Nucleophilicity

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Reversing the Stereoselectivity of a Palladium-Catalyzed O-Glycosylation through an Inner-Sphere or Outer-Sphere Pathway**

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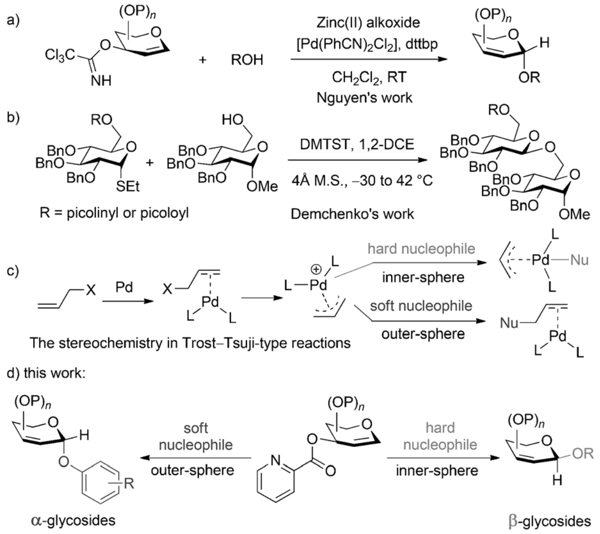
Abstract: *An efficient and concise method for the construction of various O-glycosidic bonds by a palladium-catalyzed reaction with a 3-O-picoloyl glucal has been developed. The stereochemistry of the anomeric center derives from either an inner-sphere or outer-sphere pathway. Harder nucleophiles, such as aliphatic alcohols and sodium phenoxides give β-products, and α products result from using softer nucleophiles, such as phenol.*

Recent advances in our understanding of the indispensable roles of carbohydrates in all major life forms over the past decades have generated a great demand to synthesize these complex biomolecules. Hence, efficient glycosylation methods through the usage of little to no activators are highly sought after, especially one that offers high yields and stereoselectivities.[1] At present, palladium-catalyzed O-glycosylation[2] with glycals as donors[3–5] has received less attention compared to traditional glycosyl donors,[6] mainly because of the difficulty in generating the palladium/π-allyl intermediates from the electron-rich glycal scaffold and the low reactivity.[7] Recent reports focused on the use of trichloroacetimidate[8] as a directing group[9] and a zinc reagent[10] was chosen to soften the O-nucleophiles (Scheme 1 a). However, the rearrangement by-products[3b,11] reduced the yields and additives often complicate the reaction process. Another promising directing group was *O*-picoloyl which is reported to strongly coordinate metal centers[12] as well as undergo selective glycosylation with pyranosyl donors through hydrogen-bond assistance (Scheme 1 b).[13] In the majority of palladium-catalyzed glycosylation reactions, the selectivity could be controlled by either the nature of the ligand[3a] or palladium source.[14] In contrast, the poor affinity of the O nucleophile for the metal center also played an important role in the stereochemical outcome. As demonstrated by Tsuji and Trost,[15] softer nucleophiles prefer an outer-sphere mechanism in which nuclephilic substitution from opposite face of palladium complex is the dominant pathway. Harder nucleophiles, on the contrary, directly attack the metal center with subsequent reductive elimination to form the product (Scheme 1 c).[16] To investigate the effect of the above factors in the reaction with a specific glycal system, we proposed a palladium-catalyzed glycosylation strategy with an *O*-picoloyl moiety as a directing group at the C3-position of a glycal-type donor (Scheme 1 d).



Scheme 1. The stereocontrol of glycosylation and palladium chemistry. 1,2-DCE = 1,2-dichloroethane, DMTST = dimethyl(methylthio)sulfonium triflate, M.S. = molecular sieves.

First, the picoloyl glucal donor **1** was prepared from 4,6-*O*-(*para*-methoxy)benzylideneglucal and picolinic acid. For optimizing the reaction conditions, the soft nucleophile 3,4,5-trimethoxyphenol (**2a**) was chosen as the acceptor.[17] The reaction was expected to proceed through an outer-sphere pathway with the palladium approaching the allylic system from the β face. Hence, the α-product **3a** should be the major isomer (see Scheme 2). The optimized reaction conditions with soft nucleophiles, that is, phenols, were found to be 10 % [Pd(PPh$_3$)$_4$] as a catalyst and 20 % dppb as a ligand in CH$_2$Cl$_2$ at 60 °C for 48 hours (see the Supporting Information). With the optimized reaction conditions established, we expanded the substrate scope with respect to the phenol-type nucleophiles. As seen in Scheme 2, unsubstituted phenol gave a lower yield (**3b**) compared to those obtained with electron-donating groups. Steric effects influenced the yield as 2-ethyl phenol afforded **3c** in 80 % yield and 2-benzyl phenol gave **3d** in 72 %. Notably, the reaction showed reasonable tolerance to halogen substituents (**3e–i**). Phenols with *para*-substituted groups provided O-glycosides with similar results, even with bulky *tert*-butyl or phenyl moieties (**3k,l**). Because of a strong

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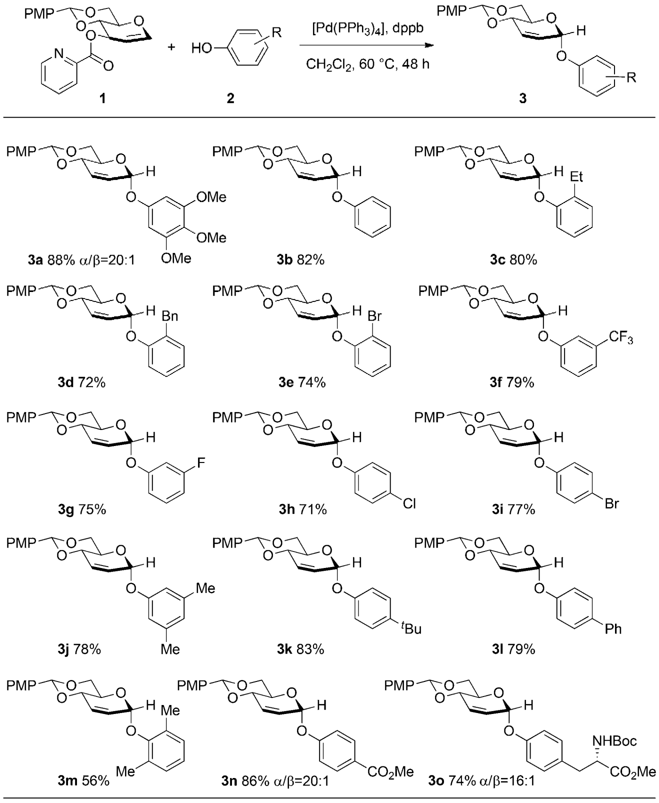
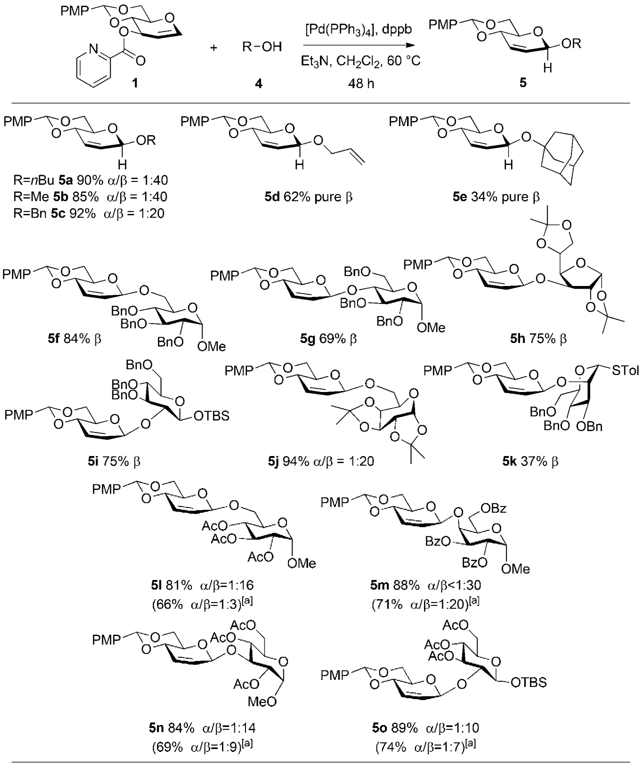


Scheme 2. Substrate scope of O-glycosylation with phenol acceptors. Boc = *tert*-butoxycarbonyl, dppb = 1,4-bis(diphenylphosphino)butane, PMP = *para*-methoxyphenyl.



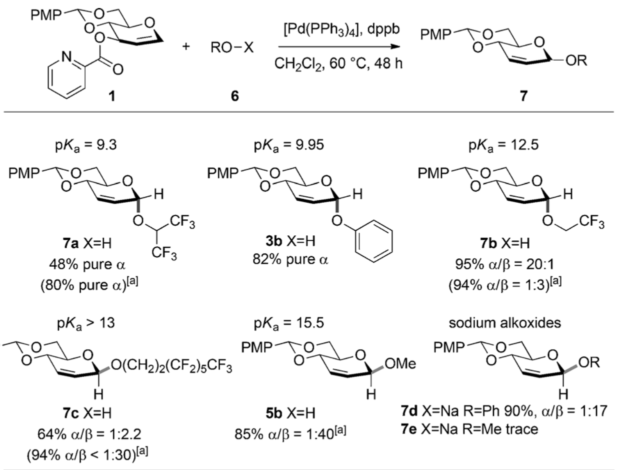
Scheme 3. Substrate scope of O-glycosylation with alcohol acceptors. [a] Reaction was conducted without Et$_3$N. TBS = *tert*-butyldimethylsilyl.

steric effect, 2,6-dimethyl phenol gave a much lower yield (**3m**). An electron-poor substituted phenol afforded **3n** in 86% yield with a α/β ratio of 20:1. However, phenols with cyano or nitro substituents gave only trace amounts of desired products because of their higher acidity or possible complexation with palladium. Additionally, Boc-L-tyrosine methyl ester was successfully introduced to the anomeric carbon atom, thus affording the desired product in 74% yield with a α/β ratio of 16:1 (**3o**). In all cases, α-isomers were the major products and the stereochemistry was confirmed by X-ray analysis of **3g**. In addition, attempts to replace the 4,6-*O*-*p*-methoxybenzylidene on donor **1** with other protecting groups, including benzyl and di-*tert*-butylsilyl, resulted in poorer yields and selectivity.

Next, a harder nucleophile, 1-butanol (**4a**), was selected as the glycosyl acceptor to test the utility of this method and to examine our hypothesis on an inner-sphere mechanism in which the nucleophile directly attacks the palladium center to give the β isomer as the major product under identical reaction conditions. The predominant β selectivity suggested that the reaction mechanism with a hard nucleophile as the acceptor was different from that with soft nucleophiles (see the Supporting Information). Further optimization to improve the β selectivity led to an improved selectivity of α/β = 1:40 when Et$_3$N was used.

We set out to expand the substrate scope with representative aliphatic alcohols as seen from Scheme 3. Methanol and benzyl alcohol were first tested and the reactions furnished excellent yields and selectivity (**5b** and **5c**). However, allylic alcohol gave lower chemical yield because of the interruption of coordination between palladium and the double bond of the glycal donor (**5d**). When a sterically hindered acceptor, such as tertiary 1-adamantanol, was subjected to the optimized reaction conditions, β selectivity was obtained, albeit with low yield (**5e**). The applicability of this method was demonstrated by syntheses of various disaccharides. For glucosyl acceptors with electron-donating protecting groups, the character is similar to that of an electron-rich alcohol. Excellent β selectivity was obtained for all substrates. Reaction with a 6-OH primary acceptor (**5f**) gave a slightly higher yield than that of secondary acceptors (**5g–i**). An electron-rich galactosyl acceptor (**5j**) and mannosyl acceptor (**5k**) were then examined and both reactions were found to be predominantly β selective. The steric hindrance led to the lower yield of mannosyl acceptor. In addition, glycosyl acceptors with electron-withdrawing protecting groups were subjected to the optimized reaction conditions (with or without Et$_3$N) and the results indicated that all substrates gave the desired products in lower chemical yield and unsatisfactory β selectivity in the absence of Et$_3$N (**5l–o**). The addition of Et$_3$N resulted in significant improvement on stereo-outcomes of the reactions. Notably, the selectivity for acceptors with electron-withdrawing groups was poorer than that of electron-donating groups.

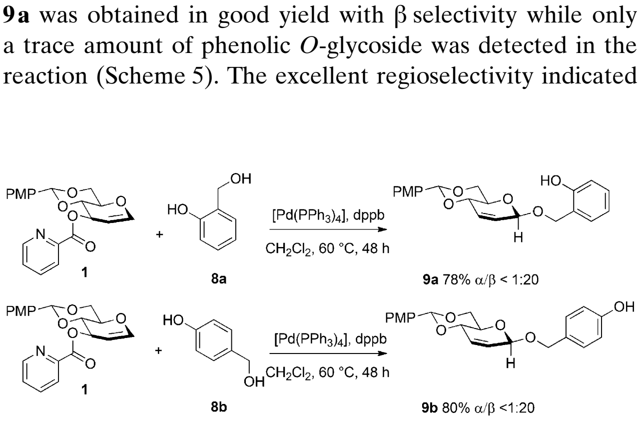
The significant difference in selectivity between two types of nucleophiles prompted us to do more studies. It was mentioned that the pK_a value of an alcohol exhibited good correlation to its nucleophilicity and thus can be used to



Scheme 4. Survey of pK_a values and stereoselectivity. [a] Reaction was conducted with 2.2 equivalents of Et$_3$N.

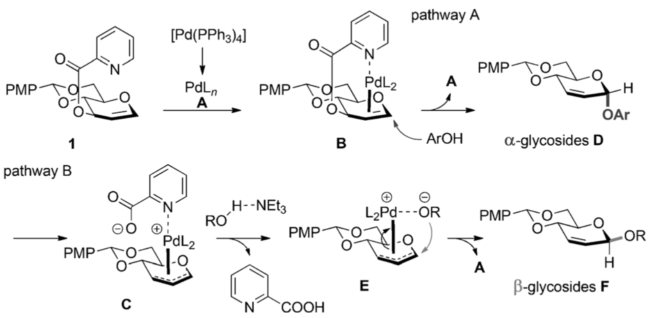
predict the stereoselectivity for this type of reaction.[15,16] As seen from Scheme 4, selected examples were presented to demonstrate the effect of pK_a values. Firstly, hexafluoro-2-propanol (**6a**), having a pK_a value similar to that of phenol (**2b**), was found to give exclusive α selectivity. Secondly, the pK_a value of 2,2,2-trifluoroethanol is 12.5, which is between that of an aliphatic alcohol and phenol, and it reacted to afford the product with α selectivity in the absence of a base. In the meantime a mixture with α/β = 1:3 was obtained when Et$_3$N was added (**7b**). Thirdly, the acceptor **6c**, having a pK_a value greater than 13, is similar to that of an aliphatic alcohol, and as expected the reaction gave a mixture in the absence of Et$_3$N. However the β-isomer ratio increased upon addition of base. Although the results illustrated that the addition of a base could increase β selectivity, it is deemed impractical because of the vulnerability of **1** under strongly basic conditions. Hence, sodium phenoxide (**6d**) was used in place of phenol and the major product turned out to be the β isomer (**7d**). Notably, the reaction was faster and could be completed in 12 hours. Unfortunately, the reaction gave only a trace amount of the product **7e** when strongly basic NaOMe was employed.

2-hydroxybenzyl alcohol (**8a**) was selected as a glycosyl acceptor for competitive reactions. The aliphatic *O*-glycoside **9a** was obtained in good yield with β selectivity while only a trace amount of phenolic *O*-glycoside was detected in the reaction (Scheme 5). The excellent regioselectivity indicated that the glycosylation between **1** and an aliphatic hydroxy group was much faster than with a phenoxy group. A similar result was obtained when the compound **8b** was employed as the acceptor and the β selectivity could be confirmed by X-ray analysis of **9b** (see the Supporting Information).



Scheme 5. Competitive reactions.

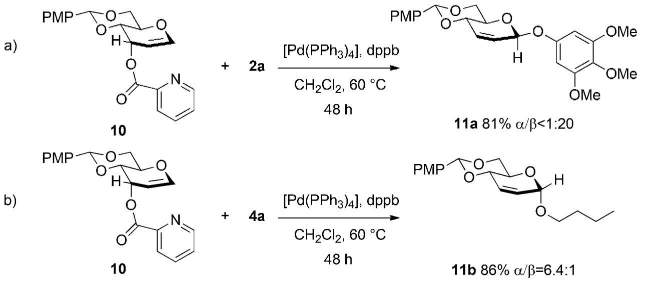
Based on the above results, a plausible mechanism for **1** is proposed as shown in Scheme 6. Firstly, the intermediate **B** is formed through the coordination of the palladium species **A** with both of the double bonds of the glucal and the nitrogen atom of the picoloyl group, which is positioned at the β face.[3b,11] In pathway A, nucleophilic addition of soft nucleophiles such as phenol occur at the allylic carbocation and the α-isomer **D** is afforded because of the steric bulk of the palladium(0) complex shielding the β face. Regeneration of **A** completes the catalytic cycle. In pathway B, removal of the picoloyl group generates the intermediate **C** as a palladium/π-allyl complex. In this structure, the palladium ion is considered to be a harder Lewis acid, while the allylic carbocation site is considered a softer Lewis acid. Aliphatic alcohols or phenoxide, having stronger nucleophilicity, prefer to coordinate to the palladium(II) center to generate the intermediate **E**. The presence of triethylamine likely enhances the nucleophilicity of the acceptor and facilitates its addition to the palladium(II) center. Following intramolecular nucleophilic addition, the β-isomer **F** is formed. At the same time, **A** is regenerated, thus finishing the catalytic cycle.[15] Formation of picolinic acid was indeed detected by monitoring the reaction with selective 1D-TOCSY NMR spectroscopy (see the Supporting Information).



Scheme 6. Proposed mechanism of stereoselective O-glycosylation.

To confirm the correlation between palladium complexation and stereoselectivity, the C3 epimer of **1** (**10**) was employed to reverse the stereo-outcome of the reaction (Scheme 7a). With an axial substituent at C3, the palladium catalyst should coordinate to **10** from the α face. According to our proposed mechanism, **2a** should give more β product whereas **4a** should provide more α isomer. Gratifyingly, the β-glycoside **11a** was obtained with a α/β ratio of less than 1:20 and the α-glycoside **11b** was obtained with a α/β ratio of 6.4:1 in high yield (Scheme 7b). This result could serve as a proof of concept to the mechanism.

In conclusion, we have developed a new strategy for efficient and stereoselective O glycosylation. The picoloyl group in the glycosyl donor served both as a leaving group and a coordinating group. Various acceptors were examined and



Scheme 7. Reversing the stereoselectivity with the allal donor **10**.

most of them gave the desired products in good yields and excellent stereoselectivities. The selectivities were effectively controlled by the nucleophilicity of the acceptors. Harder nucleophiles like an alcohol and sodium phenoxide follow an inner-sphere pathway to give β products, while α products were favored when using softer nucleophiles, such as phenol. For phenolic O-glycosides, both α-type and β-type could be achieved by this method. Aliphatic O-glycosides and disaccharides were obtained with excellent β-selectivity. Competitive reaction studies suggested that the glycosylation with stronger nucleophiles through an inner-sphere pathway was more rapid than weaker nucleophiles, which proceed by an outer-sphere pathway.

Experimental Section

The picoloyl glucal donor **1** (0.1 mmol), nucleophile (0.2 mmol), Et_3N (2.2 equiv or none), $[Pd(PPh_3)_4]$ (0.01 mmol) and dppb (0.02 mmol) were dissolved in CH_2Cl_2 (2 mL) in a sealed tube under a nitrogen atmosphere. The solution was heated at 60°C for 48 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to give the desired *O*-glycosides.

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