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Palladium-Catalyzed Decarboxylative Allylation/Wittig Reaction: Substrate-Controlled Synthesis of *C*-Vinyl Glycosides

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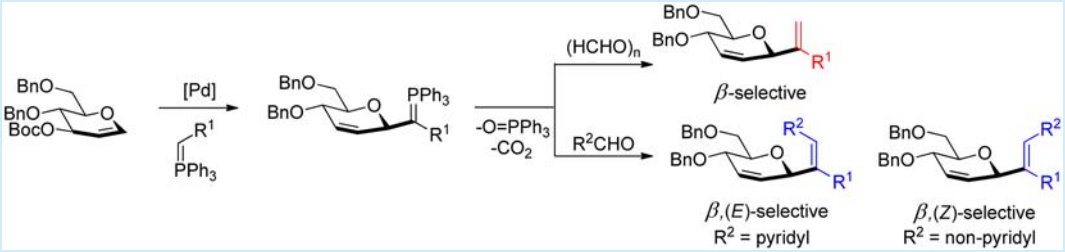
Supporting Information



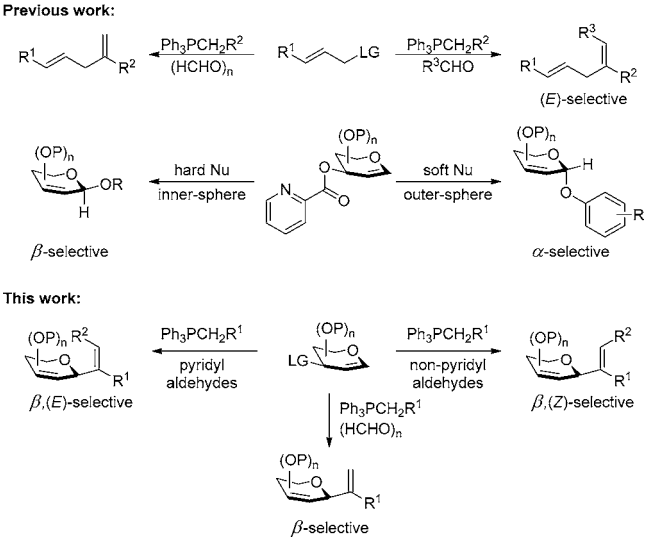
ABSTRACT: A palladium-catalyzed one-pot Tsuji–Trost type decarboxylative allylation/Wittig reaction has been developed to synthesize *C*-vinyl glycosides. Screening of various aldehydes led to formation of β,(*E*)-selective *C*-vinyl glycosides with pyridyl group containing aldehydes and β,(*Z*)-selective *C*-vinyl glycosides with nonpyridyl aldehydes. A plausible mechanism is proposed based on the coordination effect of the aldehydes.

Over the past decade, transition metal-catalyzed coupling reactions, such as Pd-catalyzed Heck type[1] and Tsuji–Trost type reactions,[2] have become popular strategies to construct glycosidic bonds.[3] Although the first palladium-catalyzed *C*-glycosylation was reported close to 40 years ago, the reaction is not widely used.[4] One of the reasons for this is the difficulty of forming π-allyl palladium species from the electron-rich enol ethers.[5] It was only when Pd-catalyzed decarboxylative allylation was recently reported[6] that further advances on its application to *C*-glycosides were reported. Notably, this reaction is able to address the challenge of stereoselectivity despite the absence of an anomeric effect.

Recent work has defined a new role for stabilized phosphonium ylides (*P*-ylides) as nucleophiles,[7] allowing their application in one-pot allylic substitution/Wittig,[8] Michael/Wittig,[9] and Mannich/Wittig[10] reactions with good regioselectivities. In these one-pot reactions, nucleophilic attack occurs first, followed by deprotonation to regenerate *P*-ylides for subsequent Wittig reaction via an oxaphosphetane intermediate. However, it is difficult to obtain tri- and tetrasubstituted alkenes via Wittig reactions efficiently, as such reactions are very sensitive to steric hindrance. The one-pot allylation/Wittig reaction as a new means of *C*-glycosylation has yet to be realized. Certainly, while the one-pot reaction seems like a potentially efficient approach, the difficulties of forming trisubstituted alkenes as well as the problems of diastereoselectivity for the anomeric and olefin selectivities must be considered.

Herein, we report a one-pot Pd-catalyzed decarboxylative allylation/Wittig reaction that can utilize the coordinating ability of aldehyde substrates to direct the diastereoselectivity (Scheme 1). Previously, we have reported our methodology to reverse anomeric selectivity through formation of an intermediate with Pd–N coordination.[2g] We postulated that such a coordinating effect of Pd could potentially control the anomeric selectivity as well as the olefin selectivity, achieving the desired overall diastereoselectivity in the desired *C*-vinyl glycosides.

Scheme 1. Reported and Current Work on Allylation and Wittig Reactions



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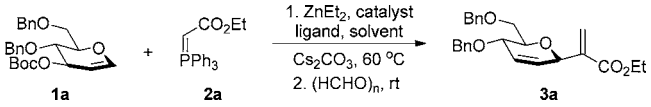
We initiated our study of one-pot allylation/Wittig reaction using glucal **1a**, *P*-ylide **2a**, and paraformaldehyde in the presence of palladium(II) acetate, 1,4-bis(diphenylphosphino)-butane (DPPB), and cesium carbonate in dimethylformamide at 60 °C (Table 1), but to our disappointment, no product was

Table 1. Optimization Results[a]



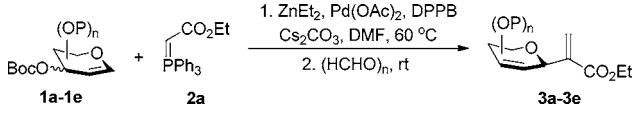
entry	catalyst	ligand	solvent	yield[b] (%)
1[c]	$Pd(OAc)_2$	DPPB	DMF	–
2	$Pd(OAc)_2$	DPPB	DMF	92
3	$Pd(OAc)_2$	DPPB	dioxane	34
4	$Pd(OAc)_2$	DPPB	DMSO	47
5	$Pd(OAc)_2$	DPPB	CH_3CN	41
6	$Pd(TFA)_2$	DPPB	DMF	69
7	$Pd(C_6H_5CN)_2Cl_2$	DPPB	DMF	80
8	$[Pd(CH_3CN)_4](BF_4)_2$	DPPB	DMF	89
9[d]	$Pd(OAc)_2$	XPhos	DMF	71
10	$Pd(OAc)_2$	DPPF	DMF	69
11	$Pd(OAc)_2$	DPPPent	DMF	70

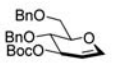
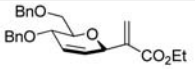
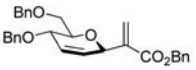
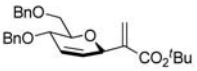
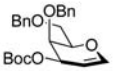
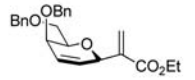
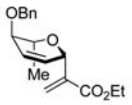
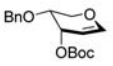
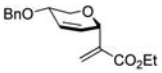
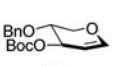
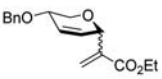
[a]Unless otherwise specified, all reactions were carried out using glucal **1a** (0.1 mmol, 1 equiv), *P*-ylide **2a** (0.15 mmol, 1.5 equiv), $ZnEt_2$ (0.15 mmol, 1.5 equiv), [Pd] 20 mol %, ligand 30 mol %, Cs_2CO_3 (0.15 mmol, 1.5 equiv) in 1.6 mL of solvent. [b]Isolated yields. [c]Without the addition of $ZnEt_2$. [d]60 mol % of ligand used.

observed (entry 1). In order to increase the compatibility between the *P*-ylide nucleophile and the soft π-allyl palladium electrophile, we attempted to soften the *P*-ylide using a $ZnEt_2$ additive[11] which proved to be successful, it providing 92% yield of the desired product (entry 2). Changing the solvents had an adverse effect on the reaction efficiency, probably because of the insolubility of the base (entries 3–5). While the Pd catalysts had no significant effect on the reaction, $Pd(OAc)_2$ gave the highest yield (entries 2, 7, 8). DPPB was found to be the most suitable ligand for the reaction (entries 2, 9–11). On the basis of these results, entry 2 was selected as the optimal set of reaction conditions. The β-stereochemical assignment was confirmed by NOE experiment based on strong observed correlation between H1 and H5 for product **3a**.[12]

With the optimal conditions in hand, we evaluated the scope of this one-pot reaction with respect to the *P*-ylide glycosyl donor and the glycosyl acceptor (Table 2). When the ethyl ester functionality of the *P*-ylide was replaced by benzyl and *tert*-butyl groups (**3a–c**), the overall efficiency of the reaction remained unaffected. Other glycals were then screened to investigate the effect of a substituent on each position. It is notable that, in all cases, the *C*-vinyl glycosides were produced with the preferred β-selectivity. As expected, **3d** had a diminished yield due to steric factors. **3e** was furnished in a lower yield due to the formation of a side product. In our case, the C6 substitutent did not have a significant effect on the control of stereoselectivity when the C3 and C4 substituents of the glycosyl acceptor were *cis* to each other, as seen in the case of arabinal (**3f**), where exclusive β-selectivity was obtained. On the other hand, when the substituents were *trans*, the effect of the C6 substituent became significant, with the absence of the C6 substituent (**3g**) leading to a decrease in stereoselectivity. Mechanistically, the palladium complex preferred to coordinate

Table 2. Scope of Glycosyl Donors and Acceptors



entry	glycal	product	yield[a] (%)
1	 **1a**	 **3a**	92
2[b]	**1a**	 **3b**	92
3[c]	**1a**	 **3c**	94
4	 **1b**	 **3d**	58
5	 **1c**	 **3e**	56
6	 **1d**	 **3f**	95
7	 **1e**	 **3g**	60 (β:α = 2:1)

[a]Isolated yields. [b]Using benzyl(triphenylphosphoranylidene) acetate. [c]Using (*tert*-butoxycarbonylmethylene) triphenylphosphorane.

to the face *trans* to the leaving group. However, when C3 and C4 were *trans* to each other, there was a steric effect between the palladium complex and the bulky C4 substituent. The two opposing stereodirecting effects accounted for a reduction in anomeric selectivity, which became significant in the absence of the C6 substituent.

To prove the applicability of the method to form trisubstituted *C*-vinyl glycosides as well as explore the effect of Pd–N coordination in the one-pot reaction, aldehydes with aromatic and heterocyclic substituents were evaluated under the reaction conditions (Scheme 2). In the course of our study, we discovered that pyridine-containing carboxaldehydes (**3h–3k**) could be successfully applied to furnish the sterically unfavored (*E*)-olefins. High efficiency was achieved when electron-donating substituents were present at the *ortho*-position to the pyridyl N (**3i–3k**), with a surprisingly high yield of 84% for the 6-(3-thienyl)-2-pyridyl group (**3j**), suggesting the presence of another factor dominating over the steric effect, which will be discussed later on. To the best of our knowledge, such a result was never reported previously and the formation of trisubstituted alkenes using the Wittig reaction is often reported with low to moderate yields due to steric factors.[8a,d] On the other hand, aldehydes without a pyridine ring, such as five-membered heterocycles (**3l–3n**) and benzaldehydes, required electron-withdrawing substituents

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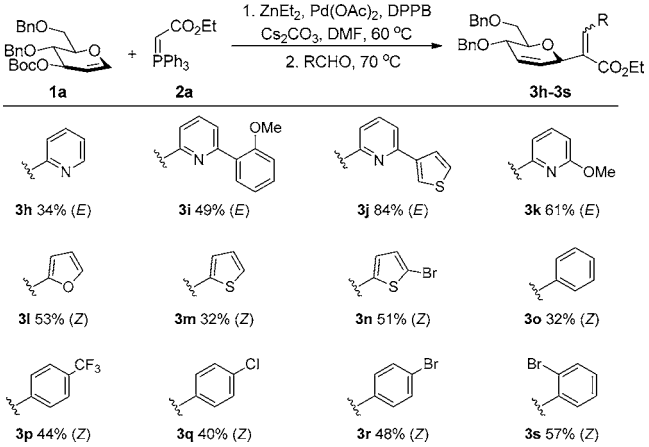
Scheme 2. Scope of Aldehydes[a]

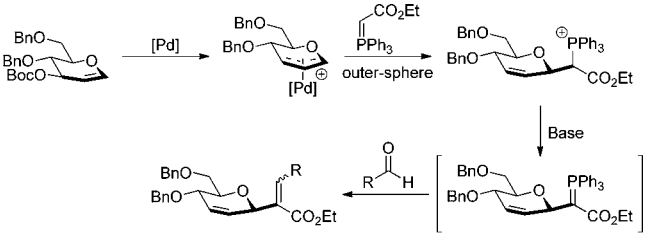


[a]Isolated yields over two steps.

(**3o**−**3s**) to promote the intermolecular Wittig reaction by enhancing the electrophilicity of the aldehydes. In such cases, the absence of coordinating effects led to the preferential formation of the (*Z*)-isomer. Aldehyde-derived Wittig selectivity is often associated with steric effects, and such cases of aldehydes of similar sizes producing opposite olefin selectivity have not been investigated. Notably, all of the products were obtained with exclusive β-selectivity at the anomeric position.

Based on the observed diastereoselectivity, the following mechanistic pathways are proposed. As the nucleophile used is a soft *P*-ylide, the Tsuji−Trost reaction proceeds via an outer sphere mechanism which gives rise to β-selectivity (Scheme 3).

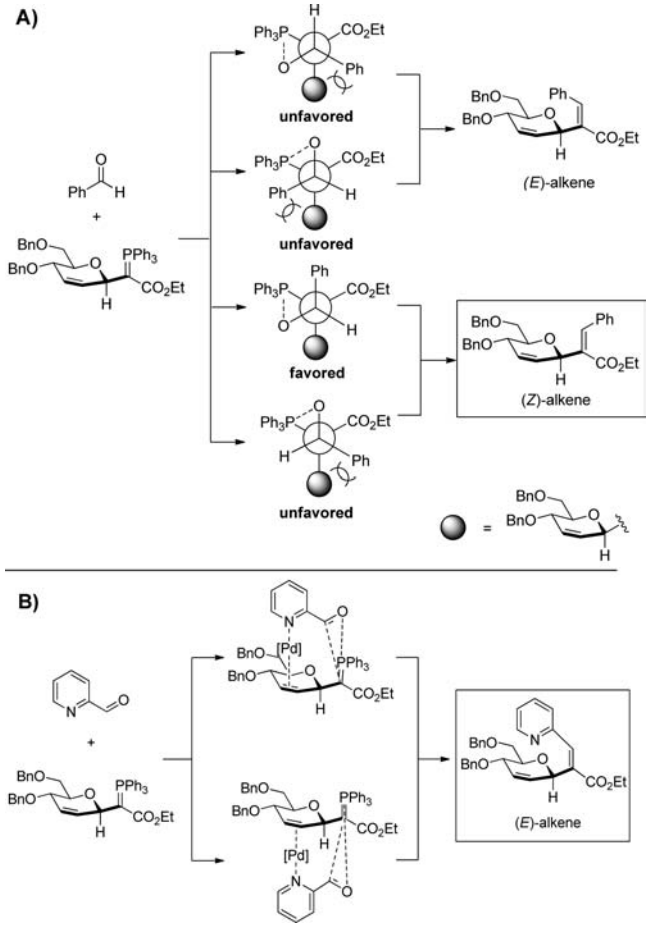
Scheme 3. Proposed Mechanism



For the Wittig reaction, the olefin selectivity is dictated by the substitutents on the aldehydes (Scheme 4). For the nonpyridyl type aldehydes, such as those with phenyl, furyl, and thienyl moieties, the reaction proceeds via the typical intermolecular Wittig reaction to give (*Z*)-alkenes. This (*Z*)-selectivity can be explained using the Newman projection of the puckered four-membered oxaphosphetane intermediate formed from the [2 + 2] cycloaddition, whereby the bulky sugar moiety prefers to have minimal gauche interactions with the aldehyde substituent. The favored (*Z*)-stereoselectivity arises from the preferred formation of oxaphosphetane with the aldehyde substituent *anti* to the sugar group (Scheme 4A).

On the other hand, when aldehydes with pyridyl groups are employed, we propose that there is some degree of Pd−N coordination,[13] leading to a reversal in olefin stereoselectivity. This is supported by the surprising formation of sterically unfavorable (*E*)-selective glycosides and increased yields with pyridyl promoted nucleophilicity due to the electron-donating substituents. Pd−N coordination allows the Wittig reaction to

Scheme 4. Proposed Key Oxaphosphetane Intermediates Accounting for (*Z*)-/(*E*)-Selectivity



proceed via a pseudointramolecular reaction by bringing the *P*-ylide and aldehyde into close proximity for [2 + 2] cycloaddition, overcoming the opposing steric factors in the typical Wittig reaction, which usually limits the efficiency of the formation of trisubstituted alkenes (Scheme 4B).

In summary, we have reported a palladium-catalyzed one-pot decarboxylative allylation/Wittig reaction to furnish diastereoselective *C*-vinyl glycosides. The diastereoselectivity arises from the successive formation of two stereocenters and was dependent on the coordinating ability of the aldehydes. Based on the formation of β,(*E*)-selective and β,(*Z*)-selective *C*-vinyl glycosides when pyridyl and nonpyridyl aldehydes were employed respectively, we have proposed two pathways: the pseudointramolecular pathway based on Pd−N coordination and the classic intermolecular pathway in the absence of coordination. This methodology has potential to be applied in synthesizing *C*-vinyl glycosides in high efficiency with controlled diastereoselectivity. These *C*-vinyl glycosides could be subjected to downstream functionalization, making them useful synthetic precursors for synthesizing pharmaceutical and natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03697.

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Procedures for one-pot reaction and characterization of isolated products; NMR spectra of products as a proof of diastereoselectivity for isolated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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