

## Recent developments in palladium-catalyzed oxidations

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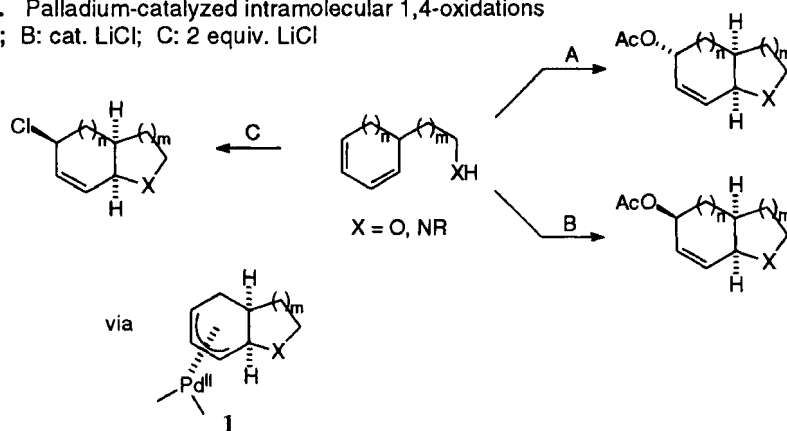
**Abstract:** The palladium-catalyzed intramolecular 1,4-oxidation of conjugated dienes has been extended to carbon-carbon bond formation. Two different methods were developed. In the first method, a vinylpalladium intermediate is generated in the side chain which adds to the diene. In the other method an allylsilane is used as nucleophile in the side chain. The first type of reaction leads to a 1,4-anti addition of carbon and a chloride and the second to a 1,4-syn addition of carbon and chloride to the 1,3-diene.

### Introduction

The palladium-catalyzed 1,4-oxidation of conjugated dienes was developed in our laboratory a few years ago.<sup>1</sup> This type of reaction leads to stereodefined 1,4-functionalized products which are synthetically useful building blocks and key intermediates. Recent extensions to intramolecular reactions have offered efficient pathways to fused heterocyclic rings in a stereocontrolled manner (Scheme 1).<sup>2</sup> The 1,4-addition to the diene is highly regio- and stereoselective and by a ligand control (added LiCl) a useful dual stereocontrol is obtained. The reactions proceeds via a ( $\pi$ -allyl)palladium intermediate **1**, which in many cases was isolated as a fully characterized.

**Scheme 1.** Palladium-catalyzed intramolecular 1,4-oxidations

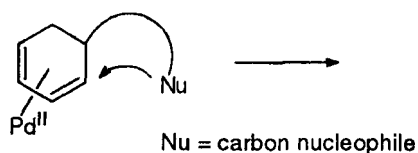
A: no LiCl; B: cat. LiCl; C: 2 equiv. LiCl



### C-C Bond Formation via Vinylpalladation

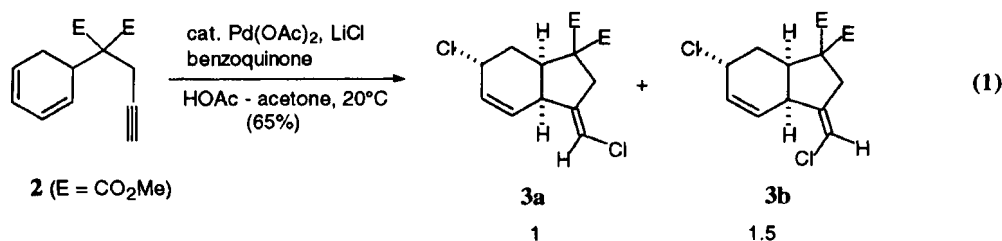
An extension of these intramolecular reactions to carbon nucleophiles (Scheme 2) was highly desirable. Initial attempts to use stabilized carbon nucleophiles in the side chain failed. We therefore tried another

**Scheme 2.** C—C bond formation?

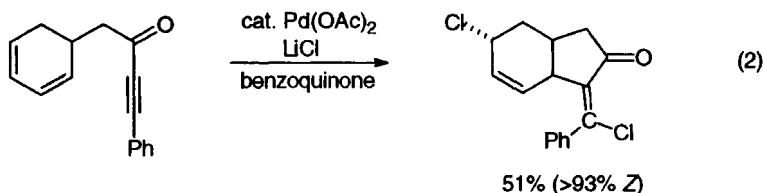


approach to obtain carbon-carbon bond formation. This approach involved generation of a vinylpalladium species in the side chain followed by a Heck-type carbopalladation to give a ( $\pi$ -allyl)palladium intermediate. A vinylpalladium species can be obtained from an acetylene via a chloropalladation reaction. In this way a palladium(II) catalyst could be used.

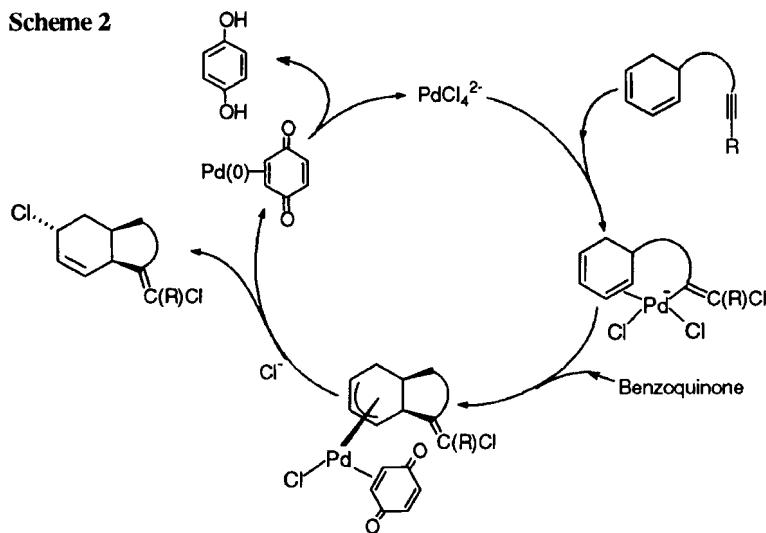
The requisite starting material **2** was prepared and subjected to the reaction conditions for palladium(II)-catalyzed 1,4-oxidation using an excess of LiCl. We were pleased to find that 1,4-addition products **3a** and



**3b** were formed in the way that we had anticipated.<sup>3</sup> The structures of **3a** and **3b** were established by their <sup>1</sup>H NMR spectra and for **3b** an X-ray crystal structure was also determined. It was found that the 1,4-addition to the diene had occurred trans. Another example of this carbocyclization is given in equation 2.

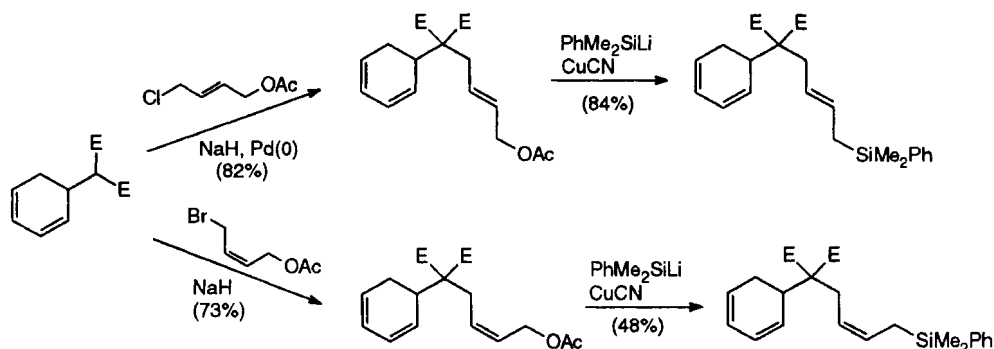


The mechanism of these carbocyclizations is given in Scheme 2. Chloropalladation of the acetylene in the side chain produces a vinylpalladium species, which undergoes a Heck-type reaction to give a ( $\pi$ -allyl)-palladium complex. Subsequent attack by a chloride anion gives the product. A syn vinylpalladation of the diene followed by a trans attack by chloride account for the stereochemistry of the product observed.



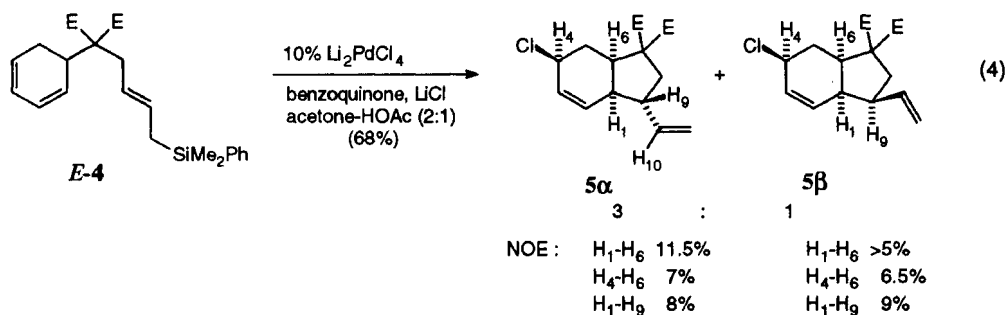
#### C-C Bond Formation via Nucleophilic Attack by an Allylsilane

After the vinylpalladation studies we turned our attention to allylsilanes. Allylsilanes are known to be useful masked carbon nucleophiles and they undergo reactions with aldehydes and ketones, usually with the catalysis of a Lewis acid.<sup>4</sup> It occurred to us that allylsilanes may be useful nucleophiles in the palladium(II)-catalyzed 1,4-oxidations of 1,3-dienes. Interestingly, they tolerate the presence of a weak acid without being hydrolyzed, which is of great importance for such an application since the Pd(0)-quinone intermediate formed in the catalytic 1,4-oxidation reactions requires the presence of weak acid to undergo the redox reaction to Pd(II) and hydroquinone.<sup>5</sup> The requisite starting materials were prepared according to Scheme 3.

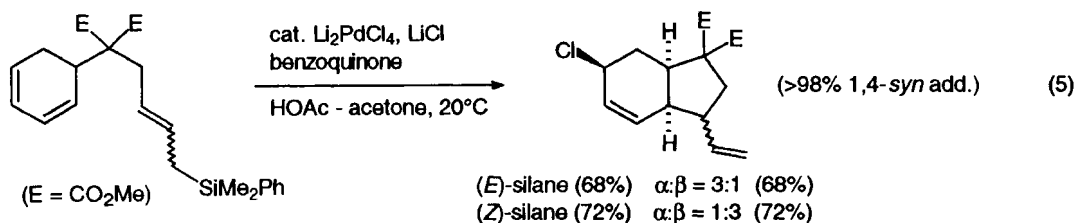
Scheme 3. Preparation of allylsilanes (E = CO<sub>2</sub>Me)

Reaction of allylsilane *E-4* with LiCl and benzoquinone employing Li<sub>2</sub>PdCl<sub>4</sub> as catalyst produced 1,4-addition products **5α** and **5β** (eq. 4).<sup>6</sup> It is a highly stereoselective 1,4-addition and in both isomers the carbon and chloride have added syn across the diene. The isomers differ only in the configuration at the vinyl substituted carbon. A 3:1 mixture between the isomers with the vinyl group down ( $\alpha$ ) or up ( $\beta$ ), respectively, was obtained. It is interesting to note that the stereochemistry of the 1,4-addition is opposite to that obtained in the carbocyclization via vinylpalladation (cf. eqs. 2 and 3, and Scheme 2).

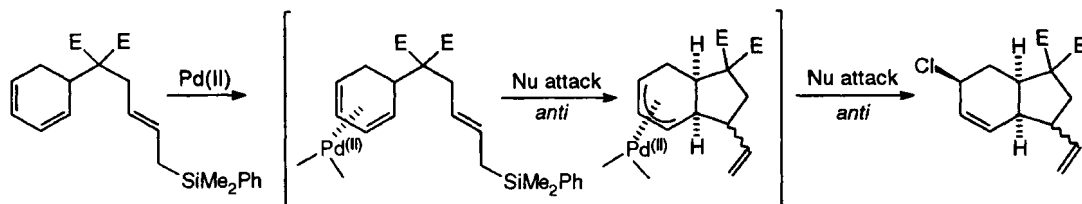
**Allylsilanes as Carbon Nucleophiles.** Highly stereoselective 1,4-syn addition to diene (>98%)



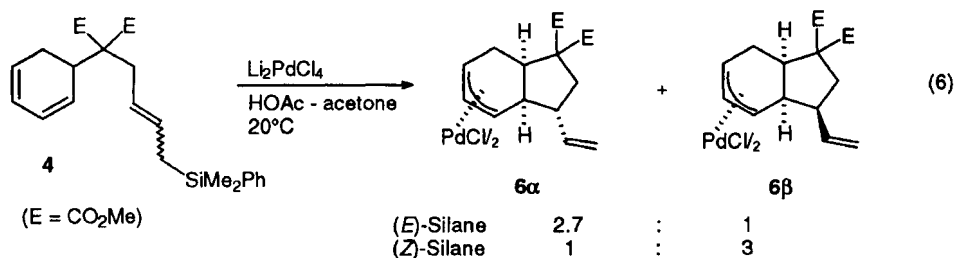
An interesting effect of the allylsilane double bond stereochemistry on the vinyl group stereochemistry was observed. It was found that the *E*-isomer gave the  $\alpha$ -vinyl product as the major isomer, whereas the *Z*-isomer produced predominantly the  $\beta$ -vinyl isomer.



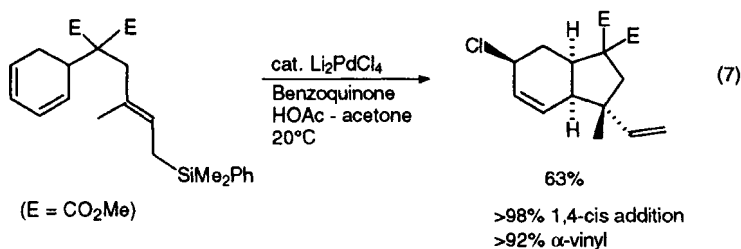
The proposed mechanism for the allylsilane carbocyclization is shown in Scheme 4. Coordination of the diene to Pd(II) generates a diene complex which is electrophilic enough to be attacked by the allylsilane. Presumably a chloride attack on the silyl group triggers the reaction. The reaction results in a ( $\pi$ -allyl)palladium intermediate via a trans carbocyclization. Subsequent attack by chloride then gives the 1,4-cis-addition product observed.

Scheme 4. Mechanism of Pd-catalyzed 1,4-addition with allylsilane (E = CO<sub>2</sub>Me)

Support for the mechanism in Scheme 4 follows from the isolation and characterization of  $\pi$ -allyl complexes **6 $\alpha$**  and **6 $\beta$**  from allylsilane *E*- and *Z*-**4** (eq. 6). A trans carbopalladation was established from these complexes and to the best of our knowledge this is the first example of nucleophilic attack by an allylsilane on a metal-olefin complex, and importantly the attack occurs trans.



With an additional methyl group at the double bond of the allylsilane the reaction now also became stereoselective with respect to the stereochemistry of the vinyl group ( $\alpha$  or  $\beta$ ). In this reaction (eq. 7) the relative stereochemistry between four stereogenic centers is created in one single reaction.<sup>7</sup> It is thought that the methyl group on the double bond further depresses the attack by the less favored  $\pi$ -face of the allylsilane by steric interaction with one of the carbomethoxy groups.



**Acknowledgments.** I wish to express my sincere appreciation to my coworkers whose names appear in the reference list, for their efforts in exploring the chemistry outlined in this review. Financial support from the Swedish Natural Science Research Council and the Swedish Research Council for Engineering Science is gratefully acknowledged.

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