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# Excited-State Palladium-Catalyzed Radical Migratory Mizoroki-Heck Reaction Enables C2-Alkenylation of Carbohydrates

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## Abstract

Excited-state palladium catalysis has emerged as a promising strategy for developing novel and valuable reactions. Herein, we report the first excited-state Pd-catalyzed radical migratory Mizoroki-Heck reaction that enables C2-alkenylation of carbohydrates using readily available 1-bromosugars and alkenes. The reaction tolerates a wide variety of functional groups and complex molecular architectures, including derivatives of natural products and marketed drugs. Preliminary mechanistic studies and DFT calculations suggest the involvement of visible-light-induced photoexcitation of Pd species, 1,2-spin-centered shift (SCS) process, and Heck-type cross-coupling reaction. The reaction expands the reactivity profile of excited-state Pd catalysis and provides a streamlined protocol for the preparation of a wide variety of C2-alkenylated carbohydrate mimetics to aid the discovery and development of new therapeutics, agrochemicals, and materials.

## Graphical Abstract

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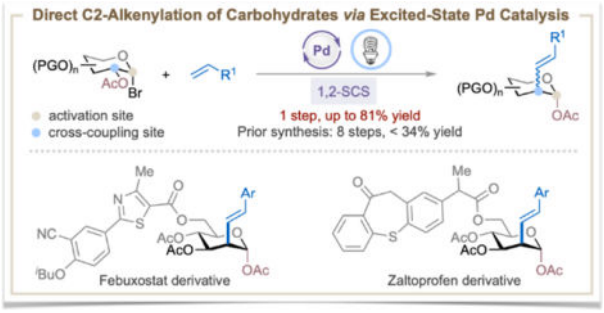
Supporting Information

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




Carbohydrates are involved in a wide range of biological processes, including their role in glycolipids and glycoproteins, where they serve as ligands for cell-cell interactions or as receptors for toxins, antibodies, viruses, and bacteria.[1] A growing body of literature links the sugar composition of various glycoconjugates to numerous diseases such as cancer, viral infections, diabetes, and neurological disorders.[2] The selective modification of carbohydrate scaffolds to enhance or alter the biochemical properties of the parent glycoconjugates is, therefore, an appealing strategy with which to develop novel therapeutics.[3] Indeed, many pharmaceuticals, vaccines, cell surface engineering agents, and imaging probes contain carbohydrate moieties and mimetics, such as C2-functionalized 2-deoxy sugars.[3a–c, 4] However, synthesis of these glycomimetics is often labor-intensive and time-consuming. For example, the current state-of-the-art synthesis of C2-alkenylated carbohydrates starting from 1-bromosugars requires 8 steps with less than 34% overall yield (Figure 1A).[5] Consequently, a strategy that enables one-step access to C2-substituted carbohydrates from readily available starting materials would be of considerable value to medicinal and process chemists.

Excited-state palladium catalysis has emerged as a powerful tool in organic synthesis because of its ability to access both open-shell (one-electron) and closed-shell (two-electron) reactivities under irradiation of visible light.[6] Exploitation of this type of hybrid reactivity has led to a wide range of carbon-carbon and carbon-heteroatom bond forming reactions, including radical Mizoroki-Heck reactions.[7] Although elegant excited-state Pd-catalyzed 1,5-, 1,6-, and 1,7-radical migratory Mizoroki-Heck (RMMH) reactions have been developed to remotely install an alkenyl group,[7n, 7p] the corresponding 1,2-RMMH reaction remains elusive (Figure 1B). Inspired by the seminal work of Giese, who showed that 1-glycosyl radical could undergo a 1,2-spin-center shift (SCS) with concomitant acyloxy migration to form the deoxypyranosan-2-yl radical,[8,9] we questioned whether we could merge the excited-state Pd-catalyzed radical Mizoroki-Heck reaction with the 1,2-SCS process to achieve a direct, catalytic C2-alkenylation of carbohydrates from readily accessible 1-bromosugars (Figure 1B). Accomplishment of such a reaction would be significant and novel because it (i) represents the first example of excited-state Pd-catalyzed RMMH reaction that proceeds through a 1,2-SCS mechanism, (ii) significantly streamlines the synthesis of C2-alkenylated carbohydrates from an 8-step procedure to a single step protocol, (iii) expands the reactivity profile of excited-state Pd catalysis, and (iv) provides a new approach to the synthesis of unnatural carbohydrates and late-stage functionalization

of glycoconjugates, which will be useful for modern glycomimetic synthesis and drug discovery.

Achieving the proposed reaction is, however, challenging because it requires precise control of the kinetics of the Mizoroki-Heck coupling reaction and the 1,2-SCS process to minimize premature C1-alkenylation.[7q] Indeed, initial attempts using 1-glucosyl bromide (**1a**) and styrene (**2a**) as model substrates and our reported reaction conditions[7y] gave only the C1-alkenylated products. Nevertheless, after further optimization of the reaction, we found that exposing **1a** (1.00 equiv) and **2a** (2.00 equiv) to visible light (34 W blue LEDs) in the presence of $Pd(PPh_3)_4$ (10.0 mol%), xantphos (20.0 mol%) and $K_3PO_4$ (2.00 equiv) in benzene at 0.025 M at 90 °C for 14 h afforded the desired C2-alkenylated 2-deoxyglucoside (**3a**) in 83% yield with an axial/equatorial (ax:eq) selectivity of 4.2:1 (Table 1, entry 1). The $Pd(PPh_3)_4$ catalyst is essential for the desired reactivity: when it was replaced with $Pd(OAc)_2$, only 19% of the desired product was formed, and in its absence the reaction failed completely (entries 2 & 3). Conventional Ru- and Ir-based photocatalysts also failed to give the desired products (entries 4 & 5). The xantphos (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(di-phenylphosphane) ligand also plays an important role in promoting the reaction and its removal significantly decreased the reaction yield (entry 6), suggesting that xantphos-ligated Pd complexes may possibly be active catalysts. The identity of the base was critical because the absence of $K_3PO_4$ or its replacement with DIPEA or $Cs_2CO_3$ dramatically diminished the reaction efficiency (entries 7–9). Conducting the reaction at room temperature (rt) gave the undesired C1-alkenylated product, indicating that elevated reaction temperatures promote the 1,2-SCS process (entry 10). Control experiments showed that both light and an oxygen-free environment were crucial for the success of the reaction (entries 11–12).

With the optimized conditions in hand, we first investigated the substrate scope of alkene derivatives (Table 2A). Styrenes with both electron-withdrawing and electron-donating substituents, including trifluoromethyl, cyano, *tert*-butyl, methoxy, and methyl groups on different positions of the phenyl ring were well tolerated under the standard conditions, affording the corresponding products **3a**-**3e** and **3i**-**3k** in 56–80% yield with moderate ax:eq selectivity. Reactions of styrenes with other substituents such as chloro (**2f**), phenoxy (**2g**), boronic ester (**2h**), and *N*-methylphthalimide (**2p**) also gave good yields. Multi-substituted substrates showed good compatibility under the reaction system and gave the desired products **3l**-**3n** in yields of 55–80%. An extended aromatic ring, such as 2-vinylnaphthalene (**2o**) was a viable substrate and furnished the desired product **3o** in a moderate yield. Alkenes bearing ferrocene and heterocyclic moieties, including pyridine, carbazole, and benzothiophene, gave the corresponding products **3q**-**3u** in 45–84% yield.

We next examined the scope of 1-bromosugars using 2-methylstyrene (**2k**) as a coupling partner (Table 2B). D-Glucoside derivatives protected with acetyl or *tert*-butyldimethylsilyl groups were well tolerated and formed the desired products **3k** and **4b** in 76–80% yield. D-Xylose, D-galactoside, D-glucuronic acid, and L-fucoside derivatives reacted under the standard conditions, affording the corresponding products **4c**-**4f** in moderate to good yields. A substrate with a fused ring structure at C4 and C6 positions was also compatible, forming product **4g** in 65% yield. The ester migrating group could be extended beyond an acetoxy

group to (hetero)aryl ester groups with different electronic properties, delivering the desired products **4h**-**4k** in 47–70% yield. Disaccharides, such as D-melibiose, D-maltose, and D-cellobiose derivatives, could also be used (**4l**-**4n**), further establishing the utility of the transformation.

Late-stage modifications of biologically active molecules are often a key to identifying medicinal agents.[10] To demonstrate the use of the excited Pd-catalyzed C2-alkenylation of carbohydrates in late-stage synthetic applications, a range of natural product- and drug-glycoconjugates were subjected to the standard conditions (Table 3). 1-Bromoglucosyl-conjugated drug molecules such as Febuxostat (an anti-hyperuricemic drug), Ibuprofen (non-steroidal anti-inflammatory drug, NSAID), Probenecid (anti-gout), Zaltoprofen (NSAID), Adapalene (antiacne agent), and L-Menthol (decongestant and analgesic) were all successfully alkenylated at the C2 position, affording the corresponding products **7a-7f** in 45–79% yield with moderate stereoselectivity. Alkenes bearing natural products such as oleanolic acid and glucofuranose were also viable substrates, furnishing the desired products **7g** and **7h** in 64% and 81% yield, respectively.

The C2-alkenylated carbohydrate products are synthetic intermediates useful for the preparation of a wide array of glycomimetics (Table 4). For example, alkene in product **3k** could be fully reduced to the saturated alkane derivative **8a** in a 96% yield. Under ozonolysis conditions, C2-enal **8b** was formed. Treatment of **3k** with 3-chloroperoxybenzoic (*m*-CPBA) in DCM at rt gave the desired epoxide **8c** in 80% yield. C2-alkenylated carbohydrate products are also good glycosyl donors for *N*-, *O*-, *S*-, and *C*-glycosylation, forming the corresponding products **8d**-**8g** in 56%−90% yield with up to >99% α-selectivity.

To gain a better understanding of the reaction mechanism, we performed a series of mechanistic studies. Stern-Volmer luminescence quenching experiments revealed that a 1-bromosugar quenches the excited Pd catalyst more efficiently than styrene (Figure S2). The addition of a radical scavenger such as 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or butylated hydroxytoluene (BHT) inhibited the reaction (Figure 2A). These results and the isolated 1-TEMPO-glucosyl adduct **3a'** indicate the formation of a 1-glycosyl radical intermediate during the reaction. Subjecting substrates 1,2-*cis*- and 1,2-*trans*-2-iodosugars (**9a**-eq and **9a**-ax, respectively), to the standard reaction conditions gave the desired product **3a** in similar yield and stereoselectivity (Figure 2B) as the parent reaction (Table 1, entry 1), suggesting that a C2-radical species is the common intermediate. Kinetic isotope effect (KIE) studies using either a mixture of **2e** and **2e**-$d_2$ or **2e**-$d_1$ afforded a value of 1.84 and 2.14, respectively, showing a primary kinetic isotope effect (Figure 2C).[11] Light ON/OFF experiments and the measured quantum yield ($\phi = 0.15$) (Figure 2D) suggested that an extended radical chain mechanism is unlikely. Alkene formation could proceed through three different reaction mechanisms: (i) Pd-catalyzed β-hydride elimination, (ii) palladoradical hydrogen atom abstraction, or (iii) bromine atom transfer followed by HBr elimination. DFT calculations showed that the recombination of benzylic radical **IV** with [$Pd^{I}$]Br followed by the β-hydride elimination is the most favorable reaction pathway for this transformation (Figure 2E and Figures S9–S13 in the SI), which is consistent with our experimental data.

Based on these results, a plausible catalytic cycle is proposed in Figure 2F. Photoexcitation of the [$Pd^0$] catalyst furnishes excited *[$Pd^0$] that abstracts a bromine atom from 1-glycosyl bromide **1,** forming alkyl radical/Pd(I) species **II**. This radical species **II** undergoes 1,2-spin-center shift (SCS) *via* a conformational change (**IIa**) and a concerted [2,3]-acyloxy rearrangement (**IIb**),[7y] affording C2-radical/Pd(I) intermediate **III**. Subsequent radical addition of **III** to alkene substrate **2** produces radical intermediate **IV**, which recombines with Pd(I) followed by $\beta$-hydride elimination, furnishing the desired product **3** and H[$Pd^{II}$]Br complex. Base-assisted HBr reductive elimination of H[$Pd^{II}$]Br regenerates the active [$Pd^0$] catalyst, closing the catalytic cycle.

In summary, we report the first excited-state Pd-catalyzed radical migratory Mizoroki-Heck reaction proceeding through the 1,2-SCS pathway, enabling the direct C2-alkenylation of carbohydrates from readily available 1-bromosugars and alkene derivatives. The reaction (i) significantly streamlines the synthesis of C2-alkenylated glycomimetics, (ii) has high functional group tolerance and broad substrate scope, and (iii) is amenable to late-stage functionalization of complex molecules such as natural product- and drug-glycoconjugates. The resulting C2-alkenylated carbohydrates can serve as versatile synthetic intermediates and glycosyl donors. Preliminary mechanistic studies and DFT calculations suggest a mechanism involving photoexcited Pd species, 1,2-SCS process, and Mizoroki-Heck cross-coupling reaction. We anticipate this excited Pd-catalyzed radical migratory cross-coupling strategy can be extended to other related C2-functionalization of carbohydrates and reactions beyond carbohydrate chemistry.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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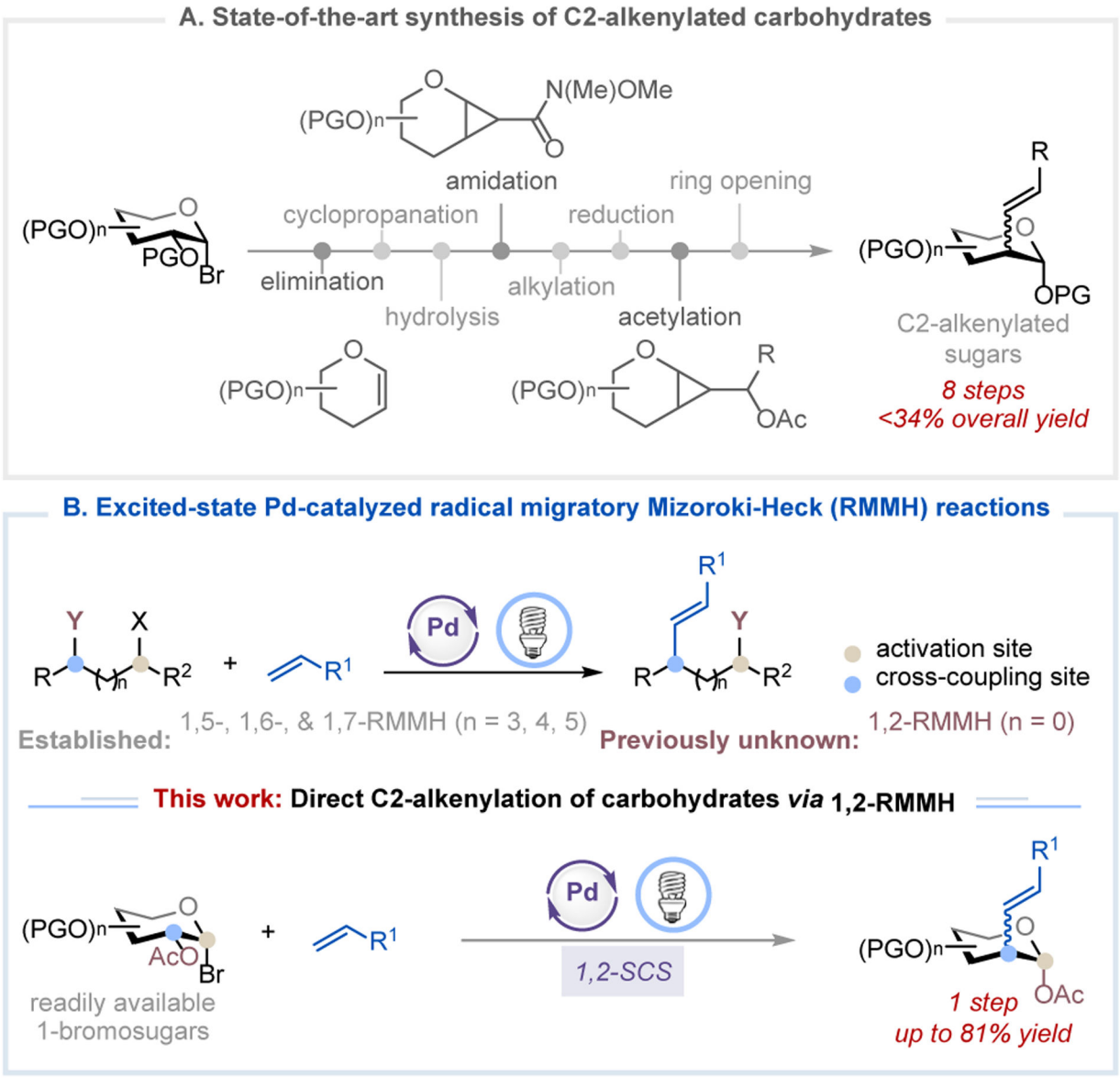



**Figure 1.**

Excited-state Pd-catalyzed radical migratory Mizoroki-Heck reaction *via* 1,2-SCS pathway enabling C2-alkenylation of carbohydrates. PG = protecting group.

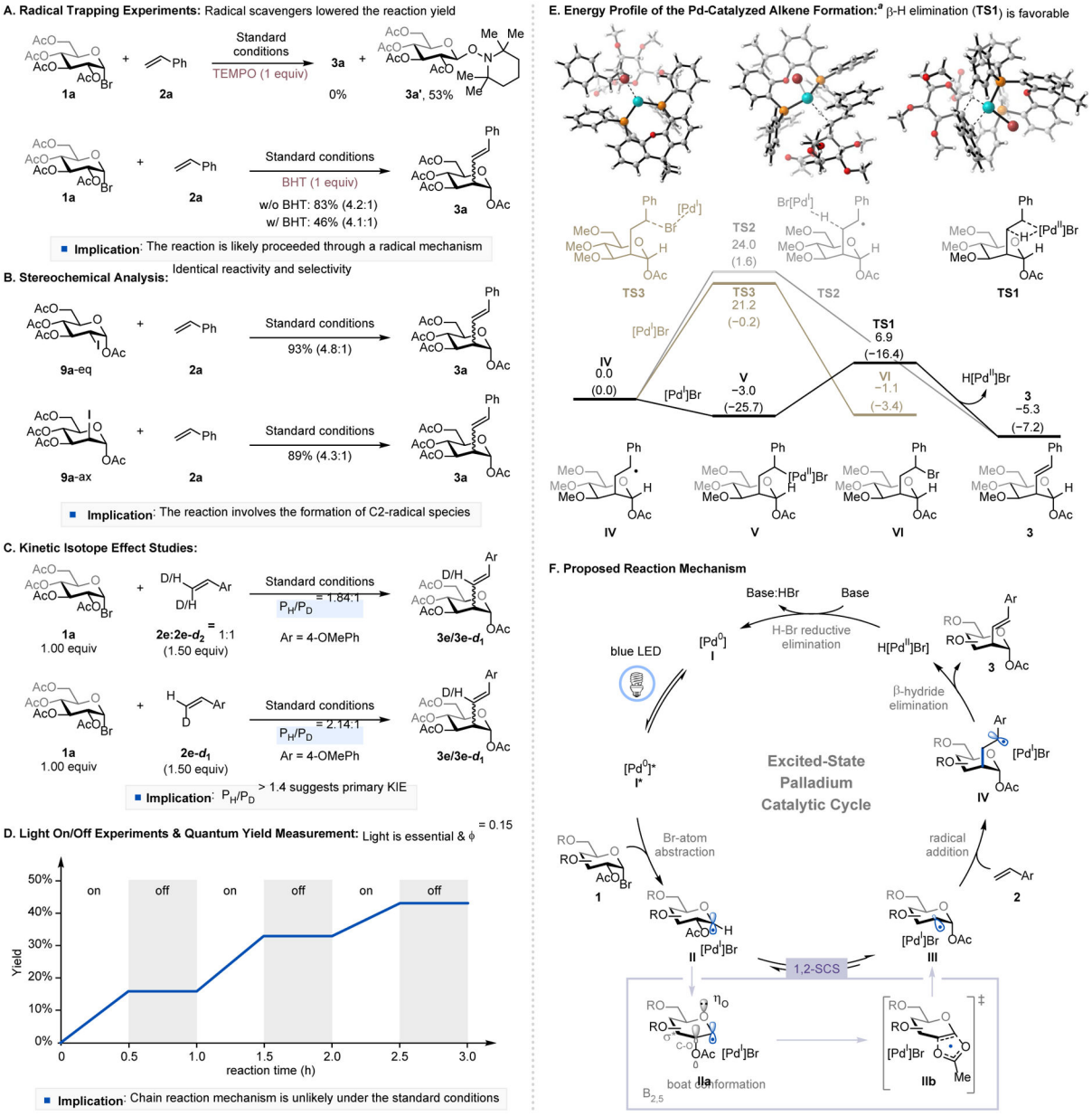
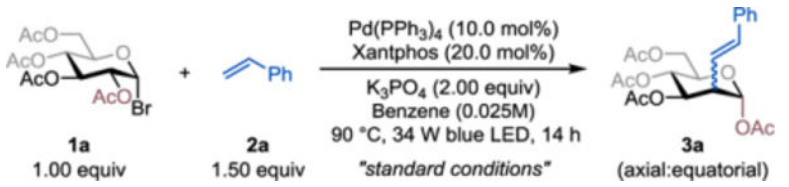



**Figure 2.**

Mechanistic studies and a proposed reaction mechanism. [a]DFT calculations were performed at the M06/SDD-6-311+G(d,p)/SMD//B3LYP-D3/SDD-6-31G(d) level of theory using a simplified model of the glucosyl radical(**1**), where the OMe groups were used in place of the OAc groups at the C3, C4, and C6 of the pyranose ring.

**Table 1.**

Selected Optimization Experiments.[a]

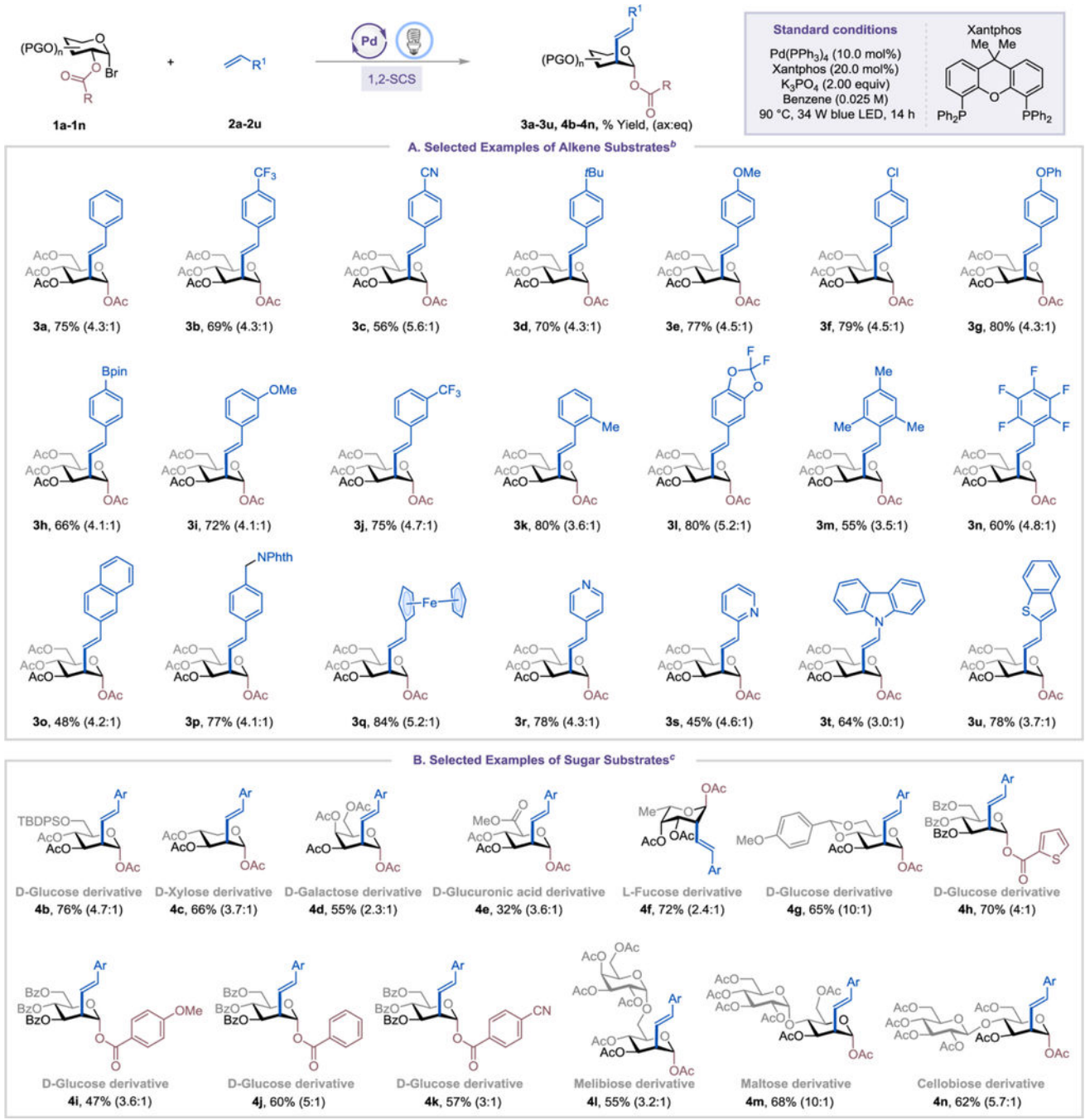



| Entry | Deviation from the standard conditions | Yield (%) | ax:eq |
|---|---|---|---|
| 1 | none | 83 | 4.2:1 |
| 2 | $Pd(OAc)_2$ instead of $Pd(PPh_3)_4$ | 19 | 4.8:1 |
| 3 | no $Pd(PPh_3)_4$ | <2 | - |
| 4 | $Ru(bpy)_3(PF_6)_2$ | <2 | - |
| 5 | $Ir(PPy)_2(dtbbpy)PF_6$ | <2 | - |
| 6 | no Xantphos | 30 | 4.2:1 |
| 7 | DIPEA instead of $K_3PO_4$ | 52 | 4.2:1 |
| 8 | $Cs_2CO_3$ instead of $K_3PO_4$ | 67 | 4.2:1 |
| 9 | no Base | 8 | 4.2:1 |
| 10 | room temperature | <2 | - |
| 11 | with air | <2 | - |
| 12 | no light | <2 | - |

[a]See the Supporting Information (SI) for experimental details. Yields of **3a** and axial:equatorial (ax:eq) ratios were determined by $^1$H NMR analysis using dibromomethane as the internal standard.

**Table 2.**

Substrate Scope of Alkene and Sugar Derivatives[a]




*J Am Chem Soc*. Author manuscript; available in PMC 2023 March 02.

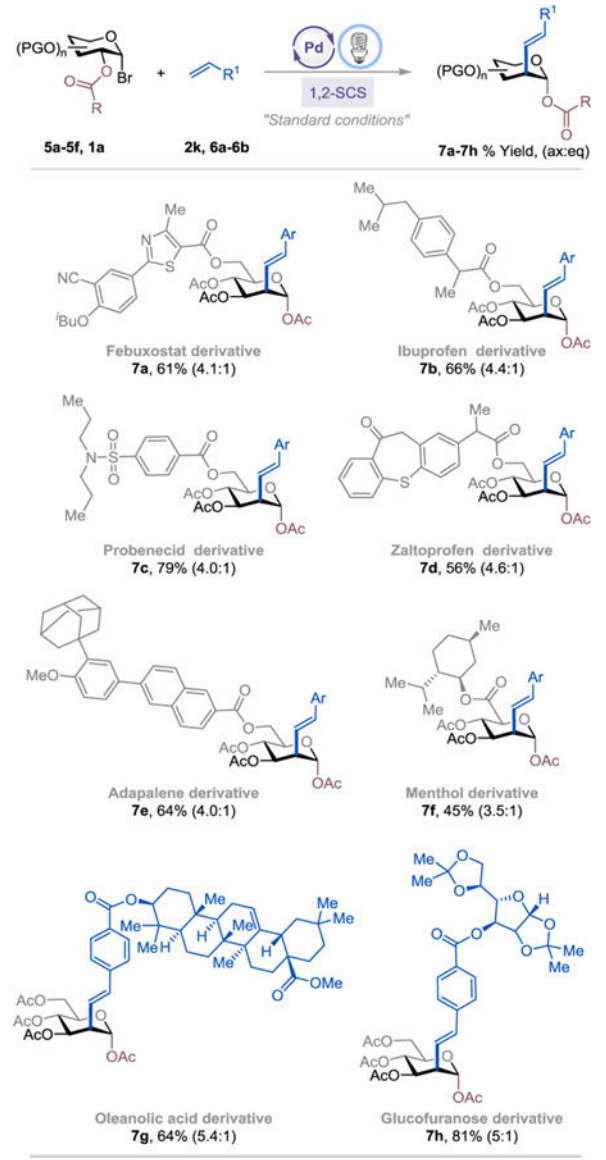
[a] See SI for experimental details. The isolated yield and axial:equatorial (ax:eq) ratio are indicated below each entry.

[b] Use **2a** as bromosugar substrate.

[c] Use 1-methyl-2-vinylbenzene (**2k**) as coupling partner. Ar = 2-MePh.

**Table 3.**

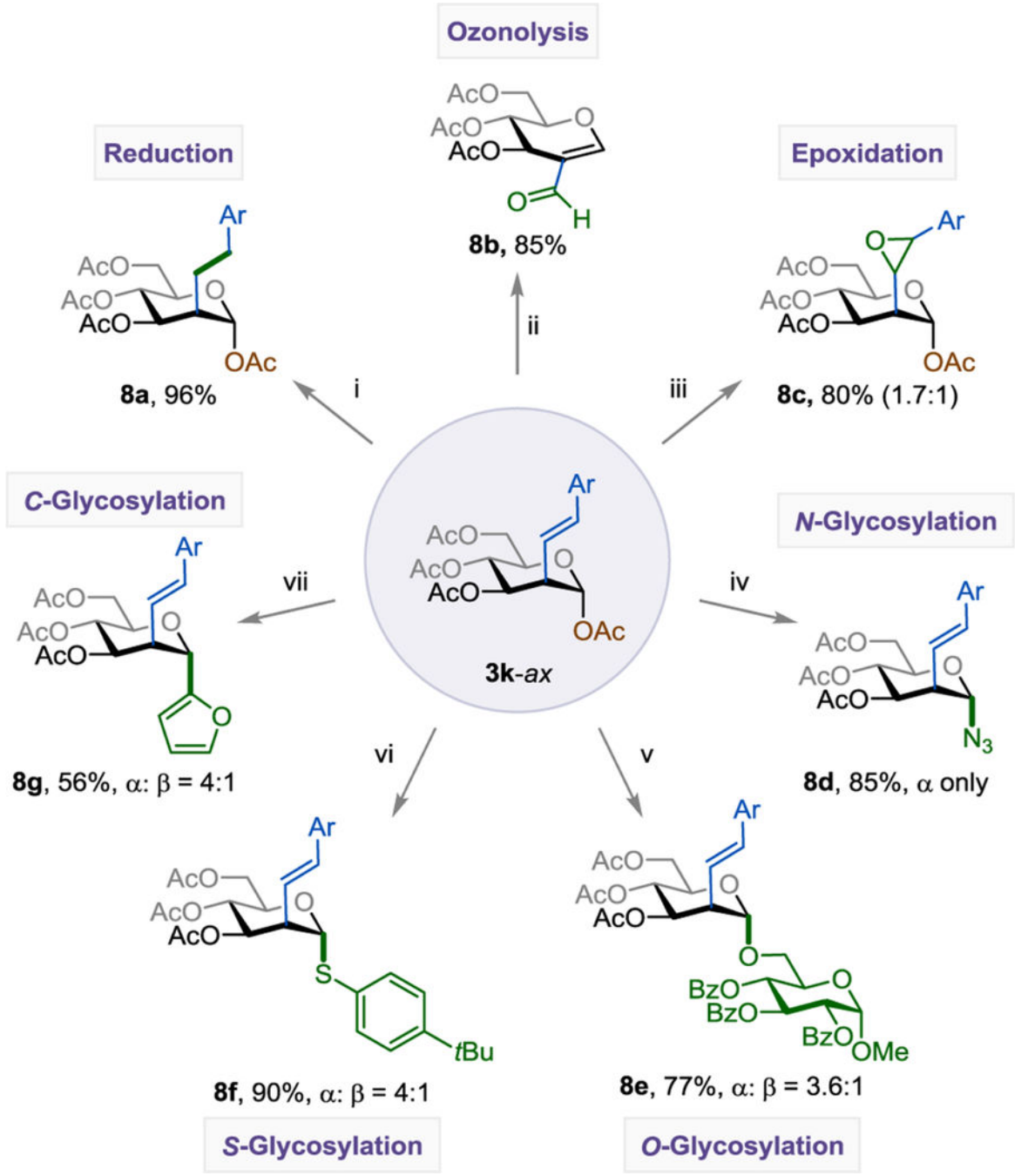
Selected Examples of Late-Stage Functionalization of Natural Product/Drug Glycoconjugates.[a]




[a]See SI for experimental details. The isolated yield and axial:equatorial (ax:eq) ratio are indicated below each entry.

**Table 4.**

Post-Functionalization of C2-Alkenyl Sugar.[a]




[a]See SI for experimental details. The isolated yield and axial:equatorial (ax:eq) ratio are indicated below each entry. Reaction conditions: (i) Pd/C (10 mol%), EtOAc (0.100 M), $H_2$ (1 atm), rt, 3h; (ii) 1. $O_3$ (1 atm), DCM (0.100 M), –78 °C, 45 min; 2. $PPh_3$ (2.00 equiv); (iii) *m*-CPBA (2.00 equiv), DCM (0.100 M), rt. 24h; (iv) $BF_3$•$Et_2O$ (1.20 equiv), $TMSN_3$ (1.20 equiv), DCM (0.100 M), 0 °C – rt, 2h; (v) $BF_3$•$Et_2O$ (1.20 equiv), (2*R*,3*R*,4*S*,5*R*,6S)-2-(hydroxymethyl)-6-methoxytetrahydro-2H-pyran-3,4,5-triyl tribenzoate (1.20 equiv), DCM (0.100 M), 0 °C – rt, 2h;

(vi) $BF_3$•$Et_2O$ (1.20 equiv), 4-*tert*-butylbenzenethiol (1.20 equiv), DCM (0.100 M), 0 °C – rt, 2h; (vii) $BF_3$•$Et_2O$ (1.20 equiv), furan (1.20 equiv), DCM (0.100 M), 0 °C – rt, 2h.