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Synthesis and Application of Palladium Precatalysts that Accommodate Extremely Bulky Di-*tert*-butylphosphino Biaryl Ligands

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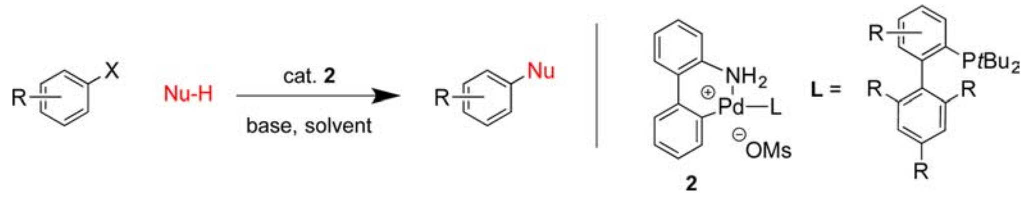
ABSTRACT



A series of palladacyclic precatalysts that incorporate electron-rich di-*tert*-butylphosphino biaryl ligands is reported. These precatalysts are easily prepared, and their use provides a general means of employing bulky ligands in palladium-catalyzed cross-coupling reactions. The application of these palladium sources to various C−N and C−O bond-forming processes is also described.

Dialkylphosphino biaryl compounds have emerged as privileged ligands for a wide range of palladium-catalyzed cross-coupling processes. Di-*tert*-butylphosphino biaryls represent a subset of this ligand class with catalysts based upon them having demonstrated a unique ability to induce extremely challenging and important processes efficiently, including the construction of C−C,[1] C−N,[2] C−O,[3] and C−F bonds.[4] In general, structural features of these ligands facilitate difficult reductive eliminations, thus contributing to their overall effectiveness. The formation of the catalytically active LPd(0) species, however, is less efficient when using these ligands. Two common methods have been utilized to overcome this issue: (1) water-mediated reduction of Pd(II) precursors[5] and (2) ligand and $Pd_2(dba)_3$ premixing.[6] Neither approach is ideal, as they both require an extra equivalent of ligand, and more importantly, the catalyst activation step involves an additional operation conducted in a second reaction vessel. Thus, we sought a simple, general approach to generating active catalysts based on these ligands.

Addressing the difficulty of efficient formation of active catalytic species, we have developed a family of air- and moisture-stable palladacycles, shown in Scheme 1, that allow for quantitative formation of the desired monoligated Pd(0) species.[7] These precatalysts are easily prepared using standard techniques and provide highly active catalysts for use in a broad array of synthetic applications. Under the basic conditions commonly employed in cross-coupling reactions, these complexes undergo deprotonation and reductive elimination to generate LPd(0) along

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(1) Strotman, N. A.; Chobanian, H. R.; Guo, Y.; He, J.; Wilson, J. E. *Org. Lett.* **2010**, *12*, 3578.

(2) (a) Rosenberg, A. J.; Zhao, J.; Clark, D. A. *Org. Lett.* **2012**, *14*, 1764. (b) Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 4710. (c) Ueda, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 10364. (d) Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576. (d) Vinogradova, E. V.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *51*, 11132.

(3) (a) Salvi, L.; Davis, N. R.; Ali, S. Z.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 170. (b) Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9943. (c) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694.

(4) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.

(5) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505.

(6) Ueda, S.; Su, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *132*, 700.

(7) (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686. (b) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073. (c) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci* **2013**, *4*, 916.

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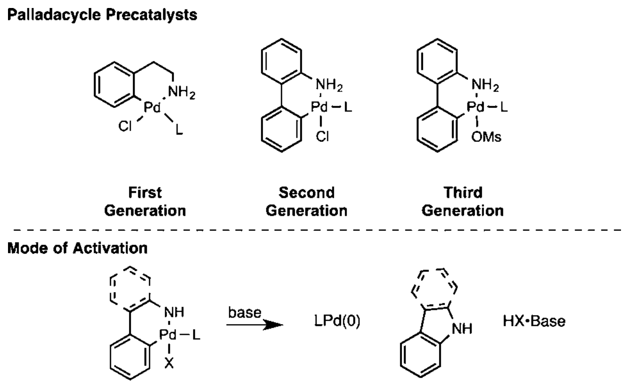
with relatively inert indoline (generation 1) or carbazole (generation 2 and 3). While precatalysts based on a number of important ligands (including R_3P, Ar_3P, BINAP, XantPhos, and dialkylphosphino biaryls) can be prepared, a means to access precatalysts based on di-*tert*-butylphosphino biaryl ligands has remained elusive. Herein, we report a general method for the synthesis of precatalysts based on these ligands and demonstrate the high catalytic efficiency of these complexes in several challenging cross-coupling reactions.

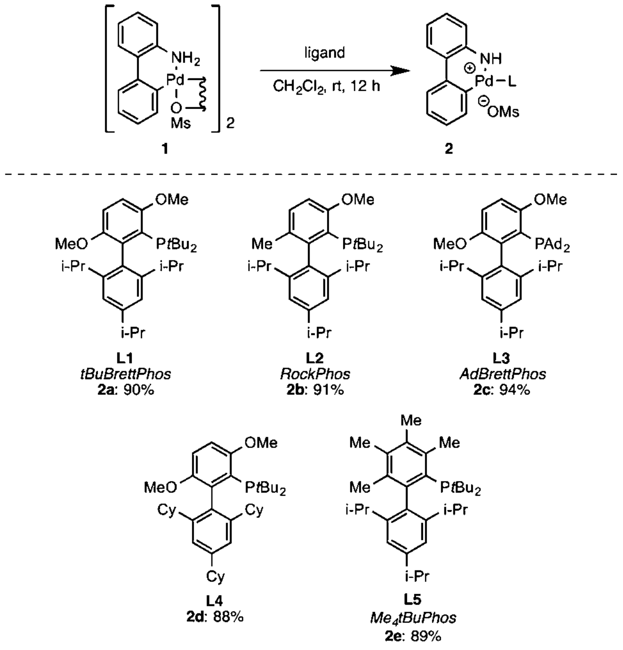
Scheme 1. Palladacyclic Precatalysts Previously Developed in Our Laboratory and Their General Activation



We recently reported the third-generation precatalysts wherein dimeric 2-aminobiphenylpalladium methanesulfonate complex **1** can be treated with a range of phosphine ligands to provide methanesulfonate precatalysts, **2**. These palladium sources are particularly useful; they allow for the direct incorporation of a range of ligands from a single intermediate and are efficiently converted to the active catalysts under very mild conditions.[7c] Initially the reported conditions for **2** were not successful for the formation of precatalysts with ligands **L1** − **L5**. As a result, we investigated a series of palladacyclic triflate precatalysts for these ligands.[8]

However, after reexamining the reaction conditions for preparing **2** we found that the use of chlorinated solvents (CH_2Cl_2 or $CHCl_3$) could be used for the incorporation of **L1**−**L5**.[9] Thus, stirring μ-OMs dimer **1** with *t*-BuBrettPhos (**L1**) in CH_2Cl_2 for 12 h at room temperature, followed by trituration of the crude material with diethyl ether, cleanly afforded the desired precatalyst in 90% yield. Additionally, this protocol could be used to form precatalyst **2** bearing **L2**−**L5** in uniformly high yields (Scheme 2). The structure of **2a** was confirmed by X-ray crystallography and is shown in Figure 1. As previously described,[7c] the palladium center is cationic with the fourth coordination site being occupied through coordinating to the *ipso* carbon of triisopropyl ring of the ligand.

Scheme 2. Preparation of Methanesulfonate Precatalysts with **L1**−**L5**



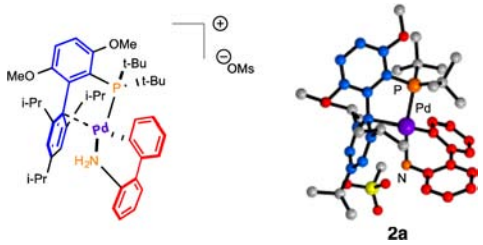
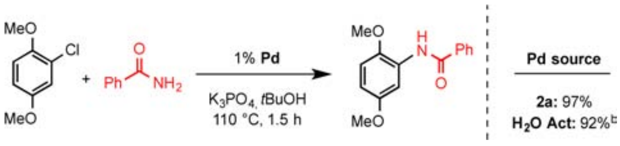


Figure 1. Crystallographically determined X-ray structure of **2a** (thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted for clarity).

Scheme 3. Comparison of Catalytic Activities of **2a** and Water Activation in the Arylation of a Primary Amide[a]



[a] General Conditions: ArCl (1 mmol), amide (1.05 − 1.2 mmol), K_3PO_4 (1.4 mmol), **2a** (1 mol %), *t*BuOH (2 mL), 110 °C, 1.5 h, isolated yields. [b] Previously reported yield.[2d]

Our reported procedure for the palladium-catalyzed amidation reaction of aryl chlorides employed a catalyst

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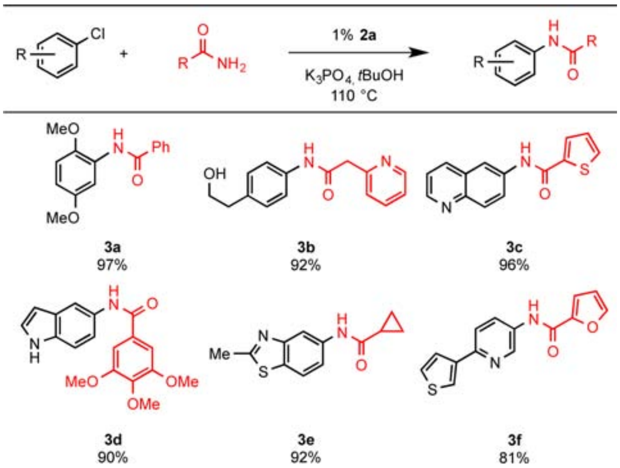
(8) Palladacyclic triflate precatalyst analogues have also been prepared. They exhibit similar reactivity but silver triflate is necessary for their preparation. See the Supporting Information for details.

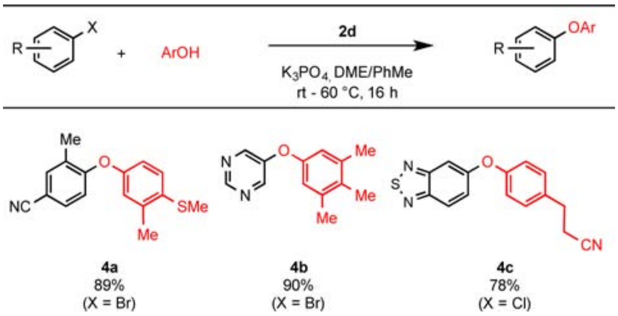
(9) The formation of precatalysts **2a**−**e** only went to completion in chlorinated solvents (CH_2Cl_2 and $CHCl_3$)

Scheme 4. Arylation of Primary Amides with **2a**[a]



[a] General Conditions: ArCl (1 mmol), amide (1.05 – 1.2 mmol), K_3PO_4 (1.4 mmol), **2a** (1 mol %), *t*BuOH (2 mL), 110 °C, 1.5 h; isolated yields, average of two runs.

Scheme 5. Arylation of Phenols with **2d**[a]

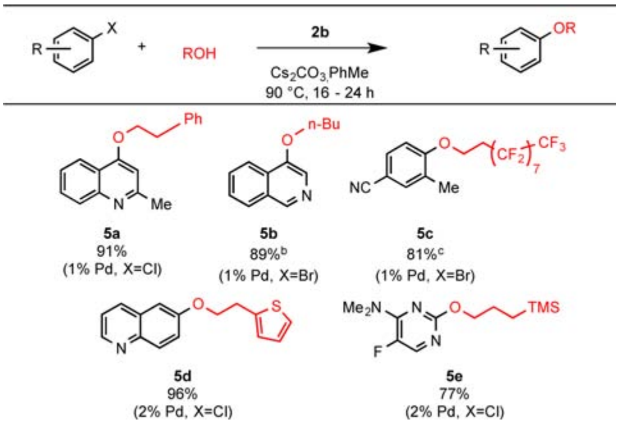


[a] General Conditions: aryl halide (1 mmol), phenol (1.5 mmol), K_3PO_4 (1.5 mmol), **3d** (1.5–2 mol %) 3:2 PhMe/DME (1 mL), rt –60 °C, 16 h; isolated yields, average of two runs.

based on **L1**.[2d] The procedure was efficient, requiring only 1 mol % palladium and relatively short reaction times; however, use of the water-mediated preactivation method was necessary to generate the active catalyst. To evaluate the efficacy of **2a**, we utilized 1 mol % of **2a** in the reaction of benzamide with 2-chloro-1,4-dimethoxybenzene (Scheme 3). Under otherwise identical conditions, the secondary amide product was obtained in slightly higher yield than previously obtained when using **2a**. As shown in Scheme 4, we further evaluated the efficiency of **2a** toward more functionalized aryl chlorides and primary amides. In general, the use of **2a** exhibited good functional group tolerance; we observed no competitive C–O bond formation or N-arylation of indole in the cases of **3b** and **3d**, respectively.

We were also interested in assessing the performance of the new precatalysts in Pd-catalyzed C–O bond-forming reactions. We previously demonstrated the coupling of aryl halides and phenols using a [(cinnamyl)PdCl]2/**L4** catalyst system.[3a] This original procedure involved the use of 0.25–3 mol % of Pd, excess **L4**, at between ambient temperature and 100 °C. However, when **2d** was used in place of [(cinnamyl)PdCl]2/**L4** (Scheme 5), the diaryl ether products were formed in good yields, under mild reaction conditions (ambient to 60 °C, 1.5–2 mol % of Pd) and without the need to add excess ligand. Similarly, utilizing a precatalysts (**2b**) derived from RockPhos (**L2**), which was previously described to be an excellent supporting ligand for the Pd-catalyzed arylation of aliphatic alcohols,[3b] we were able to couple a variety of primary alcohols with aryl halides (Scheme 6). Aryl alkyl ethers were obtained in good to excellent yields, comparable to our previously described results.[10]

Scheme 6. Arylation of Aliphatic Alcohols with **2b**[a]



[a] General Conditions: aryl halide (1 mmol), alcohol (1.5 mmol), Cs_2CO_3 (2 mmol), **2b** (1–2 mol %) PhMe (1 mL), 90 °C, 24 h; isolated yields, average of two runs. [b] 3 equiv of alcohol. [c] 1.05 equiv of alcohol.

In summary, we have developed a series of ligated palladium precatalysts that incorporate extremely bulky ligands (**L1**–**L5**). The use of these precatalysts address a number of issues in catalyst activation. They are significantly more convenient to use and obviate the need to use excess ligand to generate active LPd(0) species. These precatalysts are bench stable and easily synthesized on a large scale (10 g for **2a**). We expect that their use will expand the scope of known transformations and facilitate the discovery of new Pd-catalyzed processes.

Acknowledgment. We thank the National Institutes of Health for financial support (GM46059 and GM58160). This activity was also supported, in part, by an educational donation provided by Amgen, for which we are grateful. We thank Phillip J. Milner (MIT) for growing crystals of **2a** and **7a** and Dr. Peter Müller (MIT) for X-ray structural analysis. We thank Dr. Nathan Jui (MIT) and Dr. J. Robb

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(10) Maligres, P. E.; Li, J.; Krska, S. W.; Schreier, J,. D.; Raheem, I, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 9071. This report notes that in difficult couplings, such as in **5a**, **L2**/$Pd_2(dba)_3$ was only effective when the palladium and ligand were premixed and molecular sieves were used. The use of **2b** circumvents these issues and provides the desired product in comparable yields without molecular sieves or premixing.

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Supporting Information Available. Experimental procedures along with experimental and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare the following competing financial interest(s): MIT has patents on the ligands used in this paper from which S.L.B. receives royalty payments and has also filed patents on the methanesulfonate precatalysts.