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The Role of Reversible Oxidative Addition in Selective Palladium(0)-Catalyzed Intramolecular Cross-Couplings of Polyhalogenated Substrates: Synthesis of Brominated Indoles

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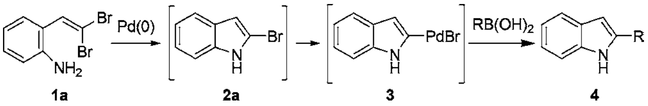
Abstract: A Pd(0)-catalyzed C−N bond-forming reaction leading to the synthesis of brominated indoles is described. The use of the phosphine ligand P*t*Bu$_3$ is necessary for reactivity. It is proposed that the bulky ligand serves to prevent inhibition of the catalyst by facilitating reversible oxidative addition into the product C−Br bond. Intramolecular coupling of a vinyl bromide in the presence of an aryl iodide can take place, demonstrating unprecedented levels of selectivity.

Palladium has recently played an increasingly important role in the synthesis of heterocycles by catalyzing C−C and C−X bond-forming reactions.[1] Most reports on this topic include a diverse range of substrates because of the high functional group tolerance of palladium catalysis. Notably absent in the vast majority of such scope evaluations is the presence of polyhalogenated substrates. This leaves a significant gap in the scope of most palladium-catalyzed heterocycle syntheses, despite the appeal of halogenated products.[2] A plausible explanation is that the Pd(0)/Pd(II) catalytic cycle gets terminated upon oxidative addition to a nonproductive carbon halide. Oxidative addition is generally considered to be an irreversible step in cross-coupling reactions, so the formed arylpalladium halide is a catalytic dead end. Herein, we present our findings on how the use of the bulky phosphine ligand P*t*Bu$_3$ can help overcome this problem for the synthesis of 2-bromoindoles and other heterocycles. Cross-coupling of a vinyl bromide in the presence of an aryl iodide is demonstrated, illustrating the power of this method.

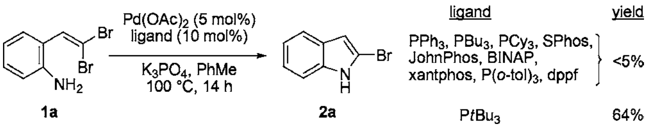
When studying the synthesis of indoles from *gem*-dibromoolefins such as **1a**, we observed that an external nucleophile (e.g., a boronic acid) was necessary for conversion of the starting material (Scheme 1).[3] Mechanistic studies suggested the intermediacy of 2-bromoindole **2a**, but this product was never observed directly in the reaction, even in the absence of boronic acid. We suspected that the active Pd(0) catalyst was undergoing irreversible oxidative addition after the first turnover to form catalytically inactive Pd(II) species **3**. The presence of a boronic acid or similar coupling partner is necessary to liberate active Pd(0) and achieve catalyst turnover.

Scheme 1. Tandem Indole Synthesis through a Brominated Intermediate



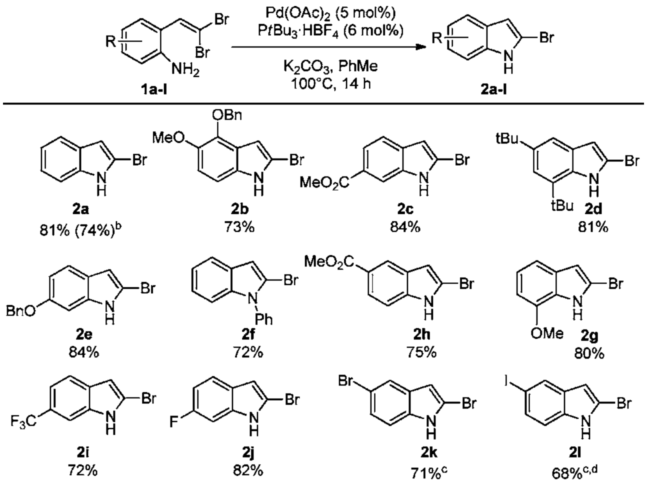
While oxidative addition of aryl bromides is generally irreversible, an exception was discovered by Hartwig and Roy,[4] who observed that treatment of an arylpalladium bromide with an excess of P*t*Bu$_3$ could induce reductive elimination to give free Pd(0). If irreversible oxidative addition of active Pd(0) into the carbon−bromide bond of **2a** to form **3** was shutting down the catalytic cycle, varying the phosphine ligand might allow regeneration of active Pd(0). A ligand screen was carried out, with most classes giving only trace amounts of product **2a** (Scheme 2). To our delight, when P*t*Bu$_3$ (protected as the BF$_4$ salt) was used, a 64% yield was obtained. The reaction was further optimized by changing the base and Pd/L ratio, and the scope was evaluated. A broad range of electron-poor, electron-rich, and sterically crowded *gem*-dibromoolefins underwent efficient C−N bond formation to form novel 2-bromoindoles (Table 1).[5,6] *Remarkably, iodoaniline **1l** containing three reactive carbon−halide bonds could be used to afford dihalogenated indole **2l** containing two reactive carbon−halide bonds*. To the best of our knowledge, this is the first report of selective cross-coupling of a vinyl bromide in the presence of an aryl iodide.

Scheme 2. Ligand Effect in the Synthesis of 2-Bromoindole



To explore the involvement of arylpalladium halide **3** in the catalytic cycle, Pd(P*t*Bu$_3$)$_2$ was mixed with an excess of indole **2a** in C$_6$D$_6$ until the starting complex was consumed, with the generation of proposed oxidative addition product **3a** and 1 equiv

Table 1. Palladium-Catalyzed Synthesis of 2-Bromoindoles



[a] Reaction conditions: **1** (0.2 mmol), Pd(OAc)$_2$ (5 mol %), P*t*Bu$_3$·HBF$_4$ (6 mol %), and K$_2$CO$_3$ (0.4 mmol) in PhMe (0.5 mL) at room temperature for 14 h. Isolated yields are reported. [b] Performed on 2 mmol scale with 10 mol % ligand. [c] For 24 h. [d] Using 10 mol % ligand.

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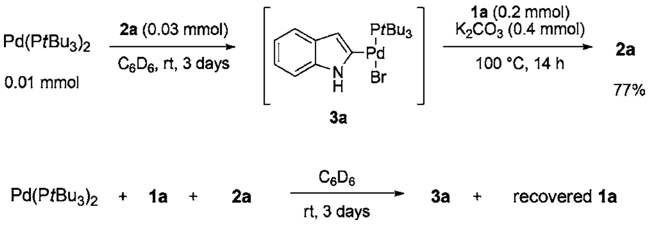
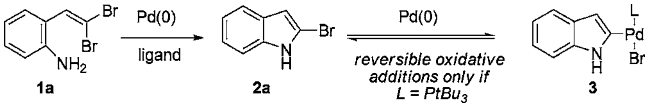
of P*t*Bu$_3$ (Scheme 3).[7] Heating the reaction mixture in the presence of excess base and **1a** gave catalyst turnover, and indole **2a** was isolated in 77% yield, suggesting that **3a** is a competent catalyst. To evaluate the site selectivity of the oxidative addition of aniline **1a** and indole **2a**, the two were mixed with 1 equiv of Pd(P*t*Bu$_3$)$_2$. Formation of product **3a** with no detectable reaction of aniline **1a** was observed, suggesting that oxidative addition preferentially occurs into the carbon−bromine bond of **2a**. These experiments support the mechanism proposed in Scheme 4. An initial Pd(0)-catalyzed C−N bond-forming reaction takes place to produce indole **2a**,[8] which then undergoes preferential oxidative addition with Pd(0) to form Pd(II) species **3**. With most ligands, this complex is catalytically inactive. If P*t*Bu$_3$ is used, free Pd(0) can be released and re-enter the catalytic cycle. Reversible catalyst inhibition was enhanced in the synthesis of polyhalogenated indoles **2k** and **2l**, which required extended reaction times. Notably, although Hartwig published his findings in 2001, the ability of P*t*Bu$_3$ to induce reductive elimination of arylpalladium bromides has not been exploited in catalysis.[9]

Scheme 3. Mechanistic Investigations



To determine whether this finding was general, we explored other intramolecular couplings of polyhalogenated substrates that our group had previously found to be problematic. The synthesis of dibromobenzofuran **6** had only been possible using copper catalysis (Scheme 5).[10] With Pd(OAc)$_2$ and P*t*Bu$_3$ in toluene at 100 °C, phenol **5** could now be converted to dibromobenzofuran **6** in 45% yield. Use of similar ligands such as PCy$_3$ and SPhos led mostly to decomposition of the starting material.

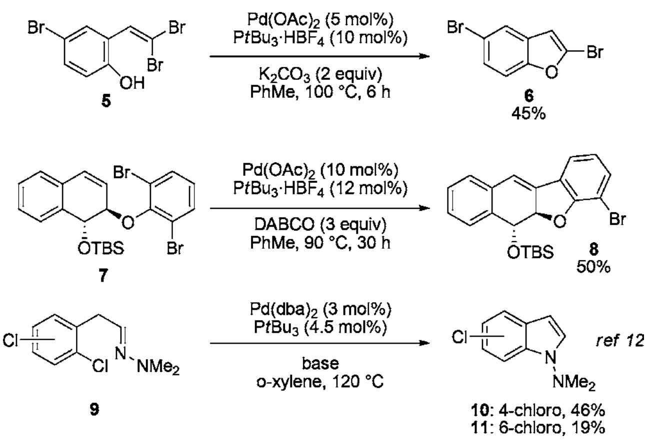
Scheme 4. Proposed Mechanism



Similarly, Heck reaction of dibrominated substrate **7** led to no coupling product under the previously optimized conditions in the absence of an external coupling partner, presumably because of irreversible oxidative addition.[11] Use of the modified conditions with P*t*Bu$_3$ allowed the formation of brominated Heck product **8** in 50% yield. Lastly, a literature search revealed a study by Watanabe in which chloroindoles **10** and **11** could be prepared from dichlorinated starting materials in 46 and 19% yield, respectively, when P*t*Bu$_3$ was used.[12] This study was published before Hartwig's work on stoichiometric reductive elimination, and the implication of reversible oxidative addition was not recognized. While the yields of these halogenated substrates were low, the sharp contrast observed between P*t*Bu$_3$ and other phosphine ligands supports the concept that the reversibility of oxidative addition plays an important role in the palladium-catalyzed synthesis of brominated substrates. Further understanding of this equilibrium may allow for a significant improvement in the scope of numerous heterocycle syntheses.

In conclusion, we have demonstrated an unusual ligand effect in the synthesis of brominated indoles. The bulky phosphine P*t*Bu$_3$ was required for conversion of starting material to be observed. We propose that the origin of this effect is the reversibility of oxidative addition into the carbon−bromine bond of the product, which has previously been demonstrated only in stoichiometric reactions. This unique mechanism allows for the selective cross-coupling of a vinyl bromide in the presence of an aryl iodide. The use of P*t*Bu$_3$ as a ligand for other coupling reactions of polyhalogenated substrates has been demonstrated. Studies of the generality of this finding, analysis of other bulky phosphine ligands, and mechanistic studies of the equilibrium between Pd(0) and arylpalladium halide are currently underway.

Scheme 5. Selective Intramolecular Cross-Couplings Utilizing P*t*Bu$_3$



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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) (a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232. (b) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944. (c) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533.
(5) While unprotected 2-bromoindoles are useful for numerous applications, their syntheses are often difficult. See: (a) Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495. (b) Techenor, M. S.; Trzupek, J. D.; Kastrinsky, D. B.; Shiga, F.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 15683. There are also several bromoindole natural products. For an overview, see: (c) Gribble, G. W. *J. Nat. Prod.* **1992**, *55*, 1353.
(6) Electron-rich 2-bromoindoles are unstable at room temperature and should be stored in dilute Et$_2$O under argon at−20 °C.
(7) While complex **3a** could not be cleanly isolated, the chemical shift was fully consistent with those of similar well-characterized complexes [e.g., the ^{31}P chemical shifts of **3a** and Pd(PtBu$_3$)(*o*-tolyl)(Br) are δ 65.1 and 64.4, respectively]. See the Supporting Information and ref 4b.
(8) We believe both *Z* and *E* oxidative additions to **1a** can lead to C−N bond formation (see ref 3).
(9) The exceptionally bulky ligand *t*Bu-Brettphos was recently used by Buchwald to induce catalytic reductive elimination of aryl fluorides. See: Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.
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