Electrospray Ionization Mass Spectrometry Detection of Intermediates in the Palladium-Catalyzed Oxidative Self-Coupling of Areneboronic Acids

María A. Aramendía* and Fernando Lafont

Mass Spectrometry Service and Organic Chemistry Department, University of Cordoba, Cordoba, Spain

Marcial Moreno-Mañas,* Roser Pleixats, and Anna Roglans

*Department of Chemistry, Universitat Autònoma de Barcelona, Cerdanyola, 08193-Barcelona, Spain*

Several intermediates of the oxidative coupling of areneboronic acids to afford biaryls have been identified by electrospray ionization mass spectrometry. Knowledge has been gained about the steps occurring after the biaryl formation and leading to the recovery of the catalytic species.

Introduction

The palladium-catalyzed preparation of biphenyl by oxidative coupling of phenylboronic acid was reported by Suzuki in 1987.[1] The reaction was performed in the presence of palladium(II) and copper(II) acetates. Later, this self-coupling was further developed by others.[2] The coupling can be performed whether in the presence of dibromo compounds[2a,b,d] or Cu(II),[2c] or in the absence of any added oxidizing agent, but the inert atmosphere is then detrimental.[2c] The Pd-catalyzed self-coupling of 4-(trifluoromethyl)phenylboronic acid, **3b** (Scheme 1), was studied by some of us under different experimental conditions and monitoring the reaction by ^{19}F NMR. As a result, we proposed a mechanistic cycle[3] which is reproduced in more detail in Figure 1. Formation of biaryls X-Ph-Ph by phenyl scrambling from triphenylphosphine ligand was also discussed[3] and will not be considered here. Oxidative addition of areneboronic acids to Pd(0) species (**2** + **3** to **5**) was considered to be achieved by an initial acid−base reaction (**2** + **3** to **4**) followed by 1,2 arene migration to an electron-deficient palladium atom (**4** to **5**). From **5** + **3** to **7** the same sequence of steps occurs. Then, intermediate **7** gives very fast reductive elimination to afford biaryls and intermediate **9**. Recovery of the catalytic species PdL_2, **2**, from **9** was not detailed in our first paper,[3] but we suggested that this could be the slow step of the catalytic cycle. Nevertheless, step **4** to **5** (and **6** to **7**) is reminiscent of the Wagner−Meerwein rearrangement. Therefore, electron-withdrawing substituents should slow it down, this step being also a candidate to be rate-determining for certain substituents at the arene ring.

A more-detailed consideration of the recovery of **2** from **9** suggests that it takes place in three steps (**9** to **11**, **11**

Scheme 1. Studied Pd-Catalyzed Self-Coupling Reactions

3a X = 3-NH_2	**8a** X = 3-NH_2	X = 3-NH_2
3b X = 4-CF_3	**8b** X = 4-CF_3	X = 4-CF_3
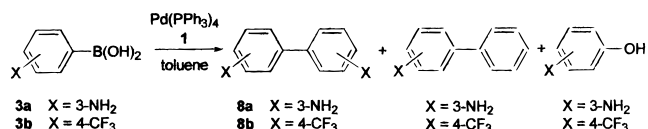
to **12**, and **12** to **2**). As a matter of fact, conventional chemical knowledge suggests that thermodynamics do not favor mechanistic steps involving direct $(HO)_2B−B(OH)_2$ elimination with respect to other requiring borate elimination.

On the other hand, electrospray ionization mass spectrometry (ESI-MS) has become a powerful tool in the identification of organic and organometallic reaction intermediates.[4] The very mild ionization conditions permit data to be acquired directly from solutions where reactions are taking place. They also allow the detection of molecular peaks without fragmentation, thus making intermediate identification possible. ESI-MS has been applied to intermediate detection of palladium-catalyzed reactions such as cross-couplings[5] and the Heck reaction.[6]

Results and Discussion

We decided to perform the self-couplings shown in Scheme 1. Our procedure was to monitor the reactions by sampling at different times and analysis with ESI-MS (positive ionization, see Experimental Section for conditions). Peaks due to intermediates containing palladium are immediately detected by the characteristic isotope distribution of the metal. Isotopic abundance of clusters was compared with calculated values.

First of all, reaction 1 (Table 1) was studied at 15, 30, 45, 60, 105, and 135 min. There was only one palladium-containing species detected by a cluster of peaks at m/z = 734−744. This intermediate was observed between 30

* Corresponding authors. Prof. Marcial Moreno-Mañas. Phone: 34-935811254. Fax: 34-935811265. E-mail: iqorb@cc.uab.es. Prof. María A. Aramendía. Fax: 34-957218606. E-mail: qo1maruj@uco.es.

(1) Miyaura, N.; Suzuki, A. *Main Group Metal Chem.* **1987**, *10*, 295.
(2) (a) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33. (b) Ye, X. S.; Wong, H. N. C. *J. Org. Chem.* **1997**, *62*, 1940. (c) Smith, K. A.; Campi, E. M.; Jackson, W. R.; Marcuccio, S.; Naeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131. (d) Yamaguchi, S.; Ohno, S.; Tamao, K. *Synlett* **1997**, 1199.
(3) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.

(4) Wilson, S. R.; Pérez, J.; Pasternak, A. *J. Am. Chem. Soc.* **1993**, *115*, 1994.
(5) Aliprantis, A. O.; Canary, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 6985.
(6) (a) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 7147. (b) Brown, J. M.; Hii, K. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 657. (c) Hii, K. K.; Claridge, T. D. W.; Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 984.
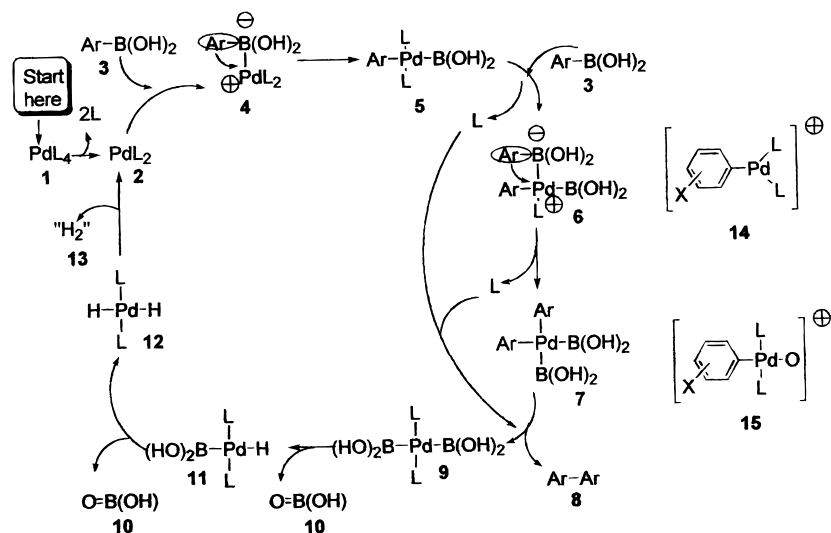
Figure 1. Mechanistic cycle for Pd-catalyzed self-coupling reactions.

Table 1. Intermediates Detected in Reactions of Scheme 1 by Electrospray Ionization Mass Spectrometry

expt[a]	**3** (mol/L)	% Pd[b]	t	detected intermediates
1	**3a** (0.022)	22	reflux	**15a**
2	**3a** (0.045)	7	reflux	**14a, 15a, 11**
3	**3a** (0.035)	100	reflux	**9, 14a**
4	**3b** (0.065)	20	rt	**14b, 15b**
5[c]	**3b** (0.030)	100	rt	**14b, 9, 4b** or **5b**

[a] All reactions in toluene. In all instances clusters due to the catalyst Pd(PPh$_3$)$_4$ were also observed at $m/z = 579$ [(OPPh$_3$)$_2$ + Na],[5] $m/z = 627-637$ [Pd(PPh$_3$)$_2$], and $m/z = 857$ [(OPPh$_3$)$_3$ + Na]. [b] As Pd(PPh$_3$)$_4$. [c] After quenching the sample with trifluoroacetic acid.

and 105 min, and structure **15a** was assigned to it. This intermediate does not belong to the cycle of Figure 1, but it is surely related to the formation of phenols in a side reaction,[2b,3] known to be produced only in the initial stages of these oxidative cross-couplings.[3] The required reductive elimination in order to form the C−O bond has some precedents.[7]

Reaction 2 (Table 1) was studied at 20, 45, and 65 min. A new and unique cluster at $m/z = 718-728$ was observed at 20 min, and it was totally consistent with structure **14a**. Although this cluster is not included in our proposed catalytic cycle (Figure 1), it could, however, arise from intermediate **5a** by cleavage, despite mild ionization conditions. Cations of type **14** have been observed by others[5,6a] in reactions where covalent ArPd-(L$_2$)−halogen complexes were postulated. Therefore, the presence of **14a** is an indication of the presence of **5a**. At 45 min, **14a** persisted and the cluster due to **15a** was already present. However, the most remarkable feature of this reaction was the formation of new clusters at $m/z = 673-683$, $687-697$, and $710-720$. The cluster at $m/z = 673-683$ is assigned to protonated intermediate **11**, in which the first postulated Pd−H bond has been formed in the way between **9** and **2**. The clusters at m/z $687-697$ and $710-720$ differ from (**11**+H) by 14 and 14+23 units. Treatment of samples includes dilution with methanol, and sodium incorporation is also a normal

event in these experiments[8] (see Experimental Section). Therefore both clusters can arise from methylation of the boronic acid moiety and sodium incorporation. Intermediate **11** is the most advanced intermediate of the catalytic cycle, and its presence explains why the oxidative coupling still operates in the absence of added oxidizing agents.

Reaction 3 (Table 1), performed in the presence of 100% molar of **1**, was the most informative, since it accelerated steps previous to the rate-determining one. This reaction was monitored at shorter times: 2, 7, and 15 min. At 2 min a very intense cluster at $m/z = 739-749$ was observed assigned to ion (**9** + Na). Moreover, a less intense cluster at $m/z = 717-727$ corresponds to the related (**9** + H). Intermediate **9** was also detected in reaction 5 with a different areneboronic acid, so its presence is independent of the nature of **3**. The ion (**9** + Na) persisted at 7 and 15 min. Besides, at 7 min intermediate **14a** was also present as in reaction 2.

Reactions of areneboronic acid **3b** featuring a substituent (4-CF$_3$) electronically very different from 3-NH$_2$ in **3a** were also monitored with time. Reaction 4 (Table 1) is similar to reaction 1, but in this case the cluster of **14b** at $m/z = 771-781$ was observed at 10 min and persisted at 20, 30, and 50 min. This is indirect evidence of the presence of **5b**. Furthermore, weak persisting signals of a cluster at $m/z = 787-797$ were assigned to **15b**, likely to be the precursor of 4-(trifluoromethyl)-phenol.[3]

Again, for **3b** use of 100% of **1** gave the most informative reaction (reaction 5, Table 1): intermediate **14b** gave strong cluster signals at 2 min. At 9 min the analyzed sample showed diminished signals for **14b**, and common intermediate **9**, already detected in reaction 3 (different areneboronic acid), was already present. Another sample taken at 9 min was quenched with trifluoroacetic acid for protonation and better detection of protonable intermediates. This made possible the detection of **5b** (or **4b**) as a cluster at $m/z = 835-845$ (**5b** + H + H$_2$O). Intermediate **14b**, in turn, gave only weak signals at 14 min, but intermediate **9** persisted. The accumulation of the latter indicates that the rate-determining is situated in the recovery of **2** from **9**. Table 2 shows a summary of

(7) (a) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787, and references therein. (b) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109.

(8) Henderson, W.; Sabat, M. *Polyhedron* **1997**, *16*, 1663.
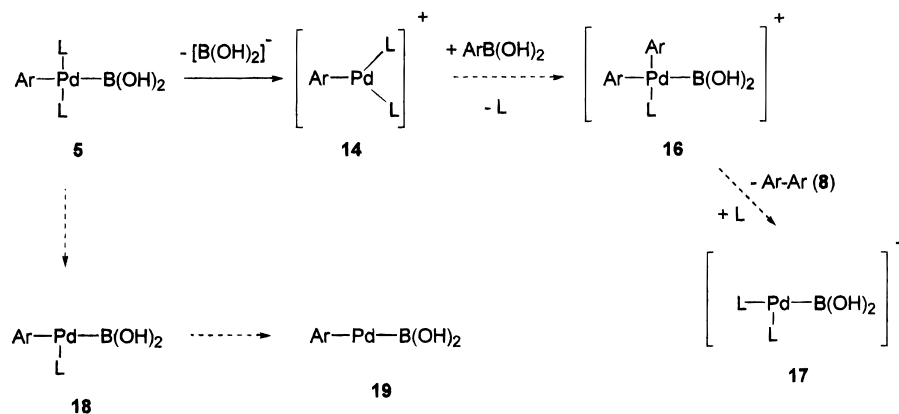
Figure 2. Ruled out pathways from **5** and **14**.

Table 2. Summary of Observed Clusters in Each of the Reactions of Scheme 1

from **3a** (X = 3-NH$_2$)	from **3b** (X = 4-CF$_3$)
(**9** + H)$^+$ m/z = 717−727	(**4b** or **5b** + H$_3$O)$^+$
(**9** + Na)$^+$ ^{a} m/z = 739−749	m/z = 835−844
(**11** + H)$^+$ m/z = 673−683	(**9** + Na)$^+$ ^{a} m/z =
	739−749
(**11** + H + CH$_3$O − OH)$^+$	(**14b**)$^+$ m/z = 771−781
m/z = 687−697	
(**11** + H + CH$_3$O − OH + Na)$^+$ ^{a}	(**15b**)$^+$ m/z = 787−797
m/z = 710−720	
(**14a**)$^+$ m/z = 718−728	
(**15a**)$^+$ m/z = 734−744	

^{a} Intermediates **9** and **11** add adventitious quantities of Na$^+$, most likely leached from glassware.[8]

observed clusters in each of the experimental reactions of Scheme 1.

The formation of intermediate **14** from Ar−Pd(L$_2$)−I has some precedents.[5,6a] The facile, required cleavage of the Pd−B bond suggests that **14** could be an intermediate in the catalytic cycle. In such a case, its logical continuation would be the oxidative addition of a second molecule of areneboronic acid to afford intermediate **16**, the precursor of biphenyls **8** (plus **17**) (Figure 2). ESI-MS evidence for possible intermediates **16** and **17**, however, could not be obtained. On the other hand, the easy decomposition of **5** could alternatively occur by loss of one ligand to form **18**, but again ESI-MS signals assignable to either **18** or **19** were not observed. Therefore, we believe that the cycle suggested in Figure 1 is a close approximation to the mechanistic cycle.

Conclusions

In summary, the following conclusions can be drawn: (i) Intermediates **5** are not detected unless acid quenching is performed. (ii) Cations **14** are detected both in reactions of **3a** and **3b**. They are probably formed by ionization of **5**. (iii) Cations **15** are formed from **14** since **15** appear when **14** disappear. Cations **15** are probably related to a side reaction affording phenols. (iv) Intermediates **7** are never detected, indicating that reductive elimination to afford biaryls **8** and intermediate **9** is fast. (v) Intermediate **9** accumulates in both cases, and therefore the rate-determining step is between **9** and **2**. (vi) Intermediate **11a** has only been detected in one case. This shows the evolution of intermediate **9** giving rise to the recovery of **2**, even in the absence of added oxidizing agents.

Experimental Section

4,4′-Bis(trifluoromethyl)biphenyl (8b) was prepared as previously described.[3]

3,3′-Diaminobiphenyl (8a). A mixture of 3-aminobenzeneboronic acid monohydrate, **3a** (0.50 g, 3.23 mmol), tetrakis(triphenylphosphine)palladium(0) (0.19 g, 0.16 mmol) and toluene (50 mL) was refluxed for 20 h (TLC monitoring). The solvent was evaporated, and the residue was chromatographed through a column of silica gel. 3-Aminobiphenyl was obtained (0.03 g, 5%) with hexanes−ethyl acetate (6:4) as eluent: mp 29−30 °C; MS (70 eV) (m/z) 169 (M$^+$, 100). 3-Aminophenol was eluted with hexanes−ethyl acetate (5:5) (0.05 g, 14%), mp 123−124 °C; MS (70 eV) (m/z) 109 (100, M$^+$), 80 (48). 3,3′-Diaminobiphenyl, **8a**, was eluted with hexanes−ethyl acetate (4:6) (0.13 g, 44%): ^{1}H NMR (250 MHz, CDCl$_3$) δ 3.70 (broad s, 4H; two NH$_2$), 6.64 (dd, J = 8.0 Hz, J = 2.2 Hz, 2H; aromatic H), 6.85 (m, 2H; aromatic H), 6.91−6.97 (m, 2H; aromatic H), 7.19 (apparent t, J = 8.0 Hz, 2H; aromatic H); MS (70 eV) (m/z) 184 (100, M$^+$), 167 (10), 92 (9).

All three compounds obtained showed mp's coincident with those reported in the *Handbook of Chemistry and Physics* and commercial catalogues.

Supporting Information Available: Mass spectra recorded during the course of reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

JO982210O