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Proton-Abstraction Mechanism in the Palladium-Catalyzed Intramolecular Arylation: Substituent Effects

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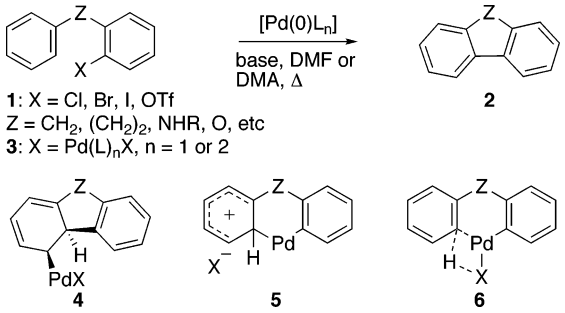
Abstract: The regioselectivity observed in the intramolecular palladium-catalyzed arylation of substituted bromobenzyldiarylmethanes as well as theoretical results demonstrate that the Pd-catalyzed arylation proceeds by a mechanism involving a proton abstraction by the carbonate, or a related basic ligand. The reaction is facilitated by electron-withdrawing substituents on the aromatic ring, which is inconsistent with an electrophilic aromatic-substitution mechanism. The more important directing effect is exerted by electron-withdrawing substituents ortho to the reacting site.

Introduction

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 has been the intramolecular version that allows the cyclization of substrates **1** to form carbo- and heterocycles **2** (Scheme 1).[1,3,4] Intramolecular arylations are also involved in reactions mediated by palladacycles.[5−7]

Scheme 1



In contrast to cross-coupling reactions,[2] less has been known on 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**,[8] which should undergo a trans β-hydrogen elimination to give **2**. σ-Allyl palladium complex **4** might be in equilibrium with the corresponding η^3-palladium complexes. Most authors have favored an electrophilic aromatic substitution (S_EAr) via intermediates **5**.[9,10] However, in one case, an intramolecular isotope effect $k_H/k_D = 3.5$ has been determined.[4a] A similar intramolecular isotope effect ($k_H/k_D = 4$) was found in the Pd-catalyzed synthesis of oxindoles that proceeds via C−H functionalization.[11] In addition, we have

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found that the arylation on nitrofluorene[12a] or nitrocarbazole[12b] gives substantial amounts of products by reaction at the positions ortho or para to a strong electron-withdrawing NO_2 group. An interesting mechanistic alternative is a σ bond metathesis via intermediates **6**,[11a] which seems more likely than processes involving C−H oxidative addition.[13]

Recently we advanced that the palladium-catalyzed arylation reaction is facilitated by electron-withdrawing substituents on the aromatic ring, which is inconsistent with an electrophilic aromatic-substitution mechanism, and have proposed a proton-abstraction mechanism for this reaction.[14] Our mechanistic proposal is in line with recent results on the intra-[4g] and intermolecular[15,16] palladium arylation that proceeds more easily with arenes or heteroarenes bearing strongly electron-withdrawing substituents. A related mechanism, in which acetate acts as the basic ligand, has been proposed for cyclometallation of benzylic amines with $Pd(OAc)_2$.[17]

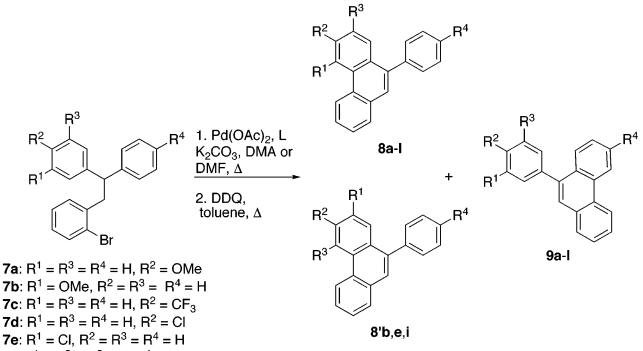
Herein we report a more thorough study on the effect of substituents that more clearly reveals the directing effect that substituents ortho to the reacting site exert on the palladium-catalyzed arylation reaction.

Results and Discussion

Effects of Substituents: Experimental Results. To determine the mechanism of the Pd-catalyzed arylation, we decided to study more precisely the effect of substituents on substrates **7a**−**l**[18] 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,[4a] using bulky phosphine **10a** as the ligand for Pd. Under these conditions, the cyclization furnished the corresponding 9,10-dihydrophenanthrenes, which in occasions were obtained along with small amounts of phenanthrenes. To facilitate determining the ratio of regioisomers by ^{1}H NMR analysis, the crude mixtures were treated with DDQ to give phenanthrenes **8a**−**l**/**9a**−**l** (Table 1). The structures of phenanthrenes **9a**,**b**,**d**,**e**,**g**,**j**,**k** were further confirmed by their independent synthesis by Suzuki couplings of 9-bromophenanthrene with the corresponding arylboronic acids.[18]

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**[19] (Table 1, entries 1 and 2). However, **10b** led to a better selectivity with substrate **7d** (Table 1, entries 6 and 7).

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



7a: $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
7b: $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
7c: $R^1 = R^3 = R^4 = H$, $R^2 = CF_3$
7d: $R^1 = R^3 = R^4 = H$, $R^2 = Cl$
7e: $R^1 = Cl$, $R^2 = R^3 = R^4 = H$
7f: $R^1 = R^2 = R^3 = F$, $R^4 = H$
7g: $R^1 = R^3 = R^4 = H$, $R^2 = F$
7h: $R^1 = R^3 = F$, $R^2 = R^4 = H$
7i: $R^1 = R^2 = F$, $R^3 = R^4 = H$
7j: $R^1 = R^3 = R^4 = H$, $R^2 = t$-Bu
7k $R^1 = R^3 = R^4 = H$, $R^2 = SiMe_3$
7l: $R^1 = R^3 = H$, $R^2 = F$, $R^4 = t$-Bu

entry	substrate	substituent(s)	L[b]	solvent	*T* (°C)	yield (%)	**8/9** (**8**/**8′**/**9**) ratio
1	**7a**	$R^2 = OMe$	**10a**	DMA	135	90	1.1:1
2	**7a**	$R^2 = OMe$	**10b**	DMA	135	93	1.1:1
3	**7a**	$R^2 = OMe$	**10a**	DMF	100	91	1.1:1
4	**7b**	$R^1 = OMe$	**10a**	DMA	135	75	1.4:1 (1.1:0.3:1)
5	**7c**	$R^2 = CF_3$	**10a**	DMA	135	71	1.3:1
6	**7d**	$R^2 = Cl$	**10a**	DMA	135	66	1.5:1
7	**7d**	$R^2 = Cl$	**10b**	DMA	135	66	2.4:1
8	**7d**	$R^2 = Cl$	**10a**	DMA	100	98[c]	2:1
9	**7d**	$R^2 = Cl$	**10a**	DMF	100	84	2:1
10	**7e**	$R^1 = Cl$	**10a**	DMA	135	54	1.9:1 (0.8:1.1:1)
11	**7f**	$R^1 = R^2 = R^3 = F$	**10a**	DMA	135	82	25:1
12	**7g**	$R^2 = F$	**10a**	DMA	135	72	1.6:1
13	**7h**	$R^1 = R^3 = F$	**10a**	DMA	135	76	19:1
14	**7i**	$R^1 = R^2 = F$	**10a**	DMA	135	62	8.2:1 (6.8:1.4:1)
15	**7j**	$R^2 = t$-Bu	**10a**	DMA	135	68	1:1.5
16	**7k**	$R^2 = SiMe_3$	**10a**	DMA	135	74	1:1.3
17	**7l**	$R^2 = F$, $R^4 = t$-Bu	**10a**	DMA	135	81	2.3:1

[a] 5% mol $Pd(OAc)_2$, 10 mol % L, and 3 equiv 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] Yield determined by ^{1}H NMR.

Cyclizations could be also carried out in DMA or DMF at 100 °C (Table 1, entries 3, 8, and 9). Remarkably, reaction of **7f** occurred almost exclusively at the trifluorophenyl ring to give **8f** (Table 1, entry 11). A single fluorine substituent in **7g** exerts a moderate control on the regioselectivity (Table 1, entry 12), similar to that of methoxyl, triflormethyl, or chloro substituents para to the arylation site. However, substrate **7h**, with fluorine substituents ortho to the arylation site (Table 1, entry 13), led to **8h** with an excellent regioselectivity (**8h**/**9h** = 19:1). The regioselectivity was ca. 8:1 with substrate **7i** (Table 1, entry 14), although in this case the yield was lower. Taking into account the fact that the two reactive positions at the phenyl ring are identical, the selectivity for the reaction ortho to a fluorine compared to the unsusbtituted aryl is ca. 14:1. Interestingly, the arylation of substrates **7j** and **7k** with *t*-Bu and $SiMe_3$ substituents, respectively, took place on the phenyl ring, with moderate selectivity (Table 1, entries 15 and 16). The arylation of substrate **7l** was expected to take place selectively at the aryl ring substituted with a fluorine with a **8l**/**9l** regioselectivity of ca. 2.4:1, calculated from the effects of entries 12 and 15 (1.6:1

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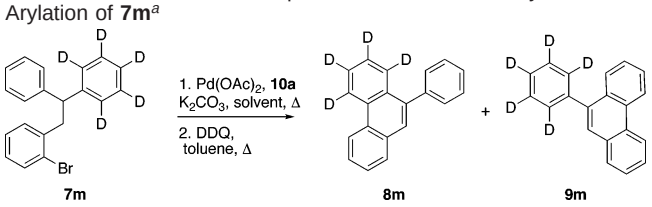
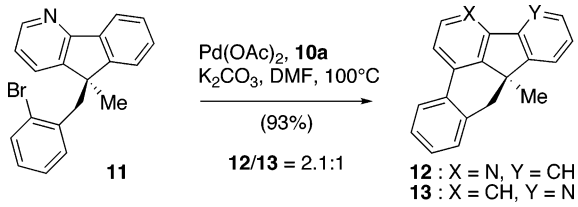
Table 2. Intramolecular Isotope Effect on the Pd-Catalyzed Arylation of **7m**[a]



entry	solvent	*T* (°C)	yield (%)	**8m**/**9m** ratio	k_H/k_D
1	DMF	100	92	0.15:1	6.7
2	DMA	135	82	0.2:1	5.0

[a] Reaction run using 5% mol $Pd(OAc)_2$, 10 mol % **10a**, and 3 equiv K_2CO_3 for 16 h.

Scheme 2



and 1:1.5, respectively). In the event, reaction of **7l** under the standard conditions led to **8l**/**9l** in a 2.3:1 ratio (Table 1, entry 17).

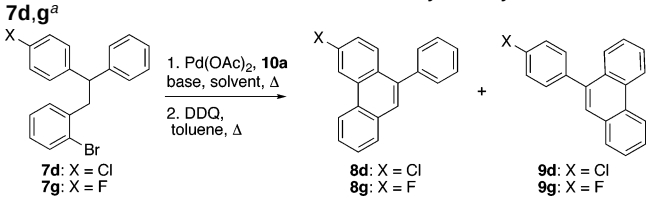
To determine the possible intramolecular isotope effects in the palladium-catalyzed arylation reaction, we subjected substrate **7m** to the standard conditions. Thus, reaction of **7m** gave 0.2:1 (135 °C) and 0.15:1 (100 °C) ratios of **8m** and **9m** (Table 2, entries 1 and 2), which correspond to intramolecular isotope effects k_H/k_D equal to 5.0 (135 °C) and 6.7 (100 °C), respectively.

These results suggested that arylation of 5*H*-indeno[1,2-*b*]-pyridine derivative **11**[18] would proceed selectively para to the pyridine ring (Scheme 2). Indeed, reaction of **11** proceeded smoothly at 100 °C to afford **12** as the major regioisomer **(12**/**13** = 2.1:1).

Effect of Base. Satisfactory results were obtained with K_2CO_3 as the base, whereas Et_3N or DBU led to unchanged starting material (Table 3, entries 2 and 3). Reduction of **7d** was observed when KO-*t*-Bu was used as the base (Table 3, entry 4). On the other hand, $KHCO_3$ and K_3PO_4 could also be used, with only small erosions in the overall yield (Table 3, entries 6 and 7). Addition of pivalic acid[15b] led to similar results (Table 3, entry 8). However, Na_2HPO_4 and NaH_2PO_4 were not effective (Table 3, entries 9 and 10). It is interesting that the regioselectivities are largely independent from the base used.

Computational Results: Overall Mechanism.[20] These experimental data are inconsistent with an aromatic electrophilic-substitution mechanism, that should drive the C−H functionalization away from the ring with electron-withdrawing fluorine substituents. The reaction features do not suit well either with the other traditionally proposed mechanisms indicated in Scheme 1, Heck-like or σ bond metathesis. Instead, the reaction seems better fitted to the mechanism we dubbed as proton-abstraction,[14] shown in Scheme 3. Variations of this mechanism have been also proposed by other authors.[13,15a,17,21,22] The defining feature

Table 3. Effect of the Base on the Pd-Catalyzed Arylation of **7d**,**g**[a]



entry	substrate	base	solvent	*T* (°C)	yield (%)	**8**/**9** ratio
1	**7d**	K_2CO_3	DMF	100	84	2:1
2	**7d**	Et_3N	DMF	100		
3	**7d**	DBU	DMF	100		
4	**7d**	K-*t*-BuO	DMF	100	*b*	
5	**7g**	K_2CO_3	DMA	135	72	1.6:1
6	**7g**	$KHCO_3$	DMA	135	68	1.5:1
7	**7g**	K_3PO_4	DMA	135	66[c]	1.6:1
8[d]	**7g**	K_2CO_3/*t*-$BuCO_2H$	DMA	100	(>95)[e]	1.7:1
9	**7g**	Na_2HPO_4	DMA	135		
10	**7g**	Na_2HPO_4	DMA	135		

[a] Reaction run using 5% mol $Pd(OAc)_2$, 10 mol % **10a**, and 3 equiv base for 16 h. [b] (1-(4-Chlorophenyl)ethane-1,2-diyl)dibenzene was observed in the crude reaction mixture. [c] Reaction time = 24 h (ca. 90% conversion). [d] Reaction carried out in the presence of *t*-$BuCO_2H$ 30 mol % for 4 h. [e] Conversion determined by ^1H NMR.

of this mechanism is that the formation of the metal−carbon bond is concerted with the breaking of the carbon−hydrogen bond, with the hydrogen being transferred to a basic center. The existence of this type of step does not fully define the mechanism, and the three variations presented in Scheme 3 can be postulated. Starting from the species resulting of the oxidative addition of the C−Br bond, the proton can be transferred either to the bromide ligand (unassisted path) or to another base in the media (assisted path), which in the computation study is hydrogen carbonate, a base that also leads to arylation (Table 3, entry 6). The external base can either coordinate previously to the metal, displacing bromide (intramolecular assisted path), or not (intermolecular assisted path).

We carried out a preliminary set of B3LYP calculations with basis set I (see computational details in the Supporting Information) on the three mechanisms of Scheme 3 on two different model systems: $[Pd(PH_3)Br(o\text{-}((CH_2)_2\text{-}C_6H_5)Ph)]$ and $[Pd(PH_3)Br(o\text{-}((CH_2)_2\text{-}C_6H_2F_3)Ph)]$; labeled as **t1a** and **t1b**, respectively (the **t** label stands for theoretical). These systems aim to reproduce the attack in either of the two rings of the system related to substrate **7f**, which gave experimentally the highest selectivity, 25:1. For each of the three mechanisms, we computed the key transition state, and the reactant and product it connects. The resulting transition states **t1aTS** for the case of the hydrogen-substituted ring are presented in Figure 1. The three geometries fit well in the proton-abstraction view: the hydrogen atom being transferred is close to halfway between carbon and oxygen (or bromine), and the three atoms are nearly in linear arrangement. The potential energy barriers corresponding respectively to the **t1a** and **t1b** systems are 43.3 and 34.5 kcal/mol (unassisted mechanism), 23.5 and 13.2 kcal/mol (intramolecular-assisted mechanism), and 17.4 and 14.4 kcal/mol (intermolecular-assisted mechanism). In all cases the species with fluorine substituents in the ring is favored, which reproduces the experimental observation and confirms the validity

(20) See Supporting Information for computational details.

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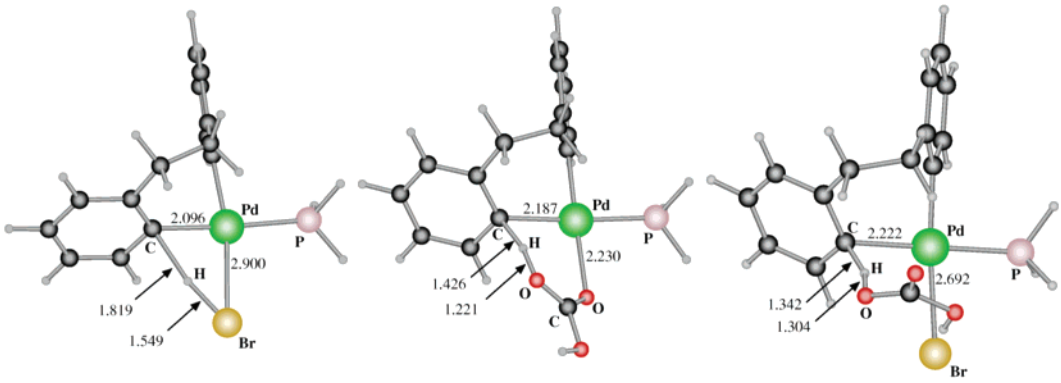
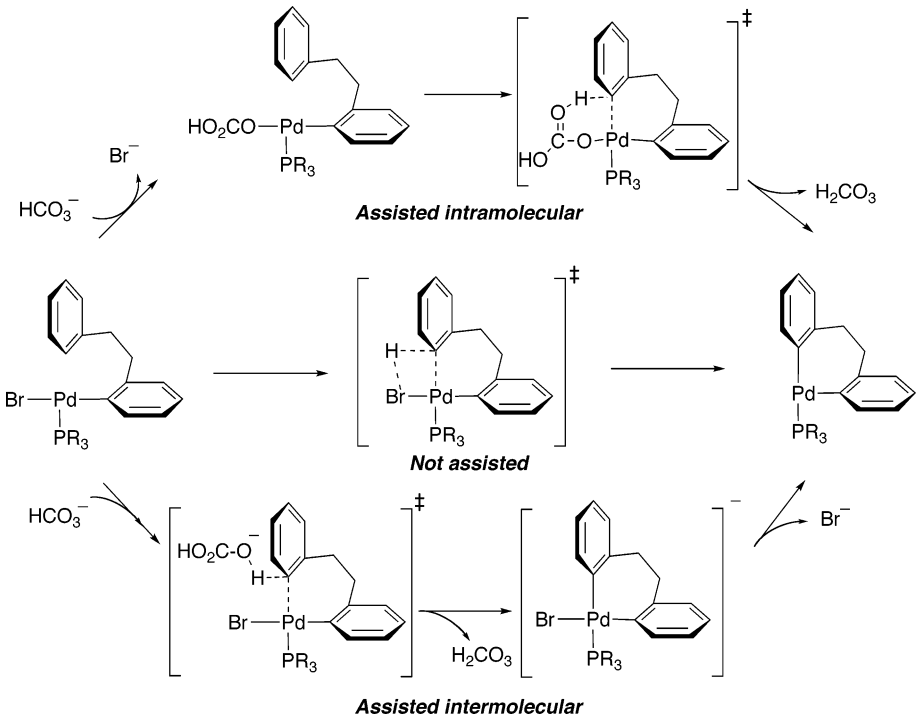


Figure 1. B3LYP optimized structures of the transition state **t1aTS** for the three mechanisms considered: unassisted (left), intramolecular assisted (middle), and intermolecular assisted (right). Selected bond distances are given in Å.

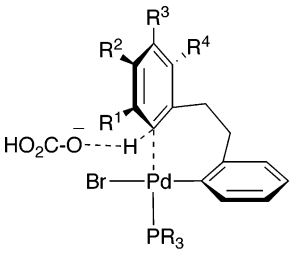
Scheme 3



of the proton-abstraction scheme. Introduction of free-energy corrections computed in gas-phase did not alter the trends in the comparison between **t1a** and **t1b**. The computed free-energy barriers for the two systems were, respectively, 37.6 and 29.5 kcal/mol (unassisted mechanism), 19.8 and 10.9 kcal/mol (intramolecular-assisted mechanism), and 15.0 and 13.1 kcal/mol (intermolecular-assisted mechanism). The results are similar, and the use of gas-phase entropic corrections for reactions taking place in solution is arguable. Because of this, we will not consider this type of corrections in the rest of the work.

The barrier for the unassisted process is more than 20 kcal/mol higher than for the assisted processes. According to these calculations, the unassisted mechanism seems thus unlikely. The experimentally observed dependence of the nature of the base on the reactivity (Table 2) points also in this direction, although the base can play other roles in the catalytic cycle. The low efficiency of the unassisted mechanism we find for our particular system is not necessarily general. In fact, Fagnou and coworkers[16b] have pointed out that the low solubility of the base may hinder its role in the reaction. If the amount of base in solution is insufficient, the assisted mechanisms may become inaccessible.

The comparison between the two base-assisted mechanisms is even less conclusive. In our preliminary communication we favored the assisted intramolecular pathway, but we revise the topic here in more detail. The lowest barrier (17.4 vs 23.5 kcal/mol) corresponds to the intermolecular mechanism for the **t1a** system with hydrogen substituents and to the intramolecular mechanism (13.2 vs 14.4 kcal/mol) for the **t1b** system with fluorine substituents. Further alterations of the otherwise similar energetics can arise from steps not computed here, namely, the replacement of bromide by hydrogencarbonate in the intramolecular mechanism, and the departure of bromide in the intermolecular mechanism (see Scheme 3). The use of hydrogencarbonate as a base is a reasonable assumption, but the dianionic carbonate could also play a role. Unfortunately, our attempts to introduce it in the calculation led to computational artifacts (see Supporting Information), and we stayed with the hydrogencarbonate model for all our studies. On the other hand,



t2a: $R^1 = R^2 = R^3 = R^4 = H$
t2b: $R^1 = R^2 = R^3 = F$, $R^4 = H$
t2c: $R^1 = F$, $R^2 = R^3 = R^4 = H$
t2d: $R^2 = F$, $R^1 = R^3 = R^4 = H$
t2e: $R^3 = F$, $R^1 = R^2 = R^4 = H$
t2f: $R^4 = F$, $R^1 = R^2 = R^3 = H$
t2g: $R^1 = F$, $R^2 = F$, $R^3 = R^4 = H$
t2h: $R^1 = F$, $R^3 = F$, $R^2 = R^4 = H$
t2i: $R^1 = R^4 = F$, $R^2 = R^3 = H$
t2j: $R^2 = R^3 = F$, $R^1 = R^4 = H$
t2k: $R^2 = R^4 = F$, $R^1 = R^3 = H$
t2l: $R^3 = R^4 = F$, $R^1 = R^2 = H$
t2m: $R^1 = Cl$, $R^2 = R^3 = R^4 = H$
t2n: $R^2 = Cl$, $R^1 = R^3 = R^4 = H$
t2o: $R^3 = Cl$, $R^1 = R^2 = R^4 = H$
t2p: $R^4 = Cl$, $R^1 = R^2 = R^3 = H$
t2q: $R^1 = SiMe_3$, $R^2 = R^3 = R^4 = H$
t2r: $R^2 = SiMe_3$, $R^1 = R^3 = R^4 = H$
t2s: $R^3 = SiMe_3$, $R^1 = R^2 = R^4 = H$
t2t: $R^4 = SiMe_3$, $R^1 = R^2 = R^3 = H$

Figure 2.

potassium hydrogen carbonate has been shown experimentally to be an efficient base in the reaction of substrate **7g** (Table 3, entry 6).

For the sake of simplicity, we will in any case choose one of the two base-assisted mechanisms for the calculations that follow. This will be the intermolecular-assisted pathway based on the smaller difference this mechanism presents between the **t1a** and **t1b** systems. For the intermolecular mechanism, the difference in potential energies is 3.0 kcal/mol (17.4 vs 14.4 kcal/mol) and this would imply a proportion of activation of fluorinated vs nonfluorinated rings of 40:1 at 135 °C, reasonably close to the experimental data of 25:1 for the **7f** substrate. For the intramolecular mechanism, the difference is 10.3 kcal/mol, which would lead to a preference of more than 700000:1. An additional experimental result in support of the intermolecular mechanism is the observation by Fagnou and co-workers[15] that the nature of the aryl halide affects significantly the regioselectivity. This seems to imply that the halide is present on the catalyst at the time of arylation, which would be incompatible with the intramolecular mechanism. A final practical issue favoring the choice of the intermolecular mechanism is that it does not require the initial replacement of Br^- by the base. This step would likely have a low barrier but is strictly not necessary in the intermolecular pathway.

The choice of one mechanism is certainly a simplification, because both mechanisms can be operative, and the preference for one of them may depend on the substrate. However, the goal here is not to discern between the two mechanisms, but to use a reasonable computational description that is able to account for the main experimental features.

It is worth noticing that these same three mechanisms were computationally analyzed in a related system by Woo, Fagnou, and co-workers in a recent work,[15a] where these mechanisms were labeled **C1**, **C2**, and **C3**. Their conclusion was that both the unassisted and the intramolecular-assisted pathways could explain the experimental results and that the intermolecular assisted pathway was not feasible. The discrepancy with our results is due to differences in the system studied, which in their case is an intermolecular arylation, with no preexistent chemical connection between the rings being coupled. These discrepancies in the computed reaction paths are further proof of the rich mechanistic complexity of these reactions.

Table 4. Computed Energy Barriers (kcal/mol) and Selectivity Ratios for the Base-Assisted Intermolecular Abstraction Reaction with Different Substrates

entry	system	substituent(s)	barrier	computed ratio	experimental ratio
1	**t2a**		12.4	1:1	1:1
2	**t2b**	$R^1 = R^2 = R^3 = F$	5.6	4400:1	25:1 (**7f**)
3	**t2c**	$R^1 = F$	6.2	2100:1	
4	**t2d**	$R^2 = F$	11.5	3.0:1	1.6:1 (**7g**)
5	**t2e**	$R^3 = F$	12.3	1.1:1	
6	**t2f**	$R^4 = F$	11.7	2.4:1	
7	**t2g**	$R^1 = R^2 = F$	5.8	3500:1	6.8:1 (**7i**)
8	**t2h**	$R^1 = R^3 = F$	5.9	3050:1	19.0:1 (**7h**)
9	**t2i**	$R^1 = R^4 = F$	5.7	3900:1	
10	**t2j**	$R^2 = R^3 = F$	10.9	6.4:1	
11	**t2k**	$R^2 = R^4 = F$	10.3	13.3:1	
12	**t2l**	$R^3 = R^4 = F$	11.4	3.4:1	1.4:1 (**7i**)
13	**t2m**	$R^1 = Cl$	9.3	52:1	0.8:1(**7e**)
14	**t2n**	$R^2 = Cl$	10.6	9.2:1	1.5:1 (**7d**)
15	**t2o**	$R^3 = Cl$	11.7	2.4:1	
16	**t2p**	$R^4 = Cl$	11.2	4.4:1	1.1:1 (**7e**)
17	**t2q**	$R^1 = SiMe_3$	21.4	1:67000	
18	**t2r**	$R^2 = SiMe_3$	12.5	1:1.1	1:1.3 (**7k**)
19	**t2s**	$R^3 = SiMe_3$	13.3	1:3.0	
20	**t2t**	$R^4 = SiMe_3$	13	1:2.1	

Computational Results: Effect of Substituents. We evaluated the barrier of the intermolecular-assisted mechanism for the variety of systems **t2** indicated in Figure 2. The tested substituents were the same as in experiment, to further check the validity of our postulated computational mechanism. Calculation also allowed the consideration of systems, for instance the whole series of monofluorinated and difluorinated systems, that are difficult to access from an experimental point of view. In this way, it is easier to analyze the sensibility of the selectivity on the substituent position. The computational model was more sophisticated for this set of calculations (see Supporting Information). The full experimental phosphines were considered through ONIOM(B3LYP:UFF) calculations. Basis set II was used for the QM region, and solvation effects were introduced through PCM calculations.

The computed barriers are summarized in Table 4. The computed value of selectivity for the parent systems **t2b/t2a** with three fluorine substituents is 2100:1, far from the 40:1 reported above with the smaller model system **t1b/t1a**, and even further from the experimental value of 25:1 found for substrate **7f**. This proves how sensitive the selectivity is to the computed barrier difference, which changes only from 3.0 to 6.2 kcal/mol. The computed selectivities are in general larger than the experimental values. In spite of the effort of considering the full experimental phosphine and the introduction of solvent effects, there are still a number of simplifications, mentioned above, that can explain this lack of quantitative agreement. Among them, we are focusing in one single mechanism (assisted intramolecular), using 1,2-diarylethane as diarene, and hydrogen carbonate as the base. The overall experimental trend in the substituent effect on selectivity is however maintained. Electron-acceptor fluorine and chlorine substituents favor in all cases the reaction, while electron-donor trimethylsilyl substituents drive the reaction toward the other ring. The effect of fluorine is in all cases much larger than that of chlorine and trimethylsilyl, with the sole exception of the case of trimethylsilyl in position R^1 (**t2q**), which will be discussed below.

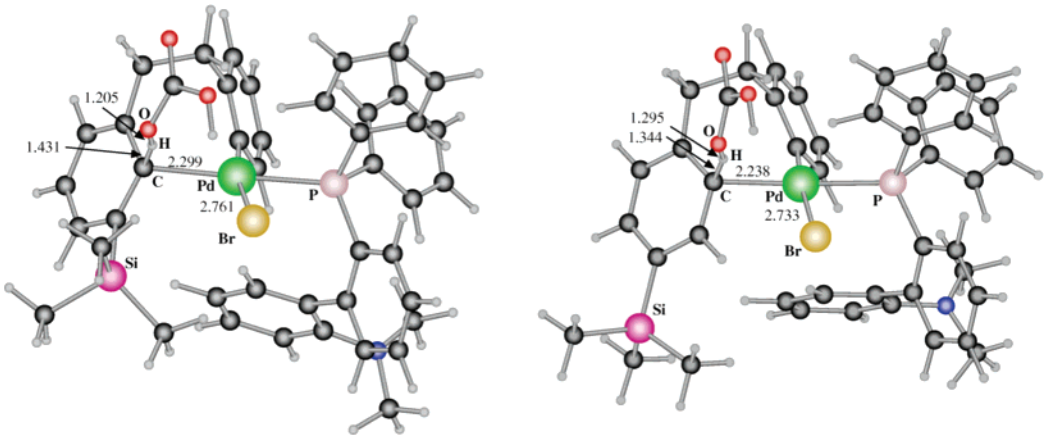


Figure 3. B3LYP optimized structures of the transition states **t2qTS** (left) and **t2rTS** (right) for the intermolecular base-assisted proton abstraction in systems with a trimethylsilyl substituent. Selected bond distances are given in Å.

Selectivity is very sensitive to the position of the substituent in the aryl ring. The example of the monofluorinated systems (Table 4, entries 3 to 6) is very clear. The effect is much larger in position 1, ortho to the C−H bond being activated. The presence of three fluorines decreases the barrier of the unsubstituted parent system from 12.4 to 5.6 kcal/mol, and the presence of only one fluorine substituent in the ortho position is sufficient to bring it down to 6.2 kcal/mol. The placement of single fluorine on any of the other three positions has in the contrary an effect always smaller than 1 kcal/mol, with barriers of 11.5, 12.3, and 11.7 kcal/mol. It is worth noticing that in the case of fluorine, the effect decreases with the distance of the fluorine from the activated C−H. The barrier is 6.2 kcal/mol for the ortho position 1, 11.5 and 11.7 kcal/mol for the meta positions 2 and 5, and 12.3 kcal/mol for the para position 3. This dependence of the effect on the distance is clearly suggesting an inductive effect. The results on the difluorine derivatives (entries 7 to 12) confirm these trends. The larger selectivity is by far associated to the presence of a fluorine in the ortho position 1 (entries 7 to 9).

The case of chlorine (entries 13 to 16) follows in general the same trends as for fluorine, albeit with smaller selectivities. This is what one would expect from an inductive effect, and this aspect of the results will not be further analyzed. The case of entry 13, where the computed ratio (52:1) appears to be opposed to the experimental value (0.8:1), deserves however some discussion. This is the case corresponding to **t2m**, with a chlorine in the ortho position. This ratio should be actually corrected to 1.6:1, as there are two identical ortho positions at the unsubstituted aryl and the 0.8 value corresponds to the reaction at the position ortho to the chlorine substituent. Upon analyzing the optimized structures, we found that the transition states for most systems, and in particular **t2m**, **t2n**, **t2o**, and **t2p**, are very similar between the real system, including the bulky experimental phosphine, and the model system with PH_3. In contrast, this is not the case for the intermediate. Specifically, **t2m** has a different conformational arrangement with the PH_3 ligand, which is used for the calculation of the solvent effects. We suspect that this is the origin of this irregular behavior, which in fact arises from a computational artifact. This could be probably corrected by geometry optimizations in solution, which we were unable to carry out.

The results for trimethylsilyl (entries 17 to 20) fit also within this model. Trimethylsilyl has an opposite effect to fluorine, in agreement with its weak electron-releasing nature, and its effect on selectivity is smaller, because it is more similar in electronic properties to hydrogen, which is the competing substituent in the other ring. A single additional factor appears in the case of trimethylsilyl, which is the steric effect. This is a bulky substituent and has a steric pressure in the position R^1 that greatly increases the energy of the corresponding transition state (21.4 kcal/mol vs 12.4 corresponding to the parent system with hydrogen substituents). The presence of this steric strain can be seen in Figure 3, where the transition states for two of the trimethylsilyl systems are shown. The steric repulsion is also probably affecting the relative order of the barriers associated to the other positions, with reaction via **t2rTS** being the least hindered (see Figure 3). In any case, it is worth noticing that it is not a purely steric effect, because even in this position the barrier is higher (by 0.1 kcal/mol) than for the case of the system with hydrogens. This difference is small, but it already gives a selectivity of 1:1.1, close to the experimental observation of 1:1.3.

Conclusion

The intramolecular palladium-catalyzed arylation has been studied on a variety of bromobenzyldiarylmethane systems. Substituents are introduced in one of the aryl rings, and this allows the investigation of their effect on the arylation process. Electron-withdrawing substituents, such as fluorine, chlorine, and trifluoromethyl favor the reaction on the substituted ring. Electronegative methoxy groups that are electron-releasing in electrophilic aromatic substitutions, behave similarly to chlorine substituents, which indicates that the main effect of substituents in this reaction is inductive. Electron-releasing substituents, like *tert*-butyl or trimethylsilyl, drive the reaction toward the unsubstituted ring. In addition, a substantial deuterium isotope effect was determined in this process. These results are incompatible with the electrophilic aromatic-substitution mechanism that had been previously favored for this type of arylation processes. There is also a strong dependence of selectivity on the position of the substituent, with the ortho position, closer to the C−H bond being cleaved, being by far the most sensitive, further suggesting that the substituents act on the selectivity

through inductive effects. The performance of DFT calculations reproduces the experimental trends and leads to the proposal of a reaction mechanism where the key step is the abstraction of a proton from the aryl ring by carbonate, hydrogencarbonate, or a related basic ligand present in the reaction media.

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

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