

A Rationally Designed Universal Catalyst for Suzuki–Miyaura Coupling Processes**

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Despite advances in the Suzuki–Miyaura cross-coupling process,^[1] the need for an operationally simple and general system remains. The minimum criteria for an optimum system that must be met include: 1) a broad substrate scope, 2) the ability to make truly hindered biaryls, 3) the ability to operate at low levels of catalyst for a range of substrates not just with the most simple examples (e.g., other than phenyl boronic acid),^[2] and 4) the ability to operate at room temperature. Moreover, it is most desirable to develop protocols that do not necessitate the use of a glovebox. Herein we report a catalyst system based on a new ligand that meets the above four criteria, has unprecedented scope, reactivity, and stability, uses only commercially available, air-stable components, and is experimentally simple to employ.

Our previous work on cross-coupling methodology demonstrated that dialkylphosphanylbiaryls were excellent supporting ligands. We have reported that these can be prepared by the addition of an aryl Grignard reagent to an in-situ-generated benzyne intermediate, followed by trapping of the newly formed organomagnesium complex with CIPR₂.^[3] The thought process that led to the design of the new ligand **1** is shown in Scheme 1.

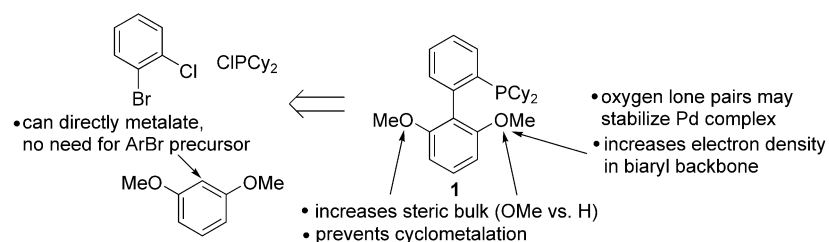
Mechanistic studies in our laboratory indicated that the elimination of *ortho* hydrogens on the bottom ring (that not bearing the dialkylphosphanyl group) was important for catalyst activity and longevity.^[4] We believe that this is due to two effects: 1) prevention of cyclometalation^[5] (to form a palladacycle), which diminishes catalyst lifetime, and 2) increased steric bulk relative to complexes with two *ortho* hydrogens. We also feel that it is important that the two methoxy groups are smaller in size than two alkyl groups as in our previously reported ligands. Moreover, the lone pairs of the alkoxy groups might interact with the Pd center and/or add electron density to the ligand backbone. The latter could be important as the interaction of the metal with the bottom ring is well documented^[6] and could help stabilize intermediate complexes.^[2c,7] Furthermore, the 1,3-dimethoxybenzene moiety offers the advantage that it can be installed by means

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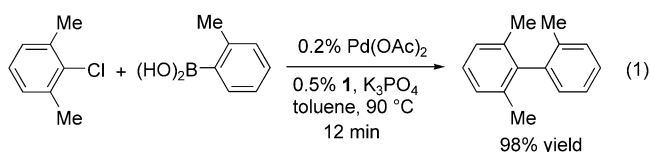
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



Scheme 1.

of direct metalation of 1,3-dimethoxybenzene, eliminating the need to use an aryl halide as the precursor for this section of the ligand. In this report we demonstrate that a catalyst employing **1** is the most active and general of those reported to date. This includes the construction of the most hindered biaryls ever prepared by Pd-catalyzed cross-coupling methods and the efficient operation at room temperature. We also present structural information consistent with our ligand-design scheme.

The Suzuki–Miyaura coupling of aryl chlorides has been reported to occur with myriad catalysts^[8] including ones that operate at low levels of catalyst and at room temperature. In order to gauge the performance of our new ligand, we decided to employ a moderately hindered substrate combination as a test case: the reaction of 1-chloro-2,6-dimethylbenzene with 2-methylphenyl boronic acid to form a biaryl that possesses three substituents *ortho* to the aryl–aryl connection [Eq. (1)].



This reaction has been studied previously by several groups.^[7a,9] However, good yields of isolated product were possible only with either high quantities of catalyst (usually 2–3 %) and/or long reaction times. In the best previously reported result, in which **2** was employed as the ligand, the reaction occurred in 3 h to give a 92 % yield of product using 1 % Pd at 100 °C.^[7a]

Using **1** as the supporting ligand with 0.2 % Pd, the reaction has a half-life of less than 2 min at 90 °C.^[10] Under these conditions, workup after 12 min provided the biaryl product in a yield of 98 % [Eq. (1)]. Increasing the L: Pd ratio to 5:1 and

heating at 100 °C for 20 h with only 0.02 % Pd furnished a 97 % yield of the desired biaryl (Table 1, entry 1). With this finding indicating the high level of activity of the catalyst system derived from **1**, we went on to examine a number of examples, which are listed in Table 1. In general, the reactions proceed at 100–110 °C in near-quantitative yield. This includes the reaction of an electron-rich aryl chloride with the very hindered 2,4,6-triisopropylphenyl boronic acid

Table 1: Suzuki–Miyaura coupling of unactivated aryl chlorides using ligand **1**.^[a]

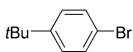
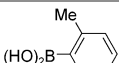
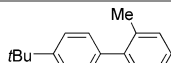
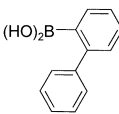
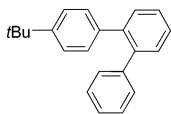
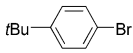
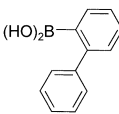
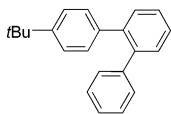
| Entry | Halide | Boronic acid | Product | Pd [mol %] | Conditions | Yield [%] ^[b] |
|-------|--------|--------------|---------|------------|---------------|--------------------------|
| 1 | | | | 0.02 | 100 °C, 20 h | 97 ^[c] |
| | | | | 0.2 | 90 °C, 12 min | 98 |
| 2 | | | | 0.05 | 110 °C, 12 h | 99 |
| 3 | | | | 1 | 100 °C, 20 h | 99 ^[d] |
| 4 | | | | 0.005 | 100 °C, 10 h | 96 |
| | | | | 0.003 | 100 °C, 24 h | 93 ^[d,e] |

[a] Reaction conditions: 1.0 equiv aryl chloride, 1.5 equiv boronic acid, 2.0 equiv K_3PO_4 , toluene (2 mL mmol⁻¹ halide), cat. Pd(OAc)₂, ligand **1**, L: Pd = 2.5:1. [b] Yield of isolated product. [c] L: Pd = 5:1. [d] In this case 2.0 equiv boronic acid and 3.0 equiv K_3PO_4 were used. [e] Here, 2.0 equiv $K_3PO_4 \cdot H_2O$ was used.

to afford the coupled product in near-quantitative yield (entry 3). This result suggests that the transmetalation step (which is often rate limiting for Suzuki–Miyaura couplings) must be facile with **1**/Pd⁰. The reaction of phenyl boronic acid can be carried out with 0.005 % Pd and a L: Pd ratio of 2.5:1. Replacing the anhydrous base with powdered $K_3PO_4 \cdot H_2O$ and using a L: Pd ratio of 5:1 permitted efficient cross-coupling at 0.003 % (30 ppm) Pd, which corresponds to a turnover number (TON) of over 31 000 for this reaction. Thus, this catalyst system shows excellent levels of activity even for the reactions of 2,6-disubstituted aryl chlorides as well as with easier substrates.

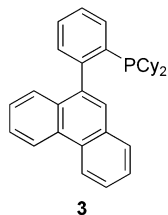
This new catalyst system was also found to be remarkably active for the cross-coupling of unactivated aryl bromides with 2-methylphenyl boronic acid (Table 2). The reaction can be carried out with 10 ppm Pd in 90 min at 110 °C to give a 98 % yield of isolated product (Table 2, entry 1). Decreasing the quantity of catalyst to 5 ppm, the process can be carried out at 100 °C in 24 h in 89 % yield. If the size of the *ortho* substituent on the boronic acid is significantly increased, here for 2-phenylphenyl boronic acid, the reaction at 10 ppm Pd can be carried out under similar conditions to provide 85 % of the desired product in 24 h (Table 2, entry 2). To our knowledge these results represent the lowest quantities of catalyst ever used to couple an *ortho*-substituted aryl boronic acid with an unactivated aryl bromide.^[11]

Table 2: Suzuki–Miyaura coupling of unactivated aryl bromides using ligand **1**.^[a]

| Entry | Halide | Boronic acid | Product | Pd [mol %] | Conditions | Yield [%] ^[b] |
|-------|---|---|---|------------|---------------|--------------------------|
| 1 |  |  |  | 0.001 | 110 °C, 1.5 h | 98 |
| | |  |  | 0.0005 | 100 °C, 24 h | 89 |
| 2 |  |  |  | 0.001 | 100 °C, 24 h | 85 ^[c] |

[a] Reaction conditions: 1.0 equiv aryl bromide, 1.5 equiv boronic acid, 2.0 equiv K_3PO_4 , toluene (2 mL mmol⁻¹ halide), cat. $Pd(OAc)_2$, ligand **1**, L: Pd = 2.5:1. [b] Yield of isolated product. [c] L: Pd = 2:1.

A particularly challenging issue in Suzuki–Miyaura coupling processes is the ability to couple sterically encumbered substrates. This is especially difficult when both of the coupling partners have one or multiple large substituents in the *ortho* positions. We recently described the first catalyst system for the Suzuki–Miyaura coupling that was capable of efficiently constructing biaryls with four *ortho* alkyl substituents.^[6a] We further described the assembly of a variety of biaryls through the formation of a C–C bond in demanding steric environments. While significant, this system had several limitations: 1) No 2,6-disubstituted aryl halides with *ortho* alkyl groups larger than methyl were effectively transformed. 2) In most instances, 4–10% Pd was necessary. 3) The most generally efficient ligand, **3**, is not commercially available.



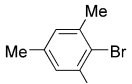
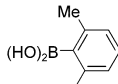
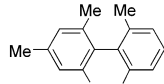
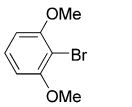
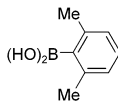
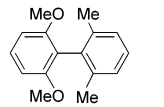
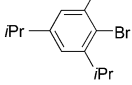
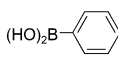
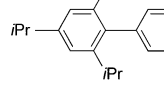
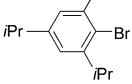
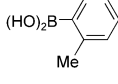
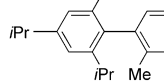
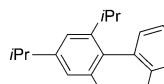
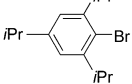
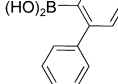
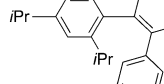
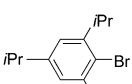
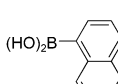
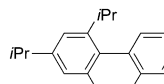
Given the remarkably high levels of catalytic activity displayed with catalysts employing **1**, we investigated its use for the preparation of hindered biaryls; a summary of our results is shown in Table 3. Our initial goal was to compare **1** with **3**. We found that for the coupling of 2-bromomesitylene with 2,6-dimethylphenyl boronic acid (**4**), the reaction rate and yield of the coupling product was nearly identical using either **1** or **3**; with 4% Pd, the coupling processes provided an 82% yield of isolated product in 18 h at 110 °C (Table 3, entry 1). Another challenging process involved the combination of **4** and very electron-rich 2,6-dimethoxybromobenzene which proceeded in 86% yield (Table 3, entry 2). We next investigated whether 2,4,6-triisopropylbromobenzene could be utilized as a substrate. To our delight, we found that using phenyl boronic acid, the very hindered aryl bromide could be converted to product with as little as 0.01% Pd in 10 h at 100 °C in nearly quantitative yield (Table 3, entry 3). To our knowledge, this is the most highly

hindered aryl bromide to be utilized in a Suzuki–Miyaura coupling process. To ascertain if this process is general with respect to the boronic acid component, we examined the reaction of 2,4,6-triisopropylbromobenzene with 2-methylphenyl boronic acid, 2-biphenylboronic acid, and 1-naphthylboronic acid; these coupling processes all proceeded in > 90% yield (Table 3, entries 4–6) using as little as 0.1% catalyst. These results indicate that the catalyst

system based on **1** is generally effective for the construction of hindered biaryls.

Among the most important and most challenging applications of cross-coupling methodology are those involving

Table 3: Suzuki–Miyaura couplings of hindered substrates using ligand **1**.^[a]

| Entry | Halide | Boronic acid | Product | Pd [mol %] | Conditions | Yield [%] ^[b] |
|-------|---|---|---|------------|--------------|--------------------------|
| 1 |  |  |  | 4 | 110 °C, 18 h | 82 ^[c] |
| 2 |  |  |  | 3 | 100 °C, 10 h | 86 |
| 3 |  |  |  | 0.01 | 100 °C, 16 h | 97 |
| 4 |  |  |  | 3 | 100 °C, 2 h | 94 |
| | | |  | 0.1 | 100 °C, 24 h | 95 |
| 5 |  |  |  | 3 | 100 °C, 18 h | 93 |
| 6 |  |  |  | 0.1 | 100 °C, 12 h | 96 |

[a] Reaction conditions: 1.0 equiv aryl bromide, 2.0 equiv boronic acid, 3.0 equiv K_3PO_4 , toluene (2 mL mmol⁻¹ halide), cat. $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone), ligand **1**, L: Pd = 2:1. [b] Yield of isolated product. [c] Here 4.0 equiv K_3PO_4 was used.

heterocyclic substrates. We have examined the use of **1** as a supporting ligand in Suzuki–Miyaura coupling with a variety of heterocycles; our results are shown in Table 4. As can be seen, the method worked well for a number of different heterocyclic bromides and chlorides including a pyrazole, tetrazole, quinoline, indole (possessing a free N–H), and pyridine. The reaction with 4-chloroquinoline was complete in 15 min at 100 °C (Table 4, entry 3). In the case of unprotected 5-chloroindole, the reaction proceeded nearly

Table 4: Suzuki–Miyaura coupling of heteroaryl halides using ligand **1**.^[a]

| Entry | Halide | Boronic acid | Product | Pd [mol %] | Conditions | Yield [%] ^[b] |
|-------|--------|--------------|---------|------------|----------------|--------------------------|
| 1 | | | | 1 | 100 °C, 24 h | 95 |
| 2 | | | | 1 | 100 °C, 24 h | 85 |
| 3 | | | | 1 | 100 °C, 15 min | 97 |
| 4 | | | | 0.1 | 100 °C, 15 h | 96 |
| 5 | | | | 0.005 | 100 °C, 24 h | 97 ^[c] |

[a] Reaction conditions: 1.0 equiv aryl chloride, 1.5 equiv boronic acid, 2.0 equiv K_3PO_4 , toluene (3 mL mmol⁻¹ halide), cat. $Pd(OAc)_2$, ligand **1**, L:Pd = 2.5:1. [b] Yield of isolated product. [c] L:Pd = 5:1.

quantitatively in 15 h at 100 °C using 0.1 % Pd (Table 3, entry 4). The coupling of 3-chloropyridine with 2-methyl phenylboronic acid produced a 97 % yield of product in 24 h at 100 °C with only 0.005 % Pd (Table 4, entry 5). We note that Beller et al. reported the coupling of 3-chloropyridine with phenyl boronic acid under similar conditions.^[2e]

Given the high reactivity of this catalyst system, we decided to explore its use in Suzuki–Miyaura cross-couplings at room temperature. Recently, Glorius et al. have shown that a carbene exhibiting “flexible steric bulk” can serve as a ligand for the room-temperature coupling of aryl chlorides.^[9c] Although a step forward, the reactions were relatively slow (24 h) and required 3 % of the palladium catalyst. Subsequently, Nolan et al. reported that with a palladacyclic carbene complex similar reactions could be carried out in 0.75–2 h using 2 % palladium catalyst.^[9d] Unfortunately, the utility of this method for many applications is compromised by the need to employ slow addition of the aryl chloride to prevent dehalogenation as a side reaction. Our results for the room-temperature Suzuki–Miyaura couplings using ligand **1** are shown in Table 5. In preliminary experiments to generate biaryl products using a 2:1 L:Pd ratio, only low conversions of the

starting aryl chlorides were observed. However, adjusting the L:Pd ratio to 1:1 dramatically accelerated the reaction and allowed smooth cross-coupling at room temperature. Thus, clean conversions to the desired biaryls were observed at room temperature in THF using powdered $K_3PO_4 \cdot H_2O$ as base. With this protocol, an indole boronic acid was successfully coupled with 1-chloro-2,6-dimethylbenzene in 2 h using 2 % catalyst (Table 5, entry 1). Introduction of an additional quantity of water (0.6 equiv) to the reaction mixtures was beneficial in many instances and allowed the efficient coupling of a variety of substituted boronic acids with electron-rich, electron-deficient, and hindered aryl chlorides at room temperature using only 0.5 % catalyst (Table 5 entries 2–5).

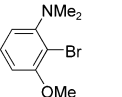
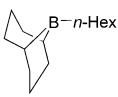
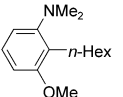
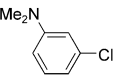
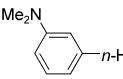
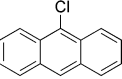
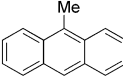
In addition to aryl boronic acids, we found that alkyl-9-BBN derivatives (BBN = 9-borabicyclo[3.3.1]nonane) as well as alkyl boronic acids could also be utilized as shown in Table 6. Interestingly, for efficient alkyl couplings the use of powdered $K_3PO_4 \cdot H_2O$ was found to be essential, and markedly lower conversions were observed with anhydrous base. Under these conditions, the process works well even with normally difficult substrates such as 3-dimethylamino-2-bromoanisole (Table 6, entry 1). Furthermore, the coupling reactions of alkyl boronic acids with aryl chlorides could be carried out at 0.05–0.1 % Pd to give near-quantitative yields of product. Thus the catalyst

Table 5: Suzuki–Miyaura couplings at room temperature using ligand **1**.^[a]

| Entry | Halide | Boronic acid | Product | Pd [mol %] | Conditions | Yield [%] ^[b] |
|-------|--------|--------------|---------|------------|------------|--------------------------|
| 1 | | | | 2 | RT, 2 h | 97 |
| 2 | | | | 0.5 | RT, 3 h | 90 ^[c,d] |
| 3 | | | | 0.5 | RT, 3 h | 96 ^[c] |
| 4 | | | | 0.5 | RT, 3 h | 98 ^[c] |
| 5 | | | | 0.5 | RT, 3 h | 80 ^[c] |

[a] Reaction conditions: 1.0 equiv aryl chloride, 1.5 equiv boronic acid, 3.0 equiv $K_3PO_4 \cdot H_2O$, THF (1 mL mmol⁻¹ halide), cat. $Pd(OAc)_2$, ligand **1**, L:Pd = 1:1, RT = room temperature. [b] Yield of isolated product. [c] H_2O (10 μ L mmol⁻¹ halide) was added. [d] Corrected yield, contains \approx 4 % 2,2'-dimethylbiphenyl.

Table 6: Suzuki–Miyaura couplings with alkylboranes and alkylboronic acids using ligand **1**.^[a]

| Entry | Halide | Alkylboron reagent | Product | Pd [mol %] | Conditions | Yield [%] ^[b] |
|-------|---|---|---|------------|--------------|--------------------------|
| 1 |  |  |  | 1 | 65 °C, 18 h | 78 ^[c] |
| 2 |  | (HO) ₂ B-Me |  | 0.1 | 100 °C, 20 h | 97 ^[d] |
| 3 |  | (HO) ₂ B-Me |  | 0.05 | 100 °C, 24 h | 99 ^[d] |

[a] Reaction conditions: 1.0 equiv aryl halide, 1.5 equiv alkylboron derivative, 2.0 equiv K₃PO₄·H₂O, cat. Pd(OAc)₂, ligand **1**, L:Pd = 2:1. [b] Yield of isolated product. [c] The reaction was carried out in THF (3 mL mmol⁻¹ halide). [d] The reaction was carried out in toluene (3 mL mmol⁻¹ halide).

1/Pd⁰ represents the most active system yet reported for this subset of Suzuki–Miyaura couplings.^[12]

To gain some insight into the high activity of our new catalyst system, we obtained an X-ray crystal structure of the [**1**/Pd⁰(dba)] complex **5** (Figure 1).^[13] A striking feature of this

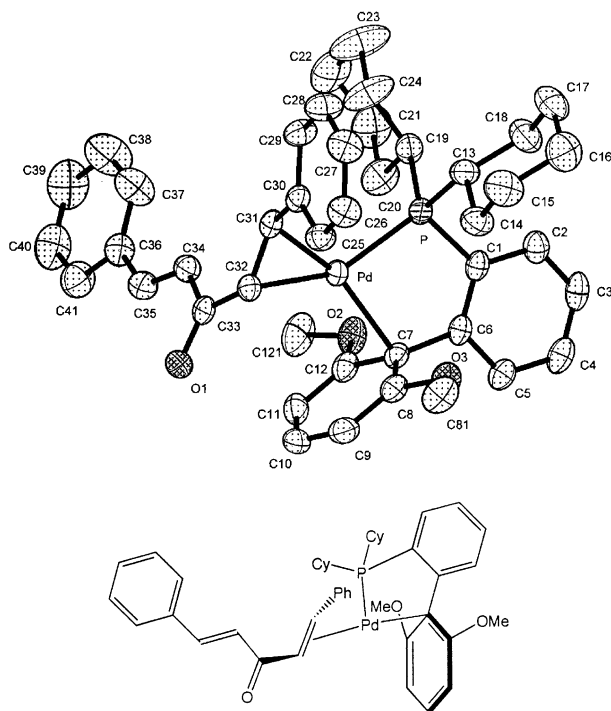


Figure 1. X-ray crystal structure of **5** (ORTEP diagram) and graphical representation. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are at 30% probability. Selected bond lengths [Å] and angles [°]: Pd–C7 2.374(3), C7–C8 1.415(4), C7–C12 1.423(4), O3–C8 1.362(3), O2–C12 1.370(4); Pd–C7–C6 110.26(17).

complex is the unusual Pd⁰ η¹-arene interaction with C7. This mode of bonding appears to be mainly a π interaction, as the Pd is located directly above C7 and only slight deviations of bond lengths in the arene that participates in this interaction, relative to the unbound arene, are observed. Fink et al. recently reported the structure of [L₂Pd⁰], L = 2-dicyclohex-

ylphosphanylbiaryl, in which a π interaction at the *ortho* carbon of the bottom (unsubstituted) ring was observed.^[6b] Related Pd^{II}–phosphane complexes have been reported in which electrophilic addition to the ipso carbon has taken place, resulting in a σ complex stabilized by an *ortho* heteroatom with lone pair(s) of electrons. In these cases, much larger distortions of the arene bonds are observed when a Pd–arene interaction is present.^[14] Two facts argue against this electrophilic-like addition occurring in the case of **5**. First, unlike the other complexes where a Pd–arene interaction is observed, the Pd center in **5** is in the zero valent state. Second, the O3–C8 and O2–C12 bond lengths are 1.362(3) and 1.370(0) Å, respectively, which are identical to those observed in an X-ray structure of [L₂PdCl₂], L = **1**,^[15] where no Pd–arene interaction exists, arguing against the donation of the lone pairs of electrons on O2 and O3 into the arene. The stability engendered by this type of interaction, as has been previously suggested,^[7a,14a] may contribute to the impressive catalytic activity^[16] and catalyst lifetime that we observe. An in-depth analysis of this structure and its relationship to the catalytic properties using **1** will be presented in a future publication.

In conclusion, we have demonstrated that tuning of steric and electronic properties have afforded a new ligand, **1**. Its application leads to a catalyst system with unprecedented scope, reactivity, and stability for Suzuki–Miyaura cross-coupling processes. Further work to apply the concepts learned in these studies to other transition-metal-catalyzed processes is underway our laboratories.

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