Nanni and Zanardi, focused on isonitriles for the synthesis of quinoxaline derivatives.[219,220]

In 2001, Bowman reported the use of radical cascade reactions with iminyl radicals in the synthesis of heteroarenes in alkaloids.[221] Previous work by the group had reported generation of C-centered radicals from precursor **230**, which subsequently attacked the nitrile (**231**) to generate iminyl radical **232**. However, the iminyl radical did not add in a 5-*exo* manner to the olefin to furnish **233**. Instead, a β-scission to the corresponding nitrile **234** occurred [Scheme 47 (i)].[222] In the publication reported in 2001, precursor **235** was subjected to irradiation with light, which generated vinyl radical **236**. Attack onto the nitrile afforded an iminyl radical (**237**). The alkaloid product **238** was achieved by 6-*endo* cyclization or 5-*exo* cyclization, followed by a neophyl rearrangement, in 21% yield [Scheme 47, (ii)].

These radical cascade reactions have also been utilized for polycyclic natural product syntheses. Applications of these protocols were reported by Bowman [Scheme 48, (i)][223] followed by Malacria [Scheme 48, (ii)][224] toward the total synthesis of Luotonin A (**239**). The mechanistic detail for these examples is conceptually similar to the mechanism shown in Scheme 47. Malacria's approach exploited unprecedented bond

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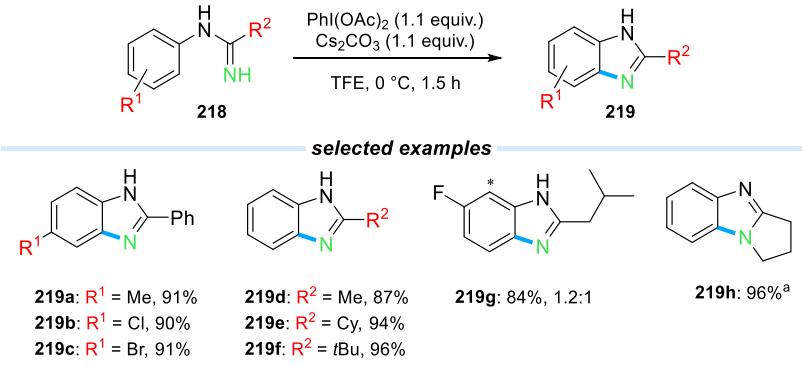
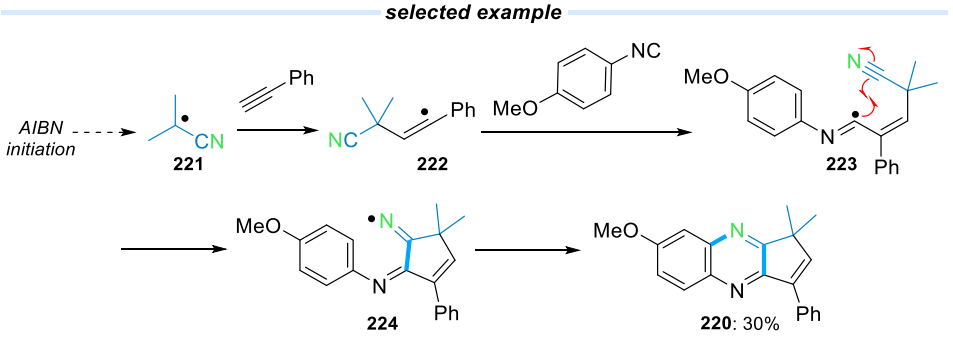
Scheme 44. Synthesis of Benzimidazoles via Cyclization of Iminyl Radicals Generated with Phenyliodine(III) Diacetate as a Reagent



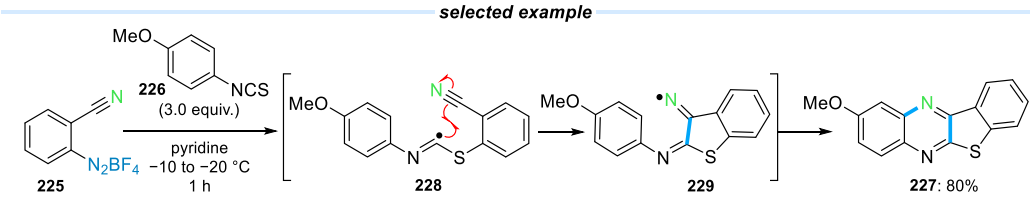
[a]Reaction conditions: $PhI(OAc)_2$ (1.1 equiv), Cs_2CO_3 (1.1 equiv), TFE, 25 °C, 2 h. The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

Scheme 45. Generation of Iminyl Radicals from Attack onto Nitriles in the Synthesis of Cyclopenta-Fused Quinoxalines[a]



[a]1.1 equiv of AIBN used.

Scheme 46. Generation of Iminyl Radicals in a [3+2] Radical Annulation Using Isothiocyanates



disconnections to construct the natural product via a radical cyclization cascade with *N*-acylcyanamides (**240**). The Malacria group also published a tin-free approach to Luotonin A (**239**) from intermediate **240**.[225] An increased yield was obtained (54%) with the addition of pyridine, under light irradiation [Scheme 48, (iii)].

The Malacria group continued their efforts in the construction of pyrimidone motifs via radical cascade reactions (Scheme 49).[225,226] In 2008, a tributyltin-mediated approach to the synthesis of polycyclic heterocycles from *N*-acylcyanamides (**241**) was reported [Scheme 49, (i)].[225] Variation of the phenyl *para*-substituent led to the desired products (**242a**−**242e**), tolerating a range of electron-poor (**242b**−**242d**) and electron-rich (**242e**) examples. Cyclization onto heterocycles was examined (**242f**), although regioisomers were obtained when *meta*-substituted substrates were used. The construction of tricyclic compounds was also described (**242g**), which proceeded well (4 examples, 66−79%). After DFT calculations, the mechanism was suggested to proceed with a 5-*exo*-trig cyclization, followed by a direct 6-*endo*-trig cyclization/re-aromatization [cf. Scheme 47, (ii)].

In 2010, the methodology was extended to the synthesis of guanidine derivatives (**243**), using aliphatic azides as precursors to NCRs (**244**) [Scheme 49, (ii)].[226] The mechanism proceeds in a similar fashion to the previously reported C-centered radical transformation [cf. Scheme 48, (ii)]. Construction of 5,6,6-tricyclic systems was successful (**243a**, **243b**), although a decreased yield was observed for the 7,6,6-tricyclic product (**243c**). It was proposed that a lower yield for **243c** was obtained due to possible competition between the cyclization event and 1,5-HAT. In varying the aromatic group, a thiophene analogue also delivered the desired product (**243d**).

In 2018, Turner and Murphy et al. reported a HAT-initiated radical addition onto nitriles (**245**), catalyzed by iron(III) acetylacetonate.[227] An iminyl radical was generated by the attack of a carbon radical onto a nitrile. Interception of the iminyl radical allowed a second cyclization to occur, producing quinazolinone derivatives. A further publication expanded the

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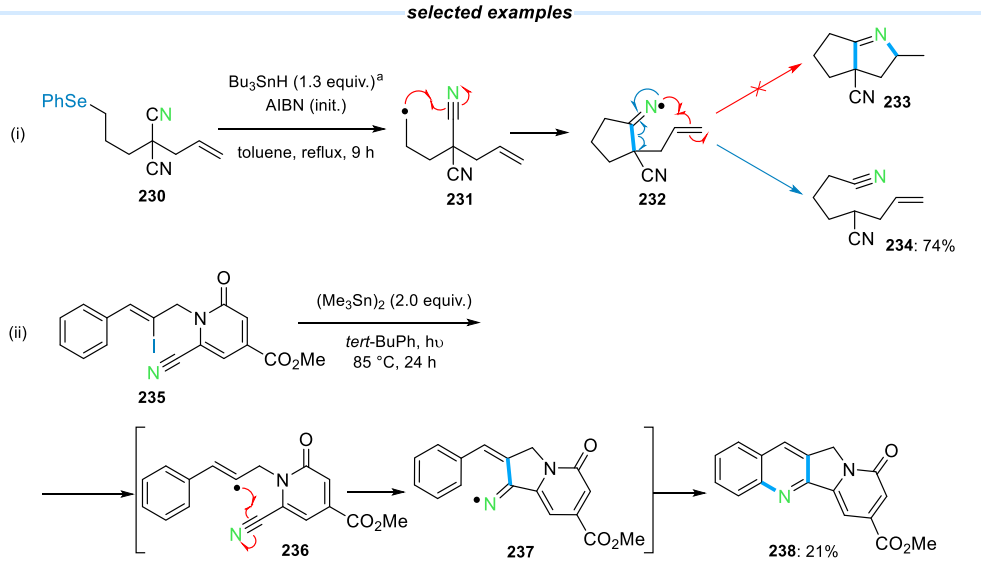
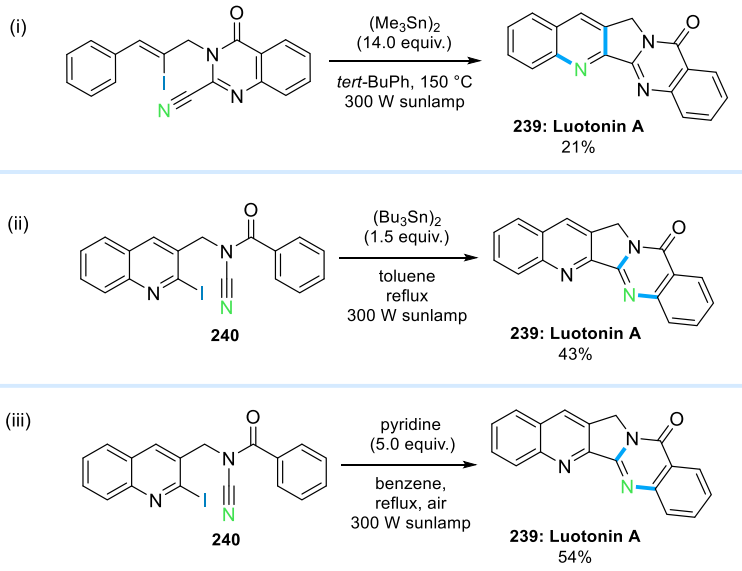
Scheme 47. (i) Generation of Iminyl Radicals from Nitriles and Their Reactivity toward Internal Olefins, and (ii) Use of Iminyl Radicals Generated by a Radical Cascade toward the Synthesis of Alkaloid Natural Products



[a]Slow addition over 3 h.

Scheme 48. Strategies toward the Synthesis of Luotonin A via Tandem Radical Cyclization



scope of the reaction for the synthesis of (spiro)quinazolinone derivatives (**245**) (Scheme 50).[228]

Diversification of the aromatic system was investigated (**246a**–**246e**). Both electron-donating (**246c**) and electron-withdrawing (**246d**, **246e**) groups were tolerated, and the corresponding quinazolinones were isolated in good yields. Reaction of heteroaromatics proved fruitful (**246f**, **246g**), despite the difficulties associated with the changed electronics of the ring. Generation and cyclization of a secondary C-centered radical onto a nitrile was also demonstrated (**246h**). The presence of heteroatoms in the spirocycle moiety led to the synthesis of spiro-tetrahydropyran (**246i**), Boc-piperidine (**246j**), and tetrahydrothiopyran (**246k**), which were isolated in good yields. Further substrates with *meta* substitution were probed to determine whether cyclization would occur at the *ortho* or *para* position, relative to the R substituent. Electron-donating groups (**246l**) favored *ortho* substitution, whereas electron-withdrawing groups (**246m**) displayed the reverse selectivity.

The application of nitriles as radical acceptors allows rapid construction of complex and diverse heterocycles. We direct the reader to a recent review by He and Yu for further information on their reactivity in synthesis.[229]

5. NON-PHOTOCHEMICAL AMINATION WITH METAL-COMPLEX N-CENTERED RADICALS

5.1. C–H Amination of (Hetero)arenes

In 2014, Baran et al. reported a novel imidation agent for direct C–H imidation of (hetero)arenes.[230] Inspired by the work of Forrester,[50] *N*-succinimidyl perester (NSP) (**247**) was selected as a redox-active NCR precursor. Ferrocene was identified as the optimal catalyst for the breaking of the O–O bond. Subsequent

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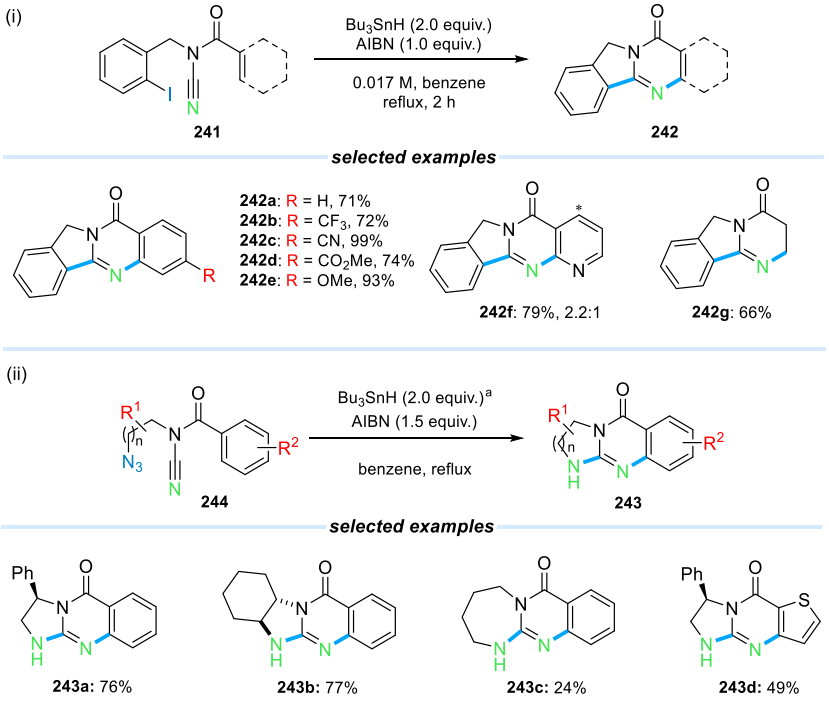
Scheme 49. Tributyltin Radical-Mediated Cyclization for the Construction of Polycyclic Heterocycles



[a]Slowly added (0.06 mol h^{-1}). The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

loss of carbon dioxide and acetone generated the imidyl radical (**248**) (Scheme 51).

Electron-rich and electron-poor pyridines were imidated (**249a**, **249b**), with the incoming group sited *meta* to the pyridine nitrogen. Unactivated aromatics (**249c**), as well as those substituted by esters (**249d**), silyl protecting groups (**249e**), ketones (**249f**), and halide (**249g**) functional groups all worked well, and the desired products were isolated in good yields. Interestingly, *ipso* substitution at the methoxy group was observed for 1,4-disubstituted aromatics (**249d**) as a side reaction (15:2). Other heteroaromatics were trialed, giving the imidated products (**249e**−**249h**). The reaction tolerated the presence of air, although consistently higher yields were obtained when run under an inert atmosphere. Pyridine **250** was subjected to a one-pot imidation and deprotection, which gave **251** in 60% yield. Furthermore, a gram-scale imidation reaction of **250** was reported, giving **249i** in 48% yield.

In 2016, the Morandi group reported the use of a hydroxylamine-derived aminating agent in the hydroamination of alkenes, catalyzed by iron(II) phthalocyanine.[231] This methodology was adapted with a novel amination reagent, *O*-(methylsulfonyl)hydroxylamine trifluoromethanesulfonate (**252**). In the recent report, use of **252** with an iron sulfate catalyst furnished the desired primary anilines (**253**) without the need for protecting groups (Scheme 52).[232]

A range of monosubstituted arenes were aminated (**253a**−**253e**) in an unselective manner, although the disubstituted anisoles trialed gave single regioisomer products (**253f**−**253i**). Unfunctionalized arenes (**253j**) and heteroaromatics (**253k**) were also successful in the reaction. Late-stage functionalization of 17β-estradiol-3-methyl ether (**253l**) and dextromethorphan (**253m**) gave the desired products in moderate yields. Mechanistic investigation revealed the strong influence of substituents on the rate of reaction, with electron-rich substrates reacting at a much faster rate than electron-poor ones. Thus, the mechanism was proposed to act through a highly electrophilic aminating agent. The Morandi group have since developed other intermolecular and intramolecular iron-catalyzed amination procedures, exploiting a range of hydroxylamine precursors.[233]

Inspired by the work of Fagnou[234] and Morandi,[231] Jiao et al. developed a novel amination reagent (**254**) to directly access primary anilines (**255**).[235] The novel reagent was easily accessed by a two-step reaction of *tert*-butyl hydroxycarbamate and the corresponding acyl chloride. All reactions were carried out in the presence of air and under mild conditions (Scheme 53).

Amination afforded electron-rich phenolic ether (**255a**−**255f**), phenol (**255g**), and acetanilide (**255i**, **255j**) derivatives in moderate yields and regioselectivities. Benzene was aminated and acetylated in a single step (**255k**), and the amination product of indolin-2-one (**255l**) was obtained in excellent yield. Heteroaromatics (**255m**, **255n**) were tolerated, although lower yields were achieved. To further demonstrate the capability of the novel aminating agent, late-stage functionalization of complex bioactive compounds such as β-D-galactopyranoside derivative (**255o**), vanillic acid methyl ester (**255p**), and Metaxalone (**255q**) was achieved. Radical scavenger experiments with TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)-oxidanyl] caused complete inhibition of the reaction, which could have suggested a radical mechanism; however, no radical adducts were isolated. Kinetic isotope experiments using acetanilide and d_5-acetanilide were consistent with a homolytic aromatic substitution mechanism (k_H/k_D = 1.0). EPR studies with 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) revealed the presence of an organic radical, which was consistent with a pathway that involved an ammoniumyl radical.

In 2019, Ritter and co-workers presented a procedure for the amination of electron-poor substrates (Scheme 54).[236] Previously reported literature which utilized ammoniumyl radical additions to arenes did not provide synthetically useful

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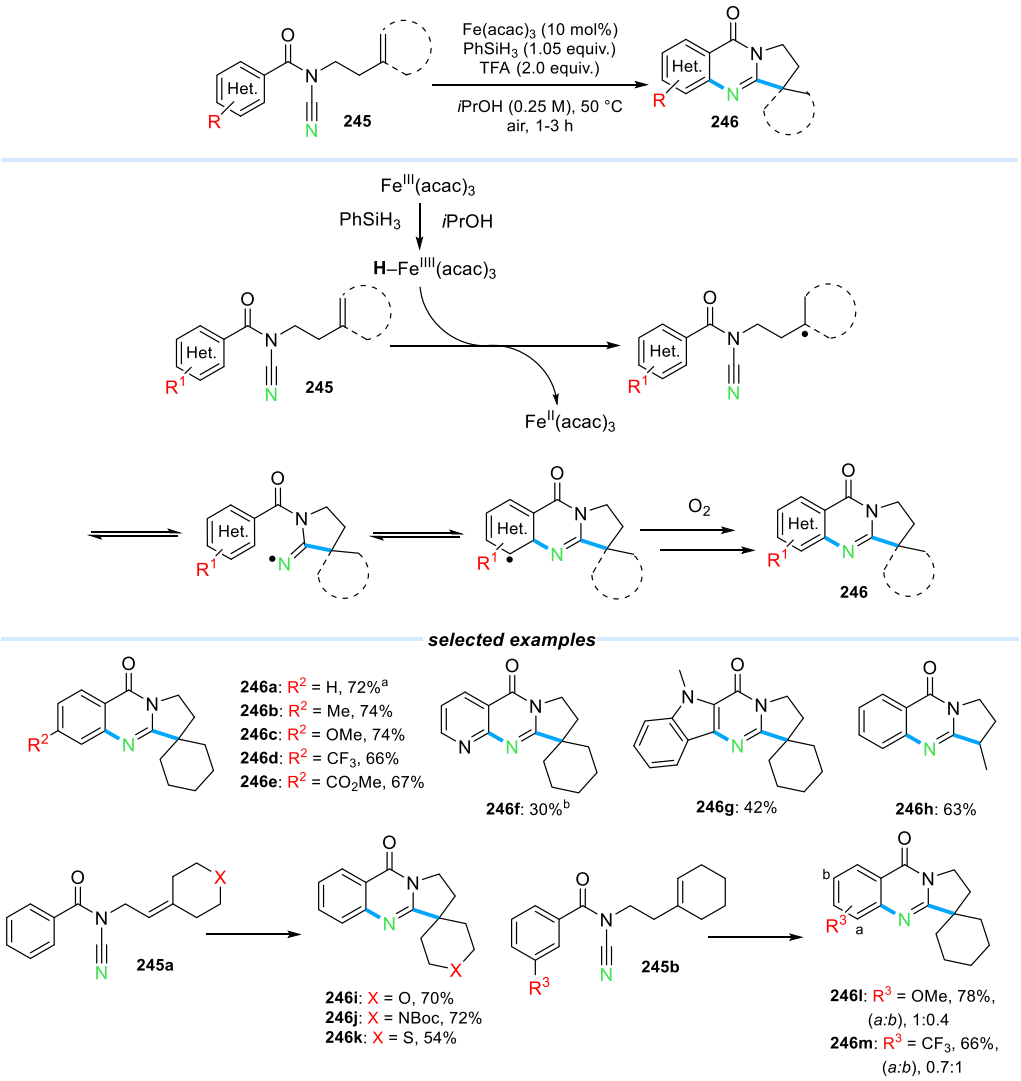
Scheme 50. H-Atom Transfer-Initiated Radical Addition onto Nitriles for the Synthesis of Quinazolinones



[a]5 mmol scale yielded 65%. [b]Reaction conditions: $Fe(acac)_3$ (20 mol%), $PhSiH_3$ (1.5 equiv), TFA (2.0 equiv), iPrOH, 80 °C, 14 h, air. 5% of 4-substituted regioisomer was also isolated. acac = acetylacetonate.

yields for electron-poor examples. It was proposed that hexafluoroisopropanol (HFIP) participated in the disruption of ion pairs by hydrogen bonding to anionic counterparts, and thus a more electrophilic cationic species was formed. The reactions were run in the presence of air, and two different iron catalysts were shown to be effective at aminating substrates under the reaction conditions.

Amination products of deactivated arenes such as nitrobenzene (**256a**), methylsulfonylbenzene (**256b**), and benzonitrile (**256c**) were isolated in very good yield and moderate regioselectivities. Quinoline derivative (**256d**) and trisubstituted arene (**256e**) also provided the desired products in good yields. Late-stage functionalization of drug molecules was demonstrated; rufinamide was aminated to afford the products **256f** in 67% yield as a 14:1 ratio of regioisomers. Investigation into the mechanism began with the cyclic voltammogram of the aminating reagent in HFIP (0.77 V vs Fc/Fc^+) and CH_3CN (1.28 V vs Fc/Fc^+). This revealed a ∼0.5 V difference in the reduction potential when strong hydrogen bonding was present with HFIP. Furthermore, swapping the counteranion to ones less capable of hydrogen bonding (e.g., PF_6) proved unsuccessful, thus proving that the triflate counterion was an important factor in the success of the reaction. Comparison between reactions run with Fe(II) as a catalyst and metal-free ones demonstrated the activating effect of HFIP. It was stated that longer reaction times were needed in the absence of the Fe(II) catalyst. When a Fe(II) catalyst is present, the ammoniumyl radical can be generated by a reductive SET; however, it was also stated that the use of an iron species as a radical chain initiator cannot be ruled out.

An analogous methodology was set out by Sanford and coworkers in 2020, who utilized hydroxylamine (**257**), an inexpensive, commodity chemical (Scheme 55).[237] Inspired by the work of Minisci,[238] initial investigation was focused around using first-row transition metal salts as redox catalysts, of which titanium salts were found to be effective.

The amination of monosubstituted arenes favored *para* substitution, and the products (**258a**−**258c**) were isolated in good yields. Unactivated arenes and anisole derivatives furnished the desired products (**258d**−**258f**) in excellent yields and as single regioisomers. The amination procedure was scaled-up to afford **258i** on a 10 mmol scale without optimization

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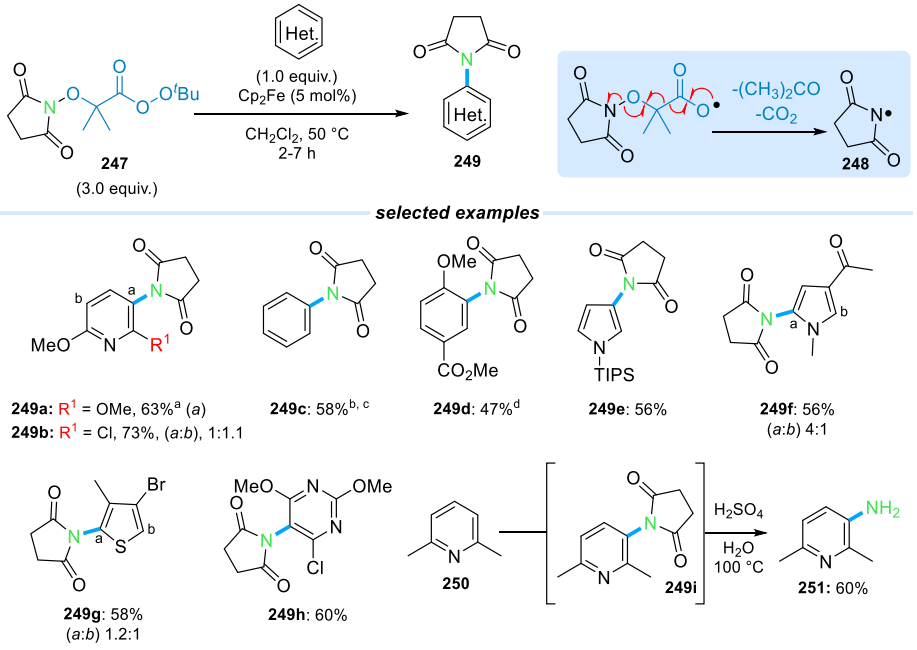
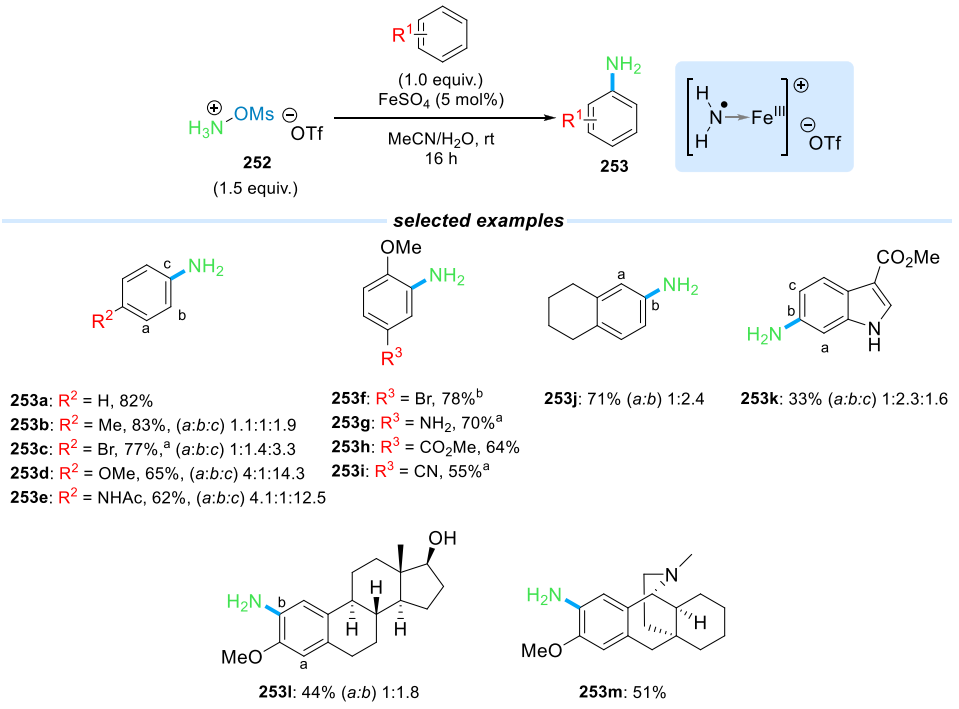
Scheme 51. *N*-Succinimidyl Perester Precursor for the C−H Imidation of (Hetero)arenes Using Ferrocene as a Catalyst



[a]2.75 equiv of NSP used. [b]4.0 equiv of NSP used. [c]Cp_2Fe (10 mol%) used. [d]*Ipso*-substitution observed as a minor product.

Scheme 52. Direct Access to Primary Anilines with *O*-(Methylsulfonyl)hydroxylaminetrifluoromethanesulfonate as an Aminating Agent



[a]4.0 equiv of aminating reagent used. [b]2.5 equiv of aminating reagent used.

(82%). Heteroaromatic substrates were also amenable, affording product thiophenes (**258j**) and benzothiazoles (**258k**) as regioisomeric mixtures. Furthermore, a number of pharmaceutically relevant structures were aminated successfully (**258l**), which demonstrated the potential for late-stage functionalization of complex intermediates. Kinetic isotope effect experiments were consistent with an aromatic substitution pathway (k_H/k_D = 1.0). Thus, the mechanism is believed to initiate via inner-sphere electron transfer to generate an electrophilic nitrogen radical. The NCR can then participate in the amination of primarily electron-rich arenes.

5.2. Difunctionalization of Olefins

In 2005, Chemler and co-workers investigated diaminations with tethered amines (**259**), promoted by stoichiometric copper(II) salts [Scheme 56, (i)].[239] The resulting sulfamide

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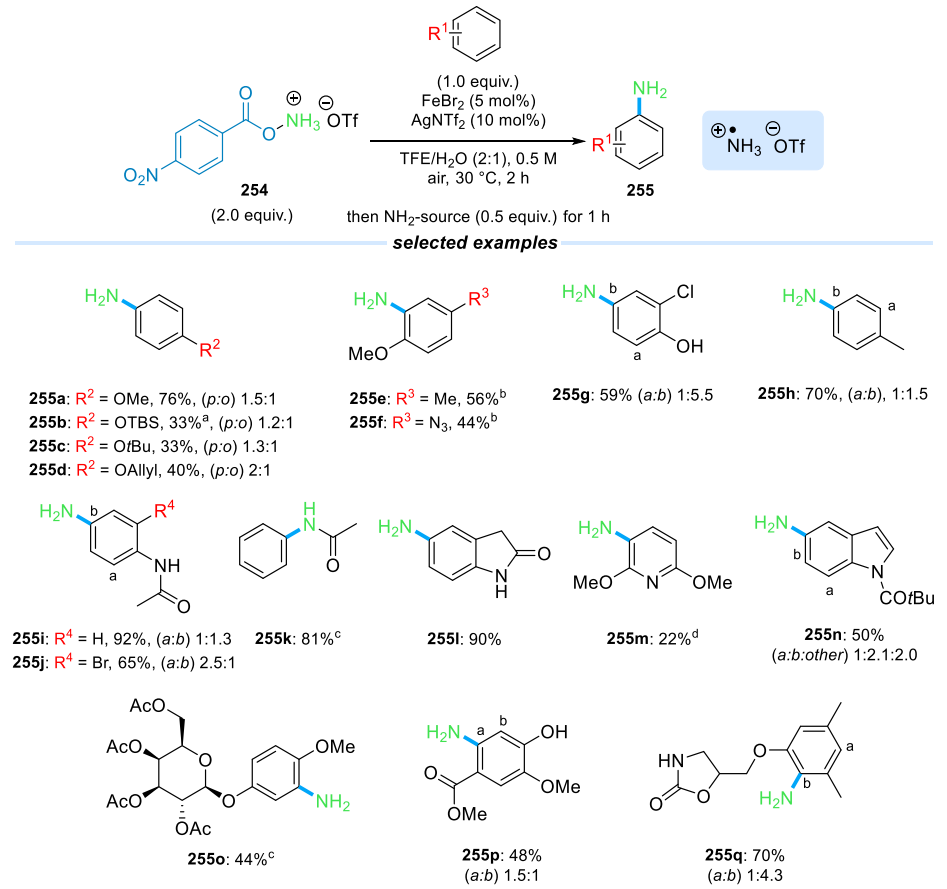
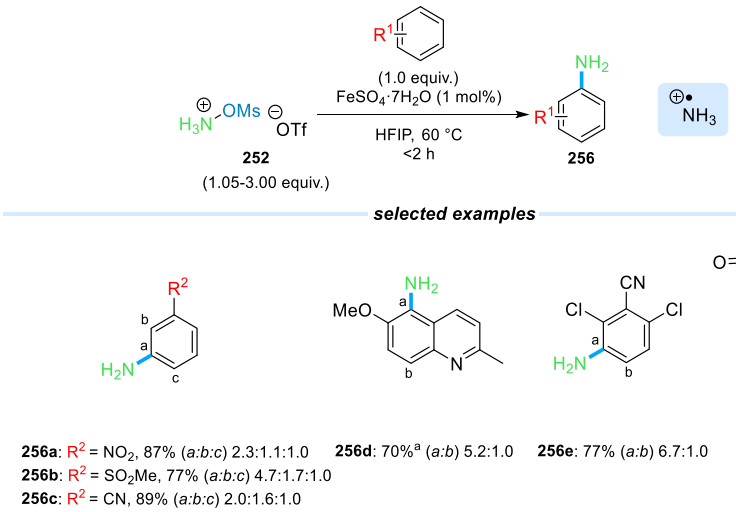
Scheme 53. Direct Access to Primary Anilines Using a Novel Redox-Active Aminating Agent



[a]1.5 equiv of NH_2 source used. [b]2.0 equiv of NH_2 source used, allowed to react for 2 h, then 0.5 equiv of NH_2 source was added and allowed to react for another hour. [c]The crude product was extracted by CH_2Cl_2 and then acetylated by acetyl chloride. [d]2.0 equiv of NH_2 source used.

Scheme 54. Amination of Electron-Poor Substrates in Hexafluoroisopropanol



[a]Performed under an atmosphere of oxygen.

260 furnished free diamine in excellent yield (93%) when subjected to reducing conditions with $LiAlH_4$. In the following years, focus was placed on the construction of imidazolidinones and pyrrolidines (**261**) from sulfonamides (**262**), and a high diastereoselectivity was achieved with substrate control [Scheme 56, (ii)].[240,241] Downstream efforts by the Chemler group have now disclosed a catalytic protocol to form indolines (**263**) from aniline derivatives (**264**) [Scheme 56, (iii)][242−244] as well as further developments in aminooxygenation[245−247] and oxidative amination of alkenes.[248,249] Other transformations such as Heck-type cascade reactions performed with copper

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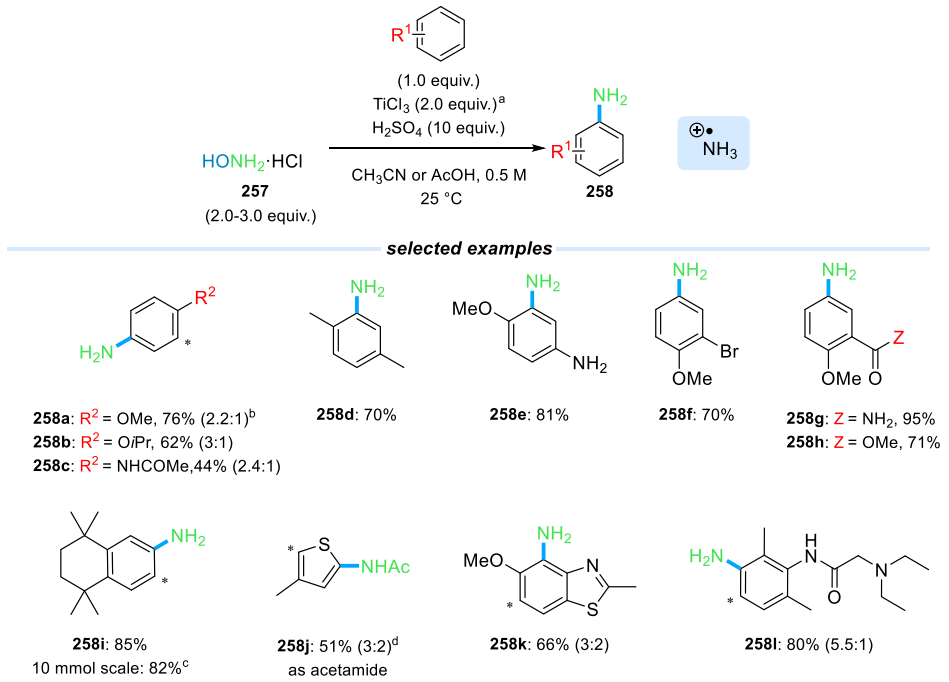
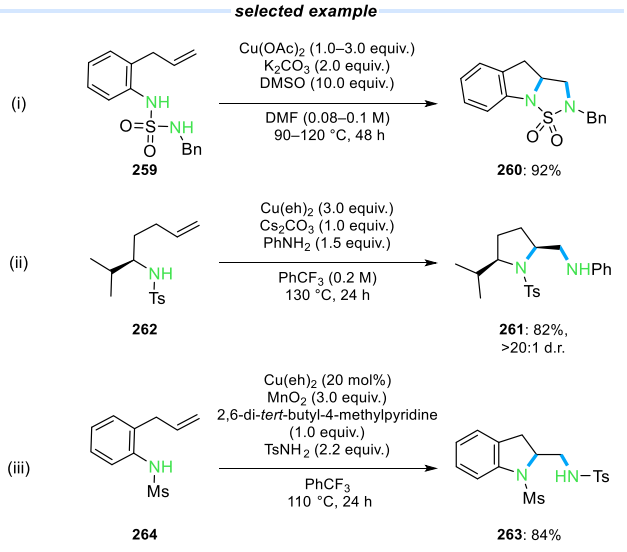
Scheme 55. Ti-Catalyzed Amination of Arenes with Hydroxylamine



[a]$TiCl_3$ (12% in HCl) was added via syringe pump (4 mL/h). Reaction was left to react until the purple color of the titanium trichloride solution persisted for more than 10 min. [b]Mono-:disubstitution ratio (2.5:1). [c]9% diamination. [d]Crude reaction was treated with acetic anhydride (1.5 equiv) and Et_3N (2.0 equiv). The C−N bond in the major isomer is shown—the minor isomer is formed at the site of the asterisk.

Scheme 56. (i, ii) Stoichiometric Copper-Promoted Diaminations and (iii) Copper-Catalyzed Diaminations, by Chemler and Co-workers[a]



[a]eh = 2-ethylhexanoate.

catalysts have been documented, notably by Chemler[244] and Bower.[250]

Work by the Shi group in 2008 looked at the use of $[Cu]^I$ catalysts for the diamination of conjugated alkenes using di-*tert*-butyldiaziridinone (**265**) as a diamination agent.[251] Previous reports by the group had used Pd(0) as the metal catalyst to diaminate the internal double-bond;[252−256] however, by using a copper catalyst, the opposite regioselectivity (diamination to the terminal position) occurred (**266**) [Scheme 57, (i)]. Shi also developed a Cu-catalyzed diamination targeting the internal double-bond regioselectively (up to >99:1) by removing the phosphine ligand [Scheme 57, (ii)].[257]

Reports on the mechanism elucidated that two pathways were in play.[257,258] These both proceeded via a copper-complexed NCR and were supported by EPR studies. Cleavage of the N−N bond (**265**) by the $[Cu]^I$ formed the copper-complexed intermediates (**268**, **A** or **B**), which are in rapid equilibrium. Looking at diamination of the internal alkenes first (left side), coordination of the $[Cu]^{III}$ (**A**) to the diene (**269**) is followed by the migratory insertion one of the complexed nitrogens in **270**. A final reductive elimination from **271** furnishes the diamination product **267** and the $[Cu]^I$ catalyst. Moving to the right-hand side of Scheme 57, the diamination of the terminal alkene proceeds through a similar mechanism, starting from aminyl radical **B**, which adds to the terminal end of the alkene to give product **266**. A review published by Shi[259] nicely summarizes the use of di-*tert*-butyldiaziridinone and related analogues for diamination of alkenes. Other applications of di-*tert*-butyldiaziridinone as an aminating agent include the α-amination of ketones[260] and esters.[261,262] Of particular note, Gong's work[262] reports the asymmetric construction of hydantoins, obtaining high ee's (90−98%) due to the formation of a chiral enolate species. Shi's attempts at formulating an asymmetric diamination method with a chiral ligand[263] or a chiral phosphate counterion[264] were somewhat successful. Other diaminating agents such as cyclic sulfamides[265] have been identified as successful diamination agents. Non-conjugated alkene substrates were also functionalized by the Shi group; their further papers featured approaches to an NK_1 antagonist,[266] synthesis of imidazolinones,[267] and use of diaziridinimines.[268] Similar protocols have been demonstrated by the Yoon group,[269,270] using copper-catalysis for aminohydroxylation transformations.

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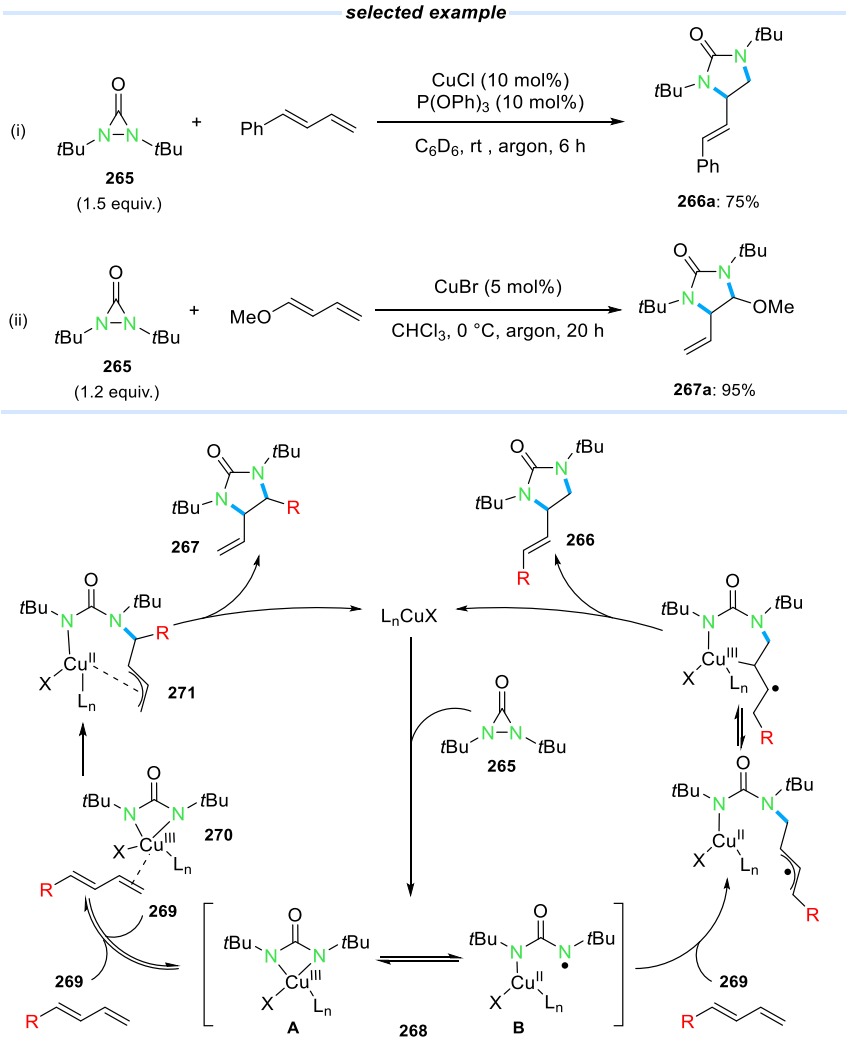
Scheme 57. Diamination of Conjugated Alkenes Using Copper-Complexed Aminyl Radicals: (i) Cu(I)-Catalyzed Diamination to the Terminal Double Bond[a] and (ii) Cu(I)-Catalyzed Diamination to the Internal Double Bond



[a]Formation of the internal regioisomer was observed in trace amounts.

Liu et al. reported catalytic asymmetric diamination of alkenes (**272**), (45 examples, up to 98% ee, Scheme 58).[271] The substrates were mainly *N*-(ϖ-styrenyl)-ureas, and the sources of the NCRs were (i) *O*-acylhydroxylamines **273** and (ii) azidoiodinanes **274**. The products are presented as **275** and **276**, respectively. Taking the first of these cases in more detail, a $[Cu]^{I}$ salt was proposed to reduce an *O*-acylhydroxylamine **273** to a carboxylate anion **278** and an aminyl radical by electron transfer. This would leave a $[Cu]^{II}$ cation and an aminyl radical. The authors represent this as an aminyl radical that is complexed to copper, and we interpret their structure as **279**, shown below. Whichever way it is represented, this is an aminyl radical source, and the aminyl radical is proposed to attack the styrene terminus to give benzyl radical **280**. Oxidation of radical **280** to the carbocation complex **281** permits the proximal urea nitrogen to cyclize, forming product **275** and regenerating a $[Cu]^{I}$ species **277** which can continue the cycle. The asymmetry is induced by the chiral phosphoric acid ligand **282a** or an analogue (e.g., **282b**).

The work of Liu has some resemblance to 2015 research reported by Shen and Wang who undertook copper-catalyzed diamination of unactivated alkenes with hydroxylamine derivatives [Scheme 59, (i)].[272] More specifically, they added benzoyloxymorpholine **283** and related substrates to γ-alkenyl *N*-alkoxyamides **284** to afford derivatives of vicinal amines such as **285** in the absence of asymmetric ligands. This was achieved with base and copper(II) acetate, and the authors proposed that a $[Cu]^{II} \rightarrow [Cu]^{III}$ oxidation provided the electron for reductive cleavage of the N−O bond of **283**. Wang et al. followed this in 2016 [Scheme 59, (ii)][273] with copper-catalyzed conversion of acids **286** to aminolactones **287** and in 2019 [Scheme 59, (iii)][274] with 3-component reactions between carboxylic acids **288**, 1-arylbuta-1,3-dienes **289**, and *O*-benzoyloxyamines like **283** to afford **290**. Other notable work from Shen and Wang detailed an aminoazidation protocol with copper(II) acetate and **274** which gave high diastereoselectivities (>20:1 d.r.).[275]

A study by the Yu group looked into the oxyamination and diamination of unactivated alkenes.[276] Isoxazolines (e.g., **291**) were derived from the corresponding β,γ-unsaturated ketoximes (**292**) [Scheme 60, (i)]. Diamination to synthesize cyclic nitrones (e.g., **293**) were also achieved when employing γ,δ-unsaturated ketoximes (**294**) as the starting material [Scheme 60, (ii)]. The proposed mechanism identified two radical intermediates; oxidation of the ketoxime (**295**) generated an

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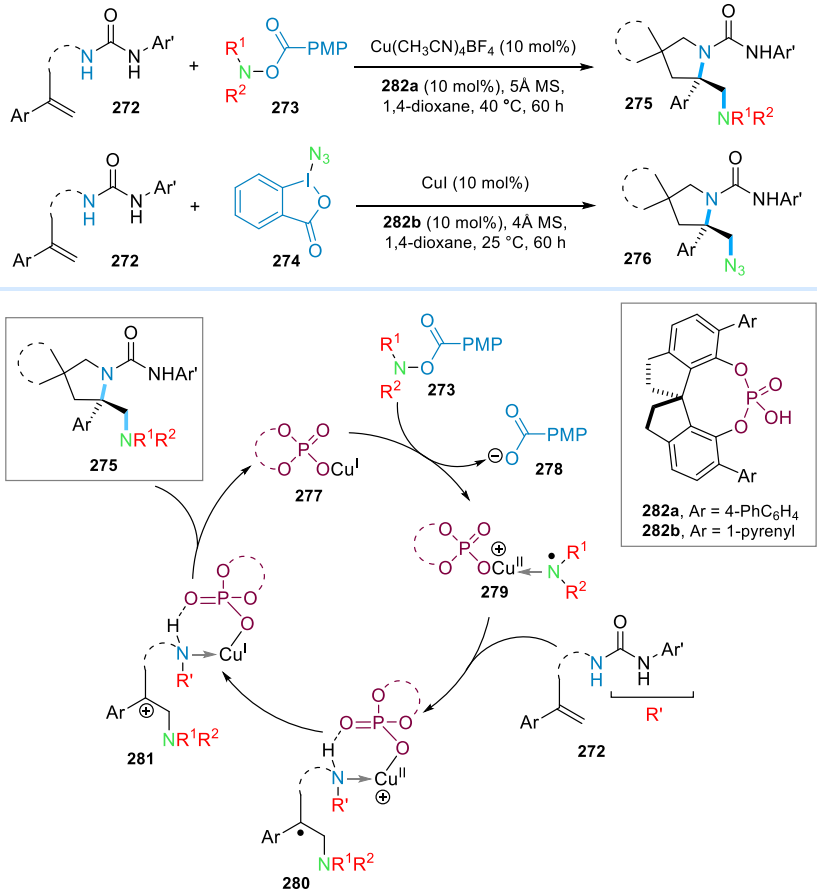
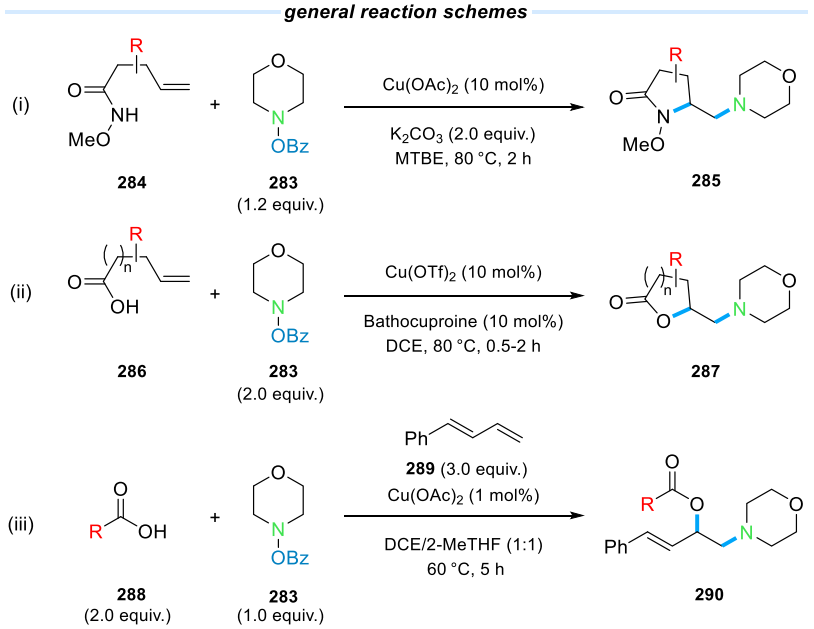
Scheme 58. Asymmetric Radical-Mediated Diamination of Alkenes Using Copper(I) Catalysts



Scheme 59. Examples of *O*-Benzoyloxymorpholines as Electrophilic Nitrogen Source in Diamination Reactions Catalyzed by Copper(II)



iminoxyl radical (**296**), which underwent a 5-*exo* cyclization, to the corresponding C-centered radical (**297**). The radical **297** then coupled to a copper-aminyl radical complex, depicted as structure **298**, in this case, to give a $[Cu]^{III}$ species (**299**). Reductive elimination provided the desired isoxazoline (**291**). The diamination proceeded through a similar mechanism, but the selectivity over oxyamination was achieved by starting with γ,δ-unsaturated ketoximes (e.g., **294**). Lengthening the chain by one carbon allowed formation of a C−N bond from **296**, constructing the corresponding nitrones (**293**).

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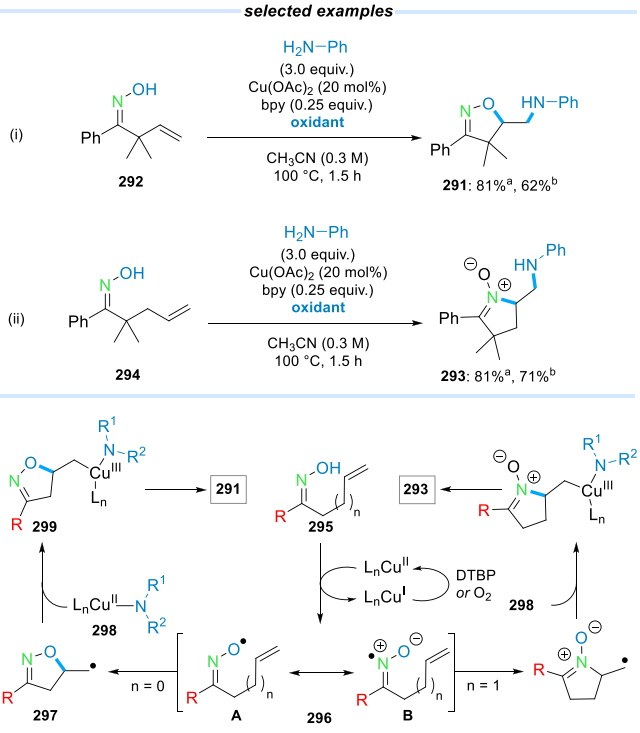
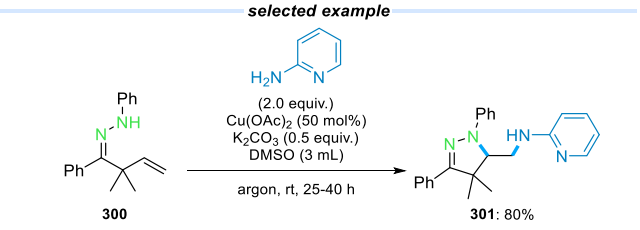
Scheme 60. (i) Copper-Catalyzed Oxyamination for the Synthesis of 4,5-Dihydroisoxazoles and (ii) Copper-Catalyzed Diamination for the Synthesis of Cyclic Nitrones



[a]Used DTBP (3.0 equiv) as the oxidant, [b]Used air as the oxidant.

In 2018, Li et al. worked on developing milder conditions to diamination of β,γ-unsaturated hydrazones (**300**) in the construction of various pyrazolines (**301**), removing the need for elevated temperatures (Scheme 61).[277] The mechanism is

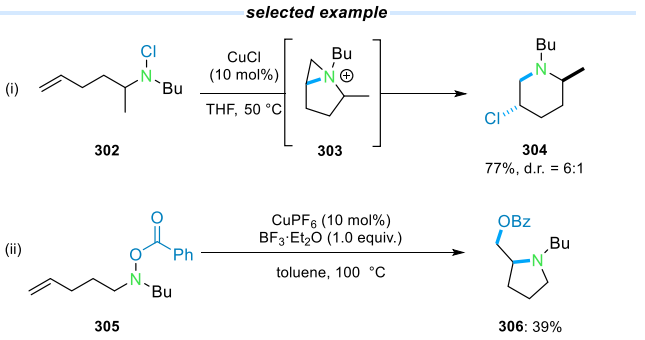
Scheme 61. Construction of Functionalized Pyrazolines via Copper-Catalyzed Diamination Reactions



believed to proceed through copper-complexed aminyl radicals, and the presence of radical intermediates was recognized with isolation of a TEMPO adduct product.

Works by Göttlich examined the use of copper catalysts as Lewis acid additives [Scheme 62, (i)].[278,279] Using *N*-chloroamines as precursors (**302**), cyclization to the corresponding pyrrolidines followed by a polar rearrangement (**303**) afforded piperidine derivatives (e.g., **304**). Although cyclization to these scaffolds had previously been published,[149] complexation to the [Cu] achieved a moderately better diastereoselectivity in the cyclization step. In the latter publication, Göttlich looked at the use of bulky chelating diamines such as TMCDA (*trans*-*N,N,N′,N′*-tetramethylcyclohexanediamine).[279] Addition of 5 equiv or more of TMCDA gave excellent diastereoselectivities (e.g., **304**, > 20:1 d.r.); however, it decreased the yield of the transformation (51%). Another report by Göttlich in 2002

Scheme 62. Early Göttlich Works on Copper-Complexed Aminyl Radicals: (i) Synthesis of Piperidine Derivatives via Cyclization of *N*-Chloroamines with Catalytic Cu(I) and (ii) Copper-Catalyzed Aminohydroxylation of Alkenes



described copper-catalyzed aminohydroxylations via complexed aminyl radicals [Scheme 62, (ii)].[280] *N*-Benzoyloxyamine precursors like **305** were activated with a Lewis acid to synthesize pyrrolidines (**306**).

In 2019, Guan, Bi, Fu, et al. reported vicinal amino-halogenation and aminoazidation reactions of alkenes (**307**)

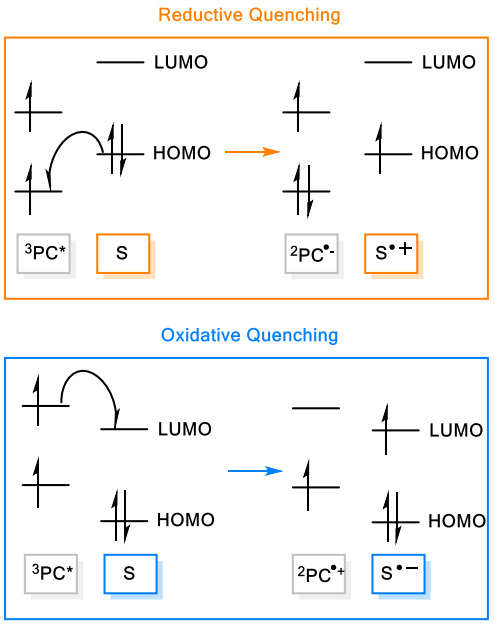


Figure 7. Reductive and oxidative quenching cycles of photoredox catalysts. S = substrate.

(Scheme 63).[281] The selected example shows difunctionalization of alkene **307** with N−Cl precursor **308**, delivering the aminohalogenation product **309**. The mechanism proceeds through coordination of the 8-aminoquinoline to the copper catalyst (**310**). Then, SET from the $[Cu]^{I}$ complex to **308**, followed by coordination of the aminyl radical, furnishes the $[Cu]^{II}$ complex **311**. An intramolecular migratory insertion of the alkene into the $[Cu]^{II}$ complex affords complex **312** and, with a subsequent reductive elimination, produces **309** and regenerates the $[Cu]^{I}$ species. A follow-up paper by Fu in 2021 described the use of *N*-bromodialkylamines for the symmetrical and unsymmetrical diamination of alkenes, making use of the same directing group shown in structure **307**.[282]

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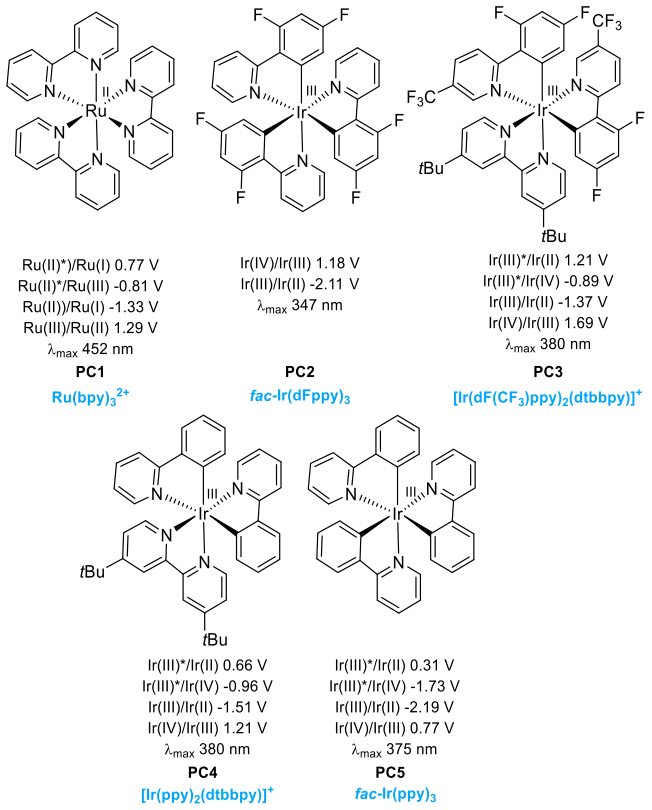
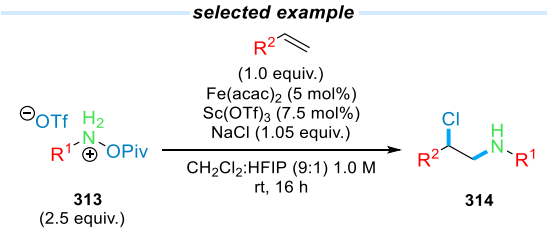


Figure 8. Types of metal photocatalysts. dFppy = 2-(2,4-difluorophenyl)pyridine, dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtbbpy = 4,4-di*tert*-butyl-2,2′-bipyridine, ppy = 2-phenylpyridine.

The same theme of copper-catalyzed amination reactions is seen in the 2020 paper of Morandi et al. in which *O*-acyl hydroxylamines **313** were activated by Fe(acac)$_2$ in the presence of a Lewis acid and NaCl to form 1-amino-2-chloro derivatives **314** from alkenes (Scheme 64).[283] The radical nature of the process is mentioned. The equation below shows formation of secondary amines in high yield, but the conditions were also adapted separately to form tertiary amines. This built upon earlier reports by the Morandi team in 2018, which formed the analogous primary amine products (cf. Scheme 52).[284]

Scheme 64. Aminochlorination of Alkenes Using Iron(II) Catalysis and an *N*-Alkyl Hydroxylamine-Derived Precursor



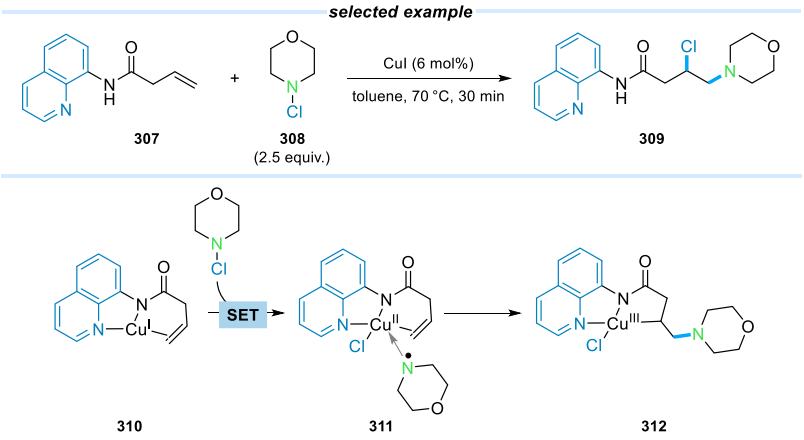
6. PHOTOREDOX CATALYSIS

Photoredox catalysis has emerged as a "hot" topic in the past 20 years and consequently has resulted in a vast literature. A powerful tool in the realm of photochemistry, it offers milder, innovative alternatives to the traditional methods of C−H amination and amination of alkenes. The idea of photoredox systems with radical chemistry was initially explored by Kellogg[285,286] and Deronzier[287,288] in the 1970s and 1980s, respectively. However, the true power of a single-electron redox process for chemical transformations had not been exploited. In 2008 and early 2009, the Yoon group,[289] Nicewicz and Macmillan,[290] and the Stephenson group[291] exposed the exciting potential of visible light in organic synthesis, pioneering the photoredox chemistry movement. Since then a plethora of organic synthetic methodologies has been discovered, relating to a diverse range of chemical transformations. A renaissance of electrochemistry has also emerged and has become a popular method of novel one-electron transformations.[292] Although this is beyond the scope of this Review, a recent review by Rovis et al.[293] has provided a critical, in-depth comparison between electrochemistry and photochemistry, highlighting their differences and similarities in radical reactions.

6.1. Photoredox Principles

Principally, "photo" refers to a photon which allows excitation of catalysts into the excited state, and "redox" refers to the reductant and oxidant properties that the catalysts possess. A photoredox catalyst acts as a vessel of charge transfer; delivery of a photon of visible light (380−700 nm) to the catalyst means that the use of higher energy UV light can be avoided. When a photocatalyst (PC) is excited, it can participate in SET processes, to and from organic molecules. It allows for nontraditional pathways to take place under relatively mild

Scheme 63. Aminohalogenation and Aminoazidation of Alkenes Using Copper Iodide



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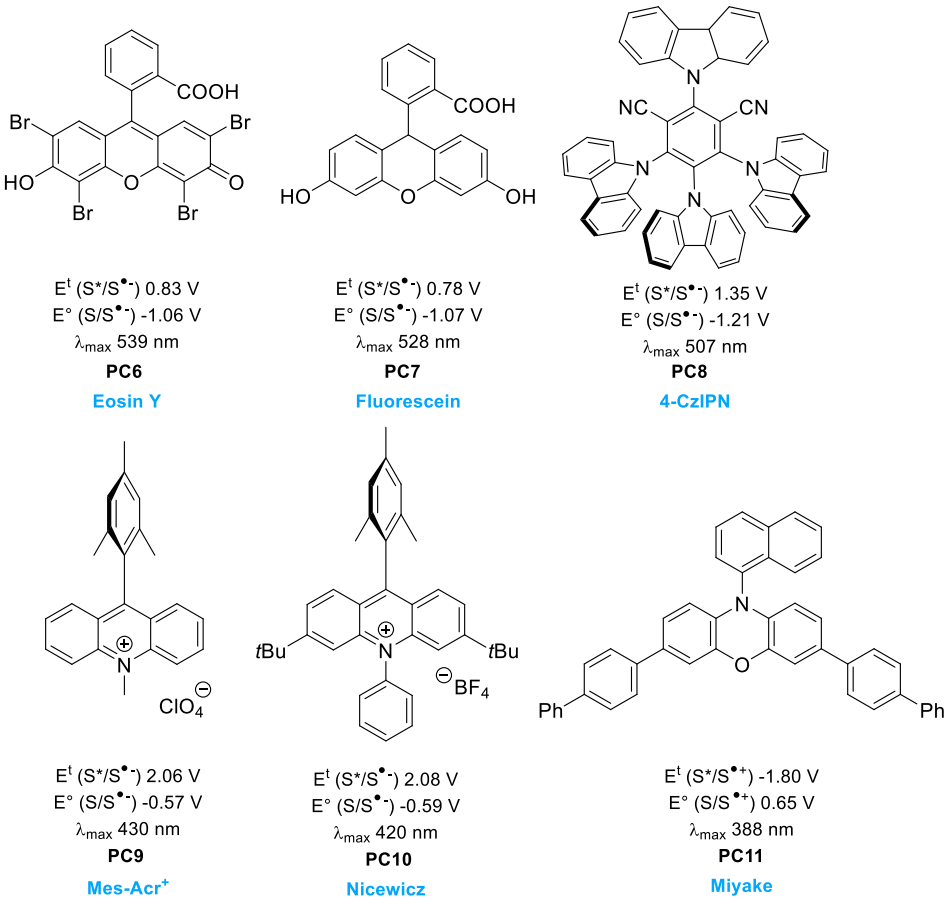

Figure 9. Examples of organic photocatalysts. 4-CzIPN = 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene, Mes-Acr$^+$ = 9-mesityl-10-methylacridinium.

reaction conditions, avoiding potential degradation and unwanted byproducts.[294] Consequently, photoredox chemistry offers a plethora of synthetic opportunities, which has been widely documented in the chemistry community.[294−302]

Redox potentials measure the potential energy difference between two electronic states and thus can be used in the comparison of one-electron processes in the ground state. This can allow suitable matching of the photocatalyst to the substrate in question. If the potentials are not matched, the photocatalyst may not be sufficiently reducing/oxidizing to provide a thermodynamic driving force for the reaction to occur. The standard Gibbs free energy can be related to the standard cell potential (E°_{cell}) of the reaction by a derivative of the Nernst equation (eq 1).[303]

Calculation of Gibbs free energy by relating the Nernst equation and standard electrode potentials of the cell:

$$\Delta G^\circ = -nFE^\circ$$
$$E^\circ = E^\circ_{D^{\bullet+}/D} - E^\circ_{A/A^{\bullet-}} \quad (1)$$

where n is the number of electrons, F is the Faraday constant, D indicates donor, and A indicates acceptor.

A positive value of E° means that the complex is an acceptor/oxidant, and conversely, a negative value of E° determines the complex is a donor/reductant; more positive or more negative values result in a stronger oxidant or reductant, respectively.[304] Due to difficulties in measurement of the redox potentials of excited state molecules, estimations are calculated from ground-state experimental values and approximations.[298,303]

Photocatalysts can undergo either a reducing or oxidizing pathway after excitation to the excited state, which is shown schematically in Figure 7.

During reductive cycling, the photocatalyst acts as an electron acceptor; on interaction with the HOMO of a substrate, an oxidation occurs and generates a substrate radical cation. On the contrary, in an oxidative cycling the photocatalyst performs as a donor, generating a radical anion of the substrate in a reductive process.

Transition metals are largely used in photoredox catalysis due to their easily accessible redox properties and long triplet lifetimes, which have been extensively reported (Figure 8). A large variety of ligands can be used in conjunction with the metal, allowing fine-tuning of redox properties of the photocatalyst. Electron-rich ligands promote oxidation in the complex whereas electron-withdrawing ligands induce reduction. Ruthenium (**PC1**) and iridium (**PC2**−**PC5**) complexes are well-known transition metal catalysts. Substantial research into their reactivities has been documented, and they are highly effective as photoredox catalysts.[300,302]

Organic photocatalysts provide an opportunity to avoid the use of transition metals in the production of APIs in the pharmaceutical sector. A number of catalysts stem from vibrant organic dyes that absorb in the visible light region (**PC6**, **PC7**) (Figure 9).[299] Advances in the development of materials for organic LEDs led to the discovery of 4-CzIPN (**PC8**),[305] which has now emerged as a powerful photoredox catalyst.[306]

Recently, interest has sparked into the synthesis of novel organic catalysts to access a wider range of redox potentials and

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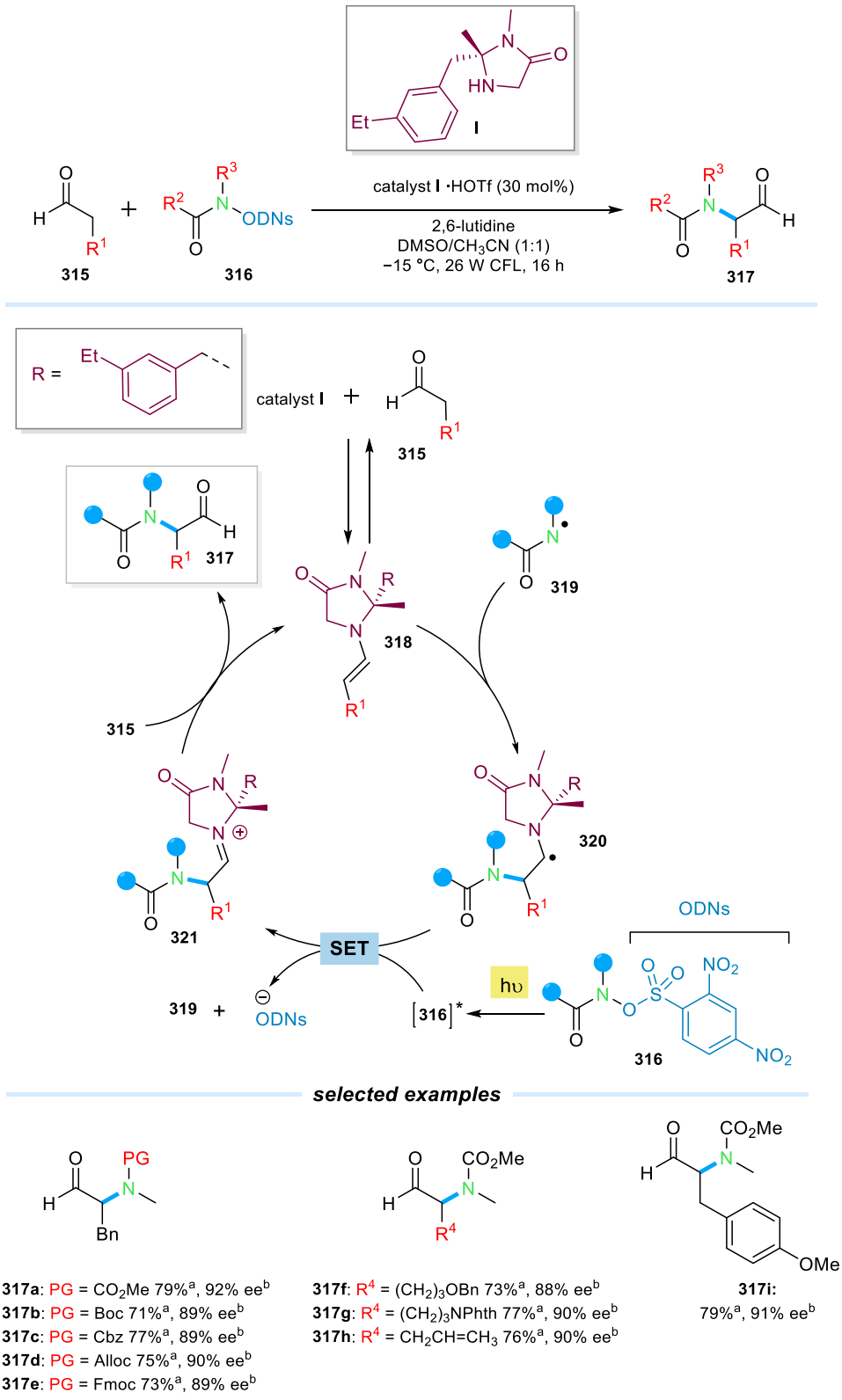
Scheme 65. Enantioselective Approach to α-Amino Functionalization of Aldehydes



[a]Stereochemistry assigned by chemical correlation or by analogy. [b]Determined by chiral HPLC analysis of the corresponding alcohol or 2-naphthoyl ester. PG = protecting group.

photophysical properties. Synthetic modification to highly conjugated molecules to generate organic catalysts was pioneered by Fukuzumi[307] in 2004 (**PC9**). Since then, the discovery of novel organic molecules that can absorb in the visible light region has been promoted by the teams of Nicewicz (**PC10**),[308] and Miyake (**PC11**),[309] which can access previously inaccessible redox potentials and are now commercially available. Extensive contribution to the field of organic

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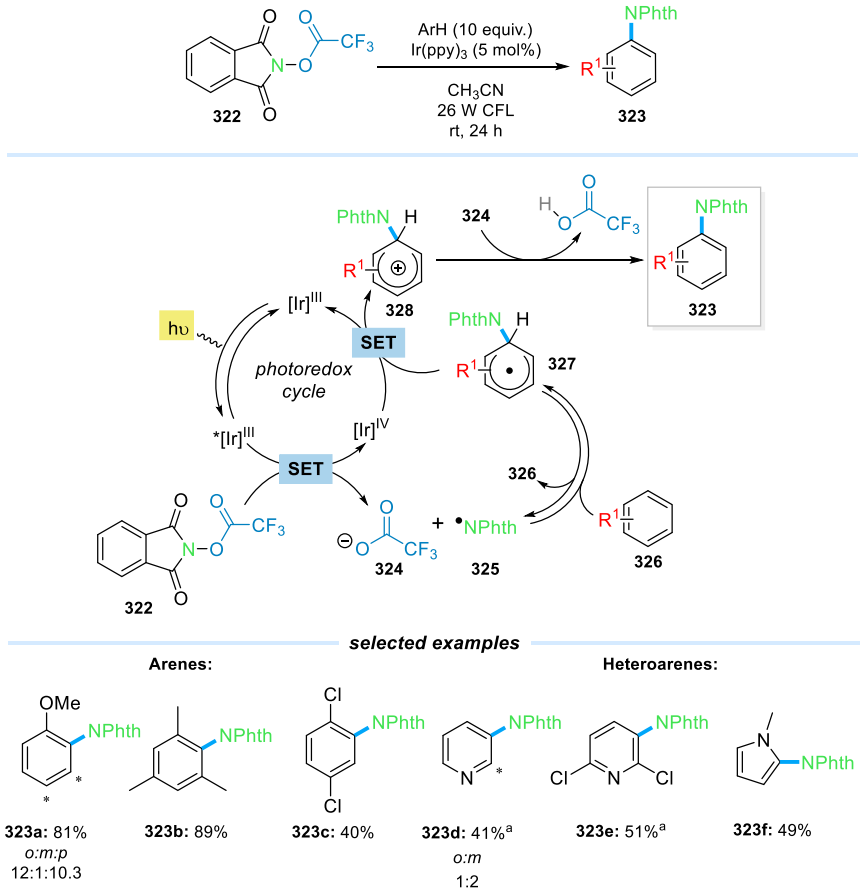
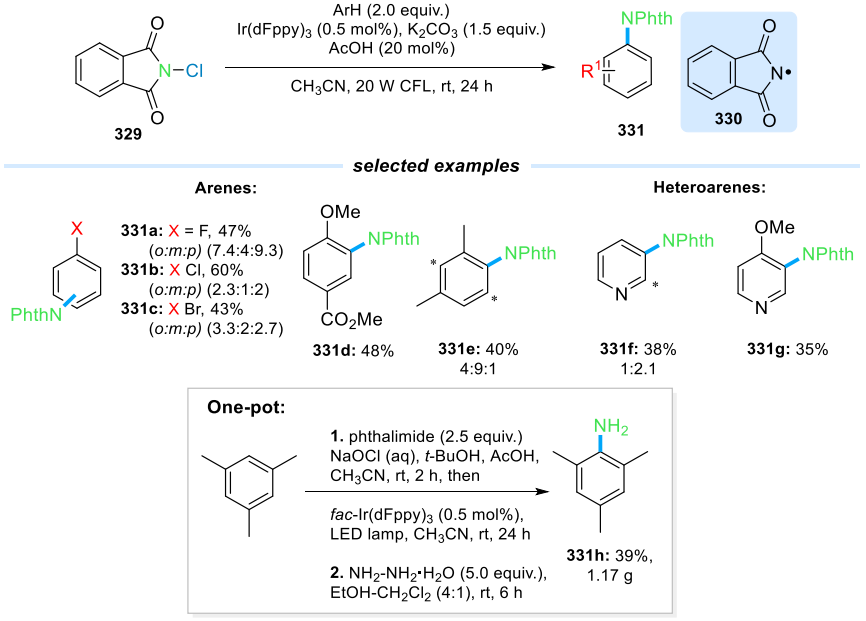
Scheme 66. N-Acyloxyphthalimides as Precursors to N-Centered Radicals in Reductive C−H Amination of (Hetero)arenes



[a]20 equiv of heteroarene, CH_3CN (0.2 M in **322**). The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

Scheme 67. *N*-Chlorophthalimide as Precursor to C−H Imidation of (Hetero)arenes[a]



[a]The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

photoredox catalysis have been reported by König[310,311] and Nicewicz and Romero[299] in some recent reviews.

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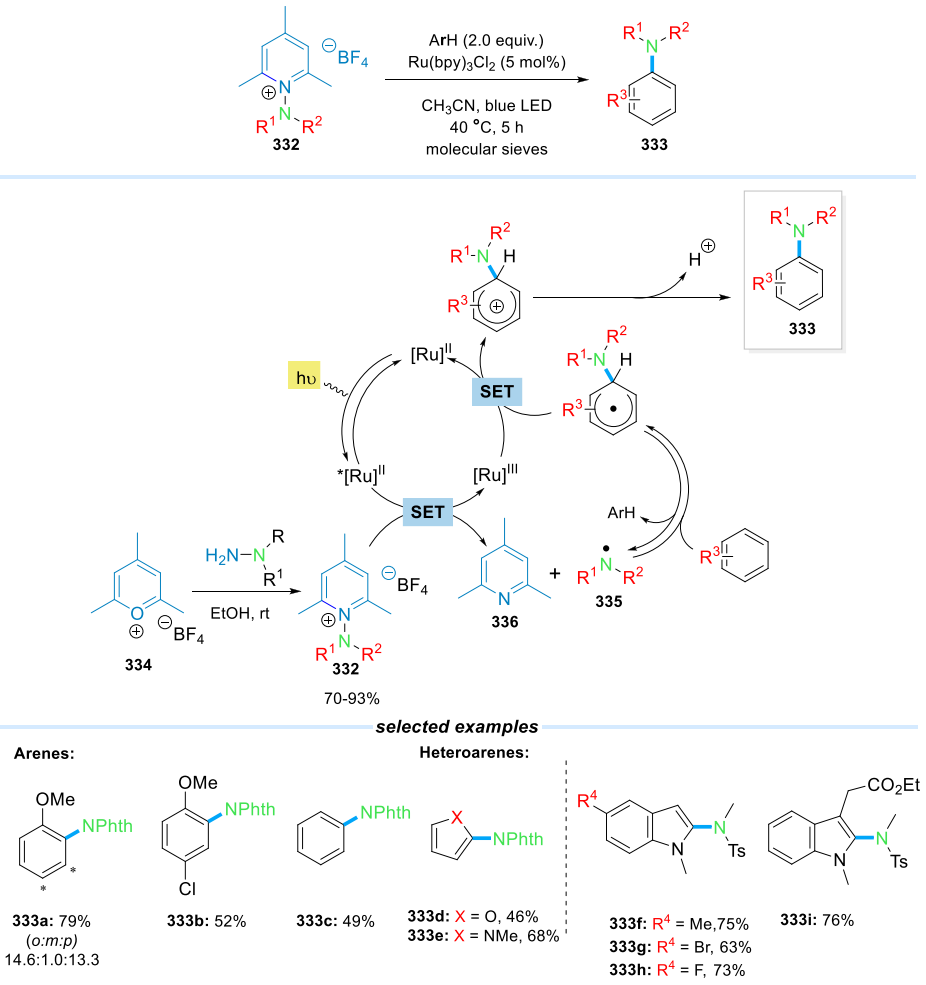
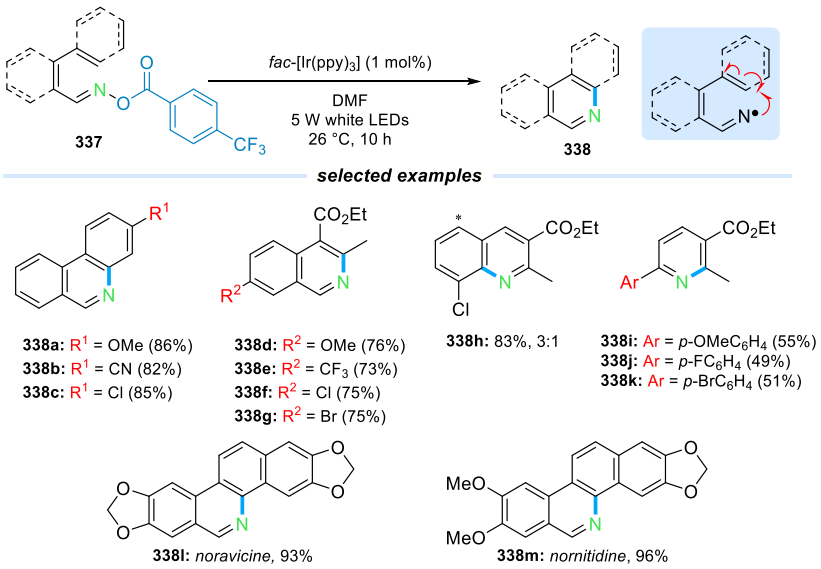
Scheme 68. *N*-Amidopyridinium Salts as C−H Amidation Reagents[a]



[a]The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

Scheme 69. Synthesis of Heteroaromatics via Cyclization of Iminyl Radicals[a]



[a]The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

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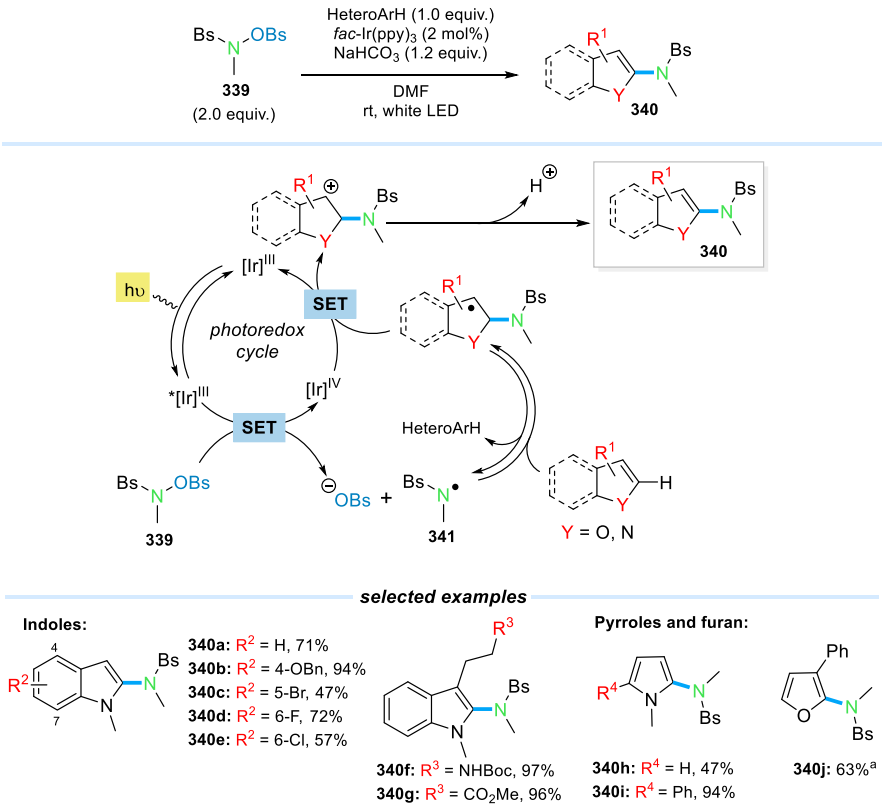
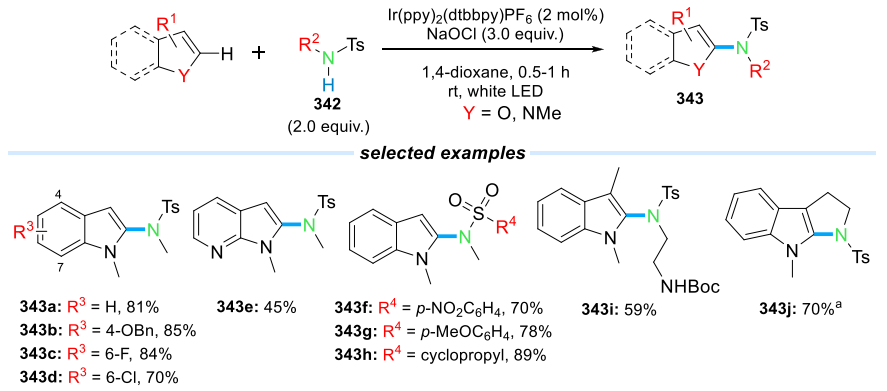
Scheme 70. Selective C−H Sulfonamidation of Heteroarenes at the C2-Position via a Sulfonamidyl Radical



[a]4.0 equiv of sulfonamide used for 4 h.

Scheme 71. Oxidative C2-Sulfonamidation of Heteroarenes via Sulfonamidyl Radicals



[a]2.0 equiv of NaOCl used.

6.2. Organocatalysis

Built upon their pioneering work in 2008, the Macmillan group presented a breakthrough, addressing asymmetric α-amination of aldehydes (**315**) with an amidyl radical precursor (**316**) and organocatalysis to afford enantioenriched α-amido aldehydes (**317**) (Scheme 65).[312] Use of a photolabile dinitrophenylsulfonyloxy (ODNs) leaving group allowed facile generation of the electrophilic NCR. The organic chiral catalyst (**I**) was the source of stereocontrol in the transformation by controlling the configuration of the enamine **318** and the direction of facial attack. Computational DFT studies revealed that the thermodynamically more stable *E*-conformation was favored (**318**), and this was confirmed by 2D nuclear magnetic resonance (NMR) studies.

Reaction of the organocatalyst **I** with aldehyde **315**, affords the enamine species **318**. Irradiation with visible light activates the NCR precursor **316**, which undergoes a reductive SET, generating amidyl radical **319**, which undergoes addition to the enamine **318**. The C-centered radical **320** results and is then oxidized by SET to yield the iminium ion **321**. Hydrolysis of **321** furnishes the α-functionalized aldehyde **317** and propagates the catalytic cycle by re-forming the imidazolidinone catalyst **I**. Several N-protecting groups with varying acid/base sensitivities were amenable to the procedure, affording products in excellent ee's (**317a**−**317e**). An array of functionalized aldehydes was tolerated, demonstrated with protected alcohol (**317f**) and phthalimide (**317g**) moieties, alkenes (**317h**), and aromatic groups (**317i**), which were also prepared in excellent ee's. This

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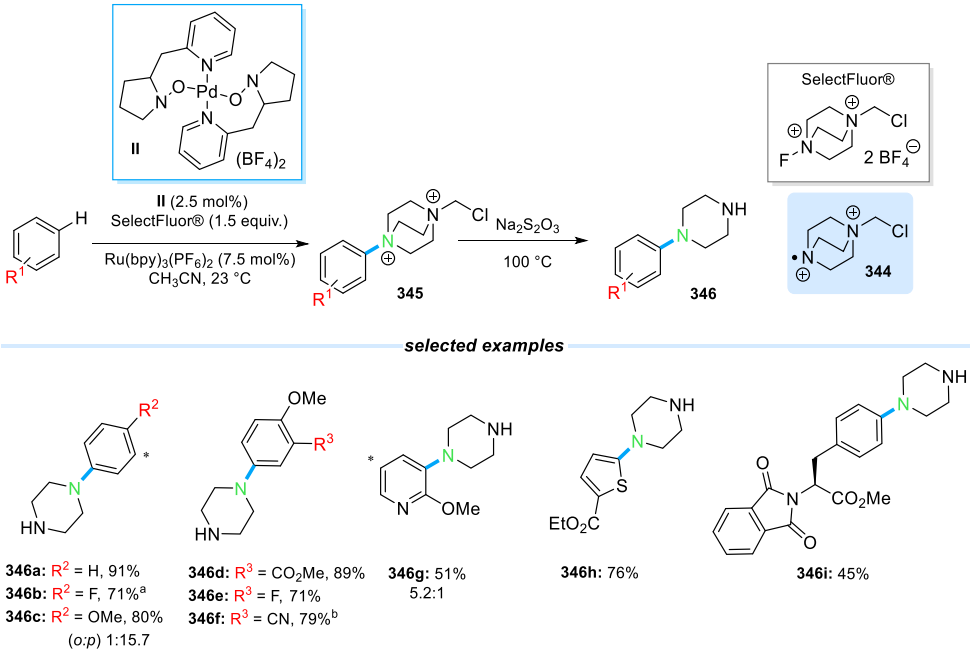
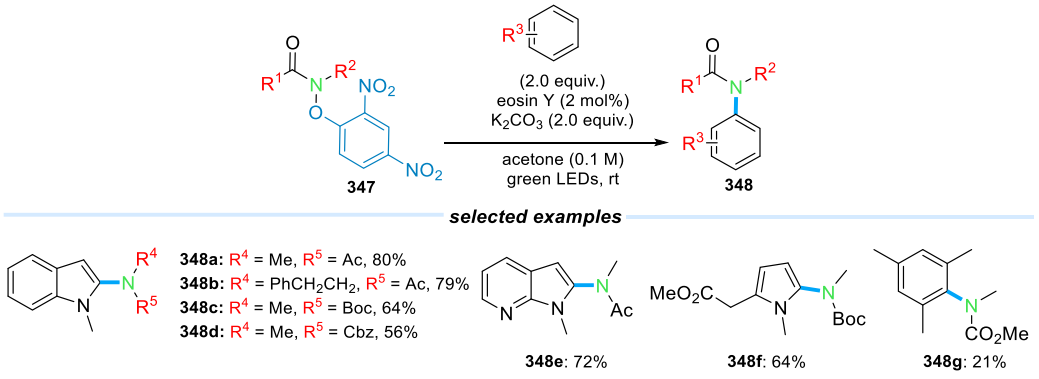
Scheme 72. Highly *para*-Selective Synthesis of Piperazine Derivatives from Selectfluor Aminium Radicals



[a]Reaction temperature of 40 °C. [b]For the first step, 2.5 equiv of Selectfluor, 5 mol% **II**, 10 mol% $Ru(bpy)_2(PF_6)_2$. The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

Scheme 73. Generation of Amidyl Radicals from *O*-2,4-Dinitrophenoxy Amide Precursors for the N-Amidation of (Hetero)aromatics



metal-free approach represents the first use of NCRs as reagents in enantioselective transformations.

6.3. Oxidative Quenching Processes

6.3.1. C−H Functionalization of (Hetero)arenes with NCRs. In 2014, Sanford et al. discovered that *N*-trifluoroacetoxyphthalimide (**322**) could perform as an imidating agent when used in the presence of visible light to yield (hetero)aromatics (**323**) (Scheme 66).[313] Following on from the work by Oda in 1991,[314,315] installation of the trifluoromethyl electron-withdrawing group on the carboxylic acid allowed a switch of reactivity, promoting the formation of a phthalimidyl radical and release of the carboxylate anion.

Photoexcitation of the $[Ir]^{III}$ catalyst generates an excited-state catalyst, which is capable of SET to precursor **322**. Fragmentation occurs, generating carboxylate anion **324** and NCR **325**. Addition of radical **325** to an arene (**326**), stimulates C−H imidation, producing radical intermediate **327**. A reductive SET to $[Ir]^{IV}$ completes the photoredox cycle and oxidizes **327** to **328**. A rapid re-aromatization furnishes the imidation product **323**. Generally, arenes with electron-donating substituents produced the corresponding products (**323a**, **323b**) in greater isolated yields compared to electron-deficient examples. This supports the idea that the radical **325** is electrophilic in nature. Tolerance of halide functionality was demonstrated by the isolation of chlorobenzene derivative (**323c**), although a lower yield was obtained. Imidation of heterocycles like pyridine (**323d**), dichloropyridine derivatives (**323e**), and *N*-methyl pyrrole (**323f**) was shown. However, a large excess of arene and a high catalyst loading were needed in order to obtain moderate yields in this process.

Later in 2014, Lee et al. proposed the use of *N*-chlorophthalimide (**329**) as a tool to initiate cleavage of N−Cl bonds (Scheme 67).[316]

N-Chlorophthalimide **329** undergoes reductive SET and fragments to furnish the corresponding NCR (**330**) and a chloride anion. An excess of 2 equiv of arene substrate was needed to induce C−H imidation of selected substrates, which afforded the desired phthalimide derivatives in moderate yields

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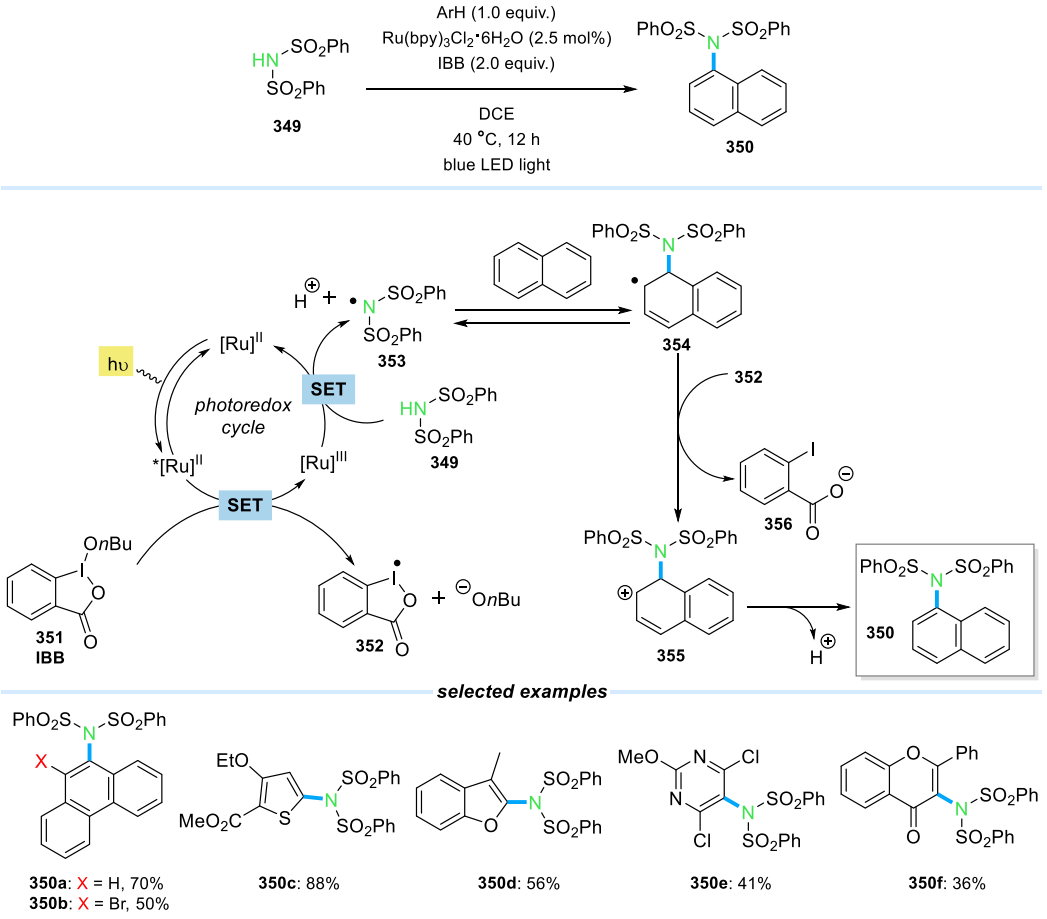
Scheme 74. Sulfonimidation of (Hetero)arenes with N-Centered Radicals Generated by Oxidation by a Photoredox Mediator[a]



[a]Naphthalene is used as a model substrate for the mechanism.

(27−60%). The substrates reported provided products that included halide functionalities (**331a**−**331c**); however, imidations occurred with poor regioselectivity. Imidation of disubstituted arenes gave moderate yields (**331d**, **331e**), and a mixture of regioisomers was obtained for **331e**. Imidation of pyridine derivatives was successful; however, a poorer yield was obtained (**331f**, **331g**). A one-pot protocol on a gram-scale was demonstrated, with the generation of the *N*-chlorophthalimide *in situ* and a subsequent Gabriel reaction to unmask the aniline moiety (**331h**).

Historically, hydrazine derivatives have been a common precursor to NCRs. Building upon this, in 2014 Studer et al. used *N*-amidopyridinium salts (**332**) for the C−H imidation of (hetero)arenes to afford aniline derivatives (**333**) (Scheme 68).[317]

The bench-stable *N*-amidopyridinium salts (**332**) were easily synthesized from pyrylium salts (**334**) and hydrazine derivatives. Irradiation by blue light with a $Ru(bpy)_3Cl_2$ catalyst induces reductive SET to hydrazine **332**, which produces NCR **335** by cleavage of the N−N bond. Release of the pyridine (**336**) was suggested to be the driving force for the formation of the radical **335**. Studer's methodology was applied to a range of electron-rich arenes and benzene with a phthalimidyl radical, which gave the imidated products (**333a**−**333c**) in moderate yields. Heteroaromatics like furan and pyrrole were amenable to imidation, and products (**333d**, **333e**) were isolated in respectable yields. Other heteroarenes, namely indole derivatives, were sulfonamidated with an *N*-methylsulfonamidyl radical giving products where alkyl (**333f**), halide (**333g**, **333h**), and ester (**333i**) motifs were featured in good yields. However, the methodology described was limited to protected amines, and no primary amines were reported.

A variety of *N*-aminopyridinium salts as precursors to NCRs have since been reported. Extensive examples have been showcased by Xu and co-workers, who developed protocols to synthesize imidazoline and oxazolidine derivatives,[318] aziridines,[319] and cyclobutanimines[320] from NCRs and olefins. More recently, Hong and co-workers reported a methodology to difunctionalize olefins with an *N*-aminopyridinium salt precursor, combining amination and alkylation of pyridines.[321]

Yu and Zhang demonstrated the use of acyl oximes (**337**) as precursors to iminyl radicals in the synthesis of pyridines, quinolines, and phenanthridines (**338**) (Scheme 69).[322]

Reduction of the acyl oxime precursors generates iminyl radicals which undergo HAS to afford N-heterocycles. Quinolines and phenanthridines with varied functionalities on the aromatic system were examined, and the products (**338a**−**338h**) were isolated in very good yields. Pyridines were also prepared, although lower yields were reported (**338i**−**338k**). The total synthesis of benzo[*c*]phenanthridine alkaloids was reported, providing noravicine (**338l**) and nornitidine (**338m**). A later publication by Yu detailed the use of *O*-(4-cyanobenzoyl)hydroxylamine derivatives in the synthesis of phenanthridines and quinolines.[323] A one-pot procedure to synthesize the precursor was established from the corresponding aldehydes and acid chlorides (27 examples, 39−88%).

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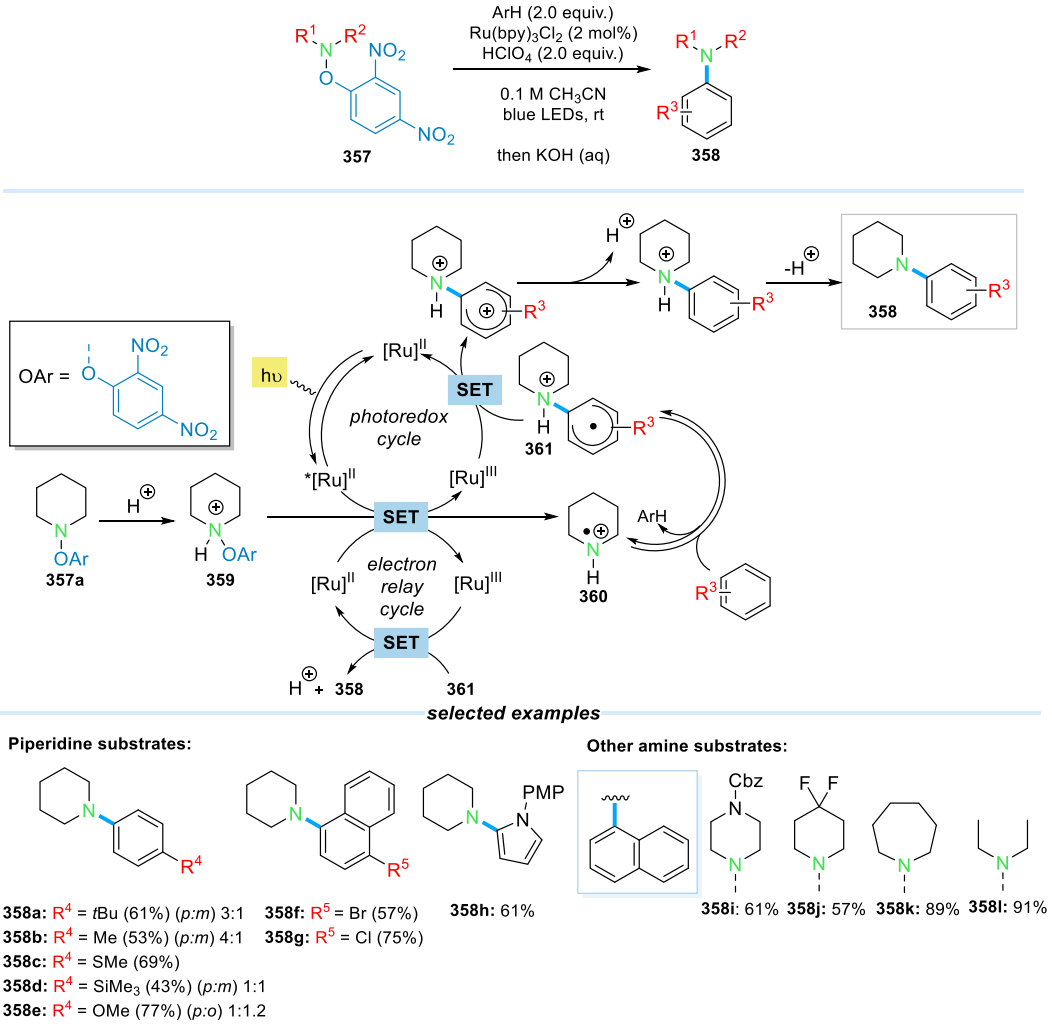
Scheme 75. Electron-Poor *O*-Aryl Hydroxylamines as Precursors to Aminium Radicals for *N*-Arylation[a]



[a]Piperidine is used as a model substrate for the mechanism.

A procedure for direct and selective sulfonamidation of heteroarenes was demonstrated by Qin and Yu (Scheme 70).[324] Generation of a sulfonamidyl radical from precursor **339** led to sulfonamidation at the C2-position on a range of indoles, pyrroles, and furan derivatives (**340**).

Reductive cleavage of the hydroxylamine derivative **339** furnishes sulfonamidyl radical **341**. A classical addition to the heteroarene species affords C2-sulfonamidation. Sulfonamidation of indole derivatives was observed in moderate to good yields (**340a**−**340g**). Other heterocycles, such as pyrroles (**340h**, **340i**) and furan (**340j**), displayed a good tolerance to the methodology. Further examples included variation of the *N*-substituent on 3-methylindole substrates which were functionalized in the presence of Bn (98%), PMB (96%), and Boc (57%) groups.

In 2016, Yu and Zhang developed the methodology previously described in Scheme 69, removing the hydroxylamine precursor.[325] The authors suggest the transformation proceeds by reduction of NaOCl by $*[Ir]^{III}$ followed by oxidation of the sulfonamide (**343**) by $[Ir]^{IV}$, generating the sulfonamidyl radical (Scheme 71). However, it is likely that NaOCl can directly react with **342**, generating the corresponding *N*-chlorosulfonamide, which is then reduced by the excited iridium complex.

N-Methyl-*para*-toluenesulfonamide sulfonamidated the C2-position of indoles to give products, both in an intermolecular setting (**343a**−**343i**) as well as in some intramolecular cases (4 examples, 50−80%, e.g., **343j**). Further heteroarene substrates were explored, as well as a wider range of sulfonamide derivatives and N-substituents. Different aromatic sulfonamides of electron-poor (**343f**) and electron-rich (**343g**) nature were explored, as well as aliphatic derivatives (**343h**), which gave very good to excellent yields. Alteration of electron density at the sulfonyl group indicated that this was not a significant factor regarding reactivity of the sulfonamidyl radical. The sulfonamidation of pyrroles and benzofuran derivatives was selective for the C2-position and afforded products in good yields (46−81% and 53−56%, respectively). The NCR species was trapped by bond formation to 2,6-di-*tert*-butyl-4-methylphenol (BHT), the product of which was isolated and characterized. Nicewicz[326] in 2015 utilized the opposite reactivity; oxidation of an electron-rich (hetero)arene counterpart generated an arene radical cation which underwent subsequent amination. Further work by Xia[327] noted a reactivity similar to that reported by Nicewicz;[326] however, Xia proposed the radical cross coupling between an NCR and an oxidized phenol counterpart. The earlier contributions by Nicewicz addressed limitations regarding

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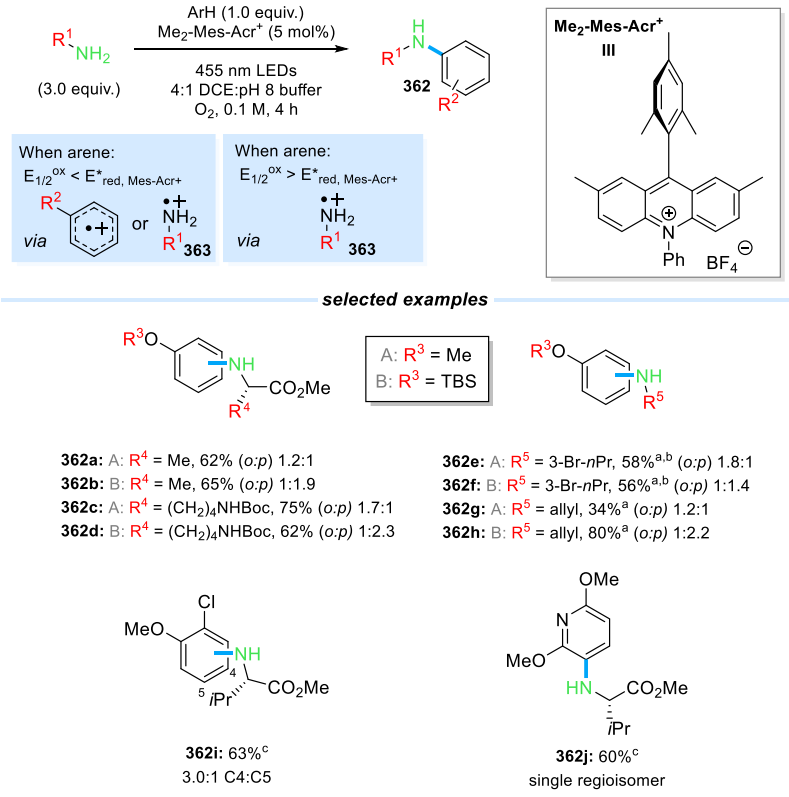
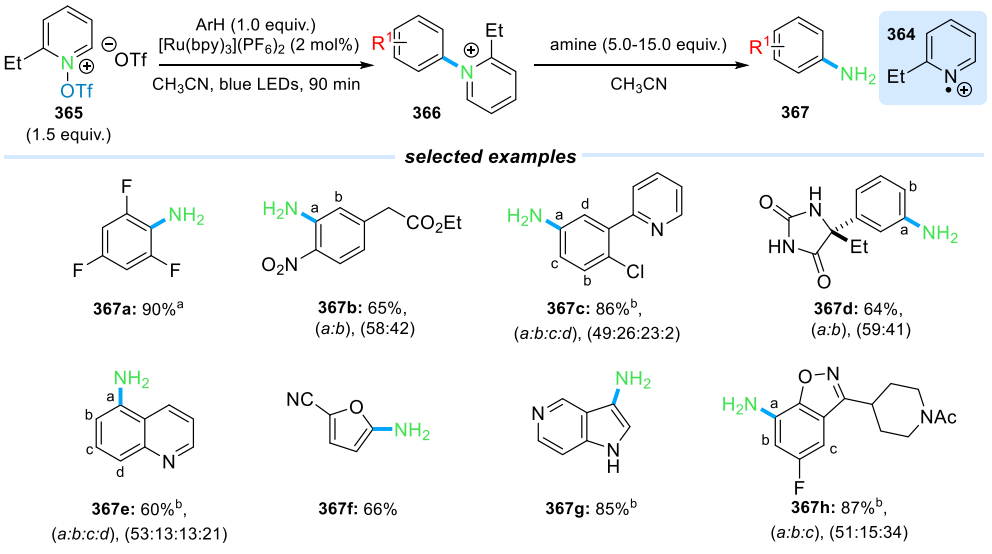
Scheme 76. Metal-Free Oxidative C−H Amination of Arenes via Aminium Radicals or Aryl Radical Cations



[a]Reaction run in DCE at 0.1 M concentration. [b]^{1}H NMR yield. [c]Reaction run with 40% TEMPO and 5 mol% tBu$_2$-Mes-Acr$^+$ for 15−26 h.

Scheme 77. One-Pot Amination Strategy with *N*-OTf 2-Ethylpyridine as a Precursor and Subsequent Zincke Aminolysis



[a]Derivatized because of the volatility of the product. [b]With 1.0 equiv of TfOH.

atom-efficiency and site-selectivity in a mild photoredox procedure; direct access to primary anilines was also achieved.

In 2016, Ritter and co-workers reported the generation of a highly electrophilic aminium radical (**344**) for the C−H functionalization of (hetero)arenes (**345**). Using Selectfluor as the precursor, highly selective *para* substitution (>99:1) was achieved (Scheme 72).[328]

A general trend was seen in computational studies; calculation of the Fukui indices indicated the position of highest electron-density on arene substrates. The doubly cationic nature of the TEDA$^{2+\bullet}$ [TEDA = *N*-(chloromethyl)triethylenediamine] radical (**344**) and an arene-to-radical charge-transfer transition state accounted for the observed selectivity. Visible light was not a necessary component of the methodology; conversely a Pd catalyst (**II**) was used to facilitate the transformation. Subsequent reduction of **345** by sodium thiosulfate gave the piperazine derivatives (**346**). A broad range of substrates with functional groups was tolerated, including methyl ethers, nitriles,

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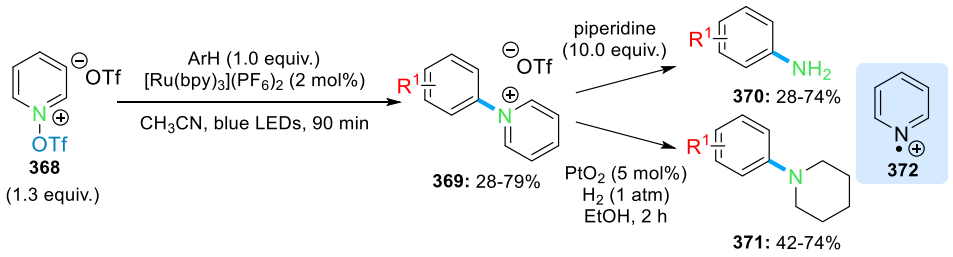
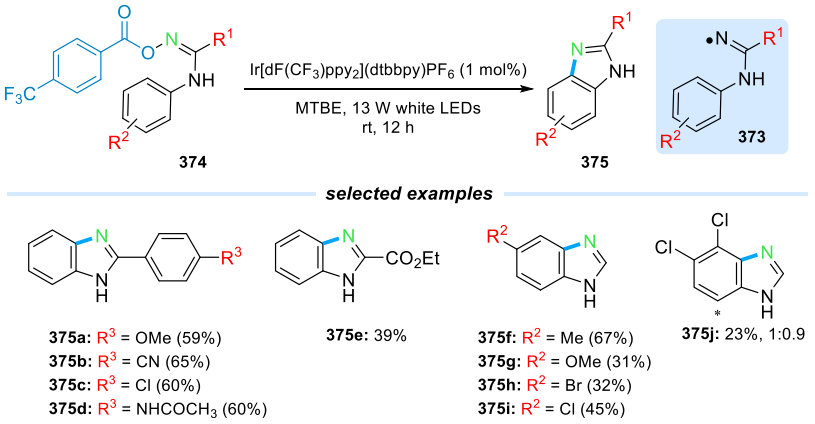
Scheme 78. N-Functionalized Pyridinium Salts as Precursors to Pyridyl Radical Cations for Amination of Arenes

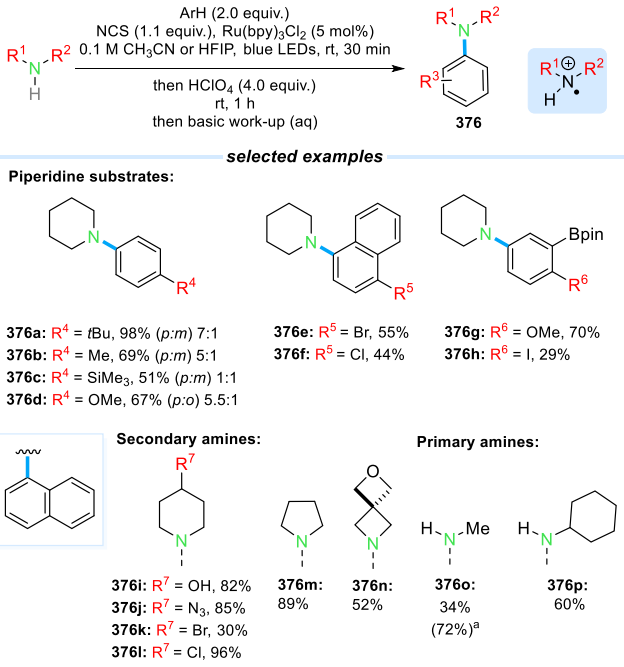


Scheme 79. Synthesis of Benzimidazoles via Amidinyl Radicals[a]



[a]The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

Scheme 80. Generation of *N*-Chloro Precursors In Situ from Corresponding Amines for the Amination of Arene Coupling Partners



[a]With *t*Bu benzene.

esters, and halide functionalities (**346a**−**346f**). Products of amination of heteroaromatics such as pyridine (**346g**) and thiophene (**346h**) were isolated in moderate yields. The proposed charge-transfer effect enabled a highly predictable *para*-amination transformation; this has valuable application in the future of C−H functionalization. Complex drug structures (**346i**) were compatible with the selective nature of this methodology, highlighting application in drug discovery.

In 2016, the Leonori group adapted their previously established intramolecular hydroamination methodology[329] to the intermolecular addition to (hetero)aromatics.[176] The use of *O*-2,4-dinitrophenoxy amide derivatives (**347**) successfully amidated a selected range of (hetero)aromatics (**348**) (Scheme 73).

Initial investigations on *N*-methylindole demonstrated the N-substituents on the NCR precursor could be modified to accommodate products bearing acetyl (**348a**, **348b**), Boc (**348c**), and Cbz (**348d**) groups, which were prepared in good yields. Further heteroaromatics were examined (**348e**, **348f**) which also gave good yields. Unactivated aromatics (**348g**) were also established, although poorer yields were obtained.

In 2017, Itami and co-workers introduced a methodology using **349** for dehydrogenative sulfonimidation of (hetero)-arenes (e.g., **350**) (Scheme 74).[330] Use of photoredox catalysis and a hypervalent iodine oxidant 1-butoxy-1λ^3-benzo[*d*][1,2]-iodaoxol-3(1*H*)-one (IBB, **351**) reagent successfully generated sulfonimidyl radicals.

The excited [Ru] photocatalyst reduces IBB (**351**) to radical **352**. To complete the redox cycle, sulfonimide **349** is oxidized to NCR **353**. This may occur through deprotonation of **349** followed by oxidation by the [Ru] catalyst. Radical **353** can add to an (hetero)arene, which results in carbon radical **354**. Oxidation of **354** with radical **352** generates carbocation **355** and the byproduct **356**. Re-aromatization of **355** results in the sulfonimidated product (**350**). Arene substrates were limited to extended π-systems with little functionalization (**350a**, **350b**). Sulfonimidations to a range of heterocycle derivatives (**350c**−**350e**), as well as a natural product, flavone (**350f**), were

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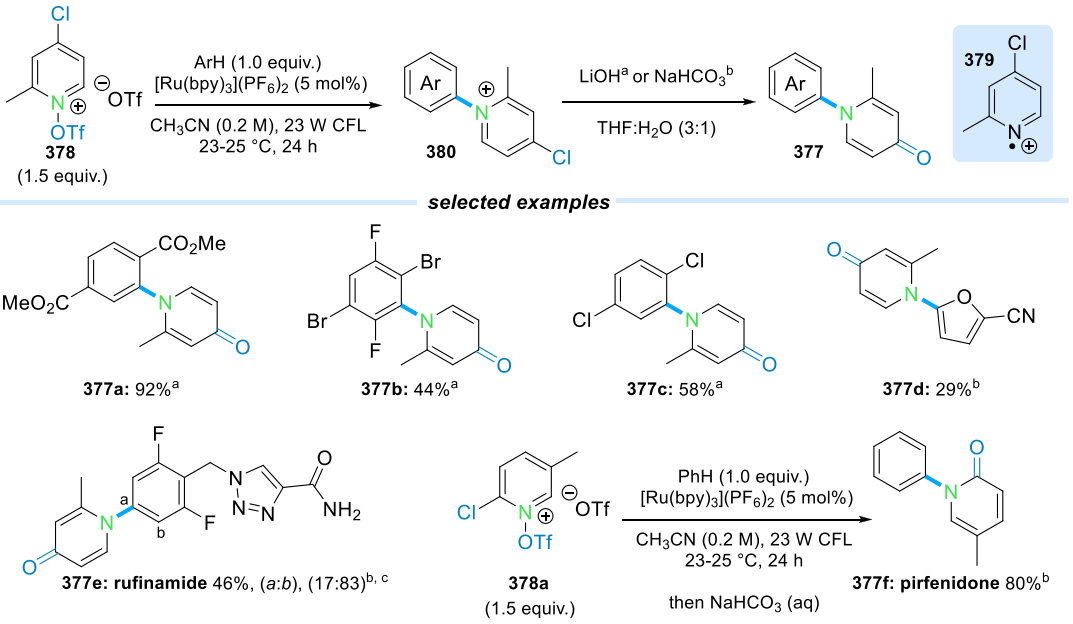
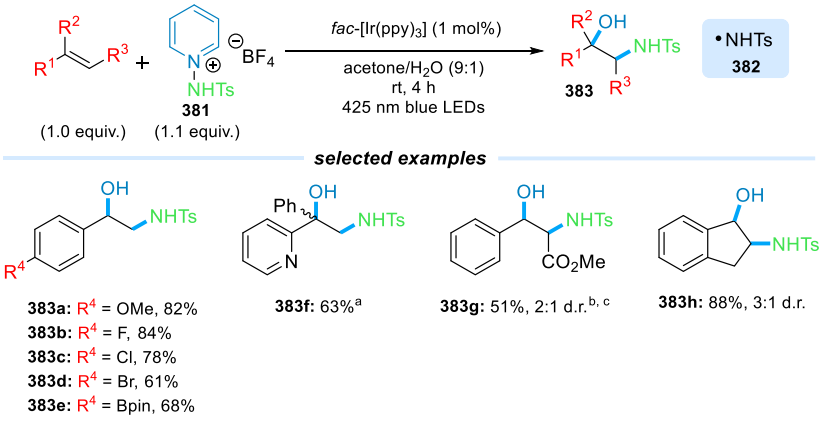
Scheme 81. Synthesis of *N*-Aryl-2- and -4-pyridones via Amination by Pyridinium Radical Cation Followed by Hydrolysis



[a]Hydrolysis with LiOH·H_2O (4−5 equiv) and *t*BuOOH (10 equiv) in THF:H_2O (3:1), 0 to 25 °C. [b]Hydrolysis conditions with $NaHCO_3$ (5−10 equiv), *t*BuOOH (10 equiv), THF:H_2O (3:1), 0 to 25 °C. [c]TfOH (1.1 equiv).

Scheme 82. Aminohydroxylation of Olefins with Pyridinium Salt Precursors



[a]Reaction time = 10 h. [b][$Ir(ppy)_2$(dtbbpy)](PF_6) (2 mol%) was used and reaction time = 12 h. [c]1.8 equiv of pyridinium precursor was used.

accomplished in the yields shown. An analogous methodology to generate NCR **353** was published by Itami et al. later that year. A metal-free approach was applied to the sulfonimidation of naphthalene substrates with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as photosensitizer, under irradiation by blue light.[331]

Leonori and co-workers expanded the use of the *O*-2,4-dinitrophenyl activating group to hydroxylamine derivatives (**357**) (Scheme 75).[332] Generation of aminium radicals permitted the amination of (hetero)arenes which, under a basic workup, yielded the corresponding anilines (**358**).

A reductive electron transfer to the protonated *O*-aryl hydroxylamine (**359**) generates the active aminium radical (**360**). A radical chain propagation begins by the addition to an arene substrate giving the radical cation (**361**). Subsequent oxidative SET and re-aromatization yields the desired protonated amine which, under basic workup conditions, affords the desired *N*-arylamine (**358**). It was proposed that an electron relay cycle was in play due to the finding that, following photoinitiation, the reaction was able to proceed in the absence of light. The authors also suggested that radical **360** would likely participate in a radical chain reaction. An array of aromatic coupling partners was successfully aminated with piperidine (**358a**−**358h**). The amine source could be altered to other secondary amines with functional motifs providing products (**358i**−**358l**) in good yields. A number of complex drug-molecules were aminated with the piperidine derivative, demonstrating the amenability of selected substrates to late-stage amination with the methodology.

In 2017, Nicewicz et al. built upon their seminal work in 2015[326] by exploring the scope of amines compatible with their mild photocatalysis strategy, furnishing aniline derivatives (**362**) (Scheme 76).[333] It was proposed that the mechanism operated through two possible radical pathways. Either the amine or arene partner was oxidized by SET to produce the active radical cation species.

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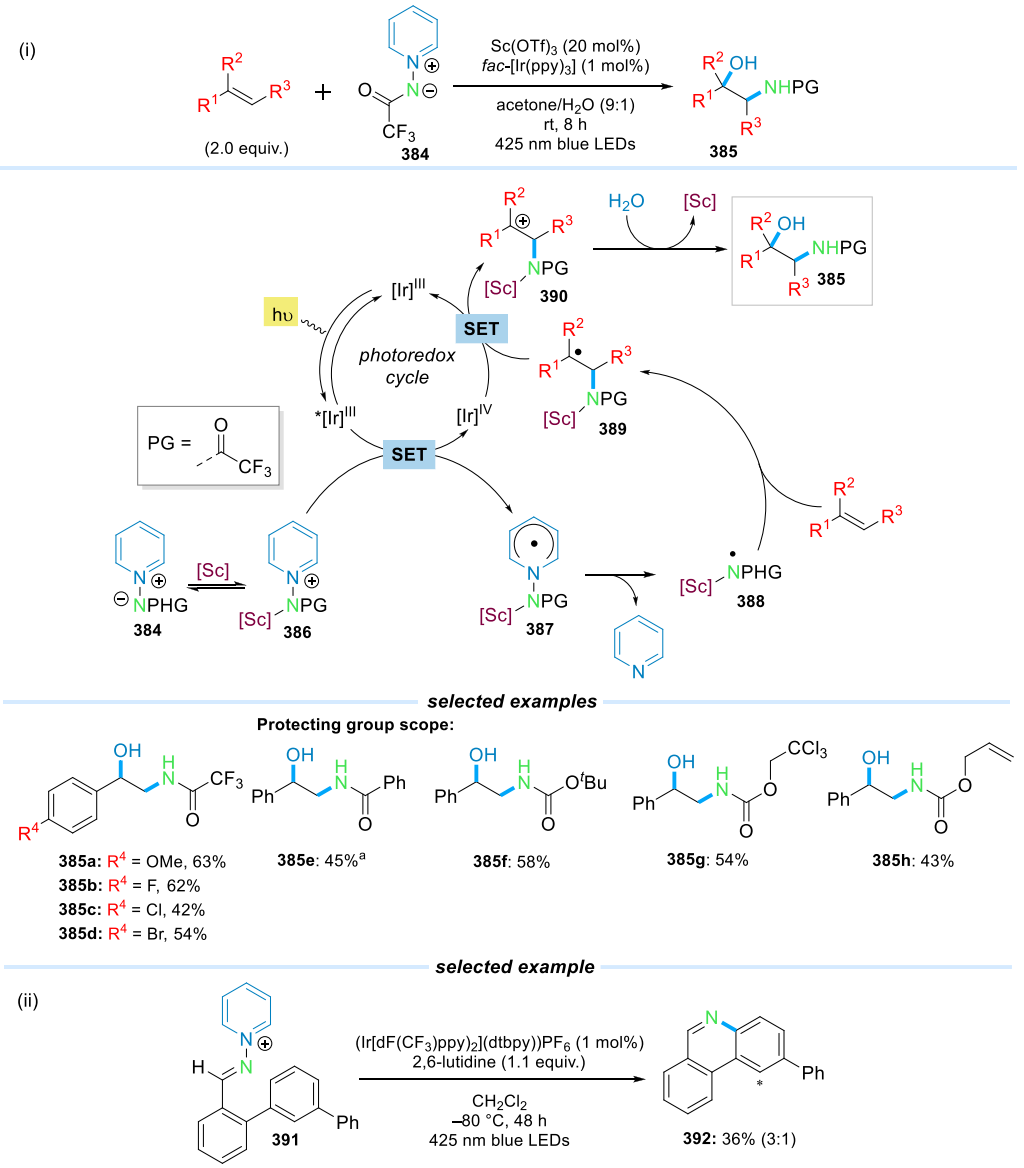
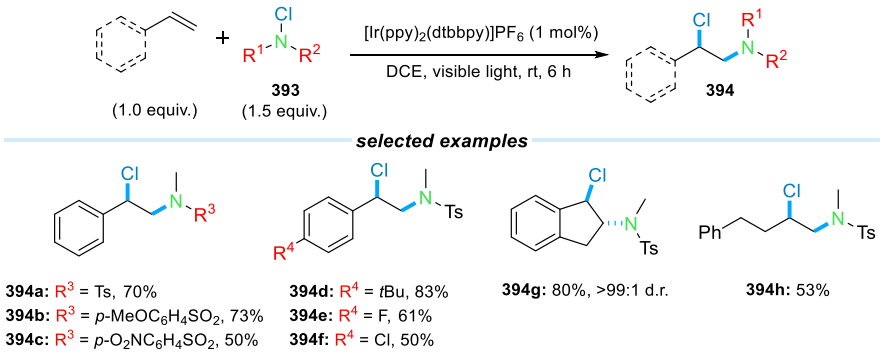
Scheme 83. (i) Lewis Acid-Catalyzed Aminohydroxylation of Olefins with Iminopyridinium Ylide Precursors and (ii) Synthesis of Phenanthridine Derivatives from Pyridinium Salts



[a]Reaction time was 24 h. The C−N bond in the major isomer is shown; the minor isomer is formed at the site of the asterisk.

Scheme 84. Chlorosulfonamidation of Olefins in the Synthesis of 1,2-Haloamine Derivatives



Electron-poor arenes were unable to be oxidized to arene radical cations, and thus the reaction primarily proceeded via the amine radical cation **363**. This was accessed by oxidation of the corresponding primary amine. Sufficiently electron-rich arenes could access either pathway. A broad selection of substrates was examined with chiral amino acids furnishing the products in

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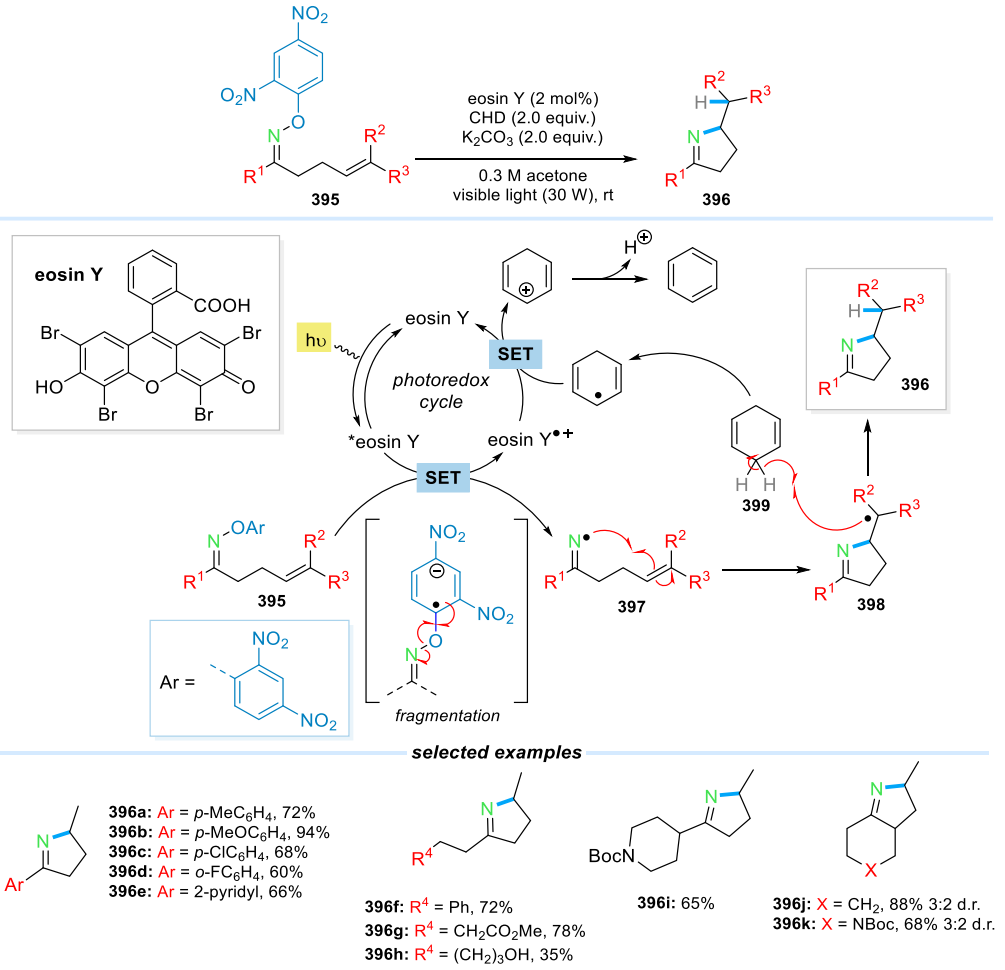
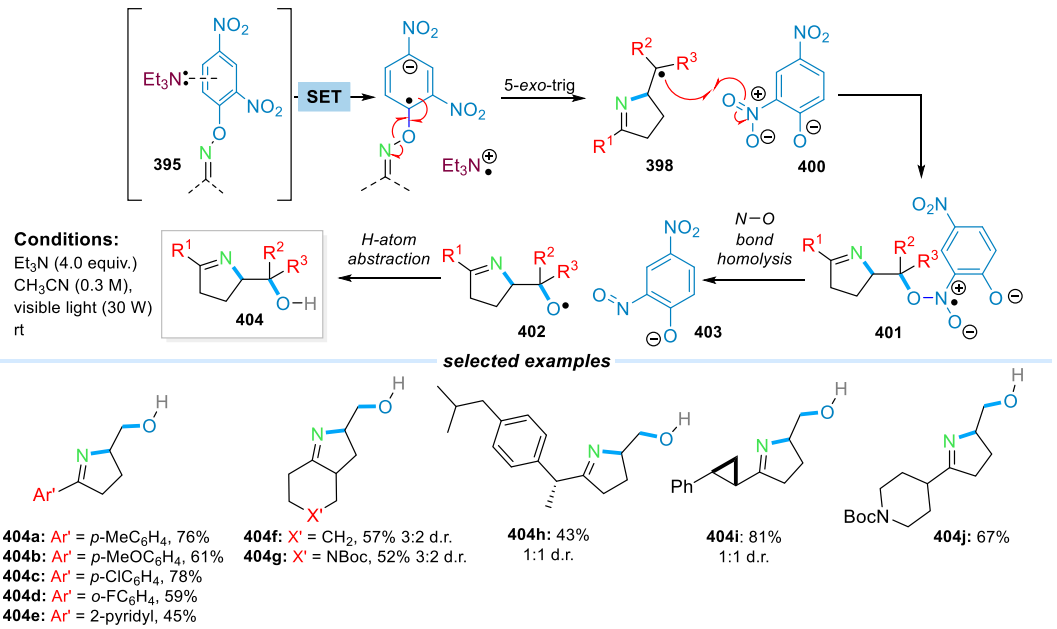
Scheme 85. *O*-Aryl Oximes as Precursors to Iminyl Radicals for the Hydroamination of Olefins



Scheme 86. Proposed Mechanism of Iminohydroxylation of Oximes with *O*-2,4-Dinitrophenyl as an Activating Group



moderate to good yields (**362a**–**362j**). No epimerization of the amino acids was observed. A number of functionalities were tolerated, including Boc groups (62–75%), halogen-containing substrates (58–78%), and a range of aliphatic (76–82%) and silyl (58–77%) protected phenols. A switch in regioselectivity was observed when R^1 = Me or TBS; a methoxy group favored

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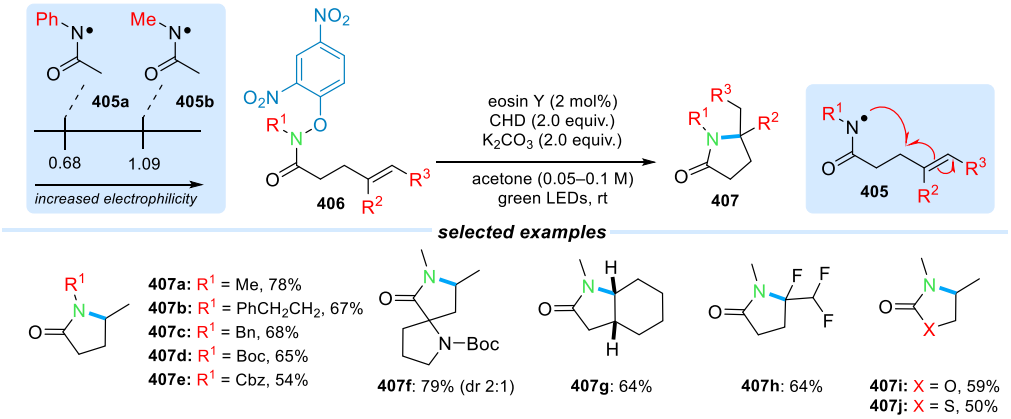
Scheme 87. Intramolecular Hydroamination with *O*-2,4-Dinitrophenyl Amides as Precursors to Amidyl Radicals



ortho substitution, whereas protection of the phenol with a TBS group favored *para* selectivity. The preference for *para* regioselectivity became prominent as phenolic protecting groups became bulkier. The methodology was also demonstrated on complex amines and arene substrates in derivatization of common drug molecules to highlight the applicability of the procedure.

Further development of aminium radical cations by the Ritter group led to the discovery of pyridyl radical cations (**364**) as precursors to aniline derivatives (Scheme 77).[334]

Reductive SET to the *N*-OTf 2-ethylpyridinium salt (**365**) generates the pyridyl radical cation (**364**), which can participate in the addition to an arene substrate, generating intermediate **366**. An *in situ* Zincke aminolysis afforded the aniline derivative (**367**). Amination of aromatics with halide functionalities (**367a**), electron-poor substituents (**367b**, **367c**), and chiral counterparts (**367d**) gave very good yields and mixed regioselectivities. Other heteroaromatic products with further functionalities were obtained in excellent yields (**367e**−**367h**). The procedure was adapted to drug molecules providing a rapid synthesis of aminated isomers, highlighting the accessibility for drug-discovery processes. It was proposed that the mechanism operated through an early transition state; hence, a poor site-selectivity is observed in the substrates reported. Despite the unselective nature of the procedure, complex molecules are successfully aminated, which provides an advantage over other generic amination methods.

A similar protocol utilizing pyridinium salt (**368**) was developed by the Carreira group, concurrently with the Ritter group (Scheme 78).[335]

The *N*-phenylpyridinium salts (**369**) were isolated in moderate to excellent yields. Anilines (via Zincke aminolysis) (**370**, 14 examples) and piperidine derivatives (**371**, 9 examples) were all accessible by a single step from the pyridinium intermediate. Further functionalization of **369** was reported in the publication, exemplifying the diverse synthetic capability of the pyridyl intermediate. EPR studies verified the generation of the pyridyl radical cation (**372**) under the stated reaction conditions.

In 2019, Wang et al. reported the mild synthesis of 2-substituted benzimidazoles under photoredox conditions.[336] Generation of amidinyl radical (**373**) was achieved from oxime ester derivatives (**374**), which underwent HAS to the corresponding benzimidazole (**375**) (Scheme 79).

Variation of the R^1 substituent provided products with *para*-substituted phenyl groups (**375a**−**375d**) and ester groups (**375e**). It was noted that an alkyl R^1 substituent (e.g., *t*Bu) did not show any desired reactivity. Evaluation of the R^2 substituent began with diversification in the *para* position of the arene radical acceptor. Alkyl substituents (**375f**) gave the best results; a lower yield was obtained for electron-donating (**375g**) and halide (**375h**, **375i**) functionalities. Regioisomers were observed when unsymmetrical arenes were employed (**375j**). No radical adducts were isolated when the reaction was exposed to TEMPO, although no reaction was observed. ^{19}F NMR revealed that irradiation with visible light was an essential component of the reaction, as no product formation was observed when the light source was turned off.

Evolution of their earlier methodology (Scheme 75)[332] has since been carried out by the Leonori group, replacing the hydroxylamine with an *N*-chloro precursor.[337] This chemistry has parallels to the classical HLF reaction (see section 2.1.1) and overcomes the multistep preparation of the *O*-aryl hydroxylamine derivatives, offering a more streamlined and atom-efficient procedure. The mechanism for the *N*-chloro substrates is analogous to the previously described mechanism in Scheme 75.

The scope of the reaction included varied aromatic coupling partners, as well as extensive examples of primary and secondary amines. A range of electron-rich arenes and heteroarenes were successfully aminated to give **376a**−**376d** (Scheme 80). Regioselectivities were successfully predicted by computationally calculated Fukui indices, which provided support for the observed *para*-selectivity. Arenes containing nitrile, halide (Cl, Br, I; **376e**, **376f**, and **376h**, and boron pinacolate (**376g**, **376h**) substituents were successfully aminated, providing handles to build further functionality into the molecule. An array of 38 examples of functionalized amines was amenable to this one-pot method (**376i**−**376p**). This methodology has established an accessible route to advanced building blocks, with a high tolerance for functional groups. It has been adapted to a flow setting and has direct application to late-stage amination of bioactive molecules, which are exemplified in the publication. The high-throughput applicability of this procedure is highlighted as it is relevant to medicinal chemistry research.

Ritter and co-workers adapted their previous protocol (Scheme 77) to directly access *N*-aryl-2- and -4-pyridones (**377**), common moieties in medicinal chemistry (Scheme 81).[338]

Reductive SET to the *N*-OTf reagent **378** generates the pyridyl radical cation **379**, which subsequently undergoes addition to a (hetero)arene, furnishing intermediate **380**.

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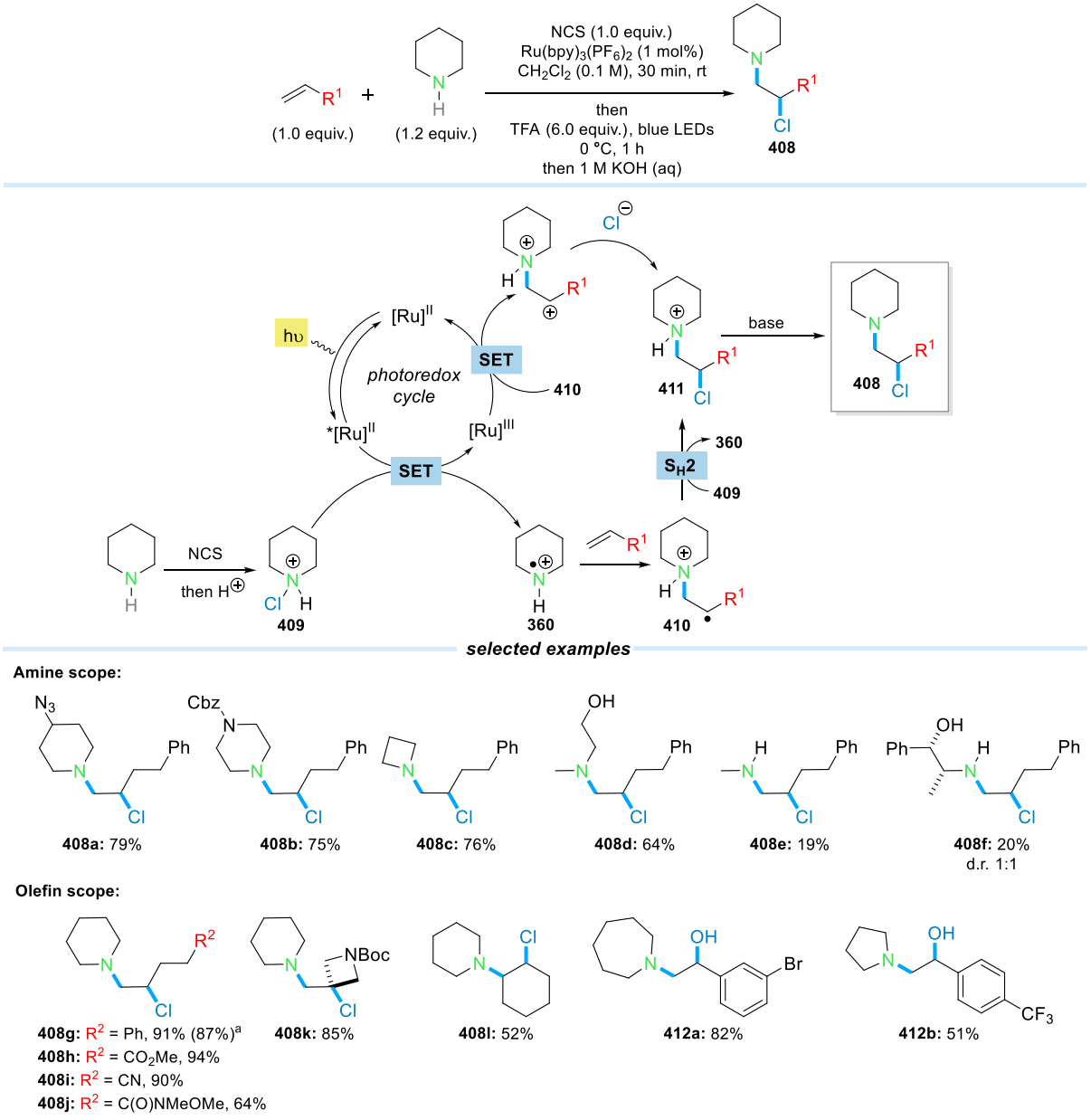
Scheme 88. Anti-Markovnikov Amination of Olefins to Afford 1,2-Chloroamine or 1,2-Hydroxyamine Derivatives



[a]Flow conditions: a higher concentration was used (0.6 M) and a reduced photocatalyst loading (0.05 mol%), 70 mmol, 3.75 min; productivity = 16.3 mmol min^{-1}; residence time = 8.7 s. Piperidine is used as the model amine for the mechanistic details.

Under selected hydrolysis conditions, a varied range of *N*-aryl-4-pyridones (**377a**−**377f**) was reported. A one-pot C−H pyridonation was achieved using 2-chloropyridinium precursor **378a** and, when followed by hydrolysis, produced pirfenidone (**377f**), an antifibrotic drug, in very good yield. Pyridinium salts have extensive application in synthesis as redox-active groups and have been highlighted on multiple occasions in this Review. For further reading on these synthetic precursors, we direct the reader to a recent review by Dagousset, Carreira, and Togni.[339]

6.3.2. Functionalization of Olefins with NCRs. A regioselective intermolecular aminohydroxylation procedure was reported by Akita and co-workers in 2015, which utilized an amidopyridinium salt (**381**) as a precursor to a sulfonamidyl radical (**382**) (Scheme 82).[340]

Reductive SET to the pyridinium salt **381** generates the active NCR **382**. Selected styrene derivatives with arene *para* substituents were examined which furnished products (**383a**−**383e**) with varied functionalities. Substitution at the R^2 and R^3 positions gave good to excellent yields with limited diastereoselectivity (**383f**−**383h**). Synthesis of product **383a** was also proved on a gram scale (76%, 1.22 g). Mechanistic probes provided evidence for a radical transformation and established that *E*- and *Z*-alkenes afforded the same products, irrespective of the original stereoisomer.

In 2016, a development of this method[340] resulted in the discovery of a photoredox/scandium(III) triflate-mediated aminohydroxylation with an iminopyridinium ylide species [Scheme 83, (i)].[341] Variation of the protecting groups on the NCR species was also examined.

Ylide **384** underwent activation with $Sc(OTf)_3$ to generate adduct **386**. Reductive electron transfer led to the radical **387**, which fragmented to a pyridine byproduct and produced the

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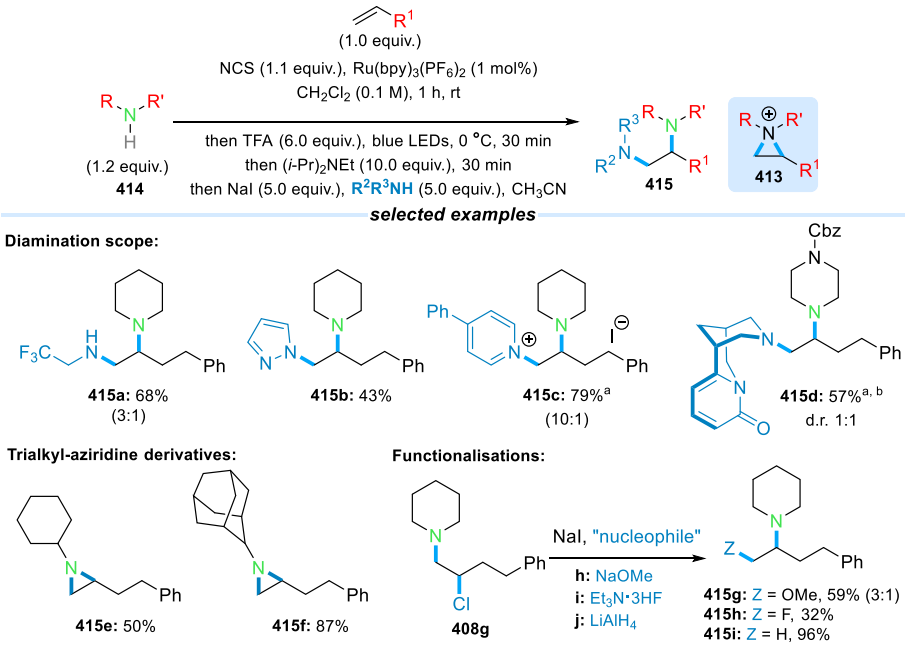
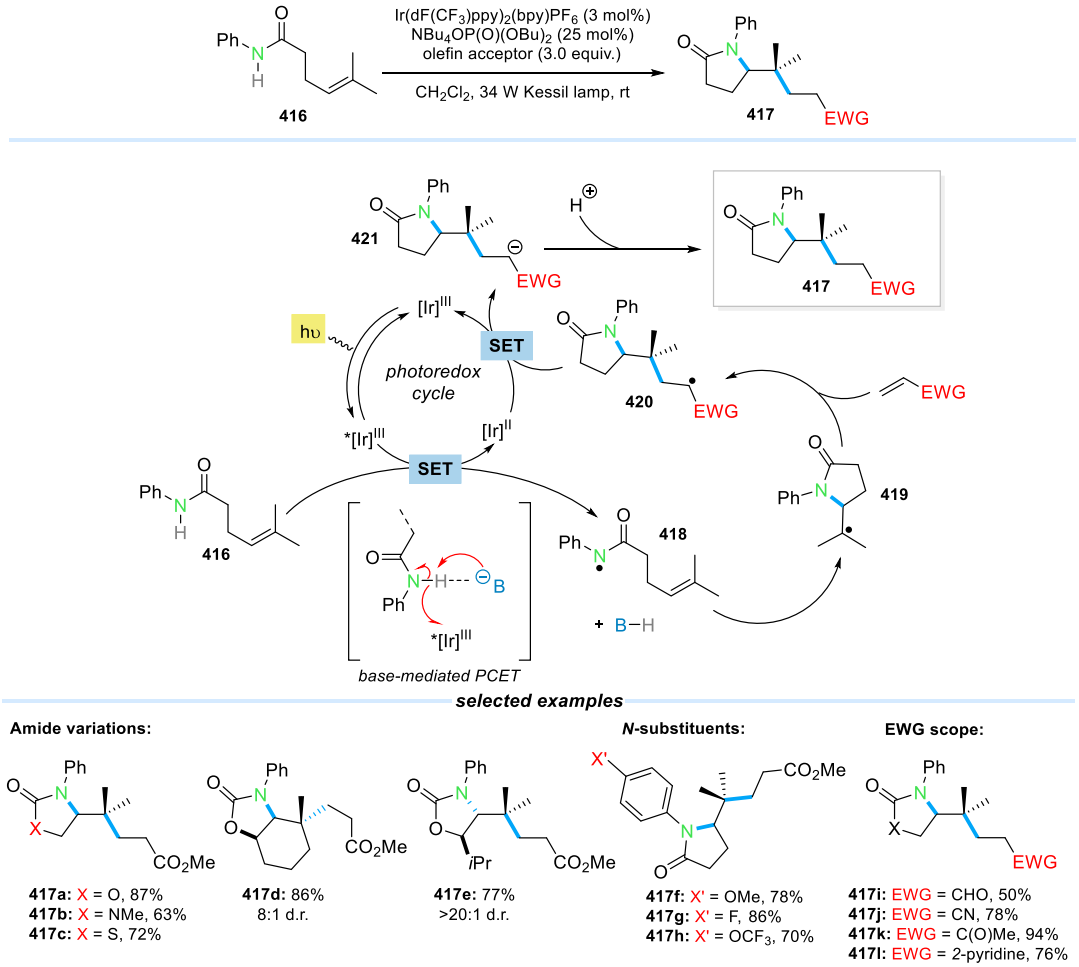
Scheme 89. Diamine Functionalization of 1,2-Chloroamine Derivatives



[a]A basic workup was performed before addition of NaI and the amine. [b]Upon addition of NaI and the amine, the mixture was warmed to 60 °C.

Scheme 90. Catalytic Proton-Coupled Electron Transfer Hydroamidation of *N*-Arylamides with Olefin Acceptors



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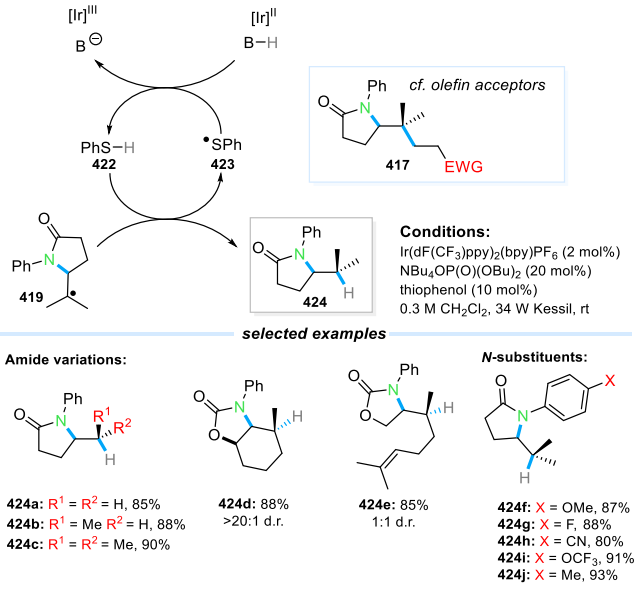
Scheme 91. Catalytic Proton-Coupled Electron Transfer Hydroamidation of *N*-Arylamides with H-Atom Donors



active NCR **388**. Addition to an olefin substrate furnished the C-centered radical **389**, which underwent subsequent oxidation (**390**). Addition of water to the cationic species **390** afforded the amidohydroxylated product **385** and regenerated the Lewis acid catalyst. Similar substrates to the previous methodology were explored.[340] Good yields were achieved for *para*-functionalized examples (**385a**–**385d**); however, they were lower compared to previous investigations. An expanded scope for N-protecting groups was explored: products bearing benzoyl (**385e**), Boc (**385f**), Troc (2,2,2-trichloroethoxycarbonyl, **385g**), and Alloc (**385h**) groups were obtained in moderate yields. More recently, the Akita group has developed a methodology with an iridium catalyst and pyridinium salts (e.g., **391**) to access phenanthridines regioselectively [Scheme 83, (ii)].[342] The transformation proceeded via an EDA complex to generate an active iminyl radical, which then underwent cyclization to afford functionalized phenanthridines (e.g., **392**).

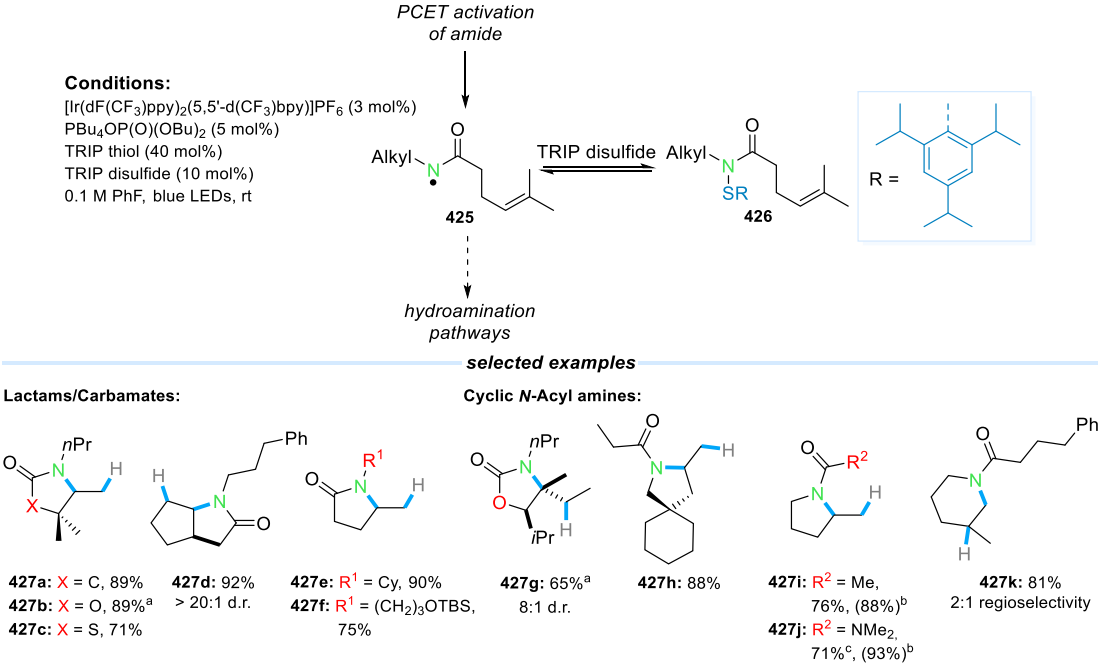
In 2015, Yu et al. reported the chlorosulfonamidation of olefins with *N*-chlorosulfonamides (**393**) (Scheme 84).[343] Irradiation with visible light generated the sulfonamidyl radical, which added to the olefin substrate in an anti-Markovnikov fashion. Propagation of the NCR with styrene derivatives afforded the 1,2-haloamine products (**394**).

Protecting group derivatives were tested, affording products **394a**–**394c** where a lower yield was obtained for the electron-deficient example (**394c**). Styrene derivatives with *para*-substituted alkyl and halide groups yielded the corresponding 1,2-haloamine derivatives in good yields (**394d**–**394f**). Sulfonamidation of 2,3-dihydro-1*H*-indene was highly diastereoselective and achieved a >99:1 d.r. for **394g** in an excellent yield. Aliphatic olefins were also examined (**394h**), although these substrates were not as efficient as the styrene derivatives.

Leonori et al. took inspiration from the work of Narasaka (cf. Scheme 23) to provide an accessible route to iminyl radicals via the SET reduction of electron-poor *O*-aryl oximes (**395**) (Scheme 85).[329] The metal-free procedure afforded hydroimination derivatives (**396**) via cyclization of the iminyl radical onto an olefin. Electrochemical studies of possible aromatic activating groups resulted in the detection of an electron-withdrawing *O*-2,4-dinitrophenyl motif, which possessed an accessible reduction potential for SET.

A simple condensation reaction of a ketone with an aryloxylamine under acidic conditions was used to access the

Scheme 92. Catalytic Proton-Coupled Electron Transfer Activation of *N*-alkyl Amides with a H-Atom Donor and a Disulfide Additive



[a]Change in reaction conditions: 0.2 mmol scale, 20 mol% $NBu_4OP(O)(OPh)_2$, 30 mol% TRIP disulfide, 0.02 M. [b]Yields reported from ^1H NMR analysis of the crude reaction mixture. [c]Change in reaction conditions: 25 mol% $PBu_4OP(O)(OtBu)_2$, 80 mol% TRIP thiol, 0.05 M.

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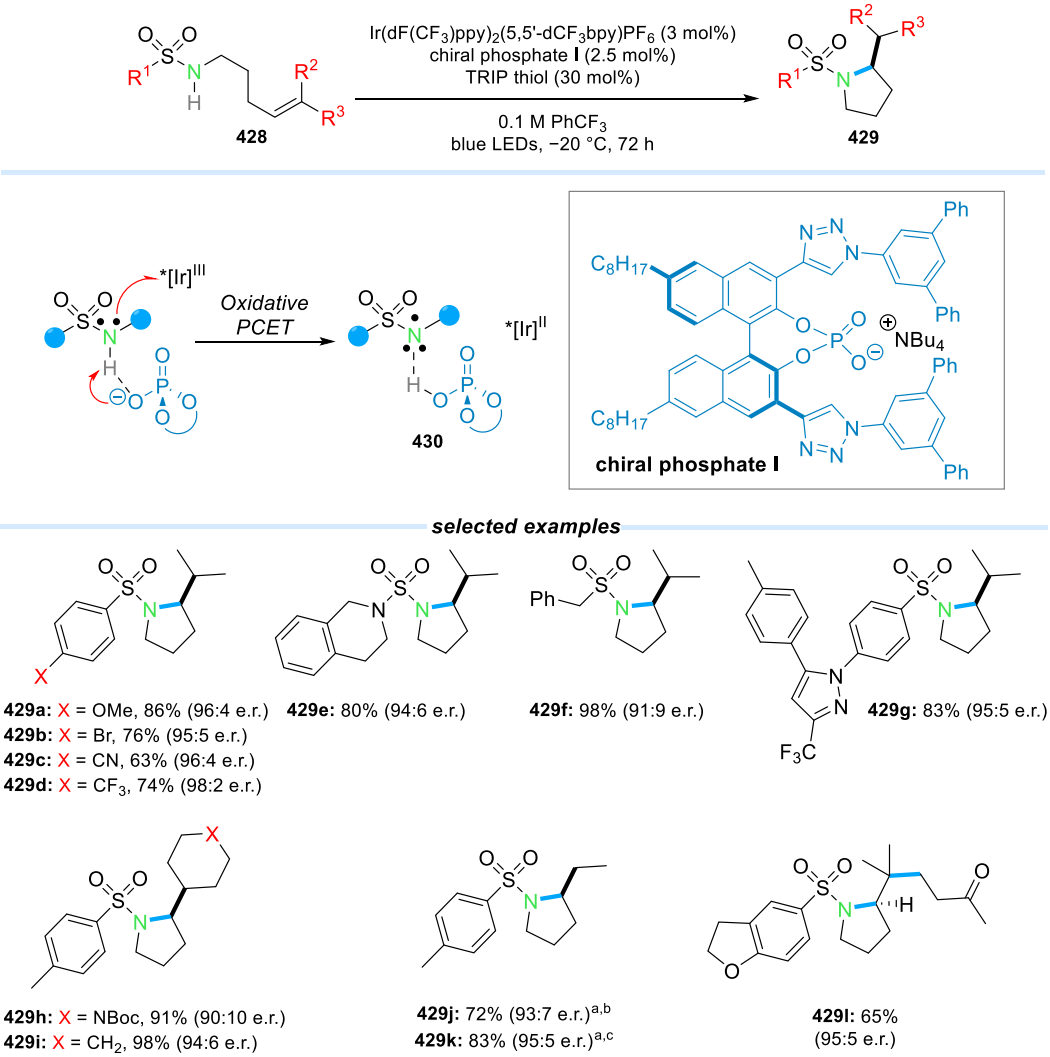
Scheme 93. Enantioselective Hydrosulfonamidation Using Oxidative Proton-Coupled Electron Transfer



[a]Reactions were run at 0 °C with TRIP thiol substituted for TRIP-disulfide. [b]From the *cis*-alkene. [c]From the *trans*-alkene.

corresponding oximes. SET reduction of the oxime **395** results in fragmentation to furnish the nucleophilic iminyl radical **397** via N−O cleavage. The iminyl radical adds to the olefin intramolecularly to form the carbon radical **398**. CHD (**399**) acts as a sacrificial H-atom donor to facilitate the drive to the desired cyclized product **396**. Aromatics adjacent to the oxime delivered the products (**396a**−**396e**) in excellent yields. Leonori et al. extended the scope of the oxime substituents to linear chain derivatives which displayed good yields (**396f**−**396h**). Boc-protected amines (**396i**, **396k**) were tolerated, and bicyclic structures (**396j**, **396k**) were synthesized with modest diastereoselectivity. In the absence of CHD, *O*-aryl oxime **395** led to unexpected oxygenated products **404** (Scheme 86).

The authors proposed that EDA complex **395** induced SET, initiating fragmentation. Once the C-centered radical **398** is generated, it could undergo addition to **400**, via attack on the NO_2 group to give intermediate **401**. It was suggested that **401** would then homolytically cleave at the N−O bond to give rise to intermediate **402** and **403** as a byproduct. However, a more likely mechanism of action would proceed through the reduction of **401**, which would heterolytically fragment to give rise to alcohol **404**. Product **403** was detected in mechanistic studies which provided evidence for the involvement of **400** in the reaction. The reaction conditions were applied to a range of imino alcohols which furnished the hydroxylated products in good yields. Arene substituents of varying electron density were tolerated (**404a**−**404e**), as well as bicyclic systems (**404f**, **404g**) and Boc protecting groups (**404g**, **404j**). Complex structures with original stereochemistry were cyclized and hydroxylated with minimal epimerization observed (**404h**, **404i**). The product from one substrate featured a quaternary center, albeit in diminished yield (29%).

Leonori et al. adapted this methodology to generate amidyl radicals (**405**) for the intramolecular hydroamidation of *O*-2,4-dinitrophenoxy amides (**406**).[176] A range of lactam derivatives (**407**) were synthesized in a transition metal-free procedure (Scheme 87).

DFT studies on the effect of the N-substituent on the electrophilicity of the amidyl radicals were carried out and defined by the local electrophilicity index values (ω_{rc}^{+}).[44] The study revealed that aryl-amidyl radicals (**405a**) are significantly less electrophilic than the corresponding alkyl-amidyl radical (**405b**). The philicity of the radicals significantly contributed to the ability of the radical to abstract a hydrogen atom; the more electrophilic the radical, the lower the barrier to H-atom abstraction. Variations of the N-substituent were effective

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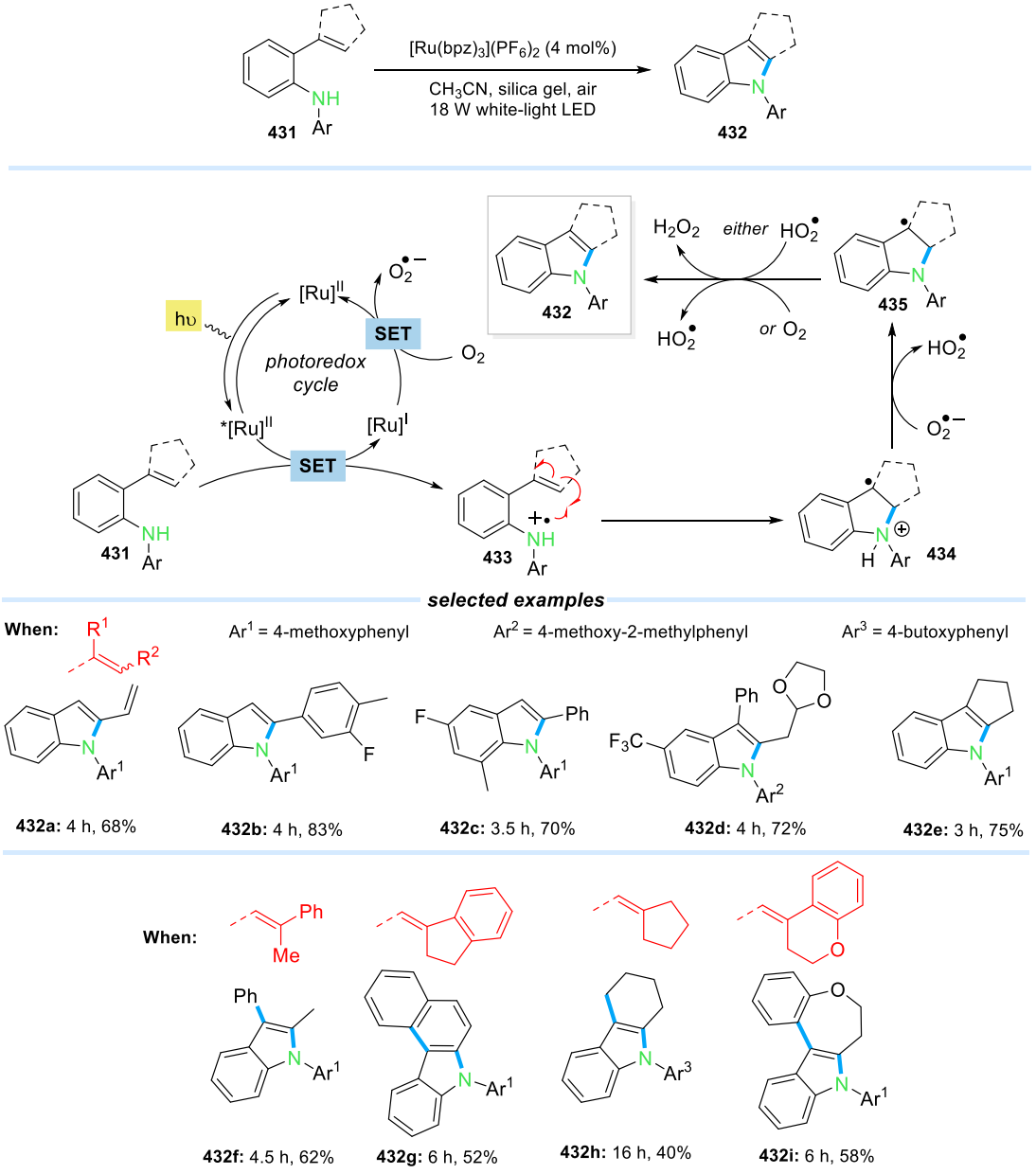
Scheme 94. Synthesis of Functionalized Indole Heterocycles via Oxidative Methods



(**407a**−**407e**), also demonstrating the tolerance to Bn, Boc, and Cbz protecting groups. Cyclization to spirocyclic (**407f**) and bicyclic (**407g**) derivatives was successful, as well as to the trifluoro-substituted product (**407h**), and good yields were obtained. Further modifications to afford carbamate (**407i**) and thiocarbamate (**407j**) examples were shown.

Applications of the *O*-2,4-dinitrophenol chromophore in photoredox chemistry have since been reported. NCR cyclization to access phenanthridine derivatives has been developed by Xie et al.[344] Wang and co-workers demonstrated the intramolecular radical cascade reaction with an amidyl radical in the synthesis of (±)-Flustramide B.[345,346] Recent adaptation from Pericàs and Frontera reported the non-covalent anion−π interaction of potassium carbonate with *N*-aryloxyamides to give amidyl radicals for intermolecular amidation, without the need for a photocatalyst.[177]

In 2020, Leonori reported a regioselective radical chain process to access unsymmetrical vicinal diamine products. Initial amination of olefins with an *N*-chloro precursor resulted in 1,2-chloroamine derivatives (**408**) (Scheme 88), which gave 1,2-diamine products when exposed to an amine source (Scheme 89).[347]

The initial amination adapted the previously reported protocol for arene amination, regarding the reductive cleavage of protonated *N*-chloroamines (**409**) to generate aminium radicals.[337] It was found that use of HFIP did not lead to the desired selectivity and TFA was found to be a suitable replacement for the previously used $HClO_4$. Addition of the aminium radical (**360**) to the alkene gave **410**, which underwent a S_H2 mechanism to achieve the chlorination of the carbon radical to give **411**. A basic workup afforded the 1,2-chloroamine derivatives (**408**). Cyclic amines gave the amination products in excellent yields (**408a**−**408c**); however, acyclic amine products (**408d**−**408f**) were isolated in lower yields. Changing the substitution pattern of the olefin showed compatibility with a number of functional groups which provided the desired

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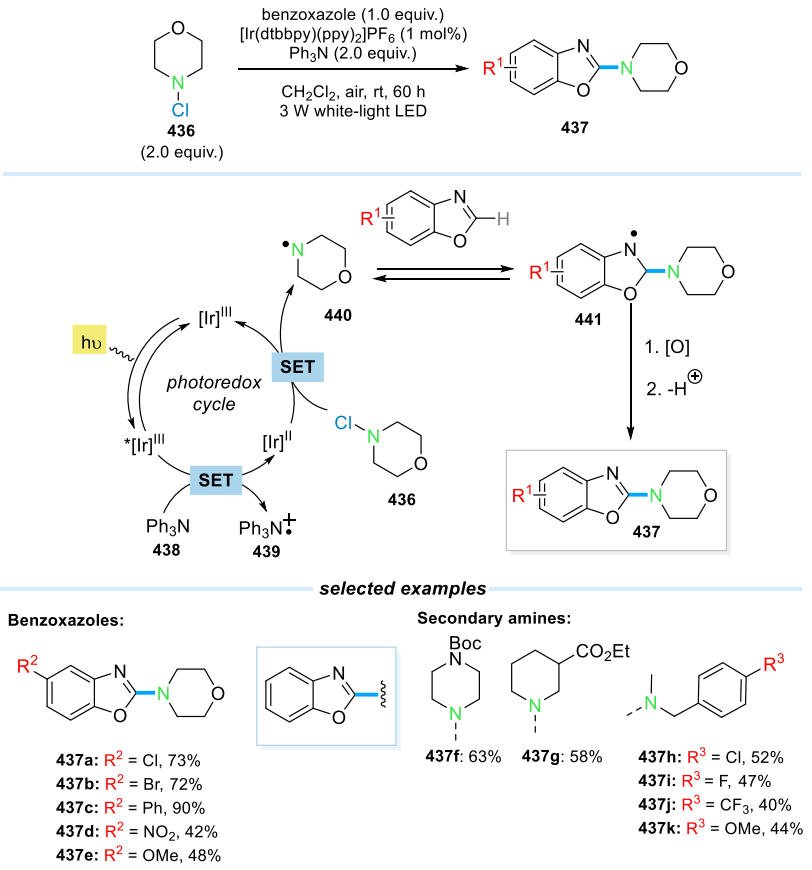
Scheme 95. Selective Amination of Benzoxazole Derivatives with Secondary Amines[a]



[a]Morpholine is used as the model amine for the mechanistic details.

products (**408h**–**408l**). The procedure was also compatible with a number of complex drug molecules. The methodology was successfully adapted to a flow reactor, which delivered the product **408g** in a short period of time and maintained an excellent yield (87%). Products obtained from styrene derivatives exhibited a difference in reactivity; thus, 1,2-amino alcohol derivatives were isolated (**412a**, **412b**) rather than the 1,2-chloroamines.

Further functionalization of the 1,2-chloroamine derivatives was demonstrated; generation of the aziridinium ion (**413**) and addition of an amine (**414**) stimulated regioselective ring-opening, affording the 1,2-diamine products (**415**) (Scheme 89).[347]

Varied amine nucleophiles were tested affording products derived from an electron-poor amine (**415a**), imidazole (**415b**), pyridine (**415c**), and the alkaloid cytisine (**415d**) in moderate to excellent yields; however, some unselective ring-opening of the intermediate **413** was observed. Upon basification, primary amine substrates were transformed into the corresponding trialkylaziridines (**415e**, **415f**) and did not undergo facile ring-opening as demonstrated with other substrates. Finally, further diversification of the aminochlorination products (**408g**) was described, where variation of the "nucleophile" allowed for the synthesis of functionalized products (**415g**–**415i**).

6.4. Reductive Quenching Processes

6.4.1. Proton-Coupled Electron Transfer. In 2015, Knowles et al. demonstrated the carboamidation of amide substrates (**416**) by irradiation with visible light and the use of an iridium catalyst. The mechanism proceeded via an oxidative concerted PCET step, furnishing the desired carboamidation products (**417**) (Scheme 90).[53] The elegant methodology was chemoselective toward amide bonds and avoided prefunctionalization of the amide or the use of strong oxidants. Although the concept of PCET had been largely established,[348,349] it had not been applied to the generation of NCRs. PCET enabled access to a lower bond dissociation energy (BDE) of a N–H amide bond, by a hydrogen-bonding interaction with a selected Brønsted base.

The excited-state photocatalyst, in combination with a phosphate base, acts as a strong oxidant to the N–H amide bond of **416** and enables the PCET process to occur. An *N*-aryl amidyl radical **418** is generated, and propagation of the radical chain occurs via an intramolecular amidation to form radical species **419**. Addition of an olefin acceptor (containing an electron-poor substituent to enable a polarity-matched reaction) results in elongation of the alkyl chain (**420**). Subsequent reduction with the reduced photocatalyst regenerates the ground-state $[Ir]^{III}$ species and the anionic species **421**. A final proton-transfer step provides the carboamidation product **417**. A range of carbamate, thiazolidinone, and fused-bicyclic derivatives were generated in very good yields (**417a**–**417c**). Substituted olefins were tolerated and displayed moderate diastereoselectivity (**417d**, **417e**). Using methyl acrylate as the olefin acceptor, the N-substituent was varied with different (hetero)arenes (**417f**–**417h**). Products were isolated in mostly good yields, and only large or *ortho*-substituted (hetero)arenes displayed a diminished yield. Various electron-poor olefin

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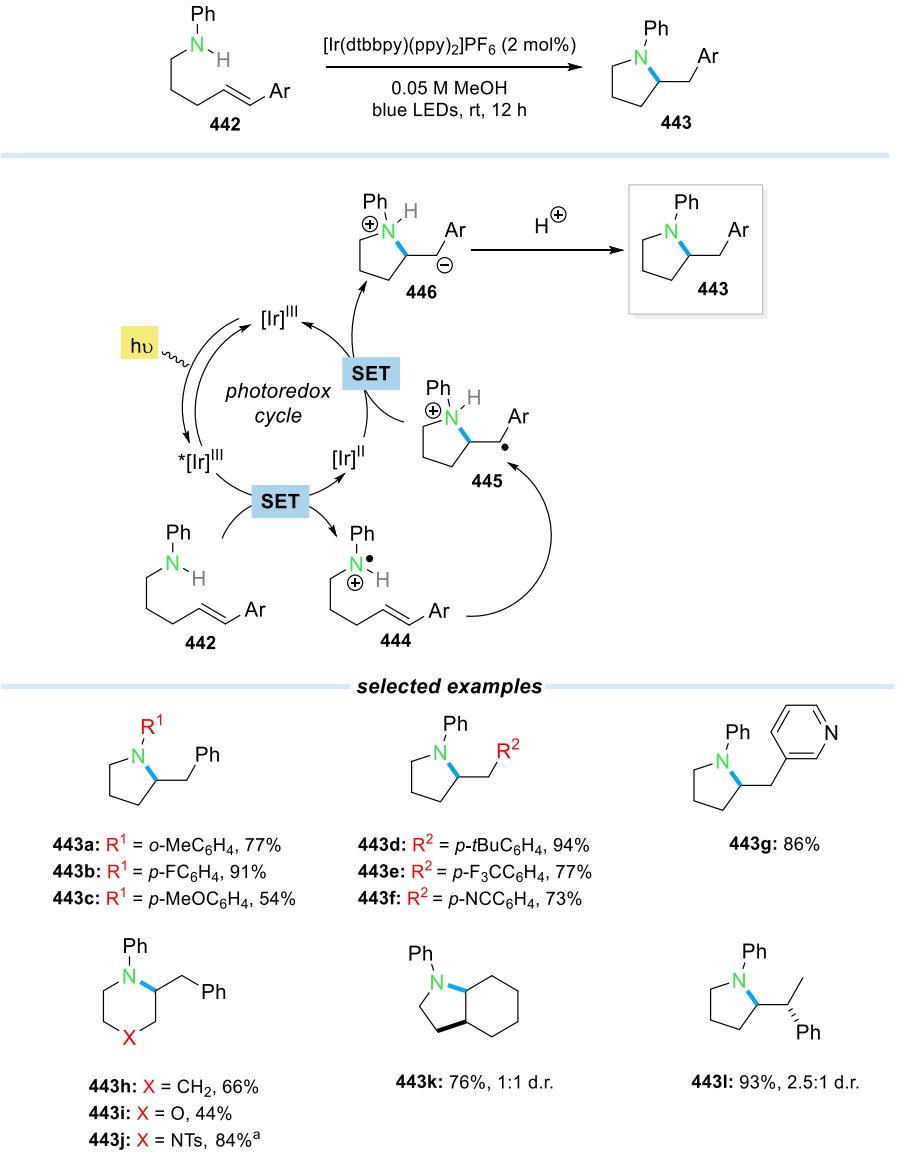
Scheme 96. Intramolecular Hydroamination of Olefins via Aminium Radicals



acceptors were examined and found to be highly effective (**417i**–**417l**).

Indeed, it was envisaged by Knowles and co-workers that a H-atom donor could be used to replace the olefin acceptor to terminate the radical propagation earlier in the mechanism (Scheme 91).[350] A thiophenol HAT catalyst (**422**) exhibited highly efficient and productive results, which could not be mimicked by other common HAT catalysts. Interestingly, it appeared that the PCET of an amide is favored over thiol H-abstraction, regardless of the difference in BDE [thiol S–H bond BDE ≈ 79 kcal/mol[351] vs amide (**416**) N–H bond BDE ≈ 99 kcal/mol[352]]. Despite the thiol having the weaker bond, the PCET activation of amides is kinetically favored over the PCET with thiols. This was recently rationalized by Knowles and co-workers when the rates of PCET and the position of hydrogen-bonding equilibria were compared between N–H and S–H bonds.[55]

Comparable to the previously described mechanism (cf. Scheme 90), the carbon-radical species **419** undergoes H-atom abstraction from a thiol catalyst, resulting in the generation of the corresponding thiyl radical (**423**) and the desired amidation product (**424**). The thiyl radical can be reduced by the $[Ir]^{II}$ catalyst, generating a thiolate anion species capable of deprotonating the phosphate base, thus regenerating the three catalytic components of this mechanism. Diverse substrates were tested, varying the amide and carbamate derivatives which were obtained in excellent yields (**424a**–**424e**). Changing electron density on the phenyl group of the N-substituents also maintained excellent yields (**424f**–**424j**). Construction of quaternary centers and generation of bicyclic structures were achieved with high diastereoselectivity. Functionalities such as unprotected alcohols and unactivated olefins were tolerated without compromising yield or stereoselectivity. It was stated that intermolecular reactions or the formation of larger rings were not favorable under these conditions.

Efforts to access *N*-alkyl amidyl radicals from this method proved unsuccessful. The BDE of an alkyl N–H bond is calculated to be significantly higher than an aniline N–H bond (alkyl N–H BDE ≈ 107 kcal/mol[353]) and precludes their application to PCET processes. In 2016, the Knowles group[354] and Rovis and Chu[355] developed a method to access an *N*-alkyl amidyl radical in a C–C alkylation transformation. The

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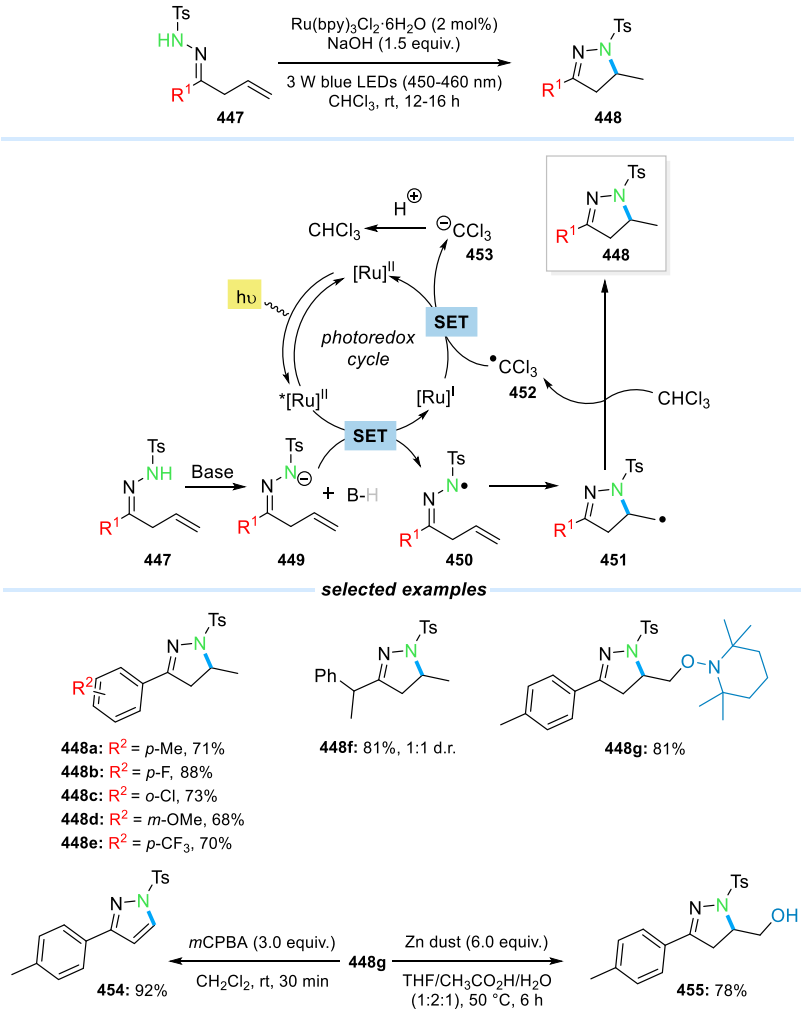
Scheme 97. Cyclization of Hydrazonyl Radicals onto Alkenes



reactivity of the amidyl radical was modulated to undergo a 1,5-HAT with a distal sp^3 C−H bond, accessing a powerful alkylation transformation. Remarkably, Knowles et al. demonstrated the approach could be adapted to intermolecular C−H functionalization examples, utilizing the hydrogen-abstraction ability of the generated *N*-alkyl amidyl radical on intermolecular C−H bonds.[354]

In 2019, Knowles adapted the method previously described in Scheme 90 and Scheme 91 to address hydroamidations of *N*-alkyl amides. Using 2,4,6-triisopropyl thiophenol (TRIP), a strategy reported by Nocera and co-workers,[356] led to an increase in the quantum yield of the reaction (Scheme 92).[357]

By introducing a disulfide trapping agent, the *N*-alkyl amidyl radical (**425**) was trapped in an equilibrium to form the N−S species **426**. Consequently, unproductive back electron transfer to the photocatalyst and undesirable mechanistic pathways were prevented, permitting a slower release of active radical into the reaction mechanism. Lactams, carbamates, thiocarbamates, and cyclic *N*-acyl amines were synthesized in good to excellent yield (**427a**−**427j**). Interestingly, a switch in ring-size favorability was noted with a 1,1-disubstituted olefin acceptor, which provided the 6-*endo*-cyclized product (**427k**) in a 2:1 regioisomer ratio with the corresponding 5-*exo*-pyrrolidine derivative.[358]

An enantioselective intramolecular hydrosulfonamidation of alkenes was developed by the Knowles group in 2020,[359] an extension from their work on intermolecular substrates in 2018.[360] It was proposed that the stereoselectivity could be controlled via the hydrogen-bonding complex with a chiral phosphate base, formed in the oxidative PCET step. This type of asymmetric induction has been previously demonstrated by the group with neutral ketyl radicals[361] and indole radical cations.[362] Starting from sulfonamides (**428**), the construction of pyrrolidines (**429**) with e.r.'s up to 98:2 was reported (Scheme 93).

Generation of the sulfonamidyl radical (**430**) via oxidative PCET resulted in cyclization to form pyrrolidine derivatives (**429**). Products derived from cyclization of aryl sulfonamides (**429a**−**429d**), sulfamides (**429e**), and alkyl sulfonamides (**429f**) resulted in good yields and high stereocontrol, which was also seen in the construction of the drug Celecoxib (**429g**). Derivatization of the alkene moiety to give products with Boc-piperidine (**429h**) and cyclohexyl (**429i**) substituents proceeded well, although a lower e.r. was achieved for **429i**. Starting from either the *cis* or *trans* alkene did not affect the stereoselectivity of the transformation, and excellent selectivities were recorded (**429j**, **429k**). Replacement of the TRIP thiol catalyst with methyl vinyl ketone resulted in excellent e.r. of the carbosulfonamidation product (**429l**). Thus, it was suggested the enantioselectivity arose in the C−N bond formation step from either formation of a PCET complex or an ion-pairing pathway (as proposed by Luo[363] and Nicewicz[364]). Upon further investigation, the enantioselectivity did not change when

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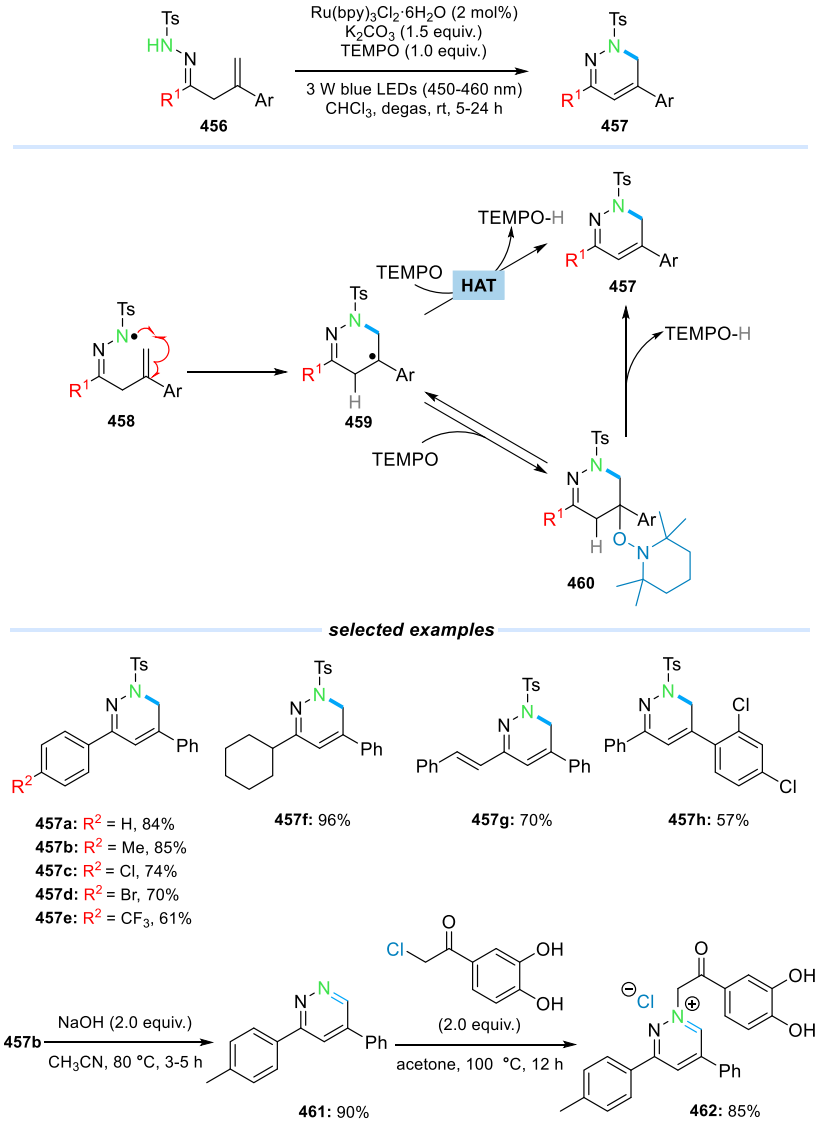
Scheme 98. TEMPO-Mediated 6-*endo*-Trig Cyclization of Hydrazonyl Radicals



the solvent dielectric was varied, therefore an ion-pairing mechanism was ruled out.

In the past 5 years, numerous reviews have been published by the Knowles group reporting the quantitative basis, applications, and chemoselectivity of PCET in organic synthesis. We direct the reader to the following publications for explicit details.[47,54,365]

6.4.2. C−H Functionalization of (Hetero)arenes with NCRs. Zheng and Maity proposed mild conditions to transform styrene-aniline derivatives (**431**) to *N*-arylindoles (**432**), utilizing oxidative photoredox conditions (Scheme 94).[366] Either full aromatization was achieved immediately to yield indole derivatives, or alternatively, a 1,2 C−C bond migration took place for geminal disubstituted alkene derivatives.

Oxidation of aniline **431** to the aminium radical **433** induces an intramolecular radical addition to the styrene moiety. Deprotonation of the carbon-radical intermediate **434** yields carbon radical **435**. Subsequent re-aromatization produces the desired indole derivatives **432**. Substrates with varied electronic contributions, substitution on the olefin and bicyclic examples were examined, affording the corresponding indoles (**432a**−**432e**) in excellent yields. A 1,2-migratory shift was observed when geminally disubstituted styrene derivatives were used (**432f**−**432i**). Products from non-cyclic (**432f**), cyclic (**432g**, **432h**), and oxacyclic substrates (**432i**) were isolated in moderate yields.

In 2014, Xiao and co-workers presented a selective amination of benzoxazole derivatives with *N*-chloroamines (**436**).[367] Amination was achieved using an iridium photocatalyst and visible light irradiation and provided C2-substituted benzoxazole products (**437**) (Scheme 95).

A sacrificial amine electron donor, Ph_3N (**438**), is initially oxidized by the excited iridium state to give an $[Ir]^{II}$ complex and **439**. The electron-rich catalyst can then reductively cleave the N−Cl bond on **436**, which generates the aminyl radical **440**. The benzoxazole can be selectively aminated at the C2-position, resulting in the NCR **441**. Oxygen or the oxidized amine additive (**439**) can oxidize NCR **441**, before a rapid re-aromatization which yields the aminated product **437**. Radical trapping experiments with TEMPO stalled the reaction, and when irradiation of the reaction with visible light was stopped, no reaction occurred. The transformation proceeded excellently with halide or phenyl functionalities present (**437a**−**437c**). However, a diminished yield was observed for electron-poor and

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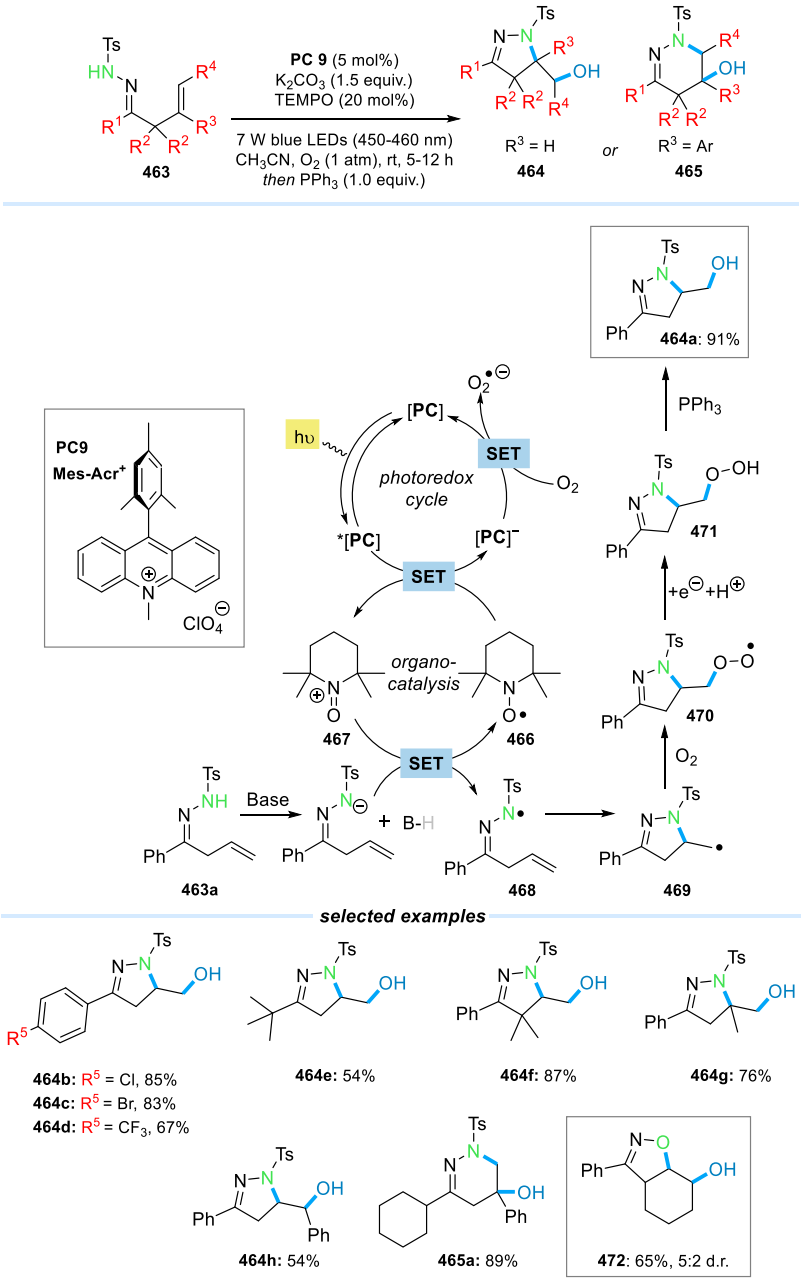
Scheme 99. Oxyamination via Hydrazonyl Radicals Using Organocatalysis (TEMPO) and Photoredox Catalysis[a]



[a]The R substituents in the mechanism have been omitted for clarity. **463a** is used as a model substrate.

electron-rich substituents (**437d**, **437e**). Cyclic amine (**437f**, **437g**) and acyclic amine (benzylamine) (**437h**−**437k**) products were furnished in moderate yields.

6.4.3. Functionalization of Olefins with NCRs. In 2014, Knowles and co-workers reported the hydroamination of alkenes (**442**) to achieve the corresponding N-heterocycles (**443**), using aminium radicals (Scheme 96).[368]

Oxidation of aniline derivatives (**442**) by a $[Ir]^{III}$ photocatalyst generates the aminium radical (**444**). Cyclization onto the olefin provides radical **445**. Reductive SET to **445** forms the carbanion **446**, which undergoes proton transfer to yield pyrrolidine derivatives (**443**). Variations of the substitution on the aniline substrates were investigated and afforded the desired pyrrolidines (**443a**−**443c**) in good yields. Further variations on the substitution of the styrene derivatives gave products (**443d**−**443f**, **443l**) as well as a pyridine variation (**443g**). Syntheses of saturated 6-membered N-heterocycles (**443h**−**443j**) and bicyclic pyrrolidines (**443k**) were also demonstrated.

Xiao and co-workers developed a protocol for the generation of hydrazonyl radicals from *β*,*γ*-unsaturated hydrazones (**447**).[369] Under basic, photochemical conditions the NCR underwent 5-*exo* cyclization, producing 4,5-dihydropyrazole derivatives (**448**) (Scheme 97).

Under basic conditions, deprotonation of the hydrazone (**447**) can occur to give hydrazone anion (**449**). Oxidative SET of **449** with the excited $*[Ru]^{II}$ catalyst furnishes the hydrazonyl radical **450**, which can rapidly undergo 5-*exo*-trig cyclization to yield the C-centered radical **451**. Transfer of a hydrogen atom from the solvent (chloroform) gives the desired 4,5-dihydropyrazole derivative (**448**). The resulting trichloromethyl

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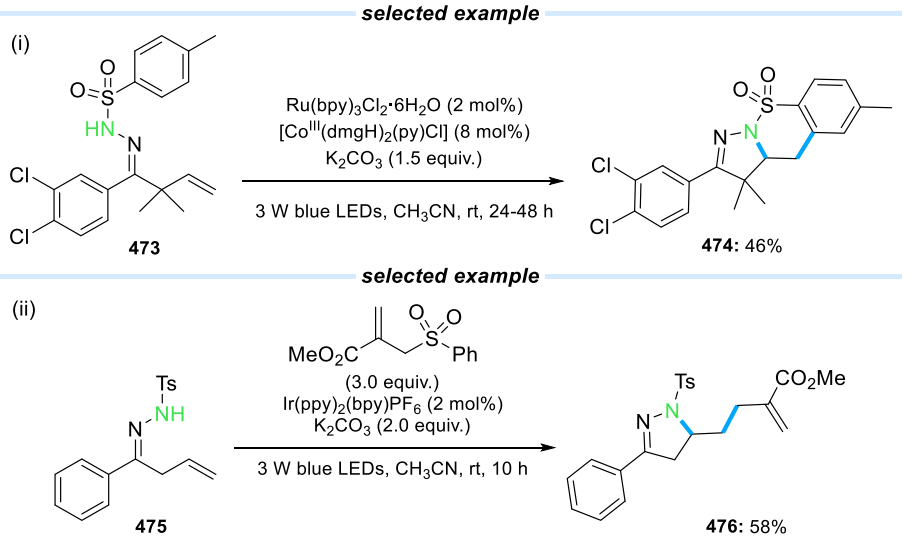
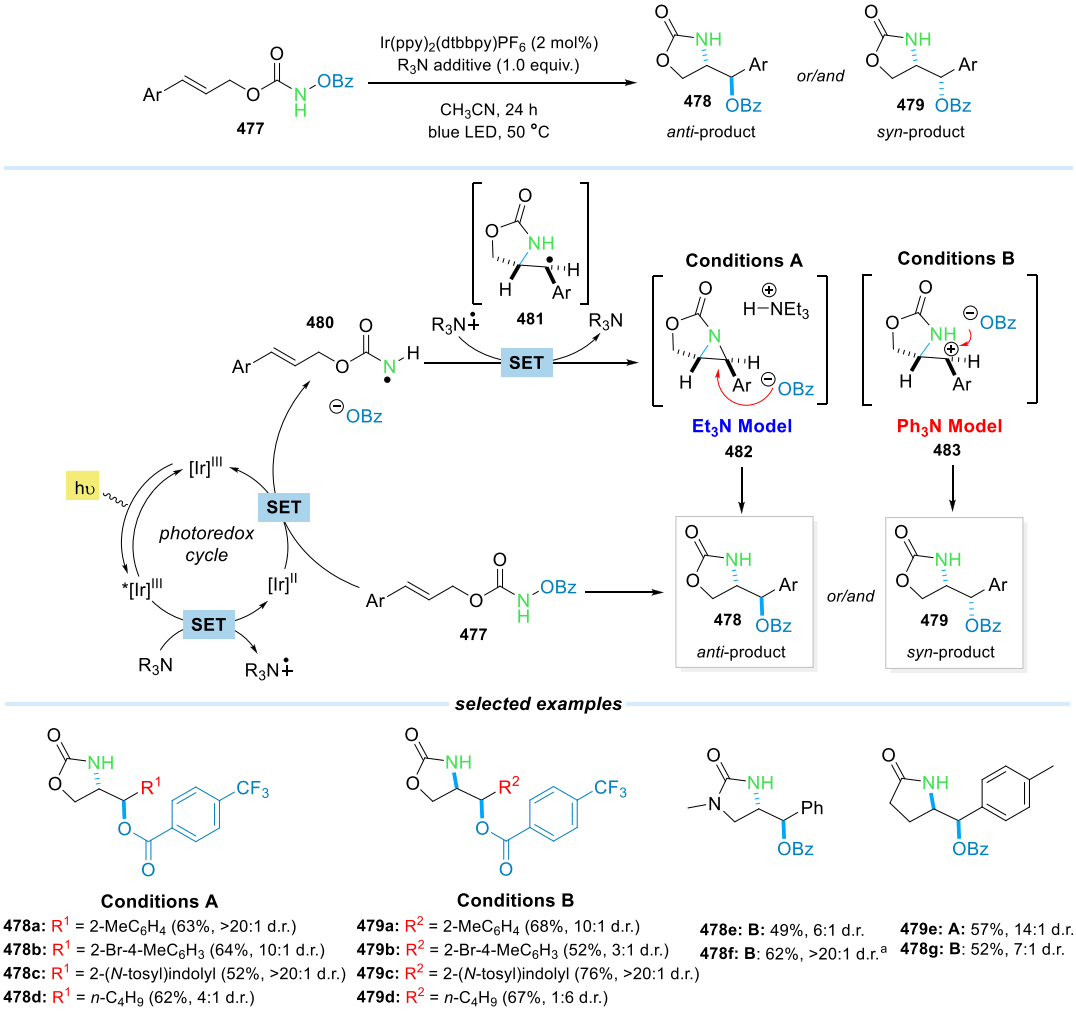
Scheme 100. Functionalization of Dihydropyrazoles via Radical Cascade Reactions: (i) Synthesis of Benzosultam Derivatives via a Secondary Radical Cyclization and (ii) Radical Cyclization Followed by Allylation with Allyl Sulfone Derivatives[a]



[a]dmg = dimethylglyoxime.

Scheme 101. Proposed Mechanism of the Diastereocontrolled Oxyamidation of Alkenes



[a]80 °C with 1.0 equiv of $PhCO_2H$.

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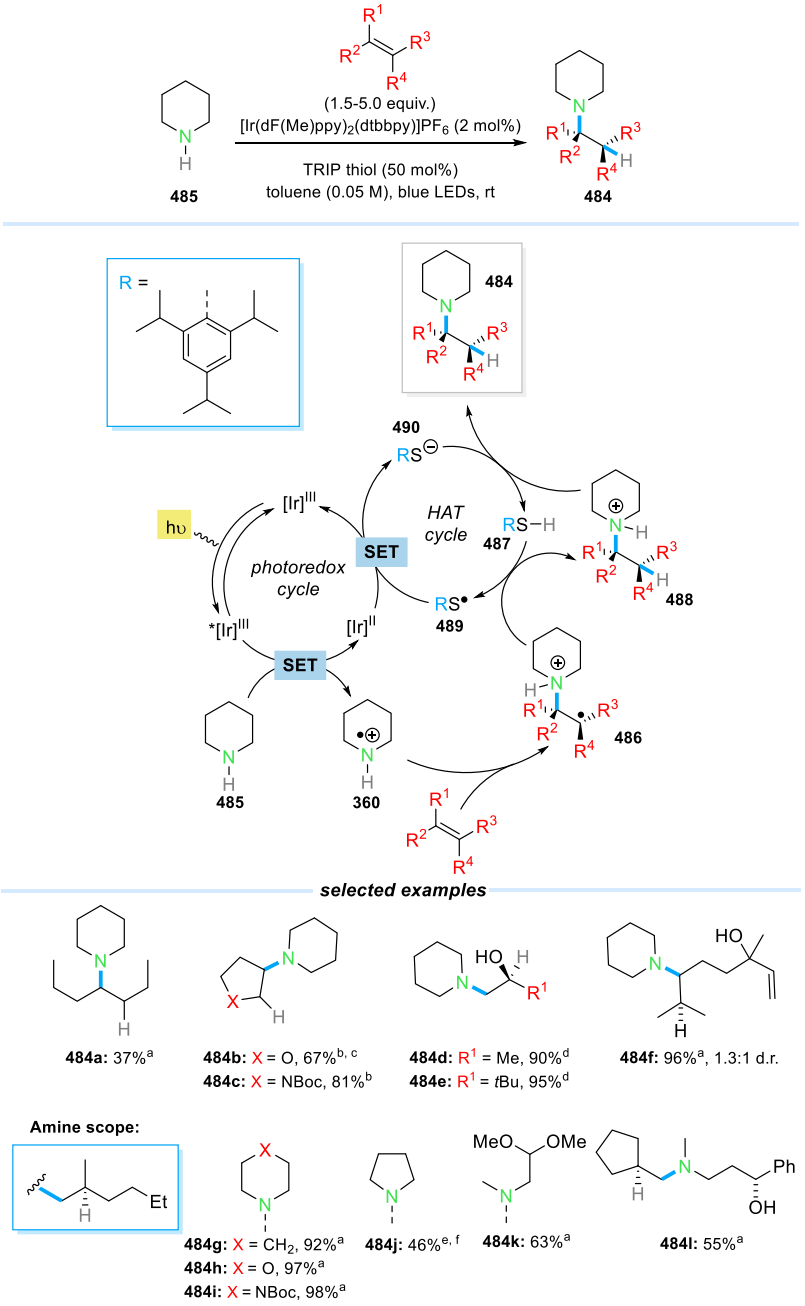
Scheme 102. Photoredox and H-Atom Transfer Catalysis for Intermolecular Hydroamination with Aminium Radicals



[a]3.0 equiv of olefin used. [b]1.5 equiv of olefin used. [c]NMR yield. [d]Substrate is a trimethylsilyl enol ether. [e]5.0 equiv of olefin used. [f]2-Methylnon-1-ene as the olefin partner. All chiral products were formed as racemates. Piperidine is used as the model amine for the mechanistic details.

radical (**452**) can regenerate the $[Ru]^{II}$ catalyst through SET, generating the anion **453** which is protonated to re-form chloroform. Phenyl substituents in the C3-position were investigated, exploring the tolerance of electron-rich and electron-poor functionalities (**448a**–**448e**). Other examples of aliphatic hydrazones gave equally good yields; however, poor diastereoselectivity was achieved (**448f**). Evidence of a radical mechanism was confirmed with TEMPO trapping of the carbon radical (**451**) to give **448g**. Pyrazole **454** was prepared by the oxidation of **448g** with *m*-CPBA (92%) or alternatively cleavage of the N–O bond was accomplished, yielding the alcohol (**455**, 78%).

In 2016, the Xiao group reported an unprecedented 6-*endo*-trig cyclization of *β*,*γ*-unsaturated hydrazones (Scheme 98).[370] Their previously established methodology detailed selectivity for 5-*exo*-trig cyclization.[369] However, computational studies revealed that 6-*endo*-trig cyclization could be achieved by using a phenyl group at the 2-position of the alkene moiety (**456**), synthesizing 1,6-dihydropyridazines. Reaction optimization revealed that using TEMPO as an additive in the reaction gave the 6-*endo* product (**457**) selectively.

The proposed mechanism of action is similar to previous work in 2014 (cf. Scheme 97).[369] A deprotonation followed by oxidative SET generates the NCR **458**, which can undergo 6-*endo*-trig cyclization, forming C-centered radical **459**. From **459**,

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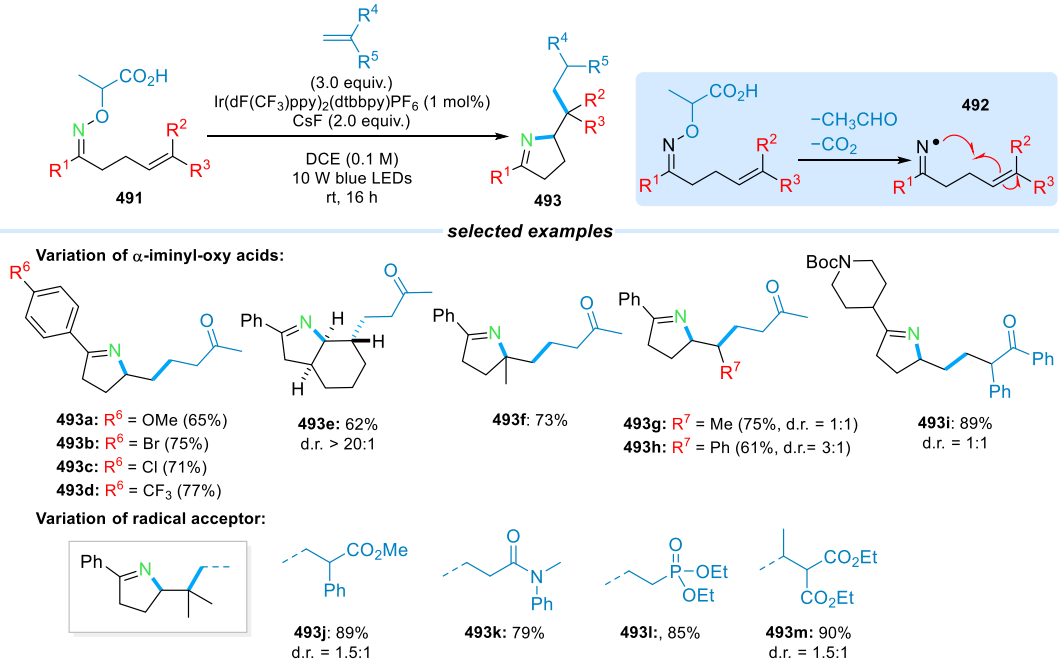
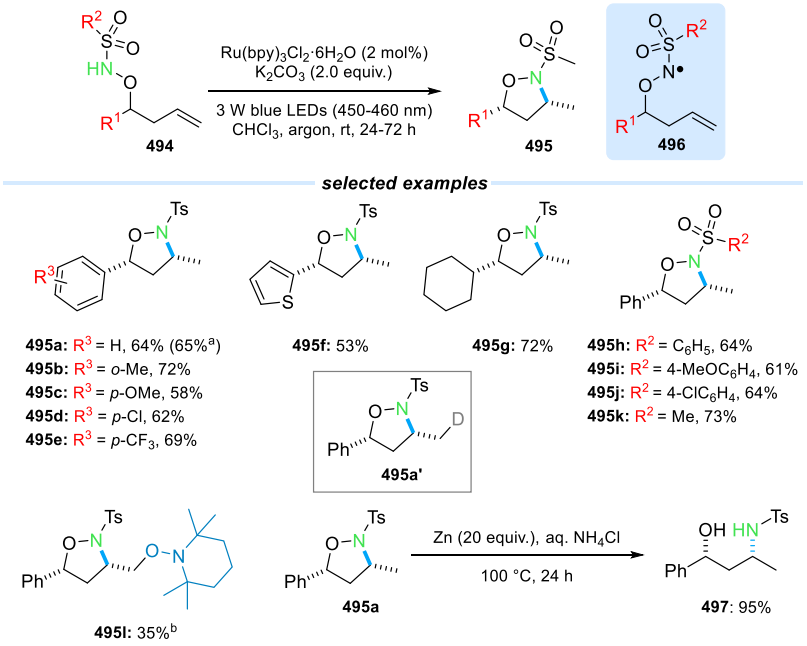
Scheme 103. Synthesis of Functionalized Pyrrolines via Iminyl Radical Cyclization Followed by Intermolecular Olefin Addition



Scheme 104. Synthesis of Isoxazolidines from 5-*exo* Cyclization of Sulfonamidyl Radical



[a]Under sunlight irradiation. [b]TEMPO (2.0 equiv) used as an additive.

two possible mechanisms were considered to reach **457**. The first pathway shows a TEMPO-mediated HAT which promotes formation of the observed product **457**. The other route proceeds through the TEMPO-trapped intermediate **460**, followed by base-induced elimination. A similar mechanism had been observed by Chiba et al. in the C−H bond oxidation of oximes and hydrazones.[371] However, in this case, computational analysis favored the HAT pathway. Substitution of the phenyl group in the R^1 position was explored to give products (**457a**−**457e**). Products derived from other alkene moieties such as alkyl (**457f**), styryl groups (**457g**), and aromatics (**457h**) were produced. No 5-*exo*-trig product was observed in any of the examples. Subjection of the 1,6-dihydropyridazine derivatives (**457b**) to basic conditions yielded the corresponding pyridazines (**461**) in excellent yields (12 examples, 76−94%). Accessing diazinium salts was demonstrated with a dihydroxyacetophenone moiety (**462**), which was proposed as a promising structure for biological activity (5 examples, 63−85%).[370] Mechanistic investigations led to the successful trapping of carbon radical (**459**) with PhSeSePh, which was produced as a mixture of the product (**457**) and the selenide adduct (61%, 1:4 ratio, respectively).

Additional investigation was made by the Xiao group into the cyclization and oxyamination of *β*,*γ*-unsaturated hydrazones

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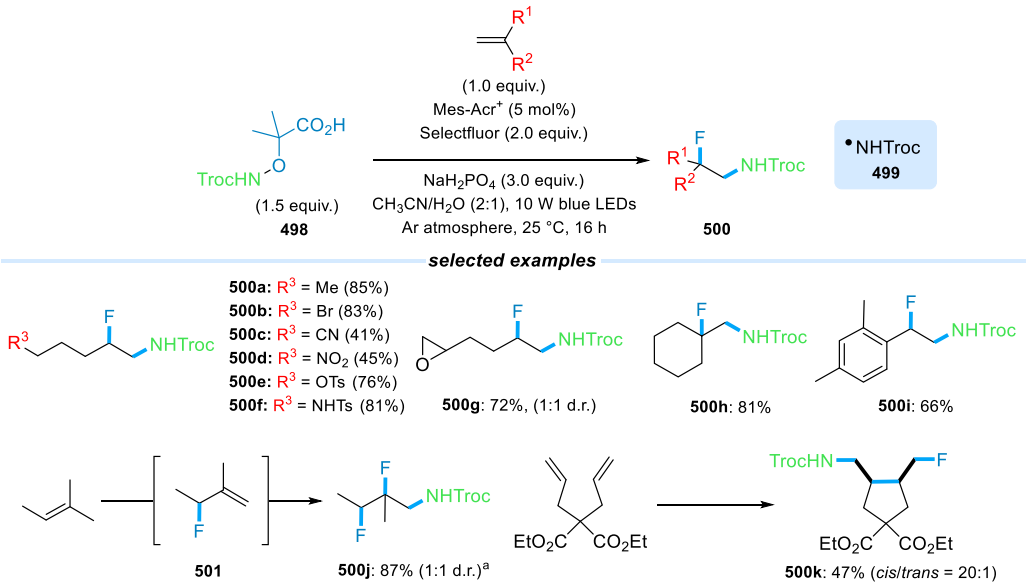
Scheme 105. Amidofluorination of Alkenes with Selectfluor



[a]3.0 equiv of Selectfluor was used.

(**463**) (cf. **455**, Scheme 97).[369,372] Inspired by the work of the Nicewicz[326] and Chen[373] groups, the publication explores the photocatalytic oxidative/TEMPO-mediated oxyamination via hydrazonyl radicals (Scheme 99).

The proposed photoredox cycle begins with a single-electron oxidation of TEMPO (**466**) to the TEMPOnium cation (**467**). The oxidizing species (**467**) generates the NCR (**468**), which undergoes 5-*exo*-trig cyclization to the C-centered radical **469**. Radical **469** is trapped with molecular oxygen (**470**) and followed by a single-electron reduction and protonation to yield **471**. A final reduction with PPh_3 furnished the oxyamination product (**464a**). The photoredox cycle can be completed upon the oxidation of the organocatalyst by molecular oxygen. Products with substitution on the phenyl group (R^1) were formed (**464b**−**464d**) as well as those featuring simple alkyl substitutions around the ring (**464e**−**464g**). Substitution at the R^4 position was also trialed, although a lower yield was obtained (**464h**). Instances of 6-*endo* cyclization (**465a**) were examined when a phenyl group was placed at the 2-position of the alkene moiety (cf. Scheme 98).[370] The report also featured the generation of O-centered radicals where the construction of isoxazoline derivatives (**472**) was described (10 examples, 60−97%). Additional reports were published which detailed the tuning of the reactivity of the C-centered radical (cf. **451**, Scheme 97). Addition of a cobalt catalyst allowed a radical cascade reaction to occur from compound **473**; cyclization of the hydrazonyl radical followed by a further cyclization onto the tosyl group afforded a series of benzosultam derivatives (**474**) [Scheme 100, (i)].[374] A 2017 publication built upon this work, adapting the conditions with similar hydrazones (**475**) to promote intermolecular capture of the C-centered radical with an allyl sulfone, producing functionalized compounds such as **476** [Scheme 100, (ii)].[375]

In 2016, Lu and co-workers presented a diastereoselective oxyamidation of alkenes (**477**) to yield carbamate products (**478**, **479**) in high diastereoselectivity. Interestingly, the stereochemistry (*anti*/*syn*) was controlled by the switching of sacrificial electron donors (Scheme 101).[376]

Mechanistic studies revealed that the transformation stalled in the presence of TEMPO, although no meaningful adducts were isolated. Tracking the reaction progress by ^{1}H NMR studies (of crude mixtures) confirmed the presence of the aziridine intermediate with either conditions **A** or **B**. DFT calculations were carried out which confirmed the experimental results relating to the observed diastereoselectivity. A proposed mechanism indicated reductive-quenching of the photocatalyst to $[Ir]^{II}$ and the oxidation of the amine additive. Reductive SET to **477** promoted cleavage of the hydroxylamine bond to generate the reactive amidyl radical species (**480**). Cyclization of the radical generated the carbon radical **481** and was followed by SET oxidation to the carbocation and the regenerated amine additive. Quenching of the carbocation generated a stable aziridine intermediate which followed one of two pathways (**482**, **483**), dependent on the amine additive. Conditions **A**, utilized Et_3N as a base to form a benzoate ion, to ring-open the aziridine in a S_N2 pathway (**482**) to afford a predominately *anti*-configuration (**478**). In conditions **B**, with Ph_3N, an effective deprotonation could not occur, and thus the reaction was proposed to proceed via a S_N1 pathway (**483**), to achieve the opposite diastereoselectivity (**479**). Starting from (*E*)-alkenes, products with alkyl (**478a**, **479a**), halo (**478b**, **479b**), and heterocyclic (**478c**, **479c**) functionalities were produced. Use of alkyl-substituted alkenes gave lower diastereoselectivity for the transformation, under both conditions (**478d**, **479d**). Non-oxazolidine cores were investigated, namely urea derivatives (**478e**, **478f**) and an amide example (**479e**, **478g**). The methodology was demonstrated on a gram scale, and it was noted that amino alcohols were accessed by hydrolysis of the products.

In 2017, Knowles and co-workers reported an intermolecular hydroamination via aminium radicals, modified from their previously described intramolecular hydroamination procedure (cf. Scheme 96). The hydroamination of unactivated alkenes with amines (**484**) was described (Scheme 102).[377]

Oxidation of amine (**485**) with photoredox catalysis generates aminium radical (**360**), which undergoes intermolecular addition to an alkene to afford the carbon radical **486**. The

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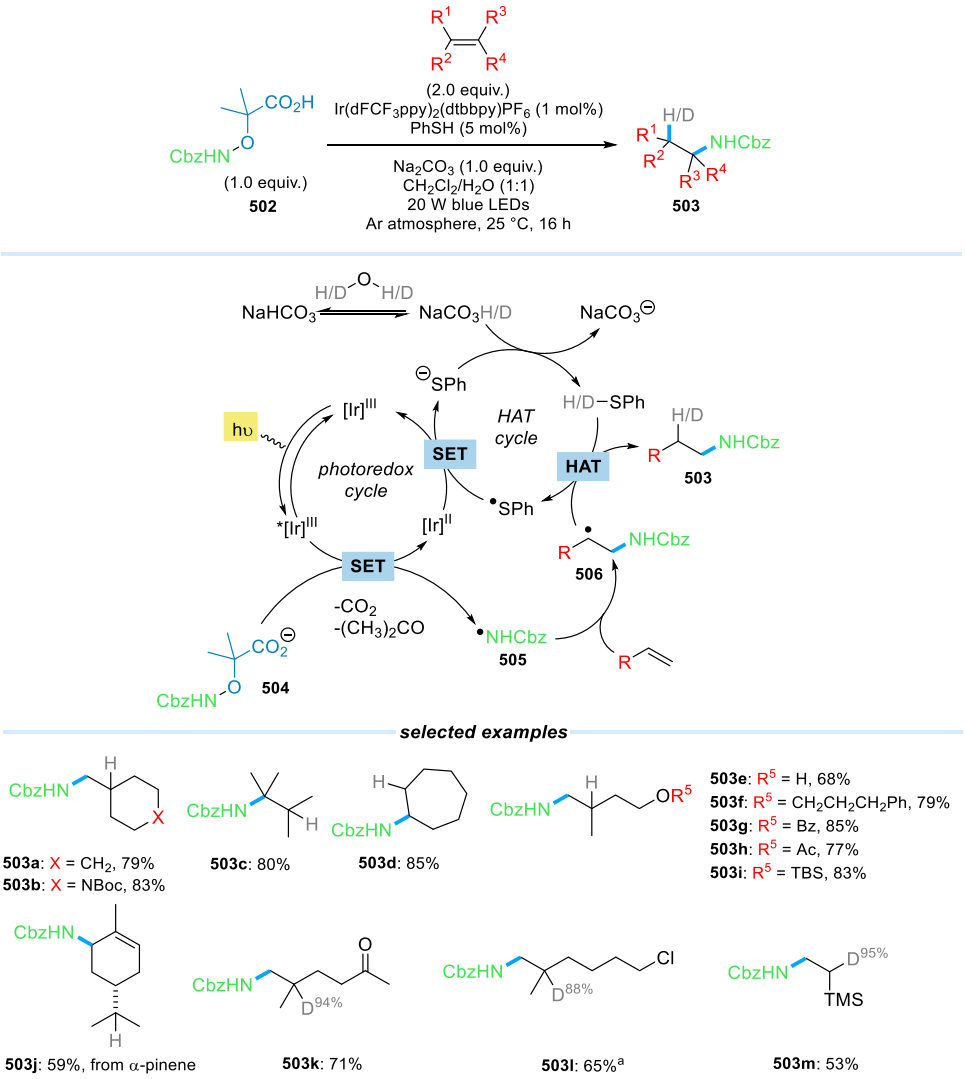
Scheme 106. Hydroamidation/Deuteroamidation of Unactivated Alkenes with Amidyl Radicals



[a]K_3PO_4 (1.0 equiv) was used instead of Na_2CO_3. R groups on the alkene in the mechanism are omitted for clarity.

TRIP thiol (**487**) acts a H-atom donor, delivering the protonated product **488** and a thiyl radical **489**. The $[Ir]^{II}$ reduces the thiyl radical (**489**) to the thiolate anion (**490**), completing the photoredox cycle. The final step is a proton transfer which produces the desired product **484** and re-forms the thiol HAT catalyst (**487**). Amination of 1,2-disubstituted aliphatic olefin (**484a**) and cyclic heterocycles dihydrofuran (**484b**) and pyrroline (**484c**) was accomplished. Use of silyl enol ethers as substrates gave the products **484d** and **484e** in excellent yields. The natural product linalool was selectively aminated, and **484f** was obtained in 96% yield. Cyclic and acyclic amines sometimes gave excellent yields of the desired products (**484g**−**484l**). This methodology is complementary to Nicewicz's work, which is focused on the oxidation of the olefin followed by addition of the amine.[378,379] The authors stated that the protocol did not tolerate aromatic amines, α-amino acid derivatives or tetramethylpiperidine. Furthermore, it was noted that primary amines were not yet amenable to this hydroamination methodology.

In 2017, Studer and co-workers introduced a new methodology to access functionalized pyrrolines via iminyl radicals (Scheme 103).[380]

Oxidation of the precursor **491** leads to a fragmentation cascade, releasing CO_2 and acetaldehyde, which produces the iminyl radical **492**. Cyclization can occur to an internal olefin acceptor, generating a transient carbon radical. The radical is quenched by the addition to an external olefin to give functionalized pyrroline derivatives (**493**). A broad range of α-iminyl-oxy acid derivatives and olefin acceptors were established (**493a**−**493m**).

In 2018, the Xiao group adapted their previous methodology,[369] using *N*-sulfonyl-*O*-butenyl hydroxylamines (**494**) for the construction of isoxazolidines (**495**) (Scheme 104).[381] Photocatalytic generation of the sulfonamidyl radical (**496**) prompted 5-*exo*-trig cyclization, which exclusively gave the *cis*-product.

The proposed mechanism is analogous to that in Scheme 97, with the participation of chloroform as a H-atom donor. The cyclization proceeded in good yield regardless of the electronic influences of the substituents (**495a**−**495e**). Other R^1 groups were examined and achieved good yields, including thiophene (**495f**) and aliphatic (**495g**) groups. Furthermore, diversification of the sulfonamide moiety did not affect the transformation (**495h**−**495k**). Radical trapping of the C-centered radical was

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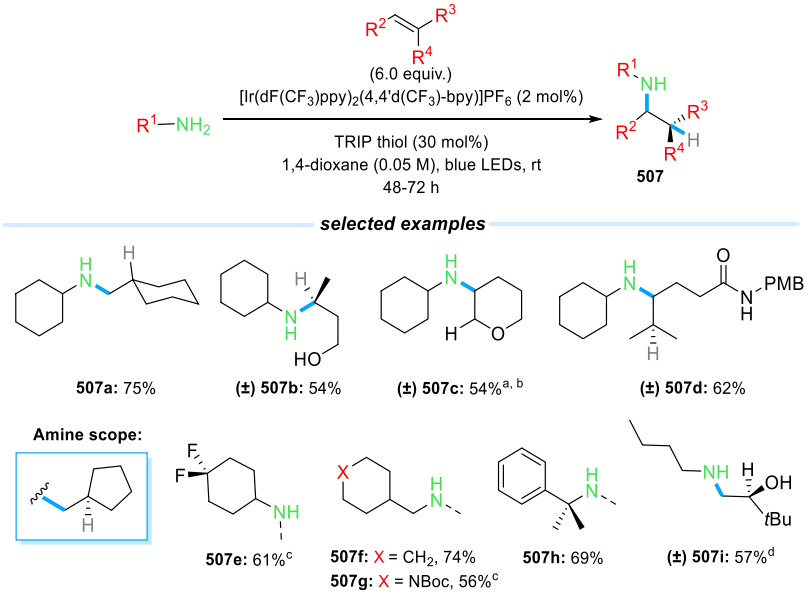
Scheme 107. Knowles's Adaptation to Intermolecular Hydroamination to Accommodate Primary Alkyl Amines



[a]3 equiv of olefin was used with 0.2 M dioxane. [b]An additional 18% of the Markovnikov addition product was also formed. [c]Amines were used as their corresponding HCl salts with 1 equiv of LiOH. [d]Substrate is the corresponding trimethylsilyl enol ether.

successful (**495l**), and use of $CDCl_3$:$CHCl_3$ (1:1) as the solvent resulted in a 6:1 ratio of **495a**:**495a′** (29%). To exemplify the synthetic potential of the reaction, **495a** was subjected to reductive conditions, using Zn to obtain the 1,3-amino alcohol derivative (**497**) in excellent yield. In the control experiments, no formation of the desired product (**495a**) was observed in the absence of visible light irradiation with LEDs. However, it was reported that synthesis of the isoxazolidine (**495a**) was achievable using sunlight as a light source; however only one example was tested (65%).

In 2018, Studer developed an intermolecular amidofluorination procedure (Scheme 105).[382] The mechanism proceeded in a similar fashion to the one shown in Scheme 103; excitation of the photocatalyst leads to the single-electron oxidation of the carboxylate (**498**). A fragmentation cascade releases CO_2 and acetone to generate the NCR (**499**). Addition to the alkene followed by F-atom transfer from Selectfluor furnished the desired amidofluorination product (**500**). Troc-protected amino-oxy acids were found to be the best precursor for the amidofluorination, although other common protecting groups were trialed (e.g., Cbz, Boc). The methodology focused on the use of organic photocatalyst (Mes-Acr$^+$, **PC9**); however, it was noted that the use of transition metal photocatalysts also delivered the desired product in good yield.

Both unfunctionalized aliphatic alkenes and functionalized alkenes afforded the desired amidofluorination products (**500a**−**500i**) in good yields. Interestingly, trisubstituted and tetrasubstituted alkenes yielded 2,3-difluoro products (**500j**) when the number of equivalents of Selectfluor was increased. An initial electrophilic fluorination of the alkene was proposed, which would result in the formation of the allylic fluoride intermediate (**501**). Subsequent amidofluorination of the migrated alkene moiety furnished the observed product **500j**. The radical nature of the transformation was supported by the formation of product **500k**, which would result from a classical 5-*exo* cyclization.

Studer's methodology was extended to the hydro- and deuteroamidation of electron-rich and unactivated alkenes, published in 2019 (Scheme 106). Utilization of a thiophenol catalyst with NCR precursor (**502**) facilitated a polarity-matched process to afford the desired hydroamidated/deuteroamidated products (**503**).[383]

Oxidative electron transfer from the carboxylate (**504**), followed by the loss of CO_2 and acetone, generates the electrophilic amidyl radical **505**. Addition to an unactivated alkene results in a nucleophilic C-centered radical (**506**). The thiophenol acts as a H-atom donor and is polarity-matched with the C-centered radical, furnishing the hydroamidated/deuteroamidated product (**503a**−**503m**). The addition of water is crucial as it acts as the formal H-atom donor, which arises due to facile proton exchange with the source of base.

In 2019, the Knowles group demonstrated that primary amines could be used for the amination of olefins (cf. Scheme 102) when used in conjunction with a more oxidizing $[Ir]^{III}$ photocatalyst (Scheme 107).[384]

The mechanism of transformation is analogous to the previously described strategy for secondary amines (Scheme 102). The use of a more oxidizing photocatalyst resulted in the ability to generate a more reactive primary aminium radical for intermolecular olefin addition. It was noted that monoamination was favored over the possible diamination pathways. Cyclohexylamine successfully aminated symmetrical (**507a**) and unsymmetrical (**507b**) aliphatic olefin partners. Interestingly, 3,4-dihydropyran yielded a 3:1 mixture of regioisomer products (**507c**). The authors proposed that Brønsted acid catalysis was in competition with the radical pathway, which occurred due to the low pK_a value of the aminium radical cation. Preparation of secondary amine **507d** was achieved in good yield, displaying the tolerance toward amide and protecting group (PMB) functionality. No further cyclization with the PMB group was observed for **507d**; therefore, PCET activation of the amide was unlikely, under these reaction conditions.[47,357] Other aliphatic primary amines were reported (**507e**−**507g**), tolerating halide and protecting group (Boc) functionalities. Notably, the cumyl group on **507h** was readily deprotected with TFA, demonstrating a complementary method to reveal a primary amine. Silyl

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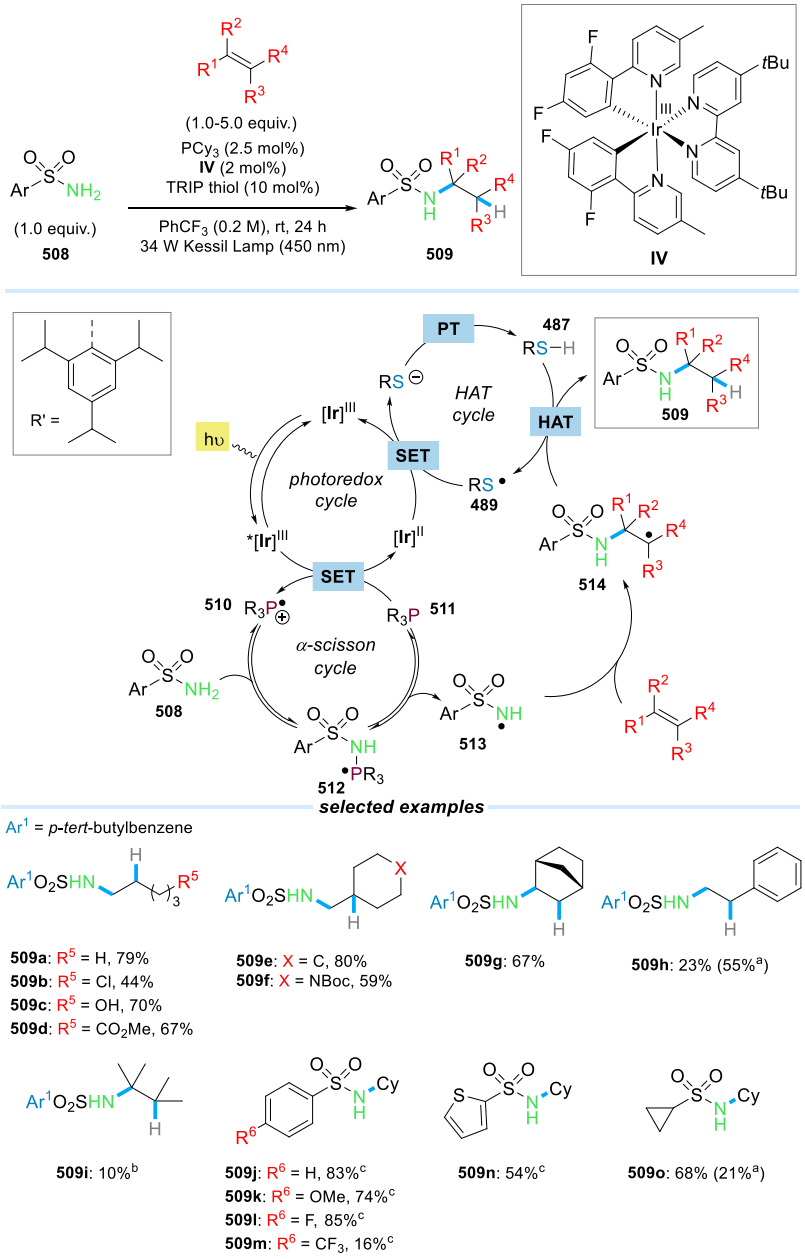
Scheme 108. Hydrosulfonamidation of Olefins with Primary Sulfonamides



1.0 equiv of olefin used, unless stated otherwise. [a]Calculated ^{1}H NMR yield compared to an internal standard. [b]3.0 equiv of olefin. [c]5.0 equiv of olefin used. dF(Me)ppy = 2-(2,4-difluorophenyl)-5-methylpyridine.

enol ethers were also compatible with the transformation, affording **507i** in good yield. More recently, the Knowles group published a perspective article on the reactivities of aminium radicals, reporting instances from 2012 to present.[385]

In 2021, the Doyle group exploited the α-scission of phosphoranyl radicals to achieve hydrosulfonamidation via sulfonamidyl radicals (Scheme 108).[386]

A thorough mechanistic investigation was pursued by the team, who explored PCET and P(V) pathways, as well as dwelling on the other possible quenching pathways of the phosphoranyl radical cation (**510**). In summary, the high pK_a and oxidation potential of sulfonamides precluded a direct deprotonation/oxidation pathway. Stern–Volmer quenching experiments revealed that quenching of the excited-state photocatalyst was driven by the presence of the trialkylphosphine only; thus, it was deemed inconsistent with a PCET mechanism. Possible phosphine(V) intermediates were synthesized and exposed to standard reaction conditions, which did not give rise to the desired products. With these observations in mind, the group proposed the following mechanism, involving three catalytic cycles. Starting with the photoredox cycle, the $[Ir]^{III}$ catalyst is excited to $*[Ir]^{III}$, which is then quenched by the trialkylphosphine (**511**) to give the phosphoranyl radical cation (**510**). Reversible addition of the sulfonamide (**508**) to the radical cation can give rise to radical **512**, then subsequent α-scission occurs to form the sulfonamidyl radical **513** and regenerates the trialkylphosphine (**511**). Addition to an alkene produces the C-centered radical (**514**), which can participate in a H-atom abstraction from the TRIP thiol (**487**), furnishing the desired product (**509**) and thiyl radical (**489**). SET to **489** is

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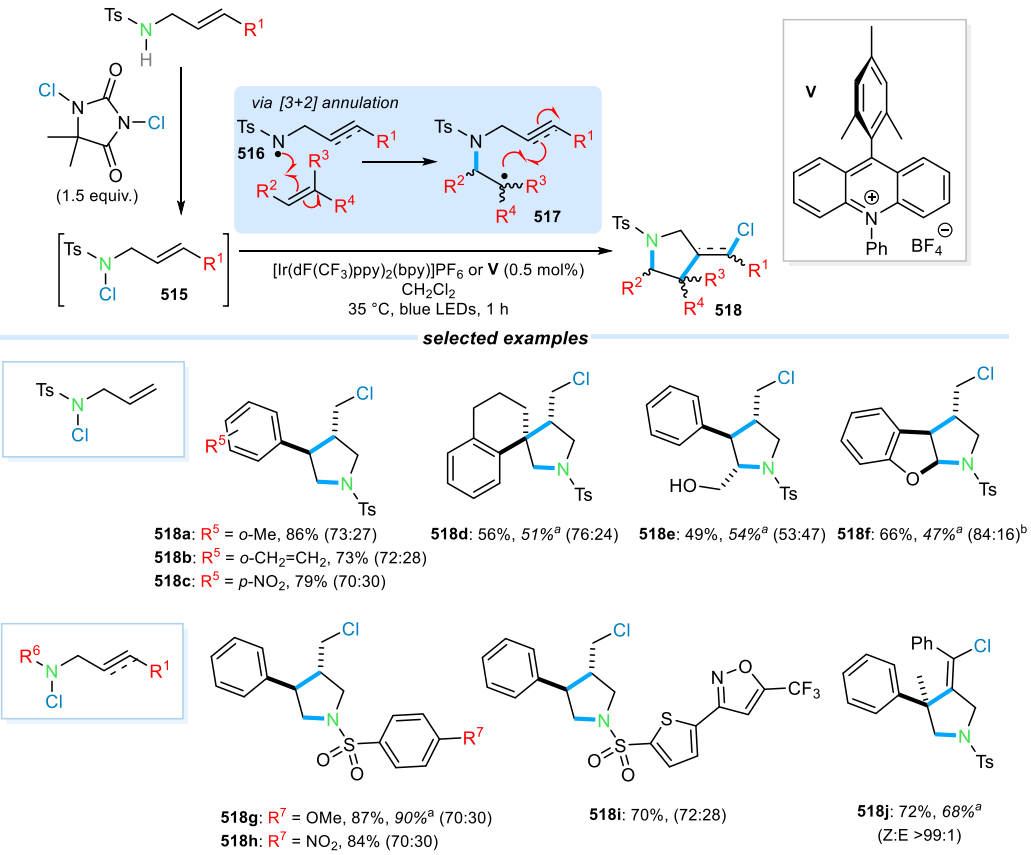
Scheme 109. Annulation of *N*-Allylamine Derivatives and Alkenes/Alkynes to Form Functionalized Pyrrolidines



Iridium catalyst used, unless stated otherwise. [a]Photocatalyst V used in 0.5 mol%. [b]Intermediate **515** isolated before photolysis was employed.

followed by a proton transfer to regenerate the TRIP thiol (**487**), completing both the photoredox and HAT cycles. The first examples show a range of olefin partners which gave the hydrosulfonamidated products, including acyclic (**509a−509d**), *exo*-cyclic (**509e**, **509f**), and *endo*-cyclic (**509g**) examples, in good yields, whereas the methodology gave only modest yields with styrene (**509h**) and sterically hindered examples (e.g., **509i**). Further elaboration of the scope of sulfonamides was also demonstrated with cyclohexene as the olefin partner (**509j−509o**).

6.5. Photosensitization

Photosensitization has been widely used as an approach to the activation of organic molecules. Although photoredox catalysis is a form of photosensitization, the two methods differ in their mechanisms of action; photosensitizers actively absorb light and transfer energy to other molecules, as opposed to photoredox catalysis, which involves the transfer of electrons.[387] IUPAC describes photosensitization as follows:[388]

> *The process by which a photochemical or photophysical alteration occurs in one molecular entity as a result of initial absorption of radiation by another molecular entity called a photosensitiser. In mechanistic photochemistry the term is limited to cases in which the photosensitiser is not consumed in the reaction.*

This approach exploits photosensitizers' ability to absorb light where organic molecules cannot.

The synthesis of functionalized pyrrolidines via a visible-light-mediated annulation of NCRs and olefins was demonstrated by the Ley group in 2017 (Scheme 109).[389]

The *N*-halo precursor **515** was generated *in situ* before being subjected to photolysis to generate the NCR **516**. Energy transfer from the photocatalyst of choice results in direct homolysis of the N−Cl bond. Subsequent intermolecular addition to an olefin occurs, generating a C-centered radical which intramolecularly adds to the *N*-allylamine double bond (**517**). A chain reaction is initiated, abstracting a chlorine atom from **515** to produce the pyrrolidine derivatives **518**. A range of intermolecular styrene derivatives were sulfonamidated (**518a−518e**) and isolated, as well as the product arising from benzofuran (**518f**). Variation of the N-substituent with other aromatic and heteroaromatic sulfonamides gave the corresponding pyrrolidines (**518g−518i**) in excellent yields with moderate selectivity. A series of alkynes was tested which gave excellent selectivity for the *Z*-alkene products (**518j**).

Exploitation of the persistent radical effect for effective intermolecular imination of olefins was demonstrated by Glorius and co-workers.[390] The Glorius group previously reported an energy transfer-enabled decarboxylative functionalization reaction which utilized reagent **519** as a source of aryl radicals. Subsequent trapping of the carbon radical with an electrophilic reagent gave the functionalized products **520** (Scheme 110).[391] To address the atom economy of the reaction, it was proposed that **521** may be used as a bifunctional reagent for the intermolecular difunctionalization of olefins (Scheme 110).

Upon energy transfer to **521** from a photosensitizer, a decarboxylative mechanism occurs to give the iminyl radical (**522**) and a carbon radical (**523**). Radical **523** reacts at the terminal end of the olefin to give an alkyl radical. Termination can then occur by coupling between the iminyl radical and alkyl

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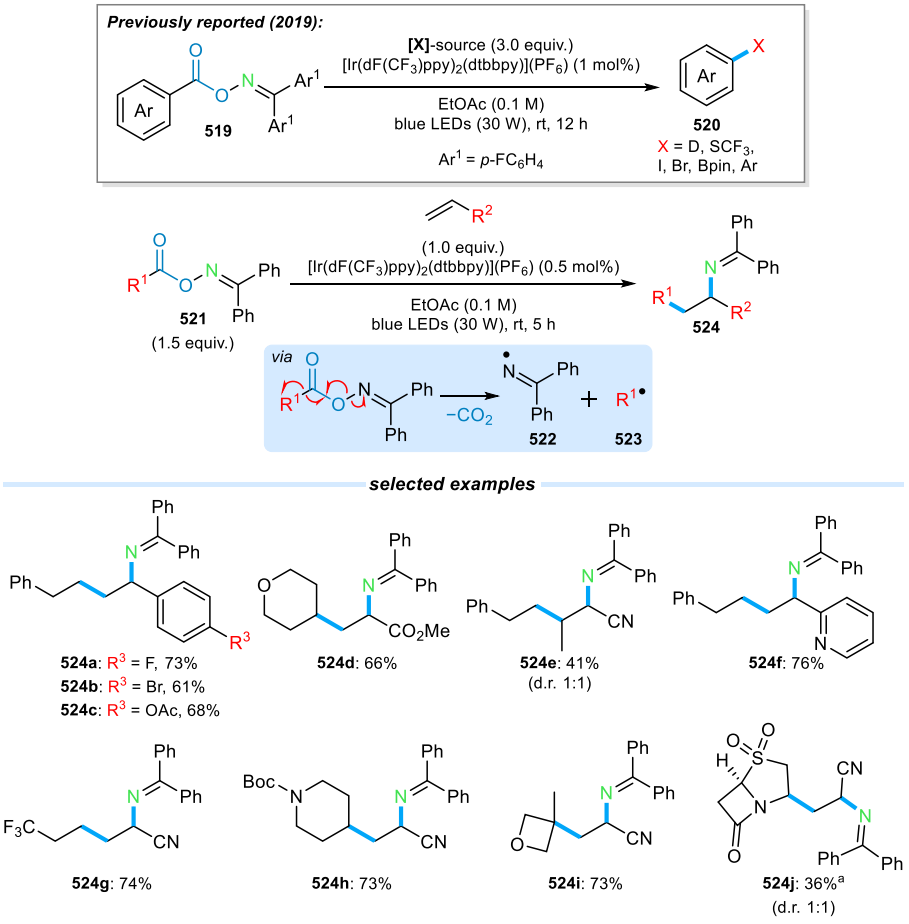
Scheme 110. Persistent Radical Effect of the Bifunctional Reagent 519 for the Difunctionalization of Olefins



[a]With 1.0 equiv of oxime ester.

radical to furnish the carboimination product (**524**). It was proposed by the group that the benzophenone-like structure of the iminyl radical allows a persistent radical effect, enabling a switch in the inherent reactivity. Thus, a selective radical−radical cross-coupling would be kinetically feasible. The persistent radical effect states that a transient and persistent radical can undergo selective radical−radical coupling, in competition with alternative pathways. It was established that SET pathways were not in play due to the high reduction potential of the benzophenone oxime species (E^{red}_{irr} = −2.05 V). This phenomenon was also observed in a previously reported publication, although instead, the iminyl radical (**522**) underwent H-atom abstraction or dimerization.[391] Imination of a range of olefin acceptors delivered the desired functionalized styrene (**524a−524c**), ester (**524d**), nitrile (**524e**), and 2-vinylpyridine (**524f**) derivatives in good yields. Primary (**524g**), secondary (**524d**, **524h**), and tertiary (**524i**) alkyl products were obtained from the corresponding carboxylic acid precursors. The methodology was applied to a plethora of natural products and drug molecules, e.g., **524j**, which achieved imination in moderate yields and a 1:1 d.r., where appropriate. Synthetic diversifications of the carboimination products were demonstrated; under acid hydrolysis or reductive conditions, a free amine was revealed.

In 2021, the Glorius group demonstrated the metal-free intermolecular oxyimination of alkenes through energy-transfer catalysis (Scheme 111).[392] Oxime carbonates (**525**) were used as precursors to O-centered radicals and NCRs in the synthesis of 1,2-oxyimination derivatives (**526**).

A variety of different NCR precursors were examined, although it was found N−O homolysis with the ester derivative **525** was the best solution to the competing decarboxylation. Thioxanthone was selected as the best photocatalyst for triplet−triplet energy-transfer-induced fragmentation to the corresponding radicals (**527** and **522**). Addition of the O-centered radical to the alkene occurred first, followed by combination of the resultant C-centered radical and **522**. Styrene derivatives led to the desired oxyimination products (**526a−526d**, **526f**) as did a pyridine derivative (**526e**). Furthermore, the methodology was amenable to the formation of quaternary centers (**526g−526i**). Investigation into different precursors proved fruitful, and iterations of the carbonate group were established (**526j**). The methodology was successfully demonstrated on a 7 mmol scale (**526k**, 71%). Acid hydrolysis of the imine (**526k**) to the ammonium chloride salt (**528**) followed by a basic hydrolysis of the carbonate to the free alcohol (**529**) gave an excellent yield. The methodologies recently published by the Glorius group offer rapid construction of difunctionalized alkenes utilizing the relatively undeveloped energy-transfer catalysis. A review was recently published by the Glorius group, detailing the synthetic utility of energy-transfer catalysis and recent applications.[393]

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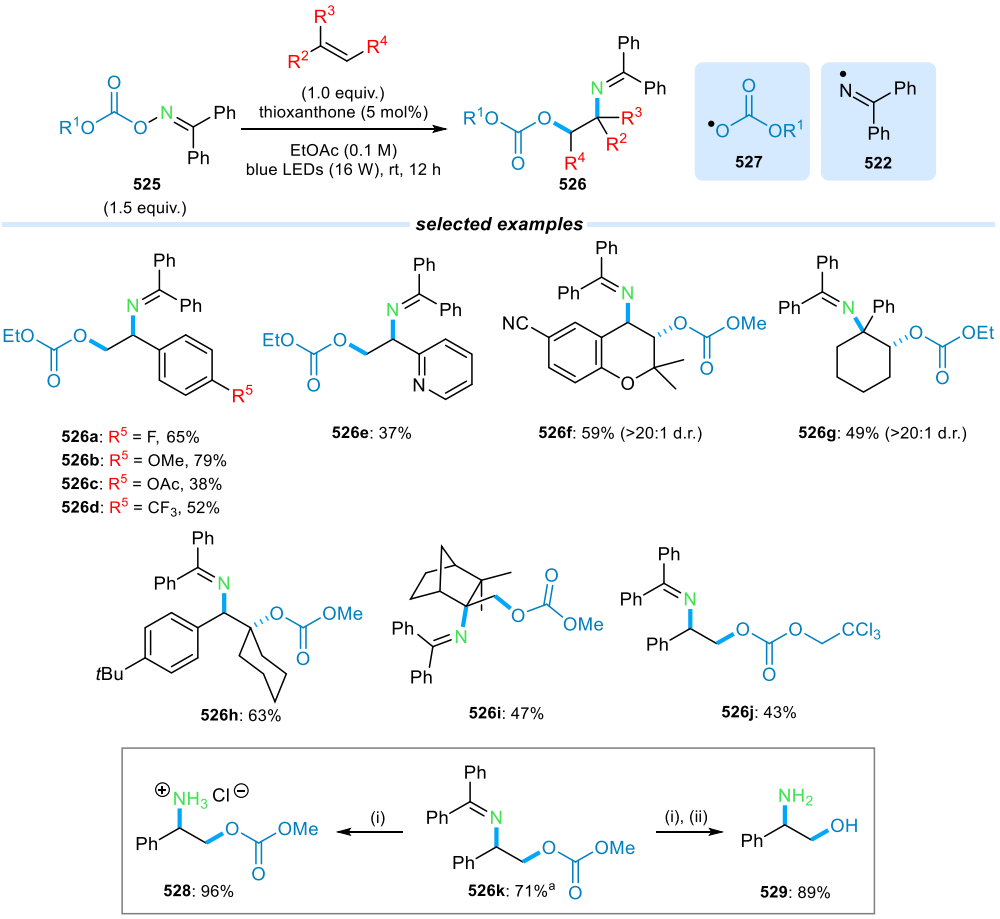
Scheme 111. Triplet−Triplet Energy Transfer for the Intermolecular Oxyimination of Alkenes with O-Centered Radicals and N-Centered Radicals[a]



[a]Reaction conditions: (i) 2 M HCl, Et_2O, (ii) 2 M KOH:MeOH (2:1), 80 °C. Reaction for **526k** was carried out on a 7 mmol scale.

7. CONCLUSION AND FUTURE PROSPECTS

Nitrogen-centered radicals have been useful intermediates in organic chemistry since their discovery. Photoredox chemistry has enhanced our understanding of NCRs, allowing milder methods for their generation and deployment. Developments in that field continue, and it is likely that they may provide a focus for wider industry-based applications of NCRs. A strong emphasis is now being placed on defining parameters (e.g., wavelength, intensity) that improve the efficiency and reproducibility of reactions.[394−397] Meanwhile, also in the area of photoredox chemistry, will the rapidly developing area of photoelectrochemistry[398−402] afford advances in the efficient generation of NCRs?

Selectivity of reactions of NCRs is a likely area of expansion. Although most NCRs themselves are planar, we have highlighted the few initial cases where complexation with chiral entities, metal-based or organic, leads to stereoselective reactions. Enantioselective and catalytic approaches by the groups of MacMillan,[312] Knowles,[359] and Liu[271] may guide and inspire further examples. Will these initial examples lead to a proliferation of fruitful studies?

This Review has cited a number of examples of C−H functionalization of arenes, and sustainable methods of C−H functionalization will likely be a growth area, particularly if further examples with excellent regioselectivity[328] can be developed. Likewise, N−H activation by proton-coupled electron transfer is still in its early stages of development and provides excellent opportunities for future growth. We hope that this Review will encourage research in this exciting area of chemistry.

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Notes

The authors declare no competing financial interest.

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Biographies

Cassie Pratley completed her integrated M.Chem. degree at the University of Bath in 2019, which included an industrial placement year at GSK, Stevenage. She subsequently undertook her final year project under the supervision of Dr. Simon Lewis, working on the synthesis of anti-austerity analogues for pancreatic cancer. In October 2019 she joined the GSK/University of Strathclyde Collaborative Ph.D. Programme, where she is currently situated in the Chemical Development Department investigating radical-mediated C−H amination methodologies under the supervision of Dr. Sabine Fenner and Prof. John Murphy.

Sabine Fenner was born in 1984 in Germany. She earned a Ph.D. in organic chemistry from the Georg-August-Universität Göttingen in 2012 in the field of transition-metal-catalyzed C−H bond functionalization under the supervision of Prof. Lutz Ackermann. She then spent two years as a DAAD postdoctoral fellow at the University of Cambridge UK in the group of Prof. Steven V. Ley, working on total syntheses of natural products. In 2014, Sabine joined the Chemical Development Department of GlaxoSmithKline in Stevenage, UK. She since has been supporting and leading projects for active pharmaceutical ingredients ranging from early to mid phase. Sabine's interests are environmental sustainability within the pharmaceutical industry, automation, and high-throughput experimentation as well as applying new manufacturing technologies.

John A. Murphy was educated at the University of Dublin (TCD) and the University of Cambridge. After Fellowships at Alberta and Oxford, he was appointed as Lecturer, then Reader, at the University of Nottingham. Since 1995, he has held the Merck−Pauson Professorship at the University of Strathclyde. His interests are in reactivity, reaction mechanisms, and synthesis.

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ABBREVIATIONS

4-CzIPN = 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
Å = angstrom
A = acceptor
Ac = acetyl
acac = acetylacetonate
ACHN = 1,1′-azobis(cyanocyclohexane)
AIBN = azobisisobutyronitrile
Alloc = allyloxycarbonyl
API = active pharmaceutical ingredient
Ar = aryl
BDE = bond dissociation energy
BHAS = base promoted homolytic aromatic substitution
BHT = 2,6-di-*tert*-butyl-4-methylphenol
Bn = benzyl
Boc = *tert*-butyloxycarbonyl
bpy = 2,2′-bipyridine
bpz = 2,2′-bipyrazine
Bs = benzenesulfonyl
Bu = butyl
Bz = benzoyl
C = Celsius
Cbz = carboxybenzyl
CFL = compact fluorescent lamp
CHD = 1,4-cyclohexadiene
D = donor
d.r. = diastereomeric ratio
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE = 1,2-dichloroethane
DDQ = 2,3-dichloro-5,6-dicyano-*para*-benzoquinone
dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine
dF(Me)ppy = 2-(2,4-difluorophenyl)-5-methylpyridine
dFppy = 2-(2,4-difluorophenyl)pyridine
DFT = density functional theory
DMAc = dimethylacetamide
DMF = *N*,*N*-dimethylmethanamide
dmg = dimethylglyoxime
DMN = 1,5-dimethoxynaphthalene
DMPO = 5,5-dimethyl-1-pyrroline *N*-oxide
DMSO = dimethyl sulfoxide
dtbbpy = 4,4-di-*tert*-butyl-2,2′-bipyridine
DTBP = di-*tert*-butyl peroxide
EDA = electron donor−acceptor
EDG = electron-donating group
ee = enantiomeric excess
eh = 2-ethylhexanoate
EPR = electron paramagnetic resonance
equiv = equivalent
Et = ethyl
EWG = electron-withdrawing group
Fmoc = fluorenylmethoxycarbonyl
h = hour
HAS = homolytic aromatic substitution
HAT = hydrogen atom transfer
HFIP = hexafluoroisopropanol
HLF = Hofmann-Löffler-Freytag
HOMO = highest occupied molecular orbital
HPLC = high-performance liquid chromatography
IBB = 1-butoxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one
IBX = *ortho*-iodoxybenzoic acid
In = initiator
LED = light-emitting diode
LUMO = lowest unoccupied molecular orbital
m-CPBA = *meta*-chloroperoxybenzoic acid
Me = methyl
m = *meta*
Mes-Acr^+ = 9-mesityl-10-methylacridinium
min = minute
Moc = methoxycarbonyl
MS = molecular sieves
MTBE = methyl *tert*-butyl ether
NBS = *N*-bromosuccinimide
NBSA = *N*-bromosaccharin
NCR = nitrogen-centered radical
NCS = *N*-chlorosuccinimide
NCSA = *N*-chlorosaccharin
NHPI = *N*-hydroxyphthalimide
NMR = nuclear magnetic resonance
NSP = *N*-succinimidyl perester
ODNs = dinitrophenylsulfonyloxy
o = *ortho*
p = *para*
PC = photocatalyst

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PCET = proton coupled electron transfer
PG = protecting group
Ph = phenyl
PhthN = phthalimide
PIDA = phenyliodine(III) diacetate
pin = pinacolato
PMB = *para*-methoxybenzyl
PMP = *para*-methoxyphenyl
ppy = 2-phenylpyridine
PTOC = *N*-hydroxypyridine-2-thione carbamate
rt = room temperature
S = substrate
SET = single-electron transfer
SOMO = singly occupied molecular orbital
t = *tert*
TBAF = tetra-*n*-butylammonium fluoride
TBS = *tert*-butyldimethylsilyl
TEDA = *N*-(chloromethyl)triethylenediamine
TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
Tf = trifluoromethanesulfonyl
TFA = trifluoroacetic acid
TFE = trifluoroethanol
THF = tetrahydrofuran
TIPS = triisopropylsilyl
TMCDA = *trans-N,N,N′,N′*-tetramethylcyclohexamediamine
TMS = trimethylsilyl
TMSI = trimethylsilyl iodide
TRIP = 2,4,6-triisopropyl thiophenol
Troc = 2,2,2-trichloroethoxycarbonyl
Ts = *para*-toluenesulfonyl
TTOC = thioxothiazolyloxycarbonyl
UV = ultraviolet
W = watts

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