

Screening Solid Bonded Metal Scavengers for Metal-Catalyzed Coupling Reactions

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Introduction

The use of palladium-catalysts in the synthesis of fine chemicals, pharmaceutical intermediates and active pharmaceutical ingredients (APIs) has become quite common in the last few decades. The number of palladium-catalyzed reactions (both achiral and chiral) available to chemists has provided access to more complex structures in fewer steps and with less waste. An unfortunate side effect of using palladium is the potential for palladium-containing impurities to remain in the desired compound after isolation. This is an especially significant problem for the pharmaceutical industry since there is a low limit for heavy metal impurities allowed in the drug substance. Traditionally chromatography and activated carbon adsorption is used for removing palladium. These techniques can be labor, solvent and time intensive. The use of metal scavengers is gaining popularity for the selective, rapid and efficient removal of metal impurities from organic compounds of pharmaceutical interest. There has, however, been no comprehensive evaluation of the various solid-supported scavengers and the factors affecting metal scavenging. Here we report the effect of solvent, time and format (batch & flow) on scavenging efficiencies of scavengers supported on varied backbones, such as silica, polystyrene, and macroporous polystyrene, in scavenging Pd from the following catalysts: Pd(OAc)₂, (Ph₃P)₂PdCl₂, Pd(PPh₃)₄ and Cu from CuI. The Metal content was analyzed using two different techniques: 1- Inductively coupled plasma optical emission spectroscopy (ICP-OES) ¹, 2- UV-Visible spectrophotometer ².

Pd(OAc)₂

A 1000 ppm solution Pd(OAc)₂ was prepared in two different solvent system [MeCN and DMF/THF (1:1)]. 3 mL of these solutions was treated with 0.5 g of bounded reagents both in batch ³ and flow through format ⁴ (table 1).

Table 1: Bounded reagents screened in scavenging of Pd(OAc)₂

Condition	Batch 2 hr. RT		Flow (gravity)	
	CH ₃ CN	DMF:THF (1:1)	CH ₃ CN	DMF:THF (1:1)
Media				
Si-Thiol	<1	<1 (1 min) ^a	<1	<1
Si-TsOH (SCX3)	1-2 ^a	3 ^b	<1	60-70
Si-Propylsulfonic acid (SCX-2)	2-3 ^a	50-60 ^b	<1	120-130
Si-Triamine	<1	<1 (30 sec) ^a	<1	<1
Si-Trisamine	<1	<1 (30 sec) ^a	<1	<1
MP-TMT	<1	1-2	<34 ^d	1-2
MP-Trisamine	<1	<1 (2-3 min) ^a	<1	<1
PS-Thiophenol	NS	2-3 ^b	-	-

^a scavenging of these catalysts from reaction mixtures was found to be complete within times indicated ^b Cloudy, difficult to filter, ^c Flow rate 1.2 mL/min, ^d Flow rate 0.25 mL/min.

Solvent: MeCN

The silica bounded scavengers, Thiol⁵, Triamine⁵ and Trisamine⁵ as well as MP-TMT ⁵ and MP-Trisamine ⁵ reduced concentration of Pd(OAc)₂ in MeCN from 1000 ppm to <1 ppm in batch format. In flow format Pd concentration was reduced to <1ppm for the silica bound scavengers but only to <34 ppm (table 1), for MP-TMT due to rapid flow (1.2 mL/min) through its large bead size (150-355 microns). By decreasing the flow rate to 0.25 mL/minute, the concentration of Pd was reduced to <1ppm. The solvent flow rate through MP-

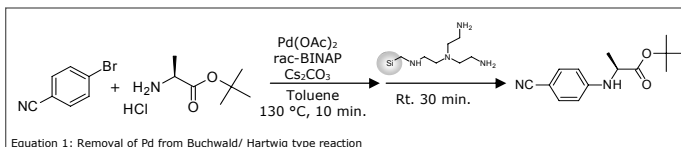
Trisamine (bead size 75-150 microns) cartridge was 0.95 mL/min, which was sufficient to lower the Pd concentration to <1ppm. The polystyrene bounded reagent Thiophenol ⁵ was inactive in scavenging Pd(OAc)₂ in MeCN, since the polystyrene back bone does not swell in MeCN (table 1).

Solvent: DMF/THF

The polystyrene based scavenger, PS-Thiophenol, completely scavenged Pd in batch format, when DMF/THF was used as solvent (Table 1). PS- type scavengers, however, were difficult to filter due to swelling.

Application

Pd(OAc)₂/ rac-BINAP (Buchwald/ Hartwig) has been used in coupling of α -amino t-butyl esters with electron deficient aryl halides. Enantioselectivity of the amino acid esters is conserved when Cs₂CO₃ is used as base ⁶. Si-Trisamine was used for quick and complete removal of Pd(OAc)₂ from this reaction mixture.



Equation 1: Removal of Pd from Buchwald/ Hartwig type reaction

ICP results from reaction mixture before and after treating with Si-Trisamine (Table 2).

	Before	After
Pd Concentration/ppm	1500	39

Pd(PPh₃)₄

Screening of bonded reagents for scavenging Pd(PPh₃)₄ was studied by treating 6 mL of a 500 ppm solution of Pd(PPh₃)₄ in DMF/THF/MeCN (1:2:1) with 0.5 g of bounded reagents both in batch ³ and flow through format ⁴. In this experiment Si-Thiol, SCX3 ⁵ (pic.1) and Mp-TMT were the most effective bounded reagents for scavenging Pd in both batch and flow format. In the case of MP-TMT cartridge rate of flow had been adjusted to 0.25 mL/minute to achieve 100% scavenging of Pd (table 3). PS-Thiophenol also was effective in reducing Pd concentration to <1 in batch format.

Table 2: Bounded reagents screened in scavenging of Pd(PPh₃)₄

	Batch 2 hr. RT	Flow (gravity)
Si-Thiol	<1 (2 min) ^a	<1
Si-TsOH (SCX3)	1-3 (cloudy)	<1
Silica	250-260	130
MP-TMT	<1 (3 min) ^a	<1 ^b
PS-Thiophenol	<1 (3min) ^a	-

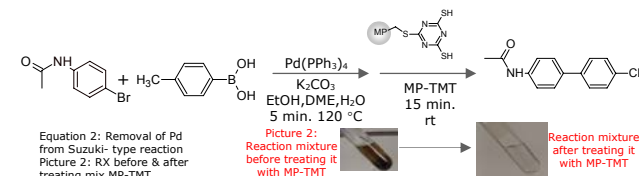
^a scavenging of these catalysts from reaction mixtures complete within times indicated, ^b Flow rate 0.25 mL/min.



Picture 1: 0.5 g of Si-Thiol, SCX3 and silica cartridges used in scavenging of 6 mL of 500 ppm of Pd(PPh₃)₄.

Application

Microwave-assisted Suzuki coupling ⁷ of phenyl boronic acid with aryl halides was used as an example to show versatility of MP-TMT in fast and efficient removal of Pd(PPh₃)₄ (Eq. 2). After completion of the reaction MP-TMT was added to reaction mixture and stirred at room temperature for 15 min ⁸. The reaction mixture color turned from brown to colorless during this time, indicating complete removal of Pd from the reaction mixture ((Pic. 2 and table 4).



Equation 2: Removal of Pd from Suzuki-type reaction
Picture 2: RX before & after treating mix MP-TMT

Picture 2: Reaction mixture before treating it with MP-TMT

Reaction mixture after treating it with MP-TMT

ICP results from reaction mixture before and after treating with MP-TMT.

	Before	After
Pd Concentration/ppm	61	5

(Ph₃P)₂PdCl₂

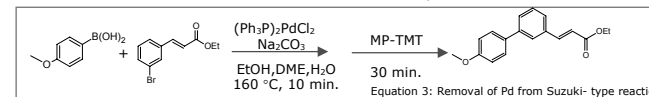
Scavenging of Pd from (Ph₃P)₂PdCl₂ was studied by treating 6 mL of a 500 ppm solution of (Ph₃P)₂PdCl₂ in DMF/THF (1:1) with 0.5 g of the solid supported scavenger. In this experiment MP-TMT, PS-Thiophenol, Si-Trisamine, Si-Triamine, PS-Trisamine, MP-Trisamine, PS-NH₂, PS-TBD and PS-Ph₃P provided complete Pd scavenging, ⁸ although the time required for complete scavenging varies (table 4, Pic. 3 ⁹).

Table 4: Time in minutes for complete scavenging of Pd from 6 mL of a 500 ppm solution of (Ph₃P)₂PdCl₂ in DMF/THF

Minutes	MP-TMT	PS-Thiophenol	Si-Trisamine	Si-Triamine	PS-Trisamine	MP-Trisamine	PS-NH ₂	PS-TBD	PS-Ph ₃ P
5-6	7		2	5	20	10	120	10	5

Application

Microwave-assisted Suzuki coupling ⁷ of phenyl boronic acid with aryl halides was used as an example to show versatility of MP-TMT in rapid and efficient removal of the catalyst from the reaction mixture (Eq. 3). After completion of reaction MP-TMT was added to the reaction mixture and stirred at room temperature for 30 minutes.



ICP results from reaction mixture before and after treating with MP-TMT.

	Before	After
Pd Concentration/ppm	200	1

CuI:

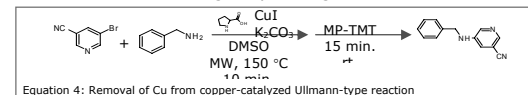
In recent years, Cu catalyzed reactions are becoming more popular due to advancements in microwave synthesizers. Here we report rapid removal of CuI using bounded reagents (table 5)

	MP-TMT	Si-Thiol	PS-Thiophenol	Si-TSOH
Minutes	3 min.	1 min	3 min.	1 min.

Table 5

Application

CuI catalyzes the amino acid promoted C-N bond formation between aryl halides and amines. The Cu was scavenged by stirring reaction mixture with MP-TMT ¹⁰.



Equation 4: Removal of Cu from copper-catalyzed Ullmann-type reaction

ICP results from reaction mixture before and after treating with MP-TMT.

	Before	After
Cu Concentration/ppm	824	2

References:

- 0.5 mL of collected solution was sent to an independent lab (GTI) for ICP analysis.
- Collected solutions were tested using GENESYS 2 UV-Vis spectrometer. Conducting UV-Vis absorption analysis at a wavelength that maximizes UV absorption of the catalysts: Pd(OAc)₂ at 462 nm, (Ph₃P)₂PdCl₂ at 410 nm and Pd(PPh₃)₄ at 465 nm.
- Batch Condition: 0.5 g of bounded reagents was placed in a glass scintillation vial with a screw cap and stirring bar. Test solution was added to vial and stirred for two hours at room temperature, and then the mixture was filtered through a syringe and washed with 0.5 mL of solvent that was used in the test.
- Flow through format: 0.5 g of bounded reagents was packed in a 3 mL syringe, and then pre-washed with 2-3 mL of MeOH. 3 mL of test solution was added to cartridge and flow through by gravity. After all the test solution passed through media, each cartridge was washed with 0.5 mL of solvent that was used in the test.
- Palladium Catalyzed Coupling of Various α -Amino t-Butyl Esters With Electron Deficient Aryl Halides Jason DeMeese, et. al. International Symposium on Medicinal Chemistry 8/15/2004
- Microwave-Promoted Palladium-Catalyzed Coupling Reactions. Mats Larhed and Anders Hallberg, J. Org. Chem. 1996, 61, 9582-9584
- Pd(PPh₃)₄ (12 mg, 0.01 mmol), 4-Bromobenzonitrile (MM, 214, 0.241 g, 1.1 mmol), 4-toluene boronic acid/MM, 135.96, 0.15 g, 1.1 mmol), and K₂CO₃ (0.21 g, 1.5 mmol) were weighed in air and transferred to a 5 mL of reactor equipped with magnetic stir bar and 4 mL of EtOH/DME/H₂O (2:7:3). The reaction mixture was heated for 5 min. at 120 °C. Then 0.5 g of MP-TMT was added to reaction mixture and stirred at RT for 15 min. Reaction mixture was filtered and eluate was concentrated by rotary evaporation followed by high vacuum to give g (90% yields) of 4-acetamidobutane.



Picture 3: Scavenging of 6 mL of a 500 ppm solution of (Ph₃P)₂PdCl₂ in DMF/THF solution with 0.5 g of bounded reagents.

- Practical Cu-catalyzed amination of functionalized heteroaryl halides. Vince S. C. Yeh, and Paul E. Wriedeman, Tetrahedron Letters 47 (2006) 6011-6016
- Amino Acid Promoted CuI-Catalyzed C-N Bond Formation between Aryl Halides and Amines or N-Containing Heterocycles
- Hui Zhang, J. Guan, Cui, Z. and Dawei, J. Org. Chem. 1997, 70, 12, 2005
- 5-Bromo-3-oxopentamide (5Brmg, 0.33 mmol), CuI (13 mg, 0.067 mmol), proline (15.5 mg, 0.134 mmol), K₂CO₃ (140 mg, 1.00 mmol) and amine (76 μ L, 0.873 mmol) were combined in a microwave tube fitted with a septum. The tube was evacuated and then filled with nitrogen several times. DMSO (2 mL) was added, and the septum was replaced with a crimped septum cap. The reaction mixture was heated in a microwave at 150 °C for 10 minutes. 0.5 g of MP-TMT was added to the reaction mixture and stirred at room temperature for 15 minutes and then filtered and washed with EtOAc. The crude material was step for ICP analysis.