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Bidentate phosphines as ligands in the palladium-catalyzed intramolecular arylation: the intermolecular base-assisted proton abstraction mechanism

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Abstract

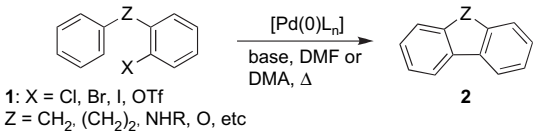
The palladium-catalyzed arylation of aryl bromides can be carried out in the presence of bidentate phosphines, such as dppm, dppe, dppf, and Xantphos under mild conditions. The experimental results and the DFT calculations fully support for this reaction a mechanism proceeding by an intermolecular proton abstraction.

Keywords: Palladium; Arylation; Phosphines; DFT calculations

1. Introduction

The arylation of arenes catalyzed by palladium is a useful alternative to methods based on cross-coupling reactions[1] for the construction of biaryls and more complex polyarenes.[2] Although much of the effort has been focused on the intramolecular arylation of substrates **1** to form carbo- and heterocycles **2** (Scheme 1),[2–4] significant progress has been done recently in the intermolecular version of this reaction.[5,6]

Recent mechanistic work does not support earlier proposals based on an electrophilic aromatic substitution (S_EAr)[7,8] for the palladium-catalyzed arylation reaction. Thus, intramolecular isotope effects k_H/k_D=3.5–4 have been determined in different processes.[4a,9] We have also reported examples in which the arylation proceeded at position *ortho* or *para* to electron-withdrawing NO_2 groups.[10]



Scheme 1.

Determining the details of this arylation is important to develop milder reaction conditions. In addition, similar mechanisms are probably followed in other reactions that proceed via palladacycles.[3d,11–13,14–18] We have recently studied the effect of substituents on the arylation process on systems **3**, which led to mixtures of **4** and **5** after aromatization of the initially formed 9-aryl-9,10-dihydrophenanthrenes using DDQ (Scheme 2).[19] Electron-withdrawing substituents X, such as fluorine, chlorine, and trifluoromethyl, favor formation of products **4**. This directing effect is particularly strong at the *ortho* position to the C–H bond being cleaved. Electronegative methoxy groups that are electron-releasing in electrophilic

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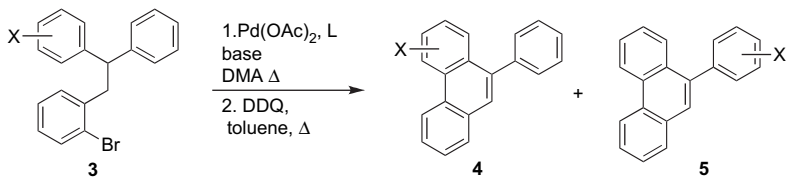
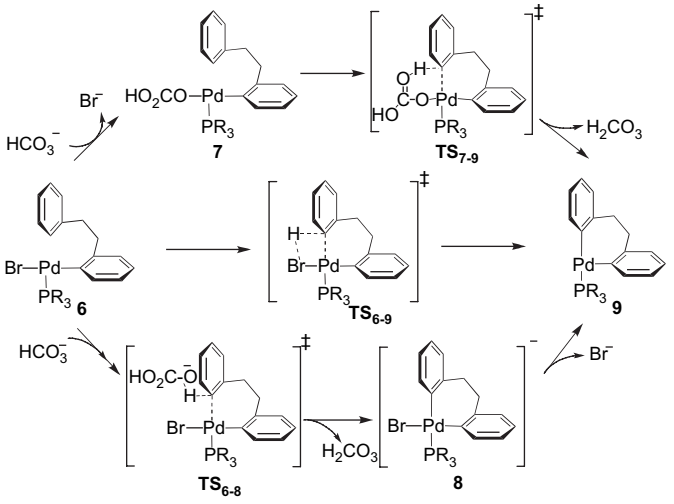


Scheme 2.

aromatic substitutions behave similarly to chlorine substituents, which indicates that the main effect of substituents in this reaction is inductive. In addition, a substantial deuterium isotope effect (k_H/k_D=5.0 at 135 °C and 6.7 at 100 °C) was determined in this process, which correlates with a linear arrangement of base and H–C in the rate-determining step.[20]

These results, which are in line with related work on other arylations[4g] and cyclometalation reactions,[21] are fully consistent with a mechanism involving a proton abstraction by the base (Scheme 3).[19,22] Although our DFT calculations done with model compound **6** excluded a direct proton abstraction through **TS$_{6-9}$** to form seven-membered ring palladacycle **9**, we could not distinguish between two base-assisted processes: an intramolecular reaction via intermediate **7** and **TS$_{7-9}$** and an intermolecular reaction via **TS$_{6-8}$** and intermediate **8**.



Scheme 3.

As part of a study to find new, milder reaction conditions for the intramolecular arylation reaction, we discovered that bidentate phosphines are excellent ligands for this process. Importantly, this result suggests that, at least in these cases, the reaction proceeds by the intermolecular base-assisted proton abstraction mechanism, which is also supported by new DFT calculations.

2. Results and discussion

2.1. Experimental results

We selected fluorinated substrate **10** to study the effect of different bases in the arylation reaction. As in our previous study,[19] to facilitate determining the ratio of regioisomers by ^{1}H NMR analysis, the crude mixtures were treated with DDQ to give phenanthrenes **11** and **12**. In addition, reduction compound **13** was observed under some reaction conditions. As the ligand, we used first 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl[23] (**14**) (see Fig. 1), which gave the best results in our previous study.[19] Using K_2CO_3 as the base in DMA at 135 °C, we obtained a 1.6:1 ratio of **11** and **12** (Table 1, entry 1).[19] When the reaction was carried out at 100 °C, a slightly better selectivity was observed (Table 1, entry 2). Under these conditions only traces of reduction product **13** were detected. Pivalic acid has been shown to be a very useful additive in palladium-catalyzed arylations, presumably by acting as a ligand to palladium as well as a base in an intramolecular base-assisted process[5b] (such as the one proceeding via intermediate **7** in Scheme 3). Therefore, we tried the reaction of **10** with potassium or cesium pivalate, formed in situ with the corresponding carbonate (Table 1, entries 3–6). The best results with ligand **14** were obtained in the presence of potassium pivalate at 100 °C (Table 1, entry 3), which led to a 1.7:1 ratio of **11** and **12** in 79% yield in only 4 h. Interestingly, a better result (86% yield) was obtained with bidentate ligand 1,1′-bis(diphenylphosphino)ferrocene (dppf) instead of **14** (Table 1, entry 6). Reactions with potassium acetate led to poorer results (Table 1, entries 7 and 8). When NaH was used as the base, almost exclusive reduction of **10** to **13** was observed (Table 1, entry 9). Sodium or potassium amidates, formed in situ with *t*-BuCONH$_2$ or *t*-BuCONHMe and NaH or KO*t*-Bu, led to lower conversions and/or extensive reduction of **10** (Table 1, entries 10–19). On the other hand, although 1,1,3,3-tetramethylguanidine led to a poor conversion, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine was an effective base for this process (Table 1, entries 20 and 21).

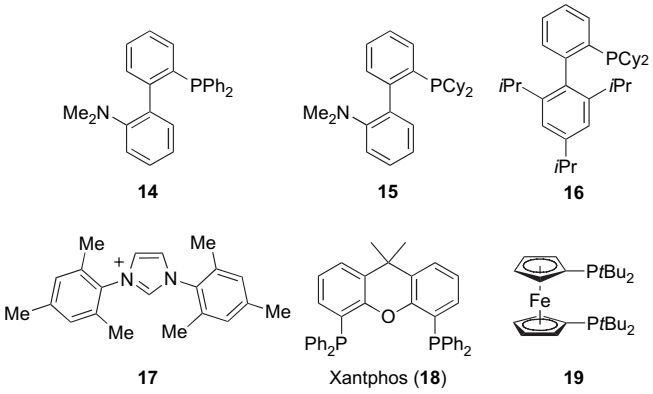
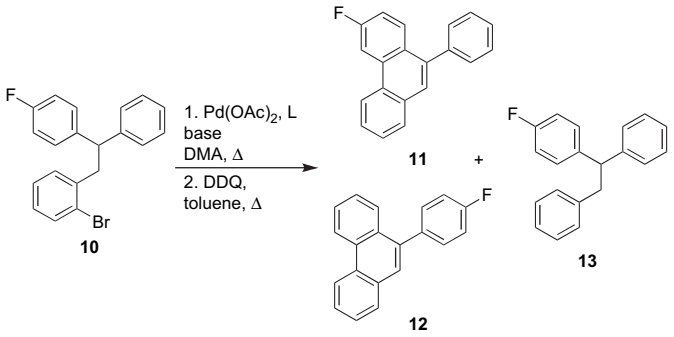


Figure 1. Ligands used for the palladium-catalyzed arylation.

Table 1
Pd-catalyzed arylation of substrate **10** with different bases[a]



Entry	Base	T (°C)	Time (h)	Conv. (%) (% **13**)	**11/12** Ratio (yield %)
1	K_2CO_3	135	16	>95 (0)	1.6:1 (72)[19]
2	K_2CO_3	100	25	92 (2)	1.7:1[b]
3	*t*-$BuCO_2H$[c]/K_2CO_3	100	4	>95 (0)	1.7:1 (79)
4	*t*-$BuCO_2H$[c]/K_2CO_3	80	42	>95 (0)	1.5:1 (75)
5	*t*-$BuCO_2H$[c]/Cs_2CO_3	80	42	84 (0)	1:4 (67)
6[d]	*t*-$BuCO_2H$[c]/K_2CO_3	100	4	>95 (0)	1.7:1 (86)
7	KOAc	80	42	52 (0)	1.5:1[b]
8	*t*-$BuCO_2H$[c]/KOAc	80	42	65 (0)	1.5:1[b]
9	NaH	135	52	>95 (95)	0.2:1[b]
10	*t*-$BuCONH_2$[c]/NaH	135	52	>95 (87)	0.1:1[b]
11	*t*-BuCONHMe[c]/NaH	135	52	>95 (98)	0.2:1[b]
12	*t*-$BuCONH_2$/NaH[e]	135	22	55 (27)	1.7:1[b]
13	*t*-$BuCONH_2$/NaH[f]	135	28	17 (11)	1.2:1[b]
14	*t*-$BuCONH_2$/NaH[g]	135	28	23 (15)	1.2:1[b]
15	KO*t*-Bu	135	22	>95 (47)	1.7:1[b]
16	*t*-$BuCONH_2$[c]/KO*t*-Bu	135	22	>95 (20)	1.7:1[b]
17	*t*-BuCONHMe[c]/KO*t*-Bu	135	22	>95 (13)	1.7:1[b]
18	*t*-$BuCONH_2$/KO*t*-Bu[f]	135	26	56 (12)	1.6:1[b]
19	*t*-$BuCONH_2$/KO*t*-Bu[g]	135	26	38 (25)	1.4:1[b]
20	$HN{=}C(NMe_2)_2$	100	22	15 (5)	1.4:1[b]
21	*t*-$BuN{=}C(NMe_2)_2$	100	22	91 (0)	1.7:1 (64)

[a] Reactions carried out with 5 mol % $Pd(OAc)_2$, 10 mol % 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl (**14**), and base (2.5 equiv). The amount of **13** was determined by ^{1}H NMR of the crude reaction mixtures.
[b] Isolated yield not determined.
[c] 0.3 equiv.
[d] Reaction with dppf (5 mol %) as the ligand.
[e] One equivalent each of amide and NaH.
[f] The sodium or potassium amidate was formed from the amide (1 equiv) and base (1 equiv) at 0 °C prior to the addition of **10** and catalyst.
[g] As in entry 13 or 18 but with 2.5 equiv each.

The fact that dppf gives the best result in the presence of pivalate anion (Table 1, entry 6) casts doubts about the role played by this carboxylate as a ligand for Pd in the intramolecular proton abstraction event. Thus, if pivalate is still coordinated to Pd, an unlikely pentacoordinate Pd(II) intermediate bearing a diphosphine ligand would be formed. We therefore decided to examine in more detail several diphosphines as well as other ligands in the arylation of **10** with K_2CO_3 as the base (Fig. 1). First, we tested several bulky monophosphines (Table 2). Thus, phosphines **15** and **16**,[24] which are structurally similar to **14**, led to extensive reduction of **10** (Table 2, entries 1 and 2). Similar results were obtained with PCy_3 (Table 2, entry 3), whereas P(*o*-Tol)$_3$ led to a poor conversion (Table 2, entry 4). P(*t*-Bu)$_3$ gave **11** and **12** in

Table 2
Pd-catalyzed arylation of substrate **10** with different ligands[a]

Entry	L	Time (h)	Conv. (%) (% **13**)	**11/12** Ratio (yield %)
1	**15**	2	>95 (30)	1.5:1[b]
2	**16**	2	>95 (72)	1:1[b]
3	PCy_3	48	>95 (40)	1.5:1[b]
4	P(*o*-Tol)$_3$	21	30 (0)	1.6:1[b]
5	P*t*-Bu_3[c]	21	>95 (0)	1.8:1 (41)
6	**17**	18	18 (0)	1.7:1[b]
7	dppf	21	>95 (0)	1.6:1 (79)
8	**18**	2	>95 (—[d])	1.7:1 (73)
9	dppm	2	>95 (—[d])	1.7:1 (77)
10	dppe	2	>95 (—[d])	1.7:1 (72)
11	dppp	2	>95 (—[d])	1.7:1 (59)
12	**19**	2	>95 (—[d])	1.7:1 (47)

[a] Reactions carried out with 5 mol % $Pd(OAc)_2$, 10 mol % L or 5 mol % L_2, and K_2CO_3 (2.5 equiv) in DMA at 135 °C. The amount of **13** was determined by ^{1}H NMR of the crude reaction mixtures.
[b] Isolated yield not determined.
[c] The HBF_4 salt was used.
[d] Traces (<1%) of **13** were detected; dppm=bis(diphenylphosphino)-methane; dppe=1,2-bis(diphenylphosphino)ethane; dppp=1,3-bis(diphenylphosphino)propane.

moderate yield (Table 2, entry 5). We also tried IMes (*N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) ligand generated in situ, although the results were poor (Table 2, entry 6). In contrast, dppf afforded the arylated products in good yield (Table 2, entry 7). Faster reactions were observed with Xantphos (**18**),[25] dppm, dppe, dppp, and ferrocenyldiphosphine **19** (Table 2, entries 8–12). The best yields were obtained with Xantphos (**18**), dppm, and dppe (Table 2, entries 8–10).

These results show that diphosphines are the ligands of choice for this transformation. In addition, the similar behavior displayed by Xantphos (**18**) and more simple diphosphines such as dppm and dppe suggest that **18** coordinates in a cis-fashion to Pd in this reaction. Indeed, it has been shown that **18** can behave as a cis- or trans-chelating ligand with Pd(II).[26,27]

We also assayed strong phosphazane bases **20**–**21** (Schwesinger bases) (Fig. 2).[28] The *t*-Bu-P$_4$ base **22** is an extremely strong nonmetallic organic base (pK_{BH^+} = 42.7 in MeCN) that can even deprotonate aromatic compounds under mild conditions.[29] Indeed, substrate **10** reacted with base **22** (1 equiv) in DMA at 80 °C for 2 h in the absence of palladium to give exclusively **11**, although the isolated yield was low (ca. 15%). Substrate **10** also reacted with strong base KHMDS, under the same conditions, to give a 0.8:1 mixture of **11** and **12** (ca. 40%), whereas NaH led only to a very low conversion (ca.

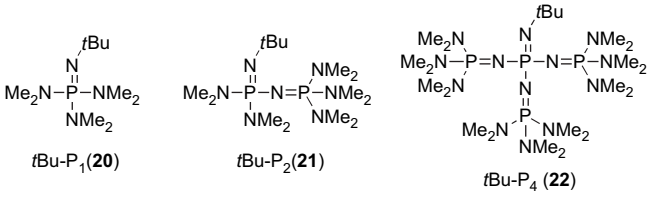


Figure 2. Phosphazene bases.

Table 3
Pd-catalyzed arylation of substrate **10** with base **20** or **21**[a]

Entry	L	Base	Time (h)	*T* (°C)	Conv. (%) (% **13**)	**11/12** Ratio (yield %)
1	dppf	**20**	6	100	>95 (—[b])	1.8:1 (78)
2	dppf	**20**	5	135	>95 (1)	1.9:1 (69)
3	dppf	**21**	22	100	23 (8)	1.9:1[c]
4	dppf	**21**	5	135	>95 (5)	1.9:1 (69)
5	—	**21**	20	135	>95 (5)	1.9:1 (64)

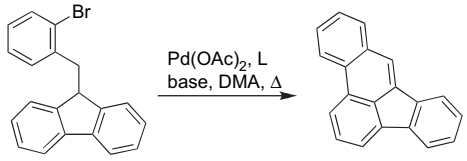
[a] Reactions carried out with 5 mol % $Pd(OAc)_2$, 5 mol % L_2, and 2.5 equiv base in DMA.
[b] Traces (<1%) of **13** were detected.
[c] Yield not determined.

8%) (DMA, 80 °C, 18 h). These reactions probably proceed via formation of the corresponding benzyne.

Using milder bases **20** and **21** only 2–6% of intramolecular arylation was observed at 135 °C in DMA after 24 h in the absence of Pd. In the presence of palladium and dppf, phosphazanes **20** and **21** gave satisfactory yields in the cyclization of **10** (Table 3, entries 1, 2, and 4). Reaction was slower in the absence of the diphosphine (Table 3, compare entries 4 and 5).

We have reported originally the cyclization of fluorene derivative **23** to give benz[*e*]acephenanthrylene (**24**) with $Pd(OAc)_2$ (5 mol %) and K_2CO_3 in DMF (130 °C, 48 h) in 52% yield.[10a] Whereas PPh_3 or $AsPh_3$ as the ligands led to poor results,[10a] the cyclization of **23** using the palladium complex with ligand **14** could be performed at 60 °C to give **24** in

Table 4
Pd-catalyzed arylation of substrate **23**[a]



23 **24**

Entry	L	Base	Time (h)	*T* (°C)	Conv. (%)	**24** (yield, %)
1	**14**	K_2CO_3	48	60	>95	62
2	**14**	*t*-$BuCO_2H$[b]/K_2CO_3	24	60	>95	73
3	**14**	*t*-$BuCO_2H$[b]/K_2CO_3	26	80	>95	58
4	dppf	K_2CO_3	24	60	>95	71
5	dppf	*t*-$BuCO_2H$[b]/K_2CO_3	24	60	>95	59
6	dppf	*t*-$BuCO_2H$[b]/K_2CO_3	26	80	>95	40
7	dppf	*t*-$BuN{=}C(NMe_2)_2$	4	100	>95	47
8	dppm	K_2CO_3	36	80	>95	44
9	dppe	K_2CO_3	25	80	>95	85

[a] Reactions carried out with 5 mol % $Pd(OAc)_2$, 10 mol % L or 5 mol % L_2, and 2.5 equiv base in DMA.
[b] 0.3 equiv.

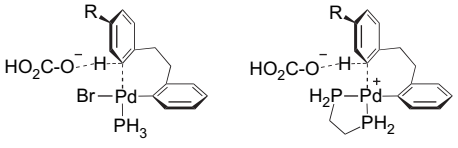
73% yield (Table 4, entry 2). In this case, the reaction with Pd/dppf proceeded with better yield in the absence of *t*-$BuCO_2H$ (Table 4, compare entries 4 and 5). The best result for the synthesis of **24** was obtained using dppe as the ligand and K_2CO_3 as the base (Table 4, entry 9).

To determine the intramolecular isotope effects in the arylation reaction, we studied the reaction of substrate **25** with $Pd(OAc)_2$ and dppf (Scheme 4). From the ratio of **26** and **27**, an intramolecular isotope effect k_H/k_D=5.3 was determined for the reaction performed at 135 °C. This value is almost identical to that found using ligand **14** (k_H/k_D=5.0) at this temperature (135 °C),[19] which suggests that the reactions in the presence of **14** and dppe proceed by the same mechanism.

2.2. DFT calculations

We carried out a series of B3LYP calculations on the reaction mechanism to confirm the seeming similarity between our previous results with monodentate phosphine ligands[19] and those found with bidentate phosphine ligands. We limit the discussion here to one of the mechanisms in Scheme 3, the base-assisted intermolecular proton abstraction going through transition state $\mathbf{TS_{6-8}}$. Our previous work discarded for this type of complexes the unassisted proton abstraction, and the intramolecular base-assisted proton abstraction seems unlikely because it would require the breaking of one of the Pd–P bonds.

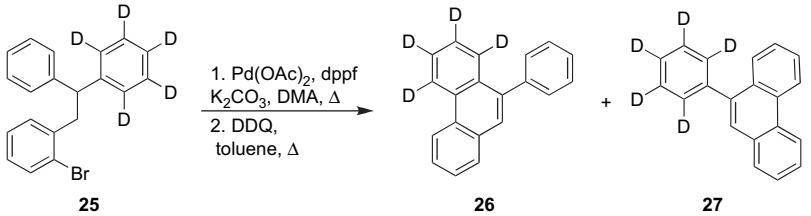
In our calculations we use the model systems presented in Figure 3, labeled as **t1a**, **t1b**, **t2a**, **t2b**. The prefix **t** stands for theoretical. Models **t1a** and **t1b** correspond to those used in our previous works, both of them with monophosphine ligands;[19] **t1a** with all hydrogen substituents in the cyclopalladated ring and **t1b** with one fluorine in the position *meta* to the metalated carbon. Models **t2a** and **t2b** are the analogous species corresponding to bidentate phosphines. We use as bidentate phosphine $H_2PCH_2CH_2PH_2$, a simplified model of dppe, where the phenyls are replaced by hydrogens, and that



t1a: R = H
t1b: R = F

t2a: R = H
t2b: R = F

Figure 3. Computational models.



25 **26** **27**

Scheme 4.

has been labeled sometimes as dhpe in previous computational studies.[30] The system we are more closely modeling is thus that with the dppe ligand, corresponding to entry 10 in Table 2, and favoring the reaction at the fluorinated ring **11** by a ratio 1.7:1. Let us recall here that the corresponding value for the system with a monodentate ligand and the same type of substitution was 1.6:1, therefore very similar.[19b]

We have decided not to include the full phosphine in the computed system, as effects were minor and it required a significant computational effort in terms of conformational analysis.[19b] Because of this, we repeat here the calculations for the monodentate phosphine model systems. The study of the bidentate systems introduces in any case a computational subtlety that must be taken into account. This is the conformation of the envelope defined by the Pd–P–C–C–P five-membered ring. The two possible conformations have been computed for the intermediate **t2aR** and the transition state **t2aTS** corresponding to system **t2a**, and the resulting geometries are shown in Figure 4. The difference between the two conformations is apparent from the position of the two carbon atoms of the chelating ligand, in the right hand side of each drawing. Conformation 2 is slightly more stable for **t2aR** (by 0.3 kcal/mol), but we decided in favor of conformation 1 because it is more stable for the rate-determining transition state **t2aTS** (by 0.8 kcal/mol).

Table 5 collects the computed barriers, measured as difference between transition state and intermediate, for the four different model systems under consideration. Three different magnitudes are presented: potential energy (E), gas phase free energy (G), and solvent-corrected potential energy (E_{PCM}). The aspect we want to highlight here is the similarity between all the computed barriers. In particular, if we compare the potential energies, we see that the difference between the two systems with hydrogen substituents (**t1a** and **t2a**) is only 0.3 kcal/mol; and the difference between the two fluorinated systems (**t1b** and **t2b**) is only 0.2 kcal/mol. Differences are larger when solvent effects are considered, but the similarity between the behavior of the two sets of systems is apparent.

Table 5
Computed barriers (kcal/mol) for the base-assisted intermolecular proton abstraction reaction with different phosphines

System	Ligand set	R	E	G	E_{PCM}
t1a	P, Br	H	19.8	18.0	19.0
t1b	P, Br	F	18.8	16.8	18.0
t2a	P, P	H	19.5	17.6	22.1
t2b	P, P	F	18.6	16.6	20.9

The drawings of the three computed structures for the two systems with the bidentate phosphines, **t2a** and **t2b**, are presented in Figures 5 and 6, respectively. The geometries respond to the patterns already reported for the complexes with monodentate phosphines. There is a nearly linear arrangement C···H···O in the transition state, with the hydrogen atom being clearly transferred from carbon to oxygen. For instance, in **t2aTS** (Fig. 5) the C–H and H–O distances are 1.429 and 1.237 Å, respectively.

In order to have a more quantitative comparison with the experimental data, we have computed theoretical selectivity ratios, and present the results of these calculations in Table 6. In order to have a single computed barrier where to evaluate the selectivity we have used a similar approach to our previous work, the barrier being estimated as $\Delta E_{PCM}+(\Delta G-\Delta E)$. In this way, the zero point energy corrections and the solute entropic corrections are taken from the gas phase calculation of the Gibbs free energy, and added to the solvent-corrected potential energy. Then, the barriers are translated into selectivities by assuming that product population will be related to the Boltzmann distribution of the energies of the

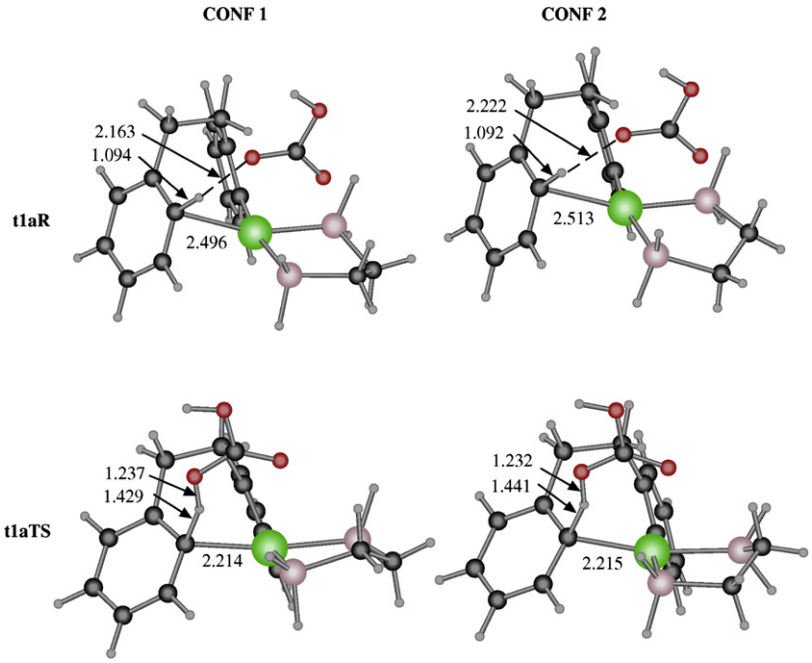


Figure 4. Computed structures for the two conformations of **t2aR** and **t2aTS**.

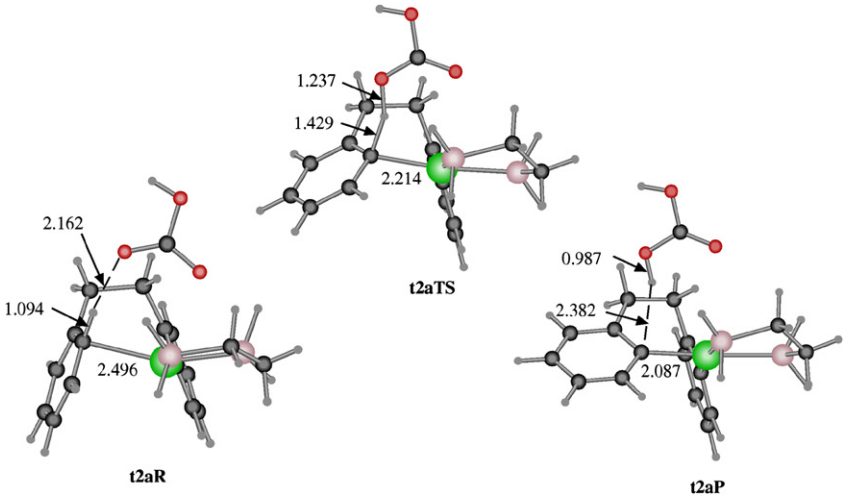


Figure 5. B3LYP structures for the reactant, transition state, and product for system **t2a**. Bond distances in Å.

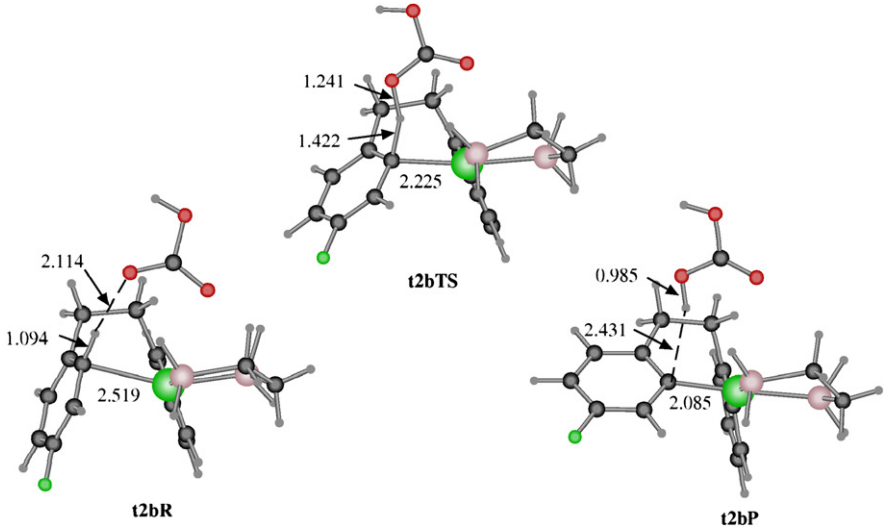


Figure 6. B3LYP structures for the reactant, transition state, and product for system **t2b**. Bond distances are in Å.

corresponding transition states.[31] The comparison between the computed and experimental ratios reported in Table 6 is satisfactory. The agreement in the absolute value of regioselectivity is certainly not perfect, with computed values around 4:1 and experimental values around 1.7:1. This is understandable because of the exponential dependence of product abundance with respect to energy differences. The encouraging result is the very similar behavior of the systems with monodentate and bidentate phosphines. The experimental ratio increases from 1.6:1 to 1.7:1 when a bidentate phosphine is used. The computed values have also a slight increase from 4.1:1 to 4.4:1. We think that this adds strong support to our hypothesis that for this particular type of systems the reaction follows an intermolecular base-assisted proton abstraction mechanism.

Table 6
Computed energy barriers (kcal/mol) and selectivity ratios for the base-assisted intermolecular proton abstraction reaction with different phosphines

System	Ligand set	R	Barrier	Computed ratio	Experimental ratio
t1a	P, Br	H	17.2	1:1	1:1
t1b	P, Br	F	16.1	4.1:1	1.6:1
t2a	P, P	H	20.1	1:1	1:1
t2b	P, P	F	18.9	4.4:1	1.7:1

A final set of calculations consisted in the evaluation of the kinetic isotope effect of the replacement of the hydrogen atom being transferred by deuterium. The computed k_H/k_D values at 135 °C for systems **t1a**, **t1b**, **t2a**, and **t2b** were 3.8, 3.7, 3.8, and 3.6, respectively. These values are again in good qualitative agreement with the experimental values of 5.0–5.3.

3. Conclusion

Bidentate phosphines, such as dppm, dppe, dppf, and Xantphos, are excellent ligands for the palladium-catalyzed arylation, which allow performing these reactions under milder conditions. Thus, for example, the arylation of fluorene **23** to give benz[*e*]acephenanthrylene (**24**) can now be carried out in 85% yield with $Pd(OAc)_2$/dppe at 80 °C in 25 h, whereas in the absence of the diphopshine a 52% yield

was achieved at higher temperature and longer reaction time (130 °C, 48 h).[10a]

Reaction with the bidentate phosphines most probably proceeds by the intermolecular proton abstraction mechanism, which is supported by the DFT calculations. Although addition of pivalic acid has a beneficial effect in many cases, the fact that the reaction occurs with a palladium complex bearing a bidentate diphosphine suggests that this carboxylate, like carbonate or bicarbonate, acts as an external base. The success of these mild bases in palladium-catalyzed arylation might actually rest on their relatively weak coordinating behavior. Additional experimental work to test this hypothesis is underway.

4. Experimental

4.1. General

All reactions were carried out under Ar. Dimethylacetamide was purchased anhydrous and packaged under N_2 (Aldrich) and was used without further purification. Thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merk GF_{234}). Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40–60 μm). NMR spectra were recorded at 23 °C on Bruker Avance 400 Ultrashield or Bruker Avance 500 Ultrashield apparatus. Mass spectra were recorded on a Waters LCT Premier (ESI) and Waters GCT (EI, CI) spectrometers.

1-Bromo-2-(2-(4-fluorophenyl)-2-phenylethyl)benzene (**10**),[19] 1-bromo-2-(2-(perdeutereophenyl)-2-phenylethyl)benzene (**25**),[19] and 9-(2-bromophenylmethyl)fluorene (**23**)[10a] were prepared according to previously published procedures. Arylation products **11**,[19] **12**,[19] **24**,[10a] **26**,[19] and **27**[19] have also been described.

4.2. General procedure for the intramolecular arylation reaction of substrate *10* using different bases and additives

A solution of the bromoarene **10**, $Pd(OAc)_2$ (5 mol %), ligand (10 mol % when 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl (**14**) was used or 5 mol % when dppf was used), base (2.5 equiv), and additive (0.3 equiv) in anhydrous DMA was heated between 80 and 135 °C (see Table 1). Once the arylation was completed the reaction mixture was cooled to room temperature. A saturated solution of NaCl was added and the organic layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated. After being analyzed by ^1H NMR to determine the amount of reduction product **13**, the crude mixture was aromatized with DDQ.

4.3. General procedure for the aromatization

A solution of the crude arylation product and DDQ (3 equiv) in toluene was heated to reflux for 16 h. The reaction mixture was cooled to room temperature, toluene was evaporated, and the reaction crude was filtered through silica using hexane as eluent. The solvent was evaporated and the residue was chromatographed (SiO_2, hexane) to give the mixture **11** and **12**.

4.4. General procedure for the intramolecular arylation reaction of substrate *10* using different ligands

A solution of the bromoarene **10**, $Pd(OAc)_2$ (5 mol %), ligand (10 mol % when monophosphines or imidazolium salt (**17**) were used or 5 mol % when diphosphines were used), base (2.5 equiv) in anhydrous DMA was heated at 135 °C. Once the arylation was completed the reaction mixture was cooled to room temperature. A saturated solution of NaCl was added and organic layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated. After being analyzed by ^1H NMR to determine the amount of reduction product **13**, the crude mixture was aromatized with DDQ.

4.5. General procedure for the intramolecular arylation reaction of substrate *10* using different phosphazenes as the base

Bromoarene **10**, $Pd(OAc)_2$ (5 mol %), and dppf (5 mol %) were dissolved in anhydrous DMA. Phosphazene base (2.5 equiv) was added dropwise via syringe and the reaction mixture was heated at 100 or 135 °C (see Table 3). Once the arylation was completed the reaction mixture was cooled to room temperature, the solvent was evaporated, and reaction crude filtered through silica using hexane as eluent. After being analyzed by ^1H NMR to determine the amount of reduction product **13**, the crude mixture was aromatized with DDQ.

4.6. General procedure for the intramolecular arylation reaction of substrate *23* using different ligands and additive

A solution of the bromoarene **23**, $Pd(OAc)_2$ (5 mol %), ligand (10 mol % when monophosphine **14** was used or 5 mol % when diphosphines were used), K_2CO_3 (2.5 equiv), and pivalic acid (0.3 equiv) in anhydrous DMA was heated at 60 or 80 °C (see Table 4). Once the arylation was completed the reaction mixture was cooled to room temperature. A saturated solution of NaCl was added and organic layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated. The residue was chromatographed (SiO_2, hexane) to give **24**.

5. Computational details

All calculations were performed with Gaussian 03.[32] The method was B3LYP.[33] The basis set was LANL2DZ for Pd and Br,[34] and 6-31+G(d) for H, C, O, F, P.[35] The basis set for Br was expanded to include polarization[36] and diffuse functions.[37] All geometry optimizations were complete, and the stationary points were identified as local minima or

transition states through the number of negative eigenvalues in their hessian matrices.

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References and notes

1. (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley: Weinheim, 2004; (b) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704–4734; (c) Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298–9307.
2. (a) Echavarren, A. M.; Gómez-Lor, B.; González, J. J.; de Frutos, Ó. *Synlett* **2003**, 585–597; (b) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253–1264; (c) Satoh, T.; Miura, M. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 1199–1207; (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238; (e) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727–2734.
3. Lead references on synthetic applications: (a) Wang, L.; Shevlin, P. B. *Org. Lett.* **2000**, *2*, 3703–3705; (b) Torres, J. C.; Pinto, A. C.; Garden, S. J. *Tetrahedron* **2004**, *60*, 9889–9900; (c) Harrowven, D. C.; Woodcock, T.; Howes, P. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 3899–3901; (d) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148–13149; (e) Shen, D. M.; Liu, C.; Chen, Q. Y. *J. Org. Chem.* **2006**, *71*, 6508–6511; (f) Kim, D.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2006**, *8*, 2313–2316; (g) Arai, N.; Takahashi, M.; Mitani, M.; Mori, A. *Synlett* **2006**, 3170–3172; (h) Wegner, H. A.; Reisch, H.; Rauch, K.; Demeter, A.; Zachariasse, K. A.; de Meijere, A.; Scott, L. T. *J. Org. Chem.* **2006**, *71*, 9080–9087; (i) Jackson, E. A.; Steinberg, B. D.; Bancu, M.; Wakamiya, A.; Scott, L. T. *J. Am. Chem. Soc.* **2007**, *129*, 484–485.
4. (a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187; (b) Lafrance, M.; Blaquière, N.; Fagnou, K. *Chem. Commun.* **2004**, 2874–2875; (c) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578–7584; (d) Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857–1860; (e) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849–2852; (f) Leclerc, J.-P.; Andre, M.; Fagnou, K. *J. Org. Chem.* **2006**, *71*, 1711–1714; (g) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590; (h) Lafrance, M.; Blaquiere, N.; Fagnou, K. *Eur. J. Org. Chem.* **2007**, 811–825.
5. (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. K. *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756; (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497; (c) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097–5100; (d) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175.
6. (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021; (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781–7786.
7. Substituent effects on the formation of five-membered ring palladacycles follow the order X=MeO>H>NO_2: (a) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, *425*, 151–154; (b) Martín-Matute, B.; Mateo, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2001**, *7*, 2341–2348.
8. (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897–2900; (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057; (c) See also: Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159–1162.
9. Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084–12085.
10. (a) González, J. J.; García, N.; Gómez-Lor, B.; Echavarren, A. M. *J. Org. Chem.* **1997**, *62*, 1286–1291; (b) Gómez-Lor, B.; Echavarren, A. M. *Org. Lett.* **2004**, *6*, 2993–2996.
11. (a) Ma, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2005**, *44*, 7512–7517; (b) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2571.
12. (a) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1988**, *346*, C27–C30; (b) Catellani, M.; Mann, B. E. *J. Organomet. Chem.* **1990**, *390*, 251–255; (c) Catellani, M.; Chiusoli, G. P.; Castagnoli, C. *J. Organomet. Chem.* **1991**, *401*, C30–C33; (d) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, *437*, 369–373; (e) Bocelli, G.; Catellani, M.; Ghelli, S. *J. Organomet. Chem.* **1993**, *458*, C12–C15; (f) Catellani, M.; Fagnola, M. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2421–2422; (g) Catellani, M.; Marmiroli, B.; Fagnola, M. C.; Acquotti, D. *J. Organomet. Chem.* **1996**, *507*, 157–162; (h) Catellani, M.; Ferioli, L. *Synthesis* **1996**, 769–772; (i) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 119–122; (j) Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* **2000**, 157–158; (k) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreño, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336–4346; (l) Motti, E.; Ippomei, G.; Deledda, S.; Catellani, M. *Synthesis* **2003**, 2671–2678; (m) Catellani, M. *Synlett* **2003**, 298–313; (n) Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759–4762; (o) Motti, E.; Rossetti, M.; Bocelli, G.; Catellani, M. *J. Organomet. Chem.* **2004**, *689*, 3741–3749; (p) Catellani, M.; Motti, E.; Faccini, F.; Ferraccioli, R. *Pure Appl. Chem.* **2005**, *77*, 1243–1248.
13. (a) Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045–1046; (b) Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745–4747; (c) Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043–2045; (d) Martins, A.; Marquardt, U.; Kasravi, N.; Alberico, D.; Lautens, M. *J. Org. Chem.* **2006**, *71*, 4937–4942; (e) Jafarpour, F.; Lautens, M. *Org. Lett.* **2006**, *8*, 3601–3604; (f) Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 14436–14437; (g) Martins, A.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 4827–4829; (h) Hulcoop, D. G.; Lautens, M. *Org. Lett.* **2007**, *9*, 1761–1764; (i) Alberico, D.; Rudolph, A.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 775–781; (j) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485–1488.
14. (a) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326–14327; (b) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506–11507; (c) Huang, Q.; Campo, M. A.; Yao, T.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 8251–8257; (d) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460–7461; (e) Zhao, J.; Campo, M.; Larock, R. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1873–1875; (f) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 701–704; (g) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 5340–5348; (h) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288–5295.
15. (a) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115–3118; (b) Masselot, D.; Charmant, J. P. H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 694–695.
16. Cárdenas, D. J.; Martín-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033–5040.
17. (a) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. *J. Am. Chem. Soc.* **2005**, *127*, 7171–7182; (b) Mota, A. J.; Dedieu, A. *Organometallics* **2006**, *25*, 3130–3142; (c) Bour, C.; Blond, G.; Salem, B.; Suffert, J. *Tetrahedron* **2006**, *62*, 10567–10581.
18. Singh, A.; Sharp, P. R. *J. Am. Chem. Soc.* **2006**, *128*, 5998–5999.
19. (a) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067; (b) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886.
20. Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2005; pp 422–428.
21. Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755.
22. The intermolecular Pd-catalyzed arylation of benzoxazoles proceeds by an entirely different mechanism involving ring-opening to form an aryl isonitrile: Sánchez, R. S.; Zhuravlev, F. A. *J. Am. Chem. Soc.* **2007**, *129*, 5824–5825.

23. Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019–6022.
24. (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696; (b) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.
25. Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081–3089.
26. Cis-chelation of **18**: van Haaren, R. J.; Goubitz, K.; Fraanje, J.; van Strijdonck, G. P. F.; Oevering, H.; Coussens, B.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Inorg. Chem.* **2001**, *40*, 3363–3372.
27. Trans-chelation of **18** to Pd(II): (a) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895–904; (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048.
28. (a) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167–1169; (b) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G.-Z.; Peters, E.-M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, 1055–1081; (c) Schwesinger, R.; Hasenfratz, C.; Schlemper, H.; Walz, L.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1361–1363.
29. Imahori, T.; Kondo, Y. *J. Am. Chem. Soc.* **2003**, *125*, 8082–8083.
30. Besora, M.; Maseras, F.; Lledós, A.; Eisenstein, O. *Inorg. Chem.* **2002**, *41*, 7105–7112.
31. Balcells, D.; Maseras, F. *New J. Chem.* **2007**, *31*, 333–343.
32. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford, CT, 2004.
33. (a) Lee, C.; Parr, R. G.; Yang, W. *Phys. Rev.* **1988**, *37*, 785–789; (b) Becke, A. D. *J. Phys. Chem.* **1993**, *98*, 5648–5652; (c) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.
34. (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299–310; (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284–298.
35. (a) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; Defrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654–3665; (b) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. V. *J. Comput. Chem.* **1983**, *4*, 294–301.
36. Höllwarth, A.; Böhme, M.; Dapprich, S.; Ehlers, A. W.; Gobbi, A.; Jonas, V.; Köhler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett.* **1993**, *208*, 237–240.
37. Check, C. E.; Faust, T. O.; Bailey, J. M.; Wright, B. J.; Gilbert, T. M.; Sunderlin, L. S. *J. Phys. Chem. A* **2001**, *105*, 8111–8116.