



Carbonylation of alkynols catalyzed by Pd(II)/2-PyPPh₂ dissolved in organic solvents and in ionic liquids: a facile entry to α -methylene γ - and δ -lactones

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Abstract—The carbonylation of terminal 3-alkyn-1-ols and 1-alkyn-4-ols by Pd(OAc)₂ associated with 2-(diphenylphosphino)pyridine (2-PyPPh₂) dissolved in organic solvents or in 1-*n*-butyl-3-methyl imidazolium ionic liquids affords quantitatively and selectively *exo*- α -methylene γ - and δ -lactones, respectively. In the case of the reactions performed in ionic liquids (biphasic conditions), the lactones were isolated by simple distillation and the ionic catalyst solution can be reused. © 2002 Elsevier Science Ltd. All rights reserved.

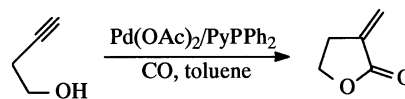
exo-Methylene lactones are represented in many biologically active natural products and are synthetically versatile starting materials widely employed in organic synthesis.¹ This importance has spurred the development of a plethora of methods for their preparation.² Amongst these methods the Pd-catalyzed homogeneous intramolecular alkoxy-carbonylation of propargyl or homopropargyl alcohols is one of the most promising and elegant approaches.³ However, in most of the cases the yields and/or selectivity in methylene lactones are low and/or the palladium catalyst cannot be recovered.

We wish to disclose herein our preliminary results on the establishment of a recyclable catalytic system for palladium-catalyzed carbonylation reactions,⁴ in particular for the synthesis of α -methylene lactones. This method is based on the use of Pd(II) compounds associated with 2-(diphenylphosphino)pyridine (2-PyPPh₂). The latter is one of the most efficient catalytic systems for the intermolecular alkoxy-carbonylation of 1-alkynes and this is reflected by its industrial use in the large-scale production of chemical intermediates including methacrylates.⁵ This system dissolved in organic solvents or in 1-*n*-butyl-3-methyl imidazolium ionic liquids⁶ catalyzes the carbonylation of alkynols to yield α -methylene- γ or δ -lactones. In the case of reactions performed in the ionic liquid, the lactones were isolated

by simple distillation and the recovered catalytic solution could be reused.

The reaction conditions for the carbonylation reaction were established after intense experimental work (solvent, CO pressure, temperature and catalyst loading). The catalytic solution was prepared by the addition of toluene (3 mL) to a mixture of 2-PyPPh₂ (0.1 mmol), *p*-toluene sulfonic acid (0.1 mmol), Pd(OAc)₂ (0.01 mmol) and hydroquinone (2–5 mg) at ambient temperature. This orange-red solution was transferred to an autoclave containing 3-butyn-1-ol (10 mmol) and then pressurized with CO (25 atm) and heated at 60°C. After 2 h the autoclave was depressurized at room temperature and the organic phase analyzed by GC, which indicated complete conversion of the alkynol (using methylbenzoate as internal standard). The α -methylene butenolide (Scheme 1) was obtained exclusively (97% yield) and the corresponding alternative six-membered lactone was not detected by GC–MS. The *exo*-methylene lactone was isolated in 80% yield after distillation under reduced pressure (0.1 bar) or extracted with diethyl ether and purified by column chromatography on basic alumina.

This protocol was successfully used for the generation of other butenolides (Table 1). Moreover, it can also be



Scheme 1. Carbonylation of homo-propargylalcohol.

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extended to the synthesis of *exo*-methylene six-membered lactones (Table 1).⁸ In all cases almost complete conversion of the alkynol was achieved and the *exo*-cyclic methylene lactones were isolated in moderate to good yields. The products were characterized by GC–MS, IR, ¹H and ¹³C NMR spectroscopy.⁹

These intramolecular carbonylation reactions are highly selective since in all cases, a single lactone isomer was detected in the crude reaction mixture (GC–MS). This high degree of selectivity can be explained on the basis of the mechanism(s) generally accepted for the carbonylation of non-functionalized 1-alkynes promoted by cationic Pd(2-PyPPh₂) complexes. Although there remains some controversy as to whether the reaction proceeds through a Pd–H or Pd–CO₂R intermediate, in both cases the regioselectivity is determined during the alkyne insertion–migration step.^{5,10} Therefore, the regioselectivity can be attributed to the steric control imposed by the 2-PyPPh₂ ligand, on the elementary alkyne insertion step into the Pd–H of Pd–C(O)OMe bond (Fig. 1), similar to that proposed earlier for the intermolecular alkoxy-carbonylation of 1-alkynes.¹⁰

This steric effect is more pronounced in the intramolecular alkoxy-carbonylation of internal alkynes such as **7** and **8** (Scheme 2) that react only sluggishly to afford the corresponding lactones **7a** and **8a** in low yields.

Table 1. Intramolecular alkoxy-carbonylation of alkynols catalyzed by Pd/2-PyPPh₂/CH₃PhSO₃H^a

Entry	alkynol	lactone	Yield (%) ^b
1			97 (80)
2			99 (75)
3			99 (80)
4			98 (70)
5			50 (40)
6			93 (30) ^c

^a Reaction conditions: Pd/2-PyPPh₂/CH₃PhSO₃H/alkynol = 1/10/10/1000; toluene (3 mL); CO (25 atm), 60°C, 2h.

^b GC yield. Isolated yield in parentheses.

^c The lactone decomposes during the purification (column chromatography).

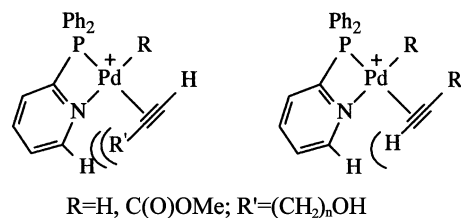
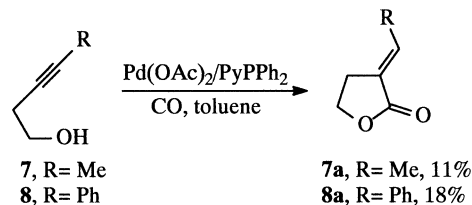


Figure 1. Steric control on the alkyne insertion step during the carbonylation reaction.

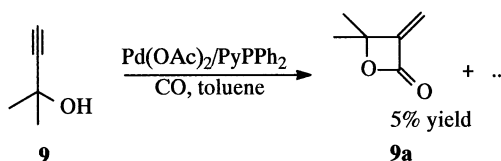
Although more than 60% alkynol conversion was observed for the carbonylation of propargyl alcohols, such as 1-methyl-2-butyne-1-ol, the desired *exo*-methylene-β-lactone was obtained in only 5% yield (Scheme 3). The side products are probably polymeric esters resulting from the successive intermolecular alkoxy-carbonylation reaction, similar to those already observed in analogous palladium-catalyzed carbonylation reactions.¹¹

Moreover, attempts to perform the intramolecular alkoxy-carbonylation of long chain alkynols, such as 8-nonyne-1-ol and 7-octyne-2-ol, have failed and the substrates were recovered almost quantitatively (>90%) after catalysis. In these cases, again, the side products are probably polymeric esters resulting from the intermolecular alkoxy-carbonylation reaction. These results are a strong indication that the intramolecular alkoxy-carbonylation reaction is under thermodynamic control, i.e. the formation of five- and six-membered lactones is favored. In opposition, the intermolecular alkoxy-carbonylation process is predominant and overrides the formation of four-, seven-membered or higher lactones.

Once the carbonylation method and its scope were established we turned our attention to the generation of a recyclable liquid–liquid biphasic catalytic system. We selected imidazolium ionic liquids (Fig. 2) as the mobile phase since this medium allows the direct transposition of homogeneous catalyzed reactions to liquid–liquid biphasic conditions without the need for ligand or metal-complex modifications.⁶



Scheme 2. Carbonylation of internal alkynols.



Scheme 3. Carbonylation of a propargyl alcohol.

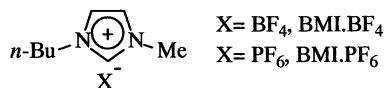


Figure 2. Imidazolium-based ionic liquids.

The ionic liquid catalytic solution was prepared by the addition of $\text{Pd}(\text{OAc})_2$, $p\text{-tolSO}_3\text{H}$ and 2-PyPPh_2 to 3 mL of 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($\text{BMI} \cdot \text{BF}_4$) or 1-*n*-butyl-3-methylimidazolium hexafluoro phosphate ionic liquids ($\text{BMI} \cdot \text{PF}_6$).⁷ The carbonylation reaction of 3-butyne-1-ol (10 mmol) was performed using the reaction conditions employed under homogeneous conditions (toluene). The alkyne conversion was determined by GC using methyl benzoate as internal standard. In both cases (reactions performed in $\text{BMI} \cdot \text{BF}_4$ and $\text{BMI} \cdot \text{PF}_6$) complete alkyne conversion was observed and the *exo*-methylene butenolide was the sole product. The lactone was isolated in good yields (>80%) by distillation under reduced pressure or by extraction with diethyl ether. In both cases the recovered ionic catalytic solution can be reused for further alkoxy-carbonylation reactions. However, a significant drop in the lactone yield was observed (from 99% on the first run to 85 and 37% on the first and second recharges using the same $\text{BMI} \cdot \text{BF}_4$ or $\text{BMI} \cdot \text{PF}_6$ ionic liquid catalytic solutions). This strongly suggests that the isolation procedures are possibly decomposing the palladium-containing catalytically active species. Work is in progress in order to avoid the ionic catalytic solution deactivation.

In summary $\text{Pd}(\text{OAc})_2/2\text{-PyPPh}_2$ dissolved in toluene (homogeneous conditions) is a simple and efficient method for the intramolecular alkoxy-carbonylation of alkynols, leading exclusively to five- or six-membered *exo*-methylene lactones. This catalytic system can also be immobilized in ionic liquids such as $\text{BMI} \cdot \text{BF}_4$ and $\text{BMI} \cdot \text{PF}_6$ (liquid–liquid biphasic conditions) without any changes in catalytic activity or selectivity.

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