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Palladium(II)-catalyzed ring expansion of a 1-alkenyl cyclopentanol

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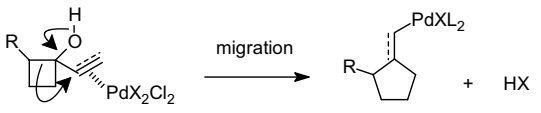
Abstract—7,7-Dimethyl-2-methylenenorbornan-1-ol, a strained bicyclic 1-alkenyl cyclopentanol, undergoes Wagner–Meerwein rearrangement to fenchone under treatment with a catalytic amount of $PdCl_2(PPh_3)_2$ in refluxing *N*-methylpyrrolidin-2-one. The described reaction constitutes the first example of the palladium(II)-catalyzed ring expansion of 1-alkenyl cyclopentanols to the corresponding cyclohexanones.

Ring-expansion reactions have a great interest in synthetic organic chemistry since they provide efficient tactics for the preparation of biologically active natural products and drugs.[1] In this sense, the palladium(II)-promoted ring-expansion reaction of 1-alkenyl or 1-alkynyl cyclobutanols to cyclopentanones is a well-known process, which has been successfully used for the construction of several interesting natural products with frameworks based on five-membered rings.[2] The reaction takes place by an initial required formation of an alkene or alkyne π-complex before migration of a (generally secondary) carbon (Scheme 1).

Related 1-alkenyl or 1-alkynyl cyclobutanol expansions can be also realized using palladium(0) catalysts. In these cases the reaction is generally initiated by a carbopalladation, using a Heck-type reaction with aryl halides,[3] or generating a π-allylpalladium intermediate by different ways (including also Heck-type reactions).[4]



Scheme 1. Palladium(II)-promoted ring expansion of 1-alkenyl or 1-akynyl cyclobutanols.

All this palladium-based ring-expansion methodology can also be applied to other strained rings, such as the three-membered ones.[5] Thus, 1-alkenyl and 1-alkynyl cyclopropanols have been expanded to the corresponding cyclobutanones by treatment with palladium(II)[5b,c] or palladium(0)[5a,d] catalysts. Unfortunately, the related expansion of less strained five-membered rings are unusual, with the exceptions of the Nagao's palladium(0)-catalyzed ring expansion of 1-(1-methoxyallenyl)cyclopentanols, via π-allylpalladium intermediates,[6a] and a more complex palladium(0)/phosphine-catalyzed ring expansion of 1-acryloylcyclopentanols of the same author.[6b]

Our approach to find a palladium(II)-catalyzed ring-expansion reaction of 1-alkenyl cyclopentanols is performed by the use of 7,7-dimethyl-2-methylenenorbornan-1-ol (**1a**) or 3,3-dimethyl-2-methylenenorbornan-1-ol (**1b**) as the starting 1-alkenyl cyclopentanols (Fig. 1), since such strained 1-alkenyl cyclopentanols have been demonstrated to exhibit a great tendency for undergoing cationic Wagner–Meerwein rearrangement to the corresponding cyclohexanones (2-norbornanones) under

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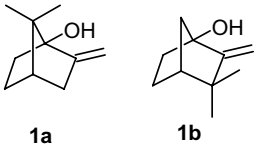
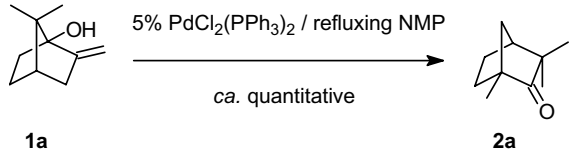


Figure 1. Selected starting strained 1-alkenyl cyclopentanols.

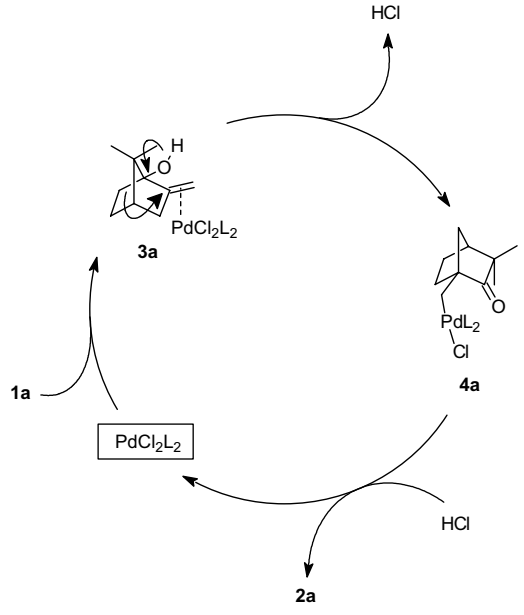
stoichiometric treatment with adequate electrophiles.[7] Additionally, both starting 1-alkenyl cyclopentanols **1a** and **1b** can be easily obtained from fenchone and camphor, respectively.[7]

We have found that 1-alkenyl cyclopentanol **1a** is able to undergo Wagner–Meerwein rearrangement to fenchone (**2a**) after treatment with a catalytic amount of $PdCl_2(PPh_3)_2$ in refluxing *N*-methylpyrrolidin-2-one (NMP) (Scheme 2), whereas analogue **1b** remains unalterated after the same palladium(II) treatment.[8]

The rearrangement shown in Scheme 2 constitutes the first example of a palladium(II)-catalyzed ring-expansion reaction of a 1-alkenyl cyclopentanol to the corresponding cyclohexanone (see catalytic cycle in Scheme 3). The unreactivity of **1b** can be attributed to the difficulty of such substrate to coordinate the palladium(II) catalyst and to form the corresponding initial required π-complex. This difficulty is due to the high steric hindrance existing around the carbon–carbon double bond of **1b** exerted by the C(3)-*gem*-dimethyl group (cf. **1a** and **1b** in Fig. 1), as well as the also high steric volume of the palladium-species bearing phosphine ligands.



Scheme 2. Palladium(II)-catalyzed ring-expansion reaction of 1-alkenyl cyclopentanol **1a**.



Scheme 3. Catalytic cycle.

In summary, the first palladium(II)-catalyzed ring-expansion reaction of a 1-alkenyl cyclopentanol has been described. Further investigations on the possible synthetic application of palladiated intermediate **4a** for the preparation of new enantiopure C(10)-substituted fenchones,[9] as well as on the possible extension of such rearrangement to other related bicyclic alcohols, are in progress.

Acknowledgements

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8. A solution of **1a** or **1b** (0.100 mmol) and $PdCl_2(PPh_3)_2$ (0.005 mmol) in NMP (1.5 mL) was refluxed for 6 h under argon atmosphere. After that, the reaction mixture was analyzed by GC/MS, showing the quantitative conversion of **1a** to **2a**, as well as the unreactivity of **1b**.
9. On the synthetic importance of enantiopure C(10)-substituted fenchones, see: García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron: Asymmetry* **2001**, *12*, 3325, and references cited therein.