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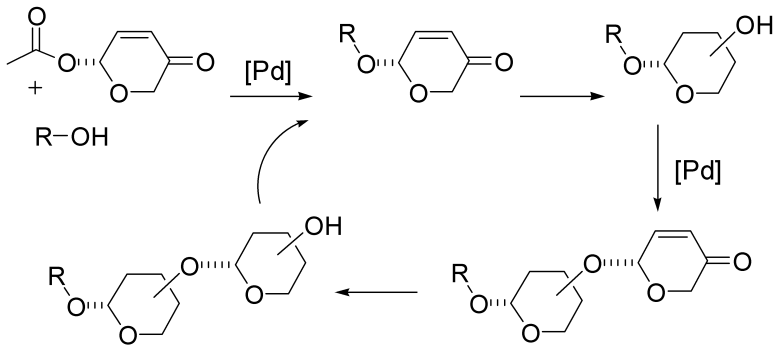

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De Novo Asymmetric Bio- and Chemocatalytic Synthesis of Saccharides − Stereoselective Formal *O*-Glycoside Bond Formation Using Palladium Catalysis

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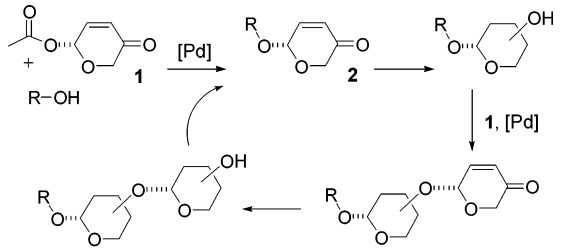
The chemical synthesis of carbohydrate domains in saccharides and glycoconjugates such as antibiotics, antitumor agents, glycoproteins, and glycolipids is now recognized as a major frontier for organic chemistry.[1] Fundamental to the synthesis of such carbohydrates and their derivatives is the selectivity of α- or *β*-*O*-glycoside bond formation which typically entails the coupling of one nucleophilic (O-donating) glycoside to another electrophilic glycosyl donor;[2,3] anomeric stereoselectivity is a complex issue usually dependent on the nature of the donor C2 substituent.[1]

Catalytic stereoselective formation of the acetal linkage onto pyranones[4] of type **1** (Scheme 1) presents a conceptually different solution to this stereochemical problem by providing a stereodefined platform whose chiral information can be relayed around the ring. Such an acetal can be a formal α- or *β*-glycoside bond depending on the enantiomer of **1**, the stereocontrol in the Pd-catalyzed step, and the chemistry used to elaborate the ring.[5]

Scheme 1. Iterative Saccharide Synthesis: Stereoselective Acetal Bond Formation Using Pd Catalysis

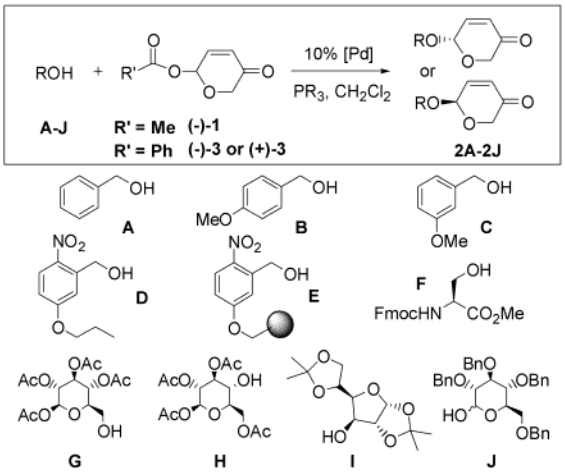


Here, we present a novel integrated approach to the de novo catalytic asymmetric synthesis of saccharides uniting two protocols: the enzymatic resolution of racemic acetoxypyranones **1**[6] with a highly stereoselective palladium-catalyzed acetal bond formation onto this embryonic sugar (Scheme 1). Resulting from subsequent steps to elaborate the ring into a diversity of natural and unnatural sugars, a free hydroxyl group can be stereoselectively coupled again to **1**, giving rise to an iterative catalytic asymmetric saccharide synthesis. A blank slate for saccharide synthesis, the versatility of this cyclic enone platform has been appreciated for some time.[7]

Despite the widespread use of phenols as nucleophiles in the palladium-catalyzed allylic substitution reaction,[8] aliphatic alcohols have received scant attention.[9,10] During early investigations, however, we found that the substitution reaction of enantiomerically pure 6-acetoxy-2*H*-pyran-3(6*H*)-one (−)-**1**[6] with simple primary and secondary aliphatic alcohols as solvent proceeded with nearly complete retention of stereochemistry.[11]

Efforts to improve the viability of this methodology resulted in the coupling depicted in Table 1. The use of 10 mol % $Pd(OAc)_2$ and triphenyl phosphite in DCM at −30 °C[12] was found to convert pyranone (−)-**1** into the benzyl alcohol adduct **2A** in high yield

Table 1. Stereoselective Acetal Bond Formation Using Pd Catalysis



adduct	donor	% yield	% ee/de	adduct	donor	% yield	% de[e]
2A	(−)-**1**	83	94[b]	**2H**	(−)-**1**	65[a]	91
2B	(−)-**1**	87	98[b,c]		(−)-**3**	57[a]	92
2C	(−)-**1**	98	99[b]		(+)-**3**	61[a]	96
2D	(−)-**1**	84	98[b]	**2I**	(−)-**1**	70[a]	97
2E	(±)-**1**	69	nd[b,d]		(−)-**3**	71[a]	82
2F	(−)-**1**	78[a]	97[b]		(+)-**3**	76[a]	95
2G	(−)-**1**	77[a]	94[e]	**2J**	(−)-**1**	60	*f*
	(−)-**3**	88[a]	94[e]				
	(+)-**3**	96[a]	98[e]				

[a] Isolated yield of unique stereoisomer. [b] 10% $Pd(OAc)_2$, $P(OPh)_3$, DCM, −30 °C; stereoselectivities were determined by chiral HPLC analysis. [c] Enantiomeric excess before chromatography. [d] Coupled to racemic **1** only. [e] 5% $Pd_2(dba)_3$, PPh_3, DCM, −10 °C; diastereoselectivities were determined from ^1H NMR. [f] Mixture of isomers.

and 94% ee. Particularly rewarding were the still higher yields and ee's for anisyl nucleophiles **B** and **C** and the *ortho*-nitrobenzyl alcohol **D**, useful mimics of benzyl linkers[1b,13] applied to the solid-phase synthesis of saccharides.[14] In preliminary experiments to apply the protocol to the solid-phase, photocleavable **E**, immobilized onto phenolic polystyrene, was also coupled efficiently to racemic **1**. Representative of Mucin-type glycosylation found in the glycopeptides of mammals and other eukaryotes,[15] adduct **2F** was also prepared with excellent stereoselectivity.

Key to the feasibility of the protocol is the success of a first iteration: a stereoselective coupling reaction of enantiopure glycosyl donor with a sugar derivative. The results are illustrated in Table 1. Initial attempts using the $Pd(OAc)_2/P(OPh)_3$ catalyst system failed, but, to our relief, use of $Pd_2(dba)_3/PPh_3$ successfully mediated formation of the desired adducts **2G**−**2J**. Primary alcohol **G**, a 6-deprotected glucopyranose, underwent coupling with (−)-**1** and both (*R*)-(−)-**3** and (*S*)-(+)-**3**[16] to afford the stereoisomers of the

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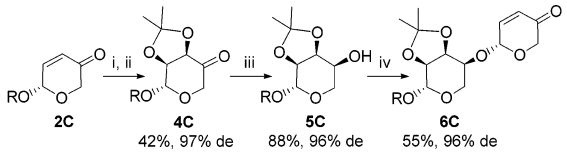
products with excellent yield (77−96%) and diastereoselectivity (94−98%). Crucially, similar success was found with the more sterically demanding substrates 4-deprotected glucopyranose **H** and 3-deprotected glucofuranose **I** bearing a secondary alcohol moiety, and good yields (57−76%) and excellent stereoselectivities (82−97%) were obtained during *both R- and S-acetal bond formation*. All adducts were isolated as unique diastereomers by simple column chromatography with the exception of that with **J**, deprotected at the anomeric center.

A preliminary application of our iterative approach is depicted in Scheme 2. Diastereoselective catalytic *cis*-dihydroxylation of enone adduct **2C** was effected by $RuCl_3/NaIO_4$,[17] and the resulting diol was protected to the dioxolane **4C** under standard conditions. Subsequent reduction using $Zn(BH_4)_2$[18] gave **5C**, a β-L-ribose.[19] Coupling of this sugar under the catalytic conditions previously described successfully afforded the disaccharide precursor **6C** with 96% de.[20]

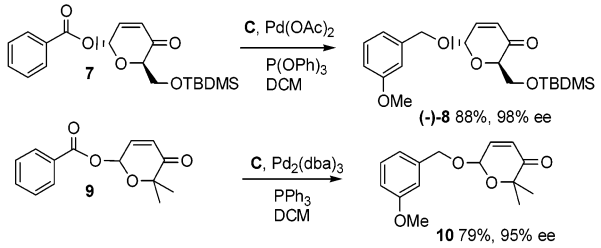
Scheme 2. Preliminary Application of Iterative Saccharide Synthesis[a]



[a] (i) $RuCl_3 \cdot 3H_2O$ (20 mol %), $NaIO_4$; (ii) 2,2-DMP, acetone, PTSA; (iii) $Zn(BH_4)_2$; (iv) (−)-**1**, $Pd_2(dba)_3$ (5 mol %), PPh_3, CH_2Cl_2.

Unsuccessful endeavors to alkylate the methylene position of **4C** led to an appraisal of prefunctionalized pyranone substrate **7** in the palladium-catalyzed allylic substitution reaction (Scheme 3). Prepared enantiopure employing a Sharpless dihydroxylation protocol,[7j] **7** indeed underwent substitution with complete retention of stereochemistry, giving **8**. 4,4-Dimethyl-substituted pyranone **9**,[7i,16] applicable to the asymmetric synthesis of L-noviose,[21] a constituent of the antibiotic novobiocin, also participated with high stereoselectivity to afford **10**.

Scheme 3. C4-Substituted Glycosyl Donors



Efforts to elaborate on this chemistry by providing a view of an iterative catalytic solid-phase protocol are ongoing.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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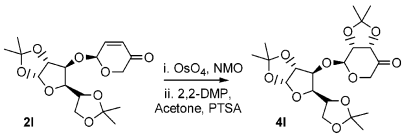

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