# Catalytic 1,2-Radical Acyloxy Migration: A Strategy to Access Novel Chemical Space and Reaction Profiles

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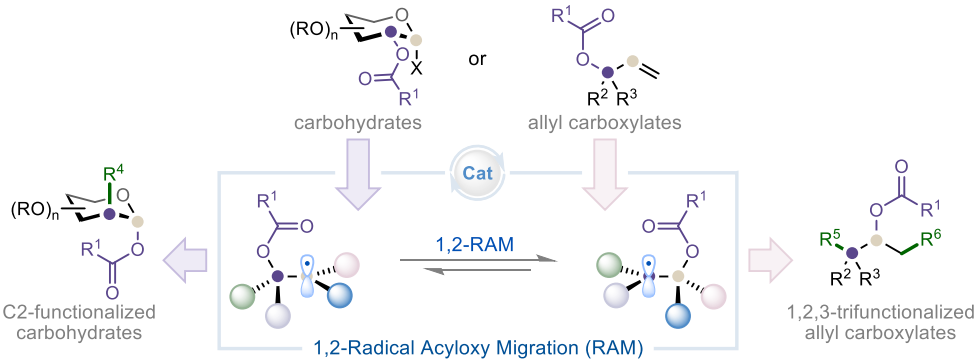
**Conspectus:** Radical migration represents a powerful strategy for reaction discovery and development in organic synthesis, offering access to unprecedented functional molecules and chemical space. In this *Account*, we highlight our contributions to the field, particularly focusing on 1,2-radical acyloxy migration (RAM), a process involving the transposition of a radical and an acyloxy group. We highlight its application in carbohydrate modification and allyl carboxylate trifunctionalization, demonstrating how this reactivity enables the streamlined synthesis of novel glycomimetics and facilitates selective 1,2,3-trifunctionalization of allyl carboxylates. These advances establish 1,2-RAM as a versatile platform for catalytic radical transformations, unlocking new opportunities in reaction development and functional molecule design.

Our approach leverages excited-state palladium and ground-state nickel catalysis to modify carbohydrates, specifically at the C2 position. This strategy enables C2-deoxy-hydrogenation, deuteration, iodination, alkenylation, ketonylation, and arylation reactions, providing direct access to unprecedented glycomimetics. These transformations streamline the synthesis of structurally diverse glycomimetics, facilitating the discovery and development of carbohydrate-based functional molecules. Furthermore, the mild reaction conditions and high functional group tolerance of these catalytic systems make them particularly attractive for late-stage functionalization, broadening their applicability in complex molecule synthesis.

Beyond carbohydrates, we have extended 1,2-RAM reactivity to achieve unprecedented 1,2,3-trifunctionalization of allyl carboxylates. By employing excited-state phosphine catalysis, we demonstrate a 1,3-carbobromination reaction accompanied by an acyloxy shift. This proof-of-concept study lays the foundation for developing a broader range of 1,2,3-trifunctionalization reactions, effectively transforming allyl carboxylates into substituted isopropyl carboxylate donors. This advancement expands the synthetic utility of allyl carboxylates, enabling the rapid construction of structurally diverse molecular scaffolds.

In summary, the 1,2-RAM reactivity opens a new avenue for reaction discovery and development, granting access to new functional molecules and chemical space. The mild conditions, broad functional group compatibility, and unique reactivity of this approach make it a valuable tool for chemical synthesis. We anticipate that merging 1,2-RAM with other catalytic platforms will further advance bond disconnection strategies, provide access to new functional molecules, and expand the frontiers of chemical synthesis.




## KEY REFERENCES


- Zhao, G.; Yao, W.; Mauro, J. N.; Ngai, M. -Y. Excited-State Palladium-Catalyzed 1,2-Spin-Center Shift Enables Selective C2-Reduction, Deuteration, and Iodination of Carbohydrates. *J. Am. Chem. Soc.* **2021**, *143*, 1728-1734.[1] Introduced excited-state palladium-catalyzed 1,2-spin-center shift enabling site-selective C2-functionalization of carbohydrates under mild conditions, providing a general platform for accessing diverse 2-deoxy sugars *via* radical-mediated reduction, deuteration, and iodination.
- Zhao, G.; Yao, W.; Kevlishvili, I.; Mauro, J. N.; Liu, P.; Ngai, M. -Y. Nickel-Catalyzed Radical Migratory Coupling Enables C2-Arylation of Carbohydrates. *J. Am. Chem. Soc.* **2021**, *143*, 8590-8596.[2] Developed ground-state nickel-catalyzed radical migratory cross-coupling of 1-bromosugars and arylboronic acids, enabling direct access to C2-aryl-2-deoxyglycosides *via* a 1,2-radical acyloxy migration (RAM) and broadening the scope of nickel-catalyzed C–C bond formation.
- Yao, W.; Zhao, G.; Wu, Y.; Zhou, L.; Mukherjee, U.; Liu, P.; Ngai, M. -Y. Excited-State Palladium-Catalyzed Radical Migratory Mizoroki–Heck Reaction Enables C2-Alkenylation of Carbohydrates. *J. Am. Chem. Soc*. **2022**, *144*, 8, 3353-3359.[3] Established excited-state Pd-catalyzed 1,2-radical migratory Mizoroki–Heck reaction for C2-

alkenylation of carbohydrates, enabling streamlined access to C2-alkenylated glycomimetics from readily available 1-bromosugars and alkenes.

- Zhao, G.; Lim, S.; Musaev, D. G.; Ngai, M.-Y. Expanding Reaction Profile of Allyl Carboxylates *via* 1,2-Radical Migration (RaM): Visible-Light-Induced Phosphine-Catalyzed 1,3-Carbobromination of Allyl Carboxylates. *J. Am. Chem. Soc*. **2023**, *145*, 8275−8284.[4] Demonstrated photoinduced, phosphine-catalyzed 1,3-carbobromination of allyl carboxylates *via* 1,2-RAM, delivering substituted isopropyl carboxylates with broad scope and highlighting new reactivity for both allyl carboxylates and phosphine catalysis.

## 1. Introduction

Radical reactions have emerged as indispensable tools in modern organic synthesis due to their unique ability to construct complex molecular architectures under mild conditions.[5-8] By circumventing the limitations of ionic mechanisms, radicals offer pathways to access intermediates that are otherwise challenging to generate. Significant advances in transition-metal catalysis,[9-13] photocatalysis,[14-17] and electrocatalysis[18-21] have propelled this area forward, allowing chemists to efficiently generate radical species, introduce new bond disconnections, and install diverse functional groups. Among these advancements, 1,n-radical functional group migrations—where radicals shift through functional groups such as (hetero)arenes, nitriles, carbonyls, alkenes, alkynes, silyls, and boron—have provided new synthetic routes for building complex molecules (**Figure 1**A).[22-26]

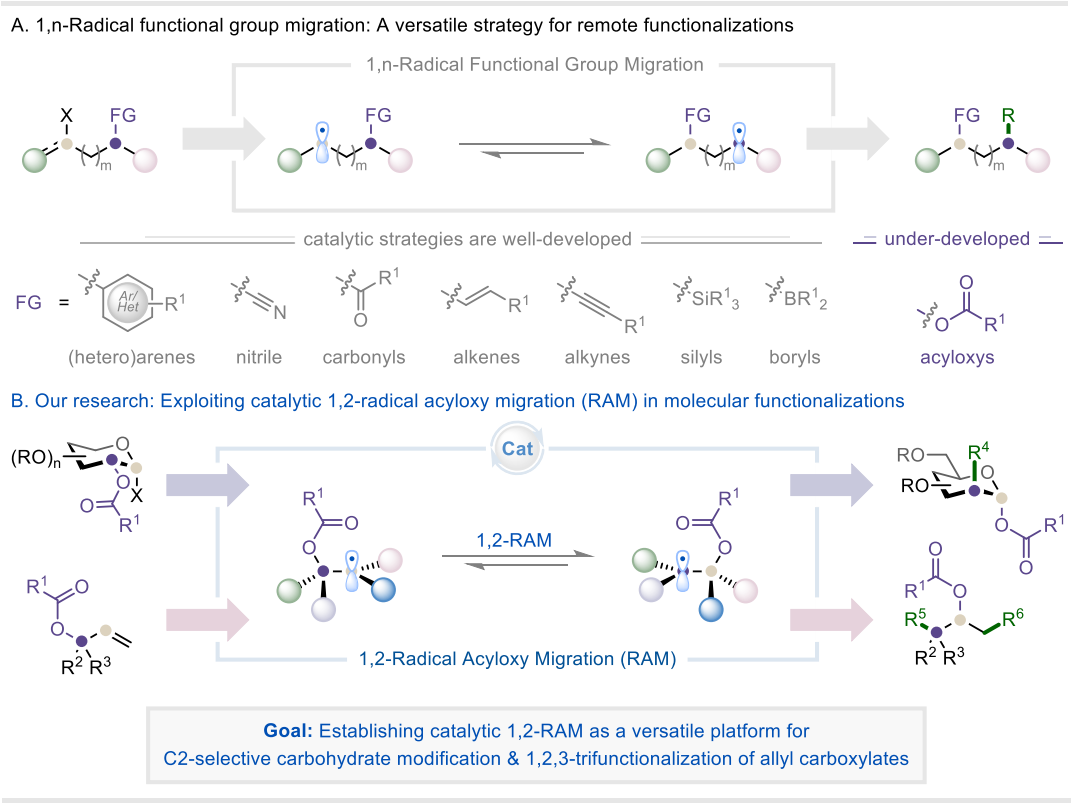



**Figure 1**. 1,n-Radical functional group migration and 1,2-radical acyloxy migration (RAM).

Within the field of radical migration chemistry, 1,2-radical acyloxy migration (1,2-RAM) holds promise for accessing new chemical spaces, but catalytic cross-coupling reactions utilizing this process remain underdeveloped.[23] Mechanistically, 1,2-RAM involves the migration of a radical from a β-position to an adjacent atom, accompanied by the transfer of the acyloxy group.[27-28] This reactivity was first recognized in the seminal work of Surzur and Tanner in the 1960s, known as the Surzur-Tanner rearrangement.[29-30] Despite its early discovery, this rearrangement has been predominantly applied to the stoichiometric synthesis of 2-deoxy sugars,[27, 31] with limited progress in catalytic applications.

Our research aims to advance catalytic radical chemistry by developing catalytic systems that harness 1,2-RAM to enable novel transformations. Specifically, we have explored 1,2-RAM as a mechanistic platform to achieve site-selective functionalization of carbohydrates and expand the reactivity of allyl carboxylates (**Figure 1**B). Achieving this would (i) create a new catalytic platform for discovering and developing novel reactions, (ii) facilitate catalytic transformations where the activation site is distinct from the coupling site, (iii) provide access to molecular architectures that are otherwise challenging or impossible to synthesize, and (iv) broaden the scope of radical chemistry, enabling the synthesis of complex molecules.

In this Account, we summarize our efforts to develop and apply catalytic 1,2-RAM reactivity for both carbohydrate modification and the functionalization of allyl carboxylates. Our findings highlight the potential of 1,2-RAM not only to expand the toolkit of radical chemistry but also to address key challenges in synthetic methodology.

## 2. Site-Selective Functionalization of Carbohydrates *via* Catalytic 1,2-RAM

Carbohydrates are abundant in natural systems, playing key roles in biological functions such as cell recognition, protein folding, neurobiology, and immune response, as well as serving as metabolic energy sources.[32] Due to their diverse functionality, carbohydrate derivatives have shown significant promise in industries ranging from materials science and agrochemicals to pharmaceuticals.[33-34] Among these, C2-functionalized-2-deoxy sugars show great promises because such structural alteration creates molecules with applications across various fields, including chiral ligand design,[35] imaging agents,[32] cell engineering tools,[36-37] LpxC enzyme inhibitors,[38] and pharmaceutical applications (**Figure 2**).[39]

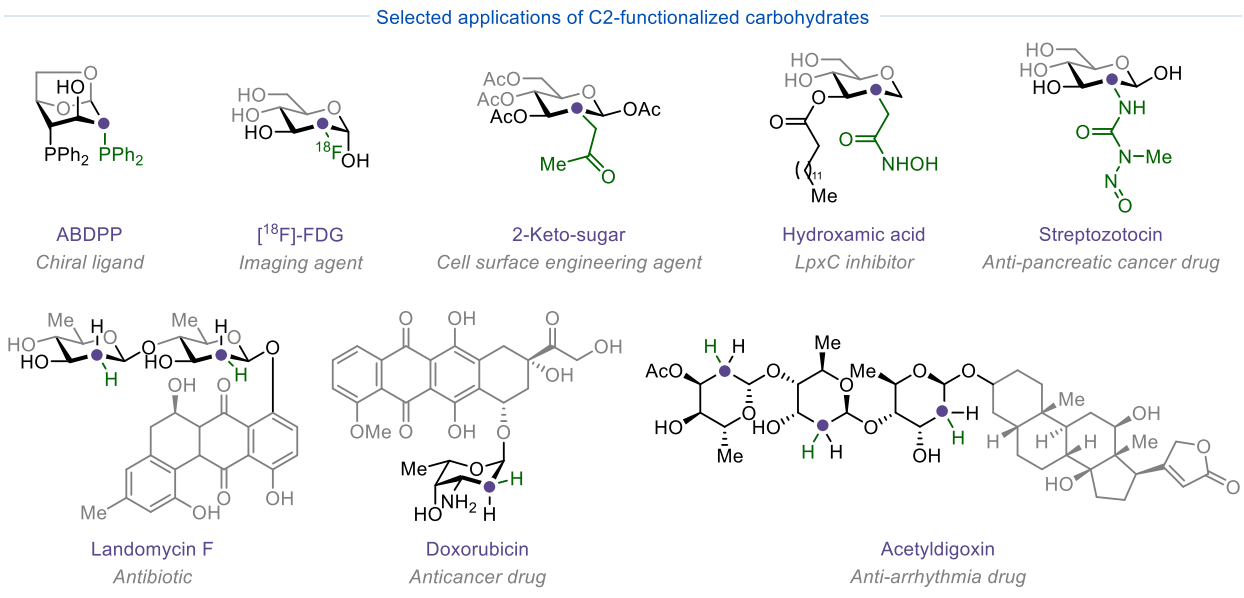



**Figure 2**. Selected applications of C2-functionalized sugars.

Given their broad applicability, modifying the carbohydrate structure to tailor physiological properties has attracted significant attention in organic synthesis.[40] However, challenges persist, particularly due to the dense array of hydroxyl groups and complex stereochemistry. Most efforts have focused on modifying the anomeric position or functionalizing peripheral hydroxyl groups, while synthesizing functionalized, unnatural carbohydrate analogs

remains difficult. Advanced methodologies like photoredox-catalyzed C-H and C-C activation have recently shown promise for direct carbohydrate modification.[41]

Despite progress, the synthesis of C2-deoxy-2-functionalized carbohydrates still relies on traditional multistep protocols (**Figure 3**A). For instance, synthesizing C2-ketonyl carbohydrates, crucial for cell surface engineering, requires an eight-step process that yields under 21% overall and involves hazardous reagents like alkyl tin and $OsO_4$.[36-37] Similarly, C2-alkenylated sugars and [$^{18}$F]-2-deoxysugars are synthesized through eight and seven linear steps, with yields below 34% and 14%, respectively.[42-43] These laborious processes highlight the need for direct, site-selective functionalization methods at the C2 position of carbohydrates. The development of such methods would not only simplify the synthesis of complex carbohydrate derivatives but also significantly accelerate drug discovery efforts by providing efficient access to biologically relevant sugar analogs.

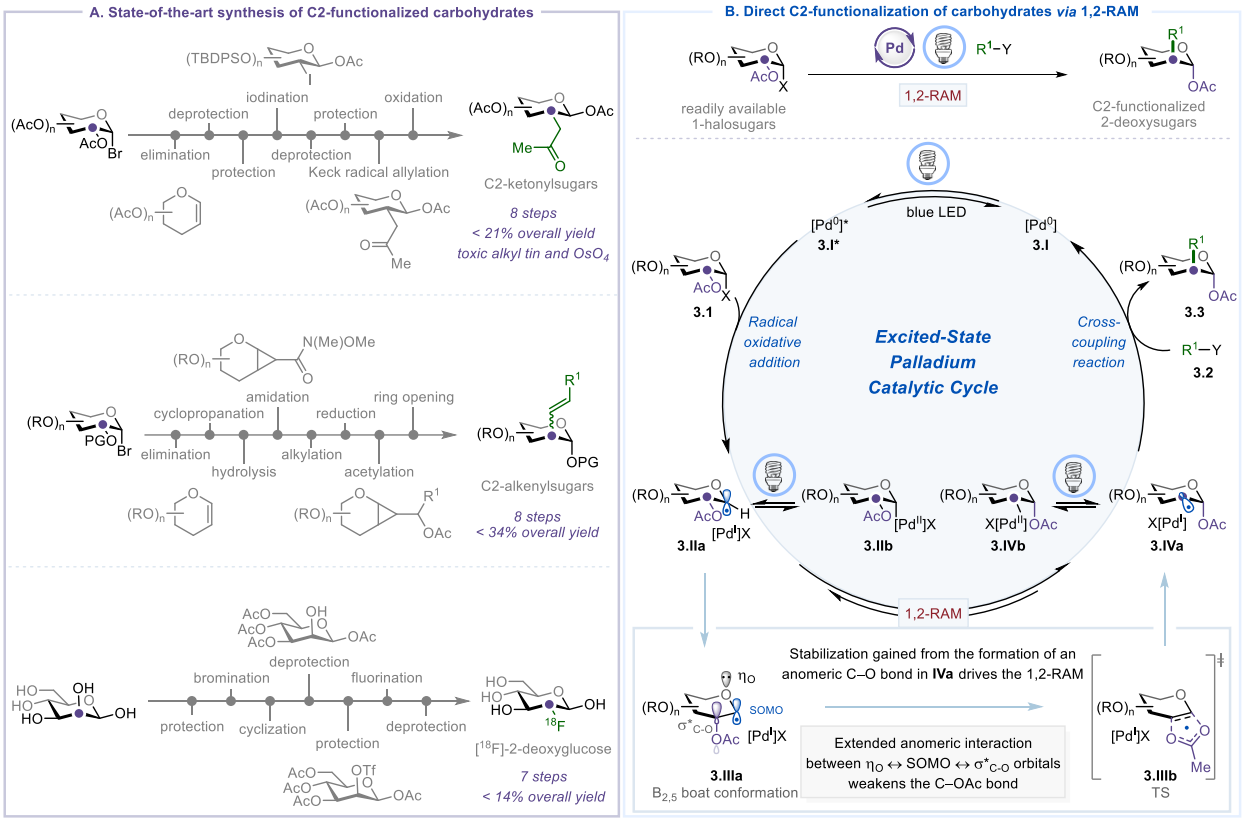



**Figure 3. A**. State-of-the-art synthesis of C2-functionalized carbohydrates; **B**. Catalytic C2-functionalization of carbohydrates through 1,2-radical acyloxy migration (RAM). Adapted with permission from Ref. 1. Copyright 2021 American Chemical Society.

In 1987, Giese demonstrated that 1-glycosyl radicals can undergo a 1,2-radical acyloxy migration, leading to the formation of a deoxypyranosan-2-yl radical.[31] Inspired by these seminal findings, we envisioned that 1,2-RAM reactivity could serve as a foundation for developing a broad range of catalytic, direct, and site-selective modifications at the C2 position of carbohydrates. To achieve this site-selective reaction, we proposed employing versatile excited-state palladium catalysis, which has recently gained significant attention due to its ability to engage in both open-shell (one-electron) and closed-shell (two-electron) reactivities upon exposure to visible-light irradiation.[44]

Our mechanistic hypothesis is illustrated in **Figure 3**B.[1] Upon visible-light irradiation, the palladium(0) photocatalyst [Pd(0)] is promoted to its excited state [Pd(0)]*, which engages in single-electron transfer with the 1-halosugar **3.1**, generating hybrid 1-glycosyl-Pd–X species **3.IIa** and **3.IIb**.[45-46] The resulting glycosyl radical **3.IIa** predominantly adopts a $B_{2,5}$ boat conformation **3.IIIa**, stabilized by hyperconjugation through an extended anomeric interaction involving the endocyclic oxygen lone pair ($\eta_O$), singly occupied molecular orbital (SOMO) and the σ*C–O orbital of the C2–OAc group.[47-48] This interaction weakens the C2–OAc bond, facilitating a concerted [2,3]-acyloxy rearrangement *via* a cyclic five-membered transition state **3.IIIb**,[27, 47] yielding the deoxypyranosan-2-yl radical **3.IVa**.[49] Although the anomeric radical is generally more stable than a secondary alkyl radical, the formation of a new anomeric C–O bond in **3.IVa** provides a thermodynamic driving force for the 1,2-RAM.[50] Under continued visible-light irradiation, the resulting alkyl radical/Pd(I)X species **3.IVa** can equilibrate with the corresponding alkyl-Pd(II)X complex **3.IVb**, enabling divergent reactivity *via* either open-shell or closed-shell pathways. We propose that these hybrid Pd intermediates can participate in various cross-coupling processes, including (i) transmetallation followed by reductive elimination or (ii) radical coupling/atom transfer followed by reduction of Pd(I)X. Both routes converge on the formation of the C2-functionalized carbohydrate product **3.3** and regenerate the ground-state Pd(0) catalyst, thereby completing the catalytic cycle.

## 2.1 Excited-State Palladium-Catalyzed 1,2-RAM Enables Selective C2-Reduction, Deuteration, and Iodination of Carbohydrates.

Guided by this mechanistic framework, we sought to develop a direct method for the exclusive synthesis of C2-deoxy carbohydrates. In 2021, we achieved this by reacting α-glucosyl bromide (1.0 equiv) with $Pd(PPh_3)_4$ (5 mol%), DIPEA (2.0 equiv) in $^{i}$PrOAc (0.050 M) under

irradiation with 24 W blue LEDs at ambient temperature for 24 hours. This approach afforded the desired product in 94% yield with >20:1 α:β selectivity at the C1 position.[1]

Applying these optimized conditions, we successfully converted a diverse array of substrates derived from L-fucose, D-xylose, D-galactose, and melibiose into the corresponding 2-deoxy sugars with excellent yields ranging from 73% to 94% (**Figure 4**). Additionally, the process demonstrated broad applicability through late-stage functionalization of natural product- and drug-conjugated sugar derivatives, such as those derived from oleanolic acid, indomethacin, and probenecid. Modifying the solvent to $d_8$-THF and the base to $Cs_2CO_3$ further expanded the method's synthetic utility, allowing the synthesis of C2-deuterated carbohydrates. These compounds, produced in 88–98% yields with high deuterium incorporation, can serve as valuable probes for studying metabolic and biosynthetic pathways,[51] as well as precursors for bioactive molecules. Intriguingly, altering the substrate to α-glucosyl iodide enabled the formation of a wide range of 2-iodo-2-deoxy sugars in high yields with up to >20:1 equatorial/axial selectivity. This adaptability highlights the synthetic versatility of our method.

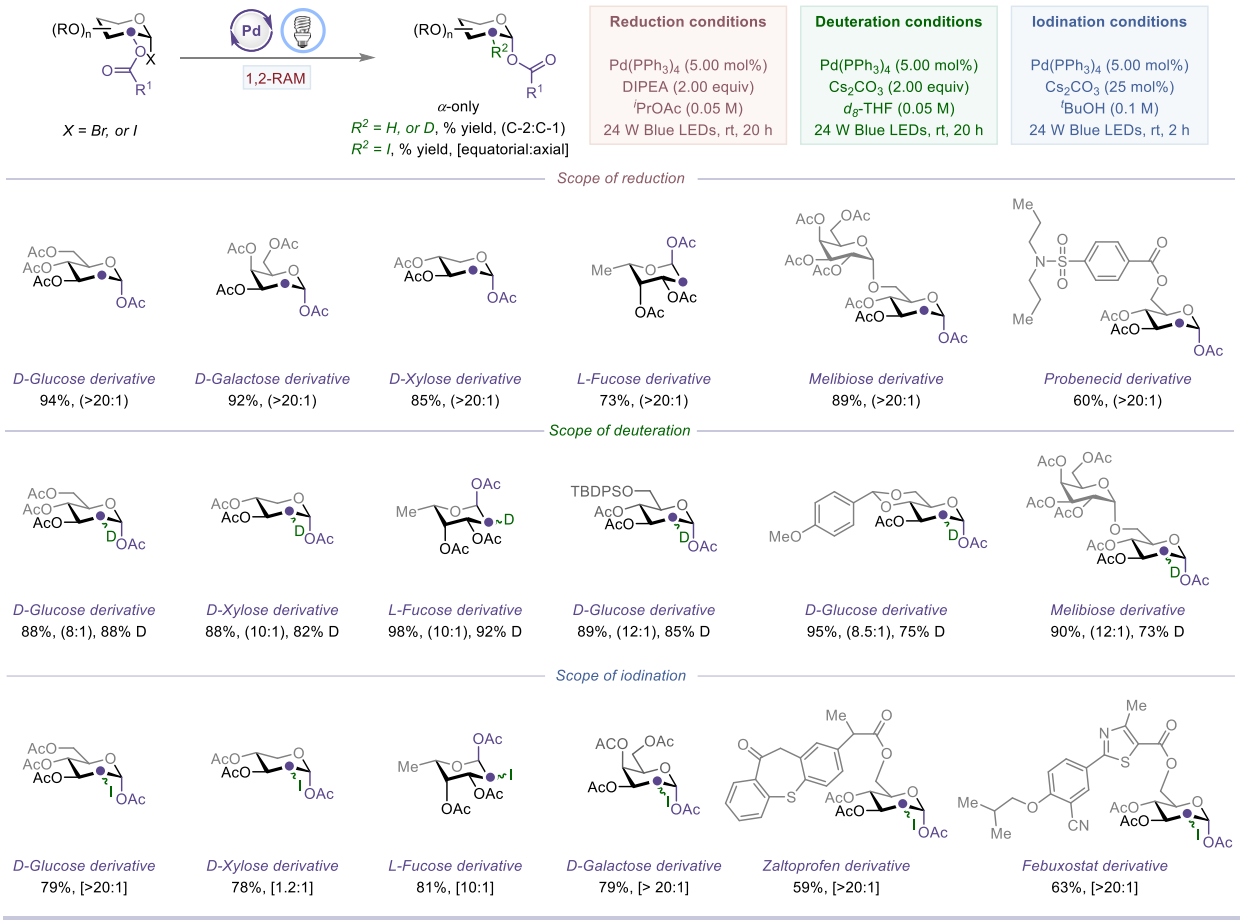



**Figure 4**. Excited-state palladium-catalyzed C2-reduction, -deuteration, and -iodination of carbohydrates. Adapted with permission from Ref. 1. Copyright 2021 American Chemical Society.

The radical nature of the reaction was confirmed by the complete inhibition observed in the presence of a radical scavenger, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO). Stern–Volmer quenching studies further supported this mechanism, demonstrating that 1-halosugars effectively quench the excited state of $Pd(PPh_3)_4$, indicating single-electron transfer (SET) from the catalyst to the 1-halo carbohydrate, effectively leading to its reduction. The low quantum yields of C2-reduction ($\Phi = 0.09$) and iodination ($\Phi = 0.24$) suggest that extended radical chain propagation is unlikely.

The key 1,2-RAM is proposed to proceed *via* one of four mechanistic pathways: (**P1**) homolytic fragmentation to generate an acyloxy radical and an alkene, followed by radical recombination; (**P2**) formation of a 1,3-dioxolanyl radical intermediate, which undergoes ring-opening; (**P3**) heterolytic cleavage to yield an alkene radical cation and an acyloxy anion, followed by recombination; or (**P4**) a concerted shift *via* a five-membered cyclic transition state (**Figure 5**).[27]

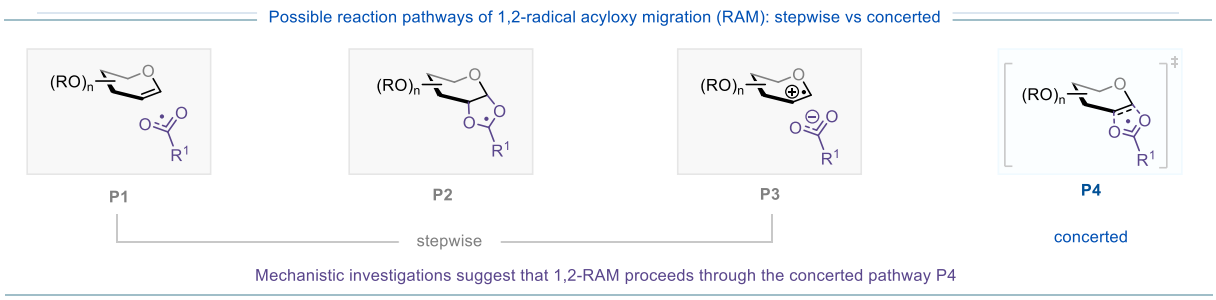



**Figure 5**. Plausible reaction pathways of 1,2-RAM.

Pathway **P1** is ruled out because the decarboxylation rate of acyloxy radicals ($k = 10^9$ s$^{-1}$)[52] far exceeds the observed migration rate ($k = 10^2$ s$^{-1}$),[50] and no decarboxylation byproducts were detected. **P2** is also unlikely, as a radical clock experiments conducted by us[1] and Woerpel[53]—using cyclopropyl and fluorenylcyclopropyl acetate-substituted substrates, respectively—yielded the desired products without evidence of the expected ring-opened byproducts. Furthermore, crossover experiments showed no formation of cross-over products, indicating either a tightly coupled "in-cage" recombination (**P3**) or a fully concerted pathway (**P4**). Given that variations in the electronic nature of the migrating group have minimal influence on the reaction rate, the data collectively support the concerted mechanism (**P4**) as the most likely pathway, consistent with both DFT calculations and prior literature reports.[50, 54]

## 2.2 Excited-State Palladium-Catalyzed Radical Migratory Mizoroki–Heck Reaction Enables C2-Alkenylation and C2-Allylation of Carbohydrates.

Following our proof-of-concept studies, we hypothesized that the C2-radical could be trapped by other radicophiles, such as alkenes, under excited-state Pd-catalyzed conditions,[45-46] to achieve the unprecedented catalytic, direct C2-alkenylation of carbohydrates. This area has traditionally been hindered by extensive protecting group manipulations and low overall yields (**Figure 3**A).[42] Achieving this reaction would streamline the preparation of this class of glycomimetics and constitute the first example of an excited-state Pd-catalyzed radical migratory Mizoroki–Heck-type reaction. One major challenge was preventing premature C1-alkenylation, which we envisioned could be mitigated by accelerating the 1,2-RAM process. Through systematic optimization, we discovered that subjecting 1-bromoglucoside and styrene to a reaction mixture containing $Pd(PPh_3)_4$ (10 mol%), Xantphos (20 mol%), and $K_3PO_4$ (2 equiv) in benzene (0.025 M), under blue LED irradiation at 90 °C for 14 hours, afforded the desired C2-alkenylated product in 83% yield with an axial/equatorial (ax/eq) selectivity of 4.2:1 (**Figure 6**).[3]

Under the optimized conditions, a wide range of 1-bromo carbohydrate substrates—including those derived from D-xylose, D-galactose, D-glucuronic acid, L-fucose, as well as disaccharides such as D-melibiose, D-maltose, and D-cellobiose—proved compatible with various alkenes. These reactions delivered C2-alkenylated derivatives in yields ranging from 32% to 80%. Additionally, our methodology demonstrated versatility in late-stage modifications of natural products and drug glycoconjugates. The resulting C2-functionalized products were amenable to further post-functionalization reactions, including reduction, epoxidation, ozonolysis, and glycosylation, enabling the synthesis of diverse glycomimetics.

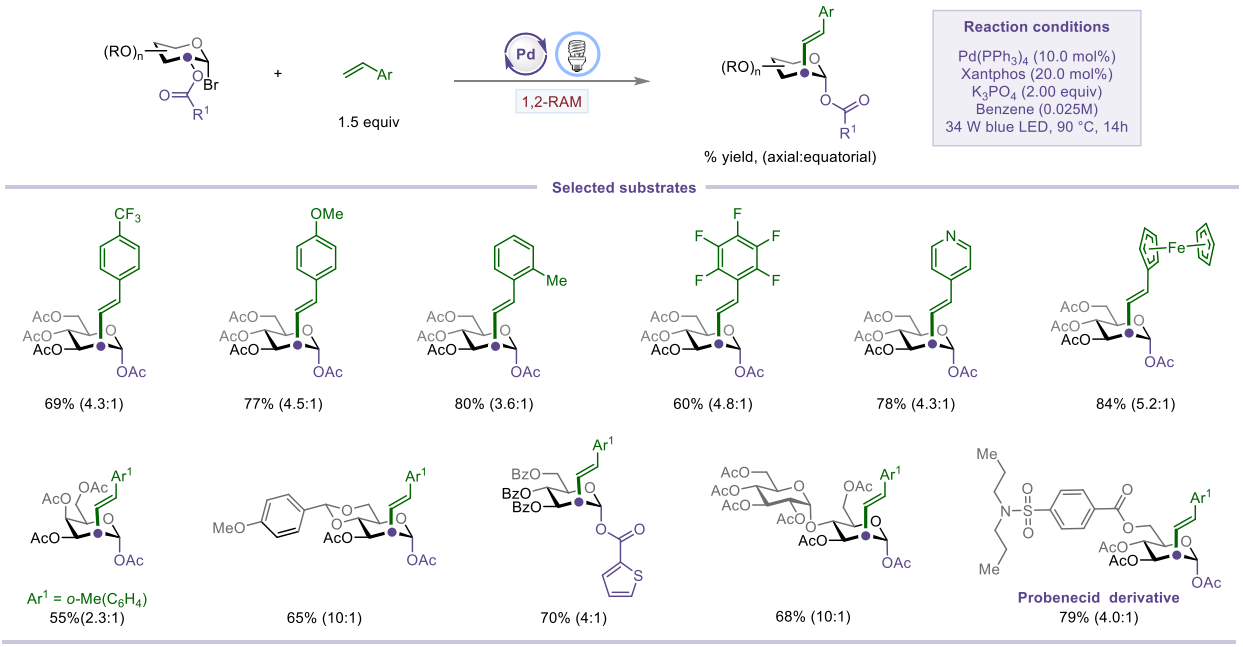



**Figure 6**. Excited-state palladium-catalyzed C2-alkenylation of carbohydrates

While the exact mechanism for generating alkenes from benzylic radicals requires further investigation, preliminary experimental and computational studies suggest that the addition of the benzylic radical to a Pd(I) complex, followed by a β-hydride elimination pathway (**7.TS1**), is favored over other potential pathways, such as hydrogen atom abstraction (**7.TS2**) or bromine atom transfer (**7.TS3**), leading to the formation of the desired product (**Figure 7**).

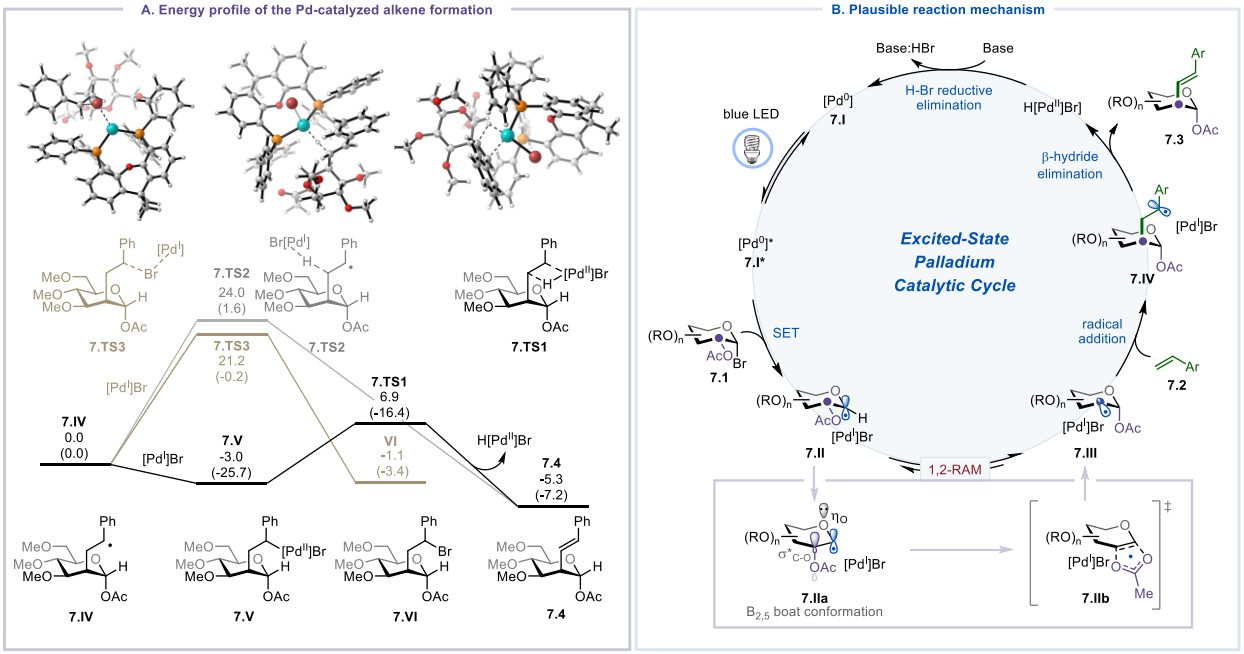



**Figure 7**. DFT calculations and plausible reaction mechanism. Adapted with permission from Ref. 3. Copyright 2022 American Chemical Society.

Interestingly, when α-alkylstyrenes were used, the reaction instead furnished C2-allylated carbohydrates, valuable intermediates for glycomimetic synthesis.[55] Under the same catalytic conditions, various α-bromosugars, including, D-galactoside, L-fucoside, D-xylose, D-glucuronic acid analogs, D-melibiose, D-cellobiose, D-maltose, as well as substrates with different C6 protecting groups (**Figure 8A**). Additionally, acyloxyl migrating group with varying electronics properties or heteroaromatic substitutents were successfully employed, yielding the corresponding products. The functional group tolerance of 1,1-alkene substrates was also explored. Notably, using D-maltose derivatives as coupling partners resulted in products with a high axial-to-equatorial ratio, reaching up to 14:1. Furthermore, activated alkenes such as α-methylstyrene derivatives, trisubstituted alkenes, including β-alkylated α-methylstyrenes, and even unactivated alkenes like 1,1-dialkyl alkenes, were successfully converted to the desired products under these conditions. Alkene derivatives containing natural products, such as glucofuranose, ibuprofen,

menthol, and oleanolic acid, were also compatible with the standard conditions (**Figure 8B**). The resulting C2-allylated sugars are not only reactive donors in glycosylation reactions but also serve as valuable synthetic intermediates for the preparation of C2-alkylated products and C2-ketonylation derivatives.

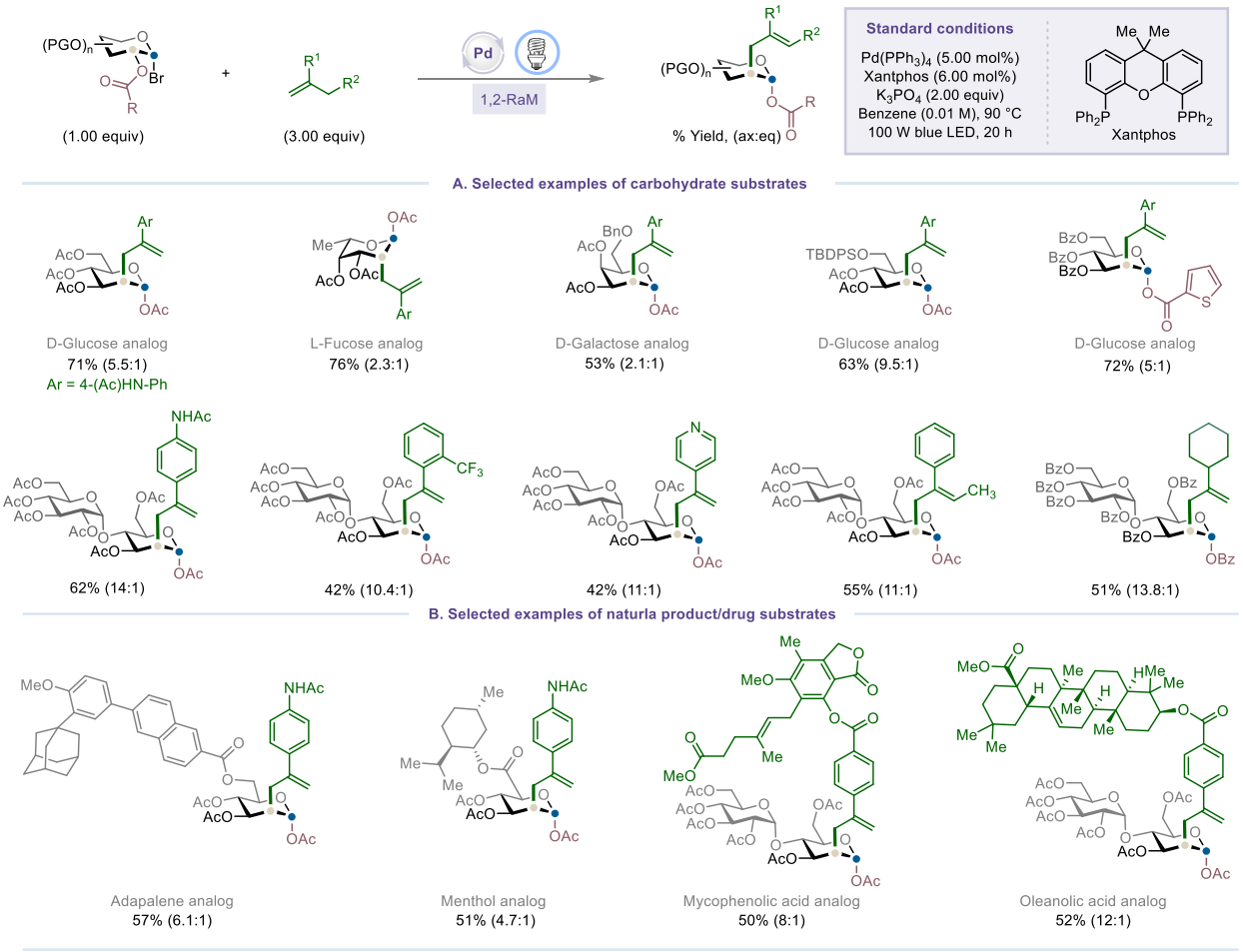



**Figure 8.** Selected scope of excited-state palladium-catalyzed allylation of carbohydrates.

Mechanistically, the allylation pathway mirrors that of alkenylation, with selectivity governed by the site of β-hydride elimination from benzyl Pd(II) intermediate **9.I**. DFT calculations revealed that hydride elimination from the less substituted carbon (**9.TS1**) is favored due to reduced steric clash with the pseudoaxial P-Ph groups of XantPhos, yielding terminal alkene

products (**9.3**). In contrast, elimination from the more hindered carbon (**9.TS2**) is disfavored due to steric repulsion from the pyranose ring (**Figure 9**).

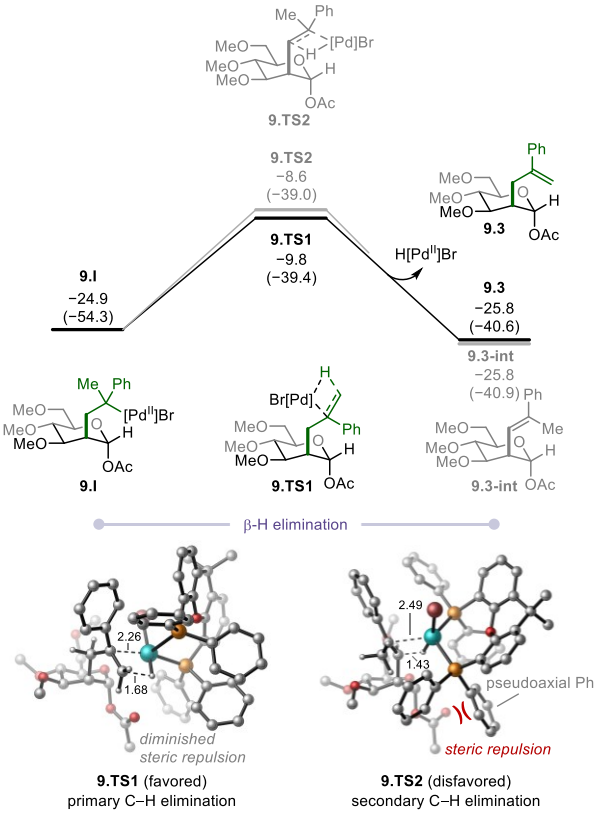



**Figure 9.** Energy profile of β-H elimination from the benzyl Pd(II) intermediate **I** that forms C2-allylated carbohydrates. Adapted with permission from Ref. 55. Copyright 2025 American Chemical Society.

## 2.3 C2-Ketonylation of Carbohydrates *via* Excited-State Palladium-Catalyzed 1,2-Radical Acyloxy Migration.

C2-ketonylated sugars are versatile probes, which have been used as isosteres of *N*-acetylated 2-aminosugars and agents for cell-surface engineering.[36-37] However, their synthesis is often lengthy, yields are low, and it requires the use of toxic reagents such as alkyl tin and $OsO_4$

(**Figure 3**A). We envisioned overcoming these limitations by trapping the C2-radical with various silyl enol ethers under excited-state Pd-catalyzed conditions. This approach allows the direct formation of C2-ketonylated sugars in one step from 1-bromosugars, the same starting materials traditionally used. Indeed, irradiation of a mixture of α-glucosyl bromide (1.00 equiv), trimethyl((1-phenylvinyl)oxy)silane (3.00 equiv), $Pd(PPh_3)_4$ (5.00 mol%), Xantphos (6.00 mol%), and KOAc (1.50 equiv) in benzene (0.015 M) under 36 W blue LED light at 90 °C afforded the desired product in 85% yield with a 4.5:1 ax:eq selectivity (**Figure 10**).[56] The scope of this transformation was examined with a wide variety of both aryl and alkyl silyl enol ethers, as well as different sugars including D-galactose, D-xylose, L-fucose, D-glucuronic acid, cellobiose, maltose, and melibiose, yielding products in 51–82% with ax:eq selectivity ranging from 2:1 to 10:1. Notably, α-glucosyl bromide derivatives of complex molecules, such as febuxostat, ibuprofen, and zaltoprofen, were also successfully ketonylated, affording 40–66% yields of the desired C2-product with ax:eq selectivity between 3.8:1 and 6.3:1.

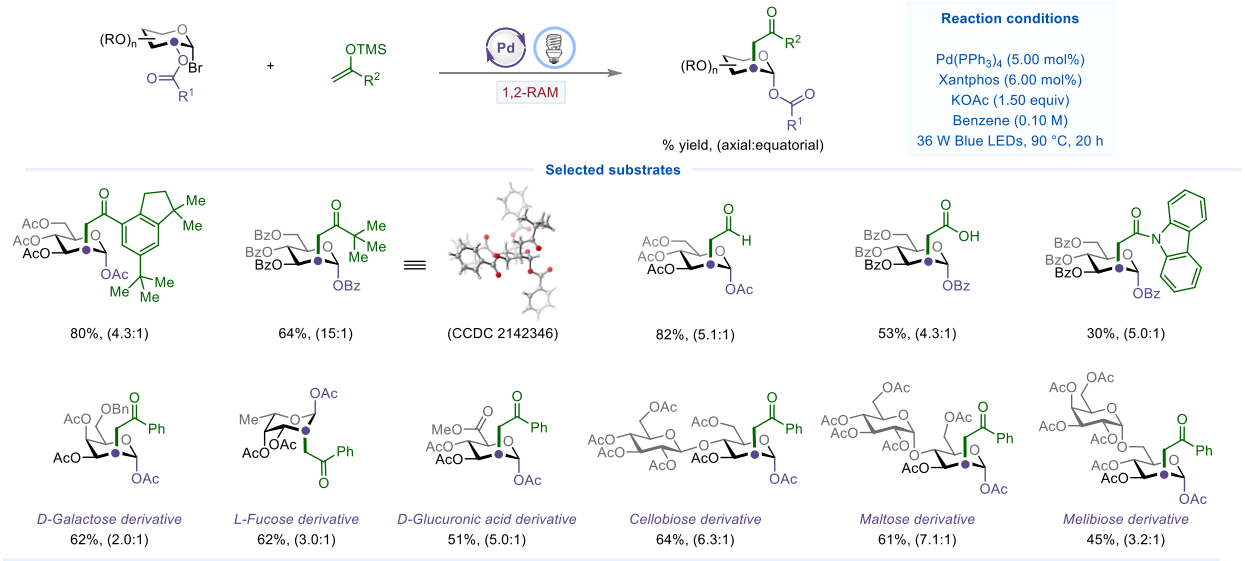



**Figure 10**. Excited-state palladium-catalyzed C2-ketonylation of carbohydrates.

Mechanistic investigations, including radical-trapping experiments, radical clock reactions, crossover experiments, quantum yield determinations, Stern–Volmer quenching studies, and computational analyses, suggested a pathway involving the reduction of 1-bromosugar by single-electron transfer from the excited palladium photocatalyst (**Figure 11**A and B). This was followed by 1,2-RAM, addition to the silyl enol ether, oxidation, desilylation, and ultimately affording the desired product (**Figure 11**C).

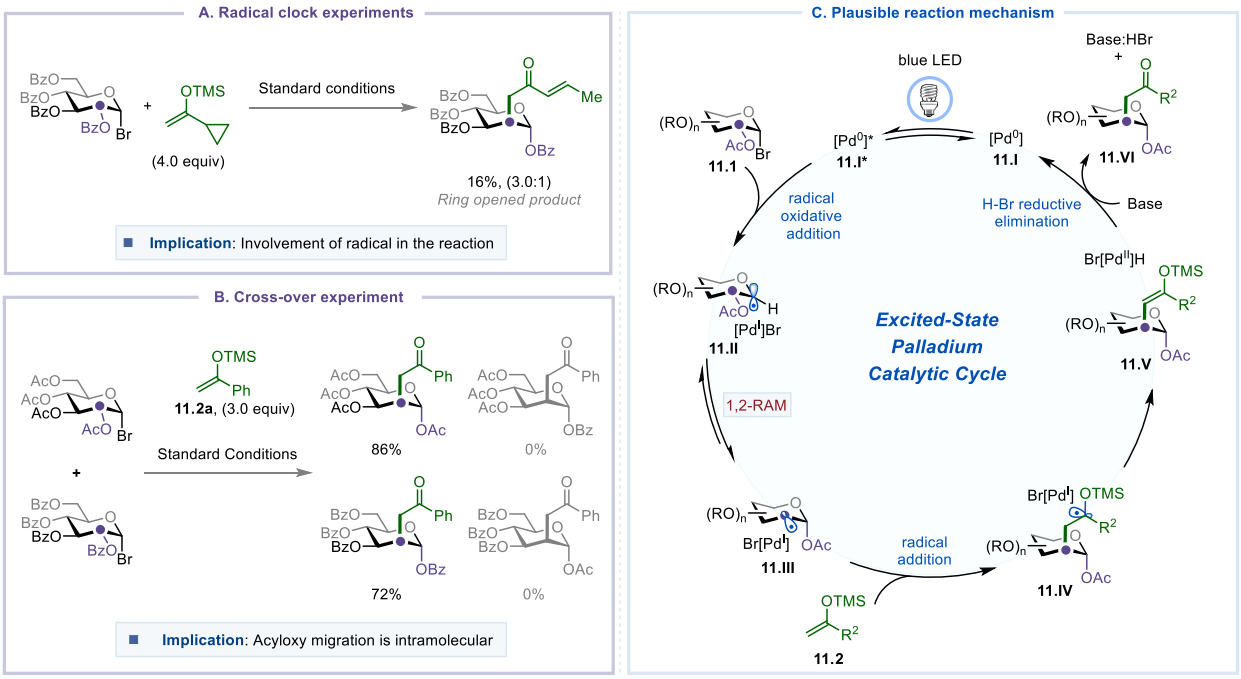



**Figure 11**. Mechanistic studies and plausible reaction mechanism.

## 2.4 Nickel-Catalyzed Radical Migratory Coupling Enables C2-Arylation of Carbohydrates.

To further expand the applicability of 1,2-RAM in organic synthesis and broaden the scope of C2-functionalization of carbohydrates, we turned our attention to nickel-catalyzed transformations.[57-61] Nickel (Ni) presents several advantages over palladium (Pd), making it an attractive choice for catalysis. Unlike Pd, Ni is earth-abundant and significantly more cost-

effective ($19.67/kg for Ni vs. $41,091/kg for Pd),[62] rendering the resulting catalytic process more sustainable (**Figure 12**A). Beyond its economic benefits, Ni possesses distinct electronic and structural properties that enable unique reactivity patterns. Its small nuclear radius,[63] high paring energy,[64] low electronegativity,[65] and low redox potentials,[66] make it well-suited for transformations that are often challenging with Pd. For example, Ni catalysts frequently adopt open-shell (radical) electronic configurations and access multiple oxidation states (0 to +4), allowing them to mediate both one-electron and two-electron processes under mild conditions.[67-68]The metalloradical reactivity of Ni introduces alternative stereo-determining pathways and helps circumvent limitations associated with traditional two-electron mechanisms. For instance, Ni catalysts can facilitate oxidative addition of sterically hindered tertiary alkyl halides, a process that is typically sluggish with Pd. As a result, Ni complexes exhibit diverse reactivity, catalyzing a wide range of C–C and C–heteroatom bond-forming reactions,[57, 61, 68] making them invaluable tools for expanding the chemical space of 1,2-RAM-mediated carbohydrate functionalization.

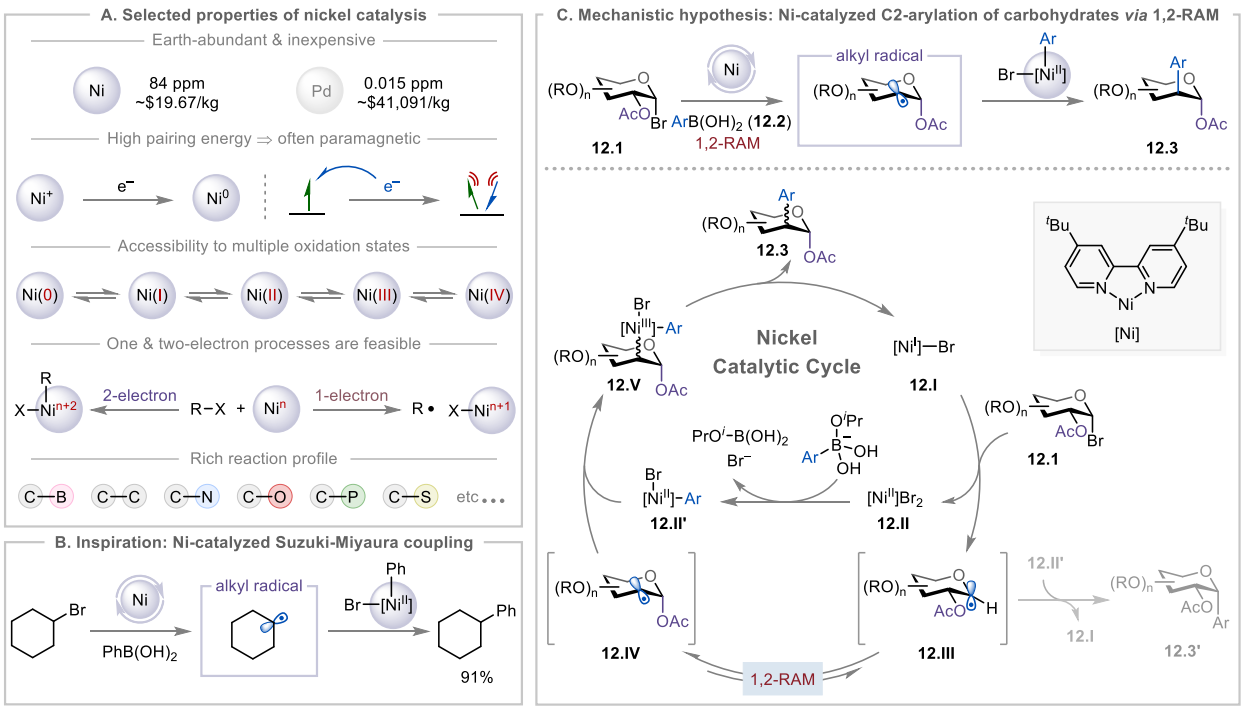


**Figure 12**. Ni-catalyzed migratory cross-coupling reaction enables the catalytic synthesis of challenging 2-aryl-2-deoxy carbohydrates.

Inspired by Fu's seminal work on Ni-catalyzed Suzuki–Miyaura cross-coupling of alkyl bromides with aryl boronic acids *via* an alkyl radical intermediate (**Figure 12**B),[69] we sought to adapt this strategy to 1,2-RAM using 1-bromosugars (**Figure 12**C). This approach enables C2-arylation of carbohydrates, providing a previously unexplored entry to glycomimetics. Our proposed mechanism begins with bromine atom abstraction from 1-bromosugars by the NiBr catalyst, generating $NiBr_2$ (**12.II**) and a glycosyl radical (**12.III**). The glycosyl radical (**12.III**) undergoes 1,2-RAM to form the deoxypyranosan-2-yl radical (**12.IV**), while $NiBr_2$ undergoes transmetallation with aryl boronic acids to produce Ni(Br)Ar (**12.II'**). Subsequent coupling of radical **12.IV** with Ni(Br)Ar yields complex C2-Ni(Br)Ar complex (**12.V**), which undergoes reductive elimination to yield the C2-arylated product, regenerating the NiBr catalyst to close the catalytic cycle.

A critical challenge arises from competing radical trapping, wherein glycosyl radical (**12.III**) is prematurely intercepted by Ni(Br)Ar (**12.II'**), leading to the C1-arylated byproduct (**12.3'**). To suppress this side reaction, systematic optimization revealed that dilute reaction conditions and elevated temperatures favor migratory coupling over premature radical trapping. Under optimized conditions, Ni-catalyzed radical migratory Suzuki-Miyaura arylation of 1-bromosugars delivered C2-arylated 2-deoxyglycosides in moderate-to-good yields (42–78%), with only minor C1-arylated side products.[2] While previous reports primarily focused on C1-arylation,[70] our strategy provides an unprecedented route to C2-arylated glycosides, expanding the chemical space of carbohydrate chemistry.

Substrate scope investigations demonstrated broad compatibility with electronically diverse aryl boronic acids and various carbohydrate derivatives, including natural product- and drug-conjugated sugars (**Figure 13**). Notably, substrate structures and ligand selection played a crucial role in stereoselectivity. D-glucose derivatives consistently favored axial C2-arylation (2.4:1 to >20:1), while D-galactose derivatives exhibited axial-to-equatorial selectivity ratios ranging from 1:6 to 1:10.

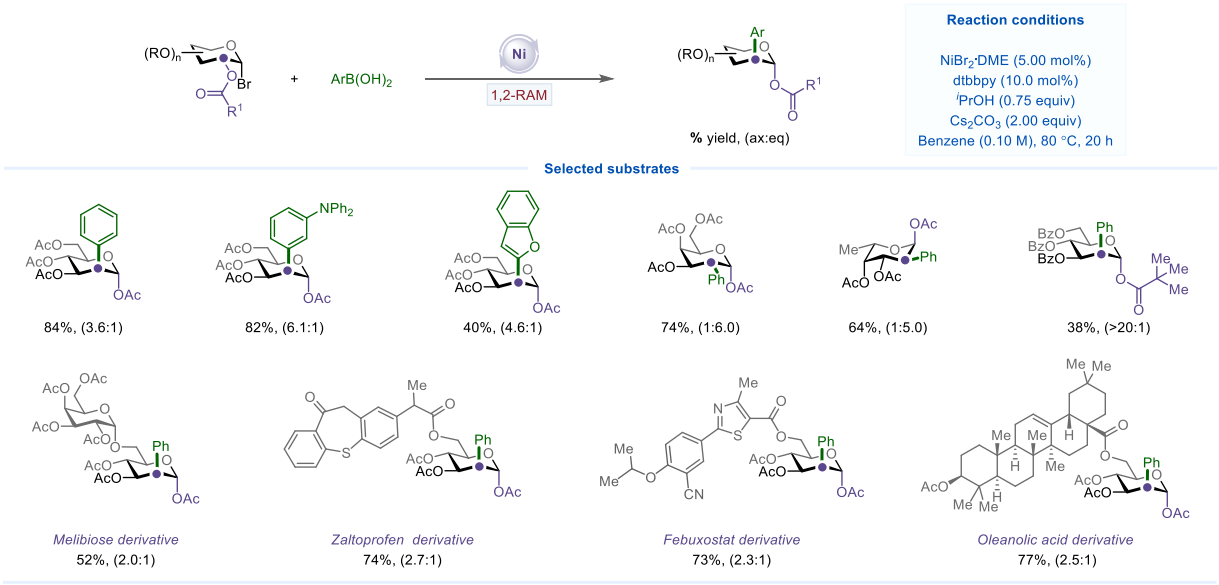



**Figure 13**. Nickel-catalyzed C2-arylation of carbohydrates *via* 1,2-RAM.

DFT calculations provided insight into stereochemical control, suggesting that addition of the Ni(Br)Ar species to the deoxypyranos-2-yl radical (**12.IV**) is a key stereodetermining step (**Figure 12**C). The square planar Ni complex preferentially facilitates axial addition, as equatorial addition induces unfavorable steric interactions with the *cis* C1-acetoxy group. Beyond computational insights, experimental mechanistic studies, including stereochemical analysis, radical trapping, and crossover experiments, further support the proposed reaction mechanism.

By leveraging radical migratory Ni-catalysis, this approach expands the synthetic toolbox for carbohydrate functionalization, providing access to novel glycomimetics with potential applications in medicinal chemistry, glycoscience, and material sciences.

## 2.5 Expanding Reaction Profile of Allyl Carboxylates *via* 1,2-Radical Acyloxy Migration (RAM): Visible-Light-Induced Phosphine-Catalyzed 1,3-Carbobromination of Allyl Carboxylates.

The application of 1,2-RAM in organic synthesis extends beyond carbohydrates to another valuable class of feedstock chemicals—allyl carboxylates. These versatile intermediates enable diverse synthetic transformations. For example, transition-metal (TM)-catalyzed two-electron redox pathways generate TM–π-allyl species, which undergo nucleophilic or electrophilic addition to furnish allylated organic compounds (**Figure 14**A).[71-72,73-74] Additionally, one-electron redox processes allow radical-mediated 1,2-difunctionalization, affording highly functionalized allyl derivatives.[75] However, a catalytic radical 1,3-difunctionalization of allyl carboxylates involving 1,2-RAM has remained elusive.

Building upon our success in 1,2-RAM on carbohydrates, we designed a strategy for catalytic radical 1,3-difunctionalization of allyl carboxylates *via* visible-light-induced phosphine catalysis. In 2019, Czekelius reported an elegant phosphine-catalyzed 1,2-difunctionalization of alkenes *via* halogen atom transfer (XAT) of iododifluoroacetates, where an electron donor–acceptor (EDA) complex formed between phosphine and iododifluoroacetate facilitated radical formation.[76] Despite these advances, activating bromodifluoroacetates using the same EDA complex mechanism has remained challenging, presumably due to the higher LUMO energy level

of bromodifluoroacetates, which weakens the HOMO-LUMO interaction between phosphine and the electrophile (**Figure 14**B).

DFT calculations support this hypothesis, revealing that the $Me_3P\cdots Br$ EDA complex is less stable ($\Delta H$ = –3.0 kcal/mol) compared to the $Me_3P\cdots I$ EDA complex ($\Delta H$ = –6.7 kcal/mol, **Figure 14**B). However, the negative enthalpy still supports the feasibility of forming a P···Br EDA complex, suggesting that an optimized catalytic system could enable its activation.

Guided by this insight, we envisioned that by merging visible-light-induced phosphine-catalyzed XAT of polyfluoroalkyl bromides with 1,2-RAM reactivity, we could achieve a novel 1,3-carbobromination of allyl carboxylates, establishing a new radical-based 1,3-difunctionalization strategy. Indeed, subjecting **14.1a** (1.0 equiv) and **14.2a** (3.0 equiv) to phosphine-catalyzed conditions in the presence of 1,1-bis(diphenylphosphino)methane (dppm, 10.0 mol%) and $Na_2CO_3$ (2.5 equiv) in 1,2-dichloroethane (DCE, 0.04 M) under 100 W blue LED irradiation at 90 °C for 24 h furnished the 1,3-bromodifluoroalkylated product **14.3a** in 86% yield (**Figure 14**C). This transformation demonstrates broad substrate scope, accommodating electron-rich and electron-deficient allyl carboxylates and enabling late-stage modifications of bioactive molecules.

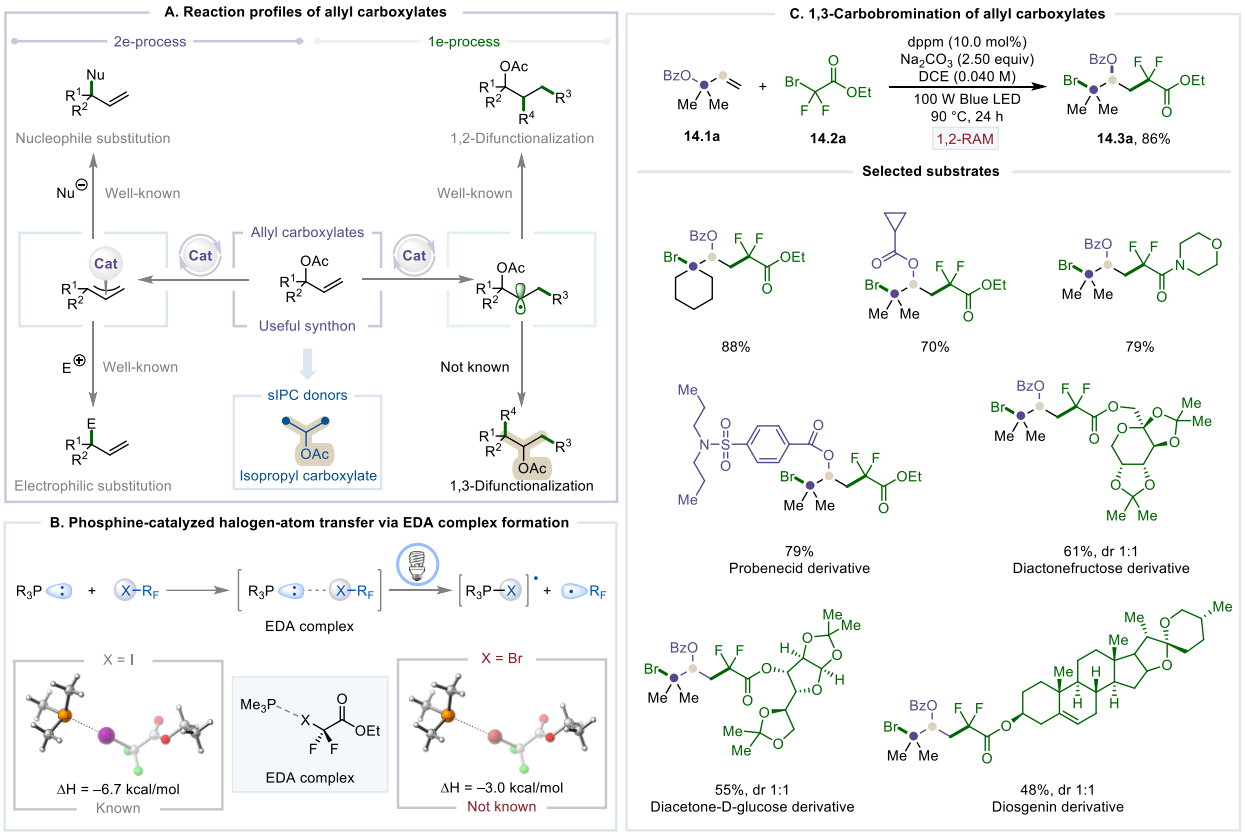



**Figure 14**. Visible-light-induced phosphine-catalyzed 1,3-carbobromination of allyl carboxylates. Adapted with permission from Ref. 4. Copyright 2023 American Chemical Society.

A series of mechanistic studies suggested a radical mechanism involving EDA complex formation and 1,2-RAM. For example, radical trap and radical clock experiments provided strong evidence for radical intermediates in the reaction pathway. Also, a $^{18}O$-labeling experiment using $^{18}O$-labeled allyl benzoate (**14.1a**-$^{18}O$) generated $^{18}O$-labeled products **14.3a**-$^{18}O$-1 and **14.3a**-$^{18}O$-2 in a 1.4:1 ratio, indicating that the 1,2-RAM process proceeds *via* both [1,2]- and [2,3]-acyloxy shifts. To further probe the reaction mechanism, we conducted NMR titration, Job's plot,[77] Benesi-Hildebrand plot,[78] which indicated the formation of an EDA complex between phosphine and bromodifluoroacetates. Moreover, DFT calculations provided insight into the reaction energetics, supporting a concerted benzoyloxy migration mechanism.

Based on these findings, we propose the following reaction mechanism (**Figure 15**): Photoexcitation of the EDA complex **15.I** generates bromo-phosphine radical species (**15.II**) and difluoroalkyl radical (**15.III**). Subsequent radical addition of **15.III** to allyl benzoate (**14.1a**) forms a secondary alkyl radical (**15.IV**), which undergoes a concerted benzoyloxy shift *via* both [1,2]- and [2,3]-transition states (**15.TS1** and **15.TS2**), affording a tertiary radical intermediate (**15.V**). Finally, Br-atom transfer from bromo-phosphine radical **15.II** to radical intermediate **15.V** delivers the desired 1,3-bromodifluoroalkylated product (**15.3**) while regenerating dppm, closing the catalytic cycle.

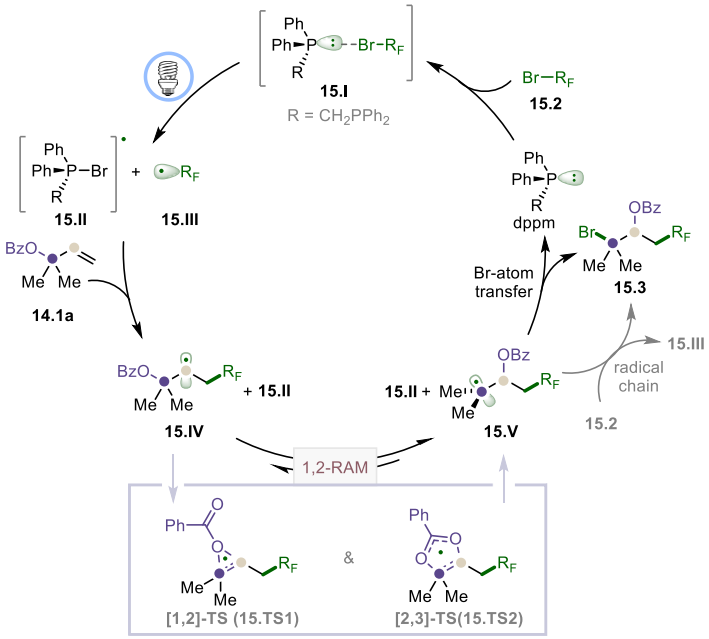



**Figure 15**. Proposed reaction mechanism for visible-light-induced phosphine-catalyzed 1,3-carbobromination of allyl carboxylates. Adapted with permission from Ref. 4. Copyright 2023 American Chemical Society.

This proof-of-concept study enables the previously elusive 1,3-carbobromination of allyl carboxylates, providing a direct route to valuable bromodifluoromethylated scaffolds. Additionally, it expands the reaction scope of allyl carboxylates and phosphine catalysis,

introducing new radical-mediated transformations that were previously inaccessible. The reaction also facilitates the synthesis of organic compounds incorporating the gem-difluoromethylene pharmacophore,[79] a privileged motif in drug discovery, thereby enhancing its potential impact in medicinal chemistry. Furthermore, this work establishes a new reaction platform in which allyl carboxylates serve as substituted isopropyl carboxylate donors, broadening their functionalization potential in organic synthesis. Collectively, these findings demonstrate how 1,2-RAM strategies enable the development of previously unattainable transformations, paving the way for further advances in synthetic and medicinal chemistry.

## 3. CONCLUSIONS AND OUTLOOK

In this *Account*, we have highlighted our recent efforts toward establishing catalytic 1,2-radical acyloxy migration (RAM) as a versatile and general platform for discovering new chemical reactivity. By integrating 1,2-RAM with excited-state palladium and ground-state nickel catalysis, we have developed a unified strategy for C2-selective modification of carbohydrates. Using readily available 1-halosugars, we achieved a broad array of transformations, including reduction, deuteration, iodination, alkenylation, ketonylation, and arylation, to access unprecedented C2-functionalized glycomimetics. These reactions exhibit broad functional group tolerance, proceed under mild conditions, and are well-suited for late-stage modification of structurally complex molecules. This work opens new opportunities for the rapid synthesis of glycomimetics, expanding chemical space and accelerating advances in the development of carbohydrate-based functional molecules.

We have also demonstrated that 1,2-RAM can be successfully merged with excited-state phosphine catalysis to achieve the first catalytic 1,3-carbobromination of allyl carboxylates

accompanied by a 1,2-acyloxy shift. This transformation enables 1,2,3-trifunctionalization of allyl carboxylates and provides access to molecules bearing the gem-difluoromethylene pharmacophore, a privileged motif in medicinal chemistry. Beyond expanding the reactivity profile of allyl carboxylates and phosphine catalysis, this approach introduces a new conceptual framework for employing allyl carboxylates as substituted isopropyl carboxylate donors, further enhancing their synthetic utility.

These proof-of-concept studies collectively highlight the potential of 1,2-RAM as a strategic platform to unlock new bond disconnections and enable radical-mediated site-selective functionalization of complex substrates. Looking ahead, we aim to extend the scope of C2-functionalization of carbohydrates to include transformations such as fluorination, amination, borylation, and alkynylation, with a particular focus on achieving precise catalyst-controlled site- and stereoselectivity. For allyl carboxylates, we will further explore diverse radical coupling partners to realize additional 1,2,3-trifunctionalization strategies and further develop their role as versatile synthetic building blocks.

Ultimately, we envision that the modular nature of 1,2-RAM will allow it to be readily merged with a broad range of radical cross-coupling platforms, enabling the introduction of diverse molecular fragments into carbohydrates and allyl carboxylates. We anticipate that continued exploration of this reactivity will expand the frontiers of radical chemistry, providing new tools for precision molecular editing, and facilitating the synthesis of functionally rich small molecules.

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**Notes**

Any additional relevant notes should be placed here.

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ABBREVIATIONS

RAM, Radical Acyloxy Migration.

REFERENCES

1. Zhao, G.; Yao, W.; Mauro, J. N.; Ngai, M. Y., Excited-State Palladium-Catalyzed 1,2-Spin-Center Shift Enables Selective C-2 Reduction, Deuteration, and Iodination of Carbohydrates. *J. Am. Chem. Soc.* **2021**, *143*, 1728-1734.

2. Zhao, G.; Yao, W.; Kevlishvili, I.; Mauro, J. N.; Liu, P.; Ngai, M.-Y., Nickel-Catalyzed Radical Migratory Coupling Enables C-2 Arylation of Carbohydrates. *J. Am. Chem. Soc.* **2021**, *143*, 8590-8596.

3. Yao, W.; Zhao, G.; Wu, Y.; Zhou, L.; Mukherjee, U.; Liu, P.; Ngai, M.-Y., Excited-State Palladium-Catalyzed Radical Migratory Mizoroki–Heck Reaction Enables C2-Alkenylation of Carbohydrates. *J. Am. Chem. Soc.* **2022**, *144*, 3353-3359.

4. Zhao, G.; Lim, S.; Musaev, D. G.; Ngai, M.-Y., Expanding reaction profile of allyl carboxylates via 1, 2-radical migration (RaM): visible-light-induced phosphine-catalyzed 1, 3-carbobromination of allyl carboxylates. *J. Am. Chem. Soc.* **2023**, *145*, 8275-8284.

5. Zhang, N.; Samanta, S. R.; Rosen, B. M.; Percec, V., Single electron transfer in radical ion and radical-mediated organic, materials and polymer synthesis. *Chem. Rev.* **2014**, *114*, 5848-5958.

6. Leifert, D.; Studer, A., The Persistent Radical Effect in Organic Synthesis. *Angew. Chem. Int. Ed.* **2020**, *59*, 74-108.

7. Galliher, M. S.; Roldan, B. J.; Stephenson, C. R. J., Evolution Towards Green Radical Generation in Total Synthesis. *Chem. Soc. Rev.* **2021**, *50*, 10044-10057.

8. Pitre, S. P.; Overman, L. E., Strategic use of visible-light photoredox catalysis in natural product synthesis. *Chem. Rev.* **2021**, *122*, 1717-1751.

9. Crossley, S. W.; Obradors, C.; Martinez, R. M.; Shenvi, R. A., Mn-, Fe-, and Co-catalyzed radical hydrofunctionalizations of olefins. *Chem. Rev.* **2016**, *116*, 8912-9000.

10. Demarteau, J.; Debuigne, A.; Detrembleur, C., Organocobalt complexes as sources of carbon-centered radicals for organic and polymer chemistries. *Chem. Rev.* **2019**, *119*, 6906-6955.

11. Mondal, S.; Dumur, F.; Gigmes, D.; Sibi, M. P.; Bertrand, M. P.; Nechab, M., Enantioselective radical reactions using chiral catalysts. *Chem. Rev.* **2022**, *122*, 5842-5976.

12. Wang, X.; He, J.; Wang, Y. N.; Zhao, Z.; Jiang, K.; Yang, W.; Zhang, T.; Jia, S.; Zhong, K.; Niu, L.; Lan, Y., Strategies and Mechanisms of First-Row Transition Metal-Regulated Radical C-H Functionalization. *Chem. Rev.* **2024**, *124*, 10192-10280.

13. Dong, X.-Y.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y., Ligand development for copper-catalyzed enantioconvergent radical cross-coupling of racemic alkyl halides. *J. Am. Chem. Soc.* **2022**, *144*, 17319-17329.

14. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C., Visible light photoredox catalysis with transition metal complexes: Applications in organic synthesis. *Chem. Rev.* **2013**, *113*, 5322-5363.

15. Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y., Metallaphotoredox: the merger of photoredox and transition metal catalysis. *Chem. Rev.* **2021**, *122*, 1485-1542.

16. Cheung, K. P. S.; Sarkar, S.; Gevorgyan, V., Visible light-induced transition metal catalysis. *Chem. Rev.* **2021**, *122*, 1543-1625.

17. Bellotti, P.; Huang, H.-M.; Faber, T.; Glorius, F., Photocatalytic late-stage C–H functionalization. *Chem. Rev.* **2023**, *123*, 4237-4352.

18. Yan, M.; Kawamata, Y.; Baran, P. S., Synthetic organic electrochemical methods since 2000: on the verge of a renaissance. *Chem. Rev.* **2017**, *117*, 13230-13319.

19. Shi, S.-H.; Liang, Y.; Jiao, N., Electrochemical oxidation induced selective C–C bond cleavage. *Chem. Rev.* **2020**, *121*, 485-505.

20. Malapit, C. A.; Prater, M. B.; Cabrera-Pardo, J. R.; Li, M.; Pham, T. D.; McFadden, T. P.; Blank, S.; Minteer, S. D., Advances on the merger of electrochemistry and transition metal catalysis for organic synthesis. *Chem. Rev.* **2021**, *122*, 3180-3218.

21. Wang, Y.; Dana, S.; Long, H.; Xu, Y.; Li, Y.; Kaplaneris, N.; Ackermann, L., Electrochemical late-stage functionalization. *Chem. Rev.* **2023**, *123*, 11269-11335.

22. Wu, X.; Ma, Z.; Feng, T.; Zhu, C., Radical-mediated rearrangements: past, present, and future. *Chem. Soc. Rev.* **2021**, *50*, 11577-11613.

23. Matsuo, B.; Granados, A.; Majhi, J.; Sharique, M.; Levitre, G.; Molander, G. A., 1, 2-Radical Shifts in Photoinduced Synthetic Organic Transformations: A Guide to the Reactivity of Useful Radical Synthons. *ACS Org. Inorg. Au* **2022**, *2*, 435-454.

24. Chen, F.; Cao, Z.; Zhu, C., Asymmetric Functionalization Harnessing Radical-Mediated Functional-Group Migration. *Angew. Chem. Int. Ed.* **2025**, *64*, e202424667.

25. Shen, X., Fluoroalkylacylsilanes as Novel Ambiphilic Donor–Acceptor Carbene Precursors. *Acc. Chem. Res.* **2025**, e202115334-202114035.

26. Zhang, Y.; Zhou, G.; Liu, S.; Shen, X., Radical Brook rearrangement: past, present, and future. *Chem. Soc. Rev.* **2025**.

27. Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q., Chemistry of β-(Acyloxy)alkyl and β-(Phosphatoxy)alkyl Radicals and Related Species: Radical and Radical Ionic Migrations and Fragmentations of Carbon−Oxygen Bonds. *Chem. Rev.* **1997**, *97*, 3273-3312.

28. Wessig, P.; Muehling, O., Spin-Center Shift (SCS)–A Versatile Concept in Biological and Synthetic Chemistry. *Eur. J. Org. Chem.* **2007**, *2007*, 2219-2232.

29. Surzur, J.; Teissier, P., Addition Radicalaire Desters Sur Les Alcools Ethyleniques. *C. R. Acad. Sci. Fr. Ser. C.* **1967**, *264*, 1981-1984.

30. Tanner, D. D.; Law, F. C., Free-radical acetoxy group migration. *J. Am. Chem. Soc.* **1969**, *91*, 7535-7537.

31. Giese, B.; Gröninger, K. S.; Witzel, T.; Korth, H. G.; Sustmann, R., Synthesis of 2-Deoxy Sugars. *Angew. Chem. Int. Ed.* **1987**, *26*, 233-234.

32. Varki, A.; Cummings, R. D.; Esko, J. D.; Stanley, P.; Hart, G. W.; Aebi, M.; Darvill, A. G.; Kinoshita, T.; Packer, N. H.; Prestegard, J. H.; Schnaar, R. L.; Seeberger, P. H., *Essentials of Glycobiology*. 2015.

33. Mishra, S.; Upadhaya, K.; Mishra, K. B.; Shukla, A. K.; Tripathi, R. P.; Tiwari, V. K., Carbohydrate-Based Therapeutics: A Frontier in Drug Discovery and Development. In *Studies in Natural Products Chemistry*, Elsevier: 2016; Vol. 49, pp 307-361.

34. Su, L.; Feng, Y.; Wei, K.; Xu, X.; Liu, R.; Chen, G., Carbohydrate-based macromolecular biomaterials. *Chem. Rev.* **2021**, *121*, 10950-11029.

35. Lu, S.; Li, X.; Wang, A., A new chiral diphosphine ligand and its asymmetric induction in catalytic hydroformylation of olefins. *Catal. Today* **2000**, *63*, 531-536.

36. Hang, H. C.; Bertozzi, C. R., Ketone isosteres of 2-N-acetamidosugars as substrates for metabolic cell surface engineering. *J. Am. Chem. Soc.* **2001**, *123*, 1242-1243.

37. Cai, L.; Guan, W.; Chen, W.; Wang, P. G., Chemoenzymatic synthesis of uridine 5′ -diphospho-2-acetonyl-2-deoxy- α -D-glucose as C2-carbon isostere of UDP-GlcNAc. *J. Org. Chem.* **2010**, *75*, 3492-3494.

38. Li, X.; Uchiyama, T.; Raetz, C. R.; Hindsgaul, O., Synthesis of a carbohydrate-derived hydroxamic acid inhibitor of the bacterial enzyme (LpxC) involved in lipid A biosynthesis. *Org. Lett.* **2003**, *5*, 539-541.

39. Bagalkot, V.; Lee, I.-H.; Yu, M. K.; Lee, E.; Park, S.; Lee, J.-H.; Jon, S., A Combined Chemoimmunotherapy Approach Using a Plasmid− Doxorubicin Complex. *Mol. Pharm.* **2009**, *6*, 1019-1028.

40. Khan, S. H., *Modern methods in carbohydrate synthesis*. CRC Press: 2020.

41. Shatskiy, A.; Stepanova, E. V.; Kärkäs, M. D., Exploiting photoredox catalysis for carbohydrate modification through C–H and C–C bond activation. *Nat. Rev. Chem.* **2022**, *6*, 782-805.

42. Munyololo, M.; Gammon, D. W.; Mohrholz, I., Extending the scope of the Ferrier reaction: fragmentation-rearrangement reactions of selectively substituted 1, 2-cyclopropanated glucose derivatives. *Carbohydr. Res.* **2012**, *351*, 49-55.

43. Fadlan, A.; Tanimoto, H.; Ito, T.; Aritomi, Y.; Ueno, M.; Tokuda, M.; Hirohara, S.; Obata, M.; Morimoto, T.; Kakiuchi, K., Synthesis, photophysical properties, and photodynamic activity of positional isomers of TFPP-glucose conjugates. *Bioorg. Med. Chem.* **2018**, *26*, 1848-1858.

44. Cheung, K. P. S.; Gevorgyan, V., Illuminating Palladium Catalysis. *Acc. Chem. Res.* **2025**, 6340-6343.

45. Kurandina, D.; Parasram, M.; Gevorgyan, V., Visible Light-Induced Room-Temperature Heck Reaction of Functionalized Alkyl Halides with Vinyl Arenes/Heteroarenes. *Angew. Chem. Int. Ed.* **2017**, *56*, 14212-14216.

46. Wang, G.-Z.; Shang, R.; Cheng, W.-M.; Fu, Y., Irradiation-induced Heck reaction of unactivated alkyl halides at room temperature. *J. Am. Chem. Soc.* **2017**, *139*, 18307-18312.

47. Dupuis, J.; Giese, B.; Rüegge, D.; Fischer, H.; Korth, H. G.; Sustmann, R., Conformation of Glycosyl Radicals: Radical Stabilization by β-CO Bonds. *Angew. Chem. Int. Ed.* **1984**, *23*, 896-898.

48. Abe, H.; Shuto, S.; Matsuda, A., Highly α-and β-selective radical C-glycosylation reactions using a controlling anomeric effect based on the conformational restriction strategy. A study on the conformation− anomeric effect− stereoselectivity relationship in anomeric radical reactions. *J. Am. Chem. Soc.* **2001**, *123*, 11870-11882.

49. Korth, H.-G.; Sustmann, R.; Gröninger, K. S.; Witzel, T.; Giese, B., Electron spin resonance spectroscopic investigation of carbohydrate radicals. Part 3. Conformation in deoxypyranosan-2-, -3-, and -4-yl radicals. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1461-1464.

50. Korth, H. G.; Sustmann, R.; Groeninger, K. S.; Leisung, M.; Giese, B., Electron spin resonance spectroscopic investigation of carbohydrate radicals. 4. 1, 2-Acyloxyl migration in pyranosyl radicals. *J. Org. Chem.* **1988**, *53*, 4364-4369.

51. He, X.; Agnihotri, G.; Liu, H.-w., Novel enzymatic mechanisms in carbohydrate metabolism. *Chem. Rev.* **2000**, *100*, 4615-4662.

52. Hilborn, J. W.; Pincock, J. A., Rates of decarboxylation of acyloxy radicals formed in the photocleavage of substituted 1-naphthylmethyl alkanoates. *J. Am. Chem. Soc.* **1991**, *113*, 2683-2686.

53. Witt, C. H.; Woerpel, K., Mechanistic Studies on the 1, 2-Spin-Center Shift in Carbohydrate Systems with a Fluorenylcyclopropyl Radical Clock. *J. Org. Chem.* **2023**, *88*, 12802-12807.

54. Zipse, H., [1, 2]-acyloxy shifts in radicals. A computational investigation of substituent and solvent effects. *J. Am. Chem. Soc.* **1997**, *119*, 1087-1093.

55. Yao, W.; Mauro, J. N.; Fu, Y.; Chen, H.; Liu, P.; Ngai, M.-Y., Excited-State Palladium-Catalyzed Radical Allylic Alkylation: Rapid Access to C2-Allyl Carbohydrates. *ACS Catal.* **2025**, *15*, 5480-5489.

56. Zhao, G.; Mukherjee, U.; Zhou, L.; Wu, Y.; Yao, W.; Mauro, J. N.; Liu, P.; Ngai, M.-Y., C2-ketonylation of carbohydrates via excited-state palladium-catalyzed 1, 2-spin-center shift. *Chem. Sci.* **2022**, *13*, 6276-6282.

57. Han, F.-S., Transition-metal-catalyzed Suzuki–Miyaura cross-coupling reactions: a remarkable advance from palladium to nickel catalysts. *Chem. Soc. Rev.* **2013**, *42*, 5270-5298.

58. Tellis, J. C.; Kelly, C. B.; Primer, D. N.; Jouffroy, M.; Patel, N. R.; Molander, G. A., Single-electron transmetalation via photoredox/nickel dual catalysis: unlocking a new paradigm for sp3–sp2 cross-coupling. *Acc. Chem. Res.* **2016**, *49*, 1429-1439.

59. Iwasaki, T.; Kambe, N., Ni-catalyzed C–C couplings using alkyl electrophiles. In *Ni-and Fe-Based Cross-Coupling Reactions*, Correa, A., Ed. Springer International Publishing: Cham, 2017; pp 1-36.

60. Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C., The merger of transition metal and photocatalysis. *Nat. Rev. Chem.* **2017**, *1*.

61. Ogoshi, S., *Nickel Catalysis in Organic Synthesis: Methods and Reactions*. John Wiley & Sons: 2020.

62. Daily Price of Metals. https://www.dailymetalprice.com/metalprices.php (accessed 9/20/2023).

63. Batsanov, S. S., Van der Waals radii of elements. *Inorg. Mater.* **2001**, *37*, 871-885.

64. Poli, R.; Cacelli, I., Orbital Splitting and Pairing Energy in Open‐Shell Organometallics: A Study of Two Families of 16‐Electron Complexes [Cp2M](M= Cr, Mo, W) and [CpM (PH3)](M= Co, Rh, Ir). Wiley Online Library: 2005.

65. Mann, J. B.; Meek, T. L.; Knight, E. T.; Capitani, J. F.; Allen, L. C., Configuration energies of the d-block elements. *J. Am. Chem. Soc.* **2000**, *122*, 5132-5137.

66. Lide, D. R., *CRC handbook of chemistry and physics*. CRC press: 2004; Vol. 85.

67. Lin, C.-Y.; Power, P. P., Complexes of Ni (I): a "rare" oxidation state of growing importance. *Chem. Soc. Rev.* **2017**, *46*, 5347-5399.

68. Diccianni, J.; Lin, Q.; Diao, T., Mechanisms of Nickel-Catalyzed Coupling Reactions and Applications in Alkene Functionalization. *Acc. Chem. Res.* **2020**, *53*, 906-919.

69. Zhou, J.; Fu, G. C., Suzuki cross-couplings of unactivated secondary alkyl bromides and iodides. *J. Am. Chem. Soc.* **2004**, *126*, 1340-1341.

70. Bokor, É.; Kun, S.; Goyard, D.; Tóth, M.; Praly, J.-P.; Vidal, S.; Somsák, L., C-Glycopyranosyl Arenes and Hetarenes: Synthetic Methods and Bioactivity Focused on Antidiabetic Potential. *Chem. Rev.* **2017**, *117*, 1687-1764.

71. Trost, B. M.; Van Vranken, D. L., Asymmetric transition metal-catalyzed allylic alkylations. *Chem. Rev.* **1996**, *96*, 395-422.

72. Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M., Iridium-catalyzed diastereo-, enantio-, and regioselective allylic alkylation with prochiral enolates. ACS Publications: 2016; Vol. 6, pp 6207-6213.

73. Kim, I. S.; Ngai, M.-Y.; Krische, M. J., Enantioselective iridium-catalyzed carbonyl allylation from the alcohol or aldehyde oxidation level using allyl acetate as an allyl metal surrogate. *J. Am. Chem. Soc.* **2008**, *130*, 6340-6341.

74. Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F., Catalytic enantioselective allylation of carbonyl compounds and imines. *Chem. Rev.* **2011**, *111*, 7774-7854.

75. Jiang, H.; Studer, A., Intermolecular radical carboamination of alkenes. *Chem. Soc. Rev.* **2020**, *49*, 1790-1811.

76. Helmecke, L.; Spittler, M.; Baumgarten, K.; Czekelius, C., Metal-free activation of C–I bonds and perfluoroalkylation of alkenes with visible light using phosphine catalysts. *Org. Lett.* **2019**, *21*, 7823-7827.

77. Job, P., A Job plot is used to determine stoichiometry ‖ Anm. *Chim.(Paris)* **1928**, *9*, 113-203.

78. Benesi, H. A.; Hildebrand, J., A spectrophotometric investigation of the interaction of iodine with aromatic hydrocarbons. *J. Am. Chem. Soc.* **1949**, *71*, 2703-2707.

79. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A., Applications of fluorine in medicinal chemistry. *J. Med. Chem.* **2015**, *58*, 8315-8359

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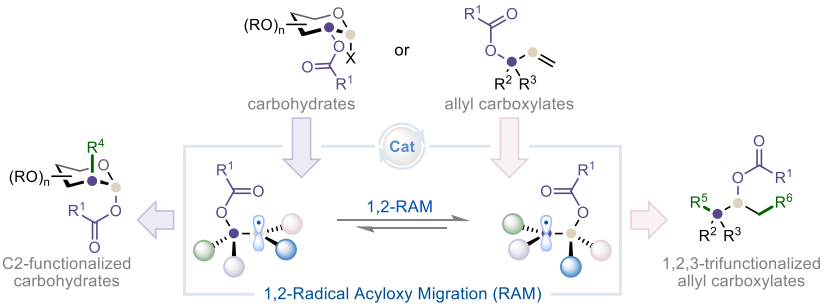
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