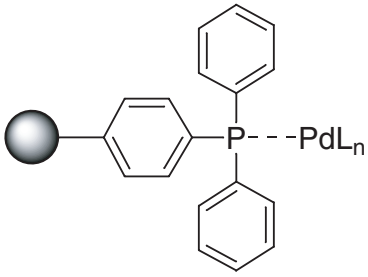
Technical Note 517

PS-PPh_3-Pd

Polymer-Bound Triphenylphosphine-Pd(0)



Chemical Name: Polystyrene Triphenylphosphine Palladium(0)

Resin Type: Poly(styrene-*co*-divinylbenzene)

Loading: Typical loading 0.1 mmol/g, minimum loading 0.08 mmol/g (ICP analysis)

Bead Size: 75 – 150 micron

Application: Catalyst for Suzuki reaction

Typical Reaction Conditions: 0.5 mol% catalyst, 16 h, 75 °C

Compatible Solvents: DMF (3.5 mL/g), THF (4.1 mL/g), DCM (4.9 mL/g) and any solvent that swells gel-type polystyrene

Storage: Cool, dry location

PS-PPh_3-Pd resin is a polystyrene-bound equivalent of the small molecule catalyst tetrakis(triphenylphosphine)palladium(0) [$Pd(Ph_3P)_4$]. The primary application for the resin is as a catalyst for Suzuki-Miyaura coupling reactions between arylboronic acids and aryl halides. PS-PPh_3-Pd may also have applications in other types of palladium-catalyzed processes in which $Pd(Ph_3P)_4$ is used. The resin was developed to perform in a manner similar to that of the well-established catalyst, while facilitating reagent handling and simplifying workup, product isolation, and removal of palladium.

The small molecule catalyst, $Pd(Ph_3P)_4$, is a standard first choice for a number of carbon-carbon bond forming reactions, including Suzuki-type cross coupling reactions.[1] The Suzuki reaction is one of the most widely practiced coupling protocols for the preparation of symmetrical and unsymmetrical biaryl compounds.[2] $Pd(Ph_3P)_4$ is preferred to other palladium catalysts for this application because of its mild reaction conditions and broad scope of reactivity. However, despite the widespread use of palladium-mediated catalytic reactions, removal of residual palladium during workup and product isolation remains a major problem. Reducing the palladium content to the parts per million (ppm) level, as is required for active pharmaceutical ingredients, is particularly challenging.[3]

PART NUMBER	QUANTITY
800473	1 g
800474	10 g
800475	25 g

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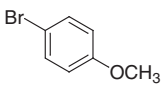
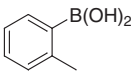
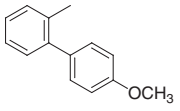
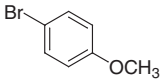
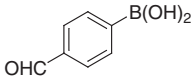
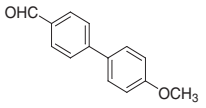
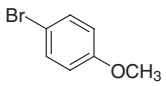
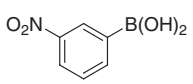
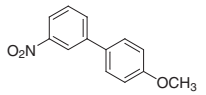
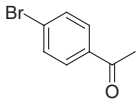
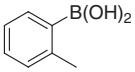
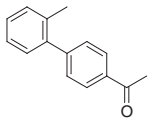
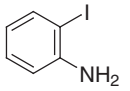
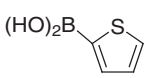
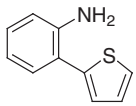
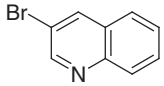
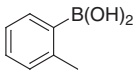
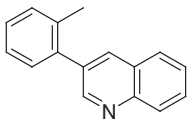
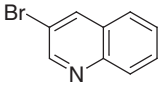
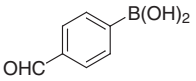
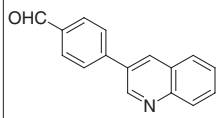
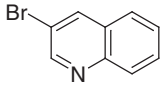
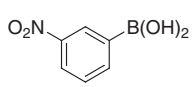
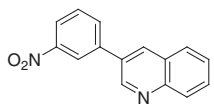
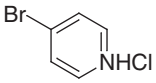
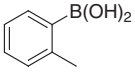
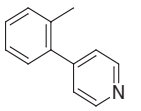
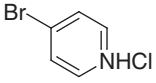
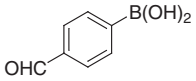
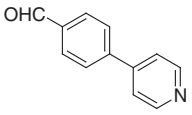
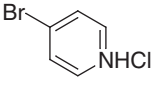
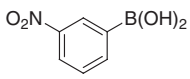
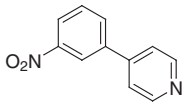
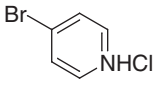
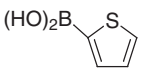
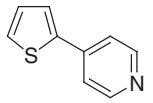
PS-PPh_3-Pd offers scope and reactivity similar to that of $Pd(Ph_3P)_4$ with the additional convenience of a polymer-supported reagent for handling and purification. Unlike the small molecule reagent, PS-PPh_3-Pd has been found to be stable to air and can be stored at room temperature for extended periods of time without degradation. The resin may be weighed out on the bench using regular weighing tools and requires no special handling techniques. Typical reaction conditions for Suzuki cross-coupling reactions of aryl bromides and iodides with arylboronic acids utilize 0.5 mol% of PS-PPh_3-Pd catalyst. The reactions are performed in a mixture of dimethoxyethane (DME) and EtOH (1:1) in the presence of aqueous K_2CO_3 at 75 °C for 16 h. After the reaction is complete, the reaction mixture is diluted with DCM and water followed by separation and filtration of the organic layer through a silica gel SPE cartridge.[4] The product is then concentrated. Using this protocol the products are typically obtained in excellent yield and purity, and contain <100 ppm residual palladium. When lower levels of palladium are required a palladium scavenging resin, MP-TMT,[5] may be employed prior to the final concentration step. Control experiments utilizing the small molecule catalyst $Pd(Ph_3P)_4$ afforded products containing palladium levels as high as 1700 ppm. When using N-heterocyclic bromides as coupling partners, the same procedure is followed except that the organic layer is loaded onto an MP-TsOH cartridge.[6] The solution is allowed to flow through the cartridge, followed by washing with methanol to remove non-basic impurities. The product is then released from the cartridge by the addition of ammonia in methanol, followed by washing with methanol. Concentration of the combined methanol solutions affords the product.

To evaluate the scope and reactivity of PS-PPh_3-Pd resin, a series of Suzuki coupling reactions were performed. Substrates included various aryl bromides and arylboronic acids, as shown in **Table 1**. Coupling reactions were carried out using 0.5 mol% of the bound catalyst. For comparison purposes, most of the reactions were also conducted with 0.5 mol% of the small molecule catalyst, $Pd(Ph_3P)_4$, as a control. In all cases, the standard protocol was followed (see Experimental Section for details), and the products analyzed by GC to determine the % conversion of starting material. The chemical purity was determined by GC and/or ^{1}H-NMR.

A range of aryl bromides, including the heterocyclic bromides, underwent high conversion to product with the series of the boronic acids studied. In most cases the results for the resin-bound catalyst were comparable to the small molecule catalyst. An exception to this trend was observed for the case of 2-iodoaniline and 2-thienylboronic acid (entry 5) where $Pd(Ph_3P)_4$ provided products in higher yield and purity than PS-PPh3-Pd. While both catalysts gave excellent results, use of the bound catalyst provided easier weighing and dispensing and afforded products with substantially lower levels of residual palladium.

Table 1: Suzuki Coupling of Aryl Boronic Acids with Aryl Halides

Entry	Aryl halide	Boronic acid	Product	PS-PPh_3-Pd Conversion (Purity) %	$Pd(Ph_3P)_4$ Conversion (Purity) %
1				97 (97)	100 (94)
2				98 (87)	97 (87)
3				98 (85)	99(90)
4				100 (95)	ND
5				51 (36)	100 (93)
6				98 (98)	76 (79)
7				89 (85)	93 (73)
8				93 (69)	99 (76)
9[a]				99 (97)	99 (89)
10[a]				99 (94)	99 (96)
11[a]				99 (90)	99 (92)
12[a]				99 (99)	99 (95)

[a]2.5 equiv of K_2CO_3 was used.

Capacity, Stability, and Handling

The palladium loading of the resin catalyst was determined by elemental analysis. Unlike the small molecule catalyst, the resin has been found to be stable to storage and use in air. The resin may be weighed out on a bench using regular weighing methods. Given its uniform density, the resin may also be dispensed by automated filling devices or manual dispensing systems such as the ArgoScoop® resin dispenser (Part Number 900131). Static electric charge may make handling difficult in dry conditions. Avoiding plastic weighing tools minimizes this effect.

Equipment List

The resin can be used in regular glass round bottom flasks with a magnetic stirrer, in polypropylene cartridges (Part Number 120-1113-C), and in 96 well plates (Part Number 121-5203). Reaction vessels can be agitated using rotary wheel devices (VWR Part Number 62404-006) or orbital shakers. Resins can be filtered in cartridges and the filtrate collected into round bottom flasks or scintillation vials ready for concentration.

Palladium Impurities in the Products

The crude products obtained by using both the bound catalyst, PS-PPh_3-Pd, and the small molecule catalyst, $Pd(Ph_3P)_4$, were tested for the presence of residual palladium. On average, the palladium levels in the products from PS-PPh_3-Pd catalyzed reactions were found to be in the 50 – 100 ppm range. Products from $Pd(Ph_3P)_4$ catalyzed reactions gave palladium levels in the 1000 – 1700 ppm range.

EXPERIMENTAL

Representative Procedure for Suzuki Reaction of Aryl Halides with Arylboronic Acid (Entry 1, Table 1)

4-bromoanisole (0.187g, 1 mmol) in DME (1 mL) was added to PS-PPh3-Pd(0) (0.05 g, 0.005 mmol, 0.10 mmol/g), followed by 2-methylbenzeneboronic acid (0.162 g, 1.2 mmol) in EtOH (1 mL), and K_2CO_3 (0.207 g, 1.5 mmol) in water (0.5 mL). The reaction mixture was agitated for 16 h at 75 °C, cooled to room temperature and diluted with DCM (1 mL) and water (2 mL). The organic layer was then passed through a silica SPE cartridge (500 mg, Part Number 460-0100-C), pre-conditioned with DCM (4 mL). The effluent was collected, the cartridge was washed with DCM (3 x 3 mL) and the combined effluent plus washings were concentrated to afford 4-(o-tolyl)anisole in 95% yield (0.19 g, GC purity 97%). The residual palladium content in the product was determined to be 90 ppm. The amount of palladium found in the control experiment using the small molecule catalyst $Pd(Ph_3P)_4$ was 1700 ppm.

Representative Procedure for Suzuki reaction of N-Heterocyclic Halides with Arylboronic Acid (Entry 6, Table 1)

3-bromoquinoline (0.208 g, 1 mmol) in DME (1 mL) was added to PS-PPh_3-Pd(0) (0.05 g, 0.005 mmol, 0.10 mmol/g), followed by 2-methylbenzeneboronic acid (0.162 g, 1.2 mmol) in EtOH (1 mL), and K_2CO_3 (0.207 g, 1.5 mmol) in water (0.5 mL). The reaction mixture was agitated for 16 h at 75 °C, cooled to room temperature and diluted with DCM (1 mL) and water (2 ml). The organic layer was then loaded onto an MP-TsOH cartridge (1g, 2.5 mmol, Part Number 800477-C30), pre-conditioned with DCM (4 mL). The solution was allowed to flow through the cartridge, which was then washed with methanol (3 x 4 mL) to remove non-basic impurities. The product was released from the cartridge by elution with a solution of ammonia in methanol (2 M, 4 mL), followed by washing with methanol (2 x 4 mL). The resulting solution was concentrated to afford 3-(*o*-tolyl)quinoline in 86% yield (0.185 g, GC purity 98%).

1. See, for example, (a) *Handbook of Reagents for Organic Synthesis Reagents, Auxiliaries and Catalysts for C-C Bond Formation,* Coates, R. M.; Denmark, S. E. Eds., Wiley, New York, **1999**, pp 596 – 604 and references cited therein; (b) Stanforth, S. P. *Tetrahedron*, **1998**, *54*, 263.
2. (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513; (b) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213; (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
3. (a) Chen, C; Dagneau, P.; Grabowski, E. J. J.; Oballa, R.; O'Shea, P.; Prasit, P.; Robichaud, J.; Tillyer, R.; Wang, X. *J. Org. Chem.* **2003**, *68*, 2633; (b) Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res. & Dev.* **1997**, *1*, 311.
4. SPE cartridge: Part Number 460-0100-C.
5. MP-TMT 10 g, Part Number 800469; MP-TMT 25 g, Part Number 800470; MP-TMT 100 g, Part Number 800471; MP-TMT 1000 g, Part Number 800472.
6. Part Number 800477-C30.

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Japanese Headquarters
Itsuwa Bldg. 6F,
2-26-9, Nishigotanda,
Shinagawa-ku, Tokyo, 141-0031, Japan
T: +81-3-5719-1239
F: +81-3-5719-1203

European Headquarters
New Road, Hengoed, Mid Glamorgan
United Kingdom, CF82 8AU
T: +44 (0) 1443 811811
F: +44 (0) 1443 816552

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