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Perspective

# Application of the Spin-Center Shift in Organic Synthesis

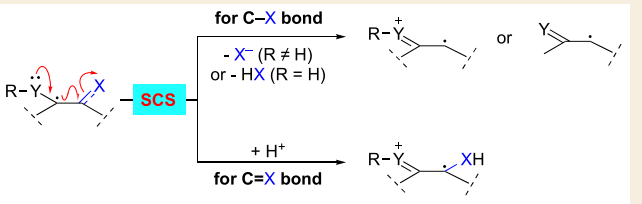
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**ABSTRACT:** Spin-center shift (SCS) is a radical process involving 1,2-radical translocation along with a two-electron ionic movement, such as elimination of an adjacent leaving group. Such a process was initially observed in some important biochemical transformations, and the unique property has also attracted considerable interest in synthetic chemistry. Experimental, kinetic, as well as computational studies have been performed, and a series of useful radical transformations have been developed and applied in organic synthesis based on SCS processes in the last 20 years. This Perspective is an overview of radical transformations involving the SCS mechanism.

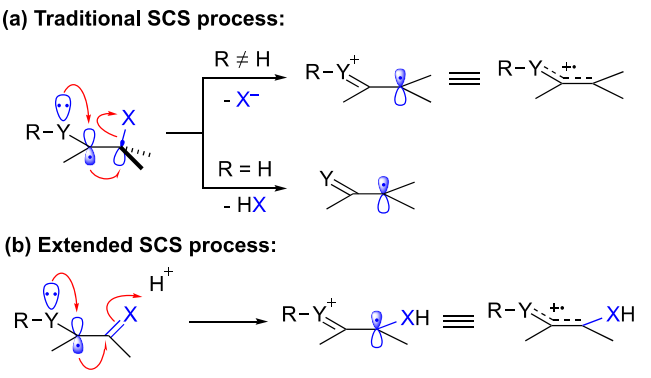



**KEYWORDS:** *spin-center shift, 1,2-radical shift, carbon−heteroatom bond activation, deoxygenation, defluorination, dechlorination*

The spin-center shift (SCS) process has been found in many important biological transformations.[1] For example, SCS is involved in ribonucleotide reductase (RNR) enzymes class (I to III)-catalyzed dehydration of ribonucleotides to 2′-deoxyribonucleotides, a process that is critical in DNA biosynthesis and repair.[2−5] In the last century, much research attention has been given to the exploration of transformations involving SCS processes.[6−9] Experimental and computational studies have been performed to uncover the reaction mechanism. These reactions were first called radical-ionic fragmentations of C−O bonds,[6] radical-induced polar substitution and elimination reactions,[7] or heterolysis of $\beta$-substituted radicals,[8] as the term "SCS" was not advanced and defined until 2007. In the review "Spin-Center Shift (SCS)—A Versatile Concept in Biological and Synthetic Chemistry",[9] Wessig gave the sharpest definition of SCS: the 1,2-radical shift accompanied by the elimination of an adjacent leaving group or the corresponding acid (Scheme 1a).

Based on previous reports and some recent studies,[10,11] a general consensus about SCS processes has been summarized: (1) the singly occupied molecular orbital (SOMO) and the $\sigma^*$-orbital of the leaving group should be in an approximate coplanar arrangement to provide sufficient orbital overlap that is essential for the efficient heterolysis of the C−X bond and the shift of the spin-center; (2) a sufficiently good leaving group is required, or Brønsted or Lewis acid or base should be added to aid the elimination of the leaving group; and (3) the existence of an adjacent electron-donating substituent/atom at the radical center is helpful to the SCS process, as it stabilizes the generated radical cation. With numerous photoredox catalysts covering a broad range of redox potentials, photoredox catalysis has emerged as a powerful platform which facilitates a myriad of organic transformations.

**Scheme 1. SCS Process**




In the last 20 years, a large number of synthetic applications have been reported based on the SCS mechanism, enabling the functionalization of various carbon−heteroatom bonds. Notably, methods based on photocatalytic reactions are found to be particularly powerful, by which more general and milder hydrogen atom transfer (HAT) and single-electron transfer (SET) reaction pathways have been established to generate radical centers that can undergo the ensuing SCS process. Although the detailed photoreaction mechanism (redox processes or chain reactions) still remains uncertain in most cases,[12] the SCS process is considered to be a solid pathway for

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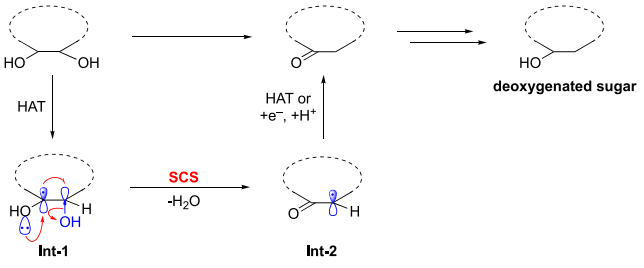
the translocation of radical centers. Based on the different types of carbon−heteroatom bonds activated, these transformations are classified into the following five aspects: C−O bond activation, C−X (halogen) bond activation, C−N bond activation, expansion of the SCS in C═O bond activation, and other reactions. In these studies, the SCS is not limited to the traditional process involving just heterolysis of carbon−heteroatom bonds. The process has been extended to 1,2-radical shift along with two-electron ionic movements, such as protonation of a C═O bond adjacent to the radical center with the forging of a new O−H $\sigma$-bond at the expense of the C═O $\pi$-bond (Scheme 1b). This Perspective provides an overview of these transformations with emphasis on the reaction mechanism and synthetic applications. It should be mentioned that radical 1,2-acyloxy migration,[6,13−21] which has recently been considered as 1,2-SCS,[18−21] is not discussed in this Perspective, considering that in the proposed reaction mechanisms no two-electron ionic movement occurs during the radical migration process.

## CARBON−OXYGEN BOND ACTIVATION

### Selective Dehydration of Carbohydrates

Stimulated by the RNR-catalyzed dehydration of ribonucleotides, organic chemists explored whether analogous dehydration of carbohydrates could be achieved in organic synthesis. The resulting products can be readily converted into deoxygenated sugars, which exist as fundamental constituents of numerous bioactive natural products and drugs.[22−24] Following this hypothesis, several selective dehydration protocols of sugars were established under photoredox conditions; the general mechanistic scenario is shown in Scheme 2. The reactions begin with HAT from the

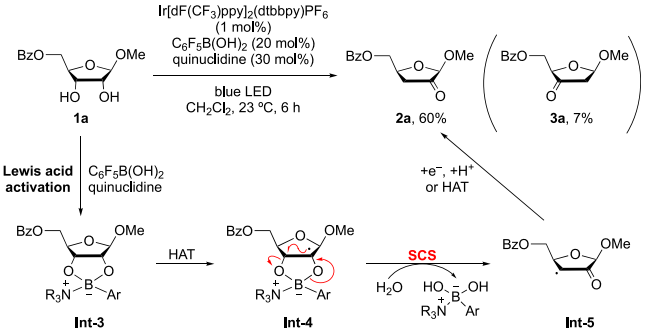
**Scheme 2. Selective Dehydration of Carbohydrates**




carbohydrates to form a carbon center radical **Int-1**. Subsequent SCS process occurs with the elimination of water to afford $\alpha$-carbonyl carbon radical **Int-2**. This, in turn, is converted into the desired dehydration products through another HAT step or a sequence of single-electron reduction and protonation process.

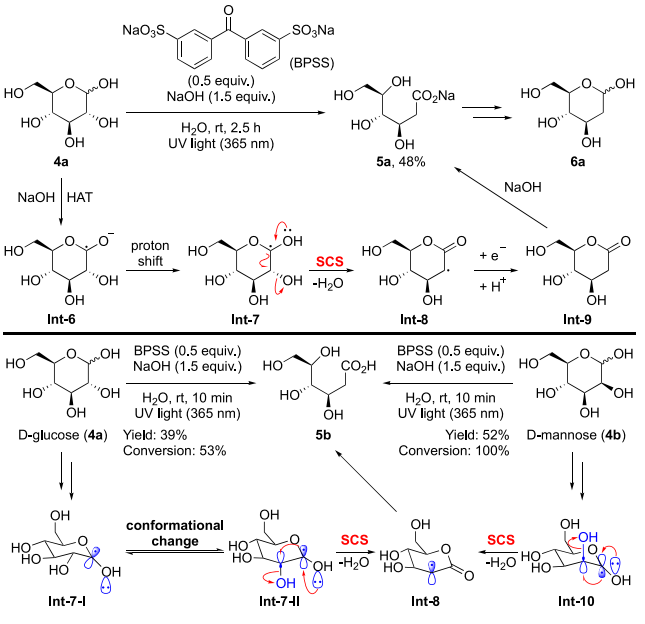
For example, selective dehydration of furanosides was realized via the collaboration of Lewis acid/photoredox catalysis to afford various 2-keto-3-deoxyfuranosides (Scheme 3),[25] thereby providing a good complement to the RNR enzyme-catalyzed dehydration of ribonucleotides.[2,26,27] In the reaction, pentafluorophenylboronic acid forms a tetracoordinate borinic ester with the *cis*-1,2-diol and quinuclidine, which is proposed to promote the hydrogen atom abstraction from the C2 position as well as activate the heterolysis of the C3−O bond in the SCS process. The site selectivity is determined in the HAT step, which is affected by the substitution pattern and electronic nature of functional groups on the substrates.

**Scheme 3. Lewis-Acid-Promoted Selective Dehydration of Furanosides**




Subsequently, Murakami and co-workers demonstrated an elegant dehydration of unprotected sugars in water by the employment of benzophenone sodium sulfonate (BPSS) as the photocatalyst under UV light irradiation (Scheme 4).[28] The

**Scheme 4. Selective Dehydration of Sugars under Basic Conditions**




reaction is amenable to an array of pyranose mono- and disaccharides. The generated 2-deoxyaldonates are in situ converted into lactones for isolation. These lactones were readily reduced to the corresponding 2-deoxy sugars. Mechanistically, deprotonation of the anomeric hydroxy group of **4a** under strong basic conditions results in weakening of the $\alpha$-C−H bond, thus enabling the hydrogen atom transfer step to give carbon radical **Int-6**.[29−32] The authors proposed that it is the protonated species **Int-7** that undergoes the SCS process with the release of water. The generated **Int-8** accepts one electron followed by a proton to produce lactone **Int-9**, which is further hydrolyzed under basic conditions to furnish 2-deoxyaldonate **5a**. Kinetic studies indicate that the reaction rate of D-glucose **4a** is lower than that of D-mannose **4b**, which may be ascribed to the slower SCS process of **Int-7-I** in comparison to that of **Int-10**. In line with the consensus about the orbital orientation in the SCS process, **Int-10** is poised to undergo SCS with the expulsion of $H_2O$ directly, whereas **Int-**

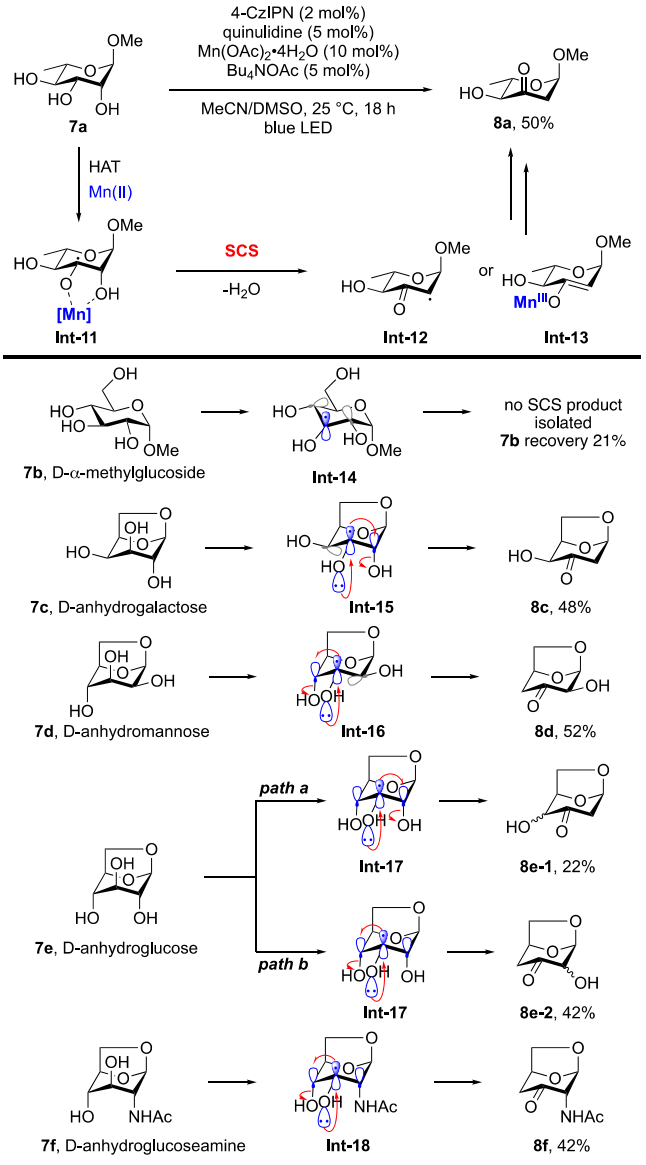


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7-**I** needs to undergo substantial conformational change to form a more stable **Int-7-II** for the SCS process to proceed.

Recently, another representative dehydration of monosaccharides was disclosed by using manganese catalyst under photoredox conditions, allowing for the concise synthesis of various deoxygenated sugars from readily available biomass-derived monosaccharides (Scheme 5).[33] In this reaction, the

**Scheme 5. Manganese-Promoted Selective Dehydration of Sugars**

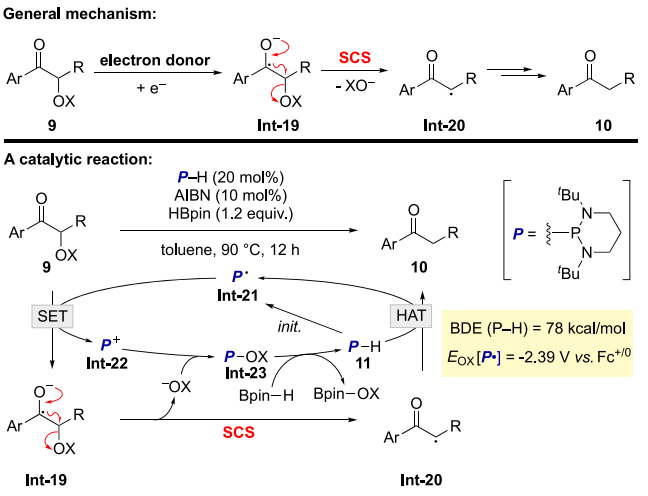



SCS process is facilitated by the $Mn^{2+}$ catalyst, although the detailed mechanism remains unclear. The authors surmised that $Mn^{2+}$ may act as a Lewis acid to induce the elimination of $H_2O$ to give **Int-12**, or it undergoes inner-sphere electron transfer as well as promotes the SCS process to deliver **Int-13**. Notably, interesting product selectivity is observed in the transformation. For example, no SCS product is formed in the case of D-$\alpha$-methylglucoside **7b**, as it lacks a hydroxyl group coplanar with the SOMO in **Int-14**. Dehydration of **7c** and **7d** proceeds efficiently with the elimination of the corresponding axial hydroxyl groups adjacent to the spin center in **Int-15** and **Int-16**, whereas the equatorial hydroxyl groups remain intact. For the reaction of **7e**, which contains two axial OH groups adjacent to the spin center in **Int-17**, ejection of both the OH groups is observed, furnishing products **8e-1** and **8e-2** as a 1:1.9 mixture. These results collectively provide strong support for the aforementioned orbital overlap prerequisite of the SCS process. The reaction of **7f** affords dehydration product **8f** exclusively, whereas no deamination product is observed, even though the $\alpha$-*N*-acetyl group (NHAc) is also coplanar with the SOMO in **Int-18**.

## Deoxygenation of Acyloin Derivatives and Lignin Degradation

Deoxygenation of acyloin derivatives is another typical transformation enabled by the SCS process (Scheme 6). In

**Scheme 6. Reductive Deoxygenation of Acyloin Derivatives**



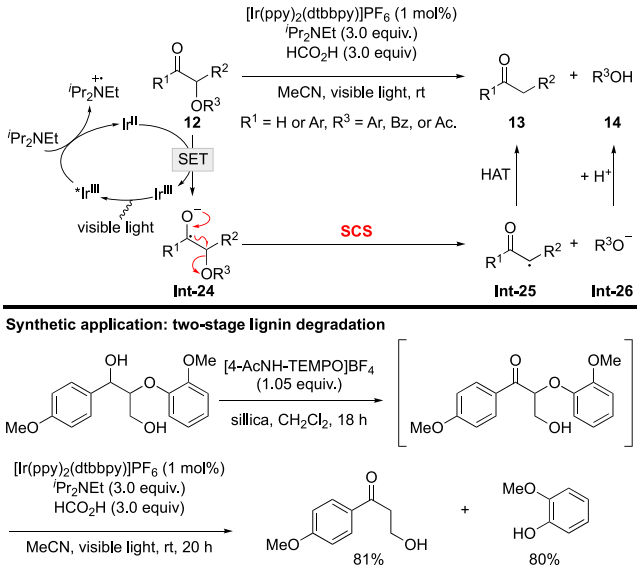

the past decade, there have been reports about deoxygenation of acyloin derivatives using stoichiometric amounts of electron donors.[34,35] For example, compounds **9** react with electron donors to give **10**. In this process, single-electron reduction of **9** affords ketyl radical anion **Int-19**. The SCS of **Int-19** gives $\alpha$-carbonyl radical **Int-20**, which is further transformed into the deoxygenative hydrogenation products **10**. Notably, the hydroxy protecting group is better as an electron-withdrawing group to promote SET to **9** and induce the departure of the anionic leaving group. Previously reported electron donors include neutral superelectron donors,[34] $Ph_2P^-$ ion, and naphthoxide ion.[35] In 2020, a phosphinyl radical-catalyzed alternative was demonstrated by Yang and Cheng.[36] With an oxidation potential of −2.39 V vs ferrocene in acetonitrile,[37] the phosphinyl radical **Int-21** is capable of reducing compounds **9**. The resulting phosphonium cation **Int-22** combines with the $XO^-$ liberated in the SCS process to afford **Int-23**. Further $\sigma$-bond metathesis between the P−O bond in **Int-23** and the B−H bond of pinacolborane regenerates diazaphosphinane **11**.[38] The P−H bond dissociation energy of diazaphosphinane **11** is about 78 kcal/mol,[37] thus enabling it as a good hydrogen atom donor. HAT from **11** to **Int-20** furnishes products **10** and regenerates the phosphinyl radical **Int-21** to close the catalytic cycle.

In 2014, Stephenson extended the above deoxygenation strategy to the selective cleavage of the C−O bond adjacent to carbonyl groups (including ketones and aldehydes) by employing $[Ir(ppy)_2(dtbbpy)]PF_6$ as the photocatalyst and *N*,*N*-diisopropylethylamine as the sacrificial reductant (Scheme


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7).[39] The protecting groups of the alcohol were extended to aryl and benzyl groups. The reaction features mild conditions

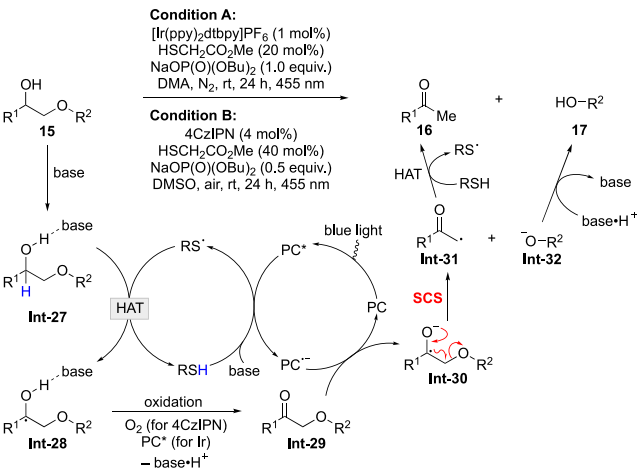
**Scheme 7. Photoinduced Selective Cleavage of the C−O Bond Adjacent to Carbonyl Groups**




and good functional group tolerance, thus allowing for its application in a two-stage lignin degradation strategy. As native lignin exits as diol form, it is selectively oxidized to the $\alpha$-alkoxyketone by [4-AcNH-TEMPO]$BF_4$ before being subjected to the visible-light-promoted C−O bond cleavage reaction.

Because of the wide existence of lignin and its application in the synthesis of value-added small molecules,[40−43] degradation of lignin has attracted tremendous research attention. In this regard, ongoing efforts have been directed to improve the two reactions involved in the two-stage lignin degradation strategy.[44−49] In 2019, König disclosed a redox-neutral one-step fragmentation protocol of diol derivatives by merging of photoredox and HAT catalysis.[50] The detailed mechanism is depicted in Scheme 8. In the presence of base, thiol catalyst is oxidized by the excited-state photocatalyst to give a thiyl

**Scheme 8. Photoinduced Redox-Neutral Fragmentation of Diol Derivatives**

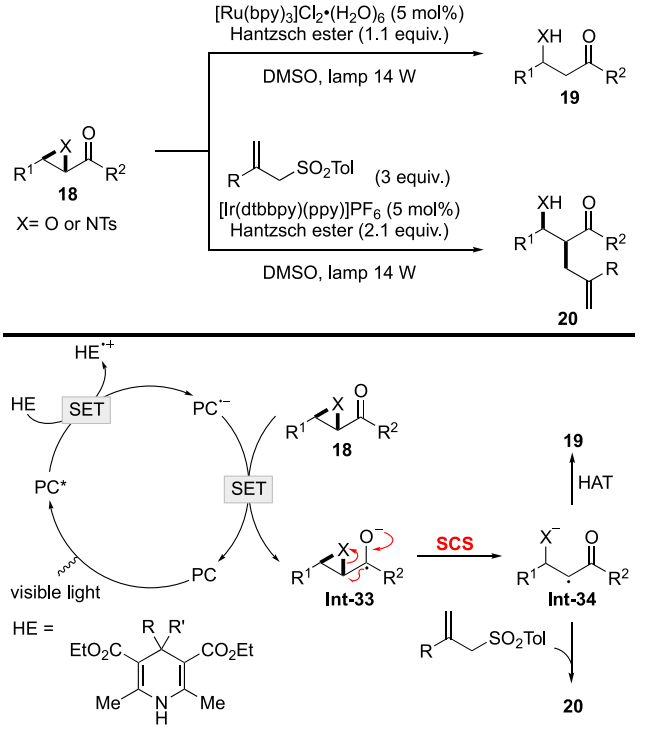



radical. Formation of hydrogen bond between **15** and base weakens the $\alpha$-C−H bond,[31,51] ensuring HAT from **Int-27** to the thiyl radical. The generated ketyl radical **Int-28** is readily oxidized by molecular oxygen or the excited photocatalyst to produce ketone **Int-29**. Single-electron reduction of **Int-29** by the reduced photocatalyst affords ketyl radical anion **Int-30**, which undergoes SCS to give carbonyl radical **Int-31** and alkoxide anion **Int-32**. HAT to **Int-31** furnishes ketone **16**, while the proton shift to **Int-32** delivers alcohol **17**. The transformation successfully combines the previously reported oxidation/deoxygenation reactions in the lignin degradation process together, thereby avoiding the use of stoichiometric amounts of external oxidant and sacrificial reductant. This protocol is applicable to a variety of diol derivatives, but lignin-branched $\beta$-O-4 model compounds did not react well under the standard conditions. The limitation was addressed by an analogous photoredox transformation performed under acidic conditions, which is amenable to both model substrates and natural lignin extracts.[52]

## Reductive Functionalizations of $\alpha$-Ketoepoxides and $\alpha$-Ketoaziridines

Photoinduced reductive ring openings of $\alpha$-ketoepoxides have been a research interest for a long time. Previously, the reactions were performed under UV irradiation.[53−57] Recently, with the rapid development of photoredox catalysis, the reactions were improved and reexamined under visible-light irradiation conditions.[58,59] For example, Fensterbank and Ollivier disclosed the reductive functionalizations of $\alpha$-ketoepoxides and $\alpha$-ketoaziridines under visible-light irradiation in 2011 (Scheme 9).[59] In the transformations, [Ir(dtbbpy)(ppy)$_2$]$^+$ or [Ru(bpy)$_3$]$^{2+}$ is employed as the photocatalyst, while Hantzsch ester serves as both the reductant and hydrogen atom donor. Quenching of the excited

**Scheme 9. Visible-Light-Induced Reductive Functionalizations of $\alpha$-Ketoepoxides and $\alpha$-Ketoaziridines**





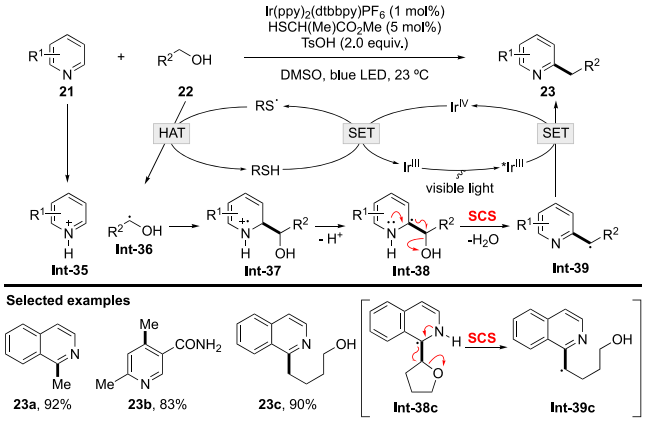

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photocatalyst by the Hantzsch ester results in the formation of reduced photocatalyst, which undergoes SET to **18** to form radical anion **Int-33**. Although not mentioned in the publication, the ring-opening process of **Int-33** involves the heterolytic cleavage of a C−O or a C−N bond along with relocalization of the spin center. Therefore, it is an SCS process. The generated **Int-34** may undergo HAT to give hydrogenated product **19**, or it can be captured by allylsufone to deliver allylation product **20**. It should be noted that the cleavage of both C−O and C−N bonds is realized via the SCS process in the transformation.

## Alkylation Reactions

In 2015, MacMillan's group implemented a protocol for alkylation of heteroarenes with unactivated alcohols as alkylating reagents based on the SCS process (Scheme 10).[60]

**Scheme 10. Alkylation of Heteroarenes with Alcohols**

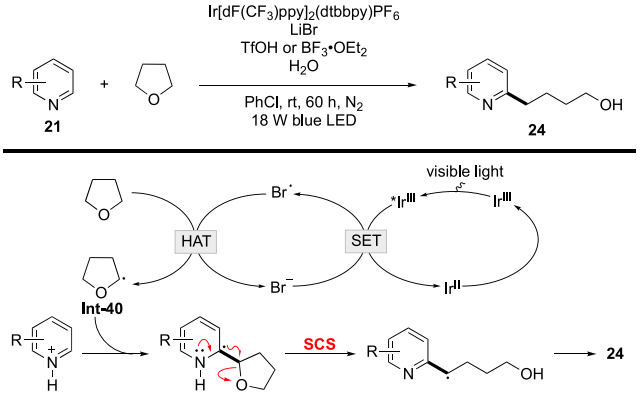



The reaction harnesses dual photoredox/HAT catalysis to generate a thiyl radical, which undergoes polarity-matched HAT with alcohol **22** to afford $\alpha$-oxy radical **Int-36**.[61] Minisci-type addition to electron-deficient **Int-35** forms aminyl radical cation **Int-37**, which is prone to undergo deprotonation to give $\alpha$-amino radical **Int-38**. The SCS of **Int-38** occurs to generate benzylic radical **Int-39** with the elimination of $H_2O$. Single-electron reduction of **Int-39** followed by protonation leads to the alkylation product and regenerates $Ir^{IV}$ to complete the catalytic cycle. Tetrahydrofuran proves to be a competent alkylating reagent, delivering alcohol **23c** via the cleavage of the C−O bond. This work unlocks reaction manifolds facilitated by the SCS process. In addition, it demonstrates that an $\alpha$-oxy radical could serve as a viable alkyl precursor via the SCS process, thereby opening a new perspective for an alkylation strategy. An array of novel alkylation reactions were developed based on this idea.

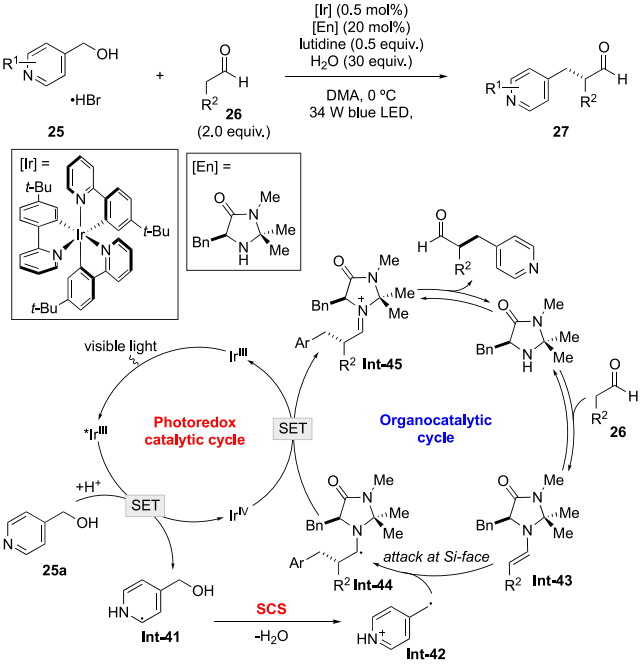
The alkylation of heteroarenes with ethers was further improved by Huang and co-workers (Scheme 11).[62] Here, LiBr was employed as the HAT catalyst in lieu of the thiol catalyst, which has an unpleasant smell.

MacMillan's group next developed an enantioselective $\alpha$-benzylation of aldehydes with alcohols through the merger of photoredox catalysis and enamine-type organocatalysis (Scheme 12).[63] In the transformation, benzylic radical **Int-42** is generated from alcohol **25** through the sequence of single-electron reduction and the SCS process. Participation of **Int-42** in the enamine organocatalytic cycle realized the enantioselective alkylation of aldehydes.

**Scheme 11. LiBr-Promoted Alkylation of Heteroarenes with Ethers**




**Scheme 12. Enatioselective $\alpha$-Benzylation of Aldehydes with Alcohols**




Further study by Wang and co-workers revealed that aldehydes and ketones are also competent alkylating reagents in the alkylation of heteroarenes (Scheme 13).[64] Mechanistically, aldehydes and ketones are converted into $\alpha$-oxy radicals by means of proton-coupled electron transfer (PCET), which then engage in the same reaction sequence shown in Scheme 10. This method provides a general route to alkylated heteroarenes from commercially available ketones and aldehydes.

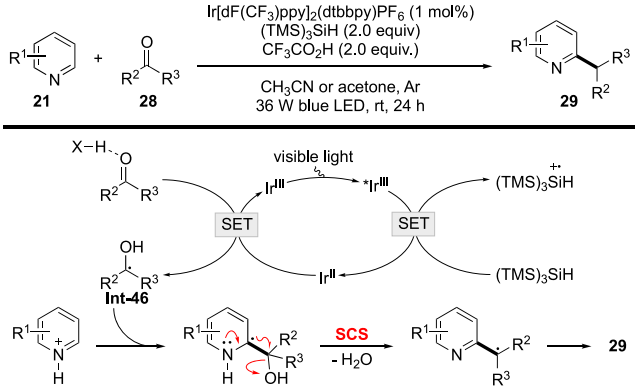
## SCS Incorporated in Complex Radical Cascade Reactions

In 2020, Ye reported a complex radical cascade reaction involving the SCS process as the key step for the cleavage of the C−O bond. As shown in Scheme 14, under the photoredox reaction conditions, ynamides **30** are converted into 2-benzhydrylindoles **31** and 3-benzhydrylisoquinolines **32** through a sequence of regioselective ketyl−ynamide coupling, Smiles rearrangement, and the SCS process.[65]

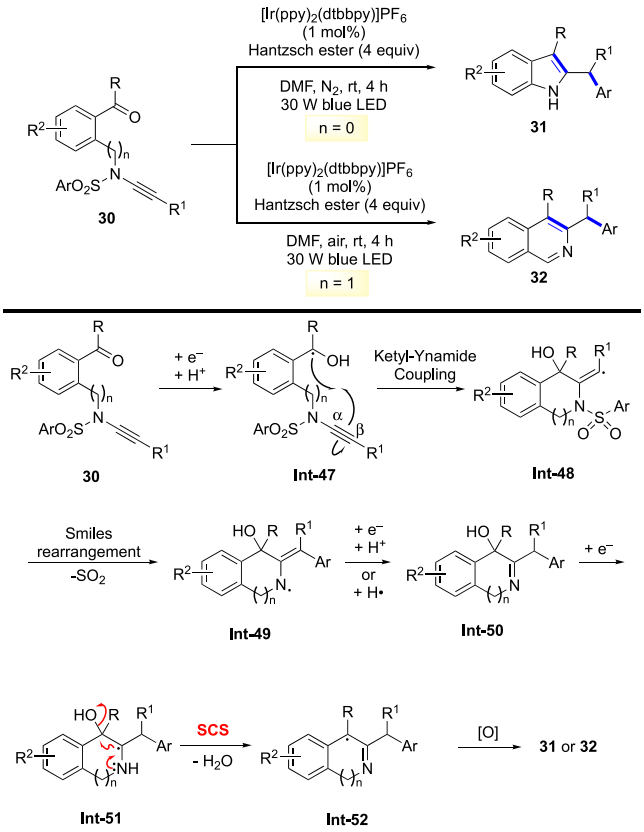


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**Scheme 13. Alkylation of Heteroarenes with Ketones and Aldehydes**



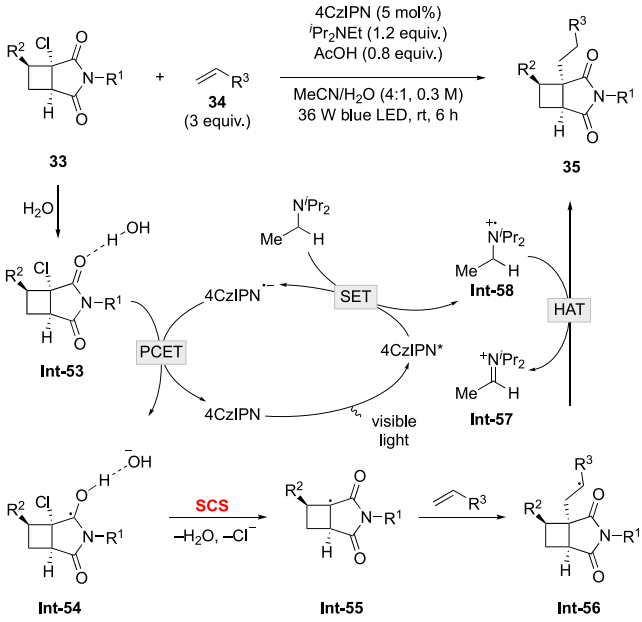

**Scheme 14. SCS Incorporated in Complex Radical Cascade Reactions**




## CARBON–HALOGEN BOND ACTIVATION

In the last century, there were reports of detailed mechanistic and kinetics studies on heterolysis of C−Cl and C−Br bonds via the SCS process.[66−68] However, the synthetically useful applications remained scarce. Recently, the strategy was exploited by Aggarwal and co-workers to forge a C−C bond on cyclobutanes and construct quaternary stereocenters under photoredox catalysis (Scheme 15).[69] The protocol allows for the synthesis of densely functionalized cyclobutanes with complete control of the diastereoselectivity. Mechanistically, SET from $^{i}Pr_2NEt$ to the excited photocatalyst 4CzIPN* affords the reduced photocatalyst $4CzIPN^{\bullet-}$ and amine radical cation **Int-58**. With the aid of water, **Int-53** undergoes PCET with $4CzIPN^{\bullet-}$ to form the protonated ketyl radical **Int-54**.

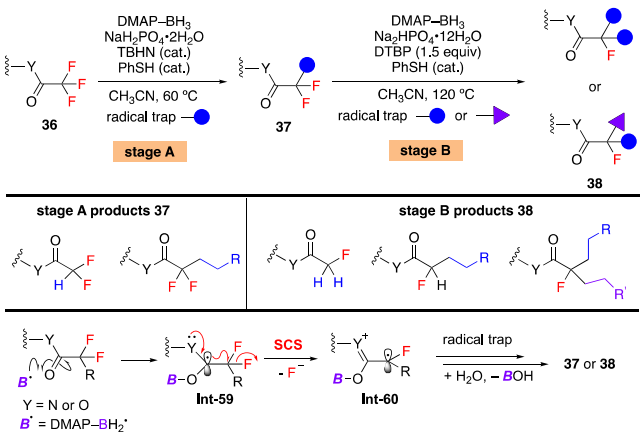
**Scheme 15. SCS-Promoted C−Cl Bond Functionalization**




SCS of **Int-54** facilitates the expulsion of water and chloride. The ensuing cyclobutyl radical adds to the alkene with high diasteroselectivity to afford **Int-56**. Eventually, HAT from **Int-58** to **Int-56** furnishes the highly functionalized cyclobutanes **35**.

Compared with C−Cl and C−Br bonds, the C−F bond is much more difficult to activate by the SCS process due to the poor leaving ability of fluoride.[70−72] Previously, there were only limited reports about biological observations of C−F bond cleavage via the SCS process.[73,74] In 2021, this tactic was realized by Wang and Houk to sequentially functionalize the C−F bond of trifluoroacetamides and esters (Scheme 16).[75]

**Scheme 16. Sequential C−F Bond Functionalizations of Trifluoroacetamides and Acetates via SCS**




Addition of a boryl radical to the carbonyl oxygen atom generates carbon radical **Int-59**. SCS takes place with the heterolytic cleavage of the C−F bond. The resulting alkyl radical **Int-60** can be trapped to form a variety of partially defluorinated compounds. A thorough computational study was performed to investigate the reaction mechanism. Charge and electron spin transfers during the SCS process were demonstrated, the results of which support the fact that C−F

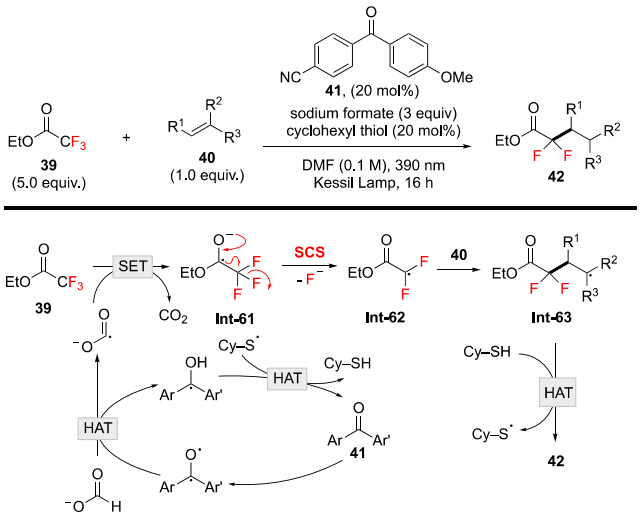


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bond cleavage is a heterolytic process. The role of $NaH_2PO_4$ in assisting the SCS process was also proven experimentally and theoretically. These studies deepen the understanding about the SCS process. Using this strategy, the Wang group next reported the selective monodefluorinative alkylation of 3,3-difluorooxindoles.[76]

Using the SCS mechanism for C−F bond cleavage as the key step, Molander and co-workers then developed photocatalytic protocols for defluorinative alkylation of trifluoroacetates and amides (Scheme 17).[77] In the transformation, $CO_2^{\bullet-}$ derived

**Scheme 17. Photoinduced C−F Bond Functionalization of Trifluoroacetacetates and Amides**




from HAT of the formate ion serves as a strong single-electron reductant to reduce trifluoroacetate. The resulting trifluoroacetate radical anion **Int-61** is an electron-rich species, which is prone to undergo an SCS process to afford *gem*-difluoroalkyl radical **Int-62**. The following Giese reaction with alkenes furnishes $\alpha,\alpha$-difluorocarbonyl products **42**. In addition, the method is applied to trifluoroamides by introduction of Lewis acid to reduce the redox potential of trifluoroamides. Very recently, similar photochemical methods were reported by Glorius[78] and Shang.[79] Defluorinative reduction and alkylation of trifluoroacetamides and acetates as well as polyfluorinated aliphatic esters and amides are all accomplished, manifesting the versatility of the transformation.

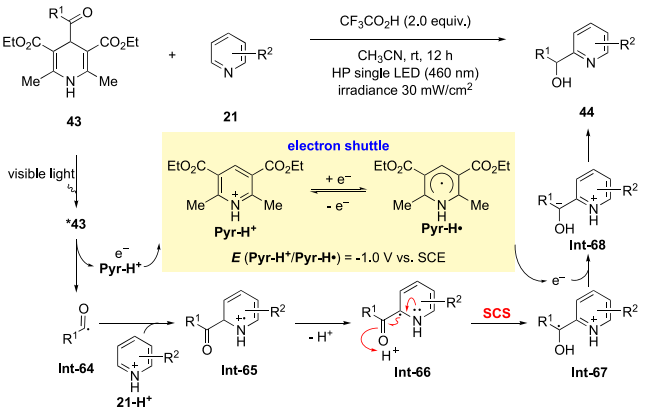
## C−N BOND ACTIVATION

The study of C−N bond activation enabled by the SCS process is quite rare. In the mechanistic investigation on SCS in the last century, little attention was diverted to the C−N bond cleavage event during exploration of the C−O bond cleavage.[80,81] In terms of biological transformations, the C−N bond cleavage via SCS is one plausible mechanism for radical *S*-adenosyl-L-methionine (SAM) enzyme DesII-catalyzed deamination of TDP-4-amino-4,6-dideoxy-D-glucose,[82−85] but this mechanism has not been confirmed. This is a crucial step in the biosynthesis of TDP-desosamine, which represents an important component in various macrolide antibiotics.[86,87] The SCS process has been underused in C−N bond functionalization in organic synthesis. To the best of our knowledge, there is only one precedent in reductive functionalization of $\alpha$-ketoaziridines, which is depicted in Scheme 9. We hope this area may attract more focus in the future.

## EXPANSION OF THE SCS IN C═O BOND ACTIVATION

The SCS process discussed in the previous sections involves the shift of the radical center along with the elimination of a leaving group. In 2019, Melchiorre extended the definition of SCS to include a carbonyl group, wherein a 1,2-radical shift proceeds along with the conversion of an adjacent C═O $\pi$-bond to a C−O $\sigma$-bond. Based on this key step, they developed an elegant hydroxyalkylation reaction of heteroarenes using 4-acyl-1,4-dihydropyridines (acyl-DHPs) **43** as the hydroxyalkylating reagents (Scheme 18).[88] In the reaction process, the

**Scheme 18. Hydroxyalkylation of Heteroarenes with Acyl-DHPs**




excited acyl-DHPs ***43** are strong single-electron reductants ($E_{red}$ about −1.1 V vs SCE in $CH_3CN$),[89] which liberate an electron and the pyridinium ion (**Pyr-H**$^+$) to generate acyl radical **Int-64**. Addition to a protonated heteroarene followed by deprotonation affords $\alpha$-amino radical **Int-66**. Upon protonation of the carbonyl oxygen atom, the spin-center shift occurs with the shift of the spin density to the adjacent benzylic carbon; meanwhile, the C═O $\pi$-bond is converted to a C−O $\sigma$-bond. This SCS process is supported by density functional theory (DFT) calculations. Single-electron reduction of **Int-67** followed by protonation yields the hydroxyalkylated heteroarene **44** aspect of radical transformations, and more interesting conversions can be expected.

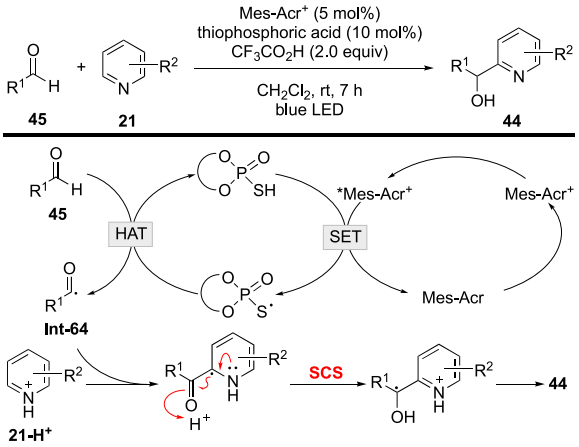
Later, Mitsunuma and Kanai described a modified equivalent by the employment of aldehydes as acyl radical precursors under synergetic photoredox/HAT catalytic system (Scheme 19).[90] The key process is also the SCS process for the translocation of the radical center and the activation of the C═O bond. The reaction is endowed with broader substrate scope, owing to the robustness of aldehydes.

## OTHER REACTIONS

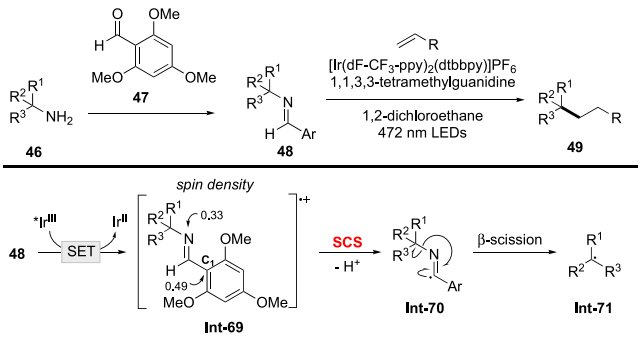
A distinct type of SCS process was disclosed by Rovis in the deaminative alkylation of $\alpha$-3° primary amines (Scheme 20).[91] Imine **48**, which is derived from condensation of $\alpha$-3° primary amines with 2,4,6-trimethoxybenzaldehyde **47**, undergoes SET to the excited $Ir^{III}$ photocatalyst. In the generated radical cation **Int-69**, the spin density is mainly located on the nitrogen atom (0.33) and $C_1$ atom (0.49) according to DFT calculations. The imidoyl C−H bond of **Int-69** is readily deprotonated with spin


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**Scheme 19. Hydroxyalkylation of Heteroarenes with Aldehydes**




**Scheme 20. Deaminative Alkylation of $\alpha$-3° Primary Amines**




center shifting to the adjacent imidoyl carbon atom. Namely, this SCS arises from deprotonation, which is quite different from traditional SCS processes that accompanied carbon−heteroatom bond heterolysis. Subsequent $\beta$-scission of **Int-70** gives rise to the alkyl radical **Int-71** that participates in the Giese reaction with electron-deficient alkenes to furnish the alkylation product **49**.

## CONCLUSION AND OUTLOOK

In summary, many synthetic applications have been reported based on SCS processes during the last 20 years, allowing for the functionalization of various carbon−heteroatom bonds. This area has encountered many breakthroughs. For example, the heterolysis of the C−F bond has been accomplished, thereby diversifying the bond types functionalized via the SCS process. The SCS process has also been extended. Traditional SCS processes are 1,2-radical translocations resulting from the heterolysis of carbon−heteroatom $\sigma$-bonds. Recently, the process is extended to the 1,2-radical shift along with a two-electron ionic movement, such as protonation of the C═O bond adjacent to the radical center with the forging of a new O−H $\sigma$-bond. Moreover, deprotonation of the C−H bond adjacent to the radical center results in the translocation of a spin center, which could also be regarded as a kind of SCS process.

Despite these advances, more achievements are anticipated: (1) SCS-promoted functionalization of C−N bonds remains underdeveloped; (2) construction of complex molecules may be accomplished through the sequential functionalization of various different carbon−heteroatom bonds; and (3) the merger of transition metal catalysis with SCS processes may provide ample opportunities to access a huge array of structurally diverse products, owing to well-developed organometallic chemistry. We look forward to the advancement of the SCS process in organic synthesis in the future.

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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