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Assessment of the Intermediacy of Arylpalladium Carboxylate Complexes in the Direct Arylation of Benzene: Evidence for C−H Bond Cleavage by "Ligandless" Species

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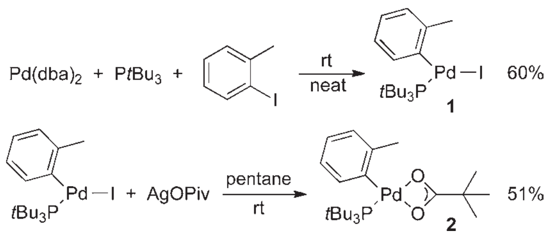
Supporting Information

ABSTRACT: Palladium-catalyzed direct arylations of benzene have been proposed to occur by the generation of a phosphine-ligated arylpalladium pivalate complex LPd(Ar)(OPiv) and reaction of this complex with benzene. We have isolated an example of the proposed intermediate and evaluated whether this complex does react with benzene to form the biaryl products of direct arylation. In contrast to the proposed mechanism, no biaryl product was formed from cleavage of the benzene C−H bond by LPd(Ar)(OPiv). However, reactions of LPd(Ar)(OPiv) with benzene and additives that displace or consume the phosphine ligand formed the arylated products in good yield, suggesting that a "ligandless" arylpalladium(II) carboxylate complex undergoes the C−H cleavage step. Consistent with this conclusion, we found that reactions catalyzed by $Pd(OAc)_2$ without a ligand occur faster than, and with comparable selectivities to, reactions catalyzed by $Pd(OAc)_2$ and a phosphine ligand.

Direct arylation, the reaction of aryl halides with arenes or heteroarenes to form biaryl or aryl-heteroaryl products, is an attractive alternative to traditional cross-coupling because it occurs without the need to prepare organometallic or main-group reagents.[1] Early efforts to develop this process focused on the direct arylation of heteroarenes,[2] arenes with directing groups,[3] and electron-deficient arenes.[4] In 2006, the direct arylation of benzene was reported by Lafrance and Fagnou.[5] Substoichiometric amounts of pivalic acid were used in the reported catalyst system, and this carboxylic acid was proposed to function as a proton shuttle during the aryl C−H cleavage step.[6]

Despite the improvements in the reaction scope, little experimental information on the mechanism of this reaction is available, especially on the mechanism of the cleavage of the C−H bonds in arenes. Phosphine-ligated arylpalladium carboxylates LPd(Ar)(OCOR) are typically proposed to react with heteroarenes or arenes to form biarylpalladium complexes through a concerted metalation−deprotonation (CMD) pathway.[7] DFT calculations of this pathway have been conducted, and these studies suggested that arylpalladium acetates are competent to undergo C−H cleavage with various heteroarenes.[8] Indeed, a recent report from Fagnou's group showed that the reaction of $(PtBu_3)Pd(Ph)(OAc)$ with 4-nitropyridine *N*-oxide formed the arylated product.[9] However, arylpalladium pivalate complexes have not been studied either experimentally or theoretically, and the reactions of isolated arylpalladium carboxylate complexes with arenes have not been conducted.

Scheme 1. Synthesis of $(PtBu_3)Pd(Ar)(OPiv)$



We report the synthesis and characterization of the phosphine-ligated arylpalladium pivalate complexes $(PtBu_3)Pd(Ar)(OPiv)$. Inconsistent with previous proposals, the reaction of isolated $(PtBu_3)Pd(Ar)(OPiv)$ with benzene does not form Ar−Ph products. However, reactions conducted with additives that displace or consume the phosphine ligand promote the formation of the arylated products, and these results and others reported herein imply the involvement of "ligandless" arylpalladium(II) species in the C−H cleavage step of the direct arylation of benzene.

The synthesis of $(PtBu_3)Pd(Ar)(OPiv)$ is outlined in Scheme 1. $PtBu_3$-ligated arylpalladium iodide **1** was prepared by the reaction of $Pd(dba)_2$ with $PtBu_3$ in neat 2-iodotoluene. Reaction of **1** with AgOPiv formed the $PtBu_3$-ligated arylpalladium pivalate **2** in good yield. Complex **2** was characterized by elemental analysis and NMR spectroscopy. The solid-state structure of complex **2** was determined by single-crystal X-ray diffraction (Figure 1). The pivalate ligand binds to the Pd center in an κ^2-mode with Pd−O bond distances of 2.124(4) and 2.301(4) Å. The longer Pd−O bond is trans to the aryl group.

The competency of complex **2** to be an intermediate in the catalytic process was then assessed, and the results of these studies are summarized in Table 1 (entry 1−3) and eq 1. To provide a benchmark to compare the reactivity of **2**, we conducted the reaction of 2-bromotoluene with benzene catalyzed by $Pd(OAc)_2$ and $PtBu_3$. This reaction formed 2-phenyl-toluene in 71% yield (eq 1). In contrast, the stoichiometric reaction of

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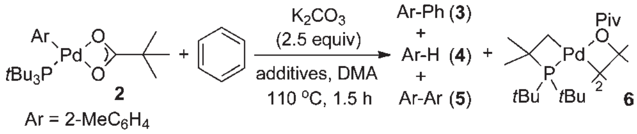
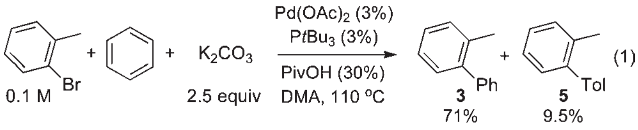
Figure 1. ORTEP drawing of $(PtBu_3)Pd(2\text{-}MeC_6H_4)(OPiv)$ with 50% ellipsoids. Hydrogen atoms have been omitted for clarity.

Table 1. Reactivity of Complex 2 with Benzene[a]



entry	concn of **2**	additives	yield of **3**	yield of **4**	yield of **5**	**3**/**5**
1	0.04 M	–	trace	27%	32%	–
2	0.003 M	–	trace	33%	20%	–
3	0.003 M	PivOH (0.03 M)	trace	45%	25%	–
4	0.04 M	$NHep_4Br$ (0.1 M)	30%	17%	23%	1.3
5	0.003 M	$NHep_4Br$ (0.1 M)	51%	31%	7%	7.3
6	0.003 M	$NHep_4OPiv$ (0.1 M)	49%	25%	5%	9.8
7	0.003 M	O_2 (0.01 M)	63%	26%	<5%	>12

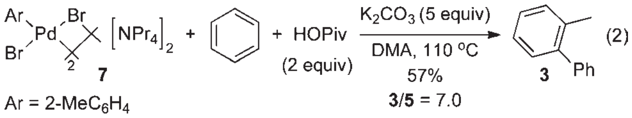
[a] Yield by GC/MS with an internal standard.



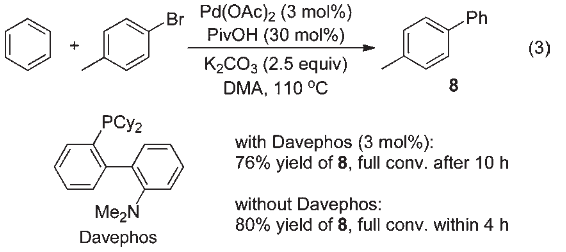
complex **2** with benzene in the presence of K_2CO_3 in DMA at 110 °C formed only trace amounts of 2-phenyl-toluene. The major organic products were toluene and 2,2′-dimethyl-biphenyl. The major organometallic product (55% NMR yield) was palladacycle **6** from intramolecular C–H bond cleavage of the phosphine ligand. Attempts to suppress the formation of 2,2′-dimethyl-biphenyl by conducting the reaction with a lower concentration of **2** that would be present in the catalytic system led to similar results. Reaction of **2** in benzene in the presence of PivOH also failed to form 2-phenyl-toluene. Thus, the $PtBu_3$-ligated arylpalladium pivalate complex **2** is not competent to be the intermediate that cleaves the arene C–H bond in the catalytic direct arylation process.

The absence of the product of the catalytic reaction in the stoichiometric reactions of arylpalladium pivalate complex **2** led us to study the effects of additives that could be present in the catalytic system on the distribution of products. The catalytic system forms a halide and pivalate anion, and it could contain adventitious oxygen. The results of reactions containing such additives are summarized in Table 1 (entry 4–7). Reactions of **2** with benzene in the presence of a soluble NR_4Br salt, the soluble NR_4OPiv salt, or O_2 formed 2-phenyl-toluene (**3**) in higher yields than in the absence of these additives. The reaction with 0.10 M added $NHep_4Br$ formed **3**, but in just 30% yield with a ratio of organic products **3**/**5** of only 1.3:1. However, the same reaction at a concentration of complex **2** (0.003 M) that would be closer to that in the catalytic system formed **3** in 51% yield. Moreover, the ratio of **3**/**5** was 7.3, and this value matched that of the catalytic system. Modest yields of **3** (49% and 63%, respectively) and good ratios of **3**/**5** were also obtained from the reaction with added $NHep_4OPiv$ or O_2. We propose that displacement of the phosphine ligand by the halide[10] or pivalate anion, or oxidation of the phosphine ligand by the oxygen generates a "ligandless" arylpalladium species that undergoes the C–H cleavage step.

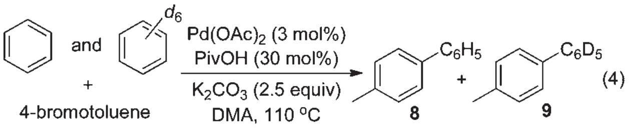
To test our hypothesis that an intermediate lacking a phosphine ligand undergoes the C–H cleavage step, a reaction of benzene with $[Pd(o\text{-}Tol)Br_2]_2^{2-}$ (**7**) lacking a phosphine ligand was conducted (eq 2) with a base and pivalic acid. The reaction of **7** with benzene in the presence of PivOH formed a 57% yield of biaryl **3**, and the ratio of **3**/**5** was again similar to that of the catalytic process (7.0).[11] These data support our hypothesis that the C–H cleavage step occurs through an arylpalladium species lacking a phosphine ligand.



If our proposal that the C–H bond cleavage step occurs by an intermediate lacking a phosphine ligand is valid, and the C–H bond cleavage step is turnover-limiting as proposed previously,[5,9] the reactions of bromoarenes with benzene should form the arylated product with faster rates when catalyzed by palladium in the absence of phosphine. Indeed, the reactions of 4-bromotoluene with benzene catalyzed by $Pd(OAc)_2$ alone occurred faster than, and with comparable selectivities to, reactions catalyzed by $Pd(OAc)_2$ and a phosphine ligand. Under published conditions with added Davephos,[5] a 76% yield of 4-phenyl-toluene was obtained, and the reaction reached full conversion after 10 h. In comparison, the same reaction catalyzed by $Pd(OAc)_2$ alone formed 4-phenyl-toluene in 80% yield after only 4 h. These results further support the proposal that C–H bond cleavage of arenes occurs by arylpalladium species lacking a phosphine ligand.[12]

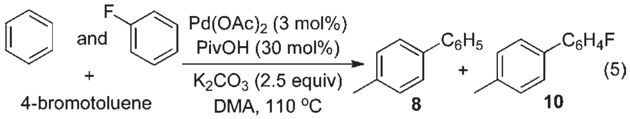


To assess further whether the C–H cleavage step occurs through such "ligandless" arylpalladium species, we studied the product distribution from the reaction of 4-bromotoluene with two distinct arenes catalyzed by $Pd(OAc)_2$ with and without a phosphine ligand. The results are provided in eqs 4 and 5. The reaction of 4-bromotoluene with benzene and benzene-d_6 catalyzed by $Pd(OAc)_2$ and Davephos formed a 5.4(1):1 ratio of $4\text{-}MeC_6H_4{-}C_6H_5$ to $4\text{-}MeC_6H_4{-}C_6D_5$. The same reaction without an added ligand formed an indistinguishable 5.6(2):1 ratio of these products (eq 4). Likewise, the selectivities from reactions of 4-bromotoluene with benzene and fluorobenzene with and without a ligand were an indistinguishable 14(2):1 and 13(1):1 (eq 5), and the ratio of ortho, meta, and para isomers of the fluorobiphenyl products were indistinguishable (23:5:1 vs 24:4:1).



(4)

	8/9
with Davephos (3 mol%):	5.4 ± 0.1
without Davephos:	5.6 ± 0.2



(5)

	10/8	o:m:p of 10
with Davephos (3 mol%):	14 ± 2	23:5:1
without Davephos:	13 ± 1	24:4:1

Finally, to assess the differences in barriers for cleavage of the C−H bond in benzene by arylpalladium species ligated by $PtBu_3$ and lacking a phosphine ligand in DMA solvent, we used density functional theory (DFT) to compute the barriers for the reaction of benzene with $(PtBu_3)Pd(Ph)(OPiv)$ and $(DMA)Pd(Ph)(OPiv)$. The calculated free energy of activation ($\Delta G^{\ddagger}$) for the reaction of $(DMA)Pd(Ph)(OPiv)$ with benzene was found to be 31 kcal/mol at 25 °C. This barrier is much lower than the 42 kcal/mol barrier computed for the reaction of $(PtBu_3)Pd(Ph)(OPiv)$ with benzene (see the Supporting Information for details). The relative magnitude of these barriers is consistent with our proposal that the arylpalladium species lacking a phosphine ligand in DMA is more reactive toward C−H bond cleavage than is the phosphine-ligated **2**.

In summary, studies of the reactions of the isolated arylpalladium pivalate complex **2** with benzene have shown that this complex is not chemically competent to be an intermediate in the direct arylation of benzene. However, reactions of **2** conducted in the presence of additives that displace or consume the phosphine ligand in **2** did form the arylated products, suggesting that a "ligandless" arylpalladium species is involved in the C−H cleavage step. This conclusion is consistent with comparisons of selectivities of catalytic reactions conducted with and without added phosphine and with DFT calculations of the barrier of the reactions of benzene with phosphine-ligated and solvent-ligated arylpalladium pivalate complexes.

We propose that the higher reactivity of the ligandless species results in large part from differences between the steric properties of **2** and those of the species formed by replacement of $PtBu_3$ with DMA or halide. All isolated arylpalladium complexes ligated by $PtBu_3$ contain only three ligands.[13] Thus, the higher coordinate species along the pathway for cleavage of the C−H bond of benzene would be expected to lie at high energy. In addition to showing that the DMA-ligated complex reacts faster than the phosphine-ligated species, our studies suggest that anionic arylpalladium species cleave the arene C−H bonds with barriers that are lower than those for neutral complexes containing hindered phosphines. This observation suggests that catalysts for direct arylation of unactivated arenes could be developed from systems containing small anionic ligands or additives. Future studies will focus on designing new methods for direct arylation of unactivated arenes based on the principles revealed by these mechanistic studies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures, spectra for all new compounds, and crystallographic data for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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DMA-d_9 or with added D_2O formed unlabeled toluene, and reactions with tetraheptylammonium pivalate form more toluene than those with pivalic acid and carbonate.

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NOTE ADDED AFTER ASAP PUBLICATION

The Supporting Information published February 11, 2011, showed coordinates for a different isomer than the one discussed in the paper. The correct Supporting Information was published February 18, 2011.