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Proton Abstraction Mechanism for the Palladium-Catalyzed Intramolecular Arylation

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The arylation of arenes catalyzed by palladium is a more direct alternative for the construction of biaryls[1] than methods based on cross-coupling reactions.[2] Particularly useful is the intramolecular version that allows one to cyclize substrates **1** to form carbo- and heterocycles **2** (Scheme 1).[1,3,4] Intramolecular arylations are also involved in reactions mediated by palladacycles.[5,6]

In contrast to cross-coupling reactions,[2] little is known about the mechanism of the Pd-catalyzed arylation. The initially formed oxidative addition complex **3** could evolve by different mechanisms via intermediates **4**−**6**. An insertion into the arene (Heck-like) would give **4**,[7] which should undergo a trans β-hydrogen elimination to give **2**. An electrophilic aromatic substitution (S_EAr) via intermediates **5** has been usually favored.[8,9] However, in one case, an intramolecular isotope effect of $k_H/k_D = 3.5$ has been determined.[4a,10] In addition, we have found that the arylation on nitrofluorene[11a] or nitrocarbazole[11b] gives substantial amounts of products by reaction at the positions ortho or para to a strong electron-withdrawing NO_2 group. An interesting alternative is a σ-bond metathesis via intermediates **6**,[10a] which seems more likely than processes involving C−H oxidative addition.[12]

To determine the mechanism of the Pd-catalyzed arylation, we decided to study more precisely the effect of substituents on substrates **7a**−**g**[13a] with an alkyl tether CH(R) between the two aryls, which should present minimum steric and/or electronic bias in this reaction. As standard conditions, we adopted those developed by Fagnou et al.,[4a] using bulky phosphine **10a** as the ligand for Pd. Under these conditions, the corresponding 9,10-dihydrophenanthrenes were obtained along with small amounts of phenanthrenes. To facilitate determining the ratio of regioisomers, the crude mixtures were treated with DDQ to give phenanthrenes **8a**−**g**/**9a**−**g** (Table 1).[13b] Satisfactory results were obtained with K_2CO_3, whereas Et_3N or DBU led to unchanged starting material. Reduction was observed with KO-*t*-Bu as the base.

Similar regioisomeric ratios (1.1−2.4:1), favoring reaction at the substituted aryl ring, were obtained from substrates **7a**−**e** bearing groups that are electron-releasing (OMe) or electron-withdrawing (CF_3, Cl) in S_EAr processes (Table 1, entries 1−10). In the case of **7a**, a similar result was obtained with ligand **10b**[14] (Table 1, entries 1 and 2). However, **10b** led to a better selectivity with substrate **7d** (Table 1, entries 6 and 7). Cyclizations could be also carried out in DMA or DMF at 100 °C (Table 1, entries 3, 8, 9, and 13). Remarkably, reaction of **7f** occurred almost exclusively at the trifluorophenyl ring to give **8f** (Table 1, entry 11). This result is clearly incompatible with the S_EAr mechanism. Reaction of **7g** gave 0.2:1 (135 °C) and 0.15:1 (100 °C) ratios of **8g** and **9g** (Table 1, entries 12 and 13), which correspond to intramolecular isotope effects $k_H/k_D = 5.0$ (135 °C) and 6.7 (100 °C).

Scheme 1

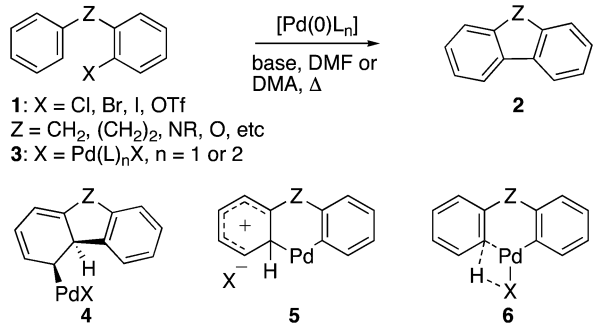
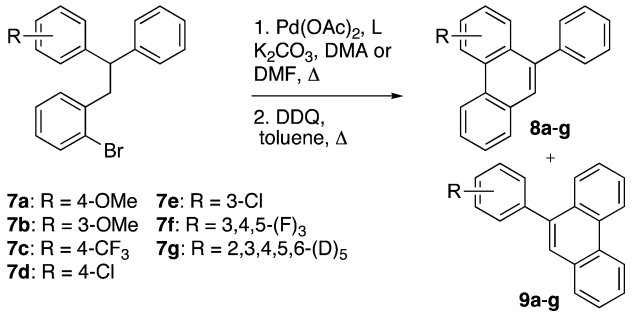


Table 1. Pd-Catalyzed Arylation of Substrates **7a**−**g**[a]



entry	substrate	L[b]	solvent	*T* (°C)	yield (%)	**8**/**9** ratio
1	**7a**	**10a**	DMA	135	90	1.1:1
2	**7a**	**10b**	DMA	135	93	1.1:1
3	**7a**	**10a**	DMF	100	91	1.1:1
4	**7b**	**10a**	DMA	135	75	1.4[c]:1
5	**7c**	**10a**	DMA	135	71	1.3:1
6	**7d**	**10a**	DMA	135	66	1.5:1
7	**7d**	**10b**	DMA	135	66	2.4:1
8	**7d**	**10a**	DMA	100	98[d]	2:1
9	**7d**	**10a**	DMF	100	84	2:1
10	**7e**	**10a**	DMA	135	54	1.9[e]:1
11	**7f**	**10a**	DMA	135	82	25:1
12	**7g**	**10a**	DMA	135	82	0.2:1
13	**7g**	**10a**	DMF	100	92	0.15:1

[a] 5% mol $Pd(OAc)_2$, 10 mol % L, and 3 equiv of K_2CO_3 for 16 h (DMA) or 24 h (DMF). [b] **10a**: 2-(Diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl, **10b**: 2-(dicyclohexylphosphino)-2′,4′,6′-(triisopropyl)biphenyl. [c] 3.7:1 ratio of 2-methoxy- (**8b**) and 4-methoxy-10-phenylphenanthrene (**8′b**). [d] Yield determined by ^1H NMR. [e] 1:1.5 ratio of 2-chloro- (**8e**) and 4-chloro-10-phenylphenanthrene (**8′e**).

We also submitted 5*H*-indeno[1,2-*b*]pyridine derivative **11**[13a] to the Pd-catalyzed arylation (Scheme 2). As anticipated from the results in Table 1, the reaction provided **12** as the major regioisomer (**12**/**13** = 2.1:1), as a result of the arylation para to the pyridine ring.

These results would fit better in a mechanism where the hydrogen from the phenyl is transferred as a proton in the step deciding the selectivity. To our knowledge, these type of processes have been

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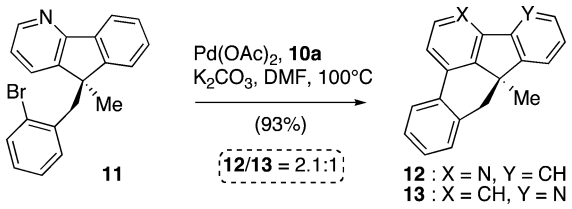
Scheme 2



seldom considered in arylation processes, with the notable exception of a recent computational work by Dedieu and co-workers, where a proton transfer assisted by a palladium center was shown to be the key step for a vinyl to aryl shift.[12]

We carried out a computational DFT study with the B3LYP method on the mechanism of the reaction.[13a] Such studies have been shown recently to provide useful insights into the mechanistic features of cross-coupling reactions.[2c,12,15] Our first set of calculations was carried out on a [Pd(PH_3)Br(*o*-(CH_2−Ph)Ph)] system, a model of the experimental system where hydrogen atoms replace the phosphine substituents and the spectator phenyl group. A single phosphine ligand was considered because of the bulky ligands used in the experiments and because in fact such mechanisms are operative for cross-coupling processes.[15c] A reactant **R1** and a transition state **TS1** could indeed be located, but the computed barrier of 43.3 kcal/mol was too high. The problem seems to be that bromide is not basic enough to abstract a proton from the phenyl, even with the assistance of the palladium center.

This particular reaction takes place in the presence of an excess of carbonate, and basic anions have been shown to replace bromine along the reaction mechanism in related processes.[2c] Therefore, we considered an alternative process where the starting species **R2** contains HCO_3^- instead of Br^-. Similar processes with formate or acetate have been reported in related palladations.[16] The computed structures for reactant **R2**, transition state **TS2**, and palladacycle **P2** are shown in Figure 1. Geometrical changes with respect to **R1** and **TS1** are minor, but the energetics are completely different. The energy barrier is as low as 23.5 kcal/mol, an acceptable value for a reaction at 100−135 °C. An additional set of calculations with three fluorine substituents in the phenyl ring produced species **R3** and **TS3**, with a lower barrier of 13.2 kcal/mol, thus confirming the experimental observation that electron-withdrawing substituents accelerate the reaction. A final set of calculations evaluated the effect of deuterium substitution for transition state **TS2**. The computed values for k_H/k_D were 4.3 at 100 °C and 3.7 at 135 °C, again in good agreement with experiment. Similar results have been obtained from a related intermolecular mechanism, with no previous coordination of hydrogencarbonate to palladium.[13a,17]

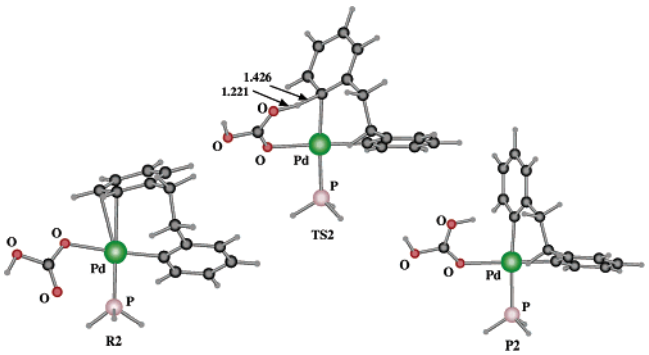


Figure 1. B3LYP optimized structures of species **R2**, **TS2**, and **P2**.

In summary, our experimental and theoretical results demonstrate that, for these systems, the Pd-catalyzed arylation does not involve an electrophilic aromatic substitution reaction. A mechanism for the Pd-catalyzed arylation involving a proton abstraction by a carbonate, or related ligand, provides a satisfactory explanation for the experimental data.

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Supporting Information Available: Experimental details, characterization data, computational details, Cartesian coordinates, Mulliken charges, and absolute energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Neither in **TS2** nor in **TS3** (nor in **TS2′** and **TS3′**, of the intermolecular pathway) does the phenyl ring present the distribution of Mulliken charges expected for an electrophilic substitution.

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