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Water-Mediated Catalyst Preactivation: An Efficient Protocol for C-N Cross-Coupling Reactions

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Abstract
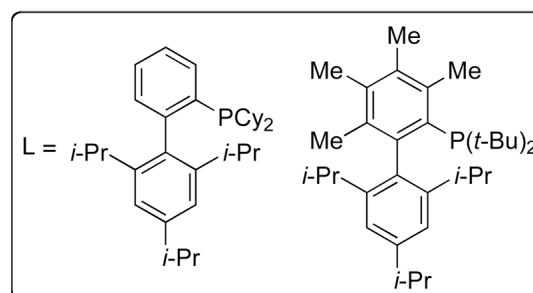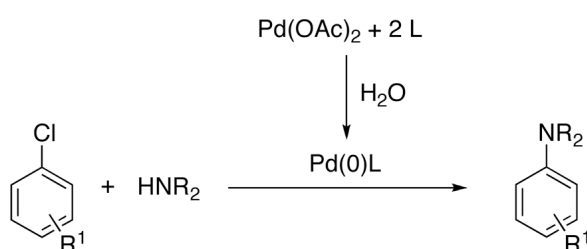
A protocol for forming a highly active Pd(0) catalyst from Pd(OAc)$_2$, water, and biaryldialkylphosphine ligands has been developed. This protocol generates a catalyst system, which exhibits excellent reactivity and efficiency in the coupling of a variety of amides and anilines with aryl chlorides.

Over the past decade great progress has been made in improving the efficiency and applicablilty of palladium-catalyzed C-N cross-coupling reactions.[1] Despite these recent advances, many limitations of these methods remain. We have previously shown that biaryldialkylphosphines, of which **1** (Figure 1) is prototypical,[2] are excellent supporting ligands in C-N cross-coupling processes. We now disclose a procedure that helps to maximize the efficiency of these ligands when used with a Pd(II) precatalyst.

The formation of an active L$_n$Pd(0) complex is most commonly accomplished in one of the following ways: 1) use of a Pd(0) source such as Pd$_2$(dba)$_3$,[3] 2) use of [(allyl)PdCl]$_2$,[4] 3) reduction of a Pd(II) salt [e.g., Pd(OAc)$_2$] using PhB(OH)$_2$,[2] a tertiary amine,[5] a tertiary phosphine,[6] or an amine substrate,[1] or 4) employment of a single component precatalyst.[7] These methods all have deficiencies when used with biaryldialkylphosphine ligands. Although Pd$_2$(dba)$_3$ has been shown to work well in combination with **1** in many instances,[2] diminished reactivity is observed due to the coordination of the dba to the palladium; this is a well known consequence of using dba containing precatalysts.[8] Attempts to use [(allyl)PdCl]$_2$ have not proven to be productive with dialkylbiarylphosphine ligands. Reduction of Pd(OAc)$_2$ with **1** is slow due to the steric hindrance of the ligand and initial results show that the use of tertiary amines or PhB(OH)$_2$ as reducing agents give slow formation of the active L$_n$Pd(0) catalyst. Lastly, reduction of Pd(OAc)$_2$ works well with primary or secondary amine substrates that have β-hydrogens. However, when non-reducing nucleophiles, such as anilines or amides, are used, formation of L$_n$Pd(0) is inefficient.

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Because of these deficiencies, we set out to develop a protocol that utilized water and **1** to reduce $Pd(OAc)_2$ and generate the active LnPd(0) complex. This type of activation was first reported in 1992 by Ozawa and Hayashi, in which they were able to reduce $Pd(OAc)_2$ in the presence of 3 equivalents of BINAP.[9] They disclosed that in the absence of water the reduction did not proceed; however, by adding extra equivalents of water the rate of activation could be accelerated. This showed that water played a direct role in the formation of the Pd(0) catalyst. Amatore and Jutand further delineated a method in which water and several different tertiary phosphines were employed as reducing agents to form a Pd(0) complex that underwent oxidative addition to aryl halides (Scheme 1).[10] In their investigations they found that water converted an intermediate phosphonium salt to the corresponding phosphine oxide in the reduction of $Pd(OAc)_2$.

We began our studies by seeking out a fast, efficient, and practical protocol for preactivation of $Pd(OAc)_2$. It was found that a highly active catalyst could be generated by heating the Pd $(OAc)_2$ (1 mol %), water (4 mol %), and **1** (3 mol %) for 1 min at 80 °C in 1,4-dioxane. The activation could be monitored visually by color change as shown in Figure 2. The resulting green catalyst solution[11] could then be transferred into a reaction vessel containing the substrates and base. Figure 3 shows the reaction of aniline and 4-chloroanisole utilizing several modes of activation. The water-mediated preactivation protocol gave a 99% GC yield, whereas $[(allyl)PdCl]_2$, $Pd(OAc)_2 / PhB(OH)_2$, and $Pd_2(dba)_3$ all resulted in yields lower than 50%. This demonstrates the efficiency in which water-mediated preactivation forms the active catalyst, without the detrimental effects of impeding ligands (eg., dba).

We next investigated the application of this protocol to amidation reactions of aryl chlorides. Our research group recently reported an efficient catalyst system for this transformation utilizing the combination of $Pd_2(dba)_3$ and ligand **2** (Figure 1). It has been proposed that with biaryldialkylphosphine ligands the rate-limiting step in amidation reactions is the "transmetallation" (amide binding and/or deprotonation).[12] We postulated that by replacing the $Pd_2(dba)_3$ with a preactivation of $Pd(OAc)_2$ a more active catalyst system could be achieved, because there would be no dba present in the reaction to compete for binding at the Pd center. By heating $Pd(OAc)_2$ (1 mol %), water (4 mol %), and **2** (3 mol %) for 1.5 min at 110 °C in *t*-BuOH a highly active catalyst was generated for these reactions. For example, whereas the coupling of either cyclohexanecarboxamide or acetamide with 4-chloroanisole using $Pd_2(dba)_3$ and **2** previously proceeded in 24 h, water-mediated preactivation decreased the reaction times to 3 h, and provided the products in excellent yields (Table 1, entries 1 and 2).[12]

We next looked at cross-couplings reactions of amides with 3-chloropyridine, which have been difficult in the past.[11,13] When the preactivation protocol was employed, formamide, nicotinamide, and 2-pyrrolidinone were all successfully coupled with 3-chloropyridine, in 3 h, using 1 mol% Pd (Table 1, entries 3, 4, and 5). Previously, the reactions with formamide and 2-pyrrolidinone had required the use of 2 mol % Pd and reaction times of 8[12] and 24 h, [13] respectively. Additionally, the latter case required the addition of Et_3B to achieve good yields.

Having established that the combination of water and **2** efficiently converted $Pd(OAc)_2$ to an active catalyst, we sought to expand the protocol to include reactions of electron-deficient anilines. Electron-deficient anilines have been difficult coupling partners due to their modest nucleophilicity and intolerance of strong base.7a,[14] By performing a preactivation of Pd $(OAc)_2$, 1, and water at 110 °C for 1 min, electron deficient 4-nitroaniline and 2-nitroaniline were successfully coupled with 4-*n*-butylchlorobenzene in excellent yields (Table 2, entries 1 and 2). Other electron-deficient anilines containing an ester or a cyano group were coupled as well in excellent yields using the newly developed protocol (Table 2, entries 3 and 4).

The chemoselectivity of the system was also briefly explored. Using 2'-aminoacetophenone ketone α-arylation was completely suppressed and exclusive C-N coupling was observed (Table 2, entry 5). This selectivity can be attributed to the high activity of the catalyst achieved utilizing water-mediated preactivation, which allows for the use of K_2CO_3.[15] The reaction of 4-aminoacetanilide also showed complete selectivity for arylation at the free aniline (Table 2, entry 6).[2] This catalyst system showed both high activity and excellent functional group compatibility.

Last, we wanted to examine the applicability of this protocol for the coupling of anilines at low catalyst loadings. There are currently very few examples of couplings with anilines and aryl chlorides below 0.5 mol % catalyst loading.[7a,7b,16] Using the preactivation protocol several examples were performed at 0.05 mol % catalyst loading in 20 min (Table 3). For example, electrondeficient 3-aminobenzotrifluoride and 4-fluoroaniline were successfully coupled with electron-rich aryl chlorides within 20 min, affording the products in excellent yields (Table 3, entries 3 and 4).

In conclusion, an efficient protocol for C-N cross-coupling reactions has been described. An active catalyst was formed by water-mediated preactivation of readily available $Pd(OAc)_2$ using biaryldialkylphosphine ligands. This new protocol allowed lower catalyst loadings, shorter reactions times, and exclusion of additives, such as Et_3B, in couplings of amides with aryl chlorides. It also gives access to a system that exhibits both high activity and excellent catalyst stability in couplings of electrondeficient anilines, and couplings of anilines at low catalyst loadings. Further studies of other applications of this protocol are currently ongoing in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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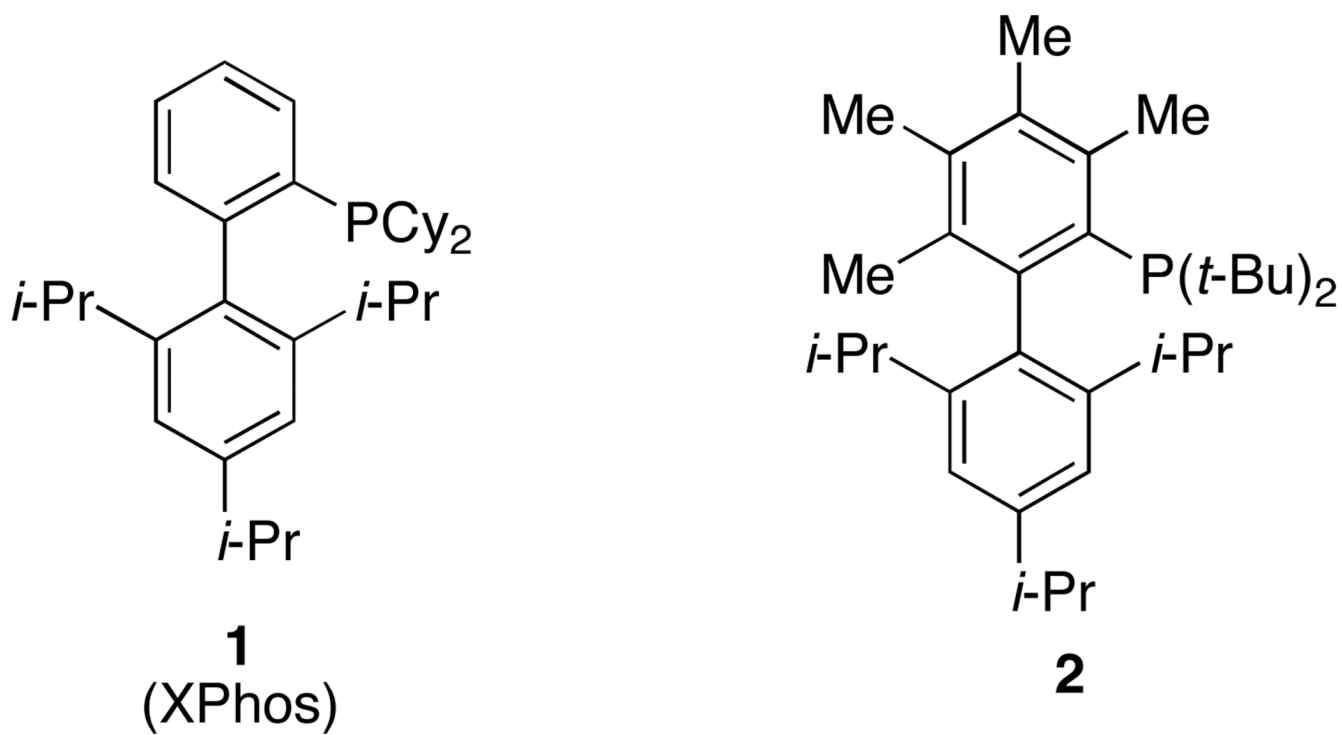
Figure 1.
Dialkylbiarylphosphine Ligands

Figure 2.
Visualization of Water-Mediated Preactivationa
[a] Reaction conditions: Pd(OAc)$_2$ (0.01 mmol), **1** (0.03 mmol), H$_2$O (0.04 mmol), 1 mL 1,4-dioxane, 80 °C.
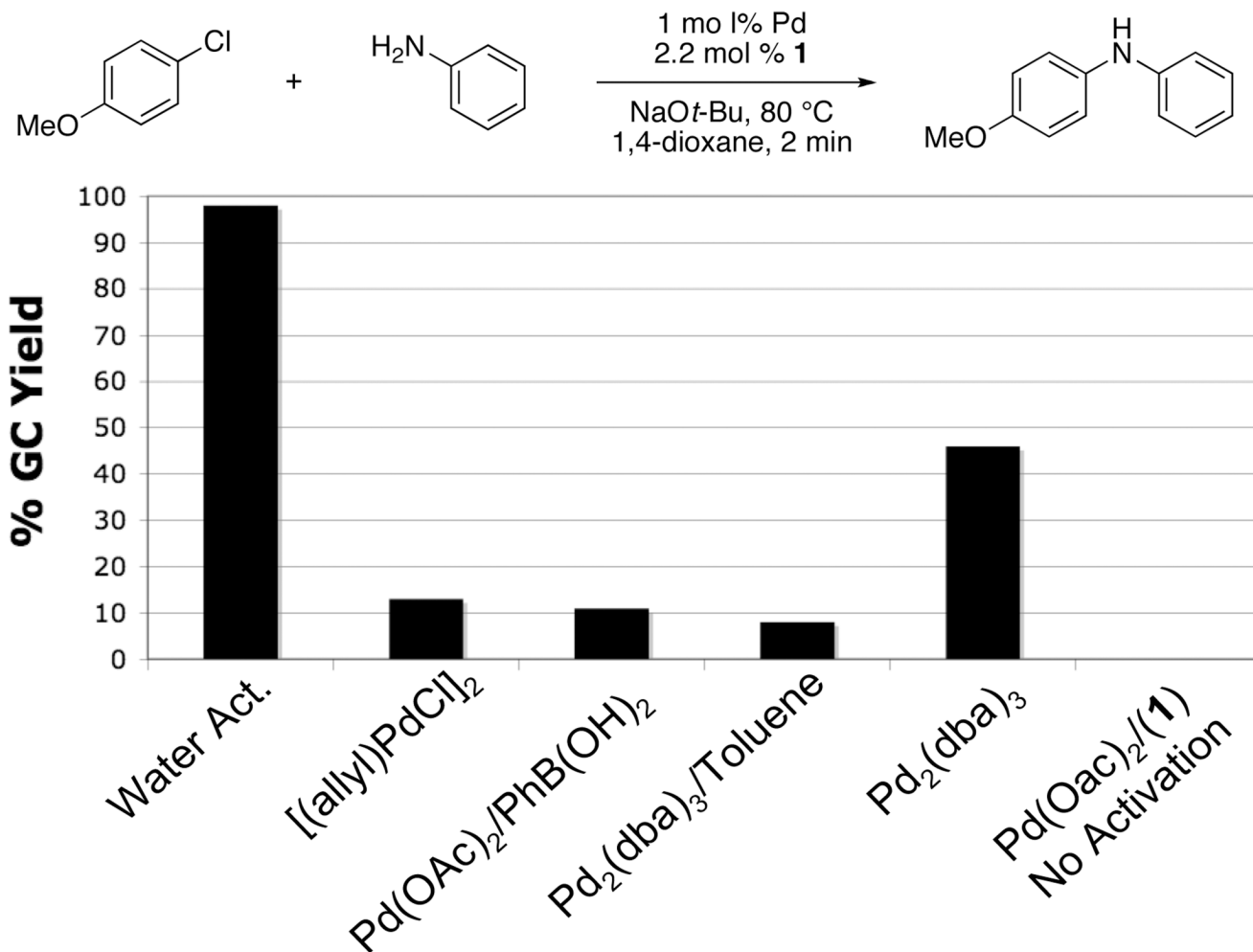
Figure 3.
Comparison of Water-Mediated Preactivation with Several Pd Sourcesa
[a] Reaction conditions: aniline (1.2 mmol), 4-chloroanisole (1.0 mmol), Pd (1 mol %), **1** (2.2 mol %), 1,4-dioxane (1 mL), 80 °C, 2 min.

$$2 \ PR_3 \ + \ Pd(II)(OAc)_2 \ \rightleftharpoons \ (R_3P)_2Pd(II)(OAc)_2$$

$$(R_3P)Pd(0) \ + \ O{=}PR_3 \ \xleftarrow[\text{-2 HOAc}]{H_2O} \ (R_3P)Pd(0)(OAc)^{\ominus} \ + \ AcOPR_3^{\oplus}$$
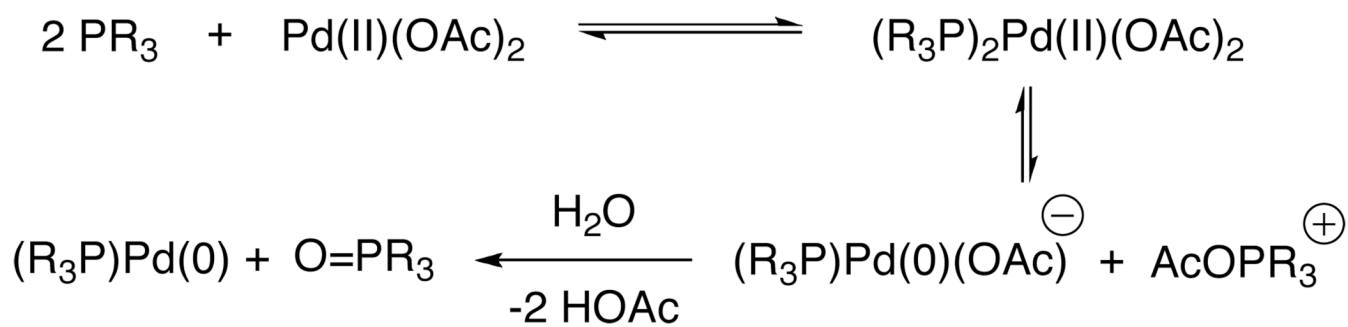
Scheme 1.
Water-Promoted Activation of Pd(OAc)$_2$

Table 1

Coupling of Amides With Aryl Chlorides
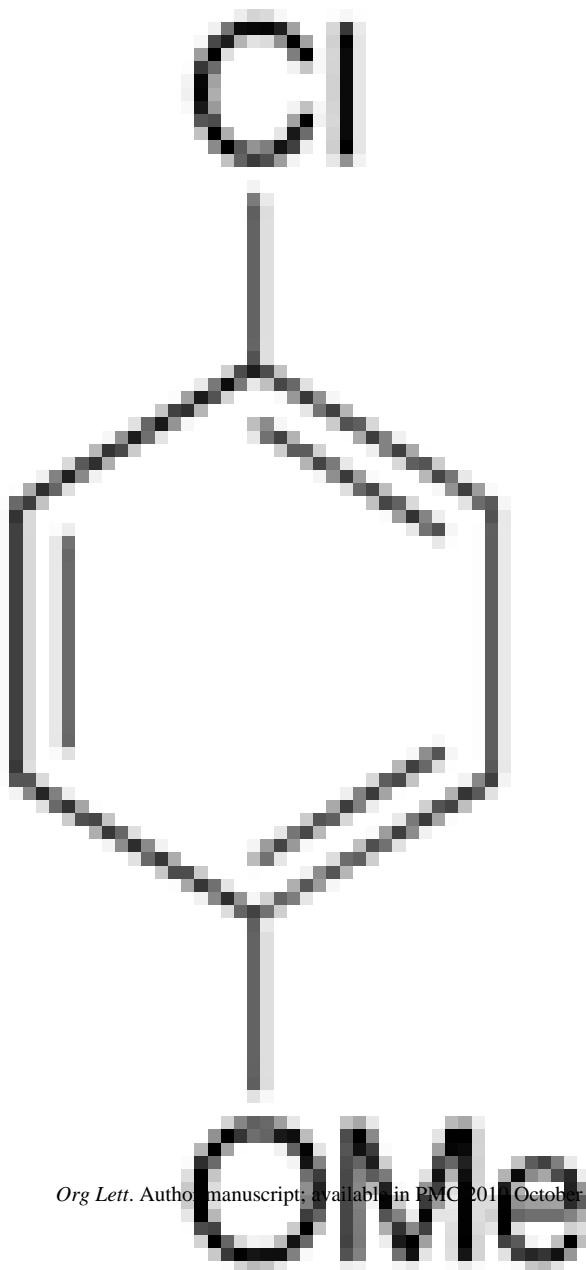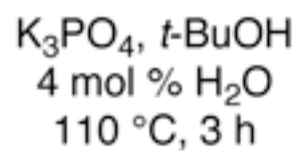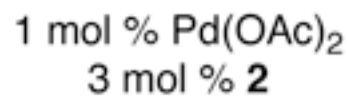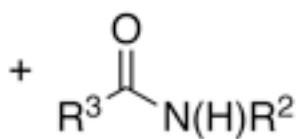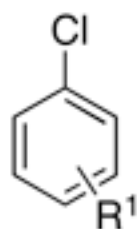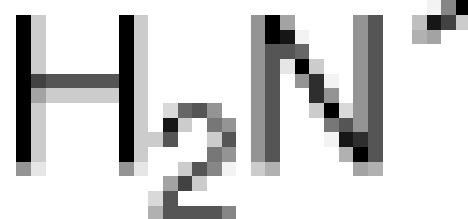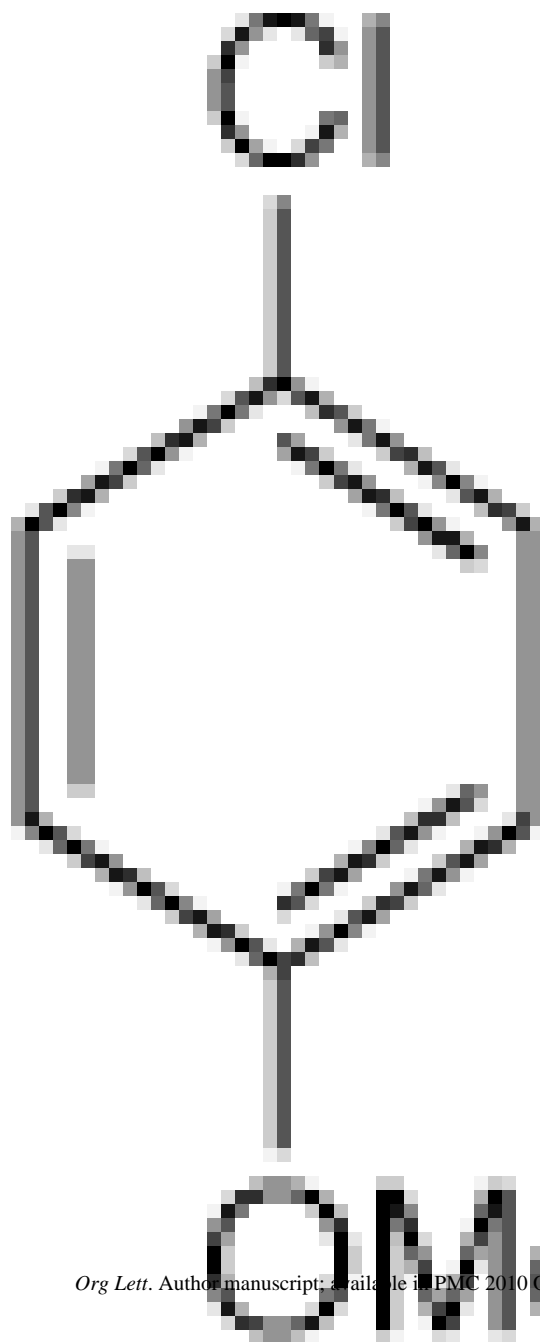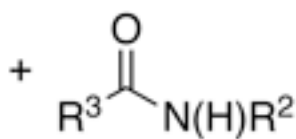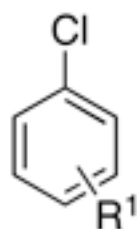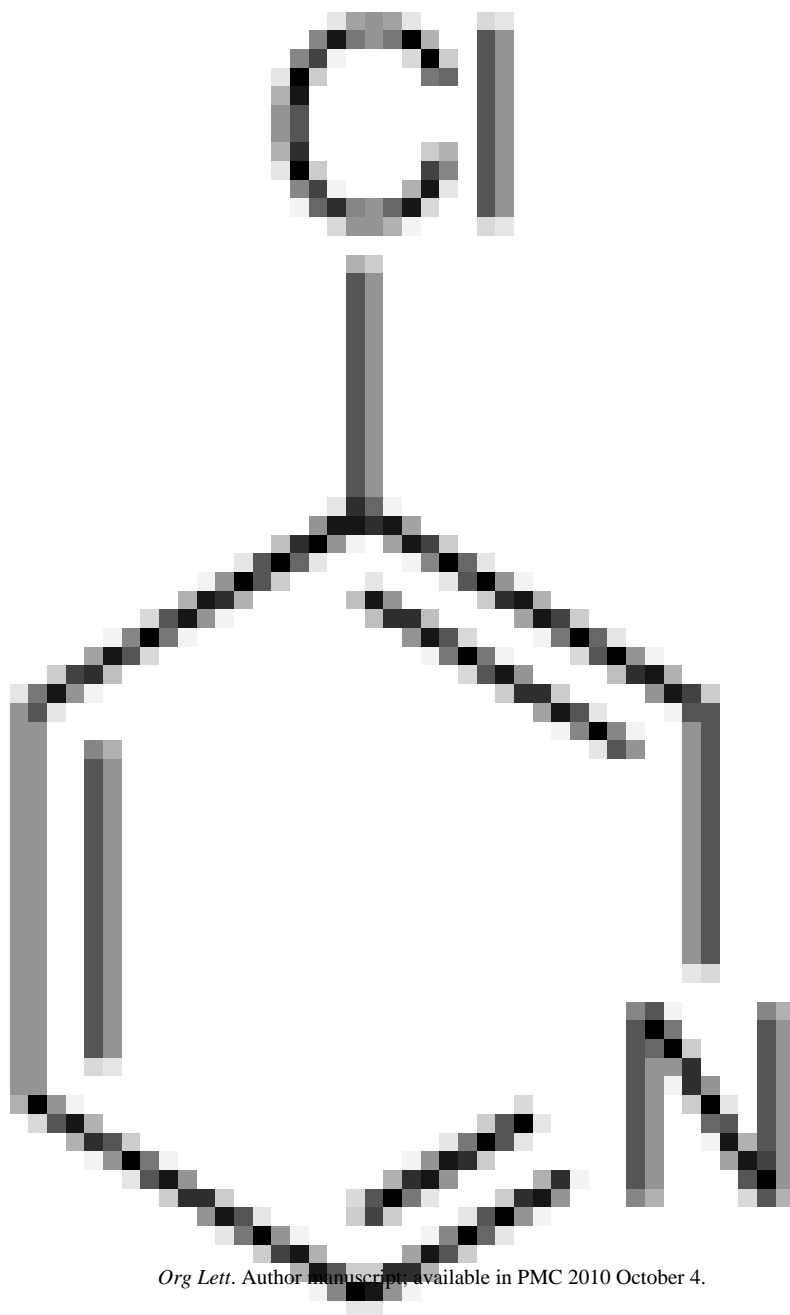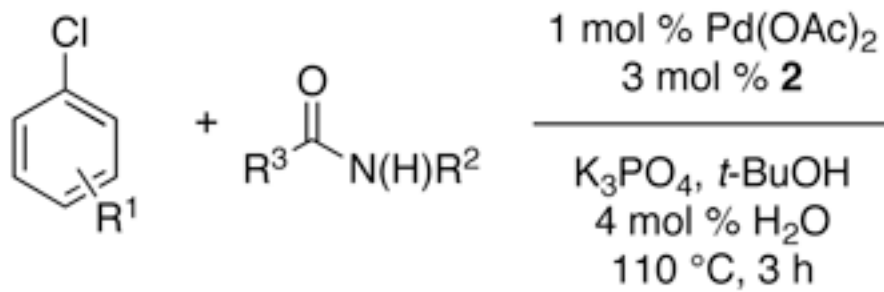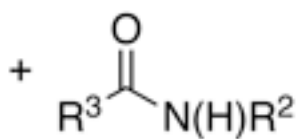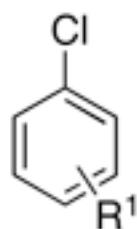
entry[a]	ArCl
1	

entry[a]	ArCl
2	

entry[a]	ArCl
3	

entry[a]	ArCl
4	

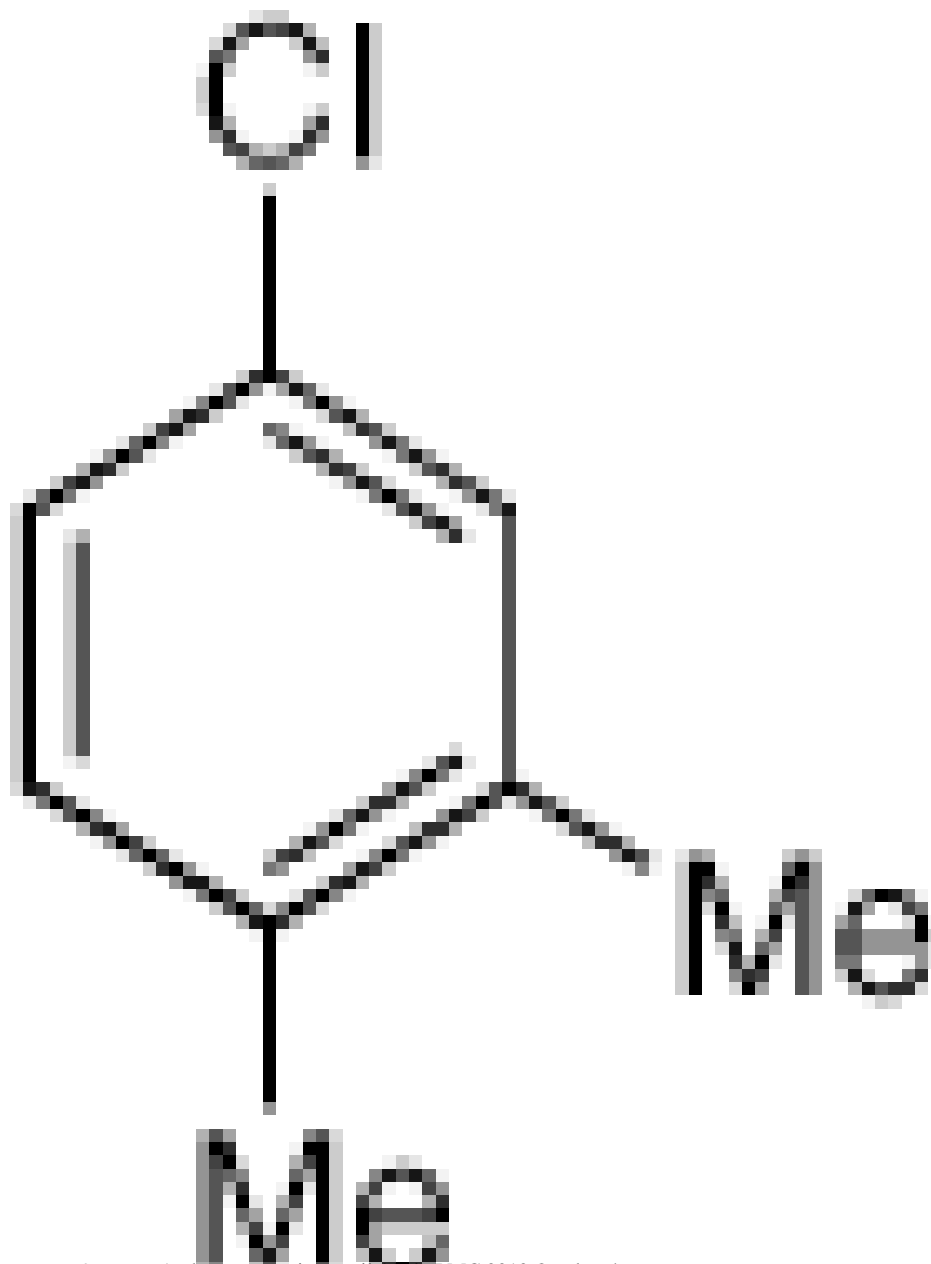| entry[a]	ArCI
5	

[a]Reaction conditions: 1.5 min preactivation at 110 °C with 4 mol % H_2O, 1 mol % Pd(OAc)$_2$, and 3 mol % **2** in 2 mL/mmol of *t*-BuOH; 1.0 equiv aryl chloride, 1.2 equiv amide, and 1.4 equiv K_2CO_3.
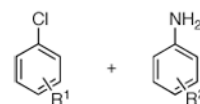
[B]Yields represent isolated yields (average of 2 runs).

[c]1.5 equiv of amide.

Table 2

Coupling of Electron-Deficient Anilines

entry[a]	ArCl
1	
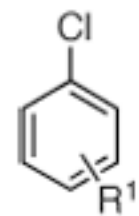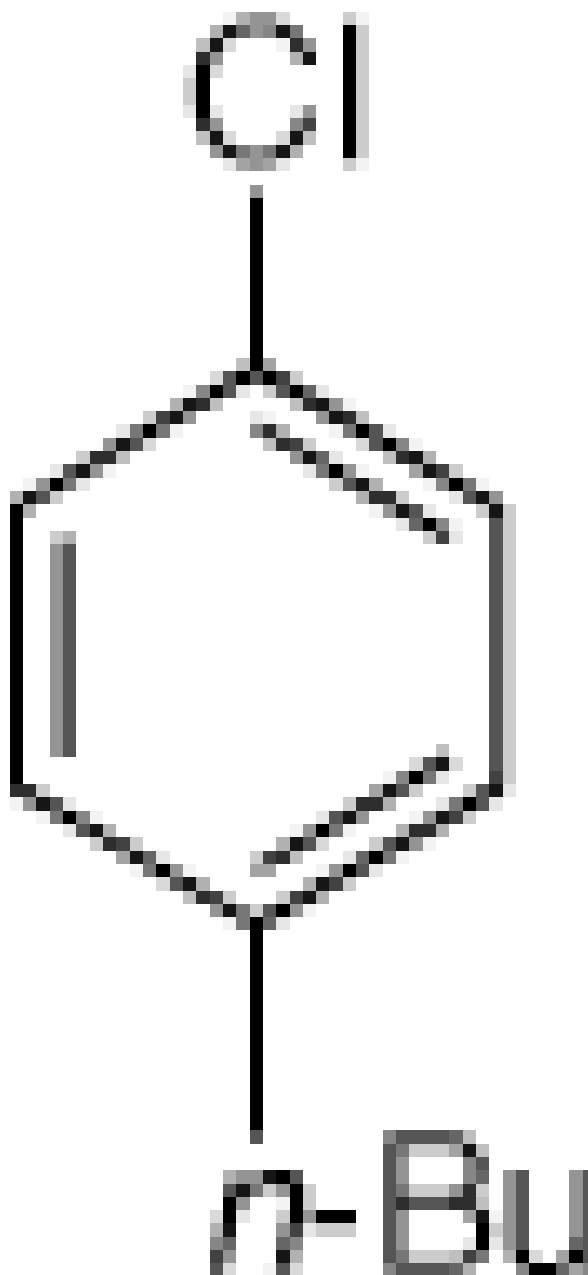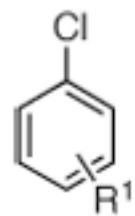
entry[a]	ArCl
2	

entry[a]	ArCl
3	

entry[a]	ArCl
4	

entry[a]	ArCl
5	

entry[a]	ArCl
6	

[a]Reaction conditions: 1 min preactivation at 110 °C with 4 mol % H2O, 1 mol % Pd(OAc)2, and 3 mol % **1** in 2 mL/mmol of *t*-BuOH; 1.0 equiv aryl chloride, 1.2 equiv amine, and 1.4 equiv K2CO3.

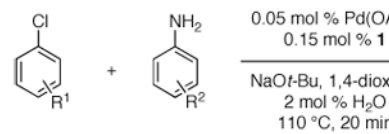[b]Yields represent isolated yields (average of 2 runs).

[c]Reaction time of 2 h.

[d]2.5 equiv of K2CO3 was used.

Table 3
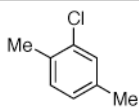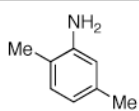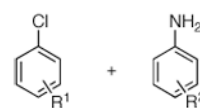
Couplings of Anilines at 0.05 mol % Catalyst Loading

| | | 0.05 mol % Pd(O/ |
| | | 0.15 mol % **1** |
Cl + NH₂ → NaOt-Bu, 1,4-diox
| | R¹ R² | 2 mol % H₂O |
| | | 110 °C, 20 mir |

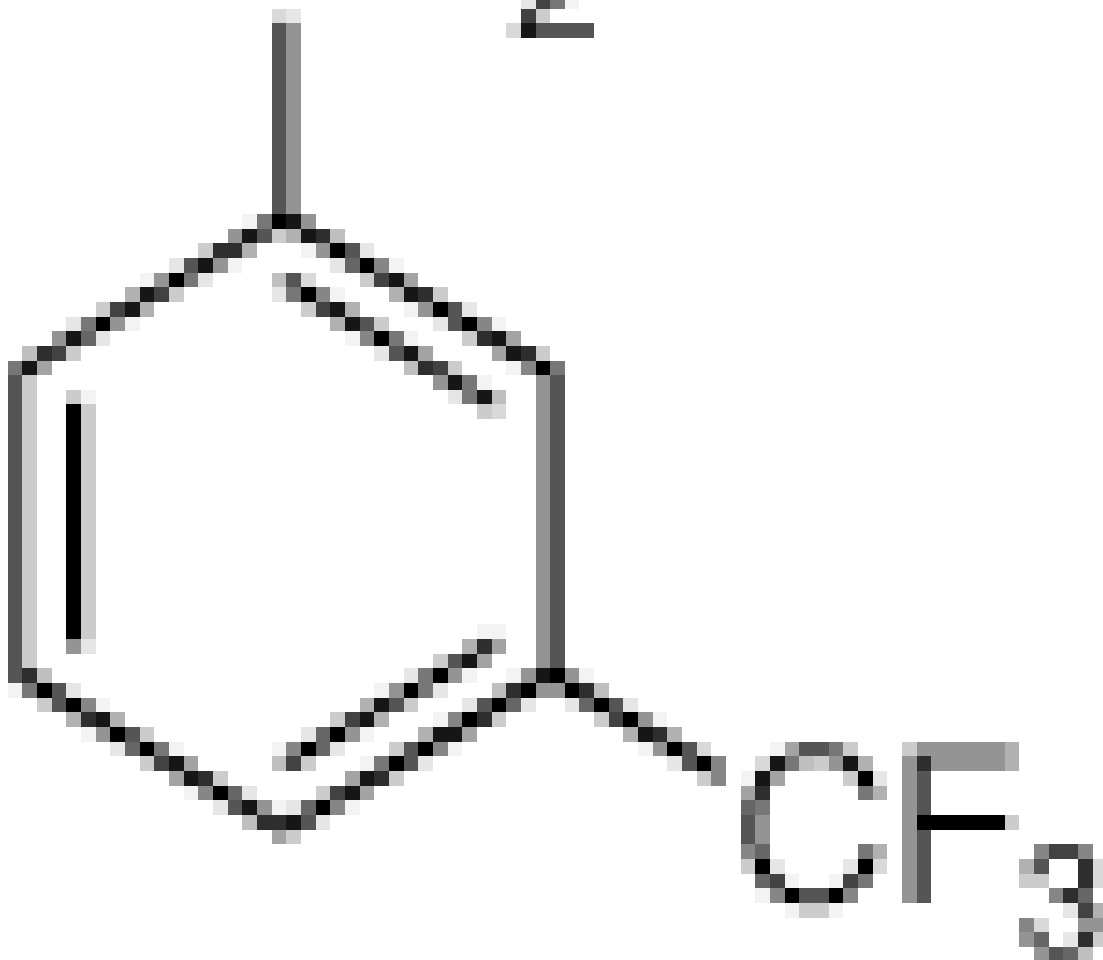| entry[a]	ArCl	aniline
1	Me⎯ Cl ⎯Me	

entry[a]	ArCl	aniline
2		

0.05 mol % Pd(OA

0.15 mol % **1**

NaO*t*-Bu, 1,4-diox

2 mol % H₂O

110 °C, 20 min

entry[a]	ArCI	aniline
3		
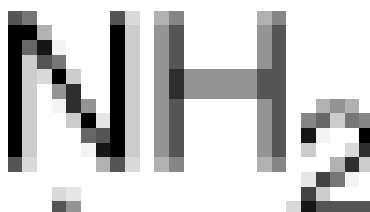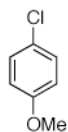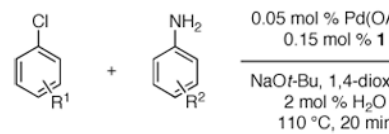
entry[a]	ArCI	aniline
4		

[a] Reaction conditions: 1 min preactivation at 80 °C with 2 mol % H_2O, 0.05 mol % $Pd(OAc)_2$, and 0.15 mol % **1** in 1 mL/mmol of 1,4-dioxane; 1.0 equiv aryl chloride, 1.2 equiv amine, and 1.2 equiv NaOt-Bu.

[B] Yields represent isolated yields (average of 2 runs).