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# Palladium on Carbon-Catalyzed Cross-Coupling of Aryl Halides with Potassium p-Tolyltrifluoroborate in Air

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## Palladium on Carbon-Catalyzed Cross-Coupling of Aryl Halides with Potassium *p*-Tolyltrifluoroborate in Air

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**Abstract:** Palladium supported on carbon (Pd/C) has been shown to be an effective catalyst for the cross-coupling of potassium *p*-tolyltrifluoroborate with a variety of aryl bromides and iodides. Yields ranging from moderate to good were obtained using Pd/C in ethanol/water mixtures with potassium carbonate as base at 50 °C under an air atmosphere.

Keywords: Cross-coupling reaction, palladium catalysis, potassium p-tolyltrifluoroborate, Suzuki–Miyaura reaction

#### INTRODUCTION

The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of aryl halides with arylboronic acids is arguably one of the most important C-C bond formation reactions.<sup>[1]</sup> Mainly because of its high functional group tolerance, the Suzuki–Miyaura reaction is often used in the final steps of complex convergent syntheses. However, in the pharmaceutical industry the amount of residual palladium contaminating final products is strictly limited, and often times extra chromatographic, crystallization, or carbon treatment steps are required to reduce palladium levels to allowed limits. EMEA guidelines categorize palladium as a Class 1 A metal with an oral

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exposure limit of 10 ppm. (See www.emea.europa.eu/pdfs/human/swp/ 444600.pdf.) One solution is to use a heterogeneous palladium catalysts (e.g., Pd/C), allowing the Pd and support to be easily filtered from the product mixture.<sup>[2,3]</sup> These heterogeneous cross-couplings have the additional advantage that no ancillary ligands (e.g., phosphine) are required, further simplifying product isolation and purification. More recent advances in the Suzuki–Miyaura cross-coupling have focused on using potassium aryltrifluoroborates as coupling partners.<sup>[4]</sup> These substrates are easily prepared in a monomeric form from readily available and inexpensive starting materials and exhibit exceptional stability to air and moisture.

In the course of our studies aimed at elucidating boron to palladium transmetalation pathways we examined the Pd supported on carbon catalyzed cross-coupling of aryl bromides with potassium aryltrifluoroborates. A number of arylbromides have been shown to cross-couple with potassium *p*-tolyltrifluoroborate using  $K_2CO_3$  as base in ethanol–water mixtures to provide biaryls in moderate to good yields.

#### **RESULTS AND DISCUSSION**

The cross-coupling of bromobenzene with potassium p-tolyltrifluoroborate was chosen as a model system. A variety of conditions were screened to optimize this Pd/C catalyzed cross-coupling reaction.



A range of bases (KOH, K<sub>3</sub>PO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>) and solvents (ethanol, methanol, NMP, THF) were examined under anhydrous conditions. In all cases, only a trace yield of biaryl products was observed. The importance of water in homogeneous catalytic reactions of aryltrifluoroborates has been established and appears to be important with Pd/C catalyzed reactions as well.<sup>[5]</sup> Once water was added to the reaction mixtures, the yields were observed to increase substantially. Thus conditions similar to those developed for arylboronic acids were found to be optimal for potassium aryltrifluoroborates.<sup>[6]</sup>

Furthermore, these cross-couplings can be performed under an air atmosphere. Provided in Table 1 are examples of the cross-coupling of 1 with a variety of aryl bromides. Aryl bromides with either electronreleasing or electron donating groups can be efficiently coupled. The cross-coupling of 4-iodotoluene did not proceed to high conversion, resulting in low yield (42%). Earlier studies have indicated CsF or KF

Aryl Halide	Product	Yield (%)
⟨Br		65
Br		63
O <sub>2</sub> N-Br	0 <sub>2</sub> N-{>	85
NCBr		65
		42

**Table 1.** Cross-coupling of potassium *p*-tolytrifluoroborate with substituted aryl halides

Note. Conditions: ethanol/water (5/1), Pd/C (10 mol%), and K<sub>2</sub>CO<sub>3</sub> (2 eq.) at 50 °C for 24 h.

provide higher yield for cross-coupling aryl iodides; however, these bases were not used in this study.<sup>[7]</sup>

#### EXPERIMENTAL

# Typical Procedure for Pd/C Catalyzed Cross-Coupling of Potassium *p*-Tolyltrifluoroborate with Aryl Bromides

Under a standard air atmosphere, 0.5 mmol (99 mg) of potassium *p*-tolyl-trifluoroborate was combined with 0.5 mmol of aryl bromide, 110 mg of

Pd/C (0.05 mmol Engelhard Escat 172 5% Pd/C dry), and 1 mmol (138 mg)  $K_2CO_3$  in a scintillation vial. To this, 3 mL of ethanol/water (5/1 volume ratio) were added along with a magnetic stirrer bar. The capped scintillation vial was heated in an oil bath at 50 °C for 24 h under constant stirring. At the end of the 24 h, the reaction mixture was diluted with 25 mL of ethyl acetate or dichloromethane and then gravity filtered to remove the Pd/C catalyst. The filtrate was washed with water (4.0 mL), then the organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the biphenyl product. Reaction screening for conversion was performed using gas chromatography–mass spectrometry. All products are known compounds, and the structures were confirmed by comparison of their <sup>1</sup>H NMR spectra with that of the known compounds.

#### CONCLUSIONS

Palladium on carbon has been shown to be an effective catalyst system for the cross-coupling of aryl bromides and potassium *p*-tolyltrifluoroborate. This cross-coupling can be accomplished using common solvents (ethanol/water) and base ( $K_2CO_3$ ) at 50 °C under an air atmosphere.

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