

An Air and Thermally Stable One-Component Catalyst for the Amination of Aryl Chlorides

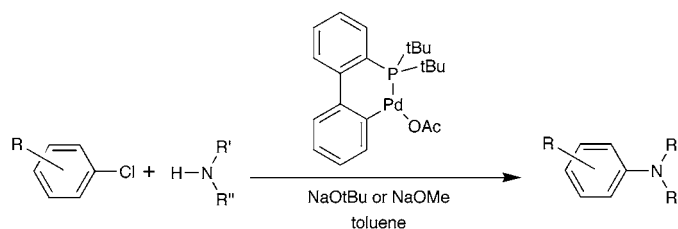
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ABSTRACT



In this paper we report a new, highly efficient palladacyclic precatalyst that is air, moisture, and thermally stable and obviates the need to employ a glovebox. We have developed a convenient one-component precatalyst for the amination of aryl chlorides that overcomes many of the limitations of those previously described.

The palladium-catalyzed amination of aryl halides and sulfonates has emerged as a valuable method for the preparation of aromatic amines.¹ Numerous ligands and catalysts have been reported to effect this type of cross-coupling. While there is a continuing push toward development of the most effective catalysts for large-scale procedures, the majority of the users are interested in small-scale application of the chemistry. In this regard, convenience, along with efficacy, is of significance.

Recently, several single-component precatalysts have been reported to be effective in catalytic aminations. These include examples based on *N*-heterocyclic carbenes,² Pd(*t*-Bu₃P)₂,³ and Pd(I)-Pd(I) dimers,^{4,5} as well as others.⁶ In this paper we report a new, highly efficient palladacyclic precatalyst that is air, moisture, and thermally stable and obviates the need to employ a glovebox. In addition, we present results

that, in contrast to those previously reported,³ indicate that catalysts employing ligand **1** are inefficient when potassium hydroxide is used as the base.

Many palladacyclic precatalysts for cross-coupling reactions have been reported in the past few years. Many of these air-stable complexes have displayed outstanding levels of activity in a variety of synthetically important transformations.⁷ As a result of some prior work in our laboratory, we wondered whether we could efficiently prepare a palladacyclic complex based on the biaryl phosphine ligands that we have developed. In fact, we found that simply stirring **1** in toluene with Pd(OAc)₂ led to the formation of the palladacycle **2** in 94% yield. Palladacycle **2**, an air- and

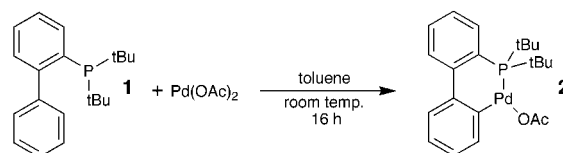


Figure 1. Synthesis of palladacycle **2**.

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Table 1. Amination of Aryl Chlorides

| entry | ArCl | amine | product | 2 (%) | time (h) | method | yield |
|-------|------|-------|---------|--------------------------------------|----------|----------------|------------------|
| 1 | | | | 0.5 | 2 | A | 97% |
| 2 | | | | 1% Pd(OAc) ₂ /2% 1 | 20 | B | 97% |
| 3 | | | | 0.5 | 2.5 | A | 98% |
| 4 | | | | 1 | 3 | A | 95% |
| 5 | | | | 0.5 | 3 | A | 96% |
| 6 | | | | 2 | 5 | A ^a | 98% ^b |
| 7 | | | | 0.5 | 2 | A ^c | 97% |
| 8 | | | | 2 | 5 | A ^a | 95% ^b |
| 9 | | | | 1 | 20 | B | 96% |
| 10 | | | | 1 | 20 | B | 94% |
| 11 | | | | 1 | 20 | B ^d | 90% |
| 12 | | | | 2 | 1 | C ^e | 81% |
| 13 | | | | 1 | 5 | C | 75% |
| 14 | | | | 1 | 2 | C | 80% |
| 15 | | | | 1 | 2 | C | 90% |

^a Method A: ArCl (1 mmol), amine (1.2 mmol), NaOtBu (1.4 mmol), toluene (1 mL), 80 °C. Method B: ArCl (1 mmol), amine (1.2 mmol), ligand (0.01 mmol), KOH (1.5 mmol), toluene (1 mL), 90 °C. Method C: ArCl (1 mmol), amine (1.2 mmol), Et₃N (0.5 mmol), NaOMe (1.4 mmol), toluene (1 mL), 60 °C. (a) 120 °C. (b) 2% of the product of double arylation was observed. (c) Et₃N (0.5 mmol) was included. (d) 3 equiv of amine. (e) Room temperature, Et₃N was not added.

moisture-stable solid, proved to be a versatile precatalyst for the amination of aryl chlorides as is described below.

As is evident from the results presented in Table 1, the use of **2** (1%) in the presence of sodium *tert*-butoxide or

sodium methoxide provides an efficient one-component system for the amination of aryl chlorides. These reactions are all set up on the benchtop and the solid components are

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weighed in the air. The reaction uses commercial solvent (Aldrich Sure-Seal), which is simply added by syringe to the reaction vessel that has been purged with argon and capped with a septum. Three different bases were used in these protocols: sodium *tert*-butoxide, sodium methoxide (both of these obtained from commercial sources), or potassium hydroxide (powdered in the air immediately prior to use). When sodium *tert*-butoxide was employed the reactions were complete in 2–5 h at 80 °C; with a 2,6-disubstituted aryl chloride 2% **2** was required and the reactions were carried out at 120 °C. The use of powdered potassium hydroxide was also effective in combination with **2**. However, in this case it was necessary to add 1% of **1** to the reaction. The reactions that use potassium hydroxide were slower than those with sodium *tert*-butoxide and were left for 20 h at 90 °C. Since it has been previously reported that **1** was an inefficient ligand for the amination of aryl chlorides when hydroxide bases were employed,³ we wondered whether there was something specific about beginning with **2**.⁸ To this end we examined the reaction of morpholine with *p*-chlorotoluene catalyzed by the combination of 1% Pd(OAc)₂/2% **1** with potassium hydroxide as base in toluene. In this case a 97% isolated yield of product was obtained. Of interest was that it was not necessary for this reaction to be carried out in the presence of a phase-transfer catalyst, although its inclusion had no deleterious effects on the reaction.

It has been widely believed that the use of alkoxide bases derived from alcohols with β -hydrogens would lead to the formation of arene from the reduction of the aryl halide. In part this was due to the suggestion that amination reactions with alkoxide bases proceed via a palladium alkoxide intermediate.⁹ While it is possible that this is true when DPPF is employed as supporting ligand, we have recently presented results that indicate that this is not the case when sodium

tert-butoxide is used as base and BINAP is the supporting ligand.¹⁰ More important was a report by workers at Novartis who described the use of both sodium methoxide and sodium isopropoxide as effective bases in palladium-catalyzed amination processes.¹¹ With **2** we have found in several instances that the use of sodium methoxide as the base leads to improved levels of functional group compatibility (entries 13–15). In particular aryl chloride substrates containing nonconjugated electron-withdrawing groups (and hence less reactive toward oxidative addition) gave good yields of products. In one instance (entry 12) we found that the reaction was complete in 1 h at room temperature; 2% of **2** was used in that case.

When the reactions involved the coupling of aniline or a substituted aniline it was necessary to use Et₃N as additive, otherwise no reaction was observed (entries 7 and 15). We believe that the Et₃N, in these cases, is the reducing agent that generates the active Pd(0) species.¹² The use of this additive also proved to be helpful in the cases where certain sensitive functional groups were present (entries 13 and 14).

In summary, we have developed a convenient one-component precatalyst for the amination of aryl chlorides which overcomes many of the limitations of those previously described. This material has recently become commercially available (Strem).

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Supporting Information Available: Experimental details for the synthesis of **2**, catalysis protocol, and product isolation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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