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Oxidative Addition of Secondary C−X Bonds to Palladium(0): A Beneficial Anomeric Acceleration

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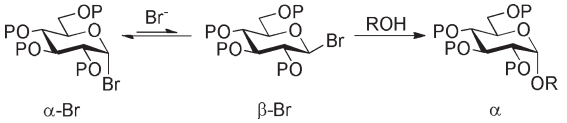
Supporting Information

ABSTRACT: The oxidative addition of secondary electrophiles to Pd(0) is significantly accelerated by anomeric effects. In contrast to cyclohexyl bromide, acetobromo-α-D-glucose undergoes invertive oxidative addition to tris(triethylphosphine)palladium(0) to generate a stable, isolable organometallic complex, $Pd(PEt_3)_2(Br)$(AcO-β-glucose), which has been fully characterized but is prone to β-acetoxy elimination.

The S_N2-like oxidative addition of secondary alkyl halides is kinetically difficult[1] and continues to hold back the universal adoption of Pd-based methods for secondary C−C, C−N, and C−O bond-forming catalysis.[2] While developments in the cross-coupling of primary alkyl electrophiles using Pd catalysts have progressed smoothly,[3] secondary electrophiles have thus far required methodologies wherein the catalyst readily adopts radical mechanisms for oxidative addition.[4,5] A noteworthy recent addition is a (Xantphos)Pd catalyst for the cross-coupling of 2°-benzyl bromide (with inversion) with aryl and vinyl Grignard reagents.[6] An additional well-recognized problem with alkyl halide electrophiles is the facility with which intermediate organometallic complexes undergo β-hydride elimination reactions. Several elegant solutions based on di- and triamine ligands (Ni)[3,7] or carefully tuned phosphines (Pd, primary alkyl-X)[3] and broad bite angle diphosphines (Pd, secondary alkyl-Br)[6] have inhibited this tendency and significantly improved the viability of such methods.

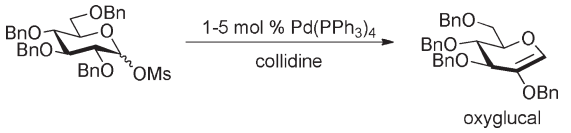
Lemieux reported more than 50 years ago that the glycosyl bromide class of secondary electrophiles was remarkable in that they could, with Br^- catalysis, react with nucleophiles as weak as secondary alcohols (Scheme 1).[8] The outcome of these studies was the development of methods for the synthesis of complex α-disaccharides, which rely on a low but steady state concentration of a reactive (lacking anomeric stabilization) β-bromo glycoside.

Scheme 1



Since anomeric effects play such a dramatic role in the invertive substitution chemistry of glycosyl halides, we questioned whether such effects could be harnessed to kinetically facilitate an S_N2-like oxidative addition of Pd(0). The feasibility of this transformation

Scheme 2



was supported by results from Scott, who showed that $Pd(PPh_3)_4$ (1−5 mol %, 50 °C) catalyzes the conversion of benzyl-protected C1-mesylates into oxyglycals via a process proposed to require C−O oxidative addition and β-hydride elimination (Scheme 2).[9] The goal of nucleophilic C−X activation was attractive in the context of a broader research theme targeting the conversion of polysaccharides into value-added chemical feedstocks. Since the leaving group in the C−O oxidative addition of a polysaccharide would necessarily be oxygen-based, the focus was on nonradical methods of activating glycosyl electrophiles.[10,11]

As expected, no reaction occurred between $Pd(PEt_3)_3$ (**1**)[12] and secondary electrophiles such as cyclohexyl bromide (Scheme 3a). In contrast, ^{31}P NMR spectroscopy showed that, over 8 h, acetobromo-α-D-glucose (**2**) reacted at room temperature with **1** to give a single isomer of $Pd(PEt_3)_2(Br)$(AcO-β-glu) (**3**), the product of invertive bromide displacement (Scheme 3b).[13] Purification of the reaction mixture by column chromatography allowed for isolation of **3**, although decomposition on the column limited the isolated yield (34%).[14]

Isolated **3** has been characterized by ^1H, ^{31}P, and ^{13}C NMR spectroscopy, and all data are consistent with formation of a single "β-glucosyl" isomer. The ^1H NMR spectrum is highlighted by seven resonances in the pyranose region (3−6 ppm), including a signal at 4.19 ppm corresponding to C_1H with $^3J_{P-H}$ = 3 and 14 Hz; the diastereotopic nature of the phosphorus nuclei

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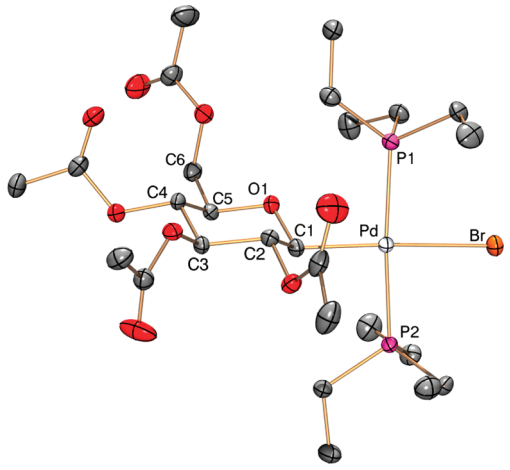
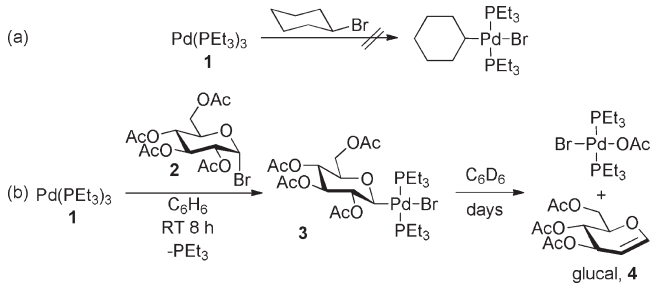


Figure 1. ORTEP of $Pd(PEt_3)_2(Br)(AcO\text{-}\beta\text{-glu})$ (**3**) (50% probability; H atoms and one molecule of the asymmetric unit omitted for clarity). Selected average bond lengths (Å) and angles (deg): Pd−C_1, 2.051; Pd−Br, 2.537; C_1−Pd−Br, 175.80; P_1−Pd−P_2, 173.08; H_1−C_1−Pd−P_1, 163.19; H_1−C_1−Pd−P_2, 13.22.

was also evident in the ^{31}P NMR spectrum (AB quartet, $^2J_{PP}$ = 404 Hz).[15] The formation of the β-anomer was additionally implied by the vicinal H_1−H_2 coupling constant ($^3J_{H_1-H_2}$ = 11 Hz), suggestive of a diaxial arrangement.[16] Single crystals of **3** were grown by slow evaporation of a hexanes solution, and X-ray diffraction confirmed the β-stereoisomer assignment and showed the pyranosyl moiety to adopt a chair conformation (Figure 1). To our knowledge, this represents the first reported crystal structure of a palladium pyranosyl complex and only the second C1-organometallic complex[10] of a fully oxygenated sugar.

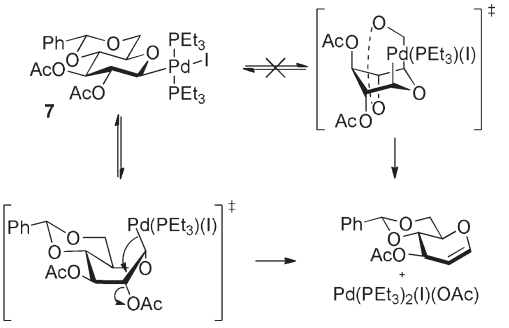
Scheme 3



Under the same conditions that produced **3**, $Pd(PEt_3)_3$ reacts even more quickly (2 h) with acetoiodo-α-D-glucose to give $Pd(PEt_3)_2(I)(AcO\text{-}\beta\text{-glu})$ (**5**). Glycosyl chloride analogues were unreactive, establishing the reactivity trend Cl ≪ Br < I.[1,17] Reaction rates were also sensitive to ligand basicity, with less electron-rich metal centers being slower to react. For example, the modestly less basic[18] $Pd(PMePh_2)_3$ required 3 days to react with acetobromo-α-D-glucose (cf. 8 h for $Pd(PEt_3)_3$), affording $Pd(PMePh_2)_2(Br)(AcO\text{-}\beta\text{-glu})$ (**6**).

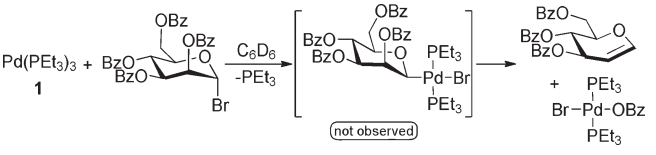
In contrast to the reactivity observed by Scott, wherein C_1-organometallic complexes generated from oxidative addition of $Pd(PPh_3)_4$ and glucosyl mesylate rapidly eliminate *β-hydride*,[9] benzene solutions of **3** slowly react via a *β-acetoxy* elimination process to give tri-*O*-acetylglucal (**4**) and *trans*-$Pd(PEt_3)_2(Br)(OAc)$ (Scheme 3). In light of this diverging behavior, we initiated mechanistic studies. Suggestive of a pre-equilibrium PEt_3-dissociation pathway were experiments showing that added phosphine, but not added bromide, significantly inhibited the β-elimination. After 14 days at room temperature, 40% conversion of **3** to **4** was observed; 5 equiv of PEt_3 and 5 equiv of Br^- led to 1−5% and 35% conversion, respectively. Noting that the stereochemistry of the sugar prevents the complex from adopting the conformation necessary for synperiplanar elimination of OAc (but not hydride) and that the Pd−C_1−C_2−OAc dihedral angle (58.1° in the crystal structure of **3**) was unsuitable for antiperiplanar elimination, we considered two possible elimination transition states: one in which the pyranosyl ring has undergone complete ring inversion to orient all substituents axially (including the monophosphine −$Pd(PEt_3)(I)$ unit), and one in which the ring has partially inverted to adopt a boat structure (Scheme 4). To distinguish between these two possibilities, a derivative of **5** was synthesized in which full ring inversion was inhibited by tethering of the C_4 and C_6 positions with a benzylidene group ($Pd(PEt_3)_2(I)$(3-AcO-4,6-benzylidene glucopyranose) (**7**)). The failure of this modification to reduce the rate of elimination (50% of **7** had undergone elimination after 1.5 days at 40 °C vs 2 days for **5**) indicated that a mechanism requiring full ring inversion was not necessary and thus suggested the likelihood of the pathway involving a boat transition state (Scheme 4).

Scheme 4



To examine how the stereochemistry of the C_2 substituent affected the stability of the C_1-organopalladium species, we carried out a reaction of α-D-mannopyranosyl bromide tetrabenzoate with **1**. In contrast to the case for the glucose-based electrophile, this reaction immediately yielded tri-*O*-benzoylglucal and $Pd(PEt_3)_2(Br)(OBz)$ (Scheme 5, confirmed by ^1H NMR spectroscopy).

Scheme 5



Finally, the sensitivity of the reaction to variation in the phosphine ligand was investigated. For example, commercially available bis(tricyclohexylphosphine)palladium(0) (PCy_3 cone angle 170° vs 132° for PEt_3) reacts with **2** to directly produce **4** and *trans*-$Pd(PCy_3)_2(Br)(OAc)$ (**8**) within 5 min at room temperature

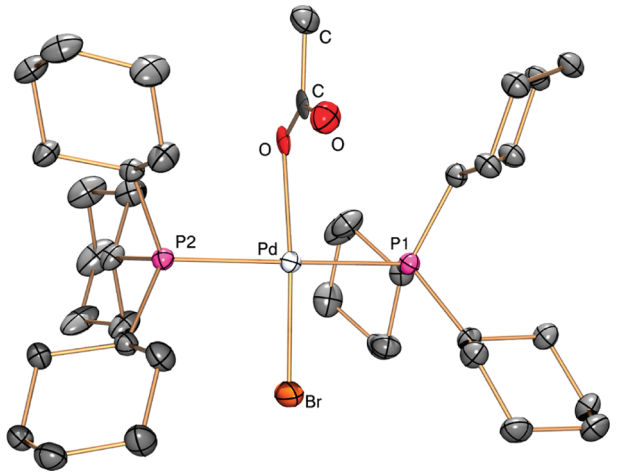
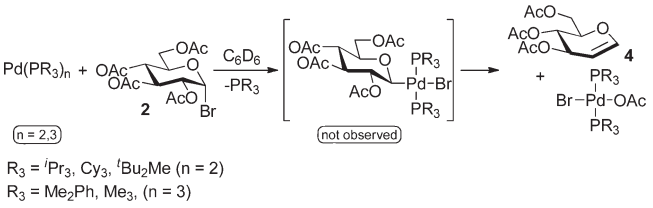


Figure 2. ORTEP of *trans*-Pd(PCy_3)$_2$(Br)(OAc) (**8**) (50% probability; H atoms and one component of the disordered OAc ligand omitted for clarity). Selected average bond lengths (Å) and angles (deg): Pd−OAc, 2.158; Pd−Br, 2.415; Pd−P_1, 2.354, Pd−P_2, 2.355, Br−Pd−OAc, 165.4; P_1−Pd−P_2, 172.4.

(Figure 2). In fact, for phosphine ligands both larger and smaller than triethylphosphine, conversion to glucal (not oxyglucal) was facile (Scheme 6). Though the target organometallic complex was not detected for PCy_3,[19] its intermediacy and rapid β-acetoxy elimination were implied. Since the elimination is dissociative in phosphine, we envision sterically bulky ligands being crowded out of the coordination sphere by a bulky pyranosyl moiety and thus accelerating the elimination; smaller ligands likely lack sufficient bulk to inhibit elimination.

Scheme 6



R_3 = ^{i}Pr$_3$, Cy$_3$, ^{t}Bu$_2$Me (n = 2)
R_3 = Me$_2$Ph, Me$_3$, (n = 3)

In summary, Pd(PEt_3)$_3$ has demonstrated a propensity toward oxidative addition of pyranosyl halides that leads to stable Pd(PEt_3)$_2$(Br)(AcO-β-glu) (**3**), the product of invertive oxidative addition. The reaction is efficient under ambient conditions and represents a rare palladium-based C(2°alkyl)−X activation and the first isolated palladium pyranosyl complex. Thermolysis has additionally shown this product to be susceptible to β-acetoxy elimination rather than β-hydride elimination. Reactivity studies are under way to test for efficacy toward valuable pyranoside functionalization.

■ ASSOCIATED CONTENT

Supporting Information. Text, figures, and tables giving characterization data and experimental details and CIF files giving X-ray crystallographic data for **3** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Even in the presence of excess PCy_3, direct conversion of **2** to **4** is observed upon treatment with $Pd(PCy_3)_2$.