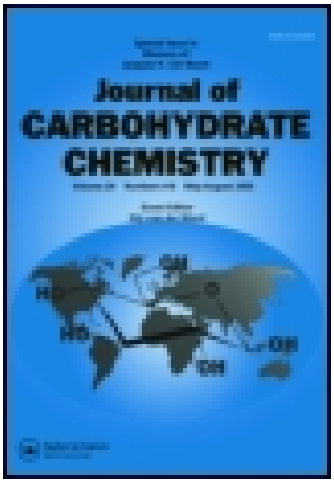

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Optimized Synthesis of Vinyl Ether Sugars and Vinyl Glycosides through Transfer Vinylation Catalyzed by (4,7-Ph_2-phen)Pd($OOCCF_3$)$_2$

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Optimized Synthesis of Vinyl Ether Sugars and Vinyl Glycosides through Transfer Vinylation Catalyzed by (4,7-Ph_2-phen) $Pd(OOCCF_3)_2$

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Sugar vinyl ethers and vinyl glycosides are conveniently synthesized by catalytic transfer vinylation with butyl vinyl ether, which serves as both the solvent and source of vinyl. The air-stable catalyst (4,7-diphenyl-1,10-phenanthroline)$Pd(OOCCF_3)_2$ is prepared in situ from commercially available components.

Keywords Vinyl sugars, Catalytic synthesis

INTRODUCTION

Vinyl glycosides and vinyl ether sugars have been employed as glycosyl donors and acceptors[1–4] and also constitute a class of potential components of sugar-based amphiphiles and surfactants or sugar-modified polymers and polymer surfaces obtained by the copolymerization of a vinyl ether sugar with a bulk alkene (e.g., styrene or propylene, methyl methacrylate, vinyl acetate, or acrylonitrile).

Early examples of vinyl sugars are 6-*O*-vinyl-1,2:3,4-di-*O*-isopropylidene-D-galacto-pyranoside,[5] obtained in 58% yield by reaction of diacetone-galactose with acetylene in sodium hydroxide melt, and 3-O-vinyl-1,2:5:6-di-

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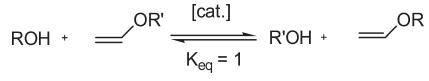
O-isopropylidene-D-glucofuranoside,[6] obtained in 22% yield by transetherification of diacetone-glucose catalyzed by mercuric acetate. More recently sugar vinyl ethers have been synthesized by preparation of the corresponding β-alkoxyvinyl sulfones followed by desulfonylation with Na/Hg amalgam.[7] Vinyl glycosides have also been prepared by transformation of vinyl acetates with Tebbe's reagent (yielding the corresponding isopropenyls),[1] by Hofmann degradation of *N*-2-trimethyl-ammonium-ethyl-*O*-glycosides,[8] through the use of selenium[9] or mercury reagents,[10] by photochemically induced rearrangement of 4-oxo-pentyl-glycosides,[11] and by acid-catalyzed alcohol elimination from mixed acetal glycosides.[12] The latter method is now also applicable to the synthesis of sugar vinyl ethers.[13] Recently we described a very *atom-efficient* and simple method for the transfer vinylation of a series of sugar substrates catalyzed by the air-stable complex (4,7-diphenyl-1,10-phenanthroline)$Pd(OAc)_2$ prepared in situ and using butyl vinyl ether as the sole reagent and solvent.[14–16] Equation (1) illustrates the reaction principle. The reaction is driven by providing either the sugar alcohol ROH or—as in the present case—the vinyl ether R′OCH=CH_2 in large excess.



(1)

We subsequently optimized this catalyst system by exchanging the counterion to the less coordinating trifluoroacetate, which reduces the reaction time required to attain equilibrium by a factor of up to eight, and successfully applied the catalyst to the synthesis of a variety of alkyl and allyl vinyl ethers.[17] Here we present the application of this optimized catalyst system to a representative series of protected monosaccharides with one, two, or three free hydroxyl functions resulting in the isolation of the corresponding vinyl glycosides and mono-, di-, or trivinyl ethers in moderate to good and in a few cases excellent yields, which may facilitate their incorporation into new sugar polymer formulations.

RESULTS AND DISCUSSION

The reaction protocol employed for the transfer vinylation was in all cases 2 mmol of sugar substrate, 0.04 mmol palladium trifluoroacetate (2 mol %), 0.04 mmol 4,7-diphenyl-1,10-phenantholine ligand, and 0.16 mmol triethyl amine dissolved in 400 mmol (200-fold excess) of butyl vinyl ether (BVE) to give a clear yellow solution, which was heated to 75°C in a sealed flask. After 5 to 12 h qualitative evaluation of TLC samples and quantitative GC of samples drawn in hourly intervals and monitored for the following 24 to 48 h showed that the equilibrium (Eq. (1)) had been established as indicated by

the constant relative concentrations of the n-butanol generated by the reactions. The presence of the auxiliary base triethyl amine prevents the formation of mixed ethyl butyl acetals catalyzed by free trifluoro-acetic acid formed in the catalytic cycle.[14,17]

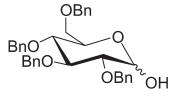
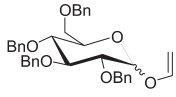
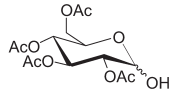
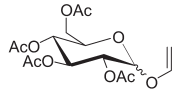
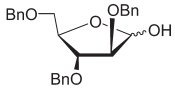
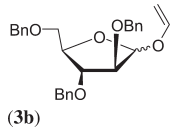
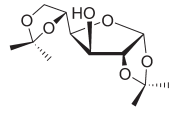
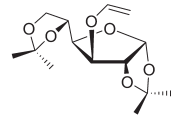
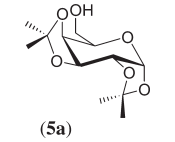
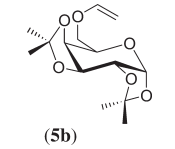
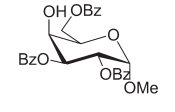
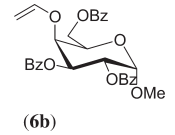
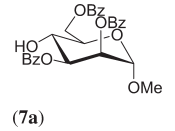
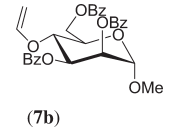
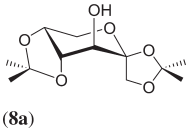
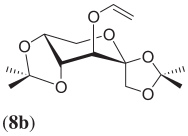
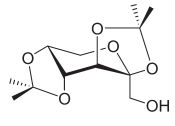
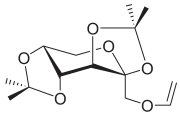
Table 1 summarizes the results obtained with this reaction protocol for the monohydroxyl substrates 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1a**), 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**2a**), 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**3a**), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**4a**), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside (**5a**), methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (**6a**), methyl 2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (**7a**), 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranoside (**8a**), and 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranoside (**9a**). Table 2 lists the results for the dihydroxyl substrates 1,2-*O*-isopropylidene-α-D-xylofuranoside (**10a**), 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**11a**), methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside (**12a**), methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (**13a**), phenyl 4,6-*O*-isopropylidene-β-D-glucopyranoside (**14a**), methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**15a**), phenyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**16a**), and the trihydroxyl substrate levoglucosan (**17a**).

The first five entries in Table 1 also compare the reaction times and yields to those achieved earlier with the nonoptimized catalyst.[14] Slightly higher yields were realized with the optimized protocol described above that employs a 200:1 rather than the 100:1 BVE-to-sugar ratio used earlier.[14]

With the exception of entry 8, 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranoside (**8a**), good to excellent yields (68%–95%) of mono vinyl ethers or vinyl glycosides are achieved with sugar substrates protected by acetals or benzyl ethers, while ester protection groups (acetate, benzoyl) result in moderate yields of 45% (**2b**, entry 2, Table 1) and 42% or 43% (**6b** and **7b**, entries 6 and 7, Table 1). As noted previously,[14] the presence of ester functionalities (**2a**, **6a**, **7a**, entries 2, 6, and 7) leads to a darkening of the reaction mixture to a more intense yellow, pointing to a coordinative interaction between either the carbonyl oxygen or possibly an ester enolate and the metal center. This can, however, not account for the lower yields with these substrates, as addition of more catalyst at equilibrium did not result in additional product formation excluding irreversible catalyst poisoning as a possible explanation.

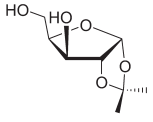
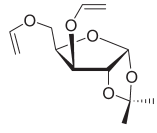
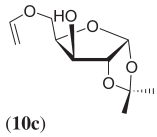
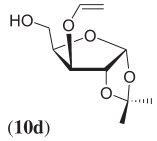
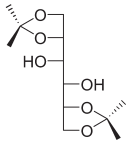
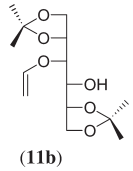
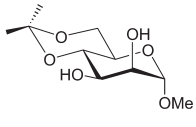
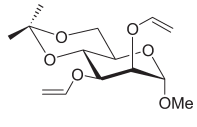
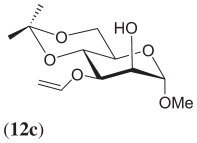
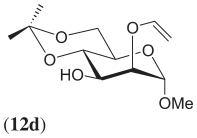
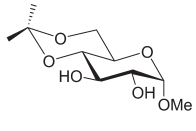
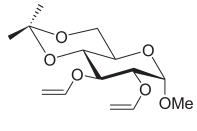
As the vinyl exchange Eq. (1) is an isodesmic reaction, the main factors governing the overall yields obtained with any of the substrates should be steric interactions within the vinylated products. However, the conformational variability and subtle structural complexity of the sugar substrates renders a general and predictive model for these interactions and quantitative rationalization of the resulting observed yields elusive. For the monohydroxyl substrates, the observed yields qualitatively scale with the steric accessibility of the free hydroxyl functions, which also correlates with the conformational flexibility of an attached vinyl group in the corresponding

Table 1: Vinylation of protected sugars with one free hydroxyl function.

Entry	Sugar substrate (#a)	Vinyl sugar (#b)	Yield with $Pd(OAc)_2$ (4–7 d)[a]	Yield with $Pd(O_2CCF_3)_2$ ≤12 h[a]
1	 (1a)	 (1b)	70% $\alpha/\beta = 9{:}1$[b]	74% $\alpha/\beta = 7{:}1$[b]
2	 (2a)	 (2b)	36% $\alpha/\beta = 6.5{:}1$[a]	45% $\alpha/\beta = 7{:}1$[a]
3	 (3a)	 (3b)	60% $\alpha/\beta = 4.4{:}1$[b]	68% $\alpha/\beta = 6{:}1$[b]
4	 (4a)	 (4b)	72%	81%
5	 (5a)	 (5b)	79%	95%
6	 (6a)	 (6b)	not det.	42%
7	 (7a)	 (7b)	not det.	43%
8	 (8a)	 (8b)	not det.	24%
9	 (9a)	 (9b)	not det.	73%

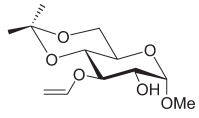
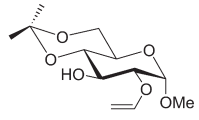
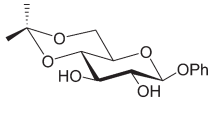
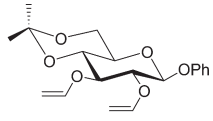
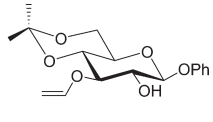
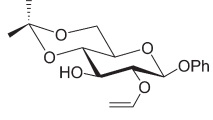
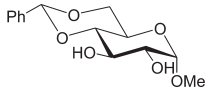
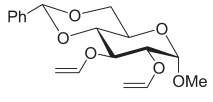
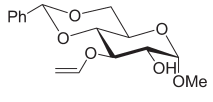
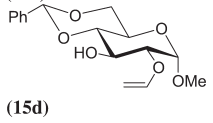
[a]Isolated yield.
[b]Anomeric ratios determined by ^{1}H NMR.

Table 2: Vinylation of protected sugars with two or three free hydroxyl functions.

Entry	Sugar substrate	Vinyl sugar	Yield and reaction time (h)[a]
1	 (**10a**)	 (**10b**)	51% (6 h)
		 (**10c**)	25% (6 h)
	Total yield of vinylated products: 82%	 (**10d**)	6% (6 h)
2	 (**11a**)	 (**11b**)	24% (6 h)
3	 (**12a**)	 (**12b**)	6% (12 h)
		 (**12c**)	30% (12 h)
	Total yield of vinylated products: 56%	 (**12d**)	20% (12 h)
4	 (**13a**)	 (**13b**)	5% (12 h)

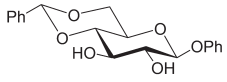
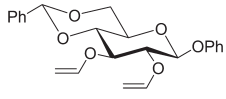
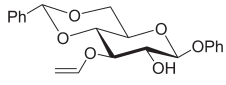
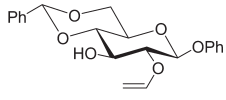
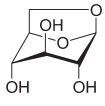
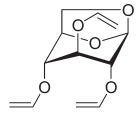
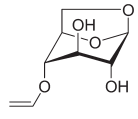
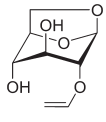
(*continued*)

Table 2: Continued.

Entry	Sugar substrate	Vinyl sugar	Yield and reaction time (h)[a]
		 (13c)	35% (12 h)
	Total yield of vinylated products: 50%	 (13d)	20% (12 h)
5	 (14a)	 (14b)	36% (24 h)
		 (14c)	21% (24 h)
	Total yield of vinylated products: 90%	 (14d)	33% (24 h)
6	 (15a)	 (15b)	24% (24 h)
		 (15c)	26% (24 h)
	Total yield of vinylated products: 66%	 (15d)	16% (24 h)

(*continued*)

Table 2: Continued.

Entry	Sugar substrate	Vinyl sugar	Yield and reaction time (h)[a]
7	 **(16a)**	 **(16b)**	13% (24 h)
		 **(16c)**	17% (24 h)
	Total yield of vinylated products: 44%	 **(16d)**	14% (24 h)
8	 **(17a)**	 **(17b)**	4% (6 h)
		 **(17c)**	13% (6 h)
	Total yield of vinylated products isolable as pure compounds: 43%	 **(17d)**	26% (6 h)

[a]Isolated yield.

product vinyl ether. For example, the lowest yield of 24% was obtained with 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranoside (**8a**) (entry 8, Table 1). A simple molecular model of **8b** suggests that the β-oriented conformationally fixed isopropylidene ring at the anomeric center hinders a free rotation of the vinyl group about the two oxygen-carbon bonds. The effect is also present in **9b**, but less pronounced, while the vinyl groups in the other sugar substrates listed in Table 1 can freely rotate. Given that the equilibrium constant in equation (1) is close to unity for all substrates, subtle differences in the entropy of the vinylated products originating from more or less restricted rotation of the vinyl group

compared to BVE could in fact account for the substantially different yields between the acetal protected vinyl sugars **4b**, **5b**, and **8b**.

Based on the results with mono-hydroxyl substrates where the best yields were achieved with acetal protecting groups (Table 1), the di- and trihydroxyl substrates investigated were limited to isopropylidene and benzylidene sugar derivatives. All possible mono- and di-vinylated products derived from compounds **10a** to **16a** (entries 1–7 in Table 2) could be separated and isolated by preparative flash column chromatography. The vinylation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**11a**), entry 2, gave the monovinylated product in 24% yield. Only one monovinylated product can be formed due to the symmetry of the starting sugar alcohol and the divinyl sugar product did not form. As with **8b**, a simple molecular model of **11b** suggests a severely hindered rotation of the vinyl group compared to BVE leading to the same explanation for the low yield discussed above. For the trihydroxyl substrate 1,6-anhydro-β-D-glucopyranoside (**17a**) (entry 8, Table 2, levoglucosan), the potential number of vinylated products is seven (three monovinylated, three divinylated, and one pervinylated) and their separation constitutes a major challenge. Of the seven products formed, we were able to purify three fractions: the trivinylated product **17b** and two separate monovinylated products **17c** and **17d**. A fourth fraction appeared to be a mixture of three divinylated products that in our hands could not be individually separated by chromatographic means (both flash and HPLC methods).

EXPERIMENTAL

General Procedure for the Transfer Vinylation of Protected Sugar Substrates Using Diacetone-α-D-glucopyranoside as an Example

In an oven-dried round bottom Schlenk flask, 4,7-diphenyl-1,10-phenanthroline (13.3 mg = 0.04 mmol) was added to butyl vinyl ether (40 g = 52 mL = 400 mmol) with stirring. Palladium(II) trifluoroacetate (13.3 mg = 0.04 mmol) was added, and the mixture left to stir at 75°C until all solids were dissolved and a clear bright yellow solution was obtained. To prevent acetylization, triethylamine (0.16 mmol) was added before addition of the sugar substrate. The sugar substrate, diacetone-α-D-glucopyranoside (520.5 mg = 2.0 mmol), was added to the mixture and allowed to react at 75°C until TLC and quantitative GC analysis for n-butanol revealed that equilibrium had been established (10 h). The reaction mixture was passed through a 10×2.5 cm plug of charcoal using ethyl acetate as the eluant (removes most of the catalyst) and concentrated under reduced pressure, and the residue was subjected to flash chromatography with various ratios of TLC pretested eluant combinations

(hexane, pentane, ether, ethyl acetate, acetonitrile, dichloromethane) yielding the pure vinylated sugars. See supporting information for details of the chromatographic separation and NMR data.

SUPPORTING INFORMATION

Sources of sugar starting materials. Detailed experimental procedures for synthesis and purification of vinylated products. Extensive collection of 1D and 2D $^{1}H/^{13}C$-NMR data and spectrum images for all new vinyl sugars synthesized (82 pages).

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