

Palladium-Catalyzed Benzene Arylation: Incorporation of Catalytic Pivalic Acid as a Proton Shuttle and a Key Element in Catalyst Design

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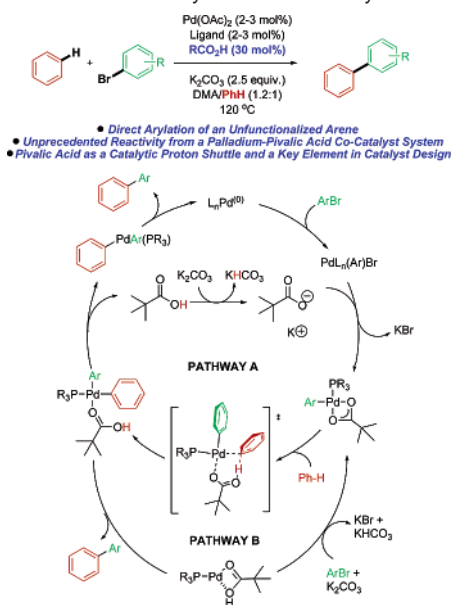
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Transition-metal catalysis has contributed significantly to the synthesis of biaryl molecules.¹ The most prominent reactions involve palladium catalysts and require differential activation of the two arene components. Recently, an emphasis on global reaction efficiency has prompted the development of reactions that are less reliant on preactivation. In this context, direct arylation, which substitutes one of the activated arenes (usually the organometallic) with an unfunctionalized arene, has attracted significant attention.² First reported nearly 20 years ago with electron-rich arenes such as indole,³ the scope of these transformations has recently undergone rapid expansion. Despite important advances, the need for directing groups⁴ or nucleophilic, electron-rich substrates⁵ is only beginning to be addressed.^{6,7} As a consequence, the application of traditional process, such as the use of phenylboronic acid as an activated benzene reagent in Suzuki couplings, remains the norm.

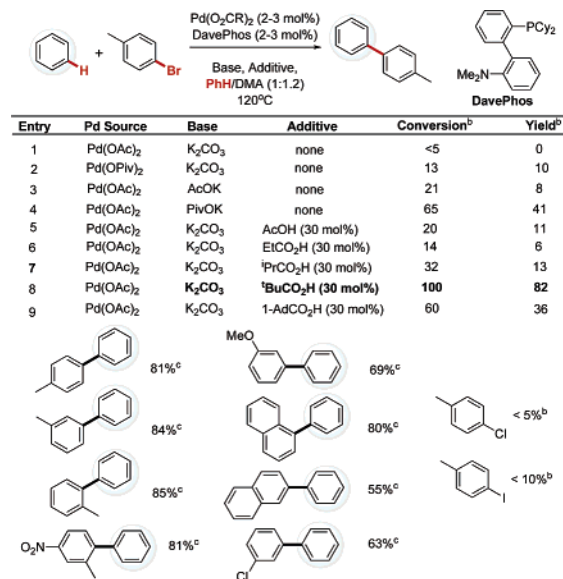
In a recent report, we described the direct arylation of electron deficient perfluorobenzenes⁷ and found that arene reactivity depended on C–H acidity, not on arene nucleophilicity. A proton abstraction mechanism, first proposed by Echavarren and Maseras,^{6c} was found to explain the reaction outcomes. Several important implications can be drawn from these studies: (1) the anionic ligand (base) is directly involved in C–H bond cleaving; (2) the anion must bind to the catalyst, but not impede the catalytic cycle by competitive occupation of vacant coordination sites;^{8,9} and, (3) the

Scheme 1. Plausible Pathways for Benzene Arylation^a



^a Two pathways are depicted: one where the pivalic acid/pivalate anion interacts reversibly with the palladium catalyst (pathway A) and another where the pivalic acid/pivalate remains bound to the palladium metal throughout the catalytic cycle (pathway B).

Scheme 2. Benzene Direct Arylation Development^a



^a Conditions: Pd(OAc)₂ or Pd(OPiv)₂ (2–3 mol %), DavePhos (2–3 mol %), K₂CO₃ (2.5 equiv). The additive and the aryl halide were heated to 120 °C in benzene/DMA (1.2:1) for 10 to 15 h (overnight). ^bDetermined by GC–MS. ^cIsolated yield using the conditions from entry 8.

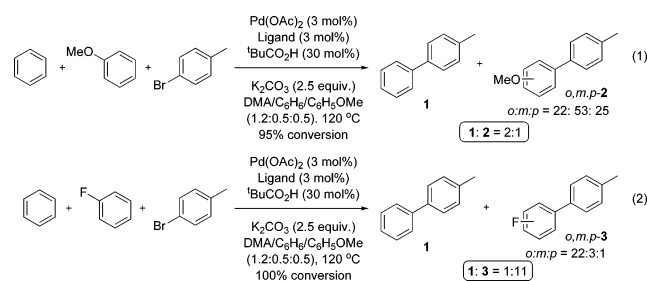
arene (benzene) which interacts with the catalyst very weakly must compete for binding to the arylpalladium(II) intermediate with the excess anion (base). Mindful of these challenges, we have been searching for more reactive catalytic systems that can extend direct arylation to include currently incompatible substrates.

Herein, we describe the development of a palladium–pivalic acid cocatalyst combination exhibiting unprecedented reactivity in direct arylation as illustrated by the first high-yielding direct metalation–arylation reactions¹⁰ of a completely unactivated arene, benzene. Experimental and computational evidence indicates that the pivalate anion is a key component in C–H bond cleaving, lowering the energy of C–H bond cleavage and acting as a catalytic proton shuttle from benzene to the stoichiometric carbonate base (Scheme 1).

Selected reactions for the development of a benzene arylation reaction are outlined in Scheme 2. Treatment of 4-bromotoluene with Pd(OAc)₂ (3 mol %), DavePhos^{11,12} (3 mol %), potassium carbonate (2.5 equiv) in a 1.2:1 mixture of *N,N*-dimethylacetamide (DMA) and benzene at 120 °C (conditions similar to those employed for perfluorobenzene arylation) gave no detectable benzene arylation (entry 1). Inspired by ongoing computational work (vide infra), Pd(OPiv)₂¹³ was examined which resulted in a 10% yield by GC–MS (OPiv = pivalate or 2,2-dimethylpropionate).

Use of KOPiv¹⁴ or KOAc as the stoichiometric bases in conjunction with Pd(OAc)₂ again revealed the superior reactivity

of pivalate which provided benzene arylation in up to 41% yield (entry 3 vs 4). Use of stoichiometric KO₂Piv and KOAc was also accompanied with unacceptable levels of hydrodebromination and homocoupling of the arylbromide.¹⁵ Reasoning that the excess carboxylate base was interfering with the catalytic activity, we investigated the use of soluble acid cocatalysts in conjunction with a stoichiometric and insoluble¹⁶ potassium carbonate base. Proper choice of the carboxylic acid is crucial. For example, use of 30 mol % acetic acid provides no benefit compared to its use in a stoichiometric amount (entries 5 vs 3). Increasing steric bulk through the use of propionic acid and 2-methylpropionic acid did not positively influence the outcome (entries 6 and 7). Gratifyingly, however, the addition of 30 mol % pivalic acid resulted in 100% conversion and 81% isolated yield (entry 8 and at the bottom of Scheme 2). Increasing the steric bulk further, as with 1-adamantyl-carboxylic acid, gave inferior results (entry 9). These conditions are compatible with a variety of aryl bromides (Scheme 2). It is noteworthy that aryl chlorides and iodides appear incompatible under the present reaction conditions and can be recovered unreacted after the typical reaction time for aryl bromides.



Mechanistic studies support the involvement of a catalytic cycle similar to that illustrated in Scheme 1. Anisole reacts to give a 22:53:25 mixture of ortho/meta/para isomers while fluorobenzene reacts to give a 22:3:1 o/m/p ratio.¹⁷ In competition studies, benzene reacts preferentially over the more electron-rich anisole in a ratio of 2:1 (eq 1) while fluorobenzene reacts preferentially over benzene in a ratio of 11:1 (eq 2). We also note the presence of a large intermolecular kinetic isotope effect of 5.5.¹⁷ The reactions with anisole indicate that there is no directing effect by the methoxy-substituent, little or no electronic bias, and a minor steric bias resulting in a small statistical preference for reaction at the meta and para positions. These same trends can also explain the preferential reaction of benzene over anisole. The reactions with fluorobenzene clearly point to an important C–H bond acidity parameter in regioselectivity and reactivity. These results are incompatible with the reactivity profiles of electrophilic aromatic substitution^{5e} and radical processes^{10,18} but correlate very well with a proton-transfer pathway.^{6c,7}

The influence of the pivalate anion on the C–H bond-cleaving transition state has been probed by DFT analysis.¹⁹ A pivalate anion results in a decrease in transition state energy of 1.3 kcal/mol compared to a bicarbonate anion (24.9 vs 26.2 kcal/mol). Thus, the enhanced reactivity of this cocatalyst system may result not only from the controlled concentration of pivalate anion, but also from favorable energetics.

In conclusion, the combination of a palladium catalyst and a catalytic amount of pivalic acid generates a highly active catalyst for the direct arylation of simple arenes. The potential of this new catalyst system is illustrated by the first examples of high-yielding catalytic benzene metalation–arylation. We are currently evaluating the breadth of arenes that will undergo reaction with this new catalyst combination and will report these findings in due course.

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Supporting Information Available: Experimental procedures and computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Hassa, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
- For recent reviews, see the following: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (e) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2005**, 1253.
- Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989**, *37*, 1477.
- For recent examples involving metallacyclic intermediates, see: (a) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (c) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (d) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112.
- For recent advances with electron-rich heterocycles, see: (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Park, C. H.; Ryabova, V.; Seregin, I. V.; Sronek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (c) Li, W. J.; Nelson, D. P.; Jensen, M. S.; Hoerner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835. (d) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700. (e) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11749.
- For recent examples of intramolecular reactions with simple arenes, see: (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K.; *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (c) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.
- Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.
- We have previously observed a poisoning effect on direct arylation by the presence of iodide salts (see ref 6a).
- In polar media, an excess of anionic ligands could result in the formation of palladate species which may prevent the arene from binding and achieving C–H bond cleavage. For a discussion of palladates in cross-coupling reactions, see: Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.
- We differentiate these reactions from arylations with aryl radicals whose generation is catalyzed by metals, see: (a) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Baidossi, M.; Ponde, D. E.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1809. (b) Fujita, K.-i.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* **2004**, 1926.
- Harris, M. C.; Geis, O.; Buckwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019.
- The choice of ligand is less crucial than the choice of base and additive. This will be discussed further in a full account of this work.
- Bancroft, D. P.; Cotton, F. A.; Falvello, L. R.; Schwotzer, W. *Polyhedron* **1988**, *7*, 615.
- Larock has employed CsOPiv as a stoichiometric base for migratory processes (ref 6b). Here, the use of Cs salts results in inferior outcomes as we have observed elsewhere (ref 6a).
- These byproducts account for the remainder of the converted mass balance in approximately equal measure. The percent conversion is based on the amount of aryl bromide consumed during the reaction.
- The solubility of K₂CO₃ was evaluated by heating it in DMA at 120 °C for 30 min followed by rapid filtration of the hot solution. Less than 1% of the K₂CO₃ had dissolved.
- See Supporting Information for experimental details.
- For pertinent mechanistic studies, see: (a) Kobayashi, M.; Minato, H.; Kobori, N. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2738. (b) Eliel, E. L.; Welvart, Z.; Wilen, S. H. *J. Org. Chem.* **1958**, *23*, 1821. (c) Davies, D. I.; Hey, D. H.; Summers, B. *J. Chem. Soc.* **1971**, 2682. (d) Beadle, J. R.; Korzeniowski, S. H.; Rosenburg, D. E.; Garcia-Slanga, B. J.; Gokel, G. W. *J. Org. Chem.* **1984**, *49*, 1591.
- B3LYP density-functional theory calculations were performed with the Jaguar 6.0 package with the LACV3P+** basis set and pseudopotential combination of Jaguar. Full details are provided in the Supporting Information.

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