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Carbohydroxypalladation Reactions in Aqueous Medium: An Efficient Route to 3-(1-Hydroxyaryl)tetrahydrofurans.

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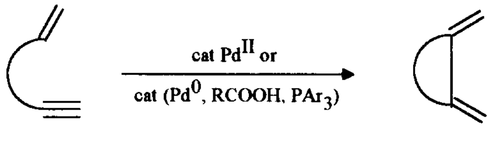
Abstract: The intramolecular carbohydroxypalladation of 1,6-enynes in aqueous medium with Pd(TPPTS)$_2$ gave 4-exomethylene-3-(1-hydroxyaryl)tetrahydrofurans or 1-exomethylene-2-(1-hydroxybenzyl)cyclopentane with good to moderate yields. © 1997 Published by Elsevier Science Ltd.

Palladium catalysis has become a major tool in organic synthesis. The emergence of numerous new useful reactions shows the importance of this metal in molecular design[1]. Among these reactions, the palladium-catalyzed cycloisomerizations of 1,6-enynes have received much attention since the early studies of Trost *et al.* in the middle of the 80's[2]. These reactions afford an efficient access to 1,6-dienes, which can be engaged in further molecular elaborations, for example in a Diels-Alder reaction.

Up to now, cycloisomerizations of 1,6-enynes can be carried out by using Pd^{II} or Pd^0 in association with a catalytic amount of a phosphine and of a carboxylic acid (scheme 1)[3]. Other transition metals have also been employed[4] as well as chiral TRAP-like phosphines[5] affording an interesting asymmetric version of these reactions.



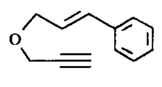
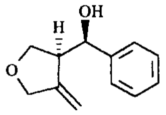
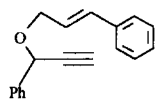
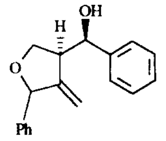
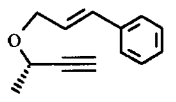
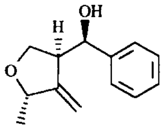
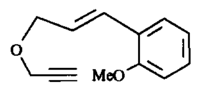
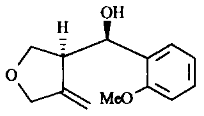
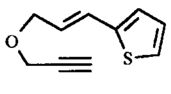
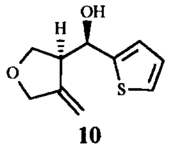
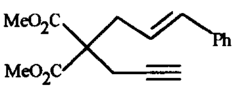
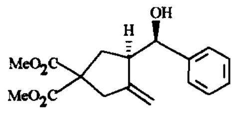
Scheme 1

We have recently established that an hydrosoluble Pd^0 species could be preformed or generated *in situ* by the association of a Pd^{II} salt (Pd(OAc)$_2$ or PdCl$_2$) and a water-soluble phosphine like TPPTS[6,7]. We have also shown that these conditions were effective in coupling reactions[8] (Heck, Sonogashira and Suzuki reactions) as well as in deprotections of allyloxycarbonates and allyloxycarbamates[9]. In the course of our study on palladium catalysis in aqueous medium, we wish now to report an unprecedented *carbohydroxypalladation reaction* allowing cyclization and hydroxyfunctionalization of 1,6-enynes:

Scheme 2

Fax: 01 44 07 10 62 E-Mail: genet@ext.jussieu.fr.

Table 1

Entry	Substrate	Product(a)	Time(h)	Yield(%)(b)
1	 **1**	 **2**	3	85(d)
2	 **3**	 **4**	7	82 (58/42 [e])
3	 **5**	 **6**	10	85 (57/43 [e])
4	 **7**	 **8**	5	47(d)
5	 **9**	 **10**	5	63(d)
6(c)	 **11**	 **12**	30	35(d)

(a) : The relative stereochemistry is not fully established.

(b) : All runs were performed using 10% PdCl$_2$, 30% TPPTS in a mixture of dioxane and water (6/1) at 80°C until complete disappearance of the starting material. Yields after purification on Florisil®.

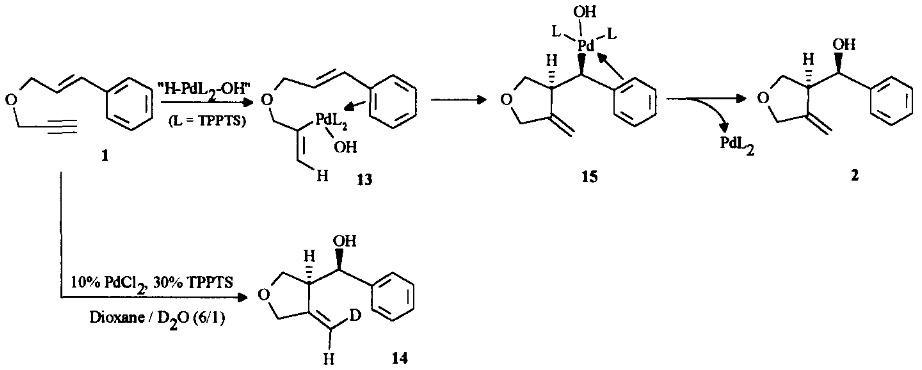
(c) : Performed in acetonitrile / water (6/1).

(d): Single diastereomer.

(e): Two diastereomers (%).

Our first attempt was directed towards the readily available propargylether **1**. When this compound was subjected to a catalytic cocktail of PdCl$_2$ (10%) and TPPTS (30%) in an homogeneous mixture of dioxane and water, we observed within a few hours the unexpected formation of secondary alcohol **2** as a single diastereomer[10,11]. The hydroxyl group was evidenced by IR and NMR spectra, and by conversion into its *t*-butyldimethylsilylether. To our knowledge, this is the first example of a diastereoselective carbohydroxypalladation reaction. As can be seen in Table 1, the reaction can be applied to propargylic substituted compounds with good yields and diastereoselectivity but with longer reaction times (entry 2 and 3). It is also possible to use substrates bearing a functionalized aromatic ring (entry 4) or even an heteroaromatic nucleus such as thiophene (entry 5). Non-oxygenated substrates may also be used but yields appear to be moderate (entry 6). Propargylamines as well as substrates deprived of any aromatic ring on the double bound did not give satisfactory results.

Although the mechanism is not clear yet, we assume the initial syn-addition of a « H-Pd-OH » species on the triple bond of the substrate leading to intermediate **13**[13]. Such an initial step is consistent with the deuterated product **14** obtained by carbohydroxypalladation of compound **1** in an homogeneous mixture of dioxane and D$_2$O. Intermediate **13** undergoes cyclization (intermediate **15**[14]) and a reductive elimination with retention of configuration[15] producing the expected alcohol **2** as a single diastereomer.



We believe that this new reaction can be profitable in numerous heterocyclic syntheses. Applications to the synthesis of podophyllotoxin and related compounds are currently in progress in our laboratory.

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References and notes

1 For an overall view on palladium catalyzed reactions see: a) Tsuji, J.; « Palladium Reagents and Catalysts. », John Wiley & Sons, West-Sussex, England, 1995. b) Malleron, J.L.; Fiaud, J.C.; Legros, J.Y. « Handbook of Palladium Catalyzed Organic Reactions. », Academic Press, Harcourt Brace & Company publishers, 1997.

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3 a) Trost, B.M.; Tanoury, G.J.; Lautens, M.; Chan, C.; MacPherson, D.T. *J. Am. Chem. Soc.* **1994**, *116*, 4255-4267. b) Trost, B.M.; Romero, D.L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268-4278.

4 Miura, K.; Funatsu, M.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 9059-9062 and references cited therein.

5 Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 662-663. (R,R)-(S,S)-TRAP = (R,R)-2,2''-Bis[(S)-1-(diarylphosphanyl)ethyl]-1,1''-biferrocene.

6 Amatore, C.; Blart, E.; Genêt, J.P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.*, **1995**, *60*, 6829-6839.

7 @ TPPTS : (m.sufonated triphenylphosphine).

8 a) Genêt, J.P.; Blart, E.; Savignac, M. *Synlett*, **1992**, 715-717. b) Genêt, J.P.; Blart, E.; Savignac, M.; Paris, J.M. *Tetrahedron Lett.*, **1993**, *34*, 4189-4192. c) Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J.P. *Tetrahedron Lett.*, **1996**, *37*, 2003-2006.

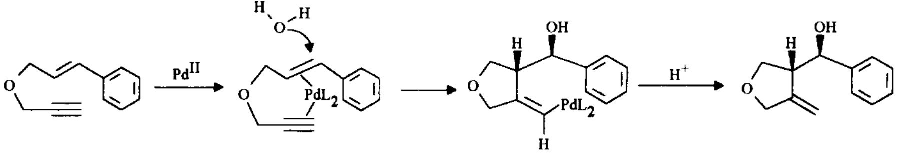
9 a) Genêt, J.P.; Blart, E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Paris, J.M.; Bernard, J.M. *Tetrahedron*, **1994**, *50*, 497. b) Lemaire-Audoire, S.; Savignac, M.; Blart, E.; Pourcelot, G.; Genêt, J.P.; Bernard, J.M. *Tetrahedron Lett.*, **1994**, *35*, 8783-8786. c) Bernard, J.M.; Blart, E.; Genêt, J.P.; Lemaire-Audoire, S.; Savignac, M. French Patents N° FR2690153 and N° FR2713687 and European Patent N° EP566459.

10 Esterification of the crude alcohol with Mosher's acid chloride followed by analysis of the ^{1}H NMR spectrum confirmed the presence of a unique diastereoisomer.

11 Typical procedure for the carbohydroxypalladation reaction in aqueous-organic medium:
Dioxane and water were degazed before the reaction. A mixture of $PdCl_2$ (mol. 10%), TPPTS (mol. 30%. Solution 32.5% weighted in water) and water (0.25 ml) were heated at 80°C under argon during 30 minutes. The dark red solution was cooled to 50°C and a solution of the substrate (1 mmol) in dioxane (1.5 ml) was added. The stirred mixture was heated at 80°C and the evolution was monitored by TLC. After completion, the solution was cooled to room temperature, then treated by 3 ml of H_2O and extracted by 4×10 ml of ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash-chromatography on Florisil®.

12 Data for compound **2** : ^{1}H NMR ($CDCl_3$; 200 Mhz; δ): 7.4 - 7.2 (5H, m, H_{arom}), 4.96 and 4.59 (2H, 2q, J = 2.1 Hz, $H_2C=$), 4.78 (1H, dd, $^3J = 6.5$ Hz and $^3J = 3.2$ Hz, HC), 4.4-4.2 (2H, m, CH_2), 4.13 and 3.86 (2H, 2dd, $^2J = 9.0$ Hz, $^3J = 4.9$ Hz and $^3J = 6.8$ Hz, CH_2), 3.1-2.9 (1H, m, HC), 2.41 (1H, d, $^3J = 3.2$ Hz, OH); ^{13}C NMR ($CDCl_3$; 50 MHz; δ): 147.98, 142.38, 128.26, 127.64, 126.35, 106.23, 74.58, 71.82, 70.27, 51.00; IR (film): 3420, 3020, 2867, 1663, 1630, 1450, 1412, 1215, 1091, 1077, 1066; MS (DCI/NH_3, m/z): 208 $(M+NH_4)^+$, 190 $(M+NH_4-H_2O)^+$, 173 $(M-H_2O+H)^+$.
Data for compound **10** : ^{1}H NMR ($CDCl_3$; 200 Mhz; δ): 7.4 - 7.2 and 7.1 - 6.8 (3H, 2m, H_{arom}), 5.05 - 4.9 (2H, m, $H_2C=$ and HC), 4.68 (1H, dd, $^2J = 2.0$ Hz and $^4J = 2.4$ Hz, $H_2C=$), 4.4 - 4.15 (2H, m, CH_2), 4.12 and 3.94 (2H, 2dd, $^2J = 9.1$ Hz, $^3J = 4.8$ Hz and $^3J = 6.7$ Hz, CH_2), 3.15 - 3.0 (1H, m, HC), 2.91 (1H, d, $^3J = 3.9$ Hz, OH); ^{13}C NMR ($CDCl_3$; 50 MHz; δ): 147.49, 146.56, 126.46, 124.79, 124.49, 106.49, 71.76, 71.00, 70.48, 51.31; IR (film): 3394, 3077, 2925, 2855, 1734, 1664, 1439, 1302, 1235, 1066; MS (DCI/NH_3, m/z): 214 $(M+NH_4)^+$, 196 $(M+NH_4-H_2O)^+$, 179 $(M+H-H_2O)^+$.

13 An alternative mechanism could be a « Wacker-type » cyclization process as depicted below:



14 Such an η^2-palladium complex has already been observed by Wang and co-workers in the insertion of norbornadiene into the aryl-palladium bond. See: Li, C.; Cheng, C.; Liao, F.; Wang, S. *J. Chem. Soc.* , *Chem. Commun.*, **1991**, 710-712.

15 The diastereoselective transfer of a deuterium atom has already been evidenced similarly by Trost and co-workers in the reductive cyclizations of 1,6- and 1,7-enynes: Trost, B.M.; Rise, F. *J. Am. Chem. Soc.*, **1987**, *109*, 3161-3163.

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