Cycloreductions *via* Alkylpalladium Intermediates: Substrate Dependent Cyclopropanations of Palladium Catalyzed Enediyne Cyclizations

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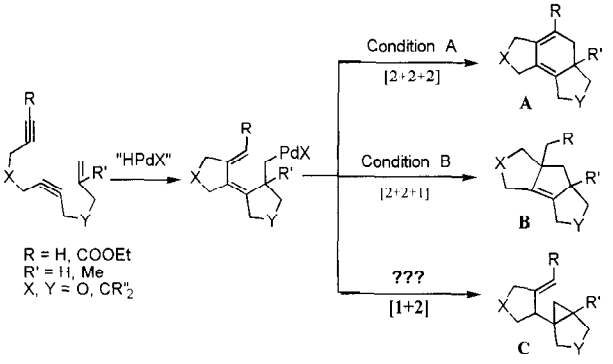
We have found for the first time that enediynes possessing an etheral oxygen in the appropriate position have been successfully cyclized via the alkylpalladium intermediates to the corresponding cyclopropane compounds.

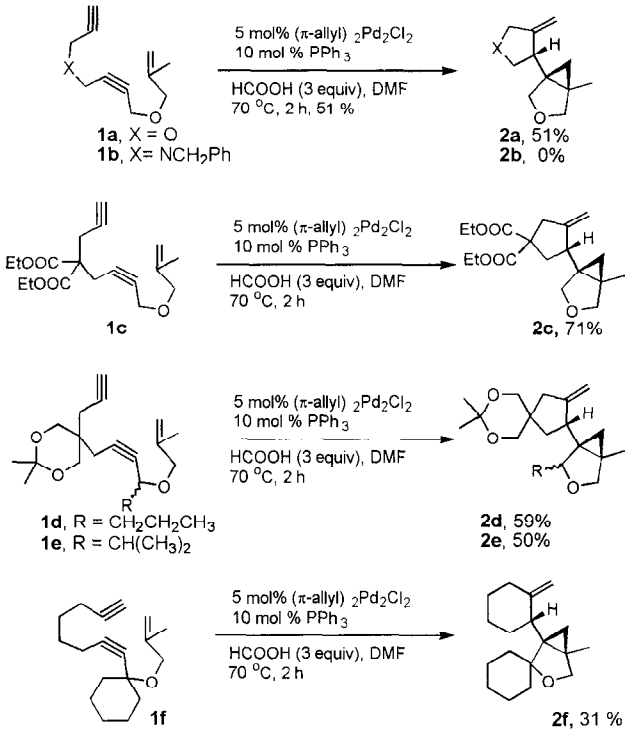
Oxidative addition of palladium(0) species with activated double bonds like haloenes and hydropalladation of palladium(II) species representing HPdX with a terminal acetylene group or an activated triple bond have been well-known to form the corresponding vinylpalladium species regioselectively in the presence of other double bonds and internal triple bonds. Such vinylpalladium species, derived from an active haloene, further underwent carbopalladation with a pendant internal triple bond and/or with the double bond to form the corresponding three-,[1] five-,[2] and six-membered rings[3] depending upon the substrates, the palladium catalysts, and the reaction conditions as shown in Scheme 1. Much effort has been put forth to the formation of the three-membered ring systems, since Negishi has unexpectedly obtained the cyclopropanation product during his study of the five membered ring system synthesis like capnellene.[4] Trost et al. reported an intramolecular [2+2+2] process which could provide the corresponding 6-membered ring systems.[5]



Scheme 1.

We have reported an important factor for altering these reaction pathways: (1) use of a catalytic amount of acetic acid as an initiator under these palladium reaction conditions resulted in formation of [m,6,n]-tricyclic compounds exclusively, as originally developed by the Trost group; (2) use of a stoichiometric amount of formic acid provided the [m,5,n]-tricyclic compounds by reductive cleavage of the alkylpalladium species.[6]

In connection with our interest, we now wish to report a novel, one-step, stereoselective cyclopropanation-reductions in

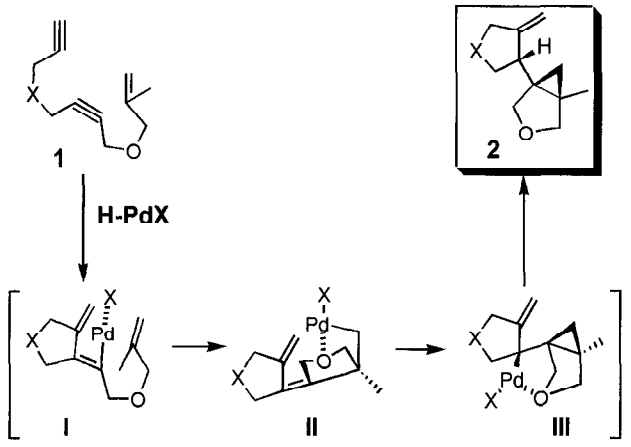


Scheme 2.

palladium catalyzed cyclizations of some structurally specific enediynes as shown in Scheme 2. When a dimethylformamide solution of substrate **1a**, 5 mol% of π-allylpalladium chloride dimer, 10 mol% of triphenylphosphine, and 3 equivalent of formic acid was stirred for 2 h at 70 °C, the corresponding cyclic product **2a** was isolated as a single isomer in 51% yield after flash chromatography. The nitrogen-containing substrate **1b** at 70 °C for 2 h under the same conditions, however, did not undergo the cyclization.[7] Enediyne **1c**, changing X to carbon skeleton, did cyclize well to the corresponding cyclopropanation product **2c** in 71% yield. Under these standard conditions, enediyne **1d** and **1e** were exclusively transformed to the product **2d** and **2e** in 59 and 50 % yields, respectively. It is important that each of these palladium catalyzed reactions exclusively afforded the corresponding cyclopropanations as a single isomer when determined by ^{1}H NMR and ^{13}C NMR data. In order to extend this method, we have studied a different type of enediyne **1f**.[8] The enediyne **1f** might be considered as a homolog of the other substrates **1a-e** employed in this study: it could form a six membered ring while the others form the five membered ring in the first step under our standard condition. As expected, the

substrate **1f** under our conditions did undergo cyclization to afford the corresponding 3-membered ring **2f** only in 31% yield. We believe that these are the first examples in which enediyne substrates under palladium catalysis form the corresponding three-membered ring systems and more examples in which the cyclization should involve a direct carbopalladation of the alkylpalladium intermediate with the conjugated double bond.

These results could be understood in terms of our proposed mechanism as shown in Scheme 3. The activated triple bond in substrate **1** regioselectively reacts with the HPdX and then with the internal triple bond to form the vinylpalladium intermediate **I**, which then further reacts with a pendant double bond stereoselectively to form the (neopentyl type) alkylpalladium intermediate **II**. Under these mild conditions, the intermediate might chaelate with the etheral oxygen, so that the subsequent carbopalladation could form the intermediate **III**. In the presence of excess formic acid, the intermediate **III** could reductively cleave to form the cyclopropanation product **2** and palladium(0) which can reform HPdX with formic acid.



Scheme 3.

In conclusion, these cyclizations *via* alkylpalladium intermediates could provide an important information to understand how the substrate structures affect the chemoselectivities in palladium catalyzed enediyne cyclizations. Further extension of this study as for a new methodology and for applications to natural product synthesis are currently underway.

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References and Notes

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7 All new compounds have been fully characterized by ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), IR, and HRMS.

8 Enediyne substrates were prepared by known procedures: see reference 5a and 6.