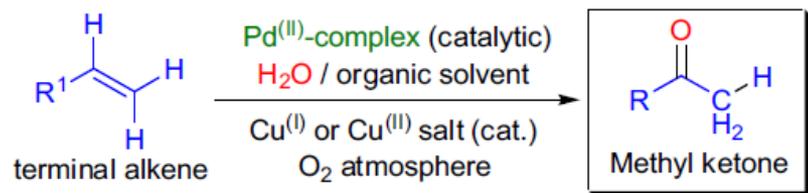


# **Wacker Oxidation**

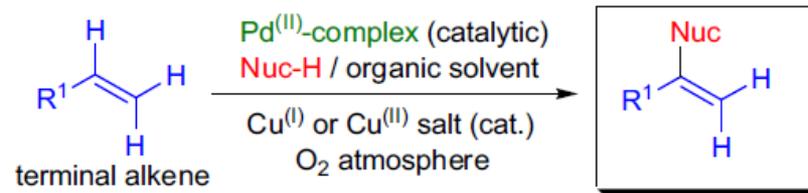
**(Tsuji-Wacker Oxidation)**

# Introduction

Wacker oxidation:



Wacker-type oxidation:

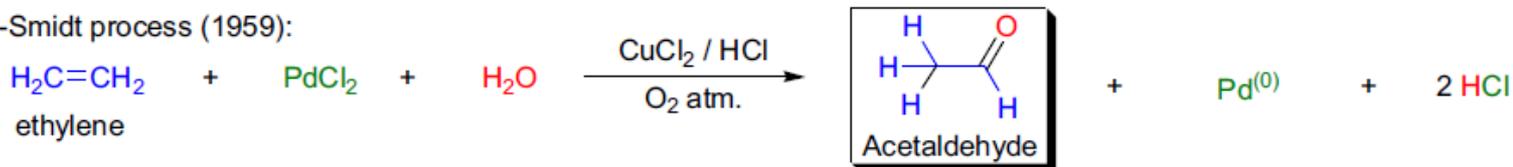


$\text{R}^1$  = alkyl, substituted alkyl;

1. The first report of the oxidation of ethylene with  $\text{PdCl}_2$  in an aqueous solution in 1894.

2. Wacker-Smidt process

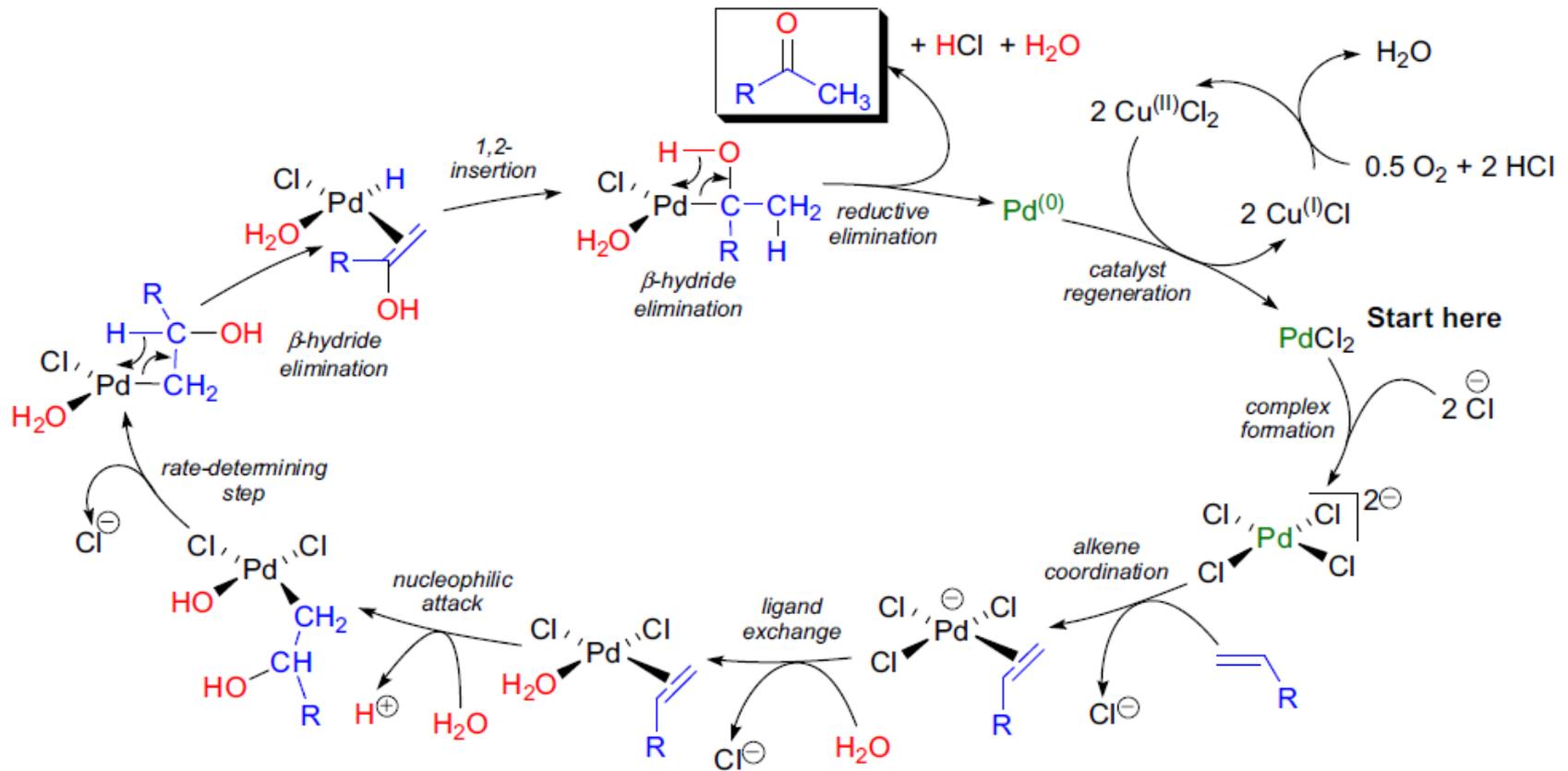
Wacker-Smidt process (1959):



3. Tsuji applied the conditions for selective oxidations of terminal olefins with multiple functional groups, and demonstrated its utility in synthesis of complex substrates in 1976.

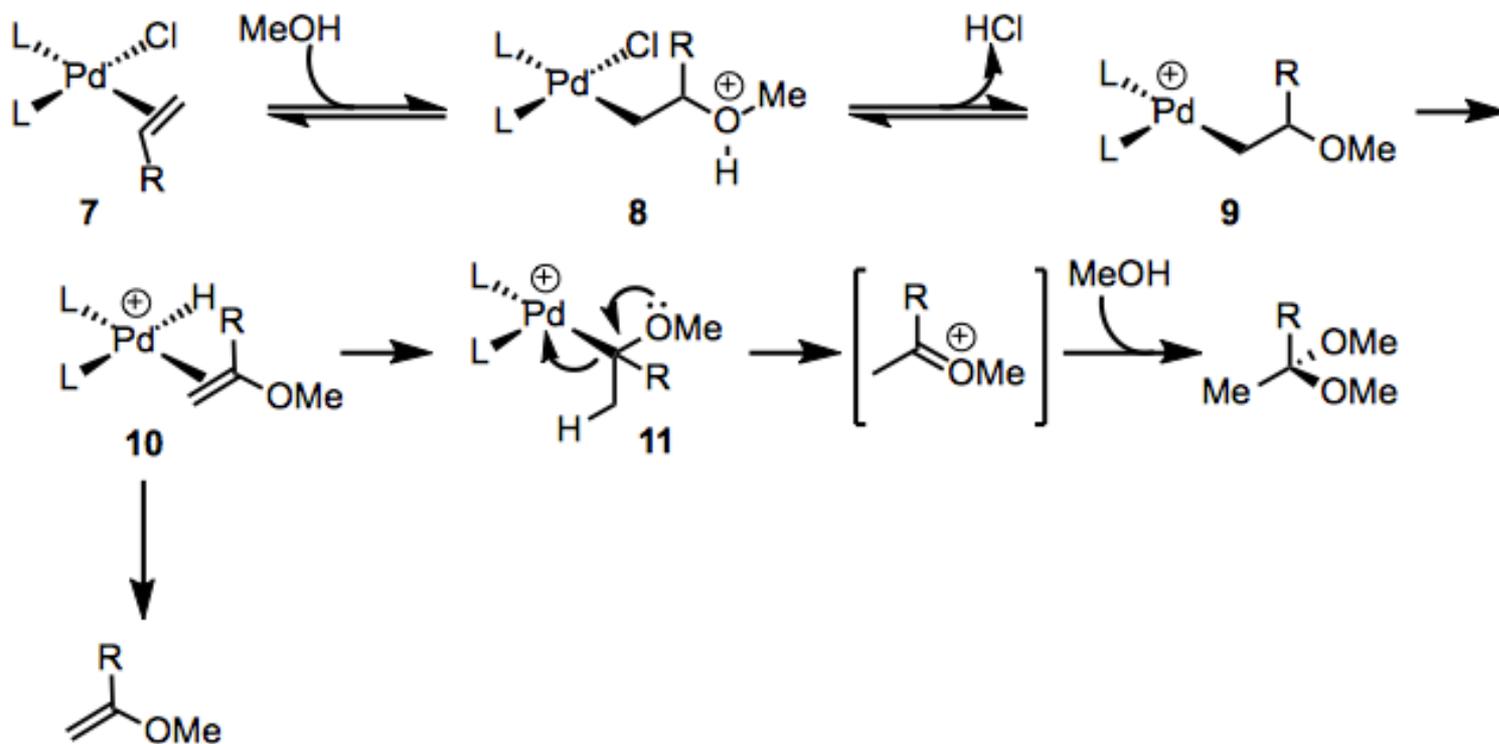
# Mechanism

## Water Nucleophile



# Mechanism

## Alcohol Nucleophile

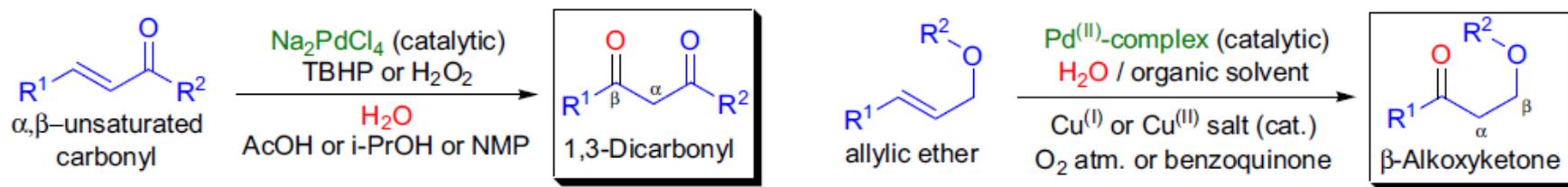


# General Features

1. The reaction is carried out in an aqueous medium in the presence of HCl;
2. Terminal alkenes react much faster than internal or 1,1-disubstituted alkenes and they are almost exclusively converted to the corresponding methyl ketones;
3. Terminal alkenes can be viewed as masked ketones for synthetic purposes;
4. Under the reaction conditions, internal alkenes are not oxidized to any appreciable extent;

# General Features

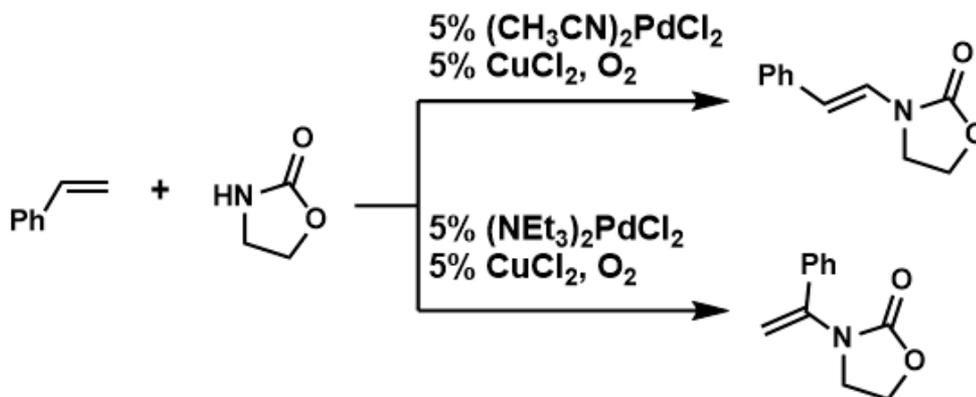
- $\alpha,\beta$ -unsaturated ketones and esters are oxidized regioselectively to the corresponding  $\beta$ -keto compounds using catalytic amounts of  $\text{Na}_2\text{PdCl}_4$  and TBHP or  $\text{H}_2\text{O}_2$  as co-oxidants;
- Allylic and homoallylic ethers are regioselectively oxidized to give the corresponding  $\beta$ - and  $\gamma$ -alkoxyketones;



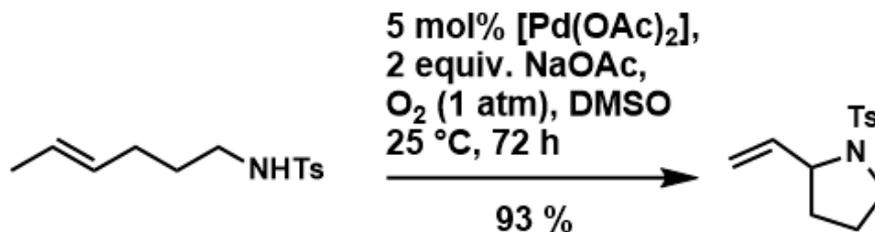
$\text{R}^1$  = alkyl, substituted alkyl;  $\text{R}^2$  = alkyl, aryl, O-alkyl

# General Features

7. When the oxidation is carried out in the presence of nucleophiles other than water, the process is called the *Wacker-type oxidation*, which can take place both inter and intramolecularly.



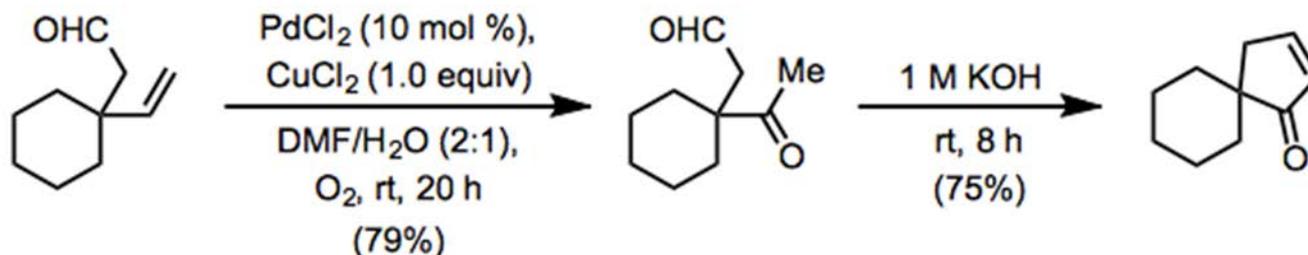
*J. Am. Chem. Soc.* 127 (50): 17888–17893



*J. Org. Chem.* 61 (11): 3584–3585

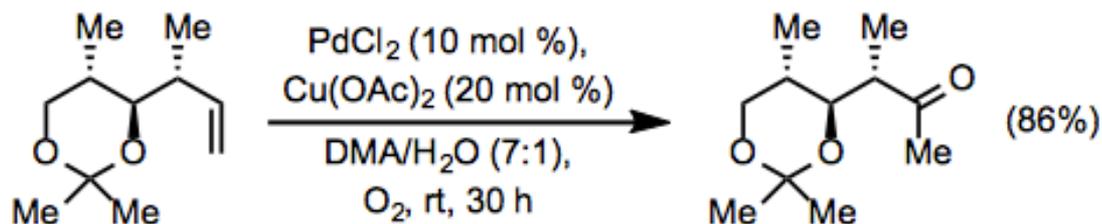
# Scope and Modifications

1. Wacker oxidation followed by intramolecular aldol condensation is a convenient method for the rapid synthesis of carbocycles.



*J. Indian Chem. Soc.* 1999, 76, 521.

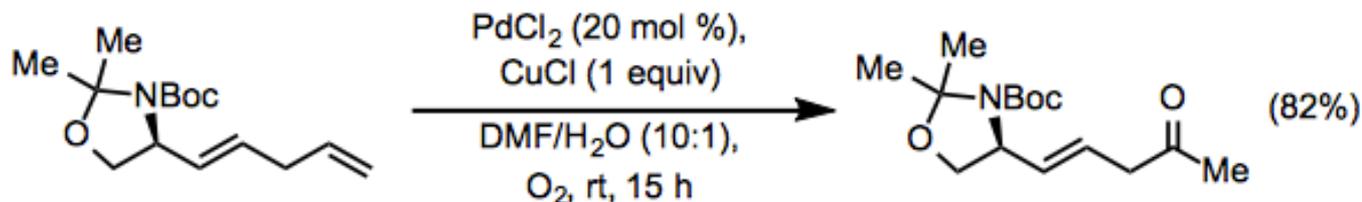
2. The original Wacker conditions can present problems for substrates containing acid-sensitive functionality, such as acetals and silyl ethers. To mitigate this issue, a method employing copper(II) acetate has been developed. Some acid sensitive groups are able to withstand the milder acetic acid generated by this method.



*Tetrahedron Lett.* 1998, 39, 8765.

# Scope and Modifications

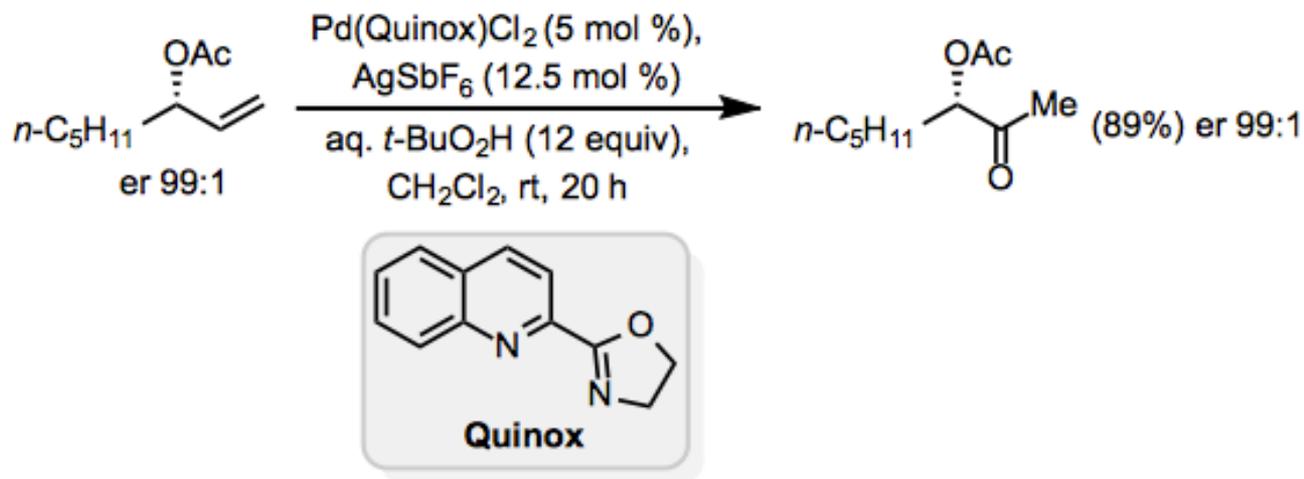
3. Unprotected amines coordinate strongly to palladium and thus cause problems for Wacker oxidations. Amines protected with electron-withdrawing substituents often do not interfere in Wacker oxidations, although they may participate in aza-Wacker cyclizations if appropriately positioned in the substrate.



*Tetrahedron: Asymmetry* 2000, 11, 3759.

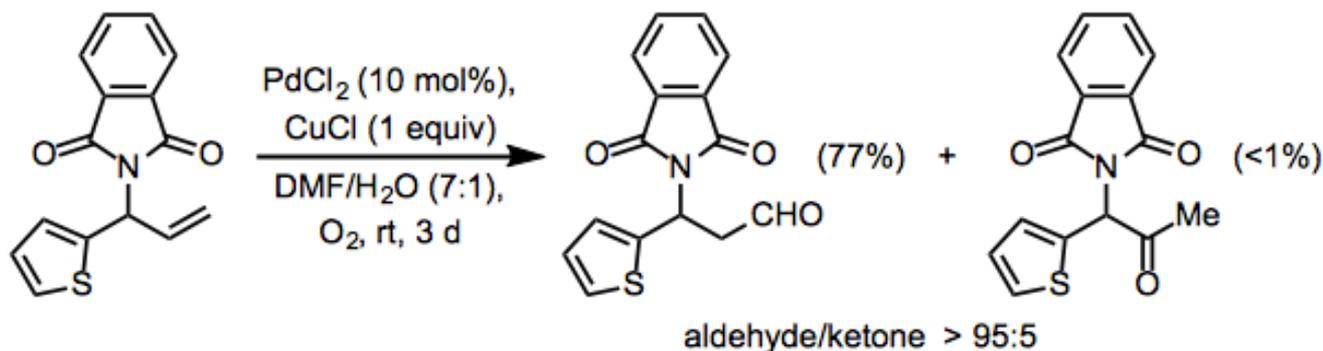
# Scope and Modifications

4. Under standard Tsuji-Wacker conditions, unprotected allylic alcohols form mixtures of methyl ketone and aldehyde products. The catalyst Pd(Quinox)Cl<sub>2</sub> was developed to allow allylic alcohols to react selectively in the presence of this catalyst to afford methyl ketones. *tert*-Butyl hydroperoxide (TBHP) is used as the oxygen source in this reaction.



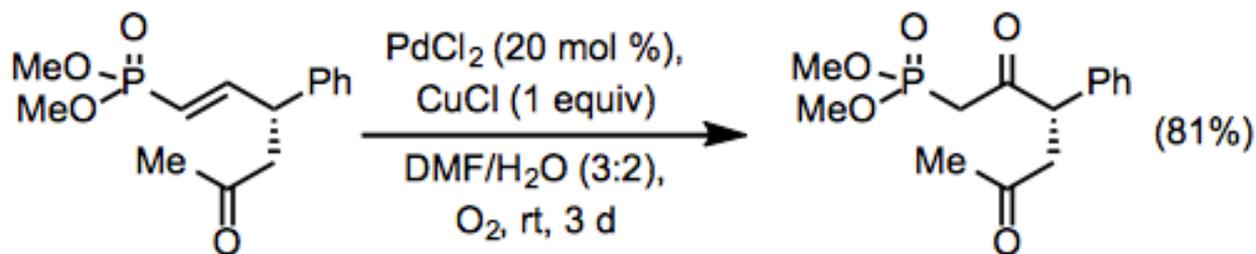
# Scope and Modifications

5. Protected allylic amines generally give higher yields of aldehyde than comparable protected allylic alcohols; These results suggest that coordination of palladium to the Lewis base is responsible for the formation of aldehydes. Using a **phthalimide** group in the allylic position, the Wacker oxidation may be rendered completely selective for aldehydes



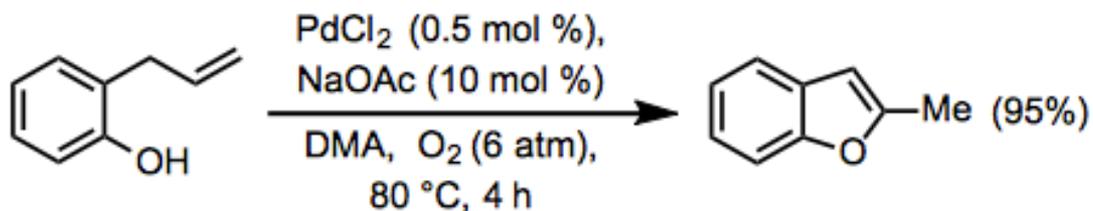
# Scope and Modifications

6. Site selectivity in reactions of internal alkenes is low unless an allylic or homoallylic Lewis base is present in the substrate. Electron-withdrawing groups can direct oxidation to the  $\beta$  position of the alkene, but relatively high catalyst loadings are required.



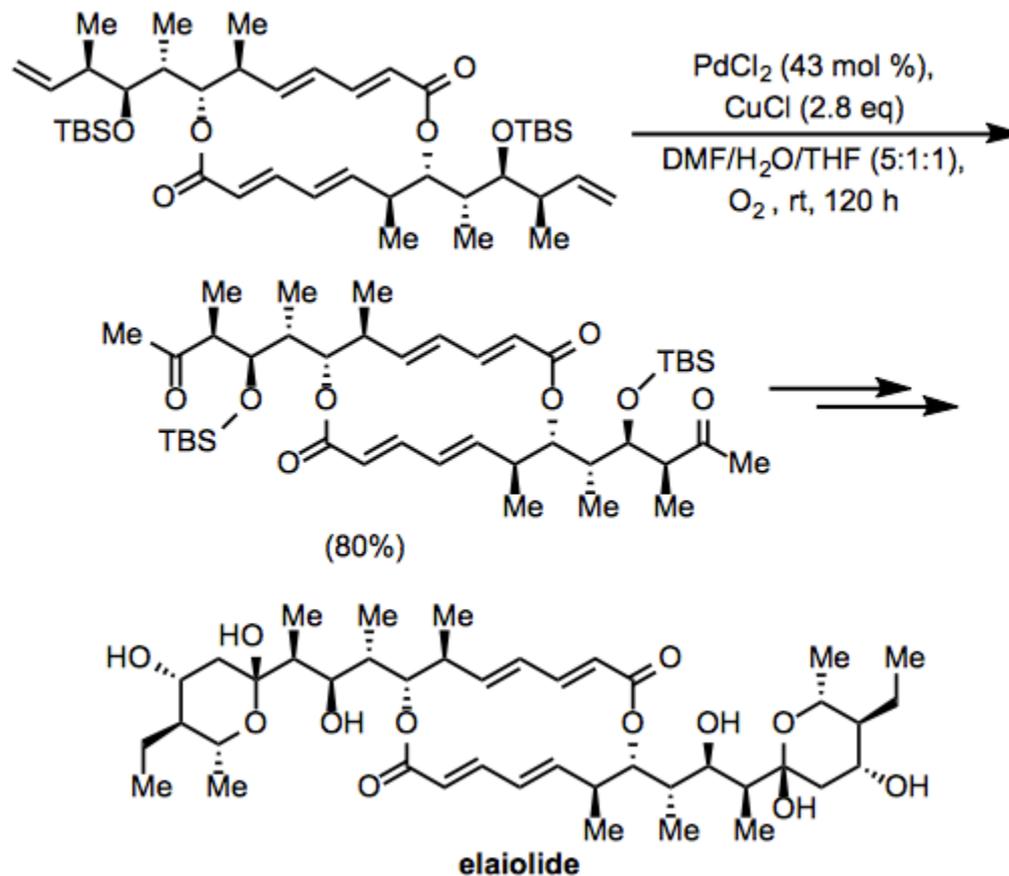
# Scope and Modifications

6. When an appropriately situated nucleophile is present in the substrate, Wacker cyclization may occur to yield an allylic or vinylic ether.



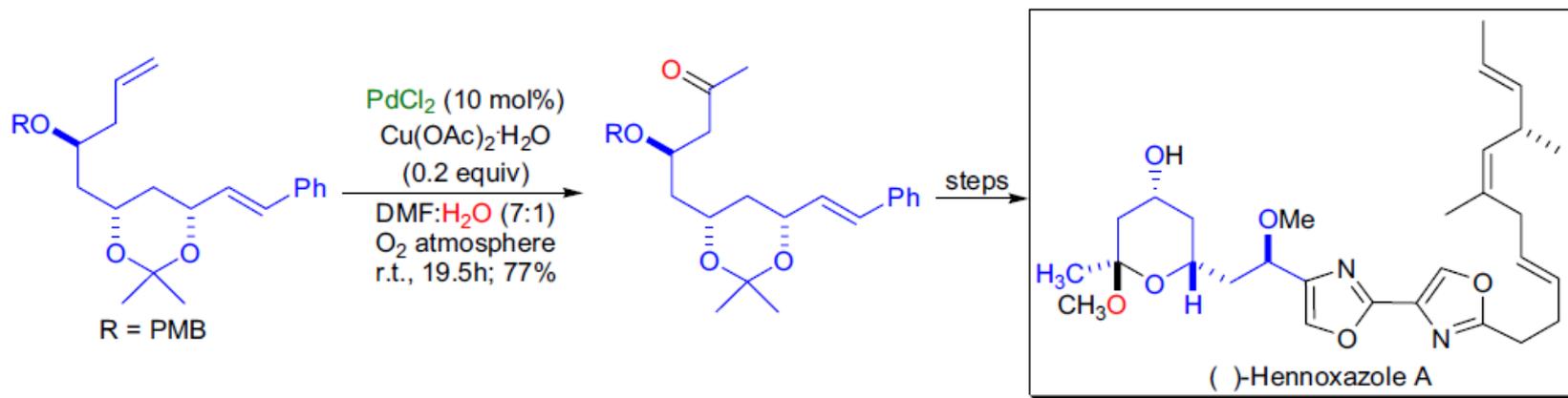
# Applications

## 1. Synthesis of the macrolide elaiolide.



# Applications

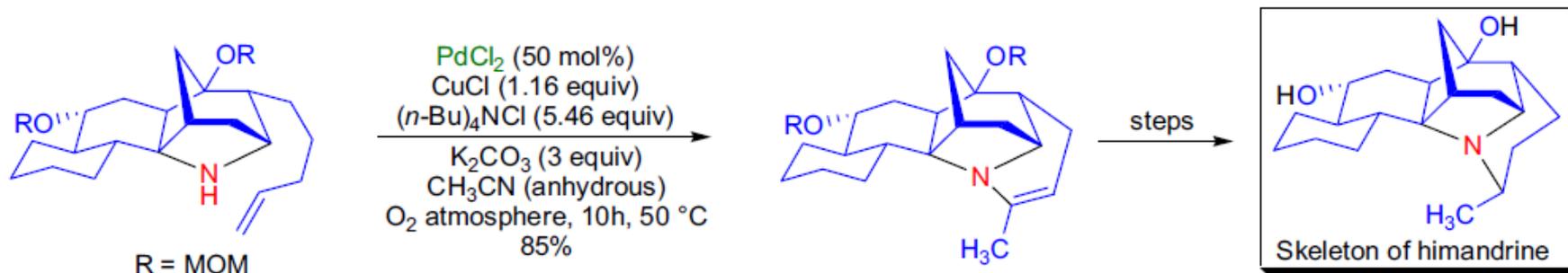
2. The antiviral marine natural product, (-)-hennoxazole A, was synthesized.



*Tetrahedron* 2001, 57, 6311-6327.

# Applications

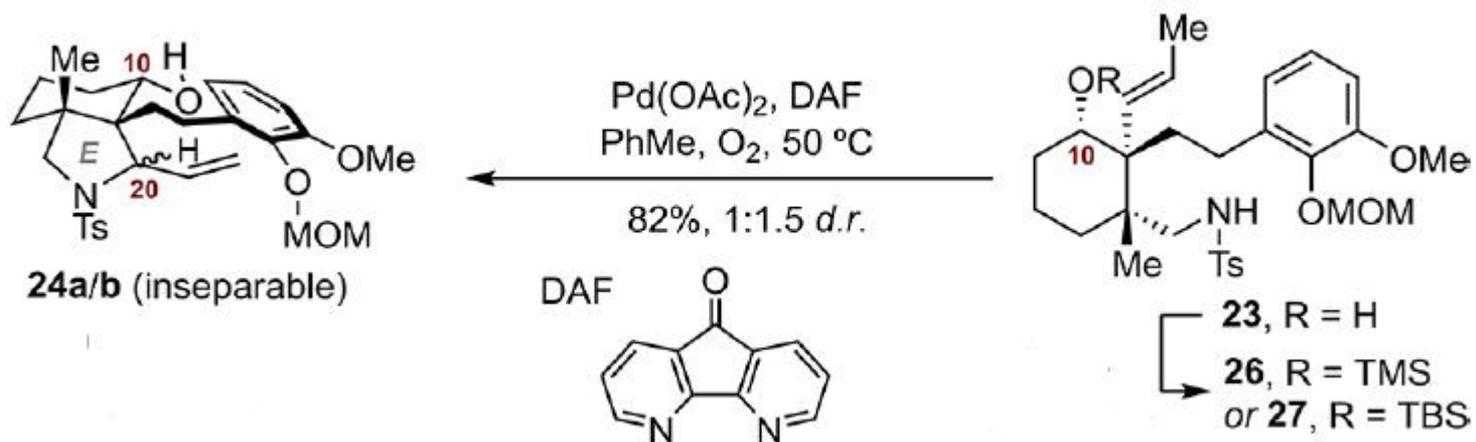
3. The first synthesis of the hexacyclic himandrine skeleton. The last six-membered heterocycle was formed *via* an intramolecular *Wacker-type oxidation* in which the terminal alkene sidechain reacted with the secondary amine functionality.



*Org. Lett.* 2004, 6, 703-706.

# Applications

## 4. Enantioselective Total Synthesis of (-)-Arcutinine



Thanks for attention!