Letter

Catalyst-Controlled Stereoselective O-Glycosylation: Pd(0) vs Pd(II)

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Catalyst-Controlled Stereoselective *O*-Glycosylation: Pd(0) vs Pd(II)

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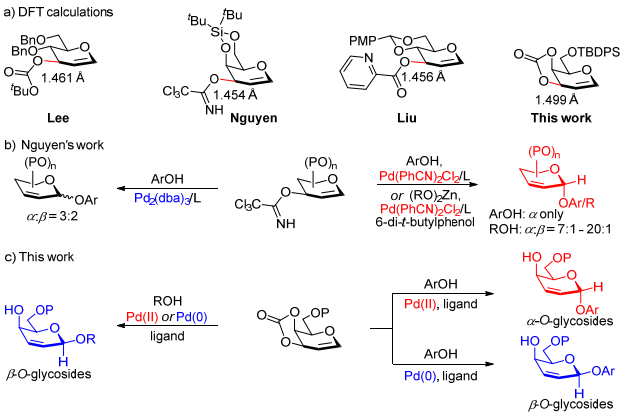
ABSTRACT: Stereoselective construction of various *O*-glycosidic bonds was first achieved by different palladium sources using 3,4-*O*-carbonate galactal as the donor to reach up to 95% yield under mild conditions. With Pd(II) catalyst coordination of this glycal donor from *β*-face directed by carbonate group, hard nucleophiles (aliphatic alcohols) gave *β*-glycosides and *α*-glycosides were obtained from soft nucleophiles (phenols). On the contrary, with Pd(0) catalyst coordinating the donor from *β*-face due to steric effect, both hard and soft acceptors could only generate *β*-glycosides via hydrogen-bond-mediated aglycone delivery.

KEYWORDS: *glycosylation, palladium, decarboxylative allylation, glycal, reaction mechanism*

Exploring highly efficient glycosyl donors for stereoselective glycosylation has been one of the main focuses in glycoscience which plays a critical role in both chemistry and biology.[1] In the past two decades, 2,3-unsaturated glycal[2] have shown great potential in directing stereoselectivity as compared to conventional saturated glycosyl donors[3] when transition metal catalysis was used.[4] The challenge of these glycal donors, however, was low reactivity and the requirement of additional activators, e.g. Et_2Zn for Lee's C3-ester glycals (Scheme 1a).[5] Later, Nguyen developed a direct *α*-*O*-glycosylation from the C3-trichloroacetimidate glycal donors but Et_2Zn was still essential for aliphatic acceptors (Scheme 1b).[6] Recently, our group reported 3-*O*-picoloyl glucal donor which could direct palladium complex to the *β*-face and give two different stereoselectivities without activators.[7] However, the selectivities totally relied on different acceptors and the reaction required a high temperature and long hours. Herein we introduced a cyclic carbonate[8] at the C3,C4 positions of galactal with an aim to form a bicyclic system with greater ring strain to increase the reactivity. Moreover, the alkoxide ion of the intermediate formed could accelerate the substitution reaction of aliphatic alcohols through H-bonding.[9] Meanwhile, a bulky C6-*O*-TBDPS group was chosen to enhance the selectivity by steric hindrance. In addition, density functional theory (DFT) calculations were also carried out to confirm our idea.[10] As shown in Scheme 1a, 3,4-*O*-carbonate D-galactal donor has the weakest and longest C-O bond (1.499 Å) at the C3 position as compared to the rest (1.454-1.461 Å).

To the best of our knowledge, reports about catalyst-controlled *O*-glycosylation were extremely rare and Nguyen's group has reported a nearly successful case (Scheme 1b) where *α*-selectivity from *β*-Pd(II) complex was directed by trichloroacetimidate and not from Pd(0) as Pd (0) could only generate α/β = 3:2 in a low yield (Scheme 1b).[6] The rapid development of transition metal chemistry provided more possibilities for catalyst-controlled glycosylation be-

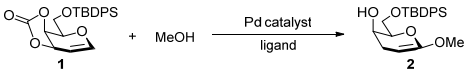


Scheme 1. Glycosyl Donors and Palladium-Catalyzed Glycosylation

cause of its unique coordination effect and the versatility in reactions, this was especially true in the case of palladium.[11] In our strategy, Pd(II) was designed to coordinate at the *β*-face directed by the carbonate group, while Pd(0) could go to the opposite direction by coordinating at the *α*-face owing to steric hindrance. From here, we successfully presented a controllable stereoselective *O*-glycosylation method using Pd(0) and Pd(II) complexes as catalysts (Scheme 1c).

Firstly, 3,4-*O*-carbonate D-galactal (**1**) was used as the glycosyl donor and the reaction was screened using methanol as the glycosyl acceptor (Table 1). Both Pd(II) and Pd(0) catalysts were found to afford exclusive *β*-selectivity in different solvents for 12 h (entries 1-7). $Pd(OAc)_2$ in THF was found to provide the best combination (entry 4) while no reaction took place in the absence of ligands (entry 8). During the ligand screening (entries 9-12), Xantphos was found to be the optimal ligand that could reduce the reaction time to 1 h (entry 12), which might be because it is a bidentate ligand with an appropriate bite angle.[12] Therefore, the optimized condi-

Table 1. Reaction Optimization for Aliphatic Alcohol[a]



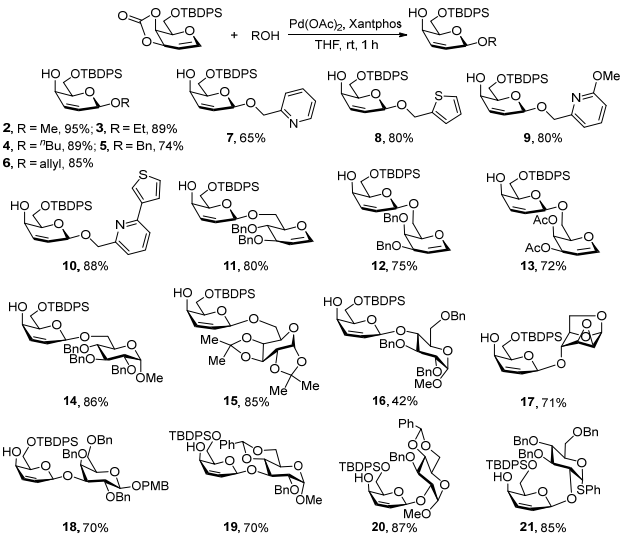
entry	catalyst	ligand	solvent	time	yield[b,c]
1[d]	$Pd_2(dba)_3$	PPh_3	THF	12 h	30%
2	$Pd(PPh_3)_4$	PPh_3	THF	12 h	88%
3	$Pd(acac)_2$	PPh_3	THF	12 h	10%
4	$Pd(OAc)_2$	PPh_3	THF	12 h	94%
5	$Pd(OAc)_2$	PPh_3	DMSO	12 h	78%
6	$Pd(OAc)_2$	PPh_3	DCM	12 h	80%
7	$Pd(OAc)_2$	PPh_3	MeCN	12 h	85%
8	$Pd(OAc)_2$	-	THF	12 h	N.R.
9[e]	$Pd(OAc)_2$	DPPF	THF	12 h	52%
10[e]	$Pd(OAc)_2$	DPPB	THF	12 h	89%
11	$Pd(OAc)_2$	$P(Cy)_3$	THF	12 h	N.R.
12[e]	$Pd(OAc)_2$	Xantphos	THF	1 h	95%

[a]Unless otherwise specified, all reactions were carried out with 0.1 mmol of **1**, 0.2 mmol of MeOH, 10 mol% Pd catalyst, 30 mol% P ligand in 2 mL solvent at room temperature. [b]Isolated yield. [c]Single isomer (β:α > 30:1 by ^{1}H NMR). [d]5 mol% Pd catalyst used and unreacted **1** was recovered. [e]15 mol% P ligand used. N.R. = No reaction. DPPB = DPPButane; DPPF = 1,1'-Bis(diphenylphosphino)ferrocene; Xantphos = 4,5-Bis(diphnyl-phosphino)-9,9-dimethylxanthene.

tion was revealed to be entry 12 and the configuration of β-*O*-glycoside **2** was confirmed by X-ray crystallography.[13]

With the optimal condition in hand, we expanded the substrate scope of glycosyl acceptors to other alcohols (Scheme 2) such as ethanol, *n*-butanol, benzyl and allyl alcohol to afford the relative products **3-6** in high yields and β-stereoselectivity. Heterocyclic alcohols which were important in drug discovery[14] were also introduced as glycosyl acceptors. They were 2-pyridinemethanol, 2-thiophenemethanol, 6-methoxyl-2-pyridine- and 6-(3-thienyl)-2-pyridinemethanol which also proceeded to give glycosides **7-10** in good yields and β-stereoselectivity respectively. The versatility of the methodology was further explored by applying it to the syntheses of disaccharides. Firstly, 3,4-dibenzyl-D-glucal was examined and the corresponding disaccharide **11** was generated in 80% yield with exclusive β-selectivity. Subsequently, other screened acceptors with 6-OH monosaccharide also gave disaccharides **12-15** in high yields and excellent anomeric selectivity. Since 4-OH glycosyl acceptors are hindered and bulkier than other carbohydrate acceptors,[15] **16** was afforded in a relatively lower yield of 42% as compared to the other substrates. Consequently, when a less crowded 4-OH acceptor 1,6:2,3-dianhydro-β-D-mannopyranose was applied in this condition, the yield of β-1,4-*O*-glycoside (**17**) was increased to 71%. β-1,3-*O*-Glycosides (**18**, **19**) could be obtained in 70% yields, while with different types of 2-OH glucose derivatives, β-1,2-*O*-glycosides (**20**, **21**) were also formed in very good yields and with exclusive selectivity.

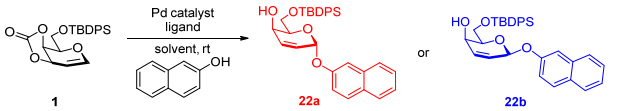
The results showed that aliphatic acceptors including monosaccharides were able to obtain glycosides in high yields with exclusive β stereoselectively. We reasoned that



Scheme 2. Alcohol Substrate Scope via Pd(II) Catalyst

our starting material containing 3,4-*O*-carbonate directed the Pd(II) complex to the β-face and through an inner-sphere pathway with hard aliphatic acceptors. Conversely, the soft phenolic nucleophiles would attack Pd-π-allyl intermediate through an outer-sphere pathway to give α-products. Therefore, 2-naphthol was used as a phenolic acceptor to optimize the condition (Table 2). The previous optimal condition (10% $Pd(OAc)_2$ as a catalyst, 15% Xantphos as a ligand in THF at room temperature for 1 hour) was able to generate the expected α-product **22a** in 71% yield (entry 1). This condition was further optimized with different ligands, solvents and Pd(II) catalyst (entries 1-7), but $Pd(OAc)_2$, Xantphos and THF remained the most suitable combination for α-glycosy-lation. As designed, the stereoselectivity was reversed to β selectivity (**22b**) when $Pd(PPh_3)_4$ was used (entry 8). The same selectivity was also

Table 2. Reaction Optimization for Phenol[a]



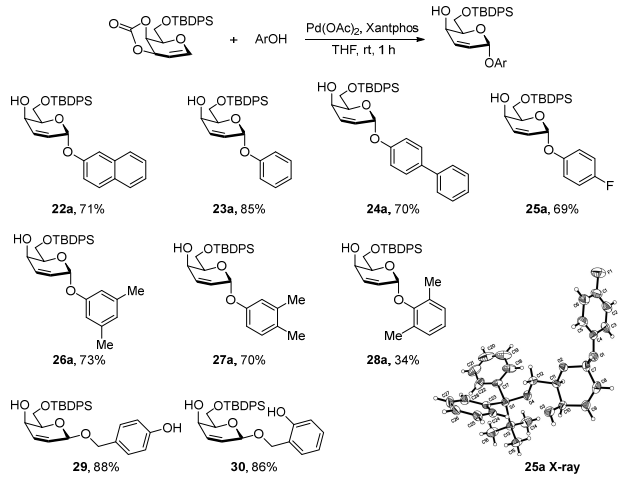
entry	catalyst	ligand	solvent	time	yield[b,c]
1	$Pd(OAc)_2$	Xantphos	THF	1 h	71% **22a**
2[d]	$Pd(OAc)_2$	PPh_3	THF	12 h	47% **22a**
3[d]	$Pd(OAc)_2$	$P(Cy)_3$	THF	12 h	N.R.
4	$Pd(OAc)_2$	DPPF	THF	12 h	14% **22a**
5	$Pd(OAc)_2$	Xantphos	DMSO	12 h	24% **22a**
6	$Pd(OAc)_2$	Xantphos	DMF	12 h	21% **22a**
7	$Pd(acac)_2$	Xantphos	THF	12 h	42% **22a**
8	$Pd(PPh_3)_4$	Xantphos	THF	12 h	66% **22b**
9	$Pd(dba)_2$	Xantphos	THF	12 h	61% **22b**
10[e]	$Pd_2(dba)_3$	Xantphos	THF	12 h	88% **22b**

[a]Unless otherwise specified, all reactions were carried out with 0.1 mmol of **1**, 0.2 mmol of 2-naphthol, 10 mol% Pd catalyst, 15 mol% P ligand in 2 mL solvent at room temperature. [b]Isolated yield. [c]Single isomer (> 30:1 by ^{1}H NMR). [d]30 mol% ligand used. [e]5 mol% Pd catalyst used. N.R. = No reaction.

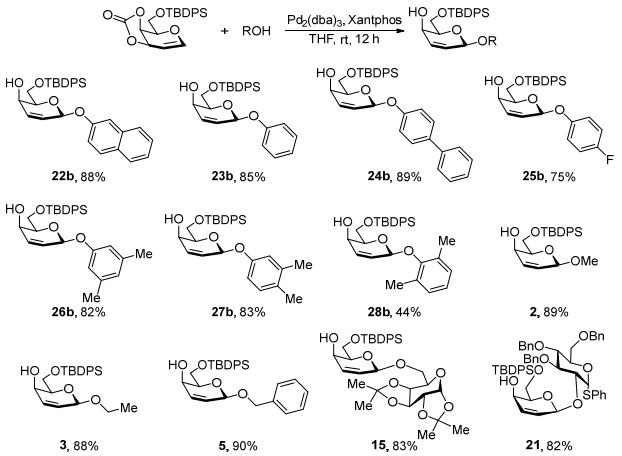
found in the other Pd(0) catalysts: $Pd(dba)_2$ and $Pd_2(dba)_3$ (entries 9, 10). The optimal condition for β-glycosylation was 5% $Pd_2(dba)_3$ as a catalyst, 15% Xantphos as a ligand in THF at room temperature for 12 hours using phenols.

To our delight, we could produce the desired α-*O*-glycosides or β-*O*-glycosides respectively by using Pd(II) or Pd(0) catalyst. To validate this hypothesis, firstly, the optimal Pd(II) condition was applied to the other phenolic substrates (Scheme 3). Notably, a variety of phenols were also able to tolerate this Pd(II) condition. For instance, phenol gave a very high yield (**23a**, 85%) with exclusive α-selectivity. 4-Phenylphenol (**24a**) and electron donating group substituted phenols (**26a**, **27a**) were able to produce good yields of 1,4-*trans*-products except for 2,6-dimethylphenol (**28a**) which showed a much lower yield due to steric hindrance. Interestingly, with a less nucleophilic, electron withdrawing group being substituted, 4-fluorophenol could also generate a good yield of α-*O*-glycoside **25a**. Comparing the reactivity between alcohols and phenols, 4-hydroxybenzyl alcohol (**29**) and 2-hydroxybenzyl alcohol (**30**) were employed to react with our glycal donor. Based on the finding, alcoholic hydroxyl group was shown with significantly higher in reactivity.

Subsequently, Pd(0) condition was also examined by the same types of phenols and some aliphatic acceptors (Scheme 4). As expected, the selectivity was reversed when compare to the corresponding phenols such as phenol (**23b**)



Scheme 3. Phenol Substrate Scope via Pd(II) Catalyst



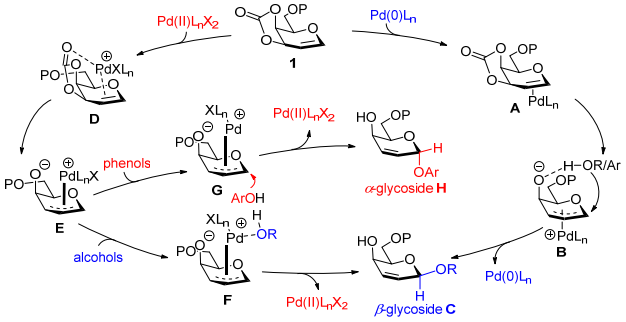
Scheme 4. Substrate Scope via Pd(0) Catalyst

4-phenylphenol (**24b**) and 4-fluorophenol (**25b**). As we screened before (Table 1), when the Pd(0) condition was applied to alcohols, only β-selectivity were observed. Both simple β-*O*-glycosides (**2**, **3**, **5**) and disaccharides (**15**, **21**) were successfully synthesized in high yields.

According to the above results, a plausible mechanism was proposed in Scheme 5. Pd(0) and Pd(II) opened up two different pathways: firstly, Pd(0) complex was coordinated to the double bond of glycal **1** to form intermediate **A** from the α-face as Pd(0) species with P-ligands was too bulky to coordinate at the β-face. Next, decarboxylation occurred and intermediate **B** was yielded at β-face for both aliphatic or phenolic acceptors due to H-bond.[16] Subsequently, nucleophilic addition formed β-*O*-glycoside **C**. On the other hand, Pd(II) species favored coordination with glycal **1** directly rather than being reduced by P-ligands to give intermediate **D** as it was more oxyphilic and could be directed by the carbonate moiety.[4a, 6] After decarboxylation and intermediate **E** was generated, the Pd complex would block H-bond formation and the pathway splits depended on the nature of acceptors. With hard nucleophile alcohols, intermediate **F** was generated by the inner-sphere pathway to give β-glycoside **C**, while for soft nucleophiles phenols, **G** was yielded to form α-glycoside **H** through the outer-sphere pathway.[7, 11a, 11b]

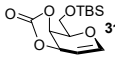
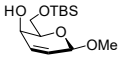
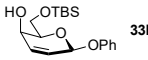
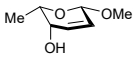
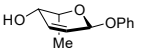
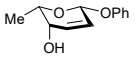
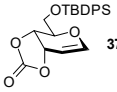
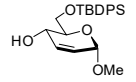
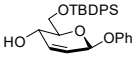
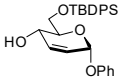
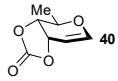
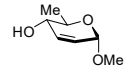
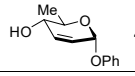
To confirm this mechanism, other glycal donors were employed as shown in Table 3. When the 6-*O*-protecting group was changed from TBDPS to a smaller TBS (entries 1-3), the stereoselectivity was consistent with glycal **1**. When L-fucal **34** was applied, α-*O*-glycoside **36a** and β-*O*-glycoside **36b** could be obtained stereoselectively in Pd(II) and Pd(0) conditions (entries 5-6) respectively. These results indicated that steric effect from C6 could not affect the selectivity but a less hindered C6-protecting group may decrease the yields due to possible side products (oligosaccharides) from further glycosylation on 4-OH of the glycosides. In order to investigate coordination relationship between glycal and palladium species, 4,6-*trans*-glycals (D-allal **37** and digitoxal **40**) were also tested (entries 7-12). The aliphatic acceptor gave α-selectivity (**38**, **41**), while the phenolic acceptor generated β-selectivity (**41b**, **44b**) in the Pd(II) condition and α-selectivity (**41a**, **44a**) in the Pd(0) condition. All the results indicated that cyclic carbonate moiety played an important role in the mechanism as we proposed Pd(0) coordinated at its *trans*-face but Pd(II) coordinated at the *cis*-face.

Competitive reactions were carried out to compare the properties of Pd(II) and Pd(0) catalysis as shown in Scheme 6. Firstly, a reaction was carried out using a mixture of Pd



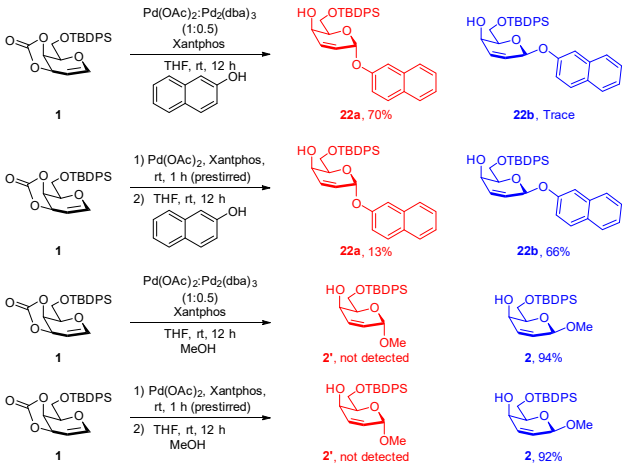
Scheme 5. Proposed Mechanism

Table 3. Mechanism Study with Different Glycals

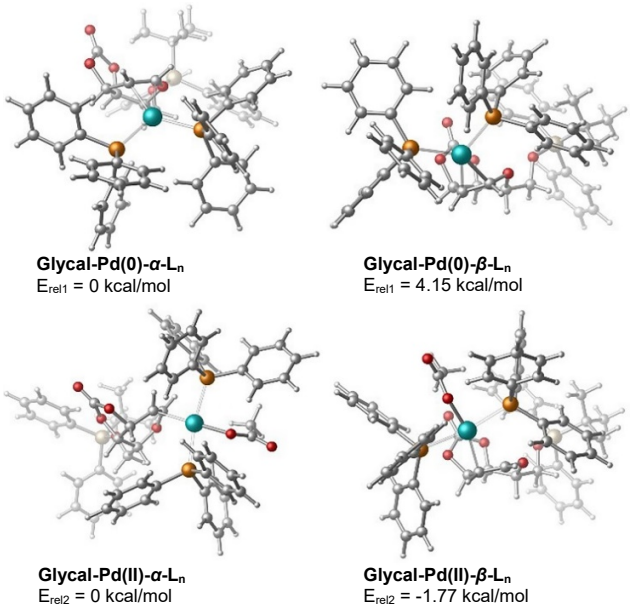
entry	glycal	acceptor	condition	glycoside	yield[a,b]
1	 **31**	MeOH	Pd(II)	 **32**	95%
2	**31**	PhOH	Pd(II)	 **33a**	61%
3	**31**	PhOH	Pd(0)	 **33b**	72%
4	 **34**	MeOH	Pd(II)	 **35**	90%
5	**34**	PhOH	Pd(II)	 **36a**	60%
6	**34**	PhOH	Pd(0)	 **36b**	58%
7	 **37**	MeOH	Pd(II)	 **38**	93%
8	**37**	PhOH	Pd(II)	 **39b**	71%
9	**37**	PhOH	Pd(0)	 **39a**	76%
10	 **40**	MeOH	Pd(II)	 **41**	89%
11	**40**	PhOH	Pd(II)	 **42b**	70%
12	**40**	PhOH	Pd(0)	 **42a**	75%

[a]Isolated yield. [b]Single isomer (> 30:1 by ^{1}H NMR).

(II):Pd(0) in 1:1 with 2-naphthol. Results showed that majority of the glycosides were able to provide α-product **22a** and hence, suggested that Pd(II) could catalyze the reaction at a much faster rate without being reduced. Next, we prestirred Pd(II) catalyst and phosphine ligands before adding glycal donor and naphthol. Then the reduced Pd(II) catalyst could only afford β:α (phenolic *O*-glycosides) in 5:1. Thus, this result illustrated that Pd(II) was not reduced in a one-pot reaction. On the other side, the aliphatic acceptor methanol demonstrated only β-selectivity under the two competitive conditions, which follows our proposed mechanism.



Scheme 6. Competitive Reactions of Pd(0)/Pd(II)



Scheme 7. Calculated Structures and Relative Energies of Plausible Glycal-Pd-Ligand Intermediates

Four plausible intermediates of galactal-palladium-ligands as proposed in our mechanism were submitted for the DFT calculation.[17] As shown in Scheme 7, the results demonstrated that Pd(0) complex preferred to stay at α-face with a relative 4.15 kcal/mol lower than β-face. On the other hand, the energy of Pd(II) complex showed 1.77 kcal/mol higher at α-face. Thus, these results also supported our proposed mechanism.

In conclusion, we have developed a novel strategy to construct α- and β-*O*-glycosidic bonds with exclusive selectivity under mild conditions through highly efficient 3,4-*O*-carbonate galactal donors. β-*O*-Glycosides could be obtained from aliphatic alcohols with both Pd(0) and Pd(II) while α- and β-*O*-glycosides could be obtained from phenols, using Pd(II) and Pd(0) respectively. Mechanistic studies with varying coordinating pathways for Pd(0) and Pd(II) was proposed and DFT calculations were also performed. A wide range of substrates such as alcohols, saccharides, phenols and glycals were employed and afforded the desired products stereoselectively in high yields. Lastly, these resultant 4-OH glycosides could potentially be acceptors for 4-branched oligosaccharides or natural product synthesis.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures, characterization data, crystallographic data and calculation details.

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REFERENCES

(1) Selected examples: (a) Jung, K. H.; Muller, M.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423-4442; (b) Kim, J. H.; Yang, H.; Park, J.; Boons, G. J. *J. Am. Chem. Soc.* **2005**, *127*, 12090-12097; (c) Zhu, X. M.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934; (d) Zhu, Y.; Yu, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 8329-8332; (e) Yasomanee, J. P.; Demchenko, A. V. *J. Am. Chem. Soc.* **2012**, *134*, 20097-20102; (f) Shu, P.; Xiao, X.; Zhao, Y.; Xu, Y.; Yao, W.; Tao, J.; Wang, H.; Yao, G.; Lu, Z.; Zeng, J.; Wan, Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 14432-14436.

(2) Selected examples: (a) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714-8715; (b) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406-12407; (c) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428-3429; (d) Zeng, J.; Ma, J.; Xiang, S.; Cai, S.; Liu, X.-W. *Angew. Chem. Int. Ed.* **2013**, *52*, 5134-5137; (e) Xiang, S.; Lu, Z.; He, J.; Hoang, K. L. M.; Zeng, J.; Liu, X.-W. *Chem. Eur. J.* **2013**, *19*, 14047-14051; (f) Sau, A.; Williams, R.; Palo-Nieto, C.; Franconetti, A.; Medina, S.; Galan, M. C. *Angew. Chem. Int. Ed.* **2017**, *56*, 3640-3644.

(3) Selected examples: (a) Yang, J.; Cooper-Vanosdell, C.; Mensah, E. A.; Nguyen, H. M. *J. Org. Chem.* **2008**, *73*, 794-800; (b) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. Eur. J.* **2010**, *16*, 1871-1882; (c) Kumar, A.; Kumar, V.; Dere, R. T.; Schmidt, R. R. *Org. Lett.* **2011**, *13*, 3612-3615; (d) Zhang, Q.; Sun, J.; Zhu, Y.; Zhang, F.; Yu, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 4933-4936; (e) Fang, T.; Mo, K. F.; Boons, G. J. *J. Am. Chem. Soc.* **2012**, *134*, 7545-7552; (f) Chu, A. H.; Nguyen, S. H.; Sisel, J. A.; Minciunescu, A.; Bennett, C. S. *Org. Lett.* **2013**, *15*, 2566-2569; (g) Sun, L.; Wu, X.; Xiong, D. C.; Ye, X. S. *Angew. Chem. Int. Ed.* **2016**, *55*, 8041-8044; (h) Park, Y.; Harper, K. C.; Kuhl, N.; Kwan, E. E.; Liu, R. Y.; Jacobsen, E. N. *Science* **2017**, *355*, 162-166.

(4) Recent reviews: (a) McKay, M. J.; Nguyen, H. M. *ACS Catal.* **2012**, *2*, 1563-1595; (b) Li, X. H.; Zhu, J. L. *J. Carbohydr. Chem.* **2012**, *31*, 284-324; (c) Li, X. H.; Zhu, J. L. *Eur. J. Org. Chem.* **2016**, 4724-4767.

(5) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336-1337.

(6) Schuff, B. P.; Mercer, G. J.; Nguyen, H. M. *Org. Lett.* **2007**, *9*, 3173-3176.

(7) Xiang, S.; Hoang, K. L. M.; He, J.; Tan, Y.-J.; Liu, X.-W. *Angew. Chem. Int. Ed.* **2015**, *54*, 604-607.

(8) (a) Khan, A.; Zheng, R.; Kan, Y.; Ye, J.; Xing, J.; Zhang, Y. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 6439-6442; (b) Khan, A.; Yang, L.; Xu, J.; Jin, L. Y.; Zhang, Y. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11257-11260.

(9) Reddy, Y. S.; Lahiri, R.; Vankar, Y. D. *Eur. J. Org. Chem.* **2012**, 4751-4761.

(10) See the Supporting Information for computation details.

(11) (a) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422; (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545-4554; (c) Mercer, G. J.; Yang, J.; McKay, M. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2008**, *130*, 11210-11218; (d) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343-18357; (e) Recio, A., III; Heinzman, J. D.; Tunge, J. A. *Chem. Commun.* **2012**, *48*, 142-144; (f) Wu, G.; Su, W. *Org. Lett.* **2013**, *15*, 5278-5281.

(12) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741-2769.

(13) Colorless syrup **2** was modified with *p*-nitrobenzoyl moiety and converted to solid growing a crystal for X-ray analysis, see the Supporting Information.

(14) Wang, S. A.; Cuesta-Seijo, J. A.; Lafont, D.; Palcic, M. M.; Vidal, S. *Chem. Eur. J.* **2013**, *19*, 15346-15357.

(15) (a) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819-6825; (b) Crich, D.; Vinod, A. U. *Org. Lett.* **2003**, *5*, 1297-1300.

(16) Azidotrimethylsilane was examined as a non-hydrogen-bonding acceptor in both Pd(0) and Pd(II) conditions. Two epimers were obtained as products, which also supported the proposed mechanism as shown in the Supporting Information.

(17) (a) Weaver, J. D.; Recio, A., 3rd; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846-1913; (b) Sperger, T.; Sanhueza, I. A.; Kalvet, I.; Schoenebeck, F. *Chem. Rev.* **2015**, *115*, 9532-9586; (c) Bai, D. C.; Yu, F. L.; Wang, W. Y.; Chen, D.; Li, H.; Liu, Q. R.; Ding, C. H.; Chen, B.; Hou, X. L. *Nat. Commun.* **2016**, *7*, 11806.

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