Catalytic Radical Reactions of Unsaturated Sugars

Giulio Goti*[a]
1. Introduction

Monosaccharides featuring a carbon-carbon double bond are valuable intermediates in organic synthesis.\[^1,2\] These unsaturated sugars provide straightforward access to a variety of glycoside derivatives as well as enantiomerically pure highly functionalized non-carbohydrate products. For example, glycals, the widest and most studied family of unsaturated monosaccharides, are extensively employed as glycosylating agents in the preparation of 2-deoxy sugars and complex oligosaccharides.\[^3,5\] and represent important precursors for the synthesis of C-glycosides.\[^6\] Unsatuated monosaccharides are relevant building block for the synthesis of natural products and biologically active molecules,\[^7\] but even their derivatives have shown great potential in medicinal chemistry. Indeed, zanamivir, a sialic acid mimic featuring an endocyclic double bond used in the therapy of flu, is a potent inhibitor of the influenza neuraminidase and probably one of the most known drugs that target glycals.\[^8\]

The well-established chemistry of C–C double bonds offers several strategies for the elaboration of unsaturated monosaccharides and, among these, transformations such as electrophilic additions, cycloadditions, rearrangements, and metallocations have found wide application.\[^1,10–13\] Radical approaches, have also been extensively investigated. These methods generally achieve the functionalization of the unsaturated monosaccharides double bond by addition of electrophilic carbon-centered and heteroatom radicals.\[^14–22\] Although providing a direct access to densely functionalized glycosides, these traditional methods typically require stoichiometric quantities of oxidants/reductants and/or dangerous and toxic reagents.

In recent years, radical chemistry has experienced an exciting and ongoing renaissance in the context of organic synthesis.\[^23\] Particularly, driven also by technological advances and breakthroughs in the fields of photo- and electrocatalysis, catalytic radical approaches have been established as powerful methods for the transformation of organic molecules.\[^24–26\] These strategies enable the controlled generation of reactive open-shell intermediates under particularly mild reaction conditions, thus overcoming limitations of traditional methods, paving the way to more sustainable processes and providing new synthetic opportunities. The carbohydrate community has recently recognized the potential of these catalytic approaches and applications to the synthesis of carbohydrates have emerged. In this Review, recent advances in the catalytic radical functionalization of unsaturated sugars are discussed. Particularly, the advantages of these catalytic methods, both in terms of reaction invention and sustainability, are highlighted. Limitations are also pointed out, suggesting new directions for further investigations.

2. Unsatuated Sugars: Scope, Structure and Reactivity

Unsaturated monosaccharides presenting a C–C double bond in their backbone are termed enoses and are classified according to the position at which the unsaturation takes place.\[^15\] This Review will survey the families of unsaturated sugars depicted in Scheme 1a. Among these, the family of glycals 1 is arguably the most studied and the most exploited for synthetic purposes. Specifically, glycals are enoses characterized by a double bond between the anomeric carbon C1 and C2. The term glycal is a trivial name introduced by Fischer and Zach in 1913 when they reported the first synthesis of a 1,2-unsaturated sugar from D-glucose, which was named D-glucal.\[^27\] In analogy, trivial names for the other saccharides are derived from the corresponding parent aldose (e.g., D-galactal for the glycal derived from D-galactose, etc.) and are commonly used.\[^28\] Glycals bearing a variety of substituents at the double bond, either at C1 or C2, are also known. Particularly, 2-hydroxyglycals 2 featuring a C–O bond at C2 present a distinct reactivity compared to unsubstituted glycals (vide infra) and have been used as versatile intermediates in the synthesis of carbohydrate analogues and natural products. Anhydro-1-enitols 3 constitute a further class of unsaturated monosaccharides. These compounds present a characteristic exo-methylene group and, given their structural similarity with glycals, are commonly referred to as exo-glycals.\[^29\] Although less exploited in synthesis than glycals, such C-glycosylidene have
inhibitors. Recently, the preparation of unsaturated sugars has attracted attention as convenient precursors in the synthesis of C-glycosides, natural products, and enzyme inhibitors. The last class of unsaturated sugars discussed within this Review is that of exo-enes. These compounds are reminiscent of eno-ses and exo-glycosides, natural products, and enzyme glycals for the presence of an exocyclic double bond α to the endocyclic oxygen, but exo-enes also retain an acetal group at C1.

A common feature to all unsaturated monosaccharides 1–4 is the enol ether moiety, which strongly dictates their chemical behavior and reactivity. The presence of such an electron-rich double bond makes these unsaturated sugars prone to oxidation or addition reactions in presence of electrophilic species. Scheme 1b summarizes the general reactivities of enoses 1–4 that will be treated throughout this Review. Particularly, glycols 1 can undergo protonation to form the oxocarbonium intermediate I, that can be readily intercepted by suitable nucleophiles at the anomeric C1 (Scheme 1b, path a). Alternatively, the same transformation can be attained via single electron transfer (SET) oxidation of glycols 1 to give the radical cation II that is also prone to nucleophilic addition at C1 (Scheme 1b, path b). The electron-rich double bond of glycol 1 can be also directly attacked by electrophilic radicals. The addition occurs at C2 to give the stabilized α-oxo radical III, that giving the resonance between the unpaired electron and the oxygen lone pair possesses a nucleophilic character (Scheme 1b, path c). On the other hand, radical addition to 2-hydroxyglycol 2 occurs at the less hindered C1 to give the nucleophilic intermediate IV (Scheme 1b, path d). Similarly, radical addition to exo-glycol 3 and exo-ene 4 proceeds at the less hindered exocyclic methylene carbon to give the corresponding stabilized α-oxo radical V or VI, respectively (Scheme 1b, path e).

3. Catalytic Radical Functionalization of Unsaturated Sugars

Recent catalytic radical approaches for the modification of unsaturated monosaccharides 1–4 rely on two main strategies: 1) electrophilic activation of the C–C double bond towards the addition of nucleophiles and 2) direct radical addition to the C–C double bond.

3.1. Electrophilic activation of Glycols

Nucleophilic addition to activated glycols is an established strategy in carbohydrate synthesis. Particularly, the addition of oxygen nucleophiles is arguably the most efficient route to 2-deoxy glycosides, relevant carbohydrate scaffolds found in many natural products, often displaying biological activity. 2-Deoxy sugars are characterized by the lack of substitution at C2, which makes their stereoselective assembly a great challenge. Although catalytic glycosylation methods using either organocatalysts or transition metal complexes have been successfully developed, complete control of the stereoselectivity and suppression of undesired side-reactions have long remained unmet goals.

In 2018, Wang and co-workers showed that a catalytic radical approach could provide a solution to this daunting problem. The authors developed a visible light-induced photoactivation method for the stereoselective conversion of glycol 1 to 2-deoxy glycosides 6 (Scheme 2). The reaction is performed with a slight excess of glycol 1 in presence of an alcohol 5 and catalytic amounts of the commercially available neutral eosin Y (EY, 1 mol %) and diphenyl disulfide 8 (2 mol %) under blue light irradiation, to give the glycosylated product 6 with excellent yields and exquisite α-selectivity. The mild conditions of such operationally simple protocol allowed to couple D-galactals with a variety of glycosyl acceptors and biorelevant molecules, including N-Boc protected serine, cholesterol, and a protected nucleotide.
Importantly, the reaction behaved well also with peracetylated \( \alpha \)-galactals \( 6 \text{a} \), generally not viable substrates under other catalytic glycosylation methods due to their tendency to form Ferrier type side products \( 7 \). Moreover, high \( \alpha \)-stereoselectivity was also observed in glycosylation of a series of variously protected more challenging \( \alpha \)-rhamnals \( 6 \text{b} \), and \( \alpha \)-glucals. A plausible reaction mechanism envisages the light irradiation of EY to give the excited EY* that acts as a photoacid. Protonation of glycal \( 1 \) gives the EY anion and the oxocarbenium ion \( I \), which undergoes nucleophilic addition with the alcohol \( 5 \) giving the intermediate \( \text{VII} \). On the other hand, light-induced homolytic cleavage of diphenyl disulfide \( 8 \) generates the thiyl radical \( 9 \), which reacts via SET with EY* giving the corresponding thiophenolate \( 10 \) and the eosin radical EY*. Thiophenolate \( 10 \) can then act as a base deprotonating the intermediate \( \text{VII} \), thus facilitating the formation of the glycosylated 2-deoxy sugar \( 6 \). Finally, thiophenol \( 11 \) reacts via hydrogen atom transfer (HAT) with EY* regenerating the active co-catalyst \( 9 \) and the EY photo-acid catalyst.

The efficient synthesis of 2-deoxy sugars from glycals was also recently accomplished by Xiong, Ye and co-workers by means of an electrocatalytic radical based method (Scheme 3).\(^{10} \) In this protocol, glycosylation between glycals \( 1 \) and alcohols \( 5 \) occurred smoothly using a catalytic amount of 3-bromopropionitrile \( 12 \) as redox mediator, in an undivided cell with a carbon and platinum electrodes as the anode and the cathode, respectively. Under these reaction conditions, \( \alpha \)-galactals and \( \alpha \)-glucals reacted with a variety of glycosyl donors to give the corresponding disaccharides with exclusive \( \alpha \)-selectivity, while \( \alpha \)-arabinals showed exclusive \( \beta \)-selectivity. Glycals could also be efficiently used as donors in the glycosylation of several natural products and drugs, as showcased by the scaled-up synthesis of glycosylated podophyllotoxin \( 6 \text{e} \). Remarkably, this methodology could be implemented with a second electrochemical glycosylation step to allow the one-pot iterative synthesis of trisaccharide \( 6 \text{f} \). The reaction mechanism was investigated by deuterium labelling experiments, cyclic voltammetry (CV) studies, and TEMPO trapping experiments. First, anodic oxidation of glycal \( 1 \) gives the radical cation \( \text{II} \) that can be intercepted by the alcohol \( 5 \) to form the radical cation intermediate \( \text{VIII} \). On the other hand, cathodic reduction of 3-bromopropionitrile \( 12 \) gives the primary radical.

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X and Br\(^-\), which can assist the deprotonation of intermediate VIII forming HBr and the radical intermediate IX. HAT between IX and HBr leads to the desired 2-deoxy glycoside 6 and bromine radical. Finally, two bromine radicals can combine to form Br\(_2\), which can react with two propionitrile radicals X to regenerate the redox mediator 12.

Recently, the same research group reported a related visible light promoted glycosylation protocol that allowed the iterative synthesis of oligosaccharides up to a 20-mer in length with excellent yields and selectivities.\[^{[41]}\]

### 3.2. Direct Radical Additions to Unsaturated Sugars

Electrophilic radicals readily add to the electron-rich double bond of enones. This strategy was recently exploited by the group of Xia to efficiently prepare 1,2-trans-2-amino-2-deoxyglycosides, widely occurring components of many oligosaccharides and glycoconjugates with important biological roles.\[^{[42]}\]

Specifically, the protocol uses catalytic TEMPO and N-fluorobenzenesulfonimide (NFSI) as a source of nitrogen-centered radicals and glycoconjugates with important biological roles.\[^{[43]}\]

The reaction is remarkable for its atom economy with excellent selectivities from >20:1 \(\beta:\alpha\) to only \(\beta\). Importantly, the authors showed that the reductive cleavage of the \(N\)-linked benzylsulfonimide group successfully led to the corresponding free amine. However, a large excess of SmI\(_2\) (20 equiv.) was required for this deprotection step. The proposed mechanism involves a SET event between the catalytic TEMPO and NFSI to give the oxidized TEMPO\(^+\) and the electrophilic nitrogen-centered radical XI. Addition of XI to glycal 1 leads to the glycosyl radical XII. This electron rich intermediate can be oxidized by TEMPO\(^+\) to give the oxocarbenium ion XIII and regenerate the catalyst. Finally, 6 β-attack of the alcohol 5 to XIII provides the 1,2-trans-2-amino-2-deoxyglycoside product 13.

With a related TEMPO-catalyzed protocol, Vankar et al. reported the synthesis of 2-azido-2-deoxy sugars from glycals using TMSI\(_2\) and a hypervalent iodine reagent.\[^{[44]}\] Similarly, an olefin diazidation protocol using a hypervalent iodine reagent in combination with a Fe\(^{3+}\) catalyst was applied by Xu and co-workers to the conversion of a \(\alpha\)-glucal derivative into the corresponding diazido compound.\[^{[45]}\]

A cascade reaction involving the addition of nitrogen-centered radicals to glycals was also reported by Hu and co-workers for the synthesis of \(C\)-glycosides, sugar mimics of great interest in medicinal chemistry for their increased stability towards hydrolytic enzymes.\[^{[46]}\] Imidate glycal derivatives 14 were reacted with styrenes or electron-deficient alkenes 15 in the presence of \([Ir(dtbpy)(ppy)_2](PF_6)\) photocatalyst and an excess of \(Pr_2NET\) under blue light irradiation to give the \(C\)-alkyl 2-amino-2-deoxy glycosides 16 (Scheme 5).\[^{[47]}\] This photocatalytic strategy provides a more sustainable alternative to classical radical methods, that generally require the use of stoichiometric toxic tin reagents and glycosyl selenides.\[^{[48,49]}\] Under these reaction conditions, \(\alpha\)-glucal and \(\alpha\)-galactal derived imidates reacted to give the corresponding 1,2-trans glycosides in high yields and exclusive \(\alpha\)-selectivity, while \(\beta\)-glycosides were obtained from \(\alpha\)-allal derivatives. Notably, the authors showed

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**Scheme 4.** Aminoglycosylation of glycals 1 catalyzed by TEMPO. NFSI: \(N\)-fluorobenzenesulfonimide.

**Scheme 5.** 1,2-trans stereoselective photocatalytic synthesis of \(C\)-alkyl 2-amino-2-deoxyglycosides 16 from glycal imidate derivatives 14.
that the dihydrooxazole ring could be cleaved upon treatment with diluted hydrogen chloride solution in methanol (0.25 M) to obtain the corresponding N-benzoyl protected C-aminoglycosides. A plausible reaction mechanism involves the SET reduction of glycal imidate 14 that, upon fragmentation with loss of a phenolate anion, gives the imidate radical intermediate XIV. Then, an intramolecular cyclization at C2 leads to the nucleophilic glycosyl radical XV, whose formation was confirmed by a TEMPO trapping experiment. Finally, the glycosyl radical XV can be intercepted by the terminal alkene 15 in a 1,2-trans stereoselective fashion, as rationalized by DFT calculations.

The synthesis of an analogous C-aryl-2-amino-2-deoxy glycoside was accomplished by Molander and colleagues. Specifically, a metallaphotoredox amidoarylation protocol of glycoside was accomplished by Molander and colleagues.

The synthesis of analogues with improved pharmacokinetic properties, oral bioavailability and metabolic stability. A plausible reaction mechanism involves the SET reduction of glycal imidate to give the excited state [Ir^{III}] that can react via SET with [Ir^{III}] giving the oxocarbenium ion XVIII and the ground state [Ir^{III}], thus closing the photocatalytic cycle. Finally, elimination of a proton from XVIII leads to the trifluoromethylated glycal 18.

To provide a more applicable and sustainable route for the trifluoromethylation of glycals, the same research group have recently developed an electrocatalytic protocol using CF_{3}SO_{3}Na as an inexpensive, readily available, and bench-stable trifluoromethyl source (Scheme 7). The reaction was performed in an undivided cell with two Pt electrodes as the anode and the cathode, using catalytic MnBr2 as redox mediator. The reaction efficiently enabled the trifluoromethylation of d-galactals, d-glucals, l-arabinals, l-rhamnals and d-xylals bearing benzyl, p-methoxybenzyl or tert-butylidimethyl silyl protecting groups (64-85% yield), while the more electron poor peracetylated d-galactal revealed to be a challenging substrate (30% yield). The role of MnBr2 as redox mediator was investigated by CV experiments, which showed MnBr2 to possess a lower oxidation potential (0.84 and 1.22 V vs Ag/AgCl) than CF_{3}SO_{3}Na (1.17 V vs Ag/AgCl), indicating that MnBr2 is preferentially oxidized at the anode catalyst and blue light irradiation. Remarkably, this catalytic approach goes beyond previous methods, as glycals are directly trifluoromethylated without the need of pre-functionalization and avoiding the use of stoichiometric perfluoroalkyl copper reagents. Under these mild reaction conditions, variously substituted d-glucal 18a, d-galactal 18b, l-arabinal and l-rhamnal 18c reacted smoothly. Interestingly, even an azido N-acetylneuraminic acid derivative, an important precursor of anti-flu drug zanamivir, successfully reacted to give the trifluoromethylated 18d in 45% yield. From a mechanistic point of view, the reaction is driven by the light irradiation of the [Ir^{III}] catalyst to give the excited state [Ir^{III}](E (Ir^{III}/Ir^{II}) = −1.73 V vs SCE) that can be oxidatively quenched by the Umemoto reagent 17 (E (17/17^+) = −0.26 V vs SCE). Then fragmentation with loss of dibenzothiophene 19 leads to the trifluoromethyl radical XVI and [Ir^{III}]. The electrophilic radical XVI can add to the glycal 1 to give the trifluoromethylated glycal 18 (Scheme 6). This method relies on the use of the Umemoto reagent 17 as radical precursor, fac-Ir(ppy)3 as photoredox mediator.
to give Mn$^{3+}$. The Mn$^{3+}$ ion can then diffuse and oxidize CF$_3$SO$_2$Na to generate the trifluoromethyl radical XVI that can add to glycal 1. Then, the so formed glycosyl radical XVII can be oxidized at the anode, generating the oxocarbenium ion XVIII. Finally, a proton elimination within XVIII gives the 2-substituted trifluoromethylated glycal 18, while protons are reduced at the cathode with release of H$_2$.

Perfluoroalkyl radicals can also be intercepted by 2-substituted glycals. As reported by Uhrig, Postigo and co-workers, 2-acetoxyglycals 2 can react with commercially available perfluoroalkyl iodides 19 under blue light illumination using (Ir(dF(C$_3$F$_7$)ppy)$_2$(dtbbpy))PF$_6$ and Cs$_2$CO$_3$ to give C-perfluoroalkylated glycosyl compounds 20 bearing perfluorinated alkyl chains at C1 (Scheme 8).[38] Fluoroalkyl iodides having 1, 4 and 6 carbon atoms were used to prepare peracetylated β-glycosyl and β-galactosyl (20a–c) derivatives in moderate yields (32–59%) and exclusive α-selectivity. 2-Acetoxy glycal derived from β-xylene reacted with n-C$_3$F$_7$I to give a mixture of the β-xyl and α-lyxo pyranoses in 1:1.4 ratio and combined 34% yield. Several mechanistic studies allowed to outline a plausible reaction mechanism (shown below for the reaction of β-galactal 2a as an example).[39] Control experiments proved that the photocatalyst is essential for the reaction to proceed. Therefore, the photoexcited catalyst [Ir$^{III}$]$^*$ is reductively quenched by Cs$_2$CO$_3$ to access the highly reducing Ir$^{III}$ complex, as proven by Stern-Volmer experiments. SET reaction between [Ir$^{III}$] (E [Ir$^{III}$/Ir$^{II}$] = −1.37 V vs SCE) and [Ir$^{III}$] (E [Ir$^{III}$/Ir$^{II}$] = −1.27 V vs SCE for C$_3$F$_7$I) is thermodynamically feasible and gives the ground state [Ir$^{II}$] and the perfluoroalkyl radical XIX that adds stereoselectively to the 2-acetoxyglycal 2a at C1. Finally, the ensuing α-oxo radical XX stereoselectively abstracts a H atom to give the C-perfluoroalkylated galactosyl 20a with an equatorial acetyl group at C2. While the nature of the H atom donor is still not fully understood, such closed catalytic cycle is supported by a quantum yield determination of Φ = 0.196.

![Scheme 8. Photocatalytic perfluoroalkylation of 2-acetoxyglycals 2.](image)

Recently, Vincent and collaborators showed that the addition of perfluoroalkyl radicals to enoles is not restricted to the use of endo-glycals.[40] Specifically, the authors reported two complementary approaches for the direct trifluoromethylation of exo-glycals 3 to obtain stereoselectively the Z-trifluoromethyl derivative 23 (Scheme 9). The Togni reagent 21 served as trifluoromethyl radical precursor in a CuI catalyzed process, using CDCl$_3$ as solvent at 120°C under microwave irradiation. On the other hand, the same transformation could be performed under blue LEDs irradiation using fac-Ir(ppy)$_3$ and the difluorinated Umemoto reagent 22. Both methods enabled the trifluoromethylation of C-glycosyldienes derived from d-arabinose, d-ribose, d-galactose, L-fucose and d-mannose, however photoredox catalysis revealed to be the most efficient strategy as its milder reaction conditions generally translated into higher yields. To gain insights on the exclusive Z-selectivity of the process, DFT calculations were performed. These studies indicated the Z-23 isomer to be more favored both thermodynamically and kinetically over the E-23 isomer, as a result of stabilizing hydrogen bonding interaction and avoidance of destabilizing steric clash.

Catalytic radical methods for the perfluoroalkylation of exo-ene unsaturated sugars are elusive. However, a photochemical defluorinative alkylation method, recently reported by Molander and co-workers, allowed the perfluoroalkylation of the methylene d-galactose derivative 4a, giving the gem-difluorinated product 26 in 74% yield and excellent diastereoselectivity, d.r. > 20:1 (Scheme 10).[41] This protocol alkenes readily trap gem-

![Scheme 9. CuI and photoredox catalysis as alternative approaches to the direct trifluoromethylation of exo-glycals 3.](image)

![Scheme 10. Photochemical gem-difluoroalkylation of the exo-ene d-galactose derivative 4a with ethyl trifluoracetate 24.](image)
difluoro α-carbonyl radicals XXI, obtained from the commodity feedstock ethyl trifluoroacetate 24 under light irradiation (390 nm) using the benzophenone derivative 25 (20 mol%) as HAT catalyst, cyclohexyl thiol as co-catalyst (20 mol%), and an excess of sodium formate as reducing agent (3 equiv.). Although limited to this single example, this precedent suggests that catalytically generated gem-difluoro α-carbonyl radicals XXI could be readily intercepted by a variety of exo- enes and, more generally, that further electrophilic radicals could engage in this kind of reactivity. Therefore, this work hints at catalytic radical strategies as powerful approaches in the development of new reactions for the functionalization of exo- ene sugars.

The addition of a hydrogen atom to the double bond of unsaturated carbohydrates represents a convenient strategy to synthesize relevant sugar derivatives.32 Following this HAT activation strategy, Kern, Compain and colleagues reported the stereoselective reaction of exo-glycols 3 and exo- enes 4 with Michael acceptors 27 to give the corresponding difficult to access C,C-glycosides 28 and 29, characterized by the presence of a stereodefined quaternary pseudoanomeric center bearing two exocyclic C-substituents (Scheme 11).33 The reaction required Fe(acac)3, as catalyst (10 mol%), an excess of PhSiH3, as reducing agent, and Na2HPO4 as a base in ethanol. Under these conditions, terminal exo-glycols derived from d-glucose 28a, d-mannose and d-threose 28b were coupled with a variety of Michael acceptors with good to complete stereo-selectivity both in the pyranose and furanose series. A d-glucose exo-ene derivative was also a competent substrate, giving the alkylated product 29a, while more sterically demanding trisubstituted exo-glycols proved recalcitrant to HAT, requiring stoichiometric quantities of Fe complex to provide the products in synthetically useful yields. From a mechanistic point of view, the reaction is mediated by catalytic Fe hydride species [Fe-H] that are formed in situ by treating Fe(acac)3 with PhSiH3 in ethanol.34 HAT from [Fe-H] to the exo-glycal 3 gives the reduced [FeI] complex and the nucleophilic glycosyl radical XXII, that can react in a Giese-type radical addition with the electron-poor alkene 27. Finally reduction and protonation of the ensuing radical intermediate XXIII regenerates the [FeIII] catalyst and gives the C,C-glycoside 28. The same mechanism is operating for the reaction of exo-ene 4.

4. Summary and Outlook

Unsaturated monosaccharides are easily accessible, versatile intermediates in organic synthesis. These sugar derivatives feature a C–C double bond that opens up multiple synthetic possibilities for their elaboration. In this regard, radical approaches have long been exploited for the functionalization of enoses, but traditional methods generally rely on harsh, poorly sustainable conditions, which limit their applicability. Catalytic radical methods instead have been recently established as greener alternatives. Relying on modern activation strategies, such as photo- and electrocatalysis, the use of catalytic organic molecules or transition metal hydride complexes, these processes achieve the functionalization of unsaturated sugars either 1) through electrophilic activation towards the addition of nucleophiles, or 2) by the direct addition of electrophilic radicals. These catalytic approaches have provided more sustainable routes to the synthesis of 2-deoxyglycosides, and amino sugars, relevant carbohydrate scaffolds found in many natural products with important biological activities. Moreover, catalytic radical methods also paved the way towards new reactivities, enabling the preparation of C-glycosides and perfluorinated sugars mimics, compounds with great importance in medicinal chemistry for their increased metabolic stability and improved pharmacokinetic properties.

Despite their great potential, catalytic radical methods for the elaboration of enoses remain largely unexplored, suggesting this research area as a fertile ground for further reaction invention. Indeed, most of the protocols reported so far only focus on the functionalization of unsubstituted glycols, while reactions involving other classes of enoses are still under-developed. Moreover, strategies involving the direct addition of open-shell intermediates to enoses have been reported only for limited types of radical species. Therefore, future advances in the field will likely allow to cover these synthetic gaps, enabling to engage a wide variety of unsaturated sugars with several radical partners to achieve new transformations. Future endeavors should also be directed in the development of stereoselective catalytic radical processes able to override the stereochemical preferences imparted by the substrates. Ideally, these new methods would also be amenable to unprotected unsaturated sugars, thus allowing to avoid tedious protection/deprotection steps that typically affect the sustainability of
photoredox catalysts should be favored, as they represent a precious transition metals. In this regard, in the development of new photocatalytic transformations the use of purely organic photoredox catalysts should be favored, as they represent a more sustainable alternative to Ru- and Ir-based complexes.

In conclusion, this Review has discussed recent catalytic radical approaches to the functionalization of unsaturated carbohydrates, highlighting the opportunities offered by these strategies in the development of new transformations of increased sustainability. This discussion will likely foster forthcoming investigations in such an exciting research field, leading to new methodological developments and applications.

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Conflict of Interest

The authors declare no conflict of interest.

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