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Mechanism of the carbopalladation of alkynes by aryl-palladium complexes

Christian Amatore [a,*], Samia Bensalem [a], Said Ghalem [b], Anny Jutand [a,*]

[a] *Département de Chimie, Ecole Normale Supérieure, UMR CNRS-ENS-UPMC 8640, 24 Rue Lhomond, F-75231, Paris Cedex 5, France*
[b] *Département de Chimie, Faculté des Sciences, Université de Tlemcen, BP 119. M-13000 Tlemcen, Algérie*

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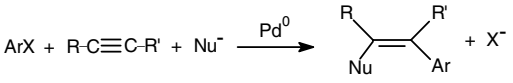
Abstract

The reaction between *trans*-$PhPdI(PPh_3)_2$ and $EtO_2C–C{\equiv}CH$ has been investigated. This carbopalladation step involved in palladium-catalyzed multicomponent reactions with alkynes gives the unusual *trans*-adduct $EtO_2C–C(PdIL_2){=}CHPh$ **1** as the major complex formed by isomerization of the primary *cis*-adduct $EtO_2C–C(PdIL_2){=}CHPh$ **2**. The carbopalladation was regiospecific. A multicarbopalladation was also observed by successive carbopalladation of $EtO_2C–C{\equiv}CH$ by the vinyl-palladium complexes themselves generated in carbopalladation steps, leading to cationic complexes.

Keywords: Carbopalladation; Multicarbopalladation; Palladium; Alkynes; Oxidative addition; Vinyl iodide

1. Introduction

Alkynes are involved in palladium-catalyzed multicomponent reactions as reported by Cacchi et al. [1] (Eq. (1)) or in Sonogashira reactions (terminal alkynes) (Eqs. (2) and (3)) [2].



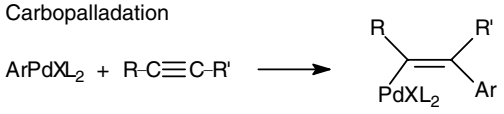
(1)

$$ArX + RC{\equiv}CH + Base \xrightarrow{Pd^0/Cu^I} ArC{\equiv}CR' + BaseH^+, X^- \quad (2)$$

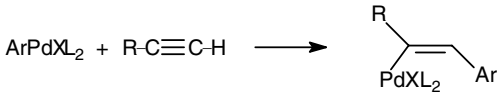
$$ArX + RC{\equiv}CH + Base \xrightarrow{Pd^0} ArC{\equiv}CR' + BaseH^+, X^- \quad (3)$$

In multicomponent reactions (Eq. (1)), one key step is the reaction of the alkyne with the aryl-palladium(II) complex formed in the *oxidative addition* of the aryl halide to a palladium(0) complex (Eqs. (4) and (5)) [1]. This step, usually named *carbopalladation*, is often considered as being rate-determining in reactions performed with aryl iodides or activated aryl bromides [1,3].

Carbopalladation



(4)



(5)

The carbopalladation involving terminal alkynes (Eq. (5)) might also be a key step in the copper-free Sonogashira reactions (Eq. (3)).

The carbopalladation is a *syn* addition which offers a *cis*-adduct in which the aryl group is transferred to the less hindered position (Eq. (5)) [1]. This reaction was

* Corresponding authors. Tel.: +33-1-4432-3872; fax: +33-1-4432-3325.
E-mail addresses: christian.amatore@ens.fr (C. Amatore), Anny.Jutand@ens.fr (A. Jutand).

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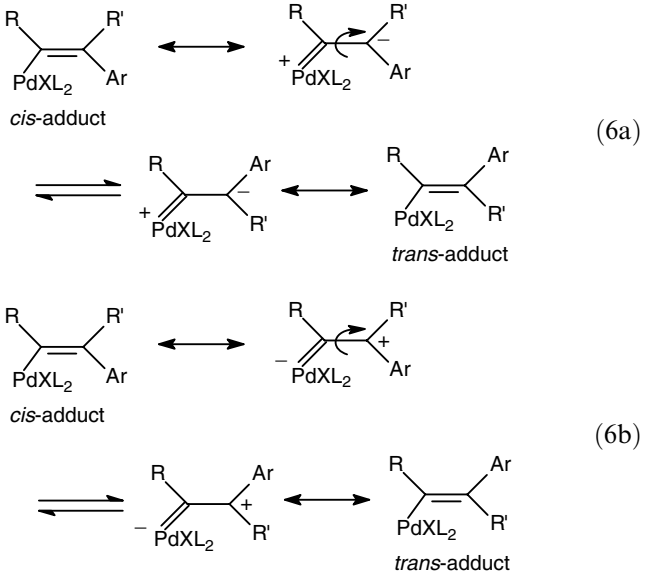
considered to be regio and stereospecific. However, some palladium-catalyzed multicomponent reactions are reported to give a mixture of products in which the Ar group and the nucleophile may be *cis* and/or *trans* [1,4]. This may arise via an isomerization of the *cis*-adduct complex first formed in the carbopalladation step via a zwitterion metal carbene (Eqs. (6a) and (6b)) [4,5]. An alternative mechanism has also been proposed via η^2-vinyl-metal complexes [6].



(6a)

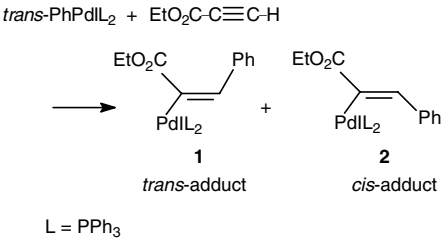
(6b)

We report herein some investigation on a carbopalladation step which shows that both *cis*- and *trans*-adducts are indeed formed. In addition, a multicarbopalladation was observed.

2. Results and discussion

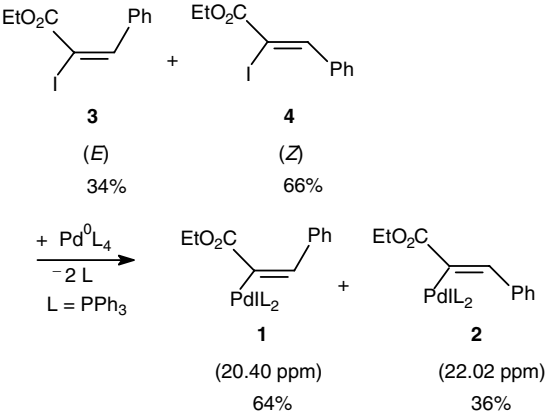
2.1. Mechanism of the carbopalladation

The reaction of *trans*-PhPdI$(PPh_3)_2$ with EtO_2C–C≡CH was monitored by ^1H NMR spectroscopy in $CHCl_3$ and by ^{31}P NMR spectroscopy in $CHCl_3$ or DMF containing 10% $CDCl_3$. A slow reaction was observed at room temperature between *trans*-PhPdI$(PPh_3)_2$ (24 mM) and EtO_2C–C≡CH (48 mM). The complex *trans*-PhPdI$(PPh_3)_2$, easily identified by the three sets of protons of the Ph group ligated to the palladium, was completely consumed after 16 h. Interestingly, when only 1 equiv. of EtO_2C–C≡CH was involved, EtO_2C–C≡CH was totally consumed after 7 h, whereas part of the complex *trans*-PhPdI$(PPh_3)_2$ was still detected (40%), suggesting that EtO_2C–C≡CH was not only consumed through its reaction with *trans*-PhPdI$(PPh_3)_2$ but participated simultaneously in another side-reaction possibly through its reaction with the complex(es) formed in the carbopalladation step (vide infra). In the early stage of the reaction, the carbopalladation gave two main complexes **1** and **2** characterized by two ^{31}P NMR singlets at 20.40 and 22.02 ppm, respectively [7]. Complex **2** (the *cis*-adduct) is the complex formed after the usual expected *syn* addition of Ph–PdI$(PPh_3)_2$ on the alkyne (Eq. (7)).



(7)

Complexes **1** and **2** have not been reported previously, so they were identified by comparison with authentic samples, independently synthesized by an oxidative addition of a mixture of (*E*) and (*Z*) vinylic iodides **3** and **4** (34/66%) to $Pd^0(PPh_3)_4$ at room temperature (Eq. (8)).

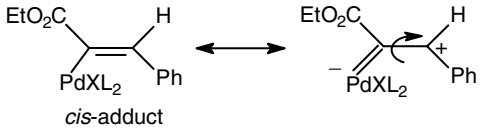


(8)

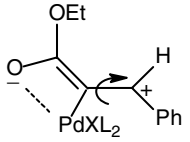
The oxidative addition being stereospecific [8], the vinyl iodides **3** and **4** should give, respectively, the vinyl-$PdIL_2$ complexes **1** and **2** in the ratio (34/66%) (Eq. (8)). The oxidative addition of the mixture of vinyl iodides **3** and **4** to $Pd^0(PPh_3)_4$ was monitored by ^{31}P NMR spectroscopy in $CDCl_3$ under stoichiometric condition (Pd/(**3**+**4**) = 1). A singlet at 20.40 ppm was first observed [7] and assigned to complex **1** because oxidative additions are reported to be faster with (*E*) than with (*Z*) vinyl halides, due to steric hindrance in the preliminary coordination of the active $Pd^0(PPh_3)_2$ to the C=C bond of the vinyl halide [8]. At longer times, a new singlet appeared at 22.02 ppm and was assigned to complex **2**, generated in the slower oxidative addition of **4**. At the end of the oxidative addition, complexes **1** and **2** were detected together but in the ratio 64/36 instead of the expected ratio 34/66. This indicates that isomerization of **2** to **1** took place during the course of the oxidative addition [9].

When the carbopalladation between *trans*-PhPdI$(PPh_3)_2$ and EtO_2C–C≡CH was monitored by ^1H and ^{31}P NMR spectroscopy in $CHCl_3$, the same ^{31}P NMR singlets at 20.40 and 22.02 ppm were observed. The two complexes **1** and **2** generated in the

carbopalladation step in Eq. (7) have then been identified. The complex **2** (*cis*-adduct) first appeared. It disappeared gradually with time while complex **1** (*trans*-adduct) appeared. The ratio of the two complexes then stabilized to 64/36% in favor of complex **1** which was eventually formed in higher amount than the expected *cis*-adduct **2**. It was then formed by isomerization of the *cis*-adduct **2** (initially formed in the carbopalladation step), as observed independently during the oxidative addition (Eq. (8)). The isomerization would proceed via one of the zwitterionic resonance forms (Eq. (9a)) [4,5] or by resonance with the ester group (Eq. (9b)).



(9a)



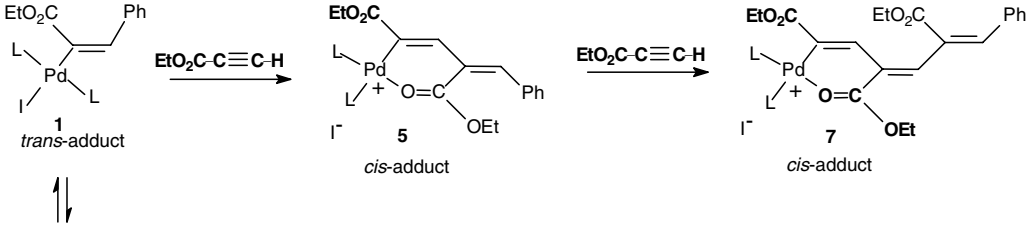
(9b)

It is worthwhile to note that the regioselectivity of the carbopalladation step is the expected thermodynamic one [1b,1c], i.e., with the $PdIL_2$ moieties located at the more hindered carbon the C≡C bond and the phenyl group at the less hindered one.

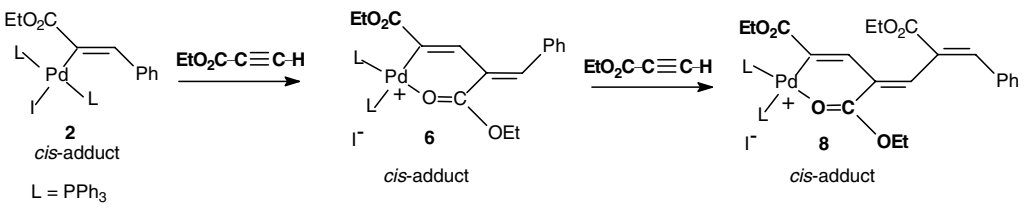
In a previous work, we reported kinetic data on the oxidative addition of phenyl iodide to $Pd^0(PPh_3)_4$ (2 mM in DMF) and established that the oxidative addition was slower in the presence of alkynes (PhC≡CH or EtO_2C–C≡CH) by complexation of the active $Pd^0(PPh_3)_2$ complex by the alkyne which generate the unreactive complex (η^2-PhC≡CH)$Pd^0(PPh_3)_2$ or the less reactive complex (η^2-EtO_2C–C≡CH)$Pd^0(PPh_3)_2$ [3]. When PhI (10 equiv.) was added to a solution of $Pd^0(PPh_3)_4$ (17 mM) in acetone-d_6 containing EtO_2C–C≡CH (1 equiv.), *trans*-$PdPdI(PPh_3)_2$ was the main complex observed at short times. The complexes formed in the carbopalladation were observed at longer times. When the amount of PhI was decreased (1 equiv.), i.e., when the oxidative addition was made slower, the complexes generated in the carbopalladation were detected together with *trans*-$PdPdI(PPh_3)_2$. This indicates that for equivalent amounts of PhI and EtO_2C–C≡CH, the time scales of the oxidative addition and carbopalladation may become closer.

2.2. Multicarbopalladation

In the carbopalladation step (Eq. (7)) performed in the presence of excess EtO_2C–C≡CH, other minor complexes appeared with time besides complexes **1** and **2**. They were detected by the presence of different sets (at least six) of quadruplets (CH_2) and triplets (CH_3) in the ^1H NMR spectrum evidencing different ethyl ester groups. The NMR spectrum also exhibited broad signals (at least four) located at low field between 7.8 and 9 ppm, characteristic of highly conjugated vinylic protons. Some of these complexes have been characterized by FAB mass spectrometry. Besides the mass of complexes **1** and **2** ($m/z = 933$ $[\mathbf{1}+H]^+$ and $[\mathbf{2}+H]^+$), other mass peaks were observed. They were indicative of successive incorporations of the EtO_2C–C≡CH unit into complexes **1** and **2**, with concomitant lost of the iodide ion ($m/z = 903$ [**1** (or **2**) + EtO_2C–C≡CH – $I]^+$; $m/z = 1001$ [**1** (or **2**) + 2EtO_2C–C≡CH – $I]^+$). The ^{31}P NMR spectrum exhibited at least three detectable sets of two doublets which were characteristic of magnetically unequivalent PPh_3, in contrast with the singlets observed for complexes **1** and **2** indicative of two magnetically equivalent PPh_3 [7]. This indicates that in each new complex, the two phosphines sit in a *cis* position on the Pd^{II} centre. New complexes **5** (or **6**) were then generated by the carbopalladation of EtO_2C–C≡CH by the vinyl-palladium complex **1** (or **2**) (Eqs. (10) and (11)). Complexes **5** (or **6**) underwent then a second carbopalladation with EtO_2C–C≡CH to give complex **7** (or **8**) (Eqs. (10) and (11)). These complexes released their iodide anion because of the internal complexation of the Pd^{II} centre by the carbonyl of the ester group, making then the two phosphines magnetically



(10)

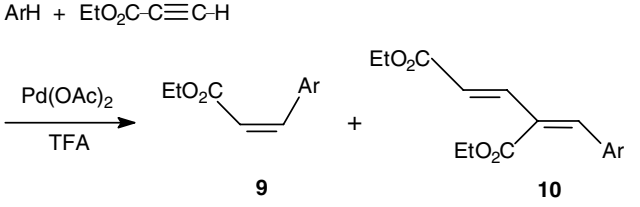


(11)

not equivalent. Such internal complexation of cationic Pd^{II} complexes by the carbonyl of an ester group was recently observed by Liu and coworkers [10] in complexes formed by multiple insertions of $EtO_2C–C{\equiv}CH$ into Pd-aryl bonds in cationic $[ArPd^{II}(P,N)(MeCN)]^+$ complexes. Due to the complex mixture of complexes and overlapping ^1H NMR signals, it was difficult to differentiate complexes **5** (or **6**) and **7** (or **8**).

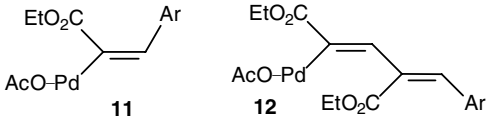
Consequently, cationic complexes were generated by successive carbopalladation steps to generate cationic complexes with two phosphines in a *cis* position. This multicarbopalladation was observed even under stoichiometric conditions so that $PhPdIL_2$ was not totally converted (40% conversion) while all the alkyne was consumed. This suggests that the vinyl-$PdIL_2$ complex **1** (or **2**) underwent a series of fast carbopalladations (Eqs. (10) and (11)) before $PhPdIL_2$ was completely converted in the first carbopalladation step.

A related *trans–cis* isomerization of the first carbopalladation product as well as a second carbopalladation have also been observed during the hydroarylation of terminal alkynes catalyzed by $Pd(OAc)_2$, as reported by Fujiwara and coworkers [11] (Eq. (12)).



(12)

In reaction (12), the postulated intermediate complex is a "ArPd(OAc)" complex which reacts with $EtO_2C–C{\equiv}CH$ to generate the *trans*-adduct **11** formed after isomerization of the primary *cis*-adduct. Compound **9** was obtained by acidic hydrolysis of **11**. A second carbopalladation step of $EtO_2C–C{\equiv}CH$ by complex the vinyl-Pd complex **11** generates the *cis*-adduct **12** whose acidic hydrolysis gives compound **10**.



3. Conclusion

The carbopalladation step between $PhPdI(PPh_3)_2$ and $EtO_2C–C{\equiv}CH$ has been investigated with the characterization of the unusual *trans*-adduct $EtO_2C–C(PdIL_2){=}CHPh$ **1** as the major complex formed by isomerization of the primary *cis*-adduct $EtO_2C–C(PdIL_2){=}CHPh$ **2**. The carbopalladation was regioselective. Those vinyl-palladium complexes undergo a first and second carbopalladation with $EtO_2C–C{\equiv}CH$, leading to cationic vinyl-palladium complexes ligated by two *cis* phosphines after release of the iodide ion due to the intramolecular complexation of the Pd^{II} centre by the ester group.

4. Experimental

4.1. General

^{31}P NMR spectra were recorded on a Bruker spectrometer (101 MHz) and ^1H NMR spectra 250 MHz, respectively. Ethyl propiolate was commercial (Acros) and used after filtration on alumina. $PdPdI(PPh_3)_2$ [12], $Pd^0(PPh_3)_4$ [13] and the vinylic iodides **3** and **4** [14] were prepared according to described procedures.

4.2. Characterization of complexes

4.2.1. *trans-Ph–PdI(PPh$_3$)$_2$*

^1H NMR (250 MHz, $CDCl_3$, TMS) δ 6.21 (t, $J=7$ Hz, 2H, *m*-H of Ph), 6.33 (t, $J=7$ Hz, 1H, *p*-H of Ph), 6.60 (d, $J=7$ Hz, 2H, *o*-H of Ph), 7.23 (t, $J=12$ Hz, $J=7$ H, *m*-H in PPh_3), 7.32 (t, $J=7$ Hz, 6H, *p*-H in PPh_3), 7.50 (dd, $J=7$ Hz, 6 Hz, 12H, *o*-H in PPh_3). ^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4) δ 23.03 (s).

4.2.2. *trans-Adduct EtO$_2$C–C[PdI(PPh$_3$)$_2$]=CHPh* ***1***

^1H NMR (250 MHz, $CDCl_3$, TMS) δ 0.97 (t, 3H, $J=7$ Hz, CH_3), 3.51 (q, 2H, $J=7$ Hz, CH_2), 7.5 (m, 18 H, H of PPh_3), 7.7 (m, 12 H, H of PPh_3), 7.85 (m, 1H, vinyl H). ^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4) δ 20.40 (s). FAB mass spectroscopy: $m/z=933$ $[\mathbf{1}+H]^+$, 805 $[\mathbf{1}-I]$, 630 $[\mathbf{1}-EtO_2C–C{=}CHPh]$.

4.2.3. *cis-Adduct EtO$_2$C–C[PdI(PPh$_3$)$_2$]=CHPh* ***2***

^1H NMR (250 MHz, $CDCl_3$, TMS) δ 1.34 (t, 3H, $J=7$ Hz, CH_3), 4.27 (q, 2H, $J=7$ Hz, CH_2), 7.5 (m, 18 H, H of PPh_3), 7.7 (m, 12 H, H of PPh_3), 8.16 (m, 1H, vinyl H). ^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4) δ 22.02 (s). FAB mass spectrum: $m/z=933$ $[\mathbf{2}+H]^+$, 805 $[\mathbf{2}-I]$, 630 $[\mathbf{2}-EtO_2C–C{=}CHPh]$.

4.2.4. *Complexes* ***5*** *(or* ***6****),* ***7*** *(or* ***8****)*

^1H NMR (250 MHz, $CDCl_3$, TMS) δ 0.7 (t, $J=7$ Hz), 0.8 (t, $J=7$ Hz), 1.02 (t, $J=7$ Hz), 1.29 (t, $J=7$ Hz), 1.51 (t, $J=7$ Hz), 3.0 (q, $J=7$ Hz); 1.02 (t, $J=7$ Hz), 3.57 (q, $J=7$ Hz), 3.8 (q, $J=7$ Hz), 4.01 (q, $J=7$ Hz), 4.41 (q, $J=7$ Hz), 4.43 (q, $J=7$ Hz). ^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4) δ 11.75 (d, $J_{PP}=19$ Hz) with 15.88 (d, $J_{PP}=19$ Hz); 23.15 (d, $J_{PP}=6$ Hz) with 26.57 (d, $J_{PP}=6$ Hz); 24.72 (d, $J_{PP}=8$ Hz) with 27.65 (d, $J_{PP}=8$ Hz). FAB mass spectra: $m/z=903$ [**5** (or **6**) $-I]^+$; $m/z=1001$ [**7** (or **8**) $-I]^+$).

Acknowledgement

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