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C–C Coupling

Palladium-Catalyzed Borylation of Aryl Chlorides: Scope, Applications, and Computational Studies**

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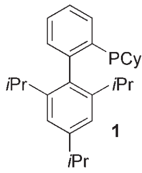
Aryl boronic acids and esters are versatile reagents for organic synthesis that are utilized in the preparation of various carbon–oxygen, carbon–nitrogen, and carbon–carbon bonds.[1] In addition, the use of organoboranes for cross-coupling processes is particularly attractive owing to their high stability and low toxicity. However, boronic acids and esters usually are prepared via intermediate alkyl and aryllithium compounds or Grignard reagents, processes that are not compatible with numerous functional groups.[2] Furthermore, the use of aryl iodides or bromides is often necessary, while the more readily available aryl chlorides[3] are often unsuitable precursors.

In recent years, the development of a variety of transition-metal-catalyzed processes has allowed for the preparation of aryl boronate esters under milder conditions.[4] In particular, numerous palladium-catalyzed methods have emerged for the conversion of aryl iodides, bromides, and triflates to the corresponding pinacol or catechol boronate esters.[5] However, only two reports[6] can be found in which unactivated aryl chlorides are suitable coupling partners, and these methods have several disadvantages: 1) High quantities of palladium catalysts (5–6 mol %) are required for many substrates. 2) Long reaction times (24–48 h) are necessary. 3) Limited substrate scope and functional-group tolerance (e.g. few or no examples with *ortho* substituents, phenols, and anilines) is exhibited. Herein, we report an active catalyst composed of Pd and dialkylphosphinobiphenyl ligands **1** or **2** that efficiently converts aryl chlorides to pinacol boronate esters and allows, for the first time, the direct "one-pot" synthesis of symmetrical and unsymmetrical biaryl compounds from two aryl chlorides. In addition, computational studies are presented that provide insight into the efficacy of biaryl monophosphine ligands in the palladium-catalyzed borylation process.



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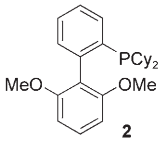

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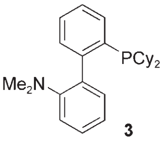

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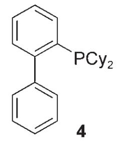

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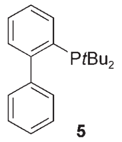

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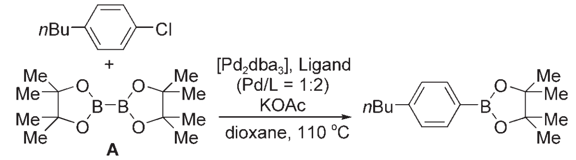
We began by optimizing the reaction parameters. We found that a variety of dialkylphosphinobiphenyl ligands could be employed to afford highly active catalysts for the borylation of 4-*n*-butylchlorobenzene (Table 1). In each instance, the desired aryl boronate ester was obtained in good or excellent yield. The optimum system, based upon [Pd$_2$dba$_3$] and XPhos (**1**), allowed for the use of relatively low quantities of catalyst and provided a quantitative yield of product in just two hours (Table 1, entry 6). We found KOAc to be the optimum base, although a variety of inorganic bases could be utilized. However, the use of K$_3$PO$_4$ or fluoride bases, despite resulting in full conversion of the aryl chloride, also led to the formation of approximately 15–20 % of the homocoupling product 4,4′-*n*-butylbiphenyl.

Table 1: Ligand optimization for the Pd-catalyzed borylation of aryl chlorides.



Entry	Ligand	mol % Pd	*t* [h]	Yield [%][a]
1	**1**	2.0	24	99
2	**2**	2.0	24	94
3	**3**	2.0	24	97
4	**4**	2.0	24	95
5	**5**	2.0	24	82
6	**1**	0.50	2	99

[a] Yield determined by GC.

To illustrate the activity of the catalyst, the borylation of an electron-rich aryl chloride, 4-chloroanisole, was examined (Scheme 1). The best previous result for the transformation of this substrate combination required 5 mol % [Pd(dba)$_2$] and a 24-h reaction time to obtain a 86 % yield of the pinacol boronate ester.[5a] However, it was found that a catalyst based upon Pd(OAc)$_2$ and **1** resulted in extremely rapid conversion (10 min) of the aryl chloride and a 97 % yield of the desired

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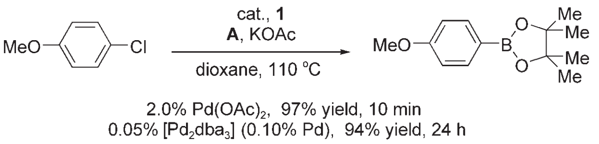
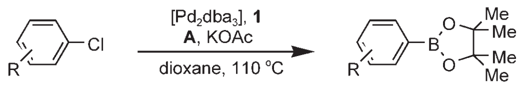
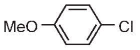
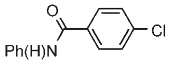
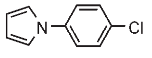
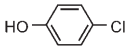
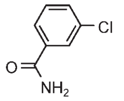
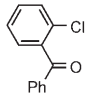
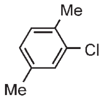
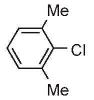
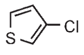
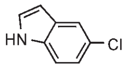
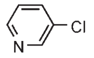


Scheme 1. Pd-Catalyzed Borylation of 4-Chloroanisole; Pd/**1** = 1:2, yields given are of isolated product.

Table 2: Palladium-catalyzed borylation of aryl chlorides at elevated temperatures.[a]



Entry	Aryl chloride	mol% Pd	t	Yield [%][b]
1		2.0 0.10	10 min 24 h	97[c] 94
2		0.50	30 min	96
3		1.0	30 min	83
4		2.0	30 min	82
5		2.0	30 min	89
6		2.0	1 h	87
7		2.0	1 h	88
8		4.0	5 h	62[d]
9		1.0	2 h	76
10		2.0	1 h	95[c]
11		2.0	5 h	82[e]

[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 1.2–3.0 equiv of **A**, 3 equiv of KOAc, dioxane (2 mL (mmol halide)$^{-1}$), cat. [Pd$_2$dba$_3$], Pd/**1** = 1:2. [b] Yield of isolated product based upon an average of two runs. [c] Pd(OAc)$_2$ used instead of [Pd$_2$dba$_3$]. [d] Dioxane/H$_2$O (10:1) used as the solvent. [e] 3-Chloropyridine was added by syringe pump over the course of 1 h.

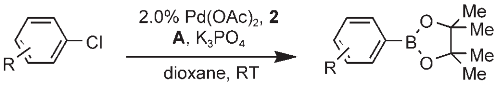
product. In addition, the process remained efficient at lower levels of palladium, as the boronate ester was produced in 94% yield after 24 h when 0.05 mol% [Pd$_2$dba$_3$] was utilized.

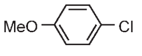
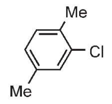
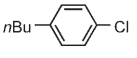
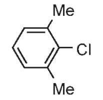
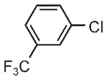
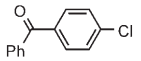
Catalyst systems based upon Pd(OAc)$_2$ or [Pd$_2$dba$_3$] and **1** as the supporting ligand proved to be highly active for the borylation of a variety aryl chlorides. In general, employing Pd(OAc)$_2$ as a precatalyst offered faster reaction rates but also resulted in the production of a greater quantity of reduced aryl halide as a by-product relative to when [Pd$_2$dba$_3$] was employed. The [Pd$_2$dba$_3$]–**1** system efficiently transformed activated aryl chlorides, such as 4-chlorobenzanilide, to the corresponding boronate esters in excellent yield and in only thirty minutes (Table 2, entry 2). In addition, the system proved to be highly active in the borylation of 4-chlorophenol (Table 2, entry 4) and 3-chlorobenzamide (Table 2, entry 5), as the desired pinacol boronate esters were furnished in 82% and 89% yield, respectively. Although *ortho*-substituted aryl halides are known to be particularly challenging substrates, the borylation of 2-chloro-*p*-xylene (Table 2, entry 7) and 2-chloro-*m*-xylene (Table 2, entry 8) under standard conditions successfully produced the corresponding boronate esters in moderate to high yield. In addition, many heteroaryl chlorides were also efficiently transformed to the desired products (Table 2, entries 9 and 10). In contrast, the borylation of 3-chloropyridine under the standard reaction conditions resulted in only a 60% conversion of the heteroaryl chloride. However, if the aryl halide was slowly added over the course of the reaction, 100% conversion was observed, resulting in an 82% yield of the boronate ester (Table 2, entry 11).

Although palladium-catalyzed borylation methods offer a higher degree of functional-group tolerance, these processes still rely upon elevated temperatures. Therefore, we sought to develop a system that could efficiently accomplish such a transformation at lower temperatures.

We discovered that our standard conditions for the borylation of aryl chlorides at elevated temperatures were inefficient at room temperature. However, when Pd(OAc)$_2$ and K$_3$PO$_4$ were employed in lieu of [Pd$_2$dba$_3$] and KOAc, the reaction proceeded in an efficient manner. Although Pd(OAc)$_2$ and **1** provided a suitable catalyst, SPhos (**2**) proved to be a better supporting ligand for the room-temperature version of this transforma-

Table 3: Palladium-catalyzed borylation of aryl chlorides at room temperature.[a]



Entry	Aryl chloride	t [h]	Yield [%][b]	Entry	Aryl chloride	t [h]	Yield [%][b]
1		24	97	4		48	79
2		48	91[c]	5		48	86
3		48	64[c]	6		48	91[c,d]

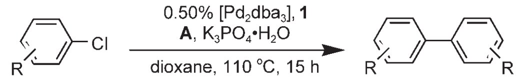
[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 3.0 equiv of **A**, 3 equiv of K$_3$PO$_4$, dioxane (2 mL (mmol halide)$^{-1}$), cat. Pd(OAc)$_2$, Pd/**2** = 1:2.5. [b] Yield of isolated product based upon an average of two runs. [c] K$_3$PO$_4$·H$_2$O used instead of K$_3$PO$_4$. [d] 3.0% Pd(OAc)$_2$ used instead of 2.0%.

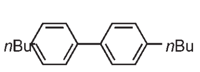
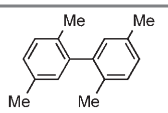
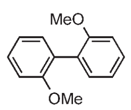
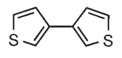
tion. For example, a catalyst based upon $Pd(OAc)_2$ and **2** allowed for the borylation of 4-chloroanisole in 97 % yield at room temperature (Table 3, entry 1). This approach was also applicable to sterically hindered aryl chlorides, such as 2-chloro-*p*-xylene and 2-chloro-*m*-xylene (Table 3, entries 4 and 5). It is noteworthy that with the latter substrate, a significantly higher yield was obtained using one-half the amount of palladium precatalyst than when the reaction was carried out at 110 °C.[7] Furthermore, activated aryl chlorides such as 4-chlorobenzophenone were efficiently converted to the corresponding pinacol boronate esters (Table 3, entry 6). This protocol represents the first Pd-catalyzed method for transforming aryl chlorides to aryl boronate esters at room temperature.

Although aryl boronate esters can be precursors to a variety of compounds, their primary application is in the synthesis of biaryl species via the Suzuki–Miyaura reaction with an aryl halide or sulfonate.[1] However, the boronate ester is typically prepared and isolated prior to the cross-coupling step. Although a few reports have utilized a "one-pot" reaction protocol combining borylation and Suzuki–Miyaura steps to synthesize biaryl compounds, these methods employ catalysts that neither display prolonged stability nor a high level of activity.[8] Consequently, previous efforts have been unsuccessful when attempting to utilize relatively unreactive aryl chlorides for the one-pot biaryl synthesis. Moreover, the addition of a second portion of palladium catalyst is necessary for the reaction to go to completion.

In our initial studies on the borylation of aryl chlorides (see above), we found that when employing bases such as K_3PO_4, approximately 15–20 % of the aryl halide was converted directly to the symmetrical biaryl compound.[9] Furthermore, if $K_3PO_4{\cdot}H_2O$ was utilized, this product was isolated in high yield. A Pd-to-ligand ratio of 1:4 was found to be optimal in order to maintain catalyst stability. Using the conditions given in Table 4, 4-*n*-butylchlorobenzene was directly converted to the symmetrical biaryl product in near-quantitative yield (Table 4, entry 1). This method was then applied to the homocoupling of an electron-rich chloride (2-chloroanisole, entry 2), a relatively hindered cloride (2-chloro-*p*-xylene, entry 3), and a heteroaryl chloride (3-chlorothiophene, entry 4), all of which were readily converted to the corresponding symmetrical biaryl compounds.

Table 4: Palladium-catalyzed preparation of symmetrical biaryl compounds.[a]



Entry	Product	Yield [%][b]	Entry	Product	Yield [%][b]
1		98[c,d]	3		77[c,d]
2		70	4		87

[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 0.50 equiv of **A**, 3 equiv of $K_3PO_4{\cdot}H_2O$, dioxane (4 mL (mmol halide)$^{-1}$), cat. $[Pd_2dba_3]$, Pd/**1** = 1:4. [b] Yield of isolated product based upon an average of two runs. [c] K_3PO_4 used instead of $K_3PO_4{\cdot}H_2O$. [d] H_2O (0.50 mL) added to the reaction mixture by syringe after 6 h.

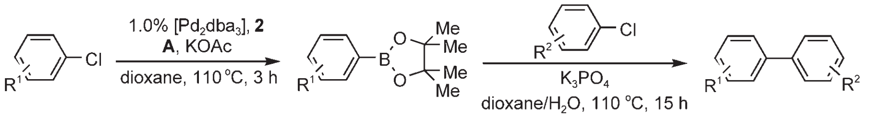
Although this method was useful for the preparation of symmetrical biaryl compounds, we sought to develop conditions for the direct synthesis of their unsymmetrical counterparts. In this endeavor, a catalyst system based upon $[Pd_2dba_3]$ and **2** proved to be effective for the borylation as well as for the subsequent Suzuki–Miyaura reaction. In this process, the substrate was subjected to standard Pd-catalyzed borylation conditions with subsequent addition of the second aryl chloride and aqueous K_3PO_4. No workup was performed nor was catalyst added prior to conducting the second reaction of the sequence. This protocol was used successfully with a variety of aryl chlorides and with a vinyl chloride (Table 5). In addition, heteroaryl chlorides could be employed in the first step (Table 5, entry 7) or in the second step (Table 5, entries 2 and 3) while maintaining good or excellent yields of the biaryl products. However, these standard conditions could not be used with many ketones, as significant α-arylation of the substrate was observed.[10] However, if KOAc was replaced with K_3PO_4 in the first step, then the biaryl species was obtained in good yield (Table 5, entry 8). These methods represent the first processes for the direct synthesis of symmetrical and unsymmetrical biaryl compounds from two aryl chlorides.

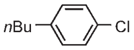
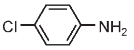
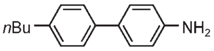
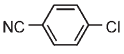
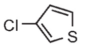
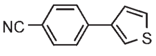
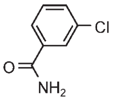
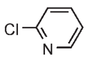
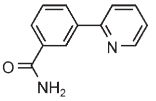
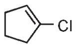
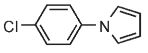
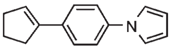
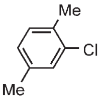
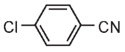
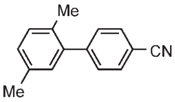
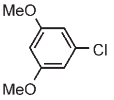
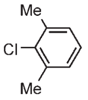
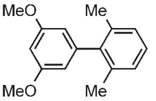
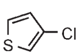
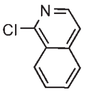
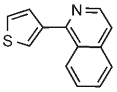
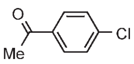
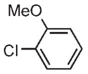
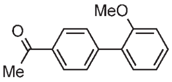
To help determine what effect biaryl phosphine ligands may have on the Pd-catalyzed borylation of aryl halides with **A**, we turned to computational chemistry. Specifically, we were interested in the common use of KOAc in Pd-catalyzed borylation reactions. All of the calculated structures described below were optimized using Gaussian 03[11] and the B3LYP[12] functional in combination with the 6-31G(d) basis set for all nonmetal atoms and LANL2DZ + ECP[13] for the Pd center.

It is possible that the use of KOAc in Pd-catalyzed borylation reactions facilitates the formation of an [LPd(Ar)-OAc] compound from an oxidative addition species (e.g. [LPd(Ar)Cl], complex **6**, Scheme 2). This type of metathesis was shown to occur in the Pd-catalyzed borylation reactions of aryl iodides and bromides by Miyaura in 1995.[14] Although the calculated free energy of reaction is $+9.2\ \text{kcal mol}^{-1}$, this metathesis may still occur because of concurrent generation and precipitation of KCl, thus shifting the reaction equilibrium to the product (Scheme 2).

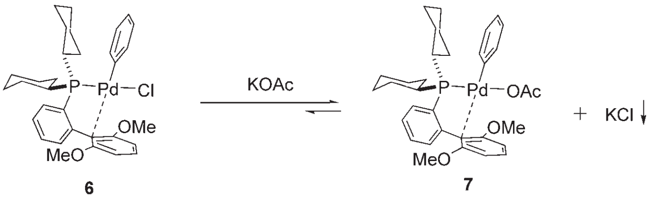
On the basis of our previous study of oxidative addition intermediates involving biaryl phosphine ligands, it is very likely that transmetalation of bis(pinacolato)-diboron occurs when complex **7** (Scheme 2) is in a geometry such that the Pd center is distal to the non-phosphine-bearing ring of the ligand.[15] The necessity for this situation is the extreme crowding around the Pd center when the Pd center is coordinated to the

Table 5: Palladium-catalyzed preparation of unsymmetrical biaryl compounds.[a]



Entry	First aryl chloride	Second aryl chloride	Product	Yield [%][b]
1				89
2				92
3				92
4				62
5				70
6				95
7				71
8				65[c,d]

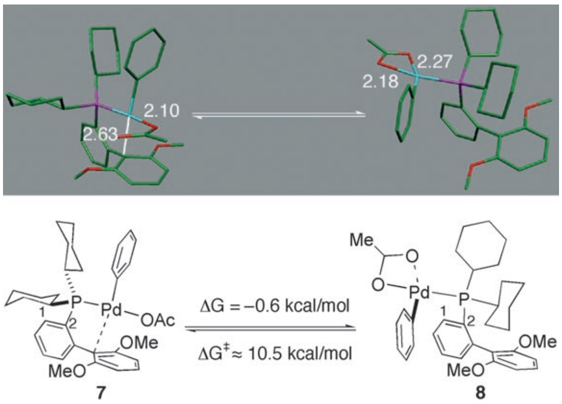
[a] Reaction conditions: 1.2 equiv of the first aryl or heteroaryl chloride, 1.0 equiv of the second aryl chloride, 1.2 equiv of **A**, 2 equiv of KOAc, 5 equiv K_3PO_4, dioxane (4 mL (mmol halide)$^{-1}$), cat. $[Pd_2dba_3]$, Pd/**2** = 1:4. [b] Yield of isolated product based upon an average of two runs. [c] K_3PO_4 used instead of KOAc in step one. [d] 2.0% $[Pd_2dba_3]$ used instead of 1.0%.



Scheme 2. Formation of [LPd(Ar)OAc].

non-phosphine-bearing ring of the ligand (Scheme 3). Specifically, a free coordination site on the Pd center needs to be made available so that coordination of the diboron species can occur. We have previously demonstrated that rotation of an oxidative addition complex (complex **6**) around the C2–P bond to a geometry such that the Pd center is distal to the bulk of the ligand is viable at room temperature ($\Delta G^{\neq} \approx 14$ kcal mol^{-1}).[16] We postulated that the barrier to rotation in complex **7** is likely similar to the barrier of rotation in complex **6**. This assertion was determined to be correct by conducting a potential energy surface scan varying the C1-C2-P-Pd dihedral angle in **7** to afford **8**. From this scan, the activation energy for rotation is approximated to be 10.5 kcal mol^{-1}.[17] Hence, an advantage of using KOAc in borylation reactions catalyzed by biaryl phosphine–Pd complexes may be that once metathesis occurs to form **7**, rotation of the Pd center such that it is distal to the non-phosphine-bearing ring of the ligand can readily occur to form **8**. This rotation is thermodynamically favored by 0.6 kcal mol^{-1}, which is due to the acetate ligand forming a κ^2 complex with the Pd center (cf. [LPd(Ph)Cl] for which $\Delta G_{\text{rotamers}} = +3.8$ kcal mol^{-1}, as the chloride ligand is unable to stabilize the Pd center when the metal center is distal to the non-phosphine-bearing ring of the ligand).[16] It is very likely that binding of the diboron species and subsequent transmetalation occurs from a species in which the Pd center is distal to the non-phosphine-bearing ring of the ligand (e.g. complex **8**). Hence, as complex **8** is more favored relative to **7**, the binding of bis(pinacolato)diboron may occur more readily in [LPd(Ph)OAc] than in a complex composed of [LPd(Ph)Cl], in which the structure analogous to **8** is thermodynamically disfavored relative to complex **6**.

From these computational studies, we attribute two features of biaryl phosphine ligands to their efficacy in promoting Pd-catalyzed borylation reactions: 1) the large nature of the ligand promotes formation of the highly reactive LPd^0 complex versus the much less reactive L$_2$Pd^0 species[18] and 2) the ability of [LPd(Ph)OAc] (derived from the oxidative addition product and KOAc) to easily access a geometry such that the Pd–arene interaction is no longer present. This situation creates an open coordination site on the Pd center and facilitates the binding of the diboron species and subsequent transfer of the borylate moiety to the Pd^{II} center with concurrent generation of pinacol boryl acetate.



Scheme 3. Kinetic and thermodynamic parameters for the rotation around the C2–P bond; O red, Pd turquoise, P purple, C green.

In summary, we have demonstrated that use of catalysts composed of Pd and ligands **1** or **2** provide highly stable and active catalysts for the borylation of aryl chlorides at elevated temperatures as well as at room temperature. We have also shown that these methods are applicable to the direct synthesis of symmetrical and unsymmetrical biaryl compounds. Furthermore, mechanistic aspects of Pd-catalyzed borylation of aryl halides with bis(pinacolato)diboron were elucidated by computational chemistry, and the effects of biaryl phosphine ligands and KOAc on the catalytic cycle were presented.

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