Published in final edited form as:

Org Lett. 2013 June 7; 15(11): 2876–2879. doi:10.1021/ol401208t.

Synthesis and Application of Palladium Precatalysts that Accommodate Extremely Bulky di-*tert*-Butylphosphino Biaryl Ligands

Nicholas C. Bruno and Stephen L. Buchwald

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Stephen L. Buchwald: sbuchwal@mit.edu

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) precursors⁵ and (2) ligand and Pd₂(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 with relatively inert indoline (generation 1) or carbazole (generation 2 and 3). While precatalysts based on a number of important ligands (including

Correspondence to: Stephen L. Buchwald, sbuchwal@mit.edu.

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>

R₃P, Ar₃P, 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.

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 (CH₂Cl₂ or CHCl₃) could be used for the incorporation of **L1** – **L5**.⁹ Thus, stirring F-OMs dimer **1** with *t*BuBrettPhos (**L1**) in CH₂Cl₂ 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.

Our reported procedure for the palladium-catalyzed amidation reaction of aryl chlorides employed a catalyst 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 % **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** towards 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 [(cinnyl)PdCl]₂/**L4** catalyst system.^{3a} This original procedure involved the use of 0.25–3 mol % Pd, excess **L4**, at between ambient temperature and 100 °C. However, when **2d** was used in place of [(cinnyl)PdCl]₂/**L4** (Scheme 5), the diaryl ether products were formed in good yields, under mild reaction conditions (ambient–60 °C, 1.5–2 mol % 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 (Table 6). Aryl alkyl ethers were obtained in good to excellent yields, comparable to our previously described results.¹⁰

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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. The authors would like to thank Phillip J. Milner (MIT) for growing crystals of **2a** and **7a** and Dr. Peter Müller (MIT) for X-ray structural analysis. We would like to thank Dr. Nathan Jui (MIT) and Dr. J. Robb DeBergh (MIT) for helpful discussions and assistance in the preparation of this manuscript. The Varian 500 and 300 MHz NMR instruments used for portions of this work were supported by the National Science Foundation (Grants CHE 9808061 and DBI 9729592, respectively). 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. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health.

References

1. Strotman NA, Chobanian HR, Guo Y, He J, Wilson JE. *Org Lett.* 2010; 12:3578. [PubMed: 20704397]
2. (a) Rosenberg AJ, Zhao J, Clark DA. *Org Lett.* 2012; 14:1764. [PubMed: 22414201] (b) Su M, Buchwald SL. *Angew Chem Int Ed.* 2012; 51:4710.(c) Ueda S, Buchwald SL. *Angew Chem Int Ed.* 2012; 51:10364.(d) Fors BP, Dooleweerd K, Zeng Q, Buchwald SL. *Tetrahedron.* 2009; 65:6576. [PubMed: 20740063] (d) Vinogradova EV, Fors BP, Buchwald SL. *J Am Chem Soc.* 2012; 134:11132. [PubMed: 22716197]
3. (a) Salvi L, Davis NR, Ali SZ, Buchwald SL. *Org Lett.* 2012; 14:170. [PubMed: 22182186] (b) Wu X, Fors BP, Buchwald SL. *Angew Chem Int Ed.* 2011; 50:9943.(c) Anderson KW, Ikawa T, Tundel RE, Buchwald SL. *J Am Chem Soc.* 2006; 128:10694. [PubMed: 16910660]
4. Watson DA, Su M, Teverovskiy G, Zhang Y, Garcia-Fortanet J, Kinzel T, Buchwald SL. *Science.* 2009; 325:1661. [PubMed: 19679769]
5. Fors BP, Krattiger P, Strieter E, Buchwald SL. *Org Lett.* 2008; 10:3505. [PubMed: 18620415]
6. Ueda S, Su M, Buchwald SL. *J Am Chem Soc.* 2012; 134:700. [PubMed: 22126442]
7. (a) Biscoe MR, Fors BP, Buchwald SL. *J Am Chem Soc.* 2008; 130:6686. [PubMed: 18447360] (b) Kinzel T, Zhang Y, Buchwald SL. *J Am Chem Soc.* 2010; 132:14073. [PubMed: 20858009] (c) Bruno NC, Tudge MT, Buchwald SL. *Chem Sci.* 2013; 4:916. [PubMed: 23667737]
8. Palladacyclic triflate precatalyst analogues have also been prepared. They exhibit similar reactivity but silver triflate is necessary for their preparation. See Supporting Information for details.
9. The formation of precatalysts **2a** – **2e** only went to completion in chlorinated solvents (CH₂Cl₂ and CHCl₃)
10. Maligras PE, Li J, Krska SW, Schreier JD, Raheem IT. *Angew Chem Int Ed.* 2012; 51:9071. This report notes that in difficult couplings, such as in **5a**, **L2**/Pd₂(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.

Figure 1.

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

Palladacycle Precatalysts **Mode of Activation**

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

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

Scheme 3.

Comparison of Catalytic Activities of **2a** and Water Activation in the Arylation of a Primary Amide.^a

^a ArCl (1 mmol), amide (1.05 – 1.2 mmol), K₃PO₄ (1.4 mmol), **2a** (1 mol %), *t*BuOH (2 mL), 110 °C, 1.5 h, isolated yields. ^b Previously reported yield.^{2d}

Scheme 4. Arylation of Primary Amides with **2a**.^a^a 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 aryl halide (1 mmol), phenol (1.5 mmol), K_3PO_4 (1.5 mmol), **2d** (1.5 – 2 mol %) 3:2 PhMe:DME (1 mL), rt – 60 °C, 16 h; isolated yields, average of two runs.

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

^a 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 alcohol. ^c 1.05 equiv alcohol