Organic LETTERS

Letter

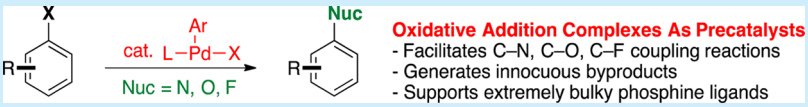
pubs.acs.org/OrgLett

Oxidative Addition Complexes as Precatalysts for Cross-Coupling Reactions Requiring Extremely Bulky Biarylphosphine Ligands

Bryan T. Ingoglia and Stephen L. Buchwald*

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

Supporting Information



ABSTRACT: In this report, we describe the application of palladium-based oxidative addition complexes (OACs) as effective precatalysts for C–N, C–O, and C–F cross-coupling reactions with a variety of (hetero)arenes. These complexes offer a convenient alternative to previously developed classes of precatalysts, particularly in the case of the bulkiest biarylphosphine ligands, for which palladacycle-based precatalysts do not readily form. The precatalysts described herein are easily prepared and stable to long-term storage under air.

The use of biarylphosphines as supporting ligands in palladium catalysis has played an important role in the development of synthetic methods that can be used to form C–C,[1] C–N,[2] C–O,[3] and C–F[4] bonds in a wide variety of settings. To facilitate the use of these ligands, we have developed several generations of palladacyclic precatalysts (**G1**–**G5**, Figure 1), which are able to accommodate a range

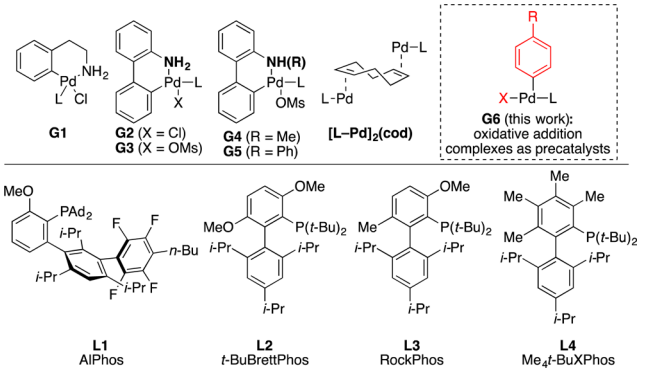


Figure 1. Evolution of precatalysts developed by the Buchwald group and selected bulky supporting ligands.

of phosphine-based ligands.[5,6] These precatalysts can be used to promote cross-coupling reactions with high efficiency. This is due, in part, to the preassociation of the ligand with the Pd center and to the rapid formation of a L–Pd(0) species under the reaction conditions. In addition, these Pd(II) precatalysts are easily handled and stable to long-term storage without the need to carefully exclude air or water.

Biarylphosphine ligands bearing bis(*tert*-butyl) and bis(1-adamantyl) phosphino groups (e.g., **L1**–**L4**) are useful supporting ligands for catalysts that promote C–O and C–F cross-coupling reactions.[7] Among other things, these ligands are believed to facilitate the challenging reductive elimination steps of these processes.[3c,4] Methods to prepare palladacycle precatalysts based on these particularly bulky ligands are less successful than with other ligands. While **G3** precatalysts containing these ligands are readily isolated, they form carbazole upon catalyst activation, which occasionally can cause inhibition of the catalyst based on kinetic and mechanistic studies.[5c,6a,8] Precatalysts of type **G4** and **G5** were prepared to address this, among other issues. However, **G4** and **G5**-based precatalysts based on **L1**–**L4** are only formed with difficulty.[5d]

As an alternative, our group has developed [L–Pd]$_2$(cod) (cod = 1,5-cyclooctadiene) precatalysts (Figure 1) which are suitable for **L1**–**L4**.[9] However, not all biarylphosphine ligands form precatalysts of this type. Furthermore, these complexes are generally air sensitive and exhibit poor solubility in organic solvents, making them less convenient to handle.[4a,9,10] Thus, we set out to find alternative Pd(II) precatalysts that would overcome these issues.

We hypothesized that a potential solution would be to use oxidative addition complexes (OACs) of general formula L–Pd(Ar)X as precatalysts. These are readily obtained by oxidative addition of aryl (pseudo)halides to an *in situ* generated L–Pd(0) species. Moreover, since they serve as presumptive intermediates on the catalytic cycle for cross-coupling processes, these OACs should be competent palladium sources for a variety of C–X bond-forming reactions.[11,12]

We were particularly interested in the use of OACs for the development of a simplified and improved protocol for the palladium-catalyzed fluorination of aryl (pseudo)halides. Previously, **L1** (AlPhos) was found to be an effective supporting ligand for the palladium-catalyzed fluorination of a broad range of aryl bromides and triflates.[4] However, preliminary investigation into the use of palladacycle precatalysts yielded poor outcomes, likely due to the formation

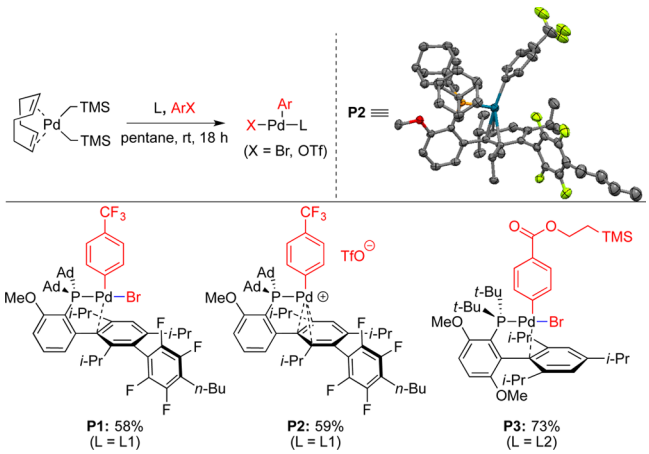
Received: April 10, 2017

DOI: 10.1021/acs.orglett.7b01082
Org. Lett. XXXX, XXX, XXX–XXX

of inhibiting byproducts (e.g., HF or carbazole) during catalyst activation, as well as the inefficiency of catalyst activation itself in the absence of a suitable exogenous base.[4c] We expected OACs to address both of these issues as no base is needed for activation, while the only byproduct is simply another aryl fluoride, which is presumably innocuous.

To test this hypothesis, precatalysts **P1**–**P3** were prepared by combining the biarylphosphine ligand, aryl bromide, or triflate, and (cod)Pd(CH_2TMS)$_2$[4] in pentane, from which the desired complex precipitated. Filtering and washing the precipitate afforded the pure complexes in moderate to good isolated yield, while the remaining free ligand may be recovered from the filtrate (Scheme 1, see Supporting Information (SI) for details).

Scheme 1. Synthesis of Oxidative Addition Complexes[a]

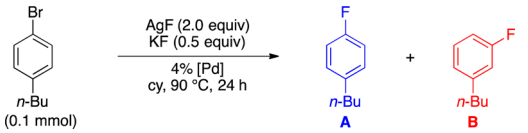


[a]Structures of OACs used as precatalysts. Crystallographically determined X-ray structure of **P2** shown (thermal ellipsoid plot at 50% probability, triflate anion and hydrogen atoms are omitted).

4-Trifluoromethylphenyl was selected as the aryl group for **P1** and **P2**, since catalyst activation via the formation of 4-fluorobenzotrifluoride under the reaction conditions was expected to be facile. Moreover, this byproduct was expected to be inert under the reaction conditions and readily removed due to its volatility. The structures of **P1** and **P2** were confirmed by NMR spectroscopy as well as by X-ray crystallography in the case of **P2**, providing the first crystal structure of a complex derived from an aryl triflate with **L1** as the supporting ligand (Figure 1). The complexes are stable under air in a benchtop desiccator in the solid state for at least 10 months, as judged by ^{31}P NMR spectroscopy.[13]

Our reported conditions for the palladium-catalyzed fluorination of aryl bromides and triflates call for [**L1**–Pd]$_2$(cod) as the source of ligand and palladium.[4a] We initially employed **P1** alone in place of the cyclooctadiene complex for the fluorination of 1-bromo-4-*n*-butylbenzene and found that it performed poorly compared to the previously developed conditions (Table 1, entries 1 vs 2). However, when exogenous cyclooctadiene was added, the yield increased substantially (Table 1, entry 3). We postulate this additive may improve the yield by stabilizing any off-cycle Pd(0) species and averting irreversible catalyst deactivation. Encouraged by this result, we examined the generality of these conditions toward the fluorination of aryl triflates. Indeed, **P1** also served as a competent precatalyst for the fluorination of aryl triflates, although small amounts of the corresponding aryl bromides were also formed, complicating isolation of the desired

Table 1. Additive Effects on the Fluorination of 1-Bromo-4-*n*-butylbenzene with P1 as Precatalyst[a]



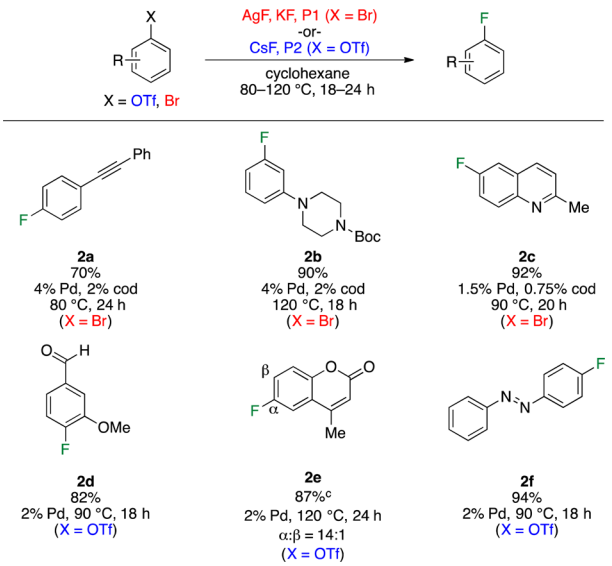
entry	[Pd]	additive	yield **A**(**B**)
1	[**L1**–Pd]$_2$(cod)		87% (5%)
2	P1		22% (1%)
3	P1	2% cod	91% (6%)

[a]Yields reported as ^{19}F NMR yields using 1-fluoronaphthalene as an internal standard: cy = cyclohexane; cod = 1,5-cyclooctadiene.

products. To address this issue, we prepared triflate analogue **P2**. For aryl triflate substrates, this precatalyst exhibits the same catalytic activity as **P1**, while avoiding the formation of aryl bromide side products. However, **P2** does not efficiently transform aryl bromides into aryl fluorides, perhaps due to inefficient activation of the precatalyst by the fluoride sources present under the reaction conditions. Thus, we employed **P1** and **P2** for the fluorination of aryl bromides and triflates, respectively. To gain a sense of the generality of these new protocols, a small collection of substrates were examined under these conditions. Substrates containing potentially sensitive functional groups, including an internal alkyne (**2a**), an aldehyde (**2c**), and an azo (**2f**) were fluorinated in good to excellent yield, with a regioisomeric side product observed only in the case of **2e** (Scheme 2).[14]

After investigating OAC precatalysts in the context of C–F bond-forming reactions, we explored the applicability of this method to other bond-forming processes. To facilitate purification of the cross-coupling product, we considered precatalysts which would produce easily removed byproducts upon activation. In particular, we designed an OAC bearing a

Scheme 2. Fluorination of Aryl Bromides and Triflates with P1 and P2[a,b]

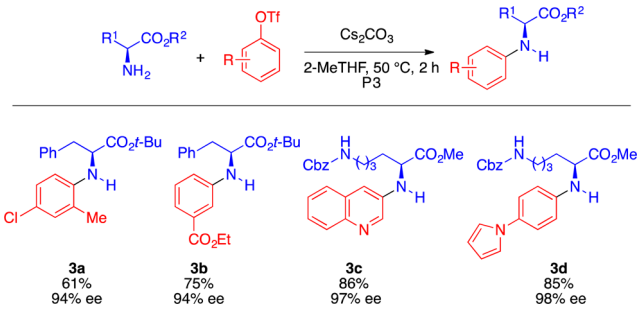


[a]Isolated yields are reported as an average of two runs. General conditions: ArBr (1.0 mmol), AgF (2.0 mmol), KF (0.5 mmol), cyclohexane (10 mL). [b]ArOTf (1.0 mmol), CsF (3.0 mmol), cyclohexane (10 mL). [c]Toluene was the reaction solvent.

DOI: 10.1021/acs.orglett.7b01082
Org. Lett. XXXX, XXX, XXX–XXX

trimethylsilyl ethyl (TMSE) ester, which can be selectively cleaved with fluoride to liberate the corresponding carboxylate, which is easier to separate from the desired product. On the basis of previously reported C−O and C−N cross-coupling processes,[3,15] **L2** (*t*-BuBrettPhos) was selected as the ligand for the precatalyst. Complex **P3** was therefore prepared as a precatalyst for these types of coupling reactions. The new precatalyst was first employed for the *N*-arylation of amino acid esters under mild and stereoretentive conditions. By employing **P3**, the desired arylation products were formed in moderate to good yields with high levels of enantioretention (Scheme 3).

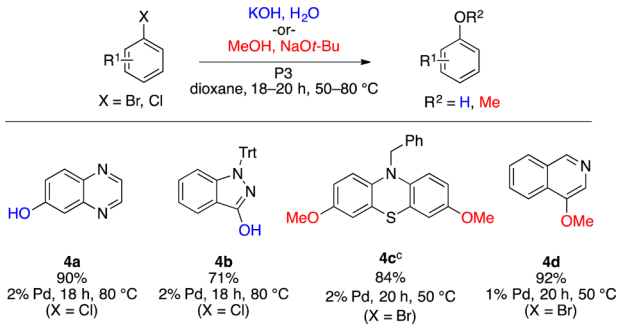
Scheme 3. Amino Acid Ester Arylation with P3[a]



[a]Isolated yields are reported as an average of two runs. General conditions: ArOTf (1.0 mmol), amino acid ester (1.1 mmol), Cs_2CO_3 (3.0 mmol), **P3** (5 mol %), 2-methyltetrahydrofuran (2 mL). Enantiomeric excess (ee, average of two runs) was determined by HPLC analysis using chiral stationary phases.

Treatment with TBAF, if necessary, was mild enough to cleave the aminated TMSE ester present in the byproduct selectively, simplifying purification of the desired product (**3b, 3d**) without eroding the enantiomeric excess and with merely one percent or less of the byproduct as judged by the ^{1}H NMR spectrum after chromatographic purification (see SI for details). Other compounds (**3a, 3c**) could be purified without the addition of fluoride. Precatalyst **P3** was also found to be suitable for the cross-coupling of oxygen nucleophiles (Scheme 4). Heterocyclic aryl halides, including a quinoxaline (**4a**), an indazole (**4b**), and an isoquinoline (**4d**), were hydroxylated or methoxylated in good yield. An *N*-benzyl dibromophenothiazine (**4c**) readily underwent coupling to afford the bis(methoxylation) product in excellent yield.

Scheme 4. Alcohol and Hydroxide Coupling with P3[a,b]



[a]Isolated yields are reported as an average of two runs. General conditions: aryl halide (1.0 mmol), KOH (3.0 mmol), H_2O (20 mmol), 1,4-dioxane (2 mL). [b]Aryl halide (1.0 mmol), MeOH (5 mmol), NaO*t*-Bu (1.2 mmol), 1,4-dioxane (2 mL). [c]Using 2.4 equiv of NaO*t*-Bu and 10 equiv of MeOH.

In summary, we have demonstrated that oxidative addition complexes based on palladium, supported by extremely bulky dialkylbiaryl phosphine ligands, can serve as active precatalysts for a wide variety of challenging, synthetically useful carbon−heteroatom bond-forming reactions. The complexes are well-characterized, easily handled outside of a glovebox, and provide a means of introducing L−Pd(0) into a reaction without the formation of potentially inhibitory byproducts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01082.

Experimental procedures and characterization data for new compounds (PDF)
Crystal data of **P2** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sbuchwal@mit.edu.

ORCID

Bryan T. Ingoglia: 0000-0002-9049-6227

Notes

The authors declare the following competing financial interest(s): MIT has patents on some of the ligands and precatalysts described in this work, from which S.L.B. as well as former or current coworkers receive royalty payments.

■ ACKNOWLEDGMENTS

We thank Aldrich for a gift of *t*-BuBrettPhos (**L2**). We thank Dr. Mycah Uehling (MIT), Dr. Nicholas White (MIT), and Dr. Yi-ming Wang (MIT) for assistance in the preparation of this manuscript. We thank Dr. Aaron Sather (MIT), Dr. Sandra King (MIT), and Anni Zhang (MIT) for providing aryl triflate starting materials for the project. We thank Dr. Kurt Armbrust (MIT) and Dr. Pedro Arrechea (MIT) for helpful discussions. We thank Jonathan Becker (MIT) for solving the X-ray structure of **P2**. The X-ray diffractometer was purchased with the help of funding from the National Science Foundation (Grant No. CHE 0946721). The Varian 500 MHz instrument used for portions of this work was supported by the National Science Foundation (Grant No. CHE 9808061). Research reported in this publication was supported by the National Institutes of Health under Award Nos. GM46059 and GM58160. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

■ REFERENCES

(1) (a) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532−7533. (b) Yang, Y.; Oldenhuis, N. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 615−619. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461−1473.

(2) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564−12649.

(3) (a) Cheung, C. W.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 3998−4001. (b) Cheung, C. W.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*,

DOI: 10.1021/acs.orglett.7b01082
Org. Lett. XXXX, XXX, XXX−XXX

5351−5358. (c) Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9943−9947.
(4) (a) Sather, A. C.; Lee, H. G.; De La Rosa, V. Y.; Yang, Y.; Müller, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 13433−13438. (b) Sather, A. C.; Buchwald, S. L. *Acc. Chem. Res.* **2016**, *49*, 2146−2157. (c) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661−1664. (d) Milner, P. J.; Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 15757−15766.
(5) (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686−6687. (b) Bruno, N. C.; Tudge, M. C.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916−920. (c) Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876−2879. (d) Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161−4166.
(6) For a class of precatalysts based on π-allyl and indenyl complexes, which have been shown to accommodate very bulky biarylphosphines, see: (a) DeAngelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J. *J. Org. Chem.* **2015**, *80*, 6794−6813. (b) Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; Tudge, M. T. *ACS Catal.* **2015**, *5*, 3680−3668.
(7) (a) Lundgren, R. J.; Stradiotto, M. *Chem. - Eur. J.* **2012**, *18*, 9758−9759. (b) Bariwal, J.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, *42*, 9283−9303. (c) DeAngelis, A.; Colacot, T. J. In *New Trends in Cross-Coupling: Theory and Applications*; Colacot, T. J., Ed.; RSC: Cambridge, U.K., 2015; pp 20−90. (d) Seechurn, C. C. C.; Li, H.; Colacot, T. J. In *New Trends in Cross-coupling: Theory and Applications*; Colacot, T. J., Ed.; RSC: Cambridge, U.K., 2015; pp 91−138.
(8) Park, N. H.; Vinogradova, E. V.; Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8259−8262.
(9) Lee, H. G.; Milner, P. J.; Colvin, M. T.; Andreas, L.; Buchwald, S. L. *Inorg. Chim. Acta* **2014**, *422*, 188−192.
(10) For a capsule-based strategy to enable convenient handling of $[L-Pd]_2(cod)$ complexes in combination with hygroscopic bases, see: Sather, A. C.; Lee, H. G.; Colombe, J. R.; Zhang, A.; Buchwald, S. L. *Nature* **2015**, *524*, 208−211.
(11) In fact, OACs have found use in the context of mechanistic experiments, see: (a) Moser, W. R.; Wang, A. W.; Kildahl, N. K. *J. Am. Chem. Soc.* **1988**, *110*, 2816−2820. (b) Wallow, T. I.; Goodson, F. E.; Novak, B. M. *Organometallics* **1996**, *15*, 3708−3716. (c) Verbeeck, S.; Meyers, C.; Franck, P.; Jutand, A.; Maes, B. U. W. *Chem. - Eur. J.* **2010**, *16*, 12831−12837.
(12) For examples of a complex with formula $(Ph_3P)_2Pd(Ph)I$ catalyzing a C−C coupling, see: (a) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273−281. (b) Sekiya, A.; Ishikawa, N. *J. Organomet. Chem.* **1976**, *118*, 349−354.
(13) Complex **P1** slowly reacts in solution with oxygen, but is stable in the solid state.
(14) Formation of regioisomeric products occurs with certain types of substrates in the Pd-catalyzed fluorination reaction.[4d]
(15) King, S. M.; Buchwald, S. L. *Org. Lett.* **2016**, *18*, 4128−4131.

DOI: 10.1021/acs.orglett.7b01082
Org. Lett. XXXX, XXX, XXX−XXX