

# Pd-PEPPSI: Water-Assisted Suzuki–Miyaura Cross-Coupling of Aryl Esters at Room Temperature using a Practical Palladium-NHC (NHC = N-Heterocyclic Carbene) Precatalyst

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**Abstract.** A Pd-PEPPSI-catalyzed (Pd = Palladium, PEPPSI = pyridine-enhanced precatalyst preparation stabilization and initiation) Suzuki–Miyaura cross-coupling of aryl esters via selective C–O cleavage at room temperature is reported. The developed catalyst system displays broad substrate scope with respect to both components under practical ambient reaction conditions using readily-available, cheap, modular, air- and moisture-stable Pd-NHC precatalyst (NHC = N-heterocyclic carbene). The use of water proved crucial for achieving high reactivity in this coupling. The catalyst system represents the mildest conditions for the Suzuki–Miyaura cross-coupling of aryl esters reported to date. The protocol also allowed for achieving TON >1,000 (TON = turnover number) in the Suzuki–Miyaura ester coupling for the first time.

**Keywords:** Suzuki–Miyaura; aryl esters; cross-coupling; C–O activation; Pd-PEPPSI

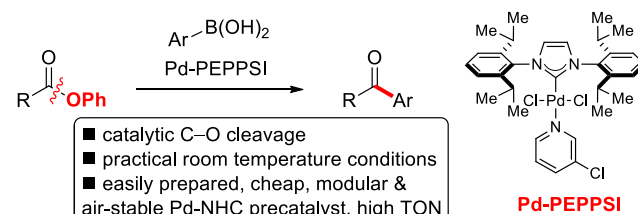
## Introduction

The development of general catalytic systems for palladium-catalyzed cross-coupling reactions has revolutionized the field of organic synthesis with a long-lasting impact on various fields of chemistry.<sup>[1–3]</sup> While these transformations typically utilize aryl halides or pseudohalides,<sup>[4,5]</sup> arguably, one of the most important developments involves cross-coupling of bench-stable carboxylic acid derivatives.<sup>[6,7]</sup> These reactions involve oxidative addition of a metal to acyl electrophile, a step which needs to overcome low reactivity of the acyl C–X bond (X = O, N), resulting from  $n_X \rightarrow \pi^*_{C=O}$  conjugation.<sup>[8]</sup>

Transition-metal-catalyzed cross-couplings of aryl esters by acyl cleavage<sup>[9,10]</sup> are of significant synthetic interest due to the ubiquity of esters as common intermediates in organic synthesis and their potential to serve as Weinreb amide equivalents with dramatically improved substrate scope under catalytic reaction conditions.<sup>[11,12]</sup> While several methods for

the cross-coupling of esters have been realized,<sup>[13,14]</sup> the development of general, robust, widely-available and operationally-convenient catalytic systems that operate under practical ambient conditions has remained a major challenge.

In 2017, our laboratory introduced a new catalytic method for the Suzuki–Miyaura cross-coupling of aryl esters<sup>[15]</sup> using widely-available Pd-PEPPSI precatalysts (Pd = Palladium, PEPPSI = pyridine-enhanced precatalyst preparation stabilization and initiation).<sup>[16]</sup> In this initial disclosure, high temperatures (80 °C), high catalyst loading (3.0 mol%), amount of base (4.5 equiv) and boronic acid (3.0 equiv) were required. Through ever-increasing effort to improve the practicality, cost and operational-simplicity of the coupling,<sup>[17–20]</sup> we identified a greatly improved catalyst system that permits for the first time to perform the Suzuki–Miyaura cross-coupling of aryl esters using readily-available, cheap and modular Pd-NHC (NHC = N-heterocyclic carbene) precatalyst under practical ambient conditions (Figure 1). The developed catalyst system represents the mildest conditions for the Suzuki–Miyaura cross-coupling of aryl esters reported to date.<sup>[21]</sup>



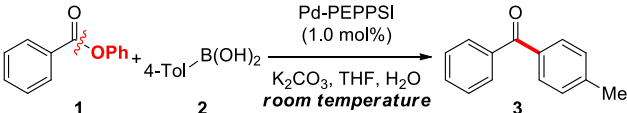
**Figure 1.** Pd-PEPPSI-Catalyzed Cross-Coupling of Aryl Esters at Room Temperature.

## Results and Discussion

Experimentally, cross-coupling of aryl ester **1** proceeds at 80 °C in 84% yield (Table 1, entry 1, <10% conversion at 23 °C).<sup>[15]</sup> We were delighted to

find that the addition of water (5.0 equiv) provided the desired diaryl ketone in excellent yield at room temperature (entry 2). Moreover, the catalyst loading could be decreased to 1.0 mol% while retaining high reaction efficiency (entry 3). Control experiments established the essential role of water concentration

**Table 1.** Optimization of the Reaction Conditions.<sup>[a,b]</sup>



Entry	Pd-PEPPSI [mol%]	H <sub>2</sub> O [equiv]	T [°C]	Yield [%]
1 <sup>[c,d]</sup>	3.0	-	80	84
2	3.0	5.0	23	94
3	1.0	5.0	23	95
4	1.0	3.0	23	36
5	1.0	10.0	23	93
6	1.0	-	23	<2
7	0.50	5.0	23	85
8	0.25	5.0	23	60

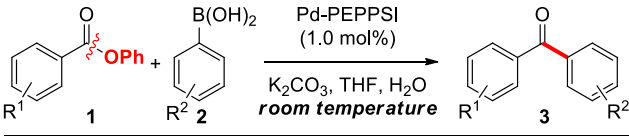
<sup>[a]</sup>Conditions: ester (1.0 equiv), Ar-B(OH)<sub>2</sub> (2.0 equiv), Pd-PEPPSI (x mol%), K<sub>2</sub>CO<sub>3</sub> (3.0 equiv), H<sub>2</sub>O (y equiv), THF (0.25 M), 23 °C, 18 h. <sup>[b]</sup>GC/<sup>1</sup>H NMR yields. <sup>[c]</sup>Ar-B(OH)<sub>2</sub> (3.0 equiv), K<sub>2</sub>CO<sub>3</sub> (4.5 equiv), 80 °C. <sup>[d]</sup>Ref. 15.

(entries 4-5), with marginal conversion observed in the absence of water under these conditions (entry 6). Furthermore, the catalyst loading could be further decreased to 0.50 mol% (entry 7) and even 0.25 mol% (entry 8), while maintaining high reactivity (vide infra). It should be noted that the developed conditions (Pd-PEPPSI, 1.0 mol%, K<sub>2</sub>CO<sub>3</sub>, 3.0 equiv, Ar-B(OH)<sub>2</sub>, 2.0 equiv, 23 °C) are superior to previous catalytic systems<sup>[13,14]</sup> in terms of reactant loading, low price and availability of Pd-NHC precatalyst. The dramatic enhancement in efficiency upon addition of water is discussed in the section below. In most cases, we observed recovery of the PhOH group after the reaction. No reaction was observed in the absence of the catalyst. We hypothesize that the bulky ligand facilitates reductive elimination of the product.<sup>[16a]</sup> The mechanism likely involves reduction to Pd(0)-NHC, oxidative addition of the acyl C–OPh bond, transmetalation and reductive elimination.<sup>[6a]</sup>

Under the developed conditions, the reaction exhibits broad scope with respect to both the boronic acid and aryl ester coupling partners (Table 2). As shown, a range of electronically-diverse boronic acids undergo efficient cross-coupling (**3a–e**). This includes electronically-deactivated 4-CF<sub>3</sub>-substituted phenyl boronic acid (**3d**), which is a challenging nucleophile in this coupling manifold.<sup>[13,14]</sup> Full selectivity in the cross-coupling of 4-CO<sub>2</sub>Me ester was observed (**3e**), attesting to the high chemoselectivity of the method.<sup>[22]</sup> In addition, steric hindrance was readily tolerated at the boronic acid component (**3f–g**). Furthermore, heterocyclic boronic acids (**3h–i**) can be readily incorporated to generate diaryl ketones in excellent yields. With respect to the ester component,

we were delighted to find that a broad range of electronically (**3c'–e'**) and sterically (**3f'**) differentiated aryl esters can participate as coupling partners in this mild room temperature protocol. Particularly notable is the functional group tolerance toward alkyl ester (**3e'**), which is a problematic substrate using strong bases, such as KOH or KO-*t*Bu,<sup>[13,14]</sup> highlighting another advantage of our protocol. Electron-deficient polyfluorinated (**3j**) and electron-rich 5-membered heterocycles substituted at the deactivating 2-position (**3k**) are well-tolerated. Finally, we determined that while the cross-coupling of a challenging aliphatic ester (**3l**) was sluggish at room temperature, this new aqueous protocol permits

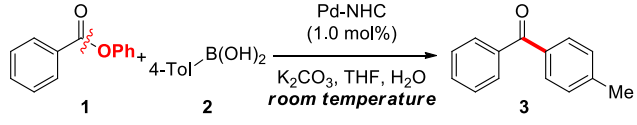
**Table 2.** Pd-PEPPSI-Catalyzed Suzuki–Miyaura Cross-Coupling of Aryl Esters at Room Temperature.<sup>[a,b]</sup>



<b>3a</b> : 73%	<b>3b</b> : 93%	<b>3c</b> : 95%
<b>3d</b> : 81%	<b>3e</b> : 66%	<b>3f</b> : R = Me, 92%
		<b>3g</b> : R = OMe, 91%
<b>3h</b> : 86%	<b>3i</b> : 97%	<b>3c'</b> : 64%
<b>3d'</b> : 95%	<b>3e'</b> : 96%	<b>3f'</b> : 60%
<b>3j</b> : 70%	<b>3k</b> : 51%	<b>3l</b> : 60% <sup>c</sup>

<sup>[a]</sup>Conditions: ester (1.0 equiv), Ar-B(OH)<sub>2</sub> (2.0 equiv), Pd-PEPPSI (1.0 mol%), K<sub>2</sub>CO<sub>3</sub> (3.0 equiv), H<sub>2</sub>O (5.0 equiv), THF (0.25 M), 23 °C, 18 h. <sup>[b]</sup>Isolated yields. <sup>[c]</sup>80 °C

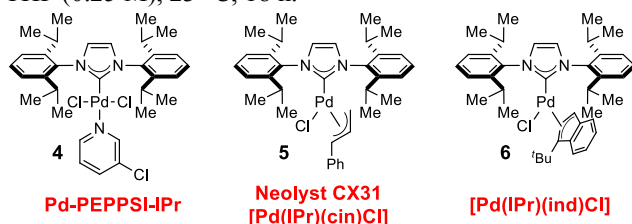
**Table 3.** Cross-coupling using various Pd-NHCs.<sup>[a]</sup>



Entry	Pd-NHC [mol%]	H <sub>2</sub> O [equiv]	T [°C]	Yield [%]
1	1.0, <b>4</b>	-	23	<2
2	1.0, <b>4</b>	5.0	23	95
3	1.0, <b>5</b>	-	23	<5

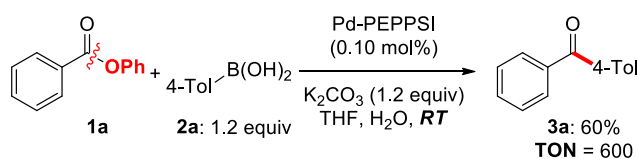
4	1.0, <b>5</b>	5.0	23	73
5	1.0, <b>6</b>	-	23	<2
6	1.0, <b>6</b>	5.0	23	94

<sup>[a]</sup>Conditions: ester (1.0 equiv), Ar-B(OH)<sub>2</sub> (2.0 equiv), Pd-NHC (1.0 mol%), K<sub>2</sub>CO<sub>3</sub> (3.0 equiv), H<sub>2</sub>O (0-5.0 equiv), THF (0.25 M), 23 °C, 18 h.

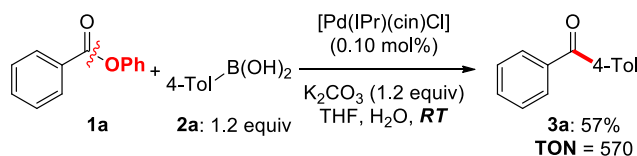


**Scheme 1.** Pd-NHC Catalysts for Room Temperature Suzuki-Miyaura Cross-Coupling of Aryl Esters.

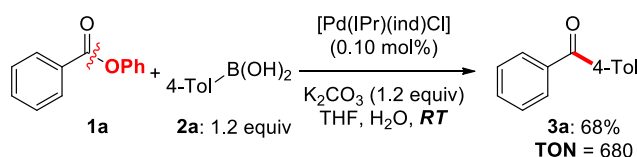
**A: Pd-PEPPSI**



**B: [Pd(IPr)(cin)Cl]**



**C: [Pd(IPr)(ind)Cl]**

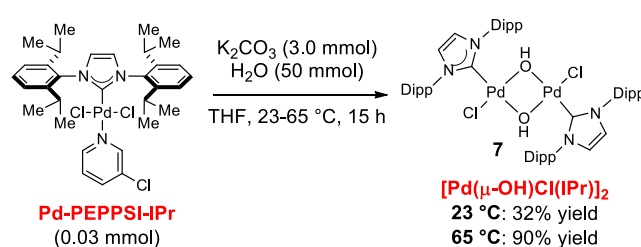


**Scheme 2.** Determination of TON in the Cross-Coupling of Aryl Esters at Room Temperature. Note: the following TON was observed at 60 °C: Pd-PEPPSI: TON = 1440; [Pd(IPr)(cin)Cl]: TON = 1640; [Pd(IPr)(ind)Cl]: TON = 1520. 4-Tol = 4-tolyl.

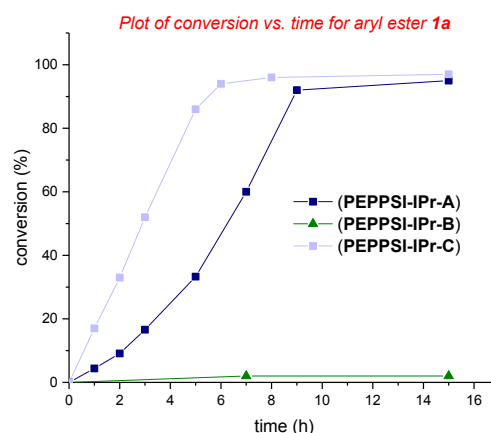
to significantly decrease catalyst loading (from 6.0 mol%<sup>[15]</sup> to 1.0 mol%) in the cross-coupling. Overall, this new catalytic system constitutes a major improvement over other available methods for the Suzuki-Miyaura cross-coupling of esters.<sup>[13,14]</sup> The method enables efficient catalysis at ambient conditions, using cheap, readily available Pd-PEPPSI catalyst<sup>[16–20]</sup> at low catalytic loading and employing a mild carbonate base under operationally-simple reaction conditions.

In order to further demonstrate the utility of this aqueous cross-coupling method, cross-coupling of aryl ester **1** in the absence and presence of water was tested using various Pd-NHC precatalysts (Table 3, Scheme 1). Generally speaking, two major classes of throw-away ligands in the Suzuki-Miyaura cross-coupling using Pd-NHC precatalysts have been developed:<sup>[16]</sup> PEPPSI-type heterocyclic ligands (**4**) and allyl-type ligands, such as [Pd(IPr)(cin)Cl] (**5**),

pioneered by Nolan and co-workers.<sup>[23]</sup> More recently, the substituted indenyl-type ligand was reported, [Pd(IPr)(ind)Cl] (**6**),<sup>[24]</sup> however, while there appear to be some advantages of this precatalyst, it remains to be seen if it will find wide applications in catalysis due to high commercial price, lengthy route to the throw-away ligand and the lack of clear benefits in the majority of cross-couplings to date. As shown in Table 3, the addition of water activates all three catalysts towards highly efficient coupling at ambient conditions (entries 1 vs. 2, 3 vs. 4, 5 vs. 6). Since the majority of modern ligand development efforts are directed at the synthesis of cheap, easily assembled, and generally-available precatalysts,<sup>[2–4]</sup> our observations highlight the potential of Pd-PEPPSI to promote elementary steps<sup>[6]</sup> in Pd-catalysis of bench-stable acyl-electrophiles with high efficiency.



**Scheme 3.** Synthesis of [Pd(μ-OH)Cl(IPr)]<sub>2</sub> from Pd-PEPPSI-IPr. Dipp = 2,6-diisopropylphenyl.

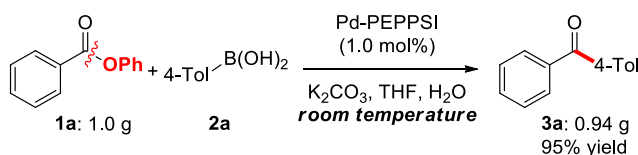


**Figure 2.** Kinetic profile of **1a**. Conditions: A) **1a**, 4-Tol-B(OH)<sub>2</sub> (2.0 equiv), K<sub>2</sub>CO<sub>3</sub> (3.0 equiv), Pd-PEPPSI (3.0 mol%), H<sub>2</sub>O (5.0 equiv), 23 °C; B) **1a**, 4-Tol-B(OH)<sub>2</sub> (2.0 equiv), K<sub>2</sub>CO<sub>3</sub> (3.0 equiv), Pd-PEPPSI (3.0 mol%), 23 °C; C) **1a**, 4-Tol-B(OH)<sub>2</sub> (2.0 equiv), K<sub>2</sub>CO<sub>3</sub> (3.0 equiv), [Pd(μ-OH)Cl(IPr)]<sub>2</sub> (1.5 mol%), H<sub>2</sub>O (5.0 equiv), 23 °C.

It is noteworthy that we observe high TON (TON = turnover number) value of 600 for the room temperature Suzuki-Miyaura cross-coupling using Pd-PEPPSI (Scheme 2). This can be compared with TON of 570 and 680 using allyl-type catalysts (**5**) and (**6**), and with TON of 1440 (**4**), 1640 (**5**) and 1520 (**6**) at 60 °C. Note that these conditions utilize close to stoichiometric amounts of both the base (1.2 equiv) and boronic acid (1.2 equiv). *To our knowledge, this*

is by far the mildest conditions for the Suzuki-Miyaura cross-coupling of esters reported to date.<sup>[13,14]</sup>

Experiments were performed to establish the role of water in the cross-coupling. Pietraszuk et al.<sup>[25]</sup> and Nolan et al.<sup>[26]</sup> independently reported the synthesis of Pd(II)-NHC hydroxide dimers,<sup>[27]</sup> and their high activity in the Suzuki-Miyaura cross-coupling of aryl halides. Subjecting the Pd-PEPPSI precatalyst to our standard cross-coupling conditions (K<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O) produces the hydroxide dimer, [Pd(μ-OH)Cl(IPr)]<sub>2</sub> (7) in appreciable 32% yield at ambient conditions (H<sub>2</sub>O, 50 mmol) and close to quantitative yield at 65 °C (Scheme 3). Kinetic studies demonstrate that the cross-coupling using [Pd(μ-OH)Cl(IPr)]<sub>2</sub> (7) proceeds at a faster rate than with Pd-PEPPSI (4) (Figure 2, conditions A-B). Note that negligible conversion is observed in the absence of water (Figure 2, conditions C). Thus, formation of the hydroxide dimer may be taking place prior to



**Scheme 4.** Large Scale Suzuki-Miyaura Cross-Coupling at Room Temperature.

reduction to the active Pd(0)-NHC species.<sup>[28]</sup> Studies on the catalytic cycle are ongoing and will be reported separately.

The scalability of this new cross-coupling protocol has been evaluated. We were pleased to find that the cross-coupling of **1a** could be conveniently carried out on a gram scale and gave the desired ketone product in 95% isolated yield (Scheme 4), attesting to the synthetic utility of the method.

Finally, it is important to point out advantages of using ester electrophiles in the cross-coupling.<sup>[6a]</sup> (1) Bench-stable ester electrophiles represent prevalent precursors in organic synthesis as well as products of many synthetic reactions, which renders them unique over alternative acyl cross-coupling precursors. (2) Moreover, the high stability of bench-stable esters provides opportunities for orthogonal cross-coupling strategies in the presence of other electrophiles. (3) Furthermore, esters are easy to prepare, while their cross-coupling is operationally-simple without taking special precautions to exclude moisture or air, which makes them attractive for practical industrial and academic applications.<sup>[3a]</sup> (4) Lastly, using easily-accessible ester precursors allows to reduce the amount of toxic waste generated during the cross-coupling manifolds. It is further interesting that the current catalytic system shows exquisite selectivity for the cross-coupling of aryl esters in the presence of their alkyl counterparts. This is due to much higher barrier to isomerization around the C–O bond in alkyl esters (C–OPh, 9.3 kcal/mol; C–OMe, 12.8 kcal/mol), which renders oxidative addition selective for the OPh electrophiles.<sup>[13c]</sup>

## Conclusions

In summary, in this Update article, we have shown the first Pd-PEPPSI-catalyzed Suzuki-Miyaura cross-coupling of aryl esters via selective C–O cleavage at room temperature. The developed catalytic system employs cheap, readily-available, air-stable and easily-assembled Pd-PEPPSI precatalyst, which shows major advantages over other Pd-NHC complexes. This new methodology has been successfully applied to the cross-coupling of a wide range of electronically- and sterically-varied aryl esters and boronic acids generating biaryl ketones in good to excellent yields under operationally-practical reaction conditions. We have shown that the activating effect of water is general, and includes PEPPSI-type and allyl-type Pd-NHC precatalysts. This protocol has also allowed for the first time to achieve TON >1,000 in the Suzuki-Miyaura cross-coupling of aryl esters. Mechanistic studies demonstrated that Pd(II)-NHC hydroxide dimer is formed under the reaction conditions, and that this species shows high catalytic activity in the cross-coupling of esters. We anticipate that the findings reported in this manuscript will have broad implications for the development of general cross-coupling methods using Pd-NHC catalysis.

## Experimental Section

**General Information.** General methods have been published.<sup>[12]</sup>

**General Procedure for the Suzuki-Miyaura Cross-Coupling of Esters at RT.** An oven-dried vial equipped with a stir bar was charged with an ester substrate (neat, 1.0 equiv), potassium carbonate (typically, 3.0 equiv), boronic acid (typically, 2.0 equiv), PEPPSI-IPr (typically, 1.0 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (typically, 0.25 M) and H<sub>2</sub>O (typically, 5.0 equiv) were added with vigorous stirring at room temperature. After the indicated time, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), filtered, and concentrated. The sample was analyzed by <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

**Representative Cross-Coupling Procedure at RT (1.0 g scale).** An oven-dried vial equipped with a stir bar was charged with phenyl benzoate (neat, 5.05 mmol, 1.00 g, 1.0 equiv), potassium carbonate (15.2 mmol, 2.10 g, 3.0 equiv), *p*-tolylboronic acid (10.1 mmol, 1.38 mg, 2.0 equiv), PEPPSI-IPr (1.0 mol%, 34.0 mg), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (0.25 M) and H<sub>2</sub>O (25.25 mmol, 0.45 mL, 5.0 equiv) were added with vigorous stirring at room temperature, and the reaction mixture was stirred for 36 h at room temperature. After the indicated time, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (80 mL), filtered, and concentrated. The sample was analyzed by <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.



Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product; 95% (0.941 g).

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