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$FeCl_3 \cdot 6H_2O$-catalyzed synthesis of substituted *cis*-2,6-tetrahydropyrans from ζ-hydroxy allylic derivatives

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ABSTRACT

A highly diastereoselective iron-catalyzed synthesis of substituted *cis*-2,6-tetrahydropyrans from ζ-hydroxy allylic derivatives is described. The $FeCl_3 \cdot 6H_2O$-induced epimerization of the formed 2-alkenyl 6-substituted tetrahydropyrans is the key reaction to account for the high diastereoselectivities observed.

1. Introduction

Substituted tetrahydropyrans (THPs) are of outstanding importance as they are ubiquitous motifs embedded in biologically relevant natural products, including antitumoral agents (Fig. 1).

As a consequence, organic chemists need efficient and complementary methods in order to build substituted THPs. A wide array of methods has been developed and some extensive reviews give an excellent overview of the different possibilities.[1] Among the existing methods to form tetrahydropyran units, the metal-catalyzed C–O bond formation is an attractive one.[1c] For our part, we focused our attention on the metal-catalyzed heterocyclization of δ-hydroxy alkenes **A** bearing an allylic leaving group. Such reactions have been reported to deliver *cis*- or *trans*-2,6-disubstituted THPs **B** depending on the conditions used (Scheme 1).

Palladium chemistry widely rules the field of δ-hydroxy alkenes heterocyclizations.[2] Two different modes of action are mainly exploited: the electrophilic character of Pd(II) complexes and the ability of Pd(0) to form π-allylic complexes.

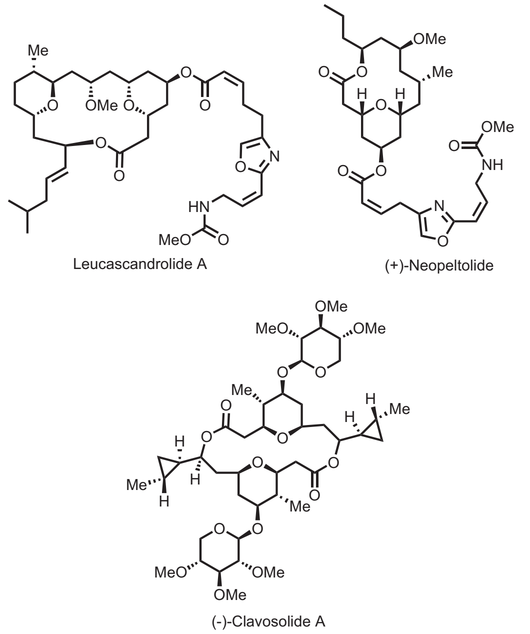

Fig. 1. Examples of natural products incorporating THP subunits.

When allylic acetates, phosphonates or carbonates, such as **C** (Scheme 2) are treated with a catalytic amount of Pd(0) complex, a π-allyl complex intermediate is produced and can be trapped intramolecularly by a δ-hydroxyl group to form a C–O bond according to a favored 6-*exo* ring-closure. In the latter process, the configuration of the newly created stereocenter is determined by the one of the initial leaving group. Indeed, during the formation of THPs **D**, the palladium preferentially coordinates to the less-hindered face of the double bond opposite to the allylic leaving

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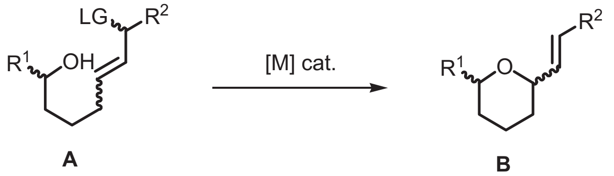
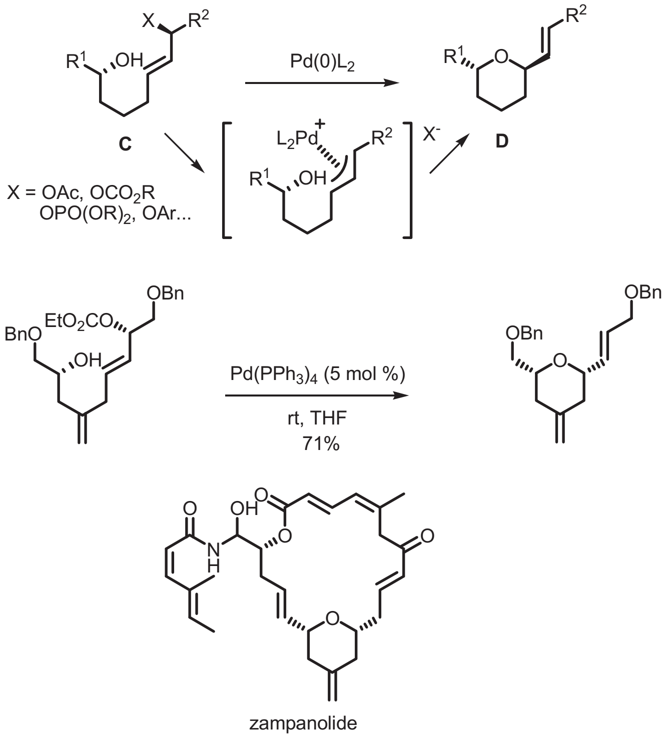


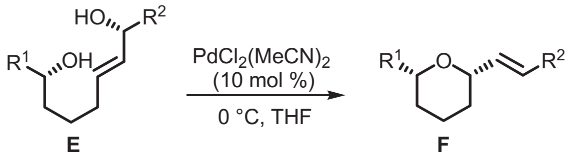
Scheme 1.



Scheme 2.

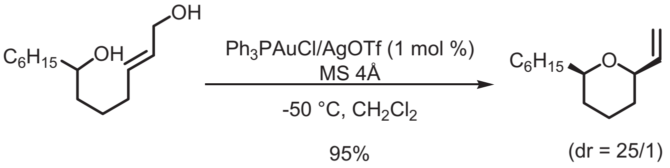
group thus forming a π-allyl cation. The δ-hydroxyl group then adds to the π-allyl cation on the opposite face to the palladium.[3] Such Pd(0)-catalyzed cyclization has been applied to the diastereoselective synthesis of a subunit of zampanolide (Scheme 2).[4]

The other strategy to form THPs exploits the electrophilic character of Pd(II) catalysts to generate π-complexes with double bonds, that can undergo an intramolecular nucleophilic addition of a δ-hydroxyl group.[5] In the presence of $PdCl_2(CH_3CN)_2$, diols of type **E** afford diastereoselectively THPs **F** with an excellent 1,3-chirality transfer (Scheme 3).[5e] The metal is first coordinated to the allylic hydroxyl group, which directs the formation of the π–Pd(II) complex on the same face of the double bond. Then, a *syn*-oxypalladation involving the δ-hydroxyl group occurs and a final *syn*-elimination can account for the perfect 1,3-chirality transfer.



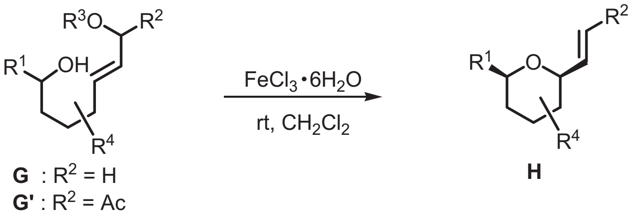
Scheme 3.

In 2008, Aponick et al. reported that a cationic gold complex, generated from $Ph_3PAuCl/AgOTf$, was able to catalyze the cyclization of 1,7-monoallylic diols to provide THPs in good yields.[6,7] When 2,6-THPs were formed, a good diastereoselectivity was observed in favor of the 2,6-*cis*-diastereomers (Scheme 4). From a mechanistic point of view, the authors proposed that the Au(I) complex activates the allylic alcohol by coordination of the oxygen and that the reaction proceeds via a S_N2' pathway.[8]



Scheme 4.

For our part, we have recently shown that $FeCl_3 \cdot 6H_2O$, an inexpensive and eco-friendly catalyst, was able to induce the cyclization of ζ-hydroxy allylic alcohols **G** and ζ-hydroxy allylic acetate derivatives **G′** to afford substituted *cis*-2,6-THPs **H** (Scheme 5).[9] Herein, we would like to report a full account of our results.



Scheme 5.

2. Results and discussion

2.1. Preparation of ζ-hydroxy allylic alcohols and derivatives G, G′

Most of the diols **G** were synthesized by utilizing a cross-metathesis reaction catalyzed by Grubbs–Hoveyda catalyst (**G**–**H**) between δ-acetoxy olefins **1a**–**d** and allylic acetates **2a** or **2b**. A subsequent methanolysis of the resulting di-acetates delivered the expected diols **3a**–**e**, which were obtained as 1/1 mixtures of the *cis*- and *trans*-diols (Table 1). It is worth mentioning that the cross-metathesis product of acetates **1c** and **2b** (Table 1, entry 4) was partially isomerized during the purification on silica gel, affording two regioisomers **3d** and the ϵ-hydroxy alkene **3d′**.[10]

A cross-metathesis involving acetate **1c** and 2-methyl-3-buten-2-ol, followed by a methanolysis, afforded diol **3f** (Scheme 6, Eq. 1). A cross-metathesis between unsaturated acetate **1c** and methyl vinyl ketone followed by a Luche reduction and a methanolysis of the acetate provided diol **3g** (Scheme 6, Eq. 2).

Both diols **3h** and its (*Z*)-isomer **3i** were prepared from the unsaturated protected alcohol **4**. The **G**–**H**-catalyzed cross-metathesis between **4** and **2b** followed by TBAF cleavage of the silyl ether afforded diol **3h** in 23% overall yield (Scheme 7). In order to access the (*Z*)-isomer **3i**, an ozonolysis was first performed on **4**. The resulting aldehyde was submitted to a Corey–Fuchs reaction and after addition of mesitaldehyde, the expected alkyne was isolated. The triple bond was partially reduced (H_2, Pd/Lindlar), affording (*Z*)-diol **3i** after cleavage of the silyl ether (28% overall yield) (Scheme 7).

Hydroxy acetates **3j**–**l** were prepared from δ-unsaturated alcohols **5a**, (1*S**,3*R**)-**5b** and (1*S**,3*S**)-**5b** after a cross-metathesis reaction with allylic acetate **2a** (Scheme 8).