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Suppression of β-Hydride Elimination in the Intramolecular Hydrocarboxylation of Alkynes leading to the Formation of Lactones

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Dedicated to Professor Masakatsu Shibasaki on occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Palladium-catalyzed intramolecular cyclization of the alkynoic acids was studied which gave the five- and six-membered lactones in moderate yields. The reaction can be conducted simply by heating a toluene solution of alkynoic acids at 100 °C in the presence of catalytic amounts of $Pd(PPh_3)_4$ and $(o\text{-tol})_3P$. The key for this transformation is the use of phosphines, instead of carboxylic acids, as an additive. Similar to our previously developed catalytic system the use of carboxylic acid, instead of $(o\text{-tol})_3P$, resulted into the exclusive formation of the diene.

Keywords: asymmetric catalysis; C–C bond formation; cross-coupling; enzyme catalysis; homogeneous catalysis

Introduction

The metal-catalyzed intramolecular cyclization of carbon and heteroatom nucleophiles with tethered activated C–C bonds such as alkenes,[1] allenes,[2] and alkynes[3] is one of the most powerful tools for the generation of carbocycles and heterocycles in an atom economical manner.[4] Although tremendous amounts of the related work have been carried out in the field of hydrocarbonation, hydroamination and hydroalkoxylation reactions,[5] very few reports are known for hydrocarboxylation reactions, partly due to the diminished nucleophilicity of the carboxylic acids.[6] Therefore, the development of suitable methods for the formation of C–C and C–X bond by these processes is highly desired.

Lactones hold an important place in the natural product field and are widely spread all over the biogenetic categories. Particularly, there are numerous examples of five- and six-membered lactones, which often exhibit pheromonal, medicinal, flavoring, or olfactory properties.[7] Recently, we have been exploring the palladium-catalyzed addition of various nucleophiles to allenes, generated *in situ* from the corresponding alkynes [Eq. (1)].[8] The addition of catalytic amounts of a carboxylic acid was crucial for the palladium-catalyzed process. We have also reported the palladium-catalyzed intermolecular hydrocarboxylation reaction between alkynes (R = Ar) and carboxylic acids which provided allyl carboxylates in good to high yields [Eq. (2)].[9] In the similar line, we envisioned that the intramolecular cyclization of alkynoic acid might afford the lactone **3** under the Pd(0)-RCOOH combined catalytic system and if the hypothesis proved realistic a new method for the synthesis of lactones would be realized. To test this possibility, the alkynoic acid **1a** was treated with $Pd(PPh_3)_4$ and benzoic acid (10 mol%) in 1,4-dioxane at 100 °C. To our disappointment, the desired lactone **3a** was not formed at all; instead the diene **2** was isolated in 92% yield [Eq. (3)]. A precise reason for this observation can be rationalized on the basis of lower nucleophilicity of the carboxylic acid oxygen which hampers the intramolecular nucleophilic attack on π-allyl palladium complex, resulting in the formation of the diene **2** *via* β-elimination process. Our initial research was focused on the study of solvents, concentration, and catalyst loading. However, in all the cases, the isomerization *via* β-hydride elimination mechanism[10] occurred giving the corresponding diene **2** exclusively.

All the attempts to suppress the β-hydride elimination product **2** by using various palladium catalysts in combination with many ligands such as dppb, dppe, dppm, and dppf failed. A challenge was to obtain the lactone by suppressing the β-hydride elimination product **2**. In the hope of finding a new catalyst system for the intramolecular hydrocarboxylation, we decided to pursue the search for alternative catalytic systems in these hydrocarboxylation reactions. We reasoned that proper tuning of ligands attached to palladium might prove beneficial for this purpose. Thus, we have undertaken a search for a suitable ligand. After studying various ligands in the absence of the external carboxylic acid additive, we found that $(o\text{-tol})_3P$ in combination with $Pd(PPh_3)_4$ gave the best results allowing us to synthesize five- and six-membered lactones [Eq. (4)]. The detailed results of the work are reported herein.

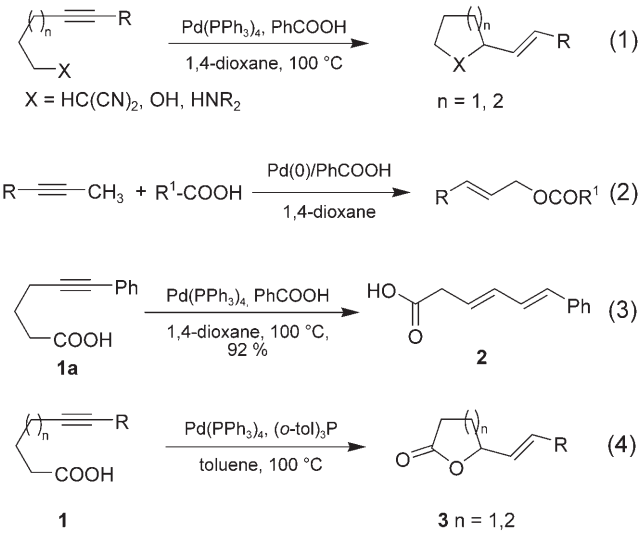
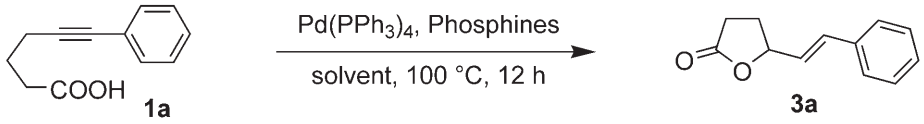


Table 1. Effect of phosphine additives on the cyclization of **1a**.[a]



Entry	Catalyst	Phosphine additive	Solvent	**1a** Yield [%][b]	**3a** Yield [%][b]
1	5% $Pd(PPh_3)_4$	10% $(o\text{-tol})_3P$	toluene	87	6
2			toluene	89	0
3	**5% $Pd(PPh_3)_4$**	**10% $(o\text{-tol})_3P$**	**toluene**	**0**	**79 (80)[c]**
4	5% $Pd(PPh_3)_4$	10% $(2\text{-furyl})_3P$	toluene	0	70 (66)[c]
5	5% $Pd(PPh_3)_4$	10% PPh_3	toluene	0	76
6	5% $Pd(PPh_3)_4$	10% $(n\text{-Bu})_3P$	toluene	0	63
7	5% $Pd(PPh_3)_4$	10% dppe	toluene	0	50[d]
8	5% $Pd(PPh_3)_4$	10% $(o\text{-tol})_3P$	benzene	21	58
9	5% $Pd(PPh_3)_4$	10% $(o\text{-tol})_3P$	THF	23	39
10	5% $Pd(PPh_3)_4$	10% $(o\text{-tol})_3P$	CH_3CN	10	51
11	5% $Pd(PPh_3)_4$	10% $(o\text{-tol})_3P$	CH_2Cl_2	4	59
12	5% $Pd(PPh_3)_4$	10% $(o\text{-tol})_3P$	1,4-dioxane	27	41
13	5% $Pd(PPh_3)_4$	5% $(o\text{-tol})_3P$	toluene	10	56
14	3% $Pd(PPh_3)_4$	10% $(o\text{-tol})_3P$	toluene	15	63
15	5% $Pd(PPh_3)_4$	10% $(o\text{-tol})_3P$	toluene	0	76[e]

[a] The reactions of **1a** (0.2 mmol) in the presence of metal catalysts and phosphine additives were carried out at 100 °C in toluene (0.1 M) for 12 h.
[b] Yields were determined by ^1H NMR spectroscopy with dibromomethane as an internal standard.
[c] Isolated yields are shown in parentheses.
[d] dppe = 1,3-bis(diphenylphosphino)-ethane.
[e] The reaction mixture was heated at 120 °C.

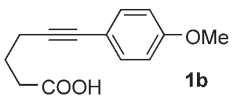
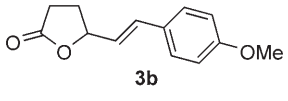
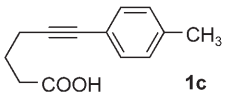
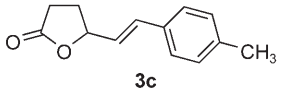
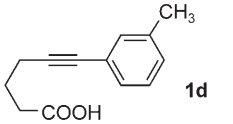
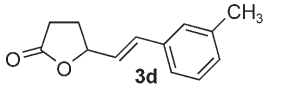
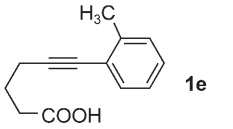
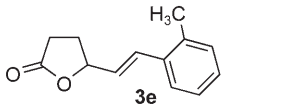
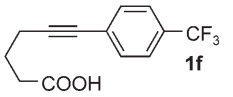
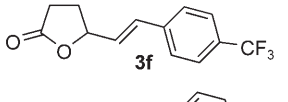
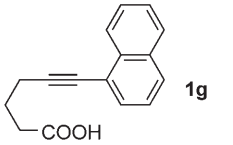
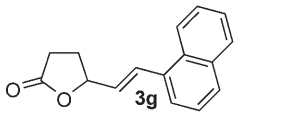
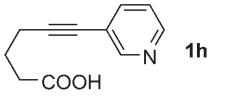
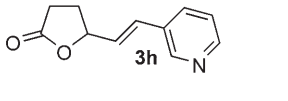
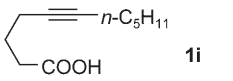
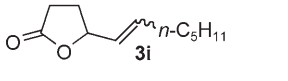
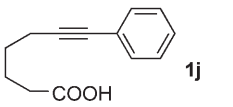
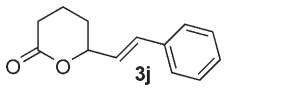
Results and Discussion

5-Hexynoic acid **1a** was selected as a substrate to optimize the cyclization process. The results are summarized in Table 1. The reaction **1a** in the absence of either $(o\text{-tol})_3P$ or $Pd(PPh_3)_4$[11] gave only trace amounts of the product **3a** or no reaction took place (entries 1 and 2). The use of 5 mol% $Pd(PPh_3)_4$ and 10 mol% $(o\text{-tol})_3P$ in toluene afforded the lactone **3a** in 80% isolated yield as the *E*-isomer (entry 3). Other phosphine ligands in the absence of external carboxylic acid were also effective for this reaction (entries 4–7). Various solvents such as benzene, THF, acetonitrile, CH_2Cl_2 and 1,4-dioxane, instead of toluene, gave the product in moderate yields (entries 8–12). Decreasing the amount of ligand and catalyst resulted in moderate yields (entries 13 and 14). The increase in reaction temperature up to 120°C gave the product in 76% yield (entry 15).

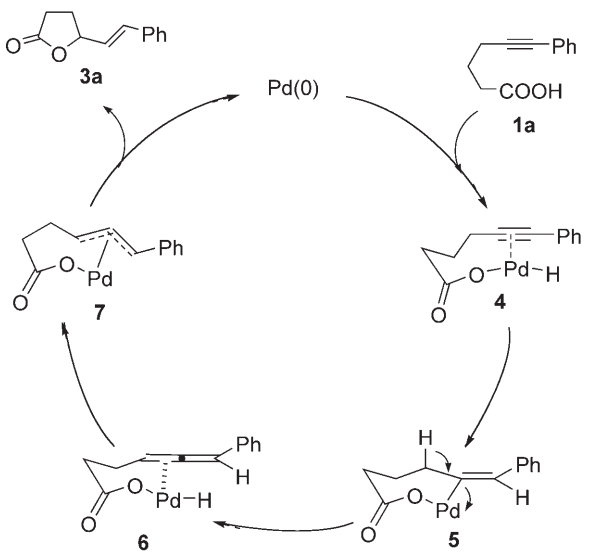
We carried out the cyclization reaction of various alkynoic acids **1** under the optimized conditions, and the results are summarized in Table 2. The substrate **1b** having a methoxy group at the *para* position of the aromatic ring afforded the corresponding cyclized product **3b** in 56% yield (entry 1). The *p*- and *m*-methyl-substituted alkynoic acids **1c** and **1d** gave the products **3c** and **3d**, respectively, in good yields (entries 2 and 3). Unfortunately, the lactone **3e** could be obtained only in a lower (30%) yield even after increasing the amount of palladium catalyst/ligand/reaction time and/or reaction temperature, and 11% of the starting material **1e** was recovered (entry 4). The reaction of the alkynoic acid **1f**, having trifluoromethyl group at the *para* position in the aromatic ring, also proceeded smoothly to afford the product **3f** in 45% yield (entry 5). The substrates **1g** and **1h** afforded the desired products **3g** and **3h**, respectively, in good yields (entries 6 and 7). The reaction of **1i**, having an *n*-pentyl group at the alkyne terminus, under the standard conditions proceeded smoothly to give a 9:1 mixture of *trans* and *cis* isomers of the lactone **3i** in good yield (entry 8). The six-membered lactone **3j** was also obtained from **1j**, albeit in somewhat lower yield. (entry 9).

A proposed mechanism for the palladium-catalyzed intramolecular cyclization of alkynoic acids is somewhat similar to our previously reported mechanism[8] and is illustrated in Scheme 1. The oxidative insertion of Pd(0) to RCOO–H bond of the acid **1a** generates catalytically active hydridopalladium complex **4**. Hydropalladation of the alkyne with the hydridopalladium species produces the vinylpalladium species **5**, which gives the substituted phenylallene **6** on β-elimination. Subsequent hydropalladation of the allene **6** gives the π-allylpalladium species **7**. Intramolecular nucleophilic substitution in the π-allylpalladium complex **7** gives the desired product **3a** along with regeneration of the catalyst. Although the precise role of the $(o\text{-tolyl})_3P$ is not clear at present, we believe that the added phosphine might be increasing the rate of oxidative addition into the carboxylic acid or helping to promote the initial hydropalladation step.

Table 2. Palladium-catalyzed cyclization of various alkynoic acids.[a]

Entry	Substrate (**1**)	Product (**3**)	Yield [%][b]
1	 **1b**	 **3b**	56
2	 **1c**	 **3c**	51
3	 **1d**	 **3d**	80
4	 **1e**	 **3e**	30[c]
5	 **1f**	 **3f**	45
6	 **1g**	 **3g**	54
7	 **1h**	 **3h**	49
8	 **1i**	 **3i**	75[d]
9	 **1j**	 **3j**	50

[a] The reactions of 1 (0.2 mmol) in the presence of $Pd(PPh_3)_4$ (5 mol%) and $(o\text{-tol})_3P$ (10 mol%) were carried out at 100°C in toluene (0.1 M) for 12 h.
[b] Isolated yields.
[c] 11% of starting material **1e** was recovered.
[d] A mixture of *trans* and *cis* isomers (9:1) was obtained. The ratio was determined by ^1H NMR spectral analysis.



Scheme 1. A plausible mechanism for the palladium-catalyzed cyclization of alkynoic acids.

Conclusions

Here, we have developed a new catalytic system for the intramolecular cyclization of alkynoic acids which affords five- and six-membered lactones in good yields. We discovered that $Pd(PPh_3)_4$ catalyst in combination with $(o\text{-tol})_3P$, in the absence of external carboxylic acid additive, suppresses the β-hydride elimination favoring the formation of lactones. Although a precise reason for the effect of added phosphine ligand is not clear at present, we are now in a position to synthesize lactones from alkynoic acids in good yields.

Experimental Section

^1H and ^{13}C NMR spectra were operated at 400 and 100 MHz, respectively, all referenced to internal tetramethylsilane (TMS) at 0.0 ppm. Reactions were monitored by thin-layer chromatography (Merck 60 F_{254}). Column chromatography was performed on neutral silica gel (60N, 100–210 μm) and elution with hexane/AcOEt (9:1) as solvent system. All starting materials were prepared in the laboratory and the details of them are described in the Supporting Information. $Pd(PPh_3)_4$ was prepared according to the literature procedure.[12] TLC was performed on aluminum-precoated plates of silica gel 60 with an F254 indicator and visualized under UV light or developed by immersion in the solution of 0.6% $KMnO_4$ and 6% K_2CO_3 in water.

General Procedure for the Synthesis of Lactones

To a 5-mL screw-capped vial equipped with a magnetic stirring bar were added the 5-heptynoic acid **1a** (37.6 mg, 0.2 mmol), $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol), $(o\text{-tol})_3P$ (6.2 mg, 0.02 mmol), and toluene (2 mL). After the mixture had been stirred for 12 h at 100 °C, TLC was taken in order to confirm complete disappearance of the starting material. The solvent was removed under reduced pressure, and the residue was purified on a short silica gel column with hexane:ethyl acetate, 9:1, as eluent to give **3a**; yield: 30.1 mg (80%).

Supporting Information

Experimental details, characterization data, ^1H NMR spectra of newly synthesized compounds are available in the Supporting Information.

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