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# Reductive Elimination of Alkylpalladium Formate Intermediates Formed in Enyne Cyclizations[1]

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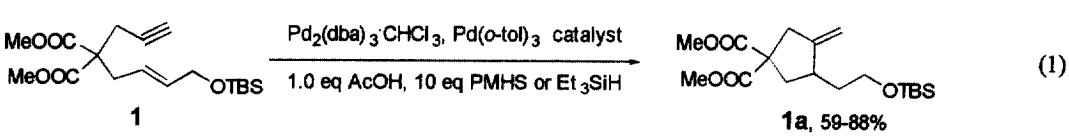
Abstract: *Various enynes under the palladium catalysts were successfully cyclized to the alkylpalladium intermediates, which then were reduced by the hydrogen in a formate ligand.* 

*Keywords: Palladium, Cyclization, Enynes, Carbocycles, Laurene*

Trost and his coworkers found that the H-Pd-X species, generated from a palladium compound and a carboxylic acid, selectively added to an activated triple bond in the presence of internal triple bonds or double bonds.[2] This remarkable observation prompted to pursue more studies on palladium catalyzed cyclization of unsaturated substrates such as enediynes,[3] triynes,[4] and enynes.[5] Recently, we have found that palladium catalyzed enediyne cyclization selectively gave either [m,6,n]- or [m,5,n]-tricyclic compounds depending on how much formic acid was used.[6] We have noted that even the alkylpalladium formates possessing a ß-hydrogen also underwent carbopalladation rather than ß-elimination. Based on this observation, we could postulate that use of an equivalent of formic acid played a dual role in initiating the catalytic reaction and also in reducing the alkylpalladium intermediate at the end of the catalytic cycle.[7] Such reduction of the $\sigma$-bonded alkylpalladium intermediates would represent a particularly useful synthetic process. Among these efforts, a silicon hydride (polymethylhydrosiloxane, PMHS) proved most efficacious source of the hydrogen donor. Enynes like **1** in the presence of $Pd_2(dba)_3$-$PPh_3$-AcOH as a catalytic system and 10 fold excess of a silicon hydride (PMHS or triethylsilane) as a reduction system could yield the cycloreduced products like **1a** in good to excellent yields as shown in eq 1.[8] Although their method was highly valuable for many enyne substrates, one critical disadvantage is the requirement of a lot excess of trialkylsilane, which should cause purification of the products to be problematic.




**1** **1a**, 59-88% (1)

An alternative method, developed by the Stork's group, involved two step processes: radical

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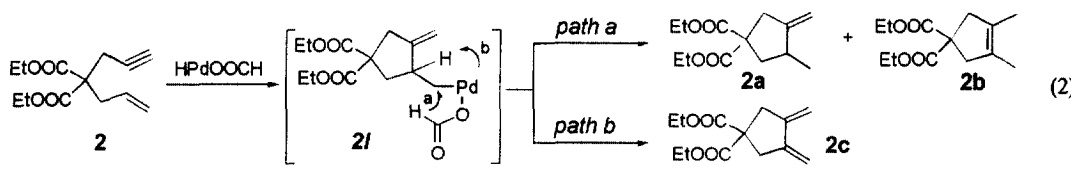
cyclization initiated by tributyltin radical and destannylation over silica gel.[9] Their method also often encountered even serious problems: a chemoselectivity problem to *5-exo-trigs* and *6-endo-trigs* and a long reaction time in destannylations.

In order to explore a new efficient enyne cycloreduction methodology and its synthetic feasibility, we have studied formic acid assisted palladium catalyzed cycloreductions of various enynes. Here we wish to report our preliminary results. Our strategy was the followings. 1) The initially formed H-Pd-OCOH could add to the terminal triple bond regiospecifically, and add to the double bond to form alkylpalladium intermediate ***2I***. 2) The alkylpalladium formate ***2I*** could undergo reductive cleavage more rapidly than $\beta$-elimination depending upon reaction condition. Diethyl allylpropargylmalonate as an enyne substrate was examined as shown in eq 2 and our results were summarized in Table 1.



(2)

**Table 1. Cycloreduction *vs* $\beta$-Elimination of Enyne 2 Using Palladium Catalysts and Formic Acid.**

| | Catalyst[a] | Equivalent of HCOOH | Solvent | Temp, °C | Time, h | Yield %[b] | Product Ratio **2a: 2b: 2c** |
|---|---|---|---|---|---|---|---|
| 1 | A | 2.5 | Toluene | 70 | 2 | 60 | 80:12:8 |
| 2 | | | *p*-Dioxane | | 2 | 70 | 3: 2: 95 |
| 3 | | | DMF | | 2 | - | 39:11:50 |
| 4 | | | $CH_3CN$ | | 2 | no rxn | - |
| 5 | | | THF | | 2 | no rxn | - |
| 6 | B | 2.5 | *p*-Dioxane | 70 | 2 | 78 | 90:9:1 |
| 7 | | 2.5-3.0 | Toluene | 80 | | 71 | 80:12:8 |
| 8 | B | 0.1 | Toluene | 90 | 1 | 62 | 3.8:0:96.2 |
| 9 | | 0.5 | | 90 | 0.5 | | 48:0:52 |
| 10 | | 1.0 | | 90 | 1.0 | 75 | 83:0:17 |
| 11 | | 10 | | 70 | 1.0 | | 20:52:28 |

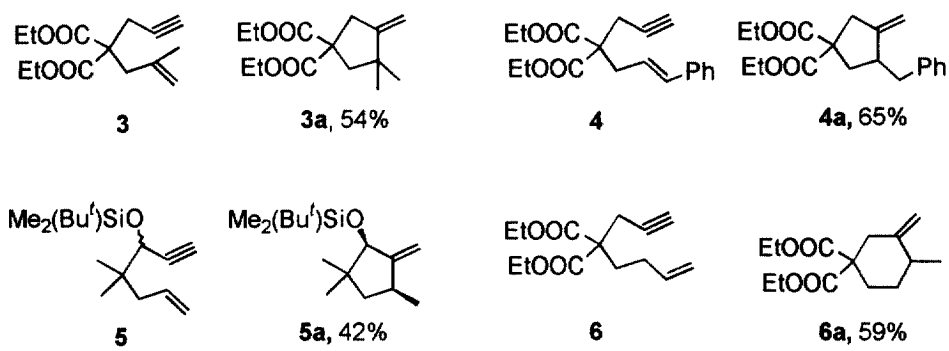
a: Catalyst A: 4 mol% $PdCl_2(PPh)_2$; catalyst B: 5 mol% $Pd(OAc)_2$, 10 mol% $PPh_3$

b: Isolated yields of the major product.

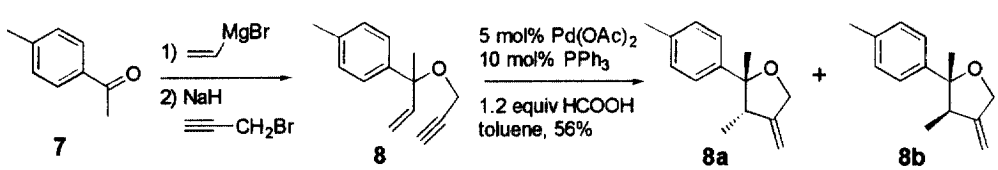
Treatment of enyne **2** with 4.0 mol% $PdCl_2(PPh_3)_2$, and 250 mol% HCOOH in dimethylformamide at 70 °C for 2 h gave a mixture of three products, **2a**, **2b**, and **2c**, in 39:11:50 ratio (entry 3). Replacing the reaction solvent caused to change the product rations dramatically. In toluene, enyne **2** gave the cycloreduced product **2a** in along with its rearranged product **2b** in highly selective manner (entry 1), although its synthetic feasibility was not yet enough due to the difficulty in purification of the desired product. In *p*-dioxane, however, $\beta$-eliminated product **2c** was formed as an almost exclusive product (entry 2). Here, solvent molecule might form a strong hydrogen bond with the formic acid, and therefore HCOOH could not play a proper role in the reaction cycle. In acetonitrile or in THF, no reactions occurred

(entry 4, 5). Choosing toluene as a standard solvent, variation of palladium catalyst systems showed us both $Pd(OAc)_2$-$PPh_3$ and $Pd(PPh_3)_4$ to be choices of this cycloreduction. Although we do not yet figure out the exact structure of the real palladium catalyst, it is evident that an optimal combination of palladium catalyst and ligand is important to complete reaction. In fact, any of palladium chloride, allylpalladium chloride dimer, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$ could not catalyze the cycloreduction in synthetically useful yields.[10] Next, we examined the role of formic acid by varying from 0.1 to 10 equivalents of formic acid (entry 8-11): using a stochiometric amount of formic acid resulted in the best cycloreduction without any rearranged product. Use of excess formic acid seemed to rearrange the first formed cycloreduced product **2a** to the thermodynamically more stable product **2b**. Under our optimized condition, the desired product **2a** could be obtained in 60-75 % isolated yield after flash chromatography.[11] One striking result was obtained when *p*-dioxane was employed as a solvent. While $PdCl_2(PPh_3)_2$ was used to yield the $\beta$-eliminated product **2c** in 70% isolated yield, $Pd(OAc)_2$ catalyst resulted in reversal in product formation to yield the cycloreduced product **2a** in 78% isolated yield (entry 2 and 6).

**Figure 1**




More enynes **3-6** were successfully applied to these optimized conditions to give the corresponding products **3a**, **4a**, **5a**, and **6a** in 42-65 % yields, respectively, as shown in Figure 1. It should be noted that the enyne **4** afforded the product **4a** in 42 % yield as a single diastereomer. With these initial results, we have applied to a short synthesis of an oxa analog of sesquiterpene laurene in three steps as shown in eq 3.[12]




(3)

Addition of vinylmagnesium bromide to 4'-methylacetophenone (7) followed by propargylation gave the enyne **8** in almost quantitative yield. Palladium catalyzed cycloreduction of enyne **4** smoothly occurred to give a mixture of oxa analogs (**8a**/**8b** = 1:3) in 56% yield[13].

In summary, we have shown that palladium catalyzed enyne cyclizations, initiated by $PdCl_2(PPh)_3$ or $Pd(OAc)_2$-$PPh_3$ as a catalyst in the presence of a stoichiometric amount of formic acid, formed

alkylpalladium formates (like ***21***) which underwent reductive elimination rather than β-elimination to give the corresponding cycloreduced products in high yields. Use of a catalytic amount rather than a stoichiometric amount of the acid under the similar condition cyclized the enynes to the corresponding dienes as reported by Trost, *et al.*. Application of this method to the natural product laurene synthesis is currently underway.

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