Communication

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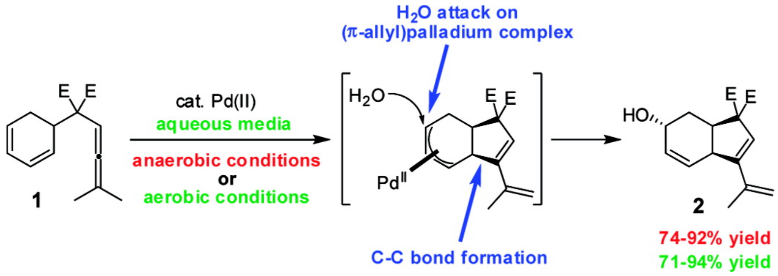

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Water as Nucleophile in Palladium-Catalyzed Oxidative Carbohydroxylation of Allene-Substituted Conjugated Dienes

Julio Piera, Andreas Persson, Xisco Caldentey, and Jan-E. Bäckvall*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

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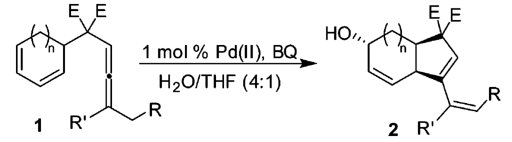
Water is an ideal solvent for chemical transformations in environmentally friendly and sustainable processes, and it offers the advantages of low cost and high safety. As a result, organic reactions in water have attracted considerable attention in recent years.[1] Although various palladium-catalyzed reactions in water are known, such as cross-coupling reactions,[2] Heck reactions,[3] allylic substitutions,[4] and oxidation of alcohols[5] and olefins,[3a,6] water is a poor nucleophile in such reactions, and synthetically useful examples of nucleophilic attack by water on (π-allyl)palladium species are still unprecedented.[7] Trost stated that "water is such a notoriously poor nucleophile in palladium-catalyzed reactions that it is an excellent solvent or cosolvent for such reactions".[8] This fact led Trost and co-workers to develop the use of triphenylsilanol[9] or carbonate[8] as water surrogates in attack on (π-allyl)palladium intermediates. In this paper, we report on an intramolecular carbohydroxylation of conjugated dienes where the C−O bond-forming reaction involves water attack on a (π-allyl)palladium intermediate.

Oxidation processes are important transformations in organic synthesis,[10] and catalytic oxidations where the terminal oxidant is either molecular oxygen or hydrogen peroxide have attracted considerable attention recently.[10,11] At present, there is a lack of efficient oxidative C−C bond forming reactions with molecular oxygen as the oxidant since these reactions are often associated with the formation of radicals, leading to side products from autoxidation. Examples of such aerobic oxidations in water are even more rare.[12] In the past few years, our group has reported on palladium(II)-catalyzed oxidative carbocyclization reactions of allene-substituted dienes[13] and enallenes.[14]

Herein we report on a palladium(II)-catalyzed oxidative carbohydroxylation of allene-substituted conjugated dienes in aqueous media. The transformation carried out formally constitutes a *trans*-1,4-carbohydroxylation of a conjugated diene and proceeds with high regio- and stereoselectivity (Scheme 1).

Scheme 1. Oxidative Carbohydroxylation of Allene-Substituted Dienes in Water



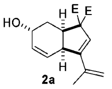
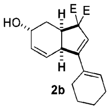
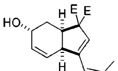
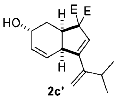
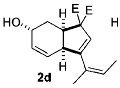
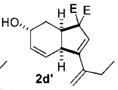
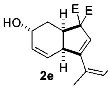
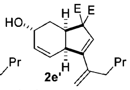
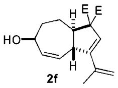
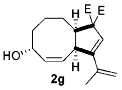
1 **2**

The requisite starting materials **1** were prepared as previously reported.[13] Reaction of **1a** with 2 equiv of *p*-benzoquinone (BQ) and 1 mol % of palladium trifluoroacetate ($Pd(TFA)_2$) in H_2O/THF 4:1 afforded **2a** in 85% yield.[15] When the reaction was performed in pure water, it proceeded very slowly, and after 24 h, only a 16% yield was obtained, the rest being unreacted starting material. This suggests that a small amount of organic solvent is required to dissolve the substrate, catalyst, and *p*-benzoquinone for obtaining a reasonable reaction rate.[16]

Next, we explored the reaction scope subjecting various substrates to the reaction conditions described above for the oxidative palladium-catalyzed carbohydroxylation of conjugated diene **1a** (Table 1, method A).

In the reaction, two new stereocenters are generated with complete stereocontrol with respect to the stereocenter already present in the starting material. Cyclohexadiene substrates **1a**−**e** and cyclooctadiene **1g** reacted to furnish *cis*-fused ring systems and *trans*-carbohydroxylation (>99% *trans*-add), whereas cycloheptadiene **1f** gave different selectivity with a *trans*-fused ring system and *trans*-carbohydroxylation (>99% *trans*-add). Conjugated dienes **1c**−**e**, where the substituents of the allene are nonsymmetric, afforded the corresponding products with a preference for formation of the product with the more substituted double bond (Table 1, entries 3−5). Substrates **2d** and **2e** were obtained as a mixture of *E*/*Z* isomers in a ratio 12:1 and 11:1, respectively.

Table 1. Palladium(II)-Catalyzed Oxidative Carbohydroxylation of **1** in Water[a]

entry	comp	product	yield (%)[b] / ratio method A	method B
1	**1a**	 **2a**	85^c 90^d	88^e
2	**1b**	 **2b**	83^c 89^d	81^e
3	**1c**	 **2c**  **2c'**	80^c **2c/2c'** 2:1	82^f **2c/2c'** 2:1
4	**1d**	 **2d**  **2d'** Method A: *E*/*Z* = 12:1 Method B: *E*/*Z* = 12:1	84^d **2d/2d'** 8:1	82^f **2d/2d'** 7:1
5	**1e**	 **2e**  **2e'** Method A: *E*/*Z* = 11:1 Method B: *E*/*Z* = 7:1	85^d **2e/2e'** 7:1	84^f **2e/2e'** 6:1
6	**1f**	 **2f**	90^c 92^d	91^e 94^f
7	**1g**	 **2g**	74^d	71^f

[a] Method A: cat. $Pd(TFA)_2$ and stoichiometric BQ was used. Method B: cat. $Pd(TFA)_2$, cat. BQ, cat Fe(Pc) under O_2 atmosphere was used. [b] Isolated yields. [c] The reactions were carried out on a 0.5 mmol scale with $Pd(TFA)_2$ (1 mol %) and BQ (2 equiv) in 4 mL of H_2O/THF (4:1) at rt for 9−12 h. [d] With 5 mol % of $Pd(TFA)_2$ and 4−6 h reaction time. [e] The reactions were carried out on a 0.2 mmol scale with $Pd(TFA)_2$ (1 mol %), BQ (5 mol %), and Fe(Pc) (1 mol %) under O_2 atmosphere in 1.5 mL of H_2O/THF (4:1) at rt for 24−48 h. [f] With 5 mol % of $Pd(TFA)_2$, 20 mol % of BQ, and 5 mol % of Fe(Pc) used in H_2O/THF (2:1) at rt for 24 h.

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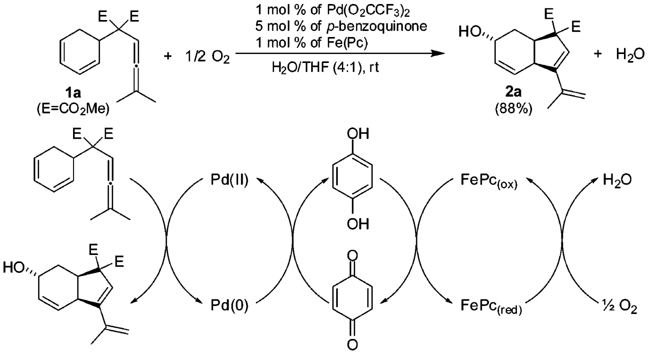
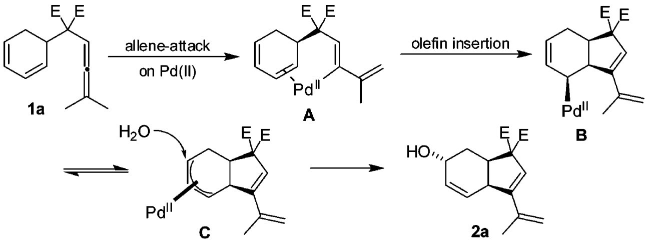
Scheme 2. Aerobic Oxidative Carbohydroxylation of Allene-Substituted Diene **1a**



Scheme 3. Oxidative Carbocyclization of Allene-Substituted Dienes



To further increase the synthetic utility of the procedure, the reaction was studied under aerobic conditions (Scheme 2). In the aerobic procedure, BQ is employed as an electron-transfer mediator in catalytic amounts and the hydroquinone (HQ) produced is continuously reoxidized to BQ by catalytic iron phthalocyanine (Fe(Pc))/O_2.[17] This procedure permits the oxidation of Pd(0) to Pd(II) by molecular oxygen under mild conditions. The aerobic oxidation of **1a** was performed in the presence of catalytic amounts of Pd(TFA)$_2$ (1 mol %), *p*-benzoquinone (5 mol %), and Fe(Pc) (1 mol %) in H_2O/THF (4:1) under O_2 atmosphere at room temperature, and the desired product **2a** was obtained in 88% yield with the same selectivity as the non-aerobic version. The reaction conditions for the aerobic oxidative carbohydroxylation were applied to the rest of the substrates with essentially the same outcome as in the non-aerobic version (Table 1, method B).

The mechanism of this reaction is similar to that of the oxidative carbocyclization of allene-substituted dienes **1** described previously.[13] Nucleophilic attack by the pendant allene of **1a** on the palladium(II) center gives vinylpalladium species **A**. Subsequent insertion of the olefin into the Pd−C$_{\text{vinyl}}$ bond leads to a (π-allyl)palladium complex (**C**), which is attacked by water from the *exo* face to yield **2a** (Scheme 3).[18−20] The high reactivity of the π-allyl complex **C** toward water attack is remarkable and may be explained by the coordination of the bicyclic hydrocarbon ligand from the *endo* face. Molecular modeling and DFT calculations[21] indicate that the terminal double bond can coordinate to palladium in **C**, and this would stabilize the transition state for nucleophilic attack and enhance the reactivity of the *endo* π-allyl complex (see Supporting Information).

Despite the increasing number of palladium-catalyzed transformations in aqueous media in the past few years, there are only limited examples of palladium-catalyzed aerobic oxidations with carbon−carbon bond formation in water. The reaction reported herein provides an example of a palladium-catalyzed oxidation leading to C−C bond formation in water with subsequent water attack on a (π-allyl)palladium intermediate. The extension into an aerobic version enhances the utility of the present method.

Acknowledgment. We are grateful for financial support from the Swedish Research Council, the Berzelius Center EXSELENT, and the Ministerio de Educación y Ciencia of Spain.

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

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(15) For the optimization of the reaction, see the Supporting Information.
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(18) The stereochemistry of compound **2a** was established by converting it to the known acetate (see ref 13a).
(19) One reviewer suggested an alternative mechanism via Pd(II)-promoted addition of H_2O into the 1,3-diene to form a (π-allyl)Pd intermediate followed by allene insertion. Attempts to generate such a (π-allyl)Pd intermediate from a 1,3-cyclohexadiene analogue to **1a**, where *n*-Bu is attached to the CHE$_2$ group in place of −CH═•═CMe$_2$, failed. Under stoichiometric conditions similar to those used in the catalytic reaction, there was no reaction with neither Pd(OAc)$_2$ nor Pd(TFA)$_2$. Further support for the mechanism in Scheme 3 was provided by monitoring the stoichiometric reaction of **1a** with Pd(TFA)$_2$ in THF-d_8 by ^{1}H NMR, which shows that the first step is formation of vinyl complex **A** (see Supporting Information). Insertion of the diene to give allyl intermediates requires BQ, and C−O bond formation is the last step of the sequence.
(20) Attack by CF_3COO^- on **C** and hydrolysis to give the **2a** is not a likely pathway since the use of Pd(OAc)$_2$ as catalyst gave 80% yield of **2a**, and the allylic acetate is completely stable under the reaction conditions.
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