Review

1,2-Radical Shifts in Photoinduced Synthetic Organic Transformations: A Guide to the Reactivity of Useful Radical Synthons

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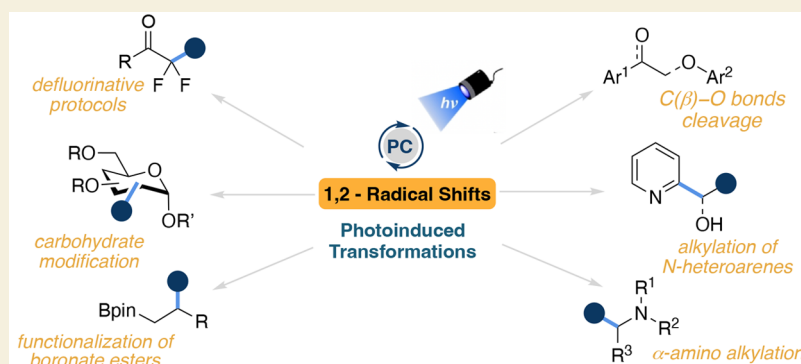
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ABSTRACT: The exploration of 1,2-radical shift (RS) mechanisms in photoinduced organic reactions has provided efficient routes for the generation of important radical synthons in many chemical transformations. In this Review, the basic concepts involved in the traditional 1,2-spin-center shift (SCS) mechanisms in recently reported studies are discussed. In addition, other useful 1,2-RSs are addressed, such as those proceeding through 1,2-group migrations in carbohydrate chemistry, via 1,2-boron shifts, and by the generation of α-amino radicals. The discussion begins with a general overview of the basic aspects of 1,2-RS mechanisms, followed by a demonstration of their applicability in photoinduced transformations. The sections that follow are organized according to the mechanisms operating in combination with the 1,2-radical migration event. This contribution is not a comprehensive review but rather aims to provide an understanding of the topic, focused on the more recent advances in the field, and establishes a definition for the nomenclature that has been used to describe such mechanisms.

KEYWORDS: spin-center shift, 1,2-radical migration, photoredox catalysis, visible light, C−F bond activation, 1,2-boron shifts, 1,2-radical shifts in oxidative processes, DNA encoded library synthesis

INTRODUCTION

The generation of open-shell radical intermediates employing photoinduced transformations is now considered a well-established and formidable synthetic tool for the construction of complex molecules in an economical and straightforward manner.[1−5] A vast amount of chemical space has been accessed under this mode of activation, which often makes use of photocatalysts (PCs) that are capable of absorbing and converting light irradiation into potential energy for the preparation of important substrates. The outstanding synthetic potential of radical intermediates generated under these protocols evidence how important the continuous development of new strategies is to achieve new advancements in this area.

Catalytic pathways in the photoredox field have been well-studied,[6] and now, the chemistry community has a clear understanding of how the activation modes take place via reductive, oxidative, and redox-neutral protocols.[7−9] To this end, the reported electrochemical characteristics of the principal photocatalysts as well as the development of new absorbing species have had a major role in this research field.[10−14] Additionally, the creativity in the design of new protocols has led to a combination of reactivities by exploring
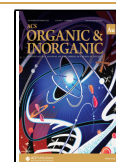
the use of dual-catalyzed routes and additives that result in a sequence of events comprising multiple modes of activation.

In this regard, many reaction pathways have been reported proceeding through 1,2-radical shifts (named in this Review as 1,2-RSs for the broadest definition), where the translocation of the spin center between vicinal atoms in a molecule takes place during the reaction. The most discussed event involving this kind of migration is the spin-center shift (SCS), a term that was first used in biochemical processes, where this concept plays a key role.[15] The most preeminent examples proceeding via SCS are related to the biosynthesis of deoxyribonucleosides and degenerative processes, such as those involved in pathogenic DNA damage. Therefore, it is a natural event taking place in many important biological redox processes.

Strictly by the mechanistic definition, an SCS event takes place in radical-based reactions where the elimination of a leaving group (mostly a hydroxy, alkoxy, or halogen group) tethered at the radical center occurs (Scheme 1a). In biological

Scheme 1. (a) Mechanism of Classical SCS Processes; (b) DNA Biosynthesis;[a] (c) Abbreviated Mechanism for 1,2-RS without Leaving Groups; (d) 1,2-Acyloxy Rearrangement via Boat Conformation in the Modification of Carbohydrates
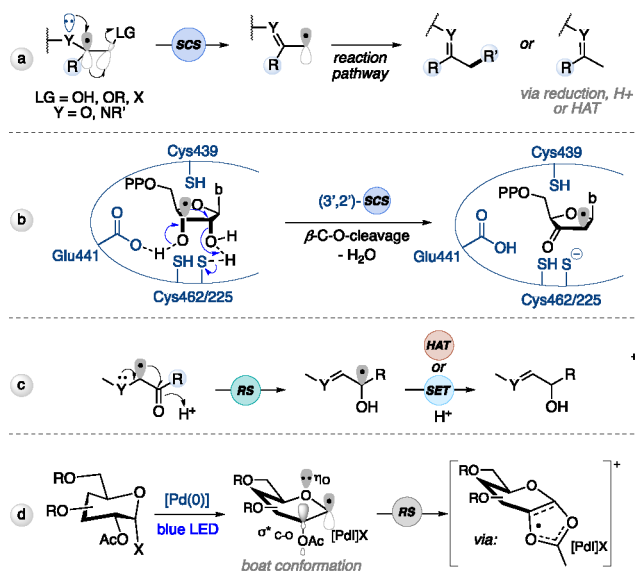
[a]SCS as a key step in the deoxygenation of ribonucleoside diphosphates (NDPs).

systems, the enzyme ribonucleotide reductase (RNR) is responsible for the deoxygenation of ribonucleoside diphosphates (dNDPs), the monomer precursor of DNA (Scheme 1b). It can be difficult to obtain direct mechanistic evidence for this step. However, many studies have demonstrated the generation of reactive intermediates via electron spin resonance (ESR) spectroscopy or radiolysis.[16] Radical clock experiments[17] have supported the SCS mechanism as the most likely pathway in synthetic transformations.

Recently, this concept has been extensively used in a range of photocatalytic transformations, and the narrow definition of the process has lost its initial meaning given the broad diversity of new reactions being reported. In 2015, Jin and MacMillan disclosed a bioinspired strategy built on the SCS concept and reported the first use of alcohols as alkylating agents for C−H

functionalization of *N*-heteroarenes.[18] This seminal work opened up new possibilities and drew attention to this particular type of radical migration.

The diffusion of the SCS concept in the field of photoredox 1,2-radical shift (RS) has led to ample use of this term. However, many reactions involving 1,2-radical delocalizations do not necessarily have a leaving group that is eliminated. In these cases, the carbon-centered radical generated from this process is further reduced and protonated or participates in a hydrogen atom transfer (HAT) event to furnish the desired product (Scheme 1c). Another mechanism that is out of the scope of the classical definition of SCS proceeds via 1,2-radical group migration, such as with an acyloxy or pyruvate migrating group. These radical-based transformations are commonly found in carbohydrate functionalization. In this regard, the exploration of the hybrid reactivity of the excited state of palladium catalysts to access one- and two-electron species has leveraged a series of functionalized carbohydrate scaffolds, which is particularly interesting given the possibilities of enhanced bioactivity of these glycomimetics. This approach has allowed the preparation of C-2-functionalized 2-deoxy sugars from commercially available substrates. Mechanistically, density functional theory (DFT) calculations have shown that conformational changes in the carbohydrate structure favor a concerted 1,2-acyloxy rearrangement mechanism via a five-membered-ring transition structure. These studies indicate that 1-glucosyl radicals adopt a preboat conformation that weakens the C-2 leaving group bond to facilitate the radical migration event to take place through an anomeric interaction between the lone-pair electrons of the endocyclic oxygen, the singly occupied molecular orbital (SOMO), and the σ* orbital of the C-2 leaving group. In these cases, the 1-glucosyl radicals can be generated via halide-atom abstraction from the α-glucosyl halides or using a hydrogen atom transfer mediator in the presence of cocatalysts, activating the leaving group in the glucosyl structure (Scheme 1d).[19]

It is worthwhile to recognize other 1,2-radical delocalizations that have been valuable in the photoredox catalysis field. Recently, 1,2-boron shifts of β-borylated radicals from 1,2-bis-boronic acids were disclosed under photoinduced protocols, leading to the formation of thermodynamically favored secondary radicals, which have been successfully explored for monofunctionalization via Giese addition and arylation reactions.

Another useful synthetic approach, which is very well established, includes the functionalization of the $C_\alpha(sp^3)$−H bonds to nitrogen atoms. This method has been adopted as a synthetic strategy that allows the direct preparation of derivatives containing the aminomethyl group and opens possibilities for chemical space diversification by introducing structural complexity. Mechanistically, through the single-electron oxidation of neutral amines, the C−H bond adjacent to the nitrogen atom is weakened to approximately 42 kcal/mol, and deprotonation can easily take place, leading to the generation of the corresponding α-aminomethyl radical.[20] Regarding this process, specific studies have demonstrated the mechanistic pathways by which the amine substrates are susceptible to form the radical cations and further provide the C−H functionalized compounds.[21−24] The application of these valuable radical synthons was well covered in previous reviews based on this topic,[25,26] and herein, more recent advances highlighting the importance of this specific type of 1,2-radical migration are covered.

This Review is not meant to be comprehensive but rather aims to provide general guidance for the design of photo-induced protocols proceeding via 1,2-RS mechanisms based on recent advances to generate useful radical synthons. This contribution complements a recently published review in the field[27] and brings to bear other useful paradigms for 1,2-RSs. Important works for C−F bond activations using $CO_2^{\bullet-}$ as a potent single-electron reductant via a combination of single-electron transfer (SET) and hydrogen-atom transfer (HAT) mechanisms are discussed. We then focus on the light-mediated modification of bioactive substrates involving both SCS/1,2-RS processes, followed by the recent reports designed for the generation of β-borylated radicals from 1,2-bis-boronic acids. These reactive radical species have been explored under classical photoredox transformations, via EDA complex formation, as well as dual Ni/photoredox-catalyzed protocols. We also address umpolung addition reactions of carbonyls to N-heteroarenes, and a summary of recent methods involving the oxidation of amines and α-silylamines is disclosed. Finally, applications of these methods to DNA Encoded Library (DEL) synthesis are discussed.

## ■ C−F BOND ACTIVATION VIA SCS AND HAT MECHANISMS USING $CO_2^{\bullet-}$

Research in C−F bond activation and subsequent functionalization to prepare organofluorine compounds is an important endeavor in organic chemistry because of the enhanced pharmacokinetic (PK) properties of such molecules, their hydrogen bonding abilities, and their enzymatic stability.[28−31] The reactivity of C−F bonds associated with consecutive defluorinations makes the selective functionalization of a single C−F bond in perfluoroalkyl groups a challenge. In this context, considerable attention has been devoted to the development of new strategies to cleave the C−F bond.[32−35] Visible light-mediated photoredox catalysis has emerged as a powerful platform for direct C−F bond activation because of the unique redox properties of the photocatalysts. Thus, Jui and co-workers reported an interesting method to perform reductive radical formations effectively using the radical anion of carbon dioxide ($CO_2^{\bullet-}$) as a powerful reductant, easily obtained from formates and thiol catalysts.[36] The strategy was successfully demonstrated for intermolecular hydroarylation of (hetero)aryl halides with unactivated olefins.

Subsequently, the work of Wang and co-workers circumvented the challenge of chemoselective defluorinative functionalization of CF_3 groups by designing a thermal two-stage process with each stage involving an SCS to trigger a C−F bond scission, leading to di- and monofluoroalkyl radicals.[17] These reactive intermediates were engaged in a sequence of transformations in the presence of different radical traps. The protocol allowed the C−F functionalization of trifluoroaceta-mides and trifluoroacetates, extending the synthetic tools available for the application of fluoroalkyl radicals beyond that of aryl difluoromethyl radicals derived from CF_3-substituted arenes.[37−41]

Using this paradigm, Yu and co-workers developed a milder alternative by exploring the advantages of photoredox catalysis for the selective carboxylation of $C(sp^3)$−F bonds in mono-, di-, and trifluoroalkylarenes and α,α-difluorocarboxylic esters and -amides with CO_2 (Scheme 2).[42] First, the mixture of triethylsilane, Cs_2CO_3, and CO_2 generates cesium formate and cesium silanolate. Next, the silanolate species 3 undergoes an SET process with the excited organophotocatalyst 2,4,6-

Scheme 2. Selective Carboxylation of $C(sp^3)$−F Bonds with CO_2 via Visible Light Photoredox Catalysis
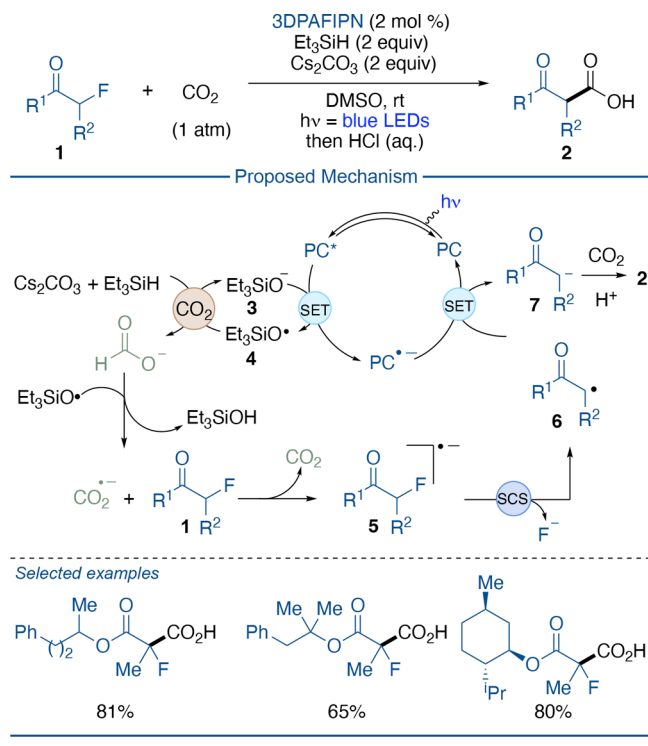
tris(diphenylamino)-5-fluoroisophthalonitrile (3DPAFIPN), generating the reduced $PC^{\bullet-}$ and a siloxy radical species 4. Subsequent HAT with the cesium formate generates the $CO_2^{\bullet-}$ radical anion ($E_v = -2.2$ V vs SCE), a strong reductant that can reduce the fluorinated substrates 1 to intermediate 5 through an SET process. A further defluorinative SCS, reduction of the corresponding difluoromethyl radical 6, and subsequent intermolecular nucleophilic attack of 7 on CO_2 provides the carboxylate products 2. Notably, these studies demonstrate the dual role of CO_2 as both an electron carrier and an electrophile. This protocol offered good functional group tolerance with a broad range of substrates. In addition to trifluoromethyl groups, a range of mono- and difluoroalkylar-enes also underwent selective C−F bond functionalization under mild and transition metal-free conditions.

In the same year, Molander and co-workers developed a robust photocatalytic protocol for the C−F bond activation of trifluoroacetates and -acetamides by taking advantage of the SCS strategy (Scheme 3).[43] This protocol merged the use of diaryl ketones as HAT catalysts and formate anion as a reducing agent to promote the efficient generation of the corresponding electrophilic difluoromethyl radicals. Mechanis-tically, the reaction proceeds through an HAT step between the excited triplet state of the diradical biaryl ketone (BP) and sodium formate, generating the $CO_2^{\bullet-}$ species. This strong reductant then accomplishes a single-electron reduction of the fluorinated carbonyl substrates 8 via single-electron transfer. Next, a defluorinative SCS of the generated intermediate 10 produces the corresponding α-defluoro carbonyl radical 11 that reacts with a range of alkenes in a Giese addition to provide the difluorinated derivatives 9 in moderate to excellent yields after HAT with cyclohexanethiol. Quantum yield experiments ($\phi = 4.9$) suggest that the reaction proceeds via a radical chain process. Furthermore, extensive experimental

Scheme 3. Photochemical Defluorinative Alkylation of Trifluoroacetates and -Acetamides

Scheme 4. Photoredox-Catalyzed Defluorinative Alkylation of Polyfluorinated Aliphatic Amides and Esters
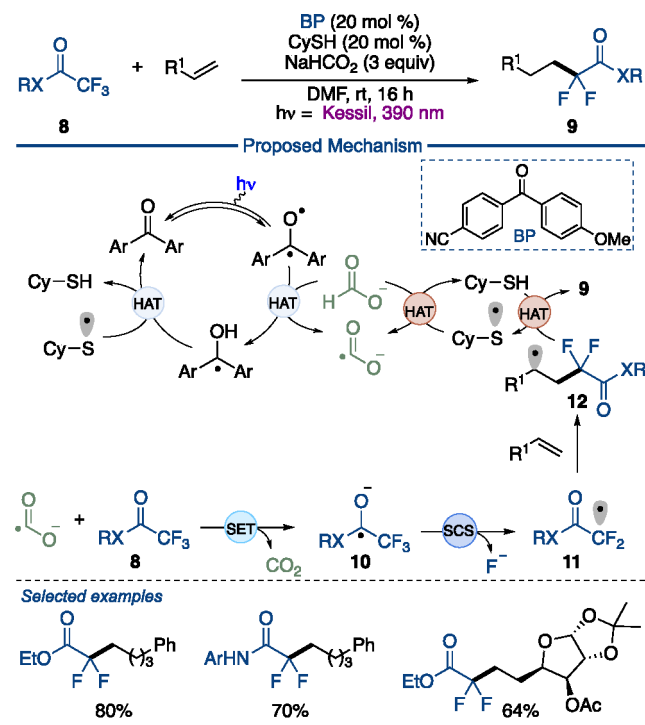
studies revealed that a catalytic loading of $Zn(OTf)_2$ lowered the reduction potential of the *N*-aryl trifluoroacetamides by 0.5 V, thus facilitating their reactivity. Moreover, ethyl difluoroacetate (E_v = −2.9 V vs SCE) and pentafluoropropionate (E_v = −2.6 V vs SCE) were also successfully engaged in defluorinative alkylation protocols and allowed access to the desired products with good to excellent yield. This protocol was demonstrated to be an operationally simple and efficient method with a demonstration of its applicability for multigram scale reactions as well. Nevertheless, electron-deficient alkenes and styrene derivatives were not suitable for this protocol.

In a similar vein, Glorius and co-workers demonstrated a photoredox-catalytic defluorinative alkylation of polyfluorinated carbonyl compounds (Scheme 4).[44] A mechanistic investigation of this transformation revealed that sodium formate is used as a reductant and base to enable the quenching of the organophotocatalyst 2,4,6-tris-(diphenylamino)-3,5-difluorobenzonitrile (3DPA2FBN). The excited photocatalyst 3DPA2FBN* is reductively quenched by the thiolate anion, generating a thiyl radical and the reduced 3DPA2FBN$^{\bullet-}$. Following similar mechanisms, the thiyl radical can produce the reductant $CO_2^{\bullet-}$ via an HAT process. Next, the polyfluorinated carbonyl compounds (esters and amides **8**) were reduced by both species (the reduced photocatalyst 3DPA2FBN$^{\bullet-}$ and the $CO_2^{\bullet-}$ radical anion), providing the carbon-centered radical intermediate **14**. Following the defluorinative SCS event and subsequent Giese addition of this radical species, diversely substituted alkenes afforded the corresponding fluorinated alkylated carbonyl products **13** under mild conditions. Notably, the utility of this method was extended to a catalytic hydrodefluorination to access CF_2H-containing compounds in an efficient manner. Interestingly, the method was also applied to an alkyne precursor as a coupling partner to obtain the defluoroalkenylation product in good yield, highlighting the potential utility of this protocol.
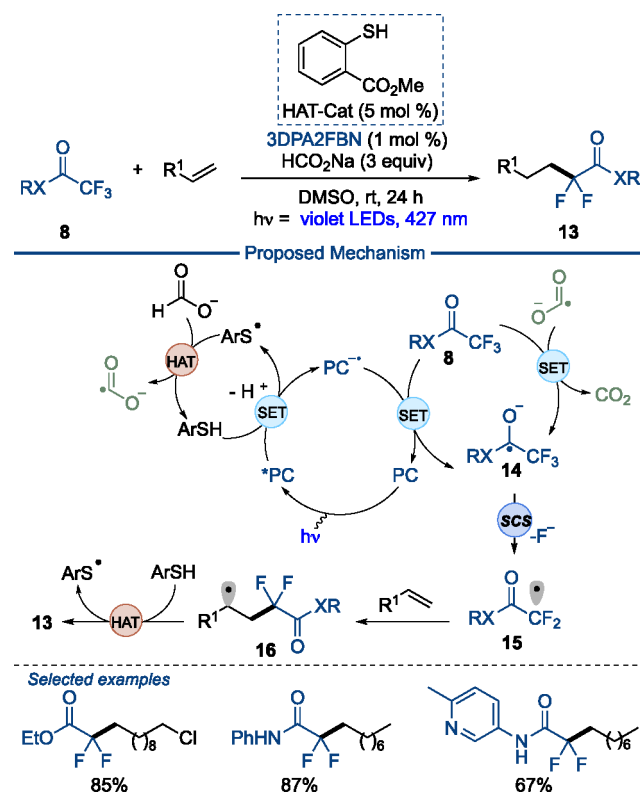
More recently, in an alternative photocatalytic protocol, Shang and co-workers described a metal-free defluoroalkylation of trifluoromethyl compounds using a readily available *O*-phosphinophenolate as the catalyst to activate the C−F bond of trifluoromethyl arenes, esters, and amides.[45] The photoexcited catalyst PO*$^{\bullet-}$ (E_v = −2.9 V vs SCE) reduces the trifluoromethyl substrates **8** to generate the difluoromethyl radical **19** via the SCS pathway, which further engages in the Giese addition in a similar manner to that previously described (Scheme 5). Alternatively, the difluoromethyl radical could be reduced with an alkylthiol HAT catalyst to afford the hydrodefluorinated products. Overall, the method shows a broad scope of trifluoroacetates and -amides for the selective C−F activation and was also applicable to the selective functionalization of the pentafluoroethyl groups. However, styrene- and acrylate-type substrates were unsuitable for this protocol because of the addition of $CO_2^{\bullet-}$ with alkenes under the reaction conditions.

The same group later highlighted the application of arenethiolates as dual-function catalysts for the photocatalytic defluoroalkylation and hydrodefluorination of trifluoromethyl compounds (Scheme 6).[46] The strong reducing power of the photoexcited thiolate (E_v = −3.31 V vs SCE) suggests that it can reduce a broad range of trifluoromethyl compounds **8** (including esters, amides, and arenes). In this case, the difluoromethyl radical **23** is produced by the oxidative quenching of the excited photocatalyst (ArS$^-$)* followed by the SCS step. The addition of the difluoro radical **23** to an alkene forms the alkyl radical **24**, which is reduced by the thiol through an HAT step to deliver the defluoroalkylation product **21**. The newly generated thiyl radical abstracts a hydrogen atom from the formate salt, leading to the $CO_2^{\bullet-}$ radical anion

## Scheme 5. Photocatalytic Defluoroalkylation of Trifluoromethyls Using Phosphinophenolate

Selected examples

85%   42%   85%
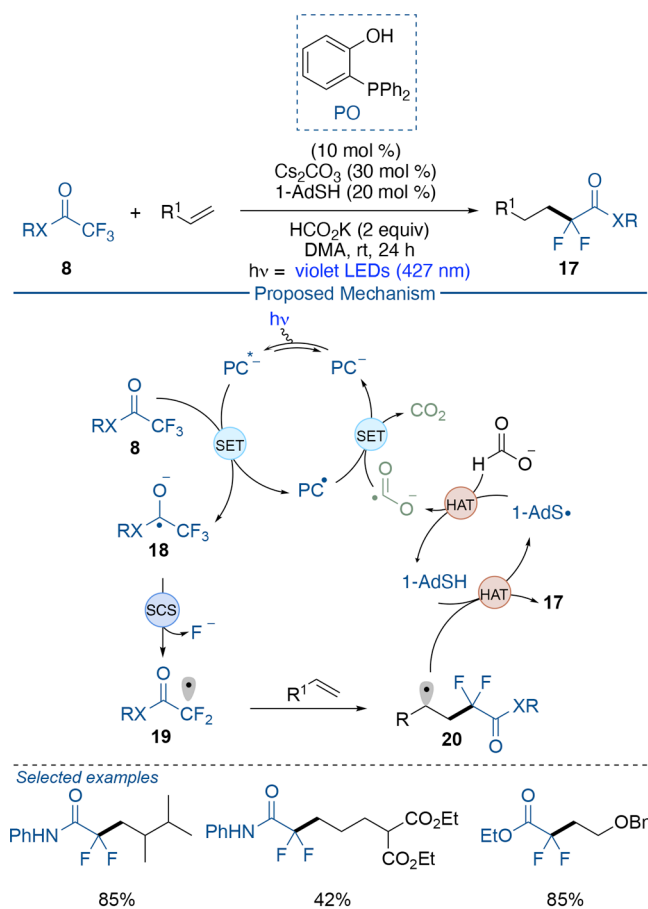
Scheme 6. Photocatalytic Defluoroalkylation of Trifluoromethyls Using Arenethiolate as a Dual-Function Catalyst

Selected examples

70%   84%   83%
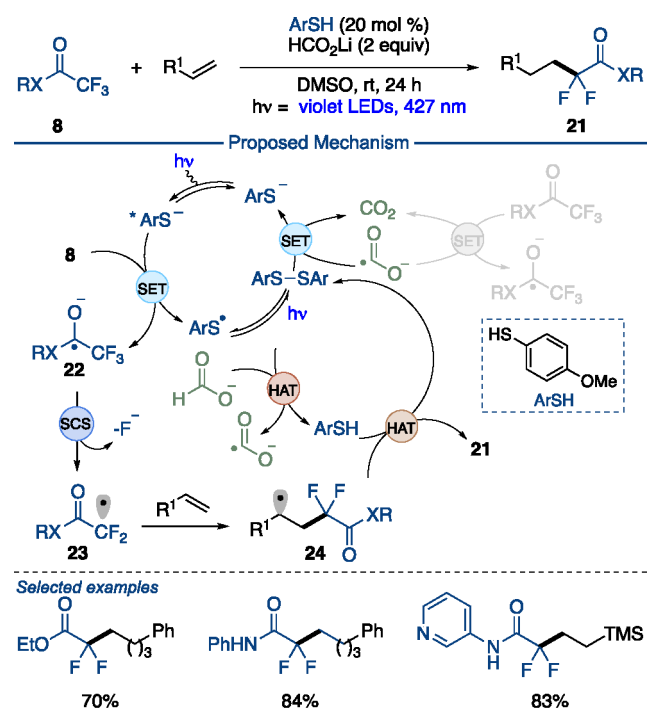
that can recycle the arenethiolate to complete the photoredox cycle. The quantum yield (Φ) of the reaction was determined to be 3.4, suggesting that a chain process was taking place to generate the difluoromethyl radical through the reduction of the trifluoromethylated substrates by $CO_2^{\bullet-}$. Notably, this method is applicable to selective monodefluorination in the absence of the alkene reagent to provide the desired hydrodefluorination products.

Zhu and co-workers contributed to the field by designing a protocol using $CO_2^{\bullet-}$ as a potent single-electron reductant of single $C(sp^3)-F$ bonds in trifluoromethylbenzimidazoles 25.[47] The transformation is mediated by a thiol-catalyzed SET reduction process and takes place under blue LED irradiation in the presence of *fac*-Ir(ppy)$_3$ as a photocatalyst. In this case, the radical intermediate 27 generated after the SET reduction step is stabilized by the aryl ring of the precursor substrate, leading to the subsequent SCS step to cleave the C−F bond and furnish the reactive radical species 29. This latter intermediate smoothly engaged in an addition reaction to a series of olefins, including electron-rich alkyl vinyl ethers and terminal and internal electron-neutral alkenes to give rise to the difluoroalkylated compounds 26 in a similar mechanism (Scheme 7) to that described in Scheme 4.

Scheme 7. Visible Light-Induced Reductive Defluoroalkylation of Trifluoromethylbenzimidazoles with Unactivated Alkenes

Selected examples

R^1 = Ph, 79%
2-F-C_6H_4, 66%
propargyl, 47%

67%   from *β*-pinene, 89%
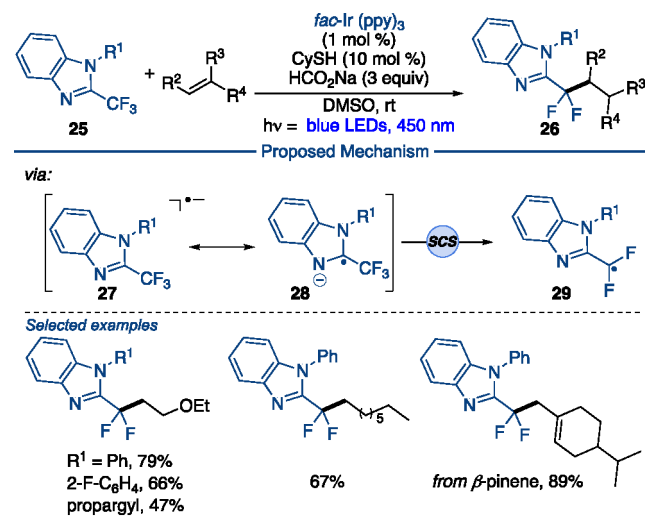
■ SCS AND 1,2-ACYLOXY/OPiv MIGRATION PROTOCOLS IN THE MODIFICATION OF BIOACTIVE SUBSTRATES

In 2019, the König group demonstrated a redox neutral fragmentation of diol derivatives such as lignin *β*-O-4 model compounds and diol monoesters via photoredox/HAT dual catalysis without the use of stoichiometric external reductants.[48]

The selective deoxygenation of this class of compounds had been previously demonstrated in a proof-of-principle approach reported by Stephenson and co-workers in 2014, where they designed a lignin degradation strategy in two steps comprising a selective [4-AcNH-TEMPO]BF$_4$-mediated oxidation followed by an Ir-mediated photoredox reductive C−O bond cleavage.[49] In König's work, the use of a photocatalyst

facilitates the selective β C(sp^3)−O bond cleavage to afford ketones, phenols, and acids effectively. Indeed, according to quenching experiments, the excited photocatalyst is reductively quenched in the presence of thiol and phosphate. Subsequently, the generated thiyl radical abstracts the α H atom of benzylic alcohol **30** to give a benzylic ketyl radical **33**, which is further oxidized to the corresponding ketone **34**. An SET reduction of ketone **34** by the reduced photocatalyst results in ketyl radical anion **35**. This intermediate is not stable, so the following β C(sp^3)−O bond cleavage takes place to form the carbonyl radical **36** and the anion of leaving group **37**, which are further converted to the final fragmentation products (Scheme 8). Despite a consistent scope, during this study, it

Scheme 8. Photoredox Selective β-C(sp^3)−O Cleavage for the Generation of Carbonyl Compounds and Phenols
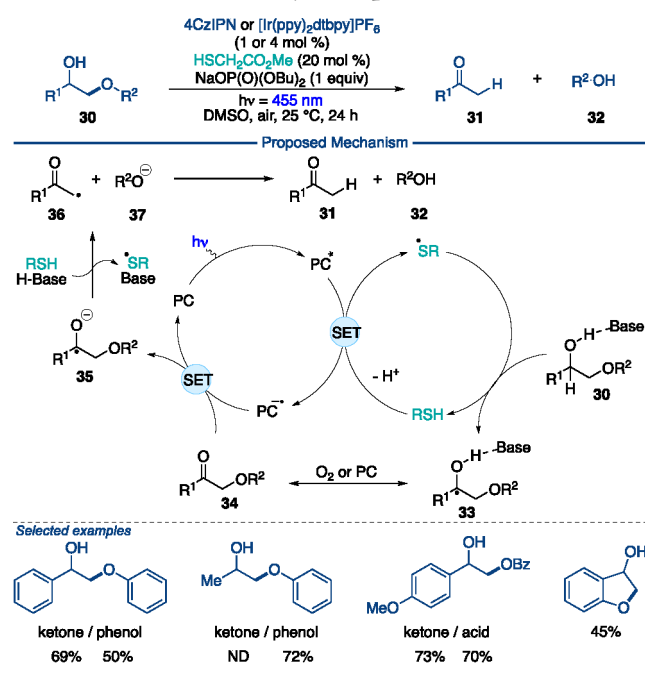
was noted that the electronic properties of both aromatic rings influence the reactivity of the substrates. Indeed, lower conversions of the starting material were observed in those instances where the aromatic ring, being part of the ketone product, was electron poor. The same trend was noted in cases where the other aromatic ring was more electron rich.

Relying on the key concept of the SCS process, Zhu and Nocera designed an elegant photocatalytic redox-neutral protocol for the selective cleavage of C(β)−O bonds in their model substrates and natural lignin extracts.[50] The reaction system was based on the PCET chemistry for the biosynthesis of deoxyribonucleotides, which proceeds via a sequence of events comprising HAT, SCS, and water elimination to give rise to the corresponding furanone at the C2-position after a final HAT to the α-hydroxyl radical located at the C3-position. A careful choice of the HAT catalyst indicated the use of the protected cystine **41** in combination with the photocatalyst [Ir-(ppy)$_2$(dtbpy)]PF$_6$ as the ideal dual-catalytic system for the generation of the bond cleavage products in nearly equimolar amounts. Contrary to the scope of the phenol moiety, the electronic effects on the ketone component predominated as expected because it is involved in the HAT step that initiates

the SCS event. Thus, electron-donating groups on the aryl ring of the ketone led to an enhanced reactivity in comparison to unsubstituted acetophenones and phenylpropanol derivatives (Scheme 9). The robustness of the protocol was next

Scheme 9. Photocatalytic Redox-Neutral Cleavage of C(β)−O Bonds in Lignin Substrates
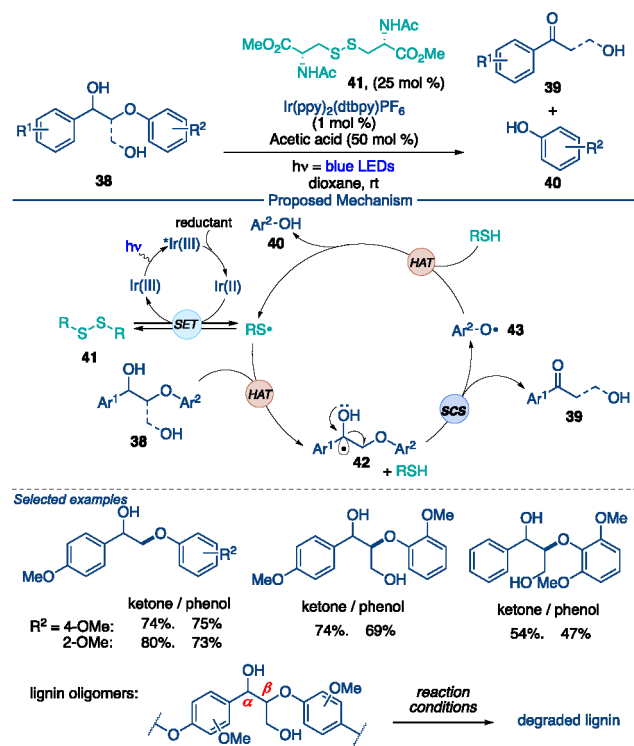
confirmed with natural lignin oligomers, and the fragmented products from the C(β)−O bond cleavage were confirmed by LC-MS analysis. A series of experiments supported the proposed reaction mechanism, which is initiated by SET from the reduced ground-state photocatalyst Ir(II) $[(E_{(Ir(III)/Ir(II))}) = -1.26$ V vs NHE] to the disulfide catalyst **41** $[(E_{(RSSR/RSSR\bullet-)}) = -1.38 \pm 0.05$ V vs NHE], leading to the formation of thiyl radicals and thiolate anion. The reduced Ir(II) is proposed to be generated via SET from the solvent (dioxane) to the excited-state *Ir(III). Next, the HAT event takes place between the thiyl radical (BDE$_{(S−H)}$ = 87 kcal/mol) and substrate **38** (BDE$_{C(\alpha)−H}$ = 85 kcal/mol in 1-phenylethanol), followed by the SCS step to give rise to the corresponding acetophenone **39** and phenoxyl radical **43**. A final HAT step between the cysteine S−H bond and phenoxyl radical **43** (BDE$_{(O−H)}$ = 90 kcal/mol) occurs to close the catalytic cycle by recycling the thiyl radical. A trapping experiment with TEMPO indicated that the formation of the phenoxyl radical **43** and acetophenone is more likely to occur than the generation of an acetophenone radical and a phenol molecule after the spin-center shift of the C(α)-radical **42**. Additionally, the reaction pathway proceeding through intermediate **43** is thermodynamically favored by 6 kcal/mol.

As previously discussed, the concept of SCS is broadly used in the context of biological transformations, especially when it comes to the conversion of ribonucleotides to deoxyribonucleotides. Building upon this, Taylor and co-workers designed a ternary catalytic system composed of an iridium photocatalyst, quinuclidine, and an organoboron catalyst. The latter

coordinates at the *cis*-1,2-diol group of the carbohydrate derivative **44**, leading to the activated species **47**, weakening the α-C−H bonds and accelerating the HAT process promoted by the quinuclidine radical cation through polarity-matching and/or ion-pairing effects (Scheme 10).[51] Addi-

Scheme 10. Boronic acid catalysis and photoredox/HAT catalysis enabling direct transformation of furanosides to 2-keto-3-deoxyfuranosides
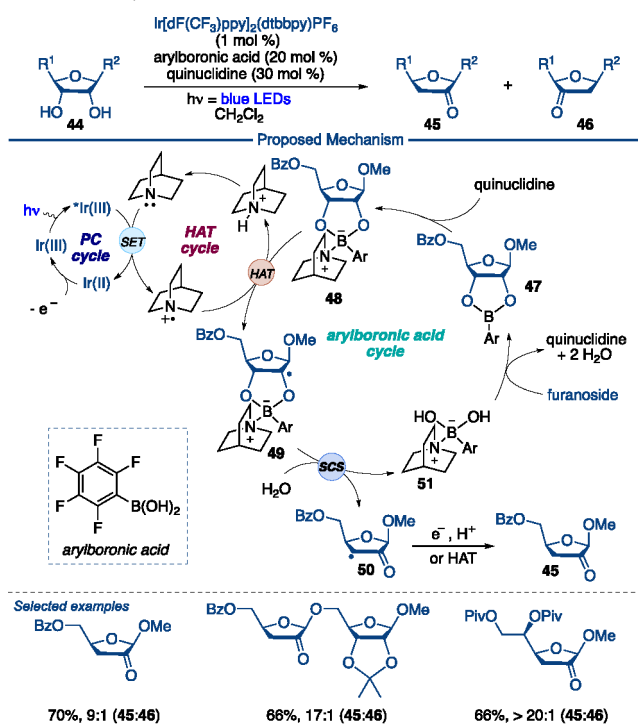

tionally, the organoboron catalyst facilitates the dehydration of the radical intermediate **49** by C−O bond cleavage. This approach offers a synthetic opportunity to access the corresponding 2-keto-3-deoxy derivatives **45** (major) selectively with the opposite regiochemistry observed for the enzyme-catalyzed processes. Both configuration and substitution patterns of the furanoside showed influences in the outcome of the redox isomerization reaction with the inductive effects of the C5-substituents playing a key role in the relative rates of hydrogen atom abstraction from C-3 versus C-2 positions.

Murakami and co-workers reported a protocol for the preparation of 2-deoxyaldonates from unprotected aldoses using benzophenone-3,3′-bis(sodiumsulfonate) as a photocatalyst (Scheme 11).[52] The deprotonated alkoxide **52** from aldose undergoes hydrogen atom transfer (HAT) by the benzophenone triplet-excited state. With the generated radicals, a proton transfer (PT) from the aldose radical anion to the ketyl radical **54** takes place. The aldose radical **55** then undergoes SCS, forming a lactone with a radical center located at C2 (**56**). Subsequently, the ketyl radical anion transfers a single electron to the lactone. A further protonation step followed by reaction with NaOH furnishes sodium 2-deoxy-aldonates **53**. Importantly, this transformation uses unprotected aldoses as substrates, a metal free photocatalyst, and aqueous media.

The selective modification of carbohydrate scaffolds is an attractive area of biological research to improve the efficiency

Scheme 11. Sodium 2-Deoxy-aldonate Preparation Reported by Murakami and Co-workers[52] Using Benzophenone Photocatalyst and UV Light
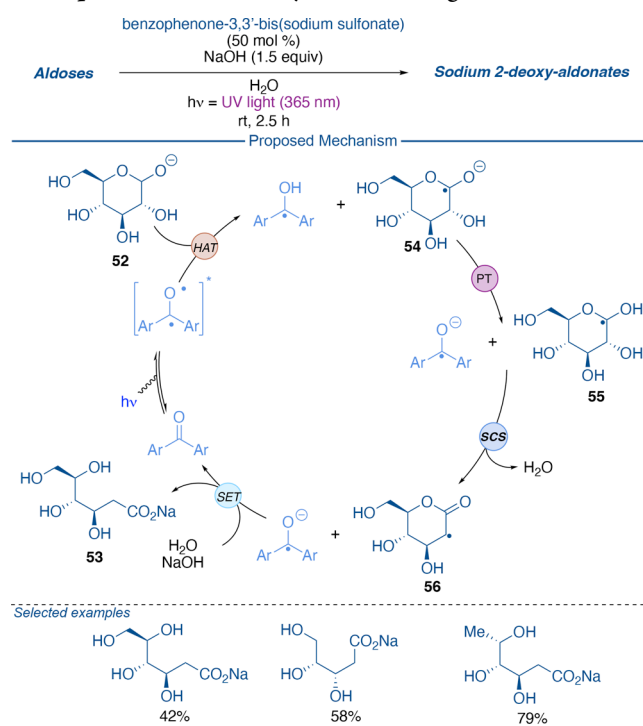
of carbohydrate-based drugs and the development of novel therapeutics. Therefore, new synthetic methods that bring essential structural changes into carbohydrate scaffolds are highly desirable. Photoredox transformations that involve 1,2-RS with acyloxy group migration to enable C2-modifications of carbohydrates are particularly prevalent in this regard.

A process that involves one or more excited catalytic species, known as excited-state catalysis, has emerged as a powerful tool in organic synthesis.[53] The Ngai group[53] utilized the excited state of a palladium catalyst for the selective C-2 reduction of carbohydrates (Scheme 12). Additionally, protocols for

Scheme 12. Excited-State Palladium-Catalyzed 1,2-RS Enabling Cross-Coupling Reactions
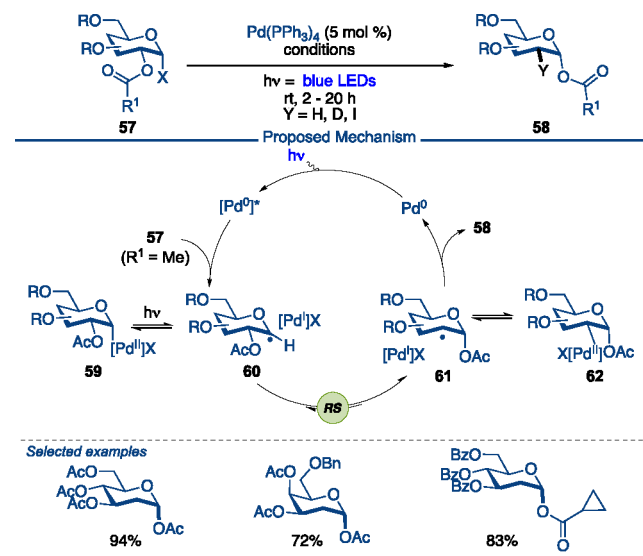
deuteration and iodination were also disclosed. Here, substrate **57** undergoes radical oxidative addition with excited state Pd⁰. The generation of the α-alkoxy-based radical **60** favors the $B_{2,5}$ boat conformation. Such an extended anomeric interaction weakens the C-2−OAc bond and promotes the 1,2-RS through a concerted [2,3]-acyloxy rearrangement, forming intermediate **61**. This intermediate is in equilibrium with the alkyl-Pd(II)X complex **62**, which can engage in substitution reactions that place H, D, or I within the carbohydrate substructure, depending on the conditions of the reaction. This protocol presents high levels of regio- and stereoselectivity, and a wide range of functional groups can be handled, including complex molecular architectures.

Recently, the same research group reported the preparation of C2-ketonyl-2-deoxysugars from 1-bromosugars and silyl enol ethers via an excited state palladium-catalyzed RS process (Scheme 13).[54] The photoexcited [Pd⁰]* abstracts the

**Scheme 13. C2-Ketonylation of Carbohydrates via Excited-State Palladium Catalysis**
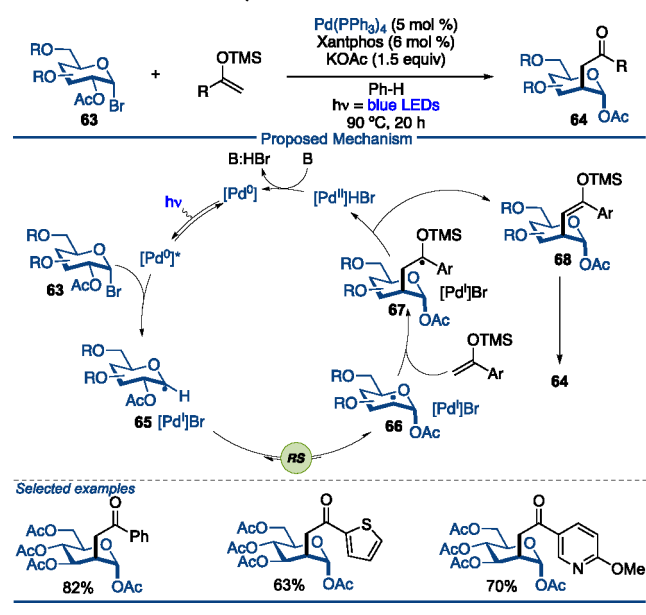
bromine atom from the corresponding 1-bromosugar **63**, generating a [Pd^I]Br complex and 1-glycosyl radical **65**. Subsequently, **65** undergoes 1,2-acyloxy migration through a conformational change, generating deoxypyranosan-2-yl radical **66**. This species adds to a silyl enol ether, furnishing intermediate **67**. Pd-catalyzed β-hydride elimination or palladoradical H-atom abstraction liberates H[Pd^{II}]Br and silyl enol ether **68**. The base-assisted HBr reductive elimination of H[Pd^{II}]Br regenerates the ground state [Pd⁰] catalyst. This transformation exhibits high atom economy and broad functional group tolerance. Importantly, this reaction is step economical and can be used for late-stage functionalization of natural product and drug glycoconjugates.

Continuing with their exploration of installing new functional groups at the C2-position of carbohydrates, the Ngai group in 2022 reported the C2-alkenylation of carbohydrates on the basis of their previously described excited-state palladium catalysis approach.[55] This Pd-catalyzed migratory Mizoroki−Heck reaction proceeds through a 1,2-RS pathway that enables a direct C2-alkenylation of carbohydrates from readily available 1-bromosugars and alkene derivatives. The

catalytic cycles involve bromine atom abstraction from bromo-sugar precursor **69** by the photoactivated *Pd(0) to deliver an alkyl radical **71** that rapidly undergoes a 1,2-RS event to generate C2-radical/Pd(I) intermediate **72**. Trapping of this radical with an activated alkene produces radical intermediate **73**, which recombines with Pd(I) followed by β-hydride elimination to furnish the desired alkenylated product **70** and H[Pd(II)]Br complex. Finally, a base-assisted HBr reductive elimination pathway is proposed to regenerate the active Pd(0) catalyst (Scheme 14). In addition to having a broad scope, the

Scheme 14. Excited-State Pd-Catalyzed C2-Alkenylation of Carbohydrates via the 1,2-Radical Migratory Mizoroki−Heck Reaction
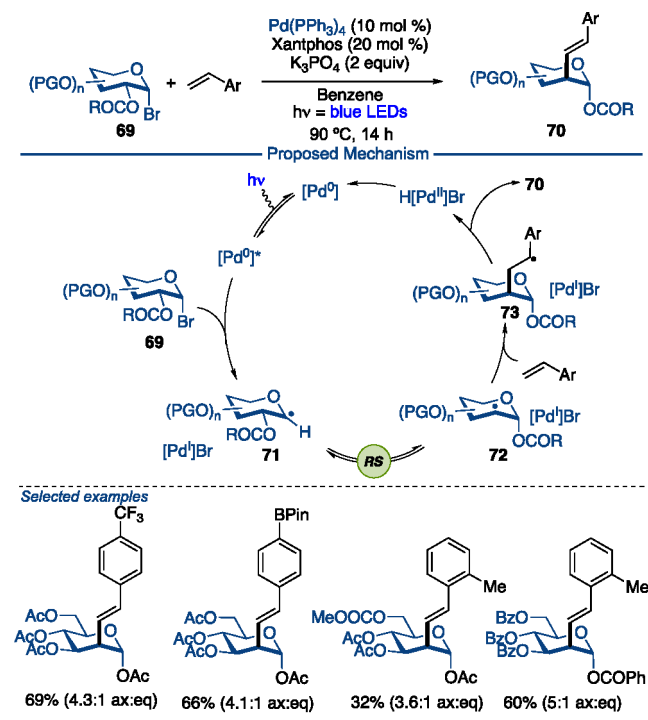

protocol considerably streamlines the synthesis of C2-alkenylated glycomimetics and is compatible with the late-stage functionalization of complex molecules and drug glycoconjugates.

With a slight diversion from their excited-state palladium catalysis approach, the Ngai group also explored the possibilities of merging nickel catalysis with radical acyloxy migration to carry out the cross-coupling of 1-bromosugars with arylboronic acid for the generation of 2-aryl-2-deoxyglyco-sides via thermal conditions.[56]

Later, Taylor and co-workers contributed to the field by reporting the preparation of ketodeoxysugars **75** from pyranoside-derived esters **74** via the combination of a photocatalyst, an HAT mediator, and a hydrogen bond acceptor as cocatalyst (Scheme 15).[57] After the HAT step, the acyl group migrates through a 1,2-dioxolane transition structure **77**, resulting in an O-acylated hemiacetal **78** that collapses to an α-keto radical **79**, which delivers the final product after reduction and protonation. Subsequently, substrate **74** restarts the catalytic cycle. On this occasion, the carbohydrate was activated with tetrabutylammonium 4-chlorobenzoate. The combination of this photoredox catalyst, an HAT mediator, and a hydrogen bond acceptor cocatalyst

Scheme 15. Synthesis of Ketodeoxysugars from Acylated Pyranosides via Photoredox/HAT Catalysis
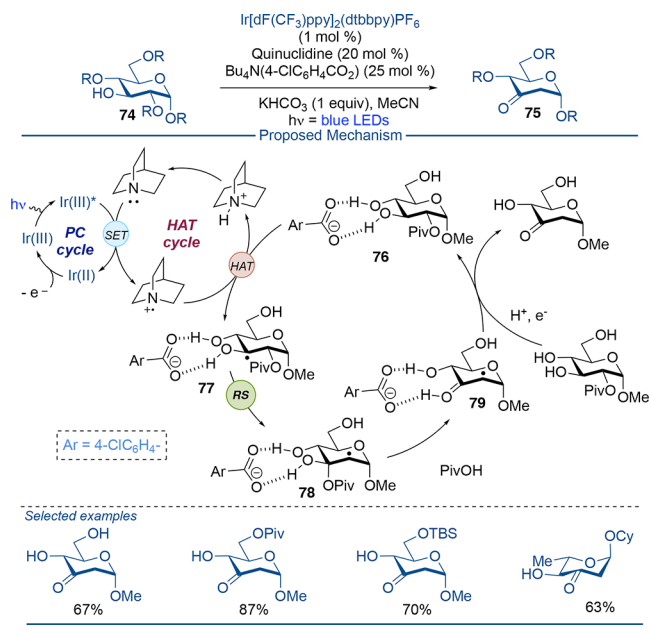
delivered interesting precursors of rare sugar components of bioactive secondary metabolites.

In 2021, Wendlandt and co-workers disclosed a dehydration protocol of monosaccharides that allowed the synthesis of deoxygenated sugars utilizing manganese(II) acetate as a catalyst under organophotoredox conditions (Scheme 16).[58] The mechanism of this reaction involves an initial formation of the sugar radical **82** via HAT mediated by the quinuclidinium radical cation followed by Mn(II)-promoted redox isomerization to afford the final deoxygenated sugars **81**. The authors propose two mechanistic scenarios for the selective dehydration step. On one hand, Mn(II) may promote radical

**Scheme 16. Redox Neutral Fragmentation of 1,2-Diol Derivatives Promoted by Visible Light**
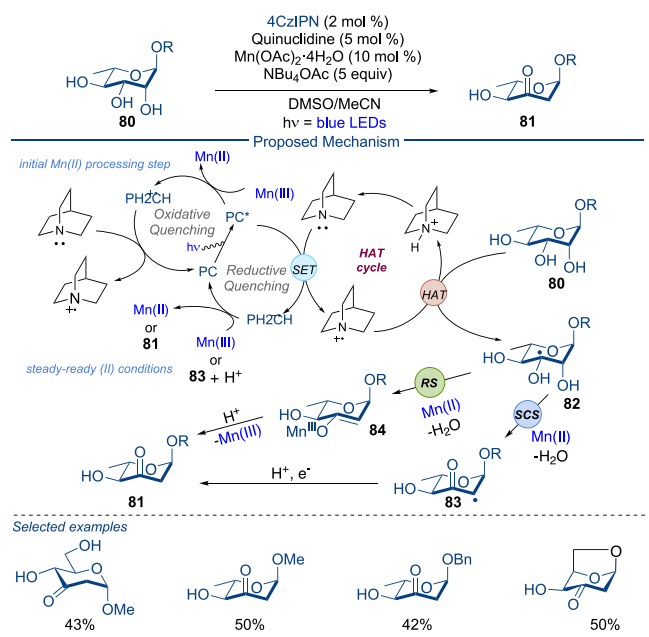
migration without an oxidation state change (**83**), followed by an outer-sphere reduction event of the radical by the reduced organophotocatalyst. On the other hand, Mn(II) may promote radical migration and inner-sphere reduction of **84** to afford **81** and Mn³⁺, which can undergo reduction by a radical anionic 4CzIPN species. A high selectivity toward the generation of products is observed without employing synthetic strategies on the basis of protecting groups. L-Rhamnose and D-α-methylmannoside as well as D-anhydrosugars were competent substrates for this transformation. Through this method, commercially available L-rhamnose served as a precursor for the synthesis of more exotic L-olivose or L-mycarose.

■ 1,2-BORON SHIFTS OF β-BORYLATED RADICALS GENERATED FROM BIS-BORONIC ESTERS

Many advances have been made in the field of photoredox chemistry using alkylboron compounds as radical precursors. Boronate esters and trifluoroborate salts can easily undergo SET oxidation to furnish useful nucleophilic alkyl radicals that can be further exploited in diverse transformations. 1,2-bis-Boronate esters are considered attractive from a synthetic point of view, because they offer two handles for functionalization and can be easily prepared from alkenes. Importantly, Aggarwal and co-workers[59] have demonstrated versatile applications of 1,2-bis-boronate esters as radical precursors under photocatalytic conditions. The β-borylated primary radical **86** generated from the photo SET oxidation step is prone to undergo a 1,2-boron shift to form thermodynamically favored secondary radical **87**. This strategy offers a pathway to functionalize the more hindered secondary position in the boronate ester in comparison to metal-catalyzed protocols, which favor functionalization at the primary positions of 1,2-bis-boronate esters given the feasibility of the boronate complex formation (Scheme 17, top).

After the same group generated a boronate complex with phenyllithium,[59] the Giese addition reaction was first reported by merging the protocol with the use of the organophotocatalyst 4CzIPN in the presence of activated olefins and *t*-BuOH in acetonitrile under blue LED irradiation (Scheme 17A).[60] The use of ortho-substituted aryllithiums was key for the single activation and addition to the 1,2-bis-boronate ester **85**. Regarding the scope of this new regioselective approach, α-secondary and α-tertiary as well as tertiary boronate esters were well tolerated. Other boron derivatives containing esters, nitriles, carbamates, and silyl ethers were successfully incorporated. Interestingly, a derivative from β-pinene provided evidence for the radical nature of the transformation, proceeding via cyclobutane ring-opening after the 1,2-boron shift step. The protocol included electron-deficient olefins and styrenes, while vinylpyridine only showed reactivity with more nucleophilic tertiary radicals. The scope also included the use of dehydroalanine with excellent diastereocontrol although in low yield. The selectivity of the method was successfully demonstrated when a 1,2,3-tris-boronate ester was employed, giving rise to the product after a sequential double 1,2-shift of two boronate esters. Mechanistically, the secondary radical species **87** generated via 1,2-boron shift adds to the activated olefins, leading to the corresponding C-centered radicals, which accept one electron from the reduced form of the photoredox catalyst. Protonation of the anions in the presence of *t*-BuOH affords the final borylated compounds **89**, which retains a functional handle for possible further transformations.

Scheme 17. Visible Light-Mediated Mono-Deboronative Functionalization of 1,2-bis-Boronic Esters
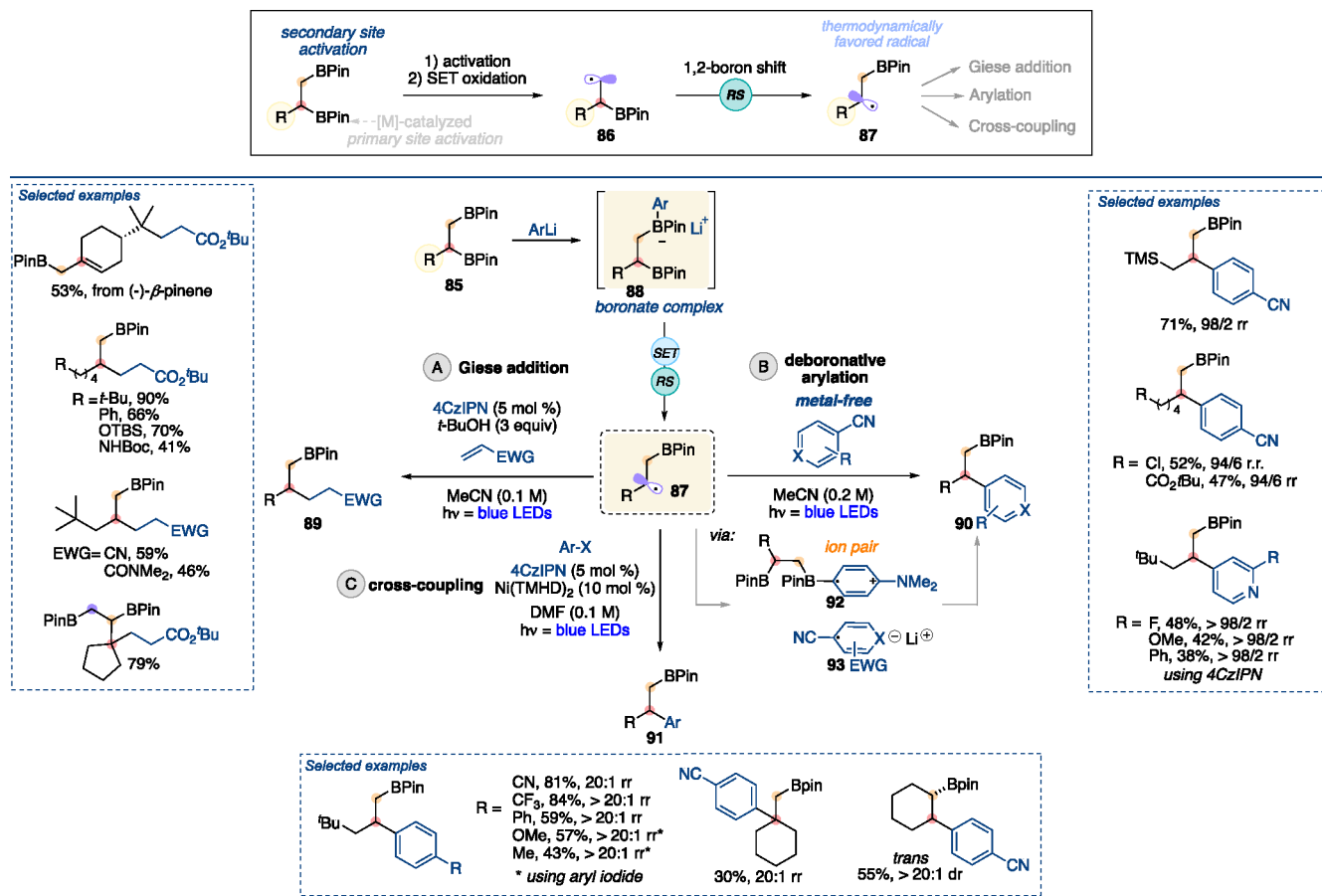
Later, the same research group developed a photoinduced metal-free deboronative arylation protocol that offers complementary regioselectivity to the traditional Suzuki−Miyaura cross-couplings. The reaction was designed to proceed via an electron donor−acceptor complex formation, and for that, the electron-rich [4-(dimethylamino)phenyl]lithium was used for the generation of the borate complex, which then couples to a series of electron-poor (hetero)aryl nitriles under blue LED irradiation in acetonitrile (Scheme 17B).[61] Importantly, for broad applications, the transformation proved to be insensitive to sterically hindered groups and tolerated diverse functional groups (halide, trimethylsilyl, esters) as well as tertiary 1,2-boronate esters.

The method's complementarity to classical cross-coupling reactions was demonstrated using cyclic-*cis*-boronate esters. In that case, the authors showed the stereodivergent synthesis of both *trans* (via a Pd-catalyzed protocol) and *cis* (via the developed photoinduced method) isomers. For the scope of the (hetero)aryl partner, the use of the organophotocatalyst 4CzIPN was crucial to achieve good yields with 4-cyanopyridines, and the products were obtained with excellent regioselectivity. The scope of the transformation was also extended to the use of monoboronate esters in the presence of (hetero)aryl nitriles. UV studies supported the generation of the EDA complex between electron-rich boronate esters and the electron-deficient aromatic ring of (hetero)aryl nitriles. Upon visible light irradiation, SET provides a radical ion pair. The radical cation **92** generates the secondary radical **87** after homolytic cleavage of the primary C−B bond followed by a

1,2-boron shift. The coupling of this transient radical with the persistent radical anion **93** then furnishes the final product **90**.

In the same year, the authors also reported the arylation of 1,2-bis-boronate esters with (hetero)aryl halides via dual nickel/photoredox catalysis, overcoming the limitations of the previous protocol regarding the use of only electron-deficient arylnitriles.[62] The use of anionic diketonate-based ligands proved to be critical for the regioselectivity of the transformation in comparison to bipyridine ligands, and the study revealed the ligand TMHD was optimal, providing the product with >20:1 rr. The effects of the ligands on the regioselectivity are in accordance with findings reported in a study by Molander and co-workers, showing a difference regarding the mechanisms for the reductive elimination step, outer-sphere (for the diketonate ligands) and inner-sphere (for the Ni-bipyridyl system).[63] Aryl bromides containing neutral or electron-withdrawing groups were well tolerated with excellent regioselectivities. However, the use of electron-rich aryl bromides led to the formation of nickel-black, furnishing poor results. This limitation was overcome by employing aryl iodides instead. In general, a range of functional groups were tolerated including cyano, trifluoromethyl, amide, fluoride, ester, and ketone. Heteroaryl halides underwent the transformation to provide the final compounds **91** in moderate yields. Regarding the diversification of the boronate species, the transformation also tolerates the use of 1,2-bis-boronate esters derived from a 1,1-disubstituted alkene and cyclic *cis*-1,2-bis-boronate esters, the latter providing the corresponding

trans products, an opposite selectivity to that found in Pd-catalyzed protocols (Scheme 17C).

CARBONYL COMPOUNDS AS RADICAL SOURCES FOR REDUCTIVE/OXIDATIVE ALKYLATION OF *N*-HETEROARENES

The rapid expansion of photocatalyzed protocols to forge C−C bonds has allowed access to different alkyl radicals generated from alkyl halides, boranes, nitriles, alcohols, amines, ethers, and others. Seminal research in the field was disclosed by Jin and MacMillan in 2015 in which they reported the use of alcohols as alkylating reagents in a Minisci benzylation reaction.[18]

Complementing the synthetic tools to achieve this C−C transformation, in 2019, Wang's group described a new catalytic activation mode that combined proton-coupled electron transfer (PCET) with spin-center shift (SCS), enabling C—H alkylation of heteroarenes from carbonyl compounds as alkyl radical equivalents.[64] This Minisci-type reaction proceeds via initial reductive PCET activation of the corresponding carbonyl compound by the photocatalyst to generate the corresponding α-oxy radicals (Scheme 18).

Scheme 18. C—H Alkylation of Heteroarenes from Carbonyl Compounds as Alkyl Radical Equivalents
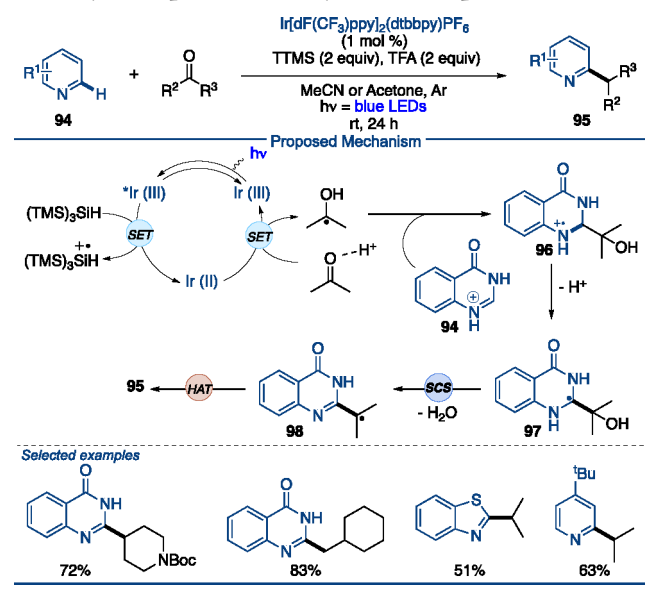

Subsequently, radical addition to the heteroarenes takes place, allowing the formation of an aminyl radical cation **96**, which undergoes deprotonation to form the α-amino radical **97**. The generated radical undergoes an SCS process, releasing H$_2$O and generating an open-shell benzylic radical **98**. Subsequently, a hydrogen atom transfer (HAT) event takes place, yielding the alkylated heteroarene **95**. The scope of this transformation extends to functionalized ketones and aldehydes. The heteroarene scope is also broad, and thus quinolines, pyridines, benzothiazolines, and imidazo[1,2-*b*]-pyridazines were successfully alkylated under the developed protocol. This approach showcased the use of ketones and aldehydes as feedstocks for the generation of alkyl radical equivalents through the carbonyl carbon.

In 2020, Huang and co-workers reported a reductive Minisci alkylation via an umpolung addition of aldehydes to *N*-heteroarenes (Scheme 19).[65] In their study, they discovered that the aldehyde component also functioned as a reductant in

Scheme 19. Reductive Minisci Alkylation/Benzylation of *N*-Heteroarenes via Umpolung of the Aldehydes
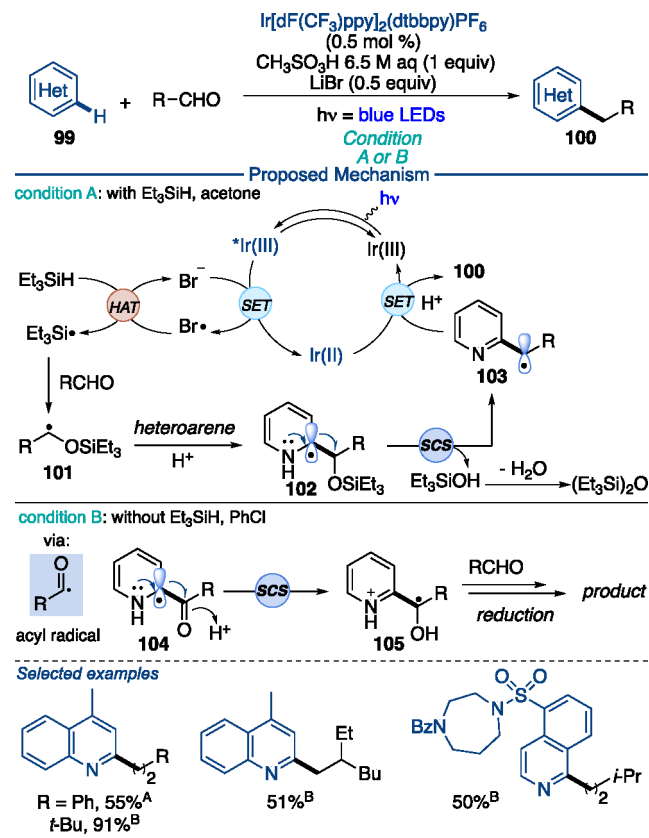

addition to its role as an alkylating reagent, allowing a reductant-free protocol in the presence of methanesulfonic acid, LiBr as an additive, and Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ photocatalyst. Alternatively, the use of Et$_3$SiH as an additional reductant led to higher yields when aliphatic aldehydes were investigated. The use of secondary aldehydes also led to the minor form of the decarbonylative alkylated product, indicating an acyl radical pathway. Nitrogen heteroarenes such as substituted quinolines, isoquinolines, benzoquinolines, or *aza*-phenanthrene were accommodated to provide the C2-alkylated compounds.

Regarding the mechanistic aspects, under both reaction conditions, bromide oxidation by *Ir(III) is the initial step, followed by an HAT between the bromine radical and the Si−H bond (condition A) or direct hydrogen abstraction from the aldehyde (condition B), to afford the silyl ether or the acyl radical, respectively. At this point, an SCS step provides either a carbon-centered radical **103** or a hydroxymethyl radical **105**, which then undergoes reduction via SET with the Ir(II) and protonation to provide the final products. A further reduction by the aldehyde may take place via a hemiacetal radical intermediate under condition B to furnish the alkylated/benzylated heteroarenes.

Considering a photocatalyst-free approach to generate acyl radicals in the context of Minisci reactions, the Melchiorre group in 2019 reported a photochemical process that exploited the excited-state reactivity of 4-acyl-1,4-dihydropyridines under the effect of blue light to obtain acyl radical species (Scheme

20).[66] According to their proposed mechanism, 4-acyl-1,4-dihydropyridines upon blue light irradiation undergo an SET

Scheme 20. Photochemical C−H Hydroxyalkylation of Quinolines and Isoquinolines
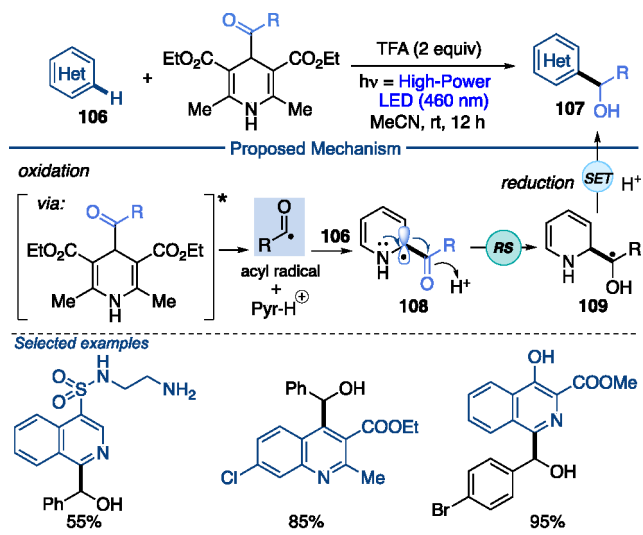

oxidation (via a Hantzsch ester pyridinium salt serving as an electron shuttle) followed by homolytic cleavage to fragment into an acyl radical and Pyr-H^{+}. Subsequently, the acyl radical adds to the protonated heterocycle **106** to generate radical intermediate **108**. Next, an RS mechanism leads to the formation of a benzylic radical intermediate **109**. Finally, SET reduction of this intermediate **109** generates the aromatized hydroxylated heterocyclic product **107** after protonation. In addition to presenting a mild and photocatalyst-free process to access acyl radicals, this method provides a mechanistically distinct approach that is slightly differentiated from a classical oxidative Minisci-type mechanism to form hydroxylated heteroarenes in an external oxidant-free condition. This method's high functional group tolerance allowed late-stage functionalization of active pharmaceutical ingredients and natural products.

In the same vein, Mitsunuma and co-workers disclosed an alternative photocatalytic oxidative Minisci protocol for the preparation of hydroxyalkylated N-heteroaromatics in 2020.[67] In their protocol, aldehydes were used as a source of an acyl radical by utilizing the HAT/RS strategy.[18,65,68] The reaction is proposed to follow a mechanistic pathway involving the generation of a thiyl radical by SET oxidation between the photocatalyst 9-mesityl-10-methylacridinium (Mes-Acr+) and thiophosphoric acid (TPA), followed by a HAT step with aldehydes (BDE ∼ 88.7 kcal/mol) to generate the corresponding acyl radical. The Minisci addition of this latter to the N-heteroarenes followed by the RS event provided the corresponding hydroxy alkylated product upon protonation. Both aromatic and aliphatic aldehydes with different functional groups were well tolerated. Regarding the scope of the N-heteroarene components, good applicability was found using isoquinolines, quinolines, and pyridines with a range of functional groups. Finally, the protocol was challenged with more complex architectures, and good results were reported when biologically active components were used. As a complementary protocol to the previous work reported by the Melchiorre group, this report showcased a milder and more

efficient method for the alkylation of N-heteroaromatics with no need for strong oxidizing reagents, thereby allowing broad functional group tolerance.[66]

In 2021, a deoxygenative reduction of carbonyl compounds under photoredox and metal-free conditions was reported by Huang's group (Scheme 21).[69] In their protocol, heteroaryl

**Scheme 21. Deoxygenative Reduction of Ketones Reported by Huang's Group[69]**
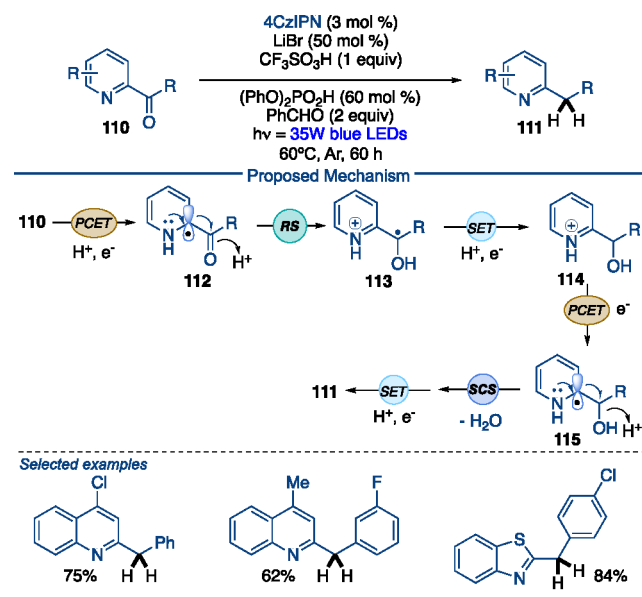
ketones undergo PCET, affording the corresponding radical **112**. Subsequently, the aromatization driven RS event occurs to generate the hydroxymethyl radical cation intermediate **113**, which after protonation followed by the SET step gives the hydroxymethylpyridine intermediate **114**. The generated intermediate proceeds through a sequential PCET, SCS, and SET to form the final alkylpyridine product **111**.

■ MISCELLANEOUS

In 2016 and 2018, the Hyster group described an enzymatic photoredox method to carry out an SCS process.[70,71] A nicotinamide-dependent enzyme, *Nicotiana tabacum* (NtDBR), catalyzes the reaction under visible light irradiation with the use of Rose Bengal (RB) as photocatalyst to promote an enantioselective deacetoxylation of α-acetoxytetralone **116** (Scheme 22). The enzyme is responsible for substrate binding in the active site and can attenuate the redox potential of **116** (X = OAc, R = Me) by approximately +157 mV, which makes the electron transfer energetically feasible. Decomposition of the ketyl radical **118** via SCS allows elimination of the acetate to form an enzyme-bound α-carbonyl radical **119**, which engages in the HAT process from an equivalent of NADPH bound within the active site to afford the product **117** with high enantioselectivity. The scope of this transformation was extended to α-bromoamides and -esters to afford the corresponding halogenated products with good yield and excellent enantioselectivity.

By exploring a sequence of events involving SET, HAT, and SCS mechanisms, Ye and co-workers disclosed a photoredox-catalyzed regioselective ketyl-ynamide coupling-triggered cascade cyclization, providing access to a series of 2-benzhydrylindoles **122** and 3-benzhydrylisoquinolines **123**

**Scheme 22. Deacetoxylation of Ketones Promoted by the Combination of Photoredox and Enzyme Catalysis**

Scheme 23. Photoredox-Catalyzed Regioselective Ketyl-ynamide Coupling
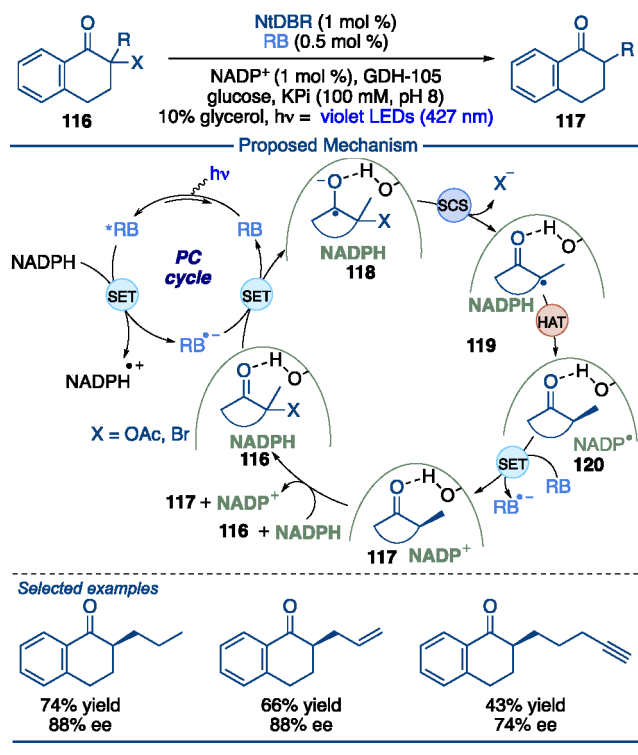
via a unique desulfonylation Smiles rearrangement (Scheme 23).[72] The tandem reaction is initiated by the reductive quenching of the *Ir(III) photocatalyst excited state by Hantzsch ester (HE), leading to HE[•+] and the highly reducing species Ir(II). The latter reduces the ynamide substrate to furnish the ketyl radical intermediate **124** after protonation by the HE[•+] species. The radical intermediate **124** then undergoes regioselective ketyl-ynamide coupling followed by a Smiles rearrangement to provide the radical intermediate **126** after extrusion of SO₂. The amidyl radical generated from this process participates in an HAT step in the presence of HE[•] to provide the reactive intermediate **127**. A single electron reduction of **126** followed by protonation is less likely to occur. Further single-electron reduction in a second photocatalytic cycle delivers the carbon-centered radical **128**, which is prone to undergo an SCS with H₂O elimination, followed by SET and protonation steps to furnish the final product **122** or the intermediate **130**, which leads to the product **123** after rearomatization. Under the developed protocol, a range of substituted ynamides was employed and included the use of the Togni reagent as a source of CF₃ radical for an intermolecular version of this transformation.

■ 1,2-RADICAL SHIFTS IN OXIDATIVE PROTOCOLS

Owing to the importance of heteroatom-containing compounds in drug discovery programs, the development of synthetic methods to functionalize such compounds readily is imperative. Because these chemical scaffolds can easily undergo an oxidative event owing to the presence of electron-rich heteroatoms such as nitrogen and sulfur in their structures, photoredox C−H activation methods have been disclosed on the basis of an oxidative mechanistic pathway that involves oxidation at the heteroatom center followed by a 1,2-RS to produce carbon-centered radicals.
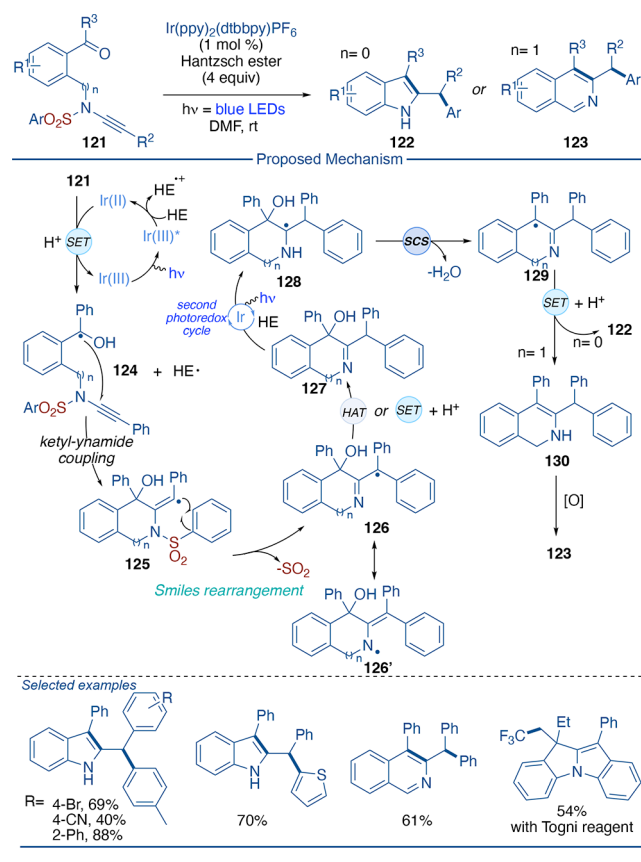
In 2020, Nicewicz's group presented a site-selective approach to carry out the C−H functionalization of bioactive piperazine compounds via an oxidative photoredox process to access C-alkylated piperazine products (Scheme 24).[73] This site-selective transformation relies on a hypothesis that involves a photoinduced electron transfer event to first oxidize the piperazine substrate **131** containing two electronically differentiated nitrogen atoms to produce a nitrogen-centered cation radical **134** at the more electron-rich locus. The radical cation intermediate undergoes deprotonation and a subsequent 1,2-RS to generate the α-amino radical **135**. Finally, the addition of this α-amino radical onto activated alkenes followed by the SET/protonation step furnishes the alkylated piperazine products. Consistent with this hypothesis, the method shows high regioselectivity for compounds that contain two electronically distinct protecting groups such as carbamate and aryl groups on the nitrogen atoms, while poor regioselectivity is observed in the case of two electronically similar carbamate groups. In addition to the electronic effect, the reaction temperature has also been shown to play a critical role in improving the regioselectivity. The report also includes computational studies to justify the hypothesis of achieving regioselectivity governed by electronic biases on the nitrogen atoms. A DFT natural population analysis was shown to predict the regioselective outcome of the reaction by measuring the electron density at both nitrogen centers in the neutral substrate along with the cation radical intermediate. The nitrogen atom that undergoes the most drastic change in electron density was predicted to be the principal site of alkylation, which is consistent with the experimentally determined result.

Scheme 24. Photoredox Site-Selective C−H Alkylation of Piperazine via Oxidative Spin-Center Shift

Scheme 25. Regioselective Photocatalytic α-Functionalization of Amines
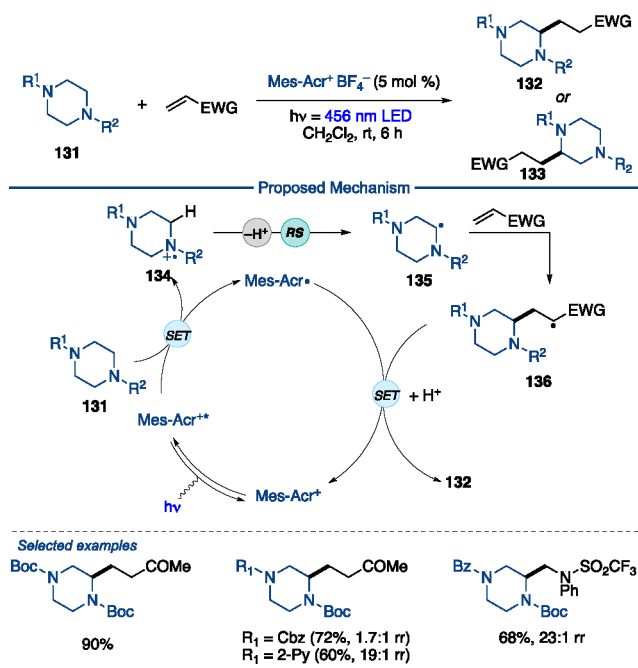
In the same year, the Ready group reported a similar oxidative 1,2-RS mechanistic protocol to achieve controllable α-functionalization of amines in which the regioselectivity is tuned by incorporating minor changes in the reaction conditions (Scheme 25).[74] In the presence of an [Ir] photocatalyst, four different alkylation products are obtained from N-aryl-N-methylaniline starting materials by simply switching the solvents or bases. On the basis of deuterium labeling and computational studies, the proposed reaction mechanism is initiated with the generation of the amine radical cation **142**, which contains two acidic protons at the α-carbons (benzylic and methyl). At this point, a solvent effect dictates the regio-outcome of the product. In CH_2Cl_2 solvent, the benzylic radical **143** formed via deprotonation/1,2-RS dominates and facilitates the formation of the benzylic alkylated product through addition into the Giese acceptors followed by a radical-polar crossover (RPC) event, while in the case of MeCN solvent, methyl radical **144** formed via the same 1,2-RS undergoes rapid Giese addition/RPC steps to generate a methyl-functionalized product as the major isomer (Scheme 25, Conditions A and B). Further, the MeCN condition was exploited to generate the doubly alkylated product **140** by adding DBU base along with two different Giese acceptors and changing the base from DBU to K_3PO_4, resulting in the formation of cyclic aldol product **141** (Scheme 25, Conditions C and D, respectively). This report, revealing the ability to exploit the reactivity of distinct C−H bonds on the basis of their acidity in a molecule to access divergent alkylated products, unveils the possibility to explore new methods that can provide a wide range of important scaffolds by selectively activating multiple reactive centers in a compound by only slightly modifying the conditions.

Later, the same group reported the photocatalyzed α-functionalization of amines using allyl bromides, benzyl bromides, and bromoacetone as the alkylating sources (Scheme 26).[75] A similar oxidative mechanism pathway is operative here by utilizing an [Ir] photocatalyst to generate the
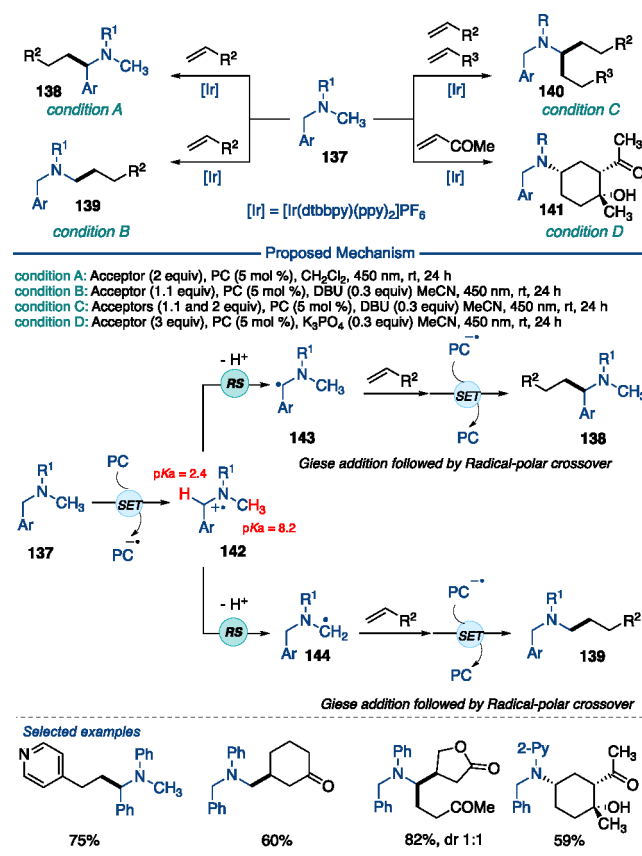
Scheme 26. Photocatalytic α-Alkylation of Amines with Alkyl Halides
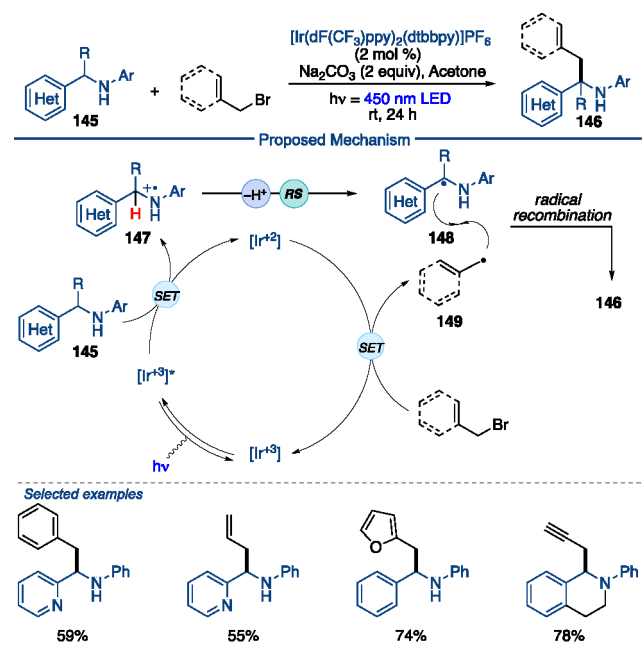
amine radical cation **147** that undergoes deprotonation followed by a 1,2-RS to provide a benzylic α-amino radical species **148**. Separately, the reduced Ir(II) species transfers an electron to the alkyl bromide to afford another carbon-

centered alkyl radical **149**. Following this, a radical recombination event between these two radicals then facilitates the formation of the desired amino-alkylation product **146**. Overall, this reported approach offers a mild, atom-economical redox neutral synthesis of α-branched amines that shows a broad scope with various functional groups on both amine precursors and alkylating reagents. Additionally, the method is synthetically attractive in that it does not require any transition metal catalyst to perform the radical–radical coupling, which is otherwise needed to facilitate an efficient capture of two reactive radical species to avoid the side processes.

Next, Alfonzo and Hande demonstrated that this photo-catalyzed oxidative 1,2-RS mechanism to generate α-alkyl heteroatom radical species is not just limited to amine substrates but also can be extended to thioether compounds.[76] On the basis of a dual catalytic approach using an acridinium photocatalyst along with a weak Bronsted base (CF₃COONa), this group demonstrated the C–H activation of thioethers to α-thioalkyl radicals and their addition to electron-deficient olefins to afford alkylated products (Scheme 27). The

Scheme 27. Photoredox/Brønsted Base-Catalyzed Alkylation of α-Thioalkyl Radicals
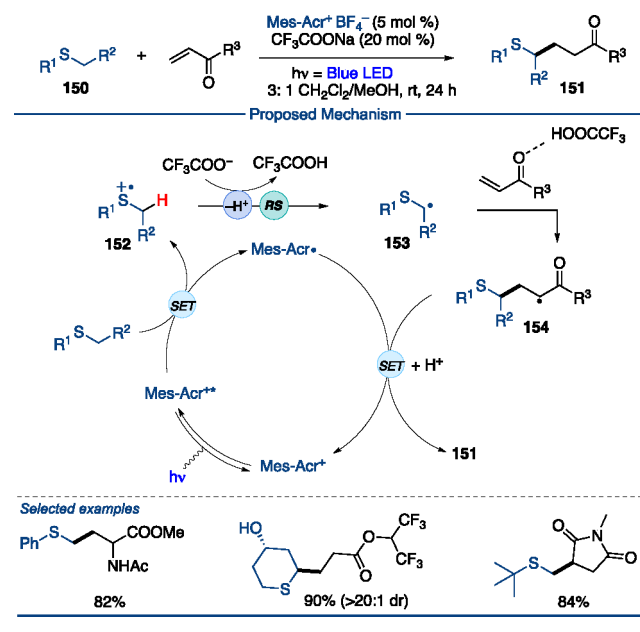

proposed mechanism involves the oxidation of thioether by acridinium photocatalyst to provide sulfide radical cation **152**. Subsequently, deprotonation followed by a 1,2-RS event generates an α-thioalkyl radical **153** that undergoes Giese addition with an electron-deficient alkene, activated by trifluoroacetic acid. Finally, alkylated product **151** is formed after an SET/protonation step. Although this method offers an excellent approach to the alkylation of thioether compounds, it is limited in terms of providing efficient regioselectivity in the case of aliphatic thioethers in which two similar C–H activation sites are present as compared to its aromatic thioether congeners.

In 2018, Rueping's group demonstrated for the first time that the solid polymeric graphitic carbon nitride (g-C₃N₄) acts as an effective photoredox catalyst for desilylative additions, allylations, and heteroarylations.[77] Because of its heterogeneous nature, this photocatalyst showed good recyclability with

reuse in multiple runs. Reactions were also conducted in a recyclable continuous flow photoreactor. Regarding the structural and electronic properties of g-C₃N₄ with a band gap of 2.7 eV and a decisive band gap adsorption at about 420 nm, visible light irradiation leads to the efficient separation of photogenerated electron–hole pairs. One-electron oxidation of α-silylamine **155** by the photogenerated hole of g-C₃N₄, followed by a desilylation process, generates an α-tertiary- or α-secondary-aminoalkyl radical **156**. This latter intermediate easily engages with alkenes or even chlorinated heteroarenes to afford, after another SET and HAT step, the desired products **158** and **160** (Scheme 28). This study presents a stable

Scheme 28. Use of Graphitic Carbon Nitride as a Heterogeneous Photocatalyst for α-Aminoalkyl Radical Additions, Allylations, and Heteroarylations
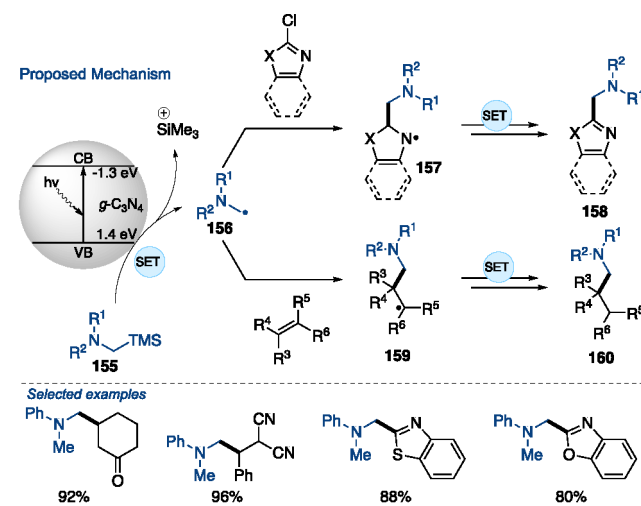

polymeric g-C₃N₄ as an alternative to homogeneous photo-sensitizers for the generation of valuable radical intermediates for applications in synthesis and catalysis.

In 2021, Xu et al. developed a regioselective coupling reaction of α-silylamines with Baylis-Hillman derivatives by visible light photoredox catalysis.[78] This catalytic system provides a convenient method for the achievement of a variety of homoallylic amines under very mild reaction conditions, although it remains limited to the use of styrene derivatives. The preparation of N-containing α,β-unsaturated carboxylate derivatives first proceeded by excitation of the photocatalyst, which is then reduced by α-silylamine **161** to produce an α-aminoalkyl radical **163**. This last intermediate reacts with Baylis-Hillman carbonate to form the corresponding alkyl radical **164**, which itself is reduced by the photocatalyst. Finally, the corresponding anion **165** induces the elimination of the acetoxy group to afford the desired product **162** (Scheme 29).

In the same vein, Fan et al. developed another visible light photoredox-promoted desilylative allylation of α-silylamines.[79] In this study, the use of a series of allylic sulfones as substrates was demonstrated for the efficient preparation of various functionalized homoallylic amines (Scheme 30). As in the previous example, the reaction mechanism starts with photo-excitation of the photocatalyst to promote the formation of the α-amino radical **168** via oxidation of the α-silylamines **166** along with the elimination of TMS⁺. After the addition of the α-amino radical to 2-phenyl allylic sulfone, the desired

Scheme 29. Photoredox Synthesis of N-Containing α,β-Unsaturated Carboxylate Derivatives Synthesized from α-Silylamine and Baylis-Hillman Adducts
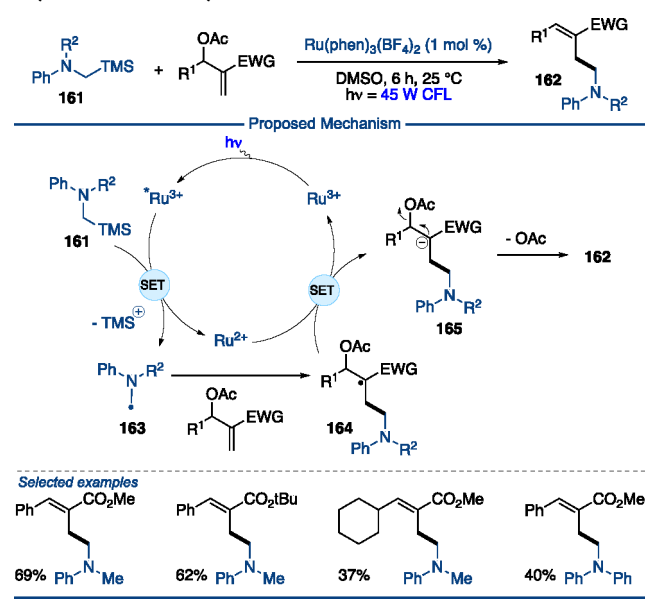
**Scheme 30. Desilylative Allylation of α-Silylamines via a Photoredox Process**
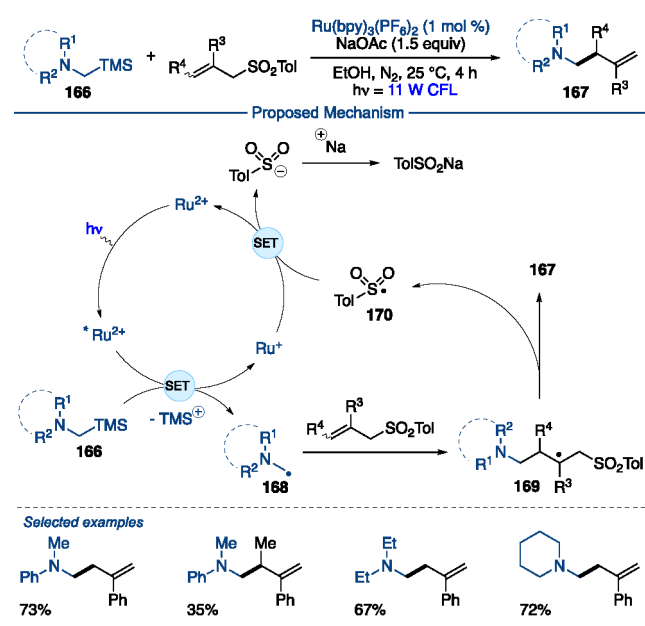
homoallylic amines **167** are formed by elimination of tosyl radical **170**, which after the reduction by Ru^I, generates TolSO$_2$Na as a byproduct. This method thus allows an alternative to the preparation of various functionalized homoallylic amines from N-arylamine derivatives, limited to the use of not only aniline derivatives but also cyclic and acyclic alkylamines.

Another recent study conducted by the Molander group took advantage of the fast desilylation of α-silylamines upon SET to develop a user-friendly and versatile route toward the aminomethylation of functionalized (hetero)aryl halides via visible light/nickel dual catalysis.[80] This general amino-alkylation strategy overcomes the intolerance of free amines

in nickel-catalyzed C−C coupling in addition to exhibiting high chemoselectivity for C−C bond formation compared to C−N bond formation. Additionally, amino acid subunits were installed with complete stereochemical fidelity at the stereogenic centers. The mechanism is initiated by the oxidation of α-silylamine **171** via SET by photoexcited 4CzIPN. The α-desilylation, facilitated by carbonate anion, promotes the generation of an α-amino radical **174**, which is then intercepted by Ni(0). After subsequent oxidative addition of an aryl halide, the resulting Ni(III) species undergo reductive elimination, offering the C−C coupled product **172** and Ni(I). Finally, SET from the reduced form of the photocatalyst to the Ni(I) regenerates the ground state 4CzIPN and Ni(0) (Scheme 31). This protocol allows a protecting group-free

Scheme 31. Visible Light/Nickel Dual Catalysis for Aliphatic Amines Synthesis
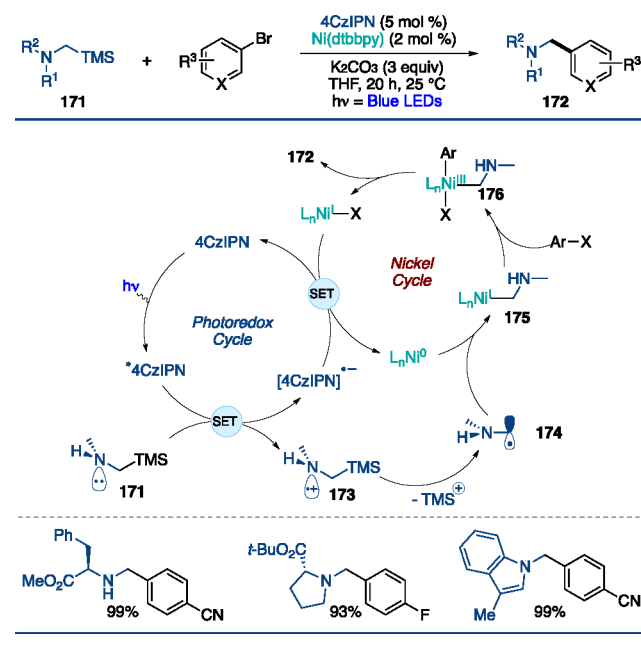
synthetic strategy for the preparation of secondary arylmethyl-amines and can be extended to the synthesis of tertiary amines from commercially available (het)aryl halides.

Photocatalytic strategies have been considered to be a milestone for functionalization of complex biomolecules, given the mild reaction conditions and robustness of the protocols. This aspect represents an ideal match to perform reactions on-DNA, which require room temperature, high dilution (1 mM), water compatibility, and near-neutral pH. Recently, DNA-encoded library (DEL) technology has received considerable attention from both the academic and pharmaceutical sectors as a novel screening modality for the rapid discovery of drug candidates. The principal advantages associated with this technology are the cost-effectiveness and time-efficiency provided by the interrogation of billions of small organic molecules against a target in a single experiment.[81]

Many advances have been achieved in the field. In 2020, the Molander group disclosed a robust photoredox cross-coupling method for alkylation on-DNA using alkyl bromides.[82] Given the importance of exploring as much chemical space as possible in DEL technology, the group then extended the strategy to incorporate structurally relevant amines on-DNA using the 1,2-RS paradigm developed for aminomethylsilanes

(Scheme 32A). The aminomethylation of (hetero)aryl bromides was developed using easily accessible amino-

which is fundamental for further applications of DEL technology.

Scheme 32. Cross-Coupling and Radical/Polar Defluorinative Amino-methylation Oxidative 1,2-Radical Shift

CONCLUSIONS

In this Review, the exploration of photoinduced transformations proceeding via key 1,2-radical shift steps has been highlighted, exposing useful strategies to generate valuable carbon-centered radical synthons. The practical applications of this paradigm were demonstrated for the challenging single activation of C−F bonds, generating difluoroalkyl radicals via SCS after the reduction of trifluoromethylated components by the powerful reductant CO_2 radical anion derived from formates. This strategy allows mild reaction conditions and is of great interest for the preparation of fluorine-containing molecules, which possess a recognized importance in the pharmaceutical field. The concept was also presented in the context of the modification of biomolecules, e.g., carbohydrates, via 1,2-RS with group migrations inspired by the biosynthesis of deoxyribonucleotides. Additionally, further applications were addressed for the selective cleavage of $C(\beta)$−O bonds of diol derivatives and natural lignin extracts. The discussion also highlighted important advances in the field in the use of 1,2-bis-boronate esters as radical precursors under photocatalytic conditions. Under this recently developed protocol, primary β-borylated primary radicals undergo 1,2-boron shifts to form thermodynamically favored secondary radicals. Such reactive species have been successfully employed in Giese addition reactions with activated olefins, in deboronative arylations with opposite regioselectivity to the traditional Suzuki−Miyaura cross-couplings via EDA complex formation, and via dual nickel/photoredox catalysis. Other versatile transformations proceeding via 1,2-radical shift combine the mechanisms of PCET, HAT, and SCS steps to enable C−H alkylation of heteroarenes from carbonyl compounds as alkyl radical equivalents under blue light irradiation. Finally, a brief overview regarding the most recent work disclosed in the field of α-amino radical generation was covered, giving the relevance and utility of this class of radical intermediates for the preparation of amine-containing compounds. Photoinduced strategies have been creatively explored by organic chemists to diversify chemical space in an unconventional way, allowing direct access to structurally important molecules under mild reaction conditions. Continuing development in the field has occurred through the design of distinct reaction mechanisms. Among these, protocols proceeding via 1,2-radical shifts represent a powerful strategy. This Review provides a base of information on the reactive radical intermediates accessed via these mechanisms as well as important photoinduced transformations and may serve as a guide for future developments in the field.

methylsilanes **177** in the presence of $[\text{Ir}\{\text{dFCF}_3\text{ppy}\}(\text{bpy})]\text{PF}_6$ as the photocatalyst. Importantly, unprotected aminomethylsilanes were successfully employed, and the reactions required short reaction times (<15 min) under open-to-air conditions. A range of heteroaryl halides were tolerated under the protocol, giving rise to synthetically useful products **178**. Some examples included an N-Boc-protected amine and aryl iodides containing free primary amines as well as tertiary amines.

Subsequently, other useful applications using α-silylamines were developed for the defluorinative alkylation via a radical/polar crossover process (Scheme 32B). In that case, the nucleophilic radical from the SET oxidation of the α-silylamine adds to the trifluoromethylated alkene to provide an α-CF_3 radical. A carbanion then is generated by the reduction of this latter species, which ultimately leads to fluoride elimination, providing the corresponding gem-difluoroalkenes **179**.

Interestingly, silylamines containing amino acid residues were incorporated, including those from proline, methionine, and tryptophan. Furthermore, a rich scope was explored, and aniline, glycoside, oxetane, and amide substructures were also found to be compatible with the transformation. Crucially, the photoredox transformations were performed under conditions in which the structural integrity of the DNA remained intact,

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Biographies

Dr. Bianca Matsuo received her B.Sc. (2015) and M.Sc. (2017) degrees in Chemistry from the Federal University of São Carlos, SP, Brazil. She completed her doctoral studies under the supervision of Professor Marcio Paixão at the same university in 2021, working on the development of radical-based protocols by means of organic photoredox catalysis. Currently, she is a postdoctoral researcher in the group of Professor Gary A. Molander at the University of Pennsylvania. Her research interests are focused on the development of new photocatalytic strategies.

Dr. Albert Granados was born in Sabadell (Barcelona, Spain). He undertook his undergraduate studies at the Universitat Autònoma de Barcelona (UAB). In 2014, he received his MSc in Electrochemistry, Science and Technology under the supervision of Prof. Iluminada Gallardo. In 2014, he joined the Vallribera group at UAB, where he received his Ph.D. with a special award. Subsequently, he pursued postdoctoral studies with Prof. Roser Pleixats and Prof. Adelina Vallribera at UAB. In 2021, he began another postdoctoral stint in the Molander group at UPenn. His research focuses on organofluorous chemistry, (photo)catalysis, and materials science.

Dr. Jadab Majhi earned a B.Sc. (Hons) in Chemistry at Ramakrishna Mission Vidyamandira (India) in 2013, and he obtained an M.Sc. in Chemistry from the Indian Institute of Technology Bombay (India) in 2015, where he conducted undergraduate research with Professor Sambasivarao Kotha. In 2021, he received a Ph.D. degree under the supervision of Professor P. Andrew Evans at Queen's University (Canada), working on the development of new stereoselective and stereospecific methods for the preparation of polysubstituted olefins and acyclic α-ternary ketones using cyanohydrins. In 2021, he joined the laboratory of Professor Gary A. Molander at the University of Pennsylvania (United States) as a postdoctoral fellow, where he is currently working on the development of new photochemical methods.

Dr. Mohammed Sharique was born in 1992 in Lucknow, India. He received his B.S.−M.S. dual degree in chemistry from the Indian Institute of Science Education and Research (IISER), Bhopal in 2014. In IISER Bhopal, he joined Dr. Alakesh Bisai's laboratory for his M.S. thesis. In 2015, he moved to UT Southwestern Medical Center, Dallas, USA to pursue his doctoral studies and joined Prof. Uttam Tambar's laboratory to work in the areas of *N*-heterocyclic carbene (NHC) organocatalysis and copper-catalyzed selective allylic alkylation reactions. Currently, he is a postdoctoral associate in Prof. Gary A. Molander's laboratory at the University of Pennsylvania, and his research involves the development of new reaction methods in the field of photoredox chemistry.

After receiving a two-year technical degree at the UIT of Créteil-Vitry in France (2013), Dr. Guillaume Levitre continued his studies with a B.Sc. in Chemistry-Biology (2014) and then received a M.Sc. in Chemistry (2016) at the Paris-Saclay University (France). From late 2016 to late 2019, he carried out his Ph.D. studies under the supervision of Dr. Géraldine Masson at the Institut de Chimie des Substances Naturelles (ICSN, France), where he developed photocatalytic and enantioselective organocatalytic processes for the synthesis of complex molecules. In 2019, he moved to the University of Geneva (Geneva, Switzerland) as a postdoctoral fellow to study rhodium and ruthenium catalysis for the synthesis and functionalization of 2-vinyloxymalonate enol ethers with Prof. Jérôme Lacour, remaining there until July, 2021. Since September 2021, he has been a postdoctoral research associate in the group of Prof. Gary Molander, investigating functionalizations of phenyl bioisosteres via photoredox processes.

Professor Gary A. Molander completed his undergraduate studies in Chemistry at Iowa State University under the tutelage of Professor Richard C. Larock. He earned his Ph.D. at Purdue University with Professor Herbert C. Brown, where later he was also a postdoctoral research associate. He undertook a postdoctoral training with Professor Barry M. Trost at the University of Wisconsin, Madison. He began his academic career at the University of Colorado, Boulder, moving to the University of Pennsylvania in 1999. Professor Molander has also served as a visiting professor in several countries. He has been recognized with several honors and awards for his contribution to the organic chemistry field, including the American Chemical Society Herbert C. Brown Award for Creative Research in Synthetic Methods (2015).

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