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Palladium-catalyzed cycloreductions of haloene-ynes in the presence of triethylsilane

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Abstract—Haloene-ynes **1** with a palladium catalyst would form the alkenylpalladium intermediates via intramolecular Heck reactions, which were reductively cleaved with triethylsilane or formate ligand to give the cycloreduction products **3** in good to excellent yields. © 2003 Elsevier Science Ltd. All rights reserved.

Alkenylpalladium species (***A***) are versatile synthetic intermediates in palladium-catalyzed reactions.[1] These (***A***) can be mainly generated from the oxidative addition of alkenyl halides (**1**) or triflates (**1**) into Pd(0) or from the addition of the alkynes (**2**) to divalent Pd(II) species.[2] Such species can further undergo carbopalladation with a pendant triple bond to generate the alkenylpalladium species (***B***). Various bromodienes were also transformed to the corresponding σ-palladium species via oxidative addition of the bromoalkene and subsequent intramolecular carbopalladation. Iterative trapping of the σ-palladium species with external nucleophiles such as hydrogen,[3] nitrogen,[4] or carbon species[5] have been reported.

These tandem processes have been offering an opportunity to develop novel synthetic strategies for complex targets. Trost and co-workers developed direct reduction of the σ-bonded alkyl- and alkenylpalladium intermediates derived from diynes by excess external hydrogen donors such as triethylsilane or polymethylhydrosiloxane (PMHS)[6] and further applied to the total synthesis of drimanes which are an important terpenoid class whose members exert broad biological activities including antibacterial, antifungal, cytotoxic, insecticidal, etc.[7] Delgado developed a tandem process utilizing nickel-promoted cyclization–quenching processes utilizing TMSCN, CO, $NaBH_4$, Et_3SiH, and others.[8]

We have long been interested in trapping σ-palladium species with external nucleophiles such as hydrogen[9] or carbon species.[10] Very recently, we found that haloene-ynes were cyclized and arylated with external arylboronic acids to give the arylated dienes in good yields. As a continuing work, we wish to report a new cycloreduction methodology of haloene-ynes involving Pd-catalyzed cyclization and subsequent reduction of the transient alkenylpalladium intermediates by external triethylsilane. To illustrate the scope of this cycloreduction by comparing with the formate-induced cycloreduction,[11] we undertook cycloreduction of various haloene-ynes in the presence of ammonium formate instead of triethylsilane. Our results are summarized in Table 1. Haloene-ynes (**1**) used in this study were designed from the preparative point of view and prepared according to the known procedures.

4-(2-Bromophenyl)-1-butyne (**1a**) and diethyl (2-bromoallyl)propargylmalonate (**1b**) were tested as bromoene-yne derivatives to give the five-membered rings. The reaction of **1a** under palladium catalysis in the presence of 2 equiv. of triethylsilane was completed in 20 h at 60°C to give the cycloreduction product **3a** in 62% (entry 1). The presence of a mineral base seems to be fundamental. We chose $Pd(PPh_3)_4$ and cesium carbonate as a catalyst and a base, and the reaction was screened in various solvents such as toluene, 1,4-dioxane, THF, ethanol, and DMF, where DMF gave the best result. The nature of a palladium catalyst was also surveyed to $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(OAc)_2$–PPh_3, $Pd_2(dba)_3$, and $Pd(PPh_3)_2Cl_2$. Based on these experiments, the optimal yield (62%) was achieved by the use of 3.0 mol% of Pd $(PPh_3)_4$ as catalyst, cesium carbonate (2.0 equiv.), trirthylsilane (2.0 equiv.) in DMF with respect to the substrate **1a**. Replacement of triethylsilane by ammonium formate gave the same product but in inferior 48% yield (entry 2).[11] Using these conditions,

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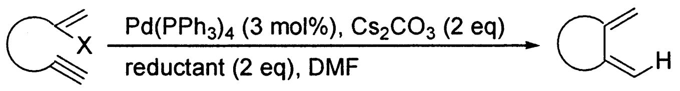
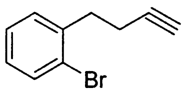
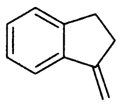
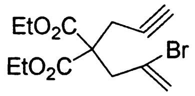
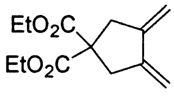
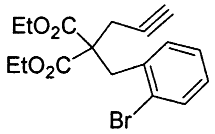
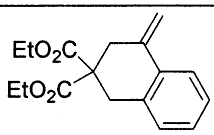
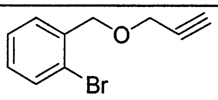
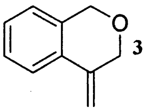
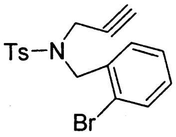
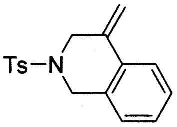
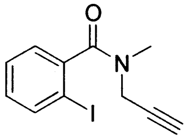
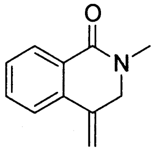
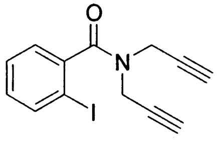
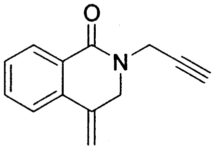
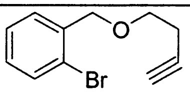
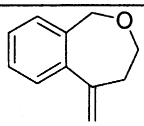
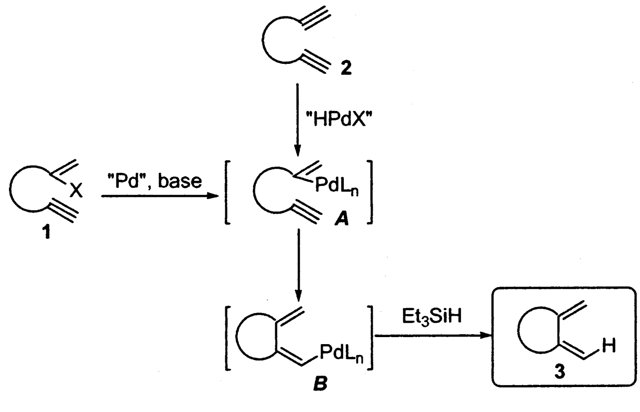
Table 1. Palladium-catalyzed cycloreduction of haloene-ynes (**1**) in the presence of triethylsilane or ammonium formate



1 **3**

	Substrates	Reductant	Temp (°C)./Time (h)	Products	% Yield
1	 **1a**	Et_3SiH	60, 20	 **3a**	62
2		HCO_2NH_4	90, 1		48
3	 **1b**	Et_3SiH	80, 4	 **3b**	72
4		HCO_2NH_4	80, 2		61
5	 **1c**	Et_3SiH	80, 4	 **3c**	85
6		HCO_2NH_4	80, 2		64
7	 **1d**	Et_3SiH	80, 4	 **3d**	54
8		HCO_2NH_4	80, 4		44
9	 **1e**	Et_3SiH	100, 12	 **3e**	65
10		HCO_2NH_4	80, 4		53
11	 **1f**	Et_3SiH	80, 24	 **3f**	82
12		HCO_2NH_4	80, 1		68
13	 **1g**	Et_3SiH	80, 12	 **3g**	80
14		HCO_2NH_4	50, 20		60
15	 **1h**	Et_3SiH	80, 3	 **3h**	48
16		HCO_2NH_4	60, 12		42

we tested Pd-catalyzed cycloreductions of a series of haloene-ynes **1b**–**h** with triethylsilane or ammonium formate as a reductant. Substrate **1b** under both conditions gave the desired product **3b** in 72 and 61% yields, respectively. Five haloene-yne derivatives **1c**–**g** were tested, which could give the six-membered rings. Diethyl (2-bromobenzyl)propagylmalonate (**1c**) gave the six-membered ring **3c** in 85 and 64% yields, respectively (entries 5 and 6). 2-Bromobenzyl propargyl ether (**1d**), an oxygen-containing substrate, also gave the corresponding six-membered ring **3d** in 54 and 44% yields, respectively (entries 7 and 8). Three nitrogen containing substrates **1e**–**g** under these conditions also gave the corresponding six-membered rings **3e**–**g** in good to excellent yields (entries 9–14).[11] Finally, 2-bromobenzyl 3-butynyl ether **1h** was prepared as a 2-bromo-1,8-enyne derivative to form the seven-membered ring. The substrate **1h** under both conditions, however, was shown to be sluggish to give the corresponding seven-membered product **3h** in 48 and 42% yields, respectively (entries 15 and 16). Various attempts were made to improve the formation of



Scheme 1.

seven-membered ring by changing the electronic and/or steric nature of the ligand on palladium complex. Instead of using $Pd(PPh_3)_4$, $Pd(OAc)_2$–dppe, $Pd(OAc)_2$–dppp, $Pd(OAc)_2$–dppb, and $Pd(OAc)_2$–(*tert*-Bu)$_3$P were tested, but non of these worked better than $Pd(PPh_3)_4$.

The reaction mechanism may be easily speculated as shown in Scheme 1. Oxidative addition of sp^2-C–X bond of the substrate **1** into Pd(0) can form the alkenylpalladium intermediates (***A***), its carbopalladation to the triple bond forms the other alkenylpalladium intermediates (***B***) which may be reduced by either triethylsilane or by the pendant formate ligand to give the desired product **3**.

In conclusion, we have accomplished a cascade Pd-catalyzed cycloreduction method of haloene-ynes. This method could be an alternative of diyne cycloreduction and enyne cyclization. Conjugated dienes or styrene derivatives obtained by this method could serve as a valuable synthetic building block.

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