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Cycloreductions *via* Alkylpalladium Intermediates: An Important Mechanistic Clue for Palladium-Catalyzed Enediyne Cyclizations

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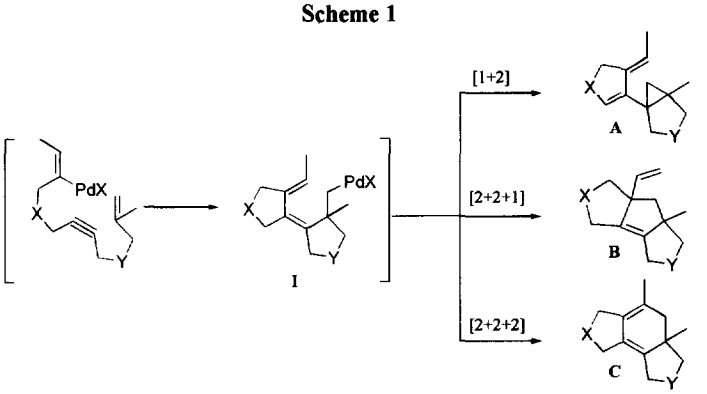
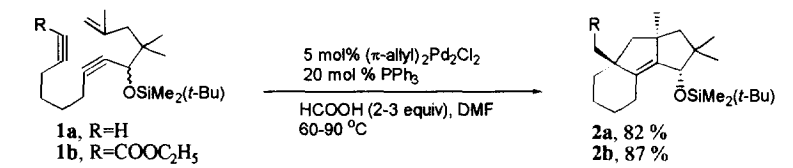
Abstract: *Various enediynes have been successfully cyclized via the alkylpalladium intermediates to the corresponding [m,5,n] tricyclic compounds.* Copyright © 1996 Elsevier Science Ltd

Palladium catalyzed cyclization has emerged as an efficient methodology which can provide various types of cyclic compounds in a very easy one step process.[1] Palladium(0) species with activated double bonds like vinyl bromide, iodide, or triflate and palladium(II) species representing HPdX with a terminal acetylene group have been known to form the corresponding vinylpalladium species regioselectively in the presence of other double bonds and internal triple bonds (Scheme 1).

Scheme 1



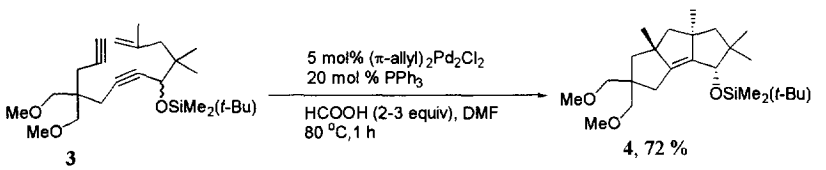
Cascade carbapalladation of these vinylpalladium species with a pendant internal triple bond could occur to form the conjugated butadienylpalladium species which then could undergo cyclizations with the double bond in three different pathways depending upon the substrates, the palladium catalysts, and the reaction conditions. Negishi et al. have attempted to synthesize the 5-membered ring system by cyclization *via* a neopentyl type alkylpalladium intermediate, but they unexpectedly obtained the cyclopropanation product for the first time.[2] Grigg and de Meijere independently reported cyclopropanation methods *via* neopentyl type alkylpalladium intermediates.[3] Later, Grigg et al. reported an intermolecular [2+2+2] process which can be diverted to 5-membered [2+2+1] or 3-membered [1+2] ring forming process.[4] Trost et al. reported an intramolecular [2+2+2] process which could provide the corresponding 6-membered ring systems.[5] Recently, we 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 [6,6,5]-tricyclic compounds exclusively, as originally developed by the Trost group; (2) use of a stoichiometric amount of formic acid provided the [6,5,5]-tricyclic compounds by reductive cleavage of the alkylpalladium species.[6] In connection with our interest in palladium catalyzed cyclizations, we now wish to report unprecedented [2+2+1] cyclizations which could provide diverse types of tricyclic [m,5,n]-tricyclic compounds from the corresponding acyclic enediynes and an important mechanistic clue in which the present cyclization should occur *via* a direct carbapalladation of the resultant alkylpalladium intermediates.



1a, R=H
1b, R=$COOC_2H_5$

2a, 82 %
2b, 87 %

(1)

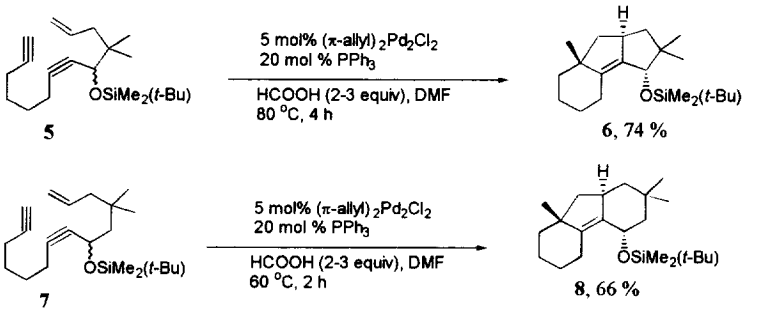


3

4, 72 %

(2)

When a dimethylformamide solution of substrate **1a**, 5 mol % of π-allylpalladium chloride dimer,[7] 20 mol % of triphenylphosphine, and 2 equivalent of formic acid was stirred for 4 h at 60 °C, the corresponding cyclic product **2a** was isolated as a single product in 82 % yield after flash chromatography (eq 1). The substrate **1b** at 90 °C for 6 h under the same conditions also cleanly underwent the cyclization to form the corresponding product **2b** in 87 % yield (eq 2).[8] These are the first example in which acyclic enediynes like **1a** or **1b under palladium catalysis** exclusively form [6,5,5]-tricyclic compounds. Under these standard conditions, enediyne **3** was exclusively transformed to the [5,5,5]-tricyclic product **4** in 72 % yield. Since each of these palladium catalyzed reactions exclusively afforded the corresponding tricyclic carbocycle as a single isomer, we have determined the relative stereochemistry of the product **2a** by using ^1H, ^{13}C, DEPT, COSY, HMQC, HMBC, NOESY NMR experiments. These data revealed that the cyclized product has the stereochemistry shown in eq 1. In order to gain more insight into the mechanism for these reactions, we have studied different types of enediynes **5** and **7**, whose structures are different from enediyne **1a** in the olefinic region.[9] Surprisingly, the substrates **5** and **7** under our conditions cleanly underwent cyclization to afford the corresponding 5-membered rings **6** and **8** without formation of any other detectable byproducts (eq 3, 4). ***We believe that these are the first examples in which the cyclization should involve neither the β-elimination nor the pallado-Diels-Alder reaction, but rather the direct carbapalladation of the alkylpalladium intermediate with a double bond.***

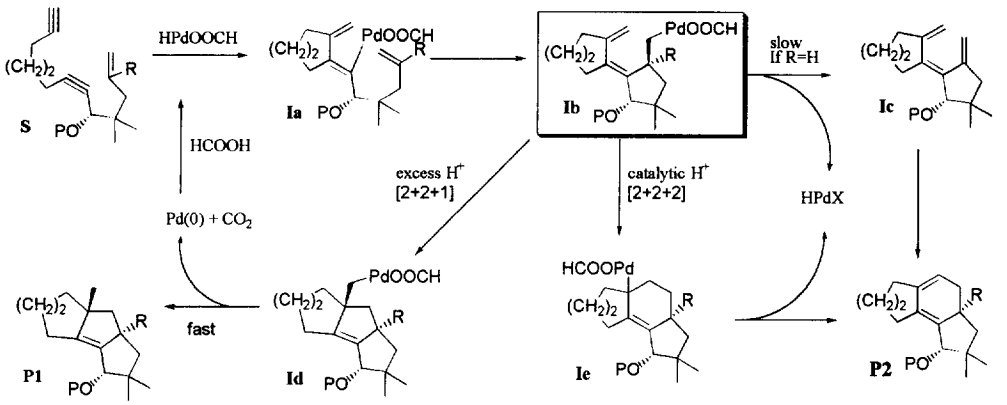


(3)

(4)

These results could be understood in terms of our proposed mechanism for the formation of the [6,5,5]-tricyclic compounds **P1** as shown in Scheme 2.

Scheme 2



The activated triple bond in substrate **S** regioselectively reacts with the HPdX and then with the internal triple bond to form the vinylpalladium intermediate **Ia**. The intermediate **Ia** then further reacts with a pendant double bond stereoselectively from the sterically unhindered face to form the (neopentyl type) alkylpalladium intermediate **Ib**. Although β-emimnation was known to be a major route for some cases,[5e] we could not detect any such products. Under these mild conditions, carbapalladation should compete over β-elimination (to **Ic**) to form the next alkylpalladium intermediates **Id** or **Ie** depending upon the reaction conditions. Thus, the intermediate **Ib** reacts with the pendant diene unit to form the intermediate **Id** and **Ie**. In the presence of only a catalytic amount of acids, the intermediate **Ib** can irreversibly cyclize to form the [6,6,5]-tricyclic product **P2** *via* the intermediate **Ie**. In the presence of excess formic acid, however, the intermediate **Id** may form the unstable intermediate **Id** which reductively cleaves to form the stable product **P1** and palladium(0) which can reform HPdX with formic acid.

In conclusion, these [2+2+1] cyclizations *via* alkylpalladium intermediates could offer an important methodology to provide [m,5,5]- and [m,5,6]-tricyclic compounds from the corresponding acyclic substrates. Further extension of this methodology and application to natural product synthesis are currently underway.[10]

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7. Allylpalladium chloride dimer was prepared according to the literature procedure. Tatsuno, Y.; Yoshida, T.; Otsuka, S. *Inorg. Syn.* **1981**, *28*, 342. For these cyclizations, allylpalladium chloride dimer was the best by far among various palladium catalysts such as $Pd(OAc)_2$, $PdCl_2$, and $(PPh_2)_4Pd$.
8. All new compounds have been fully characterized by ^1H NMR (300 MHz), ^{13}C NMR (75 MHz), IR, and HRMS and/or elemental analysis. A typical cyclization procedure is as follows. In an oven-dried 10 ml test tube with a magnetic stirr bar were placed enediyne **1a** (70 mg, 0.20 mmol), triphenylphosphine (10.6 mg, 0.04 mmol, 20 mol %), and π-allylpalladiumchloride dimer (3.6 mg, 0.01 mmol, 5 mol %) and then dry dimethylformamide (1.0 ml). The mixture was treated with commercial formic acid (0.025 ml, 0.5 mmol) and purged with a stream of argon at room temperature, and then closed with a rubber septum, and then stirred for 4 h at 60 °C. The dark solution was directly separated on flash chromatography to give the corresponding cyclized product **2a** (57.5 mg, 82 %) as a colorless liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 1H), 2.34 (ddd, *J*=12.6, 6.0, 1.8 Hz, 1H), 1.93 (ddd, *J*=12.6, 11.8, 6.0 Hz, 1H), 1.84-1.70 (m, 1H), 1.76 (d, *J*=12.6 Hz, 1H), 1.62 (d, *J*=12.6 Hz, 1H), 1.57-1.48 (m, 1H), 1.52 (d, *J*=12.9 Hz, 1H), 1.32-1.16 (m, 2H), 1.30 (s, 3H), 1.26 (d, *J*=12.9 Hz, 1H), 1.21 (s, 3H), 1.05 (s, 3H), 0.96-0.86 (m, 2H), 0.89 (s, 9H), 0.84 (s, 3H), 0.06 (s, 3H), -0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.01, 139.72, 76.58, 59.69, 54.34, 51.41, 49.16, 45.41, 44.34, 31.95, 29.92, 27.77, 25.81, 24.91, 24.81, 24.31, 22.45, 18.14, -4.54, -5.33; FT-IR ($CHCl_3$, cm^{-1}) 2955, 2928, 2858, 1463, 1371, 1254, 1084, 1069, 1043; HRMS calcd for $C_{22}H_{40}OSi$ (M^+) 348.2848, found 338.2838.
9. Enediyne substrates were prepared by known procedures: see reference 5a and 6.
10. For a representative natural product: Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* **1976**, *17*, 195.

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