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Excited-State Palladium-Catalyzed 1,2-Spin-Center Shift Enables Selective C-2 Reduction, Deuteration, and Iodination of Carbohydrates

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Abstract

Excited-state catalysis, a process that involves one or more excited catalytic species, has emerged as a powerful tool in organic synthesis because it allows access to the excited-state reaction landscape for the discovery of novel chemical reactivity. Herein, we report the first excited-state palladium-catalyzed 1,2-spin-center shift reaction that enables site-selective functionalization of carbohydrates. The strategy features mild reaction conditions with high levels of regio- and stereoselectivity that tolerate a wide range of functional groups and complex molecular architectures. Mechanistic studies suggest a radical mechanism involving the formation of hybrid palladium species that undergoes a 1,2-spin-center shift followed by the reduction, deuteration, and iodination to afford functionalized 2-deoxy sugars. The new reactivity will provide a general approach for the rapid generation of natural and unnatural carbohydrates.

Graphical Abstract

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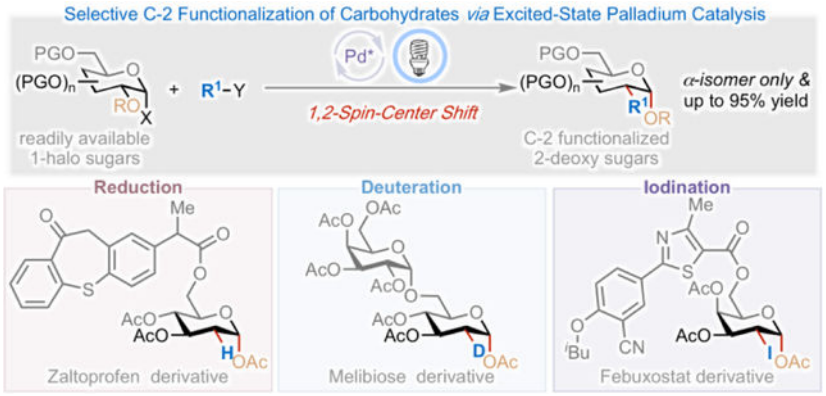
Supporting Information

Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

This paper is dedicated to Prof. Barry M. Trost on the occasion of his 80th birthday. The authors declare no competing financial interests.



Visible-light-induced excited-state palladium catalysis has emerged as a promising strategy for developing valuable reactions.[1] Seminal work by Gevorgyan,[2] Fu,[3] and Yu[4] showed that photoexcited Pd-complexes undergo rapid, radical oxidative addition into aryl/alkyl-halide bonds, forming aryl/alkyl-Pd species with hybrid reactivity in which the closed-shell Pd(II) complex is in equilibrium with an open-shell alkyl radical/Pd(I) intermediate through a reversible photoexcitation/recombination process (Figure 1).[5] This hybrid reactivity has been exploited in a range of transformations, such as desaturation reactions,[2a, 6] Mizoroki-Heck reactions,[2b, 3, 7] difunctionalization of conjugated dienes,[8] and others.[4, 9] Despite these recent advances, the application of either ground-state or excited-state Pd-catalysis to mediate 1,2-spin-center shift (SCS)[10] remains elusive. We envisioned that with a functional group such as acyloxy at the β-position, the alkyl radical/Pd(I) species could undergo a 1,2-SCS, accessing a new reaction site for further functionalization (Figure 1).[11] The establishment of such reactivity is significant because it will (i) enable unique reactions capable of the rapid generation of molecular complexity and late-stage functionalization of complex molecules; (ii) provide new strategic bond formation that leads to otherwise difficult or unobtainable molecular architecture; and (iii) guide the design and development of new chemical reactions.

Carbohydrates, the most abundant biomolecules, have indispensable roles in a wide range of biological processes, including cell-cell recognition, protein folding, neurobiology, inflammation, and infection.[12] The possibility of modifying sugar structure(s) to enhance or otherwise alter the physiological properties of the parent molecule is therefore highly attractive.[13] Selective C-2 functionalization of carbohydrates has attracted significant interest because the resulting 2-deoxy sugar derivatives, in which the C-2 hydroxyl group of sugar has been replaced by other functional groups, are ubiquitous in nature and are found in medicine, molecular imaging, cell engineering, and catalysis.[14] Conventional methods to access C-2 functionalized 2-deoxy sugars rely on the derivatization of advanced intermediates such as glycals and 1,2-epoxy- or 1,2-cyclopropyl-sugars.[15] These protocols often involve multi-step precursor syntheses and harsh reaction conditions, and have limited reaction scope. We envisaged that the establishment of excited-state Pd-catalyzed 1,2-SCS reactivity would enable a general, controllable, and selective catalytic strategy for C-2 functionalization of carbohydrates using readily available 1-halosugars.[16]

The mechanistic hypothesis of the proposed transformation is outlined in Figure 2. We envisioned that photoexcited palladium catalyst [Pd(0)]* undergoes radical oxidative addition with 1-halo sugar **1**, generating the hybrid 1-glycosyl-Pd-X complexes **IIa** and **IIb**.[2b, 3] The glycosyl radical **IIa** favors the $B_{2,5}$ boat conformation (**IIIa**) because of the hyperconjugation between the singly occupied molecular orbital (SOMO) and $\sigma^*_{C\text{-}O}$ orbital of the C-2–OAc group.[17] Such an interaction is more pronounced in glycosyl radicals because the lone pair electron of the endocyclic-*O* (η_O, anomeric interaction) raises the SOMO energy level. Such an extended anomeric interaction weakens the C-2–OAc bond and promotes the 1,2-SCS through a concerted [2,3]-acyloxy rearrangement with a cyclic five-membered ring transition state **IIIb**,[11b, 17a] forming the deoxypyranosan-2-yl radical **IVa** that prefers the ^{4}C-1 chair conformation.[18] Although the anomeric radical is more stable than the secondary alkyl radical, the molecular stability gained from the formation of an anomeric C–O bond in **IVa** drives the desired 1,2-SCS.[19] Under visible-light irradiation, the intermediate **IVa** is in equilibrium with alkyl-Pd(II)X complex **IVb**, which allows access to both open- and closed-shell reactivities. We anticipate that these hybrid Pd species can engage in a wide range of cross-coupling reactions through processes such as (i) transmetalation followed by reductive elimination, or (ii) radical coupling or atom/group transfer followed by reduction of Pd(I)X to furnish the desired C-2 functionalized carbohydrate **2** and regenerate Pd(0) catalyst, completing the catalytic cycle.

With this hypothesis in mind, we started our investigations using readily available α-glucosyl bromide (**1a**) as a model substrate. Initial experiments showed that upon exposing **1a** to 24 W blue light-emitting diodes (LED) in the presence of $Pd(PPh_3)_4$ (5.00 mol%), *N*, *N*-diisopropylethylamine (DIPEA, 2.00 equiv) in isopropyl acetate (*i*-PrOAc, 0.05 M) at room temperature for 20 h, we observed 94% yield of *α-only* product **2a** with >20:1 C-2 selectivity (Table S1, entry 1). The $Pd(PPh_3)_4$ catalyst was shown to be critical for the desired reactivity because replacing it with PPh_3, $Pd(PPh_3)Cl_2$, led to no reaction or significantly lower yield and selectivity (entries 2 & 3). We recognized that the relative rates of the intramolecular 1,2-SCS and the intermolecular hydrogen atom transfer must be controlled to achieve high levels of regioselectivity. It was envisioned that the unique inner-sphere coordination interaction between the Pd catalyst and alkyl radical could stabilize and modulate the reactivity of radical intermediates, thus minimizing the premature C-1 reduction.[1e, 20] Indeed, the use of other common Ru-, Ir-, and organic-based photoredox catalysts, where inner-sphere coordination is not feasible, proved to be ineffective and afforded the product with low yields and selectivity (entries 4–6). Reactions in acetonitrile were sluggish and were accompanied by the erosion of the regioselectivity (entry 7). Control experiments showed that DIPEA, an oxygen-free environment, and light were all essential for the desired reactivity (entries 8–10).

With the optimized conditions in hand, we next examined the scope of the reaction. In general, a wide range of α-bromosugars afforded the desired 2-deoxy sugars with up to 95% yield and >20:1 regioselectivity (Table 1A).[21] α-Glucosyl bromides with different ester protecting groups such as acetyl, benzoyl, or pivaloyl worked well (**2a**-**2c**). Other α-bromosugars, including those derived from acetylated L-fucose, D-xylose, and D-galactose, were also viable substrates (**2d**-**2f**).[22] Substrates with benzyl-, methyl-, and the acid-

sensitive *tert*-butyldimethylsilyl-protected C-6 hydroxyl groups were well tolerated, affording the desired products **2g-2i** in 72–91% yields with >20:1 C-2 selectivity. A free C-6 hydroxyl group, which is useful for further functionalization and often serves as a glycosyl acceptor, reacted smoothly and gave product **2j** in 72% yield. A fused ring structure also proved to be compatible with the reaction conditions (**2k**). The structure of the migratory ester group has little effect on the reaction efficiency because C-2 esters substituted with alkyl, aryl, or heteroaryl groups underwent excited-state Pd-catalyzed 1,2-SCS smoothly, forming the corresponding products **2l-2q** in 74–90% yields. A melibiose derivative gave the desired 2-deoxy-disaccharide **2r** in 89% yield. Notably, the reaction affords the α−2-deoxyglycosides exclusively, and the corresponding β-isomers were not observed.

The synthetic utility of this process is further highlighted by its amenability to (i) a late-stage modification of functionally dense natural product- and drug-conjugated sugar derivatives and (ii) the synthesis of deuterated 2-deoxy sugars (Table 1). For example, α-Bromoglucose derivatives of oleanolic acid, Indomethacin, Probenecid, Bezafibrate, Febuxostat, Zaltoprofen, Ibuprofen, and Adapalene reacted and afforded the desired products **2s-2z** in good yields and excellent levels of regioselectivity, demonstrating that the method can be used in the preparation of pharmaceutically relevant compounds. Furthermore, deuterium-labeled sugars are versatile probes for the study of biological processes such as metabolic and biosynthetic pathways,[23] and useful chiral building blocks for the synthesis of chiral deuterated precursors of bioactive molecules.[24] Using d_8-THF as the solvent and Cs_2CO_3 as the base under otherwise identical reaction conditions, we successfully obtained a series of (2-$^2H_1$)-2-deoxy sugars *d*-**2a**, *d*-**2d**, *d*-**2e**, *d*-**2i**, *d*-**2k**, and *d*-**2r** in yields of 88–98% and with high levels of regioselectivity and deuterium incorporation (Table 1B).

The reaction can be further extended to the synthesis of 2-iodo-2-deoxy sugars using α-iodosugars as starting materials (Table 1C). For example, α-iodosugar derivatives of D-galactose, D-glucose, L-fucose, and D-xylose were converted to the corresponding 2-iodo-2-deoxy sugars **4a-4d** with good yields and up to >20:1 equatorial/axial selectivity. The electronic nature of the migrating group had a negligible impact on reaction efficiency and stereoselectivity, as demonstrated by substrates **3e-3f** that afforded the desired products **4e-4f** in similar yields and diastereoselectivity. Disaccharide and D-galactose derivatives of pharmaceuticals such as Ibuprofen, Probenecid, Febuxostat, and Zaltoprofen could be used to generate the corresponding products **4h-4l** with >20:1 equatorial/axial ratios in good yield. Notably, other photocatalysts such as $Ru(bpy)_3^{2+}$, $Ir(ppy)_3$, and Eosin Y failed to catalyze this iodination reaction. Given that 2-iodo-2-deoxy sugars are (i) excellent glycosyl donors that control the stereochemistry of the newly formed glycosidic bond[25] and (ii) versatile intermediates for further sugar derivatizations,[26] our protocol will find a useful application in the synthesis of complex glycans for the discovery and development of new bioactive compounds.

Our mechanistic hypothesis of the excited-state Pd-catalyzed C-2 functionalization of carbohydrates depicted in Figure 2 is supported by UV-Vis measurements, Stern-Volmer quenching studies, radical trapping experiments, deuterium labeling studies, quantum yield measurements, radical clock and cross-over experiments, and kinetic studies (Figure 3). UV-Vis measurements showed the absence of any reaction between the acetylated α-glucosyl

bromide (**1a**) and the ground-state $Pd(PPh_3)_4$ (Figure 3A). Irradiation of the reaction mixture with blue LED light for 5 min, however, led to a significant bathochromic shift ($\Delta\lambda_{abs}$ = 43 nm) with a λ_{abs} at 362 nm. The UV-Vis data suggested that an excited $Pd(PPh_3)_4$ catalyst readily undergoes a radical oxidative addition with **1a**, generating a putative Pd(II)-species.[4] Stern-Volmer quenching studies demonstrated that only 1-halosugar quenches the excited $Pd(PPh_3)_4$ (Fig. S2). The radical nature of the reaction is further supported by a radical trapping experiment (Figure 3B). Deuterium labeling studies where Cs_2CO_3 was replaced by DIPEA under deuteration reaction conditions shifted the **2a**:*d*-**2a** ratio from 1.0:7.3 to 1.9:1.0, showing that DIPEA serves as a hydrogen atom donor (Figure 3C). Because the quantum yields of the C-2 reduction and iodination reactions were 0.09 and 0.24, respectively, an extended radical chain propagation is unlikely under our reaction conditions (Fig. S9 and Fig. S10).

The key 1,2-spin-center shift involving the acyloxy migration may proceed through one of the following reaction pathways: (**P1**) fragmentation to an acyloxy radical and an alkene with subsequent recombination; (**P2**) formation of a cyclic 1,3-dioxolanyl radical followed by ring-opening; (**P3**) fragmentation to an alkene radical cation and an acyloxy anion followed by recombination; or (**P4**) a concerted process involving a cyclic five-membered ring transition state (Figure 3D).[11b] The **P1** pathway can be eliminated because the decarboxylation of an acyloxy radical ($k = 10^9\ s^{-1}$)[27] is much faster than the migration ($k = 10^2\ s^{-1}$),[19] and no decarboxylation was observed in the reaction. Pathway **P2** is also unlikely because a radical clock experiment using a substrate bearing the cyclopropyl acetate group (**1m**) afforded the desired product **2m** without the formation of a ring-opening side product **2m'**. No cross-over products **5a** and **5b** were formed in cross-over experiments using substrates **1a** and **1b**, indicating that the reaction could proceed through either pathway **P3** with an "in-cage" recombination or pathway **P4**. Since the electronics of the migrating group has a negilible effect on the reaction rate, the acyloxy migration most likely proceeds through the natural, concerted pathway **P4**, and this agrees with the DFT calculations.[28]

In summary, we established and exploited the first excited-state Pd-catalyzed 1,2-SCS reaction for the synthesis of C-2 functionalized carbohydrates from readily available 1-halosugars. The reaction features high levels of regio- and stereoselectivity, broad substrate scope, and mild reaction conditions that tolerate a wide range of functional groups and complex molecular structures. Detailed mechanistic studies suggest a non-chain radical reaction mechanism involving an excited Pd catalytic species and a 1,2-SCS *via* a concerted [2,3]-acyloxy rearrangement. Given the versatile reactivity of Pd catalysts in carbon-carbon and carbon-heteroatom bond forming reactions, we anticipate that our strategy will (i) offer a general, catalytic approach for the C-2 selective functionalization of carbohydrates to access a wide array of unexplored carbohydrate mimics, establish tools that tackle fundamental questions in glycobiology, and aid the discovery and development of new therapeutics; and (ii) guide the design and development of new synthetic strategies beyond carbohydrate chemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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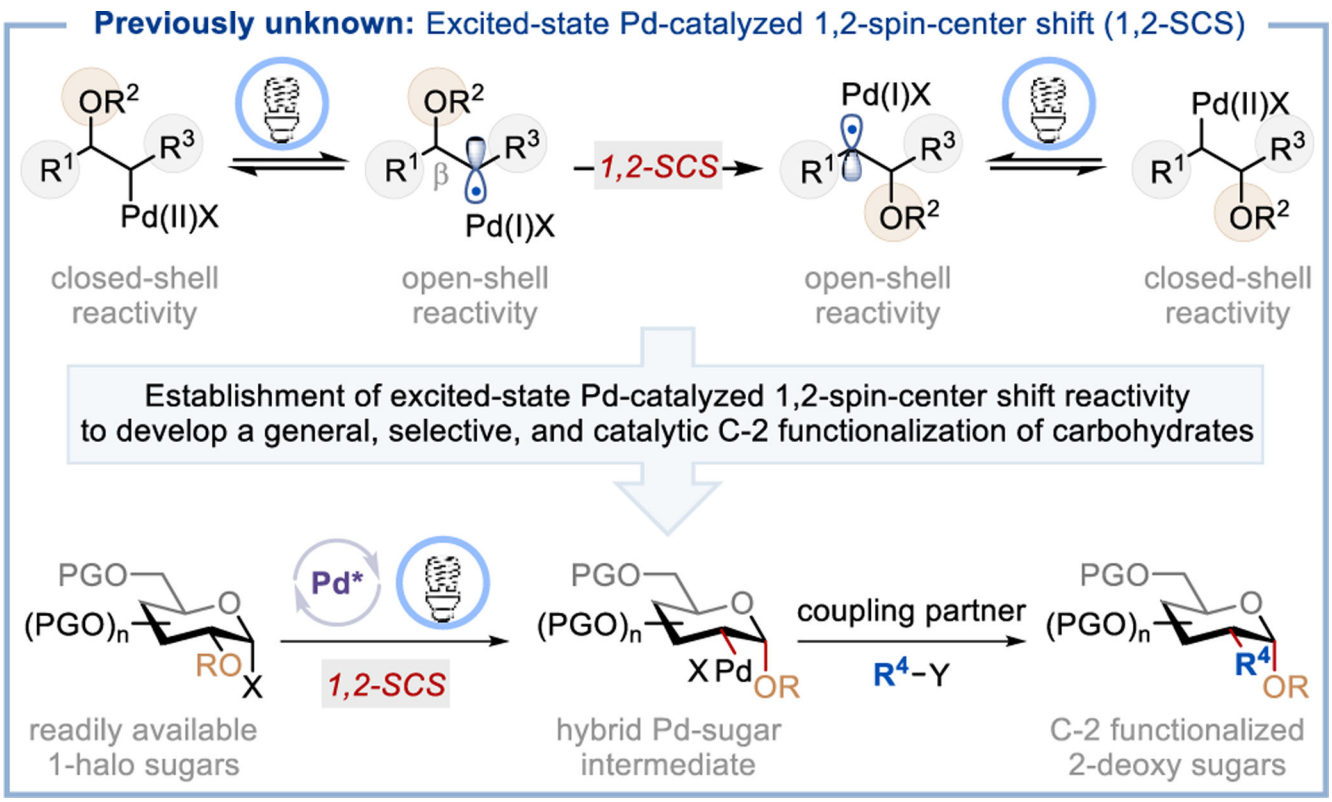


Figure 1.

Development and exploitation of excited-state palladium-catalyzed 1,2-spin-center shift for selective C-2 functionalization of carbohydrates.

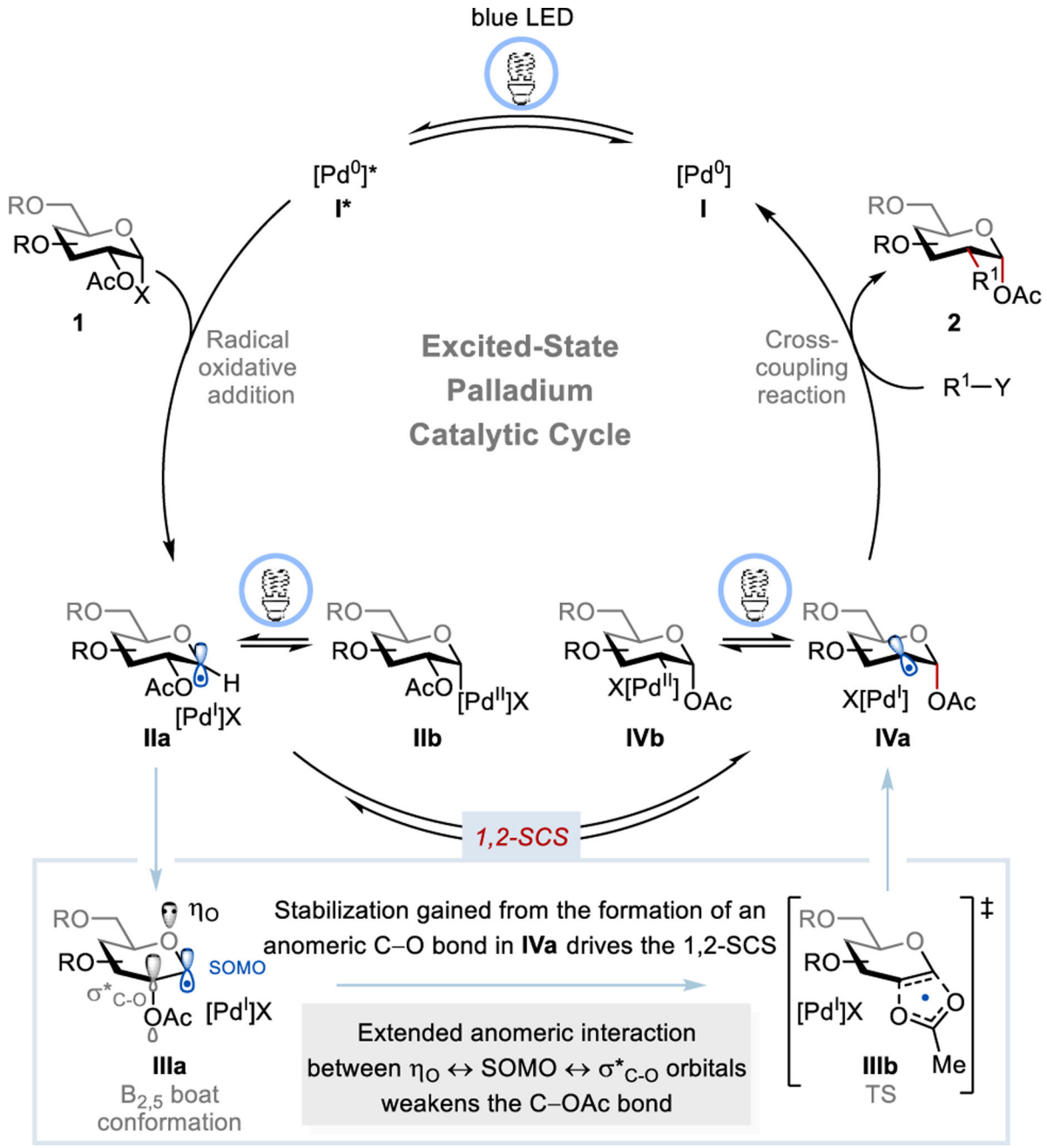


Figure 2.
Proposed catalytic cycle for the excited-state Pd-catalyzed C-2 functionalization of carbohydrates.

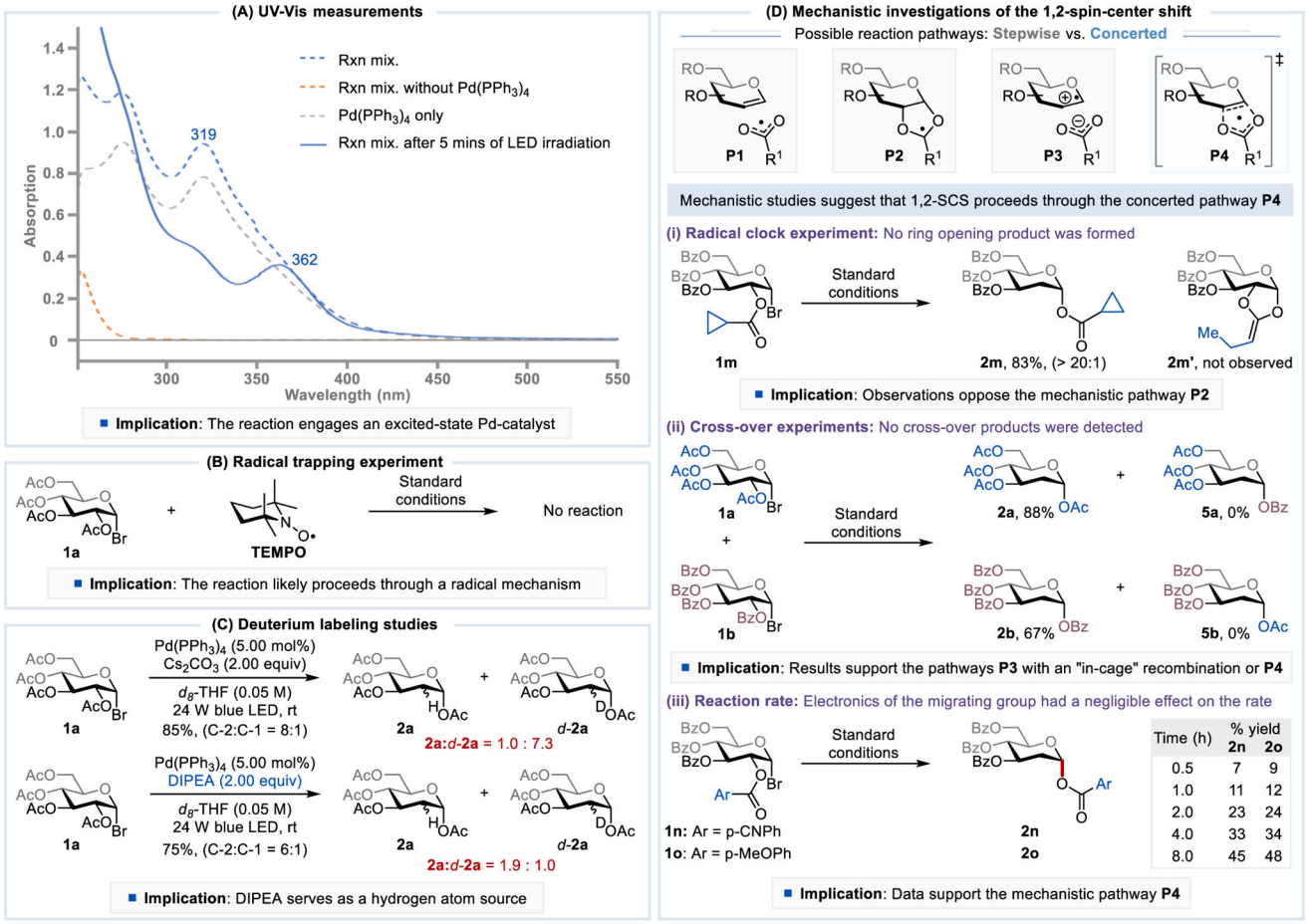
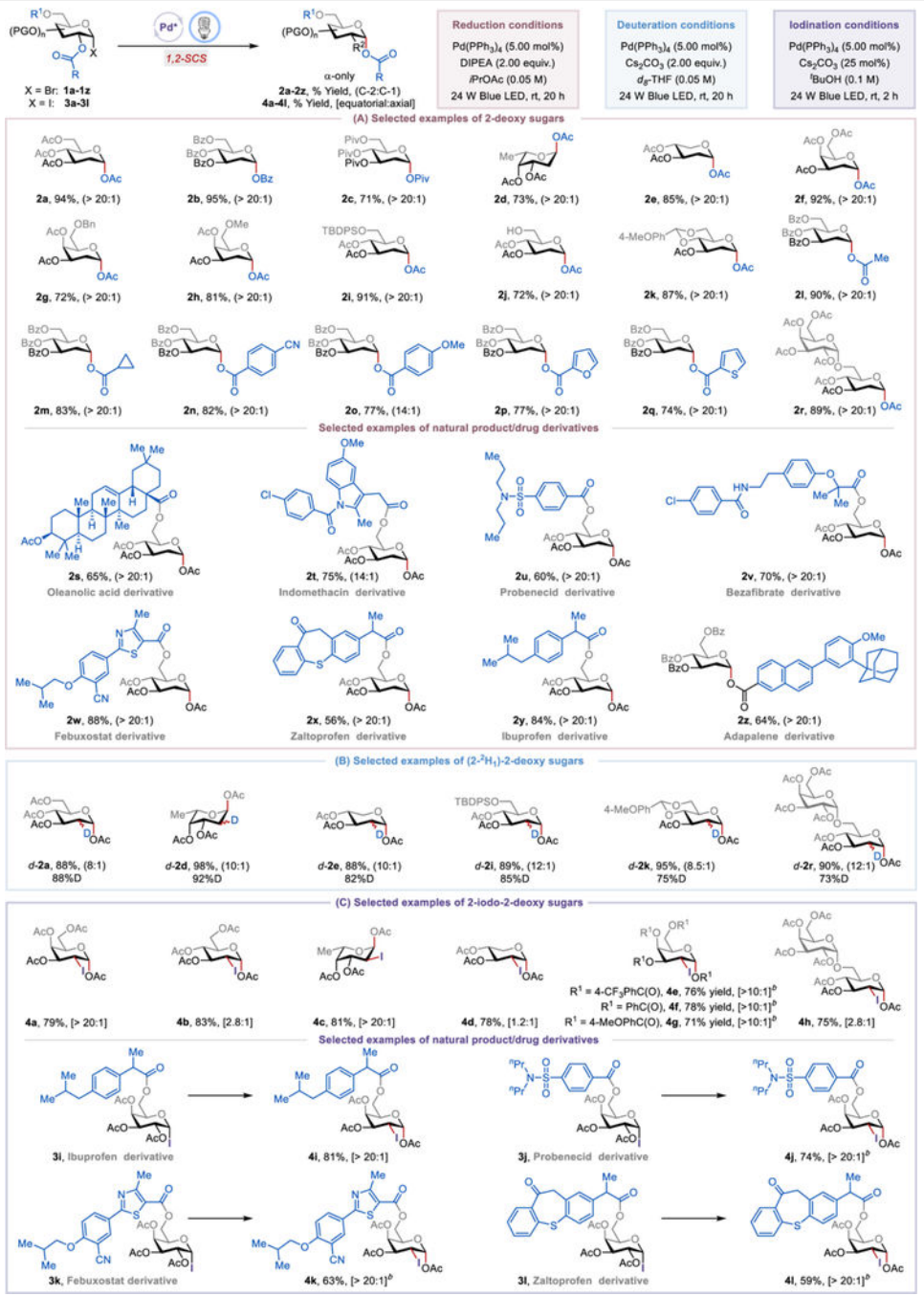


Figure 3.

Mechanistic studies of excited-state Pd-catalyzed C-2 functionalization of carbohydrates. See Supporting Information for experimental details. % of deuterium incorporation, C-2:C-1 ratio, and reaction yields were determined by ^{1}H-NMR using CH_2Br_2 as an internal standard.

Table 1.

Scope of C-2 reduction, deuteration, and iodination of α-glycosyl halides via excited-state Pd-catalysis.[a]



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[a] See Supporting Information for experimental details.

[b] % of deuterium incorporation, C-2:C-1 ratio, and equatorial:axial (eq:ax) ratio were determined by ^{1}H-NMR.

[b] Benzene instead of ^{t}BuOH was used as a solvent.