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Efficient Monophosphorus Ligands for Palladium-Catalyzed Miyaura Borylation

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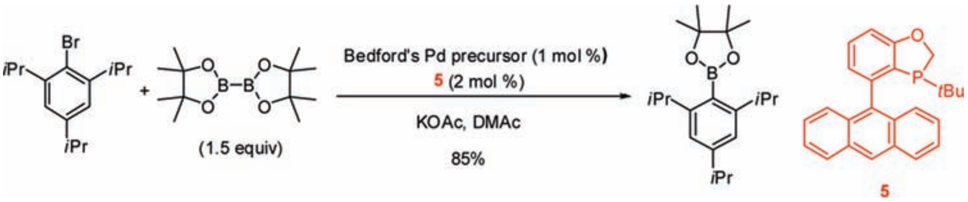
ABSTRACT



In combination with the Bedford Pd precursor, the new biaryl monophosphorus ligand 5 was efficient for palladium-catalyzed Miyaura borylation of sterically hindered aryl bromides at low catalyst loadings.

Arylboronic acids or esters are key chemical building blocks in synthetic organic chemistry that have been utilized for a variety of chemical transformations.[1] Of particular importance are their applications in transition-metal-catalyzed cross-coupling reactions, of which are the well-known Suzuki−Miyaura coupling reactions.[2] The syntheses of aryl boronic acids or esters have thus gained a great deal of attention, and a few methods have emerged.[3] One of the most common methods includes the transmetalation of aryl lithium or Grignard reagents with trialkyl borates.[4] However, this method generally requires harsh reaction conditions and is incompatible with sensitive functional groups. By using aryl halides and bis(pinacolato)-diboron as the reagents, the palladium-catalyzed Miyaura borylation is more functionality-tolerable and has become an important alternative for the synthesis of arylboronic esters.[5] A recent modification using pinacolborane as the reagent is attractive albeit with more limitations of the substrate scope.[6] Despite these progresses,[7,8] Miyaura borylation of sterically hindered aryl halides remains a very challenging task. For example, only a modest yield (72%) was achieved on the palladium-catalyzed borylation of 2-bromo-1,3,5-triisopropylbenzene at a high catalyst loading (5 mol %).[6d] We herein report the application of biaryl monophosphorus ligands **1** and **5** (Figure 1) in the palladium-catalyzed Miyaura borylation. Excellent reactivities have been achieved on a series of sterically hindered aryl bromides.

We have developed a series of conformationally rigid biaryl monophosphorus ligands containing a 2,3-dihydrobenzo[*d*][1,3]oxaphosphole substructure **1−4** and have

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(1) For recent reviews, see: (a) Merino, P.; Tejero, T. *Angew. Chem., Int Ed.* **2010**, *49*, 7164. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(2) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *36*, 343. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(3) For rhodium- and iridium-catalyzed borylation of arene C−H bonds, see a recent review: Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. C.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(4) Suzuki, A.; Brown, H. C. *Organic Syntheses via Boranes*; Aldrich Chemial Company: Milwakee, 2003; Vol. 3.

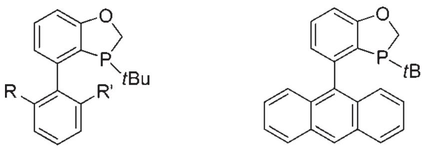
(5) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813. (c) Furstner, A.; Seidel, G. *Org. Lett.* **2002**, *4*, 541. (d) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359. (e) Xu, C.; Gong, J.-F.; Song, M.-P.; Wu, Y.-J. *Transition Met. Chem.* **2009**, *34*, 175.

(6) (a) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458. (b) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164. (c) Broutin, P.-E.; Čerňa, I.; Campaniello, M.; Leroux, F.; Colobert, F. *Org. Lett.* **2004**, *6*, 4419. (d) Murata, M.; Sambommatsu, T.; Watanabe, S.; Masuda, Y. *Synlett* **2006**, 1867. (e) Billingsley, K. L.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5589. (f) Lam, K. C.; Marder, T. B.; Lin, Z. *Organometallics* **2010**, *29*, 1849.

(7) For Ni-catalyzed borylation, see: (a) Rosen, B.; Huang, C .; Percec, V. *Org. Lett.* **2008**, *10*, 2597. (b) Moldoveanu, C.; Wilson, D. A.; Wilson, C. J.; Leowanawat, P.; Resmerita, A.-M.; Liu, C.; Rosen, B. M.; Percec, V. *J. Org. Chem.* **2010**, *75*, 5438. (c) Wilson, D. A.; Wilson, C. J.; Moldoveanu, C.; Resmerita, A.-M.; Corcoran, P.; Hoang, L. M.; Rosen, B. M.; Percec, V. *J. Am. Chem. Soc.* **2010**, *132*, 1800.

(8) With tetrahydroxydiboron as the reagent, see: Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701.

10.1021/ol2000556

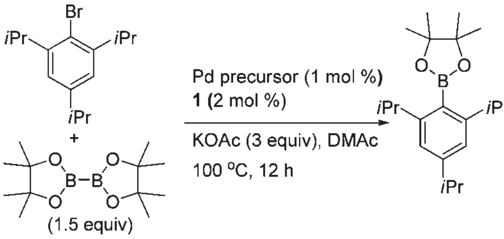


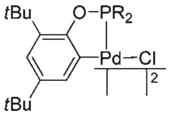
1: R = R' = OMe (BI-DIME)
2: R = R' = H
3: R = OMe, R' = H
4: R = NMe_2, R' = H

5

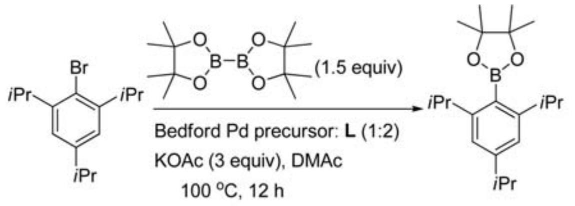
Figure 1. Novel biaryl monophosphorus ligands.

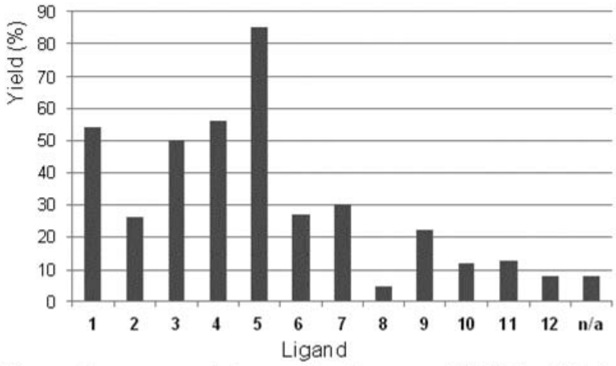
Scheme 1. Miyaura Borylation of 2-Bromo-1,3,5-triisopropylbenzene with Pd-BI-DIME Catalysts



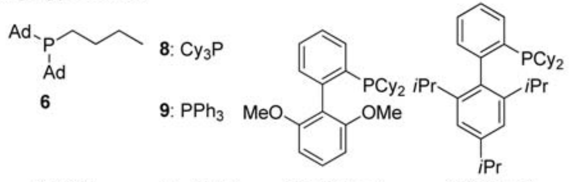
Pd precursor	yield (%)
Pd_2dba_3	13%
 R = OC_6H_3-2,4-tBu_2 (Bedford Pd precursor)	54%

Scheme 2. Ligand Survey on Miyaura Borylation of 2-Bromo-1,3,5-triisopropylbenzene[a]





[a] The reactions were carried out under nitrogen at 100 °C for 12 h, 2-bromo-1,3,5-triisopropylbenzene (1 mmol), bis(pinacolato)diboron (1.5 mmol), Bedford Pd precursor (0.01 mmol), ligand (0.02 mmol), KOAc (3 mmol), dimethyl acetamide (2 mL), averaged HPLC assayed yields based on two runs. The main side-product with ligand **1-5** was 1,3,5-triisopropylbenzene.



6

7: $PtBu_3$

8: Cy_3P

9: PPh_3

12: DPPF

10 (SPhos)

11(XPhos)

demonstrated the superior reactivity of ligand **1** (BI-DIME) for Suzuki–Miyaura couplings and Buchwald–Hartwig aminations.[9,10] The excellent reactivity of BI-DIME observed in the sterically hindered Suzuki–Miyaura coupling reactions prompted us to investigate its catalytic activities in the Miyaura borylation of sterically hindered aryl halides. 2-Bromo-1,3-5-triisopropylbenzene was chosen as the substrate of study (Scheme 1). An initial result under standard conditions (1.5 equiv bis(pinocolato)-diboron, 3 equiv KOAc, 1 mol % Pd_2dba_3, 2 mol % **1**, 100 °C, 12 h) provided a disappointingly low yield (13%). A close monitoring of the reaction course showed a good initial reaction rate (~5% conversion within 1 h). However, the reaction significantly slowed down afterward indicating fast catalyst deactivation. Although the deactivation pathway was not well understood, we envisioned that the incorporation of a sterically hindered phosphite ligand in the reaction system could increase the catalyst longevity of the reaction, a strategy successfully employed by Bedford and co-workers in Suzuki–Miyaura coupling reactions.[11] To our delight, a much improved yield (54%) was observed when the Bedford Pd precursor, a phosphite-ligated palladacycle complex,[12] was employed instead of Pd_2dba_3 (Scheme 1).

The improved yield observed in combination with the Bedford Pd precursor encouraged us to develop a more efficient biaryl monophosphorus ligand for Miyaura borylation. Although ligands **2**–**4** did not provide much improved yields, we found ligand **5** containing an anthracenyl moiety at the low aryl ring[13] provided 4,4,5,5-tetramethyl-2-(2,4,6-triisopropylphenyl)-1,3,2-dioxaborolane in 85% yield (Scheme 2). It is noteworthy that this is the highest yield reported to date on this sterically

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[9] (a) Tang, W.; Capacci, A. G.; Wei, X.; Li, W.; White, A.; Patel, N. D.; Savoie, J.; Gao, J. J.; Rodriguez, S.; Qu, B.; Haddad, N.; Lu, B. Z.; Krishnamurthy, D.; Yee, N. K.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5879. (b) Rodriguez, S.; Qu, B.; Haddad, N.; Reeves, D.; Tang. W.; Krishnamurthy, D.; Senanayake, C. H. *Adv. Synth. Catal.*, doi: 10.1002/adsc.201000878.

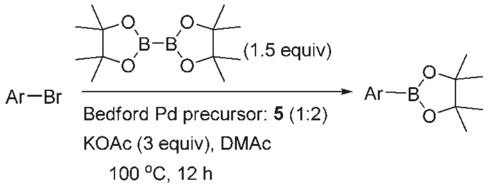
[10] For related bisphosphorus ligands, see: (a) Tang, W.; Qu, B.; Capacci, A. G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 176. (b) Tang, W.; Capacci, A. G.; White, A.; Ma, S.; Rodriguez, S.; Qu, B.; Savoie, J.; Patel, N. D.; Wei, X.; Haddad, N.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 1104.

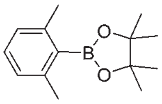
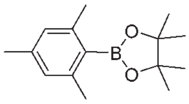
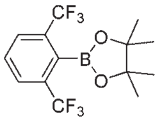
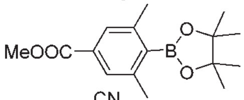
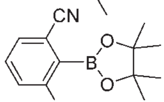
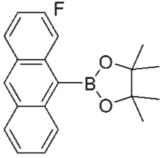
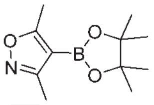
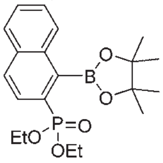
[11] Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4120.

[12] For an excellent review on palladacycles, see: Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527.

[13] See Supporting Information for a detailed synthesis.

Table 1. Miyaura Borylation of Di-*ortho*-substituted Aryl Bromides[a]



entry	product	Pd loading (mol %)	yield (%)
1		1	96
2		1	95
3		0.5	89
4		1	85
5		1	60
6		1	91
7		1	82
8[b]		1	59

[a] The reactions were carried out under nitrogen at 100 °C for 12 h, aryl bromide (1 mmol), bis(pinocolato)diboron (1.5 mmol), Bedford Pd precursor/**5** = 1:2, KOAc (3 mmol), dimethyl acetamide (2 mL), isolated yields. [b] The main side product was the debromo compound.

Scheme 3. Miyaura Borylation of 1-Bromo-4-methoxybenzene

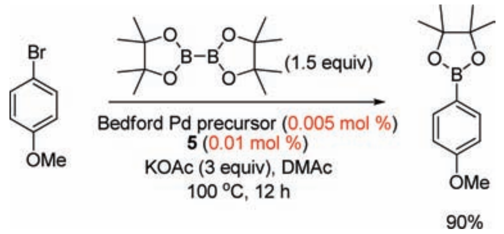
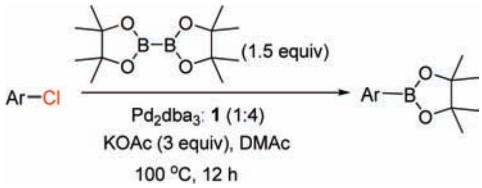
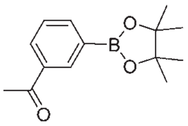
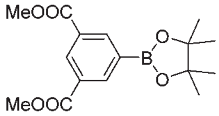
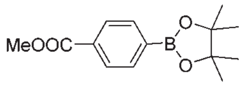
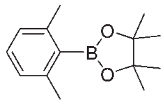


Table 2. Miyaura Borylation of Aryl Chloride with Pd_2dba_3 and Ligand **1** as the Catalysts[a]



entry	product	Pd loading (mol %)	yield (%)
1		2	82
2		2	92
3		1	86
4[b]		4	53

[a] The reactions were carried out under nitrogen at 100 °C for 12 h, aryl chloride (1 mmol), bis(pinocolato)diboron (1.5 mmol), KOAc (3 mmol), dimethyl acetamide (2 mL), isolated yields. [b] The reaction was incomplete.

hindered substrate at 2 mol % Pd loading. A series of commercially available ligands were also employed for comparison. Some commonly used monophosphorus ligands such as Ad_2PnBu (**6**), tBu_3P (**7**), Cy_3P (**8**), PPh_3 (**9**), SPhos (**10**), and XPhos (**11**) were inefficient for this reaction and all provided < 30% yields. An often applied chelating ligand DPPF (**12**) also led to a very low yield. These results clearly demonstrated the outstanding reactivity of ligand **5** for sterically hindered Miyaura borylation. We hypothesized that the unique structural and electronic properties of ligand **5** facilitate the key transmetalation step of the Miyaura borylation process. While it is not clear whether there is a rate acceleration of the catalytic cycle in the presence of both ligand **5** and the bulky phosphite from the Bedford Pd precursor,[14] the fact that a low conversion (8%) was observed with the Bedford Pd precursor alone as the catalyst suggests that the bulky phosphite ligand is less likely to promote the rate of the catalytic cycle but rather plays a role in increasing the longevity of the Pd catalyst.

To explore the synthetic utilities of ligand **5** for palladium-catalyzed sterically hindered Miyaura borylation, the combination of the Bedford Pd precursor and ligand **5** was applied in the borylation of a range of di-*ortho*-substituted aryl bromides. As shown in Table 1, excellent yields were achieved on a series of sterically congested aryl bromides at

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[14] For a report about multiligand-based Pd catalysis, see: Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914.

low palladium loadings (0.5−1 mol % Pd). Various functionalities such as $-CF_3$ (entry 3), −COOMe (entry 4), −CN (entry 5), and phosphonate (entry 8) were well tolerated. A high yield was also achieved on an oxazole substrate (entry 7).

To further demonstrate the catalytic efficiency of ligand **5** for Miyaura borylation, 1-bromo-4-methoxybenzene was subjected to borylation in the presence of 0.005 mol % Bedford Pd precursor and 0.01 mol % ligand **5**, and the desired product 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was obtained in 90% isolated yield (9000 TON). To our knowledge, this is the lowest catalyst loading reported to date in Miyaura borylation (Scheme 3).

The combination of ligand **5** and the Bedford Pd precursor was unfortunately incapable of catalyzing the borylation of aryl chlorides.[5d] This could be attributed to the π-acidity of the phosphite ligand from the Bedford Pd precursor which makes the key oxidative addition of aryl chloride more difficult.[11] Nevertheless, the palladium catalyst generated from Pd_2dba_3 and BI-DIME (**1**) proved to be efficient for the borylation of a series of aryl chlorides (Table 2) with various functionalities. For a sterically bulky aryl chloride, a higher catalyst loading (4 mol %) was required and only a moderate yield was obtained (entry 4).

In conclusion, a novel and efficient biaryl monophosphorus ligand **5** is developed for the palladium-catalyzed Miyaura borylation. In combination with the Bedford Pd precursor, ligand **5** is efficient for the borylation of a series of sterically hindered aryl bromides with various functionalities at low catalytic loadings. A turnover number up to 9000 has been demonstrated, which provides potential for practical applications. BI-DIME also proves to be efficient for the borylation of aryl chlorides. Further efforts will be focused on exploring the relationships between the ligand structures and the reactivities for Miyaura borylation, and progress will be reported in due course.

Supporting Information Available. Experimental details and NMR spectra of ligand **5** and all arylboronic ester products, general borylation procedure. This material is available free of charge via the Internet at http://pubs.acs.org.