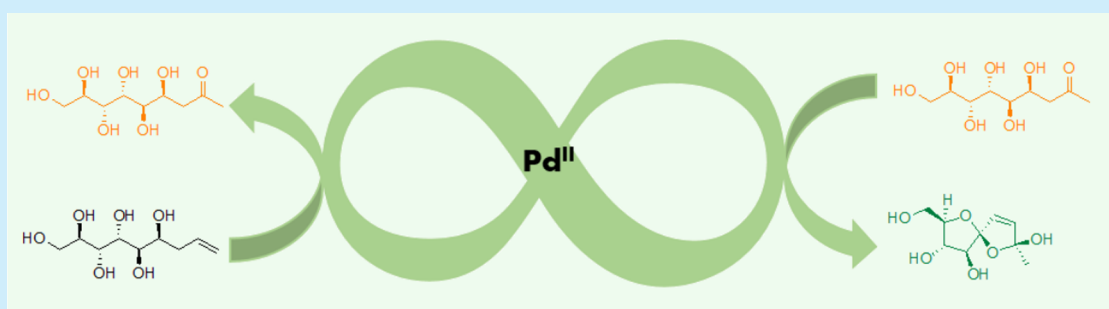


Tsuji–Wacker-Type Oxidation beyond Methyl Ketones: Reacting Unprotected Carbohydrate-Based Terminal Olefins through the “Uemura System” to Hemiketals and α,β -Unsaturated Diketones

Patrik A. Runeberg*¹ and Patrik C. Eklund*¹

Laboratory of Organic Chemistry, Johan Gadolin Process Chemistry Centre, Åbo Akademi University, Piispankatu 8, 20500 Turku, Finland

Supporting Information



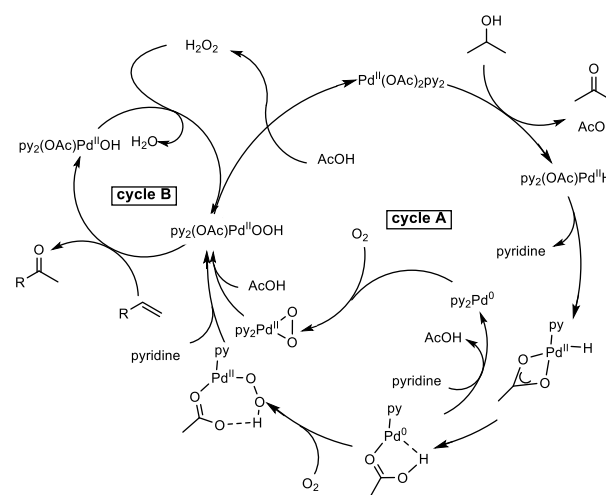
ABSTRACT: Aerobic Pd(OAc)₂/pyridine-catalyzed oxidation of unprotected carbohydrate-based terminal alkenes was studied. In accordance with previous reports, the initial reaction step gave methyl ketones. However, our substrates partially gave subsequent α,β -water elimination and alcohol oxidation to α,β -unsaturated 2,5-diketones. Upon increasing the pressure of O₂, the reaction was shifted toward formation of α,β -epoxy-2-ketones. The reactions were stereoselective and gave up to quantitative conversions. However, isolated yields were substantially lower because of the complexity of the product mixtures.

The Tsuji–Wacker oxidation, a lab-scale version of the Wacker oxidation, is a palladium(II)-catalyzed oxidation reaction for conversion of alkenes to ketones and aldehydes.^{1,2} It is an important reaction which has extensive applications in both the laboratory and industry.^{3,4} The method originally used PdCl₂ in combination with CuCl₂ in an oxygen atmosphere, but has later included also other Pd-species, such as Pd(OAc)₂. The mechanism and kinetics of the catalytic cycle has been extensively studied and reviewed.^{5–8}

A system for oxidation of alkenes to carbonyls by palladium(II) in the presence of H₂O₂ was reported in 1980.⁹ The proposed catalytic cycle formed Pd(II)OOH as the active species, which was regenerated by H₂O₂ (cycle B in Scheme 1). In a different context in 1998, Uemura et al. reported a novel aerobic Pd(OAc)₂-pyridine system for oxidation of alcohols to carbonyls and generating H₂O₂.^{10,11} The system used 2-propanol (IPA) for generating H₂O₂, releasing acetone as a side product (cycle A in Scheme 1). Furthermore, Pd(II)OOH was formed as a catalyst-species in the catalytic cycle. Thus, by adding an olefin to the reaction, Uemura et al. combined cycle A and cycle B for oxidation of olefins to carbonyls, as seen in Scheme 1.¹² The proposed mechanism of cycle A is based on studies reported by Stahl and Popp.¹³

Previously, Wacker-type palladium(II)-catalyzed oxidations of terminal olefins to α,β -unsaturated methyl ketones have also been reported. There, the elimination step, giving the α,β -

Scheme 1. Uemura System for Aerobic Wacker-Type Oxidation of Terminal Olefins



unsaturation, was shown to be acid promoted in cases where the initially formed methyl ketone product had a β -hydroxyl group. Aliphatic methyl ketone products, on the other hand,

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were suggested to form α,β -double bonds through catalytic α -hydride elimination.^{14–16} Here, we report the formation of α,β -unsaturated 2,5-diketones from carbohydrate-based poly-olefinic terminal olefins. To the best of our knowledge, no Wacker-type oxidations to these types of substrates have previously been reported.

The substrates 1–3 (Figure 1) were prepared at our laboratory according to literature procedures through metal-

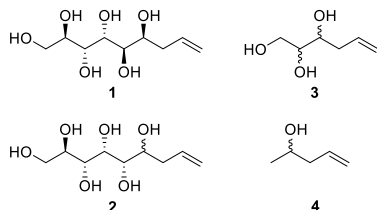
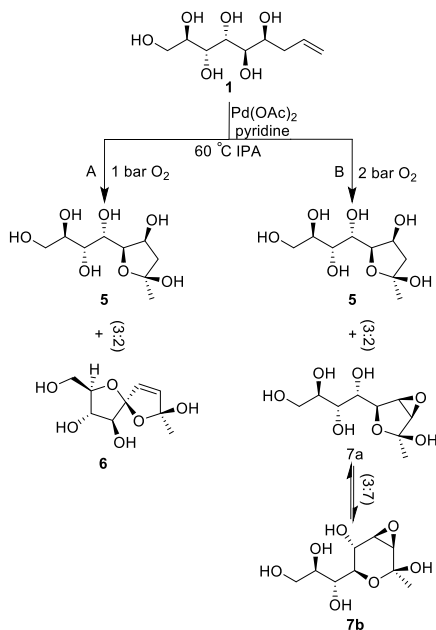


Figure 1. Substrate scope of allylated polyols.

mediated allylation of unprotected monosaccharides.^{17–19} Allylated D-mannose (**1**) was retrieved as pure *threo*-isomer through recrystallization in ethanol, while substrates **2** and **3** were used as stereoisomeric mixtures. 4-Penten-2-ol (**4**) was purchased from a commercial source as a racemic mixture. Substrate **4** was used in this study because of the simplicity of the structure.

We started our investigation using **1** as substrate in the “Uemura system”. The oxidation reaction in 1 bar molecular oxygen atmosphere for 20 h at 60 °C resulted in a quantitative conversion (observed by GC-MS and NMR) to two major products in a 3:2 ratio (Scheme 2, path A). The major product

Scheme 2. Aerobic Palladium-Catalyzed Oxidation of **1** in a 1 or 2 bar Molecular Oxygen Atmosphere



(**5**) was a hemiketal, and the other was a tetrahydrofuran-dihydrofuran bicyclic spiroketal (**6**). Both products were identified as single stereoisomers. When the reaction was performed in open air, instead of an atmosphere of molecular oxygen, the same products were again formed in a 3:2 ratio.

However, the reaction had a lower observed conversion of around 80%.

When the pressure of the oxygen atmosphere was increased to 2 bar, the reaction resulted in a quantitative conversion (observed by GC-MS and NMR) to three major products in a 15:7:3 ratio. The major product was **5** here also. However, the other products were epoxyderivatives of five- and six-membered rings (**7a** and **7b**) which were in equilibrium in a 3:7 ratio (Scheme 2, path B). Additionally, traces of degradation products were observed.

Higher pressure of O₂ only decreased the reaction selectivity. When reacted at 3 and 6 bar, the same products were formed as at 2 bar (**5**, **7a**, and **7b**) in a similar 15:7:3 ratio. However, in these cases broader mixtures of byproducts were seen in NMR analysis.

Also, when the solvent was changed to toluene, no reaction occurred (2 bar O₂). This clearly indicates that isopropanol is needed to initiate the catalytic cycles.

A proposed mechanism for the formation of products is presented in Scheme 3. The first step is the Tsuji–Wacker oxidation of the terminal alkene to the corresponding methyl ketone (**8**). The methyl ketone was partially ring closed to hemiketal **5**. Compound **8** also partially formed an enone intermediate (*E*- and *Z*-**9**) through α,β -elimination of water. In 1 bar oxygen, this intermediate may function as the substrate in the catalytic cycle A (seen in Scheme 1 for 2-propanol), forming an α,β -unsaturated diketone (**10**) which further ring closed to **6**. Palladium-catalyzed *E*-*Z*-isomerization of **9** combined with coordination to the adjacent carbonyl presumably locked **9** in *Z*-configuration during oxidation to **10**, and no *E*-isomer of **10** was observed.

At 2 bar oxygen atmosphere, epoxidation of **8** occurred, forming an epoxy-ketone (**11**) which further ring closed in equilibrium to products **7a** and **7b**. A logical explanation for the epoxide formation would be a nucleophilic attack, by H₂O₂ or other hydrogen peroxy species, on enone intermediate **9**. However, this mechanism is unlikely as the absolute configuration at the β -hydroxyl in **1** (*S*) remained in the formed epoxide. For further proof, the *erythro*-isomer of **1**, (*R*-conformation at β -position), gave an epoxide with the corresponding stereochemistry. (See the Supporting Information for more details.)

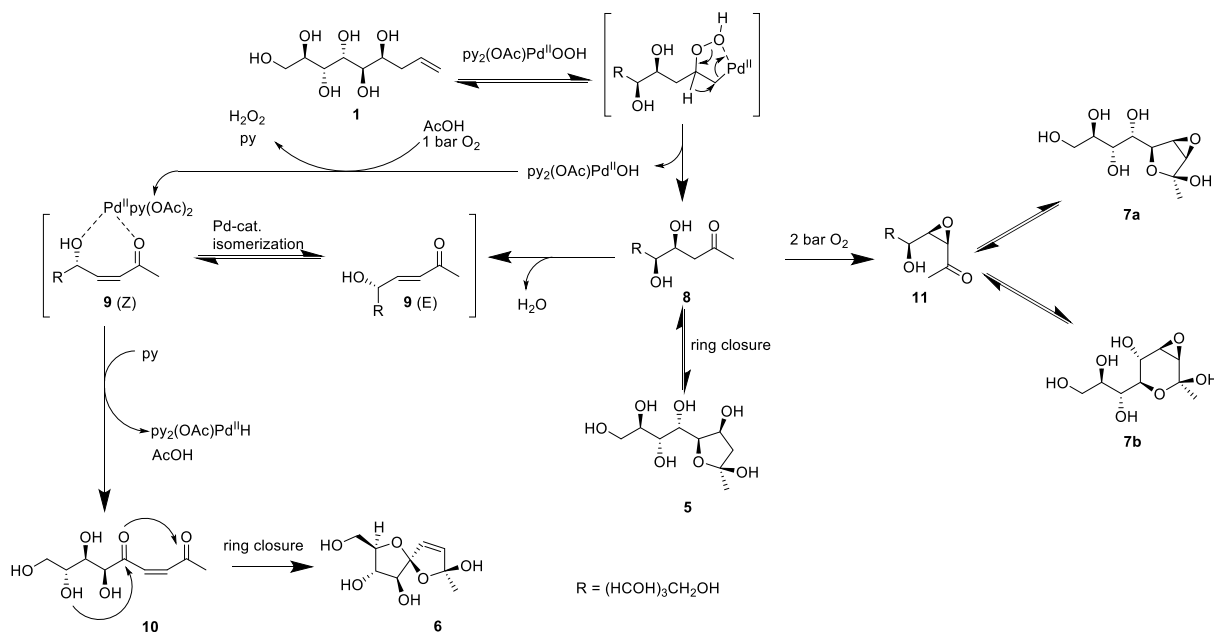
Previously, intramolecular Wacker cyclizations of alkene-ols have been reported under similar reaction conditions, forming ethers through nucleophilic attack by alcohols to C–C double bonds.²⁰ Although a similar pathway may have occurred at the double bond of a palladium-stabilized enolate-intermediate, to the best of our knowledge, no such mechanisms have previously been reported on enols. Therefore, a thorough mechanistic study is needed to fully understand the α -epoxidation step.

The reactions with **2**–**4** gave lower conversions compared to allylated D-mannose (Table 1). Also more byproducts were observed compared to **1**. This may be due to the racemic mixtures of **2**–**4**. Moreover, no other substrate formed the corresponding epoxides, even when the pressure of oxygen was increased to 2 bar. At this pressure **2**–**4** formed the same products as at 1 bar, only with higher reaction conversions.

The reaction of **3** distinguished from the others as the second major product (**14**) was formed through double water elimination of product **13**.

Substrate **4** gave the corresponding methyl ketone **15** as major product together with product **16**, which was formed

Scheme 3. Proposed Reaction Pathways for the Formation of Products

Table 1. Observed Conversions and Products after Oxidation at 1 and 2 bar Molecular Oxygen^a

substrate	0.3 eq Pd(OAc) ₂ , 0.6 eq pyridine IPA, 60 °C, 20 h 1 bar O ₂		0.3 eq Pd(OAc) ₂ , 0.6 eq pyridine IPA, 60 °C, 20 h 2 bar O ₂	
	observed conversion	major products (ratio)	observed conversion	major products (ratio)
	100%	 5 iy = 27% (3:2) 6 iy = 26%	100%	 5 iy = 17% (3:2) 7a + 7b iy = 22%
	50%	 12 iy = 0%^b (1:3) 6 iy = 10%	70%	 12 iy = 1%^b (2:3) 6 iy = 16%
	80%	 13 (1:1) 14	100%	 13 (2:3) 14
	15%	 15 (1:1) 16	35%	 15 (6:1) 16

^aiy, isolated yield after column chromatography of the crude reaction mixture. Where no isolated yield is given, the products were analyzed in a reaction mixture without further isolation. ^bProduct 12 could not be separated from product 6 and other byproducts by column chromatography. Also it was partially reacted to new mixtures of byproducts in the column.

through olefin migration. Only traces (<1%) of the corresponding olefin-ketone (3-penten-2-one) was detected.

As an observation, all ring-closed products (hemi- and spiroketals) were identified through NMR analyses in D₂O. We cannot exclude that the ring closing take place in the NMR samples because of the aqueous environment.

For isolation and unambiguous identification of the products, the reaction mixtures were purified through column chromatography using an ethyl acetate and methanol eluent system. Because of the complexity of the products and the equilibrium between different forms, the isolation and identification were difficult, and the isolated yields were substantially lower than the conversions. This was especially challenging for the isomers of product **12**, and only traces could be isolated.

For better separation, the reaction mixtures were also subjected to acetylation reactions prior to column chromatography. During the acetylations, all ring-closed products, aside from **6**, were opened and acetylated as the corresponding open-chain ketones. Products **7a** and **7b** gave a single open-chain epoxyketone. Products **5** and **12** underwent water elimination to α -unsaturated methyl ketones. The isolated yields were increased for all products, but because of water elimination, products **5** and **12** could not be retrieved through deacetylation of the isolated products. (See the [Supporting Information](#) for more details.)

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.9b02134](https://doi.org/10.1021/acs.orglett.9b02134).

Additional results, discussion, experimental procedures, characterization data, and NMR spectra for all novel compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: patrik.runeberg@abo.fi

*E-mail: paeklund@abo.fi

ORCID

Patrik A. Runeberg: 0000-0002-5636-2786

Patrik C. Eklund: 0000-0003-3040-5116

Notes

The authors declare no competing financial interest.

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