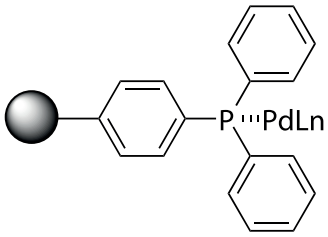
Biotage® PS-PPh_3-Pd

Polymer-supported Triphenylphosphine-Pd(0)



Key Facts

Shelf Life

Capacity (mmol/g)

BSE/TSE

Scalable

Particle Size (µm)

Thermally & Mechanically Stable

Good Laboratory Practice

Bulk Density (g/L)

Specifications

Chemical Name:	Polystyrene Triphenylphosphine Palladium(0)
Resin Type:	Poly(styrene-co-divinylbenzene)
Application:	Catalyst for Suzuki and Heck reactions
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)
Storage:	Cool, dry location

PS-PPh_3-Pd resin is a polystyrene-supported 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 Suzuki reaction is one of the most widely practiced coupling protocols for the preparation of symmetrical and unsymmetrical biaryl compounds.[2]

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.

Application

$Pd(Ph_3P)_4$ 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.

Scope and Usage

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.

Residual Pd Levels

When lower levels of palladium are required, a palladium scavenging resin, MP-TMT,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 a catch and release SCX-2 cartridge. 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.

Biotage®

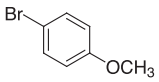
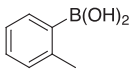
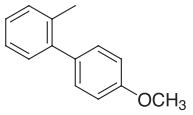
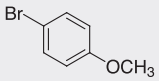
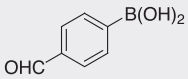
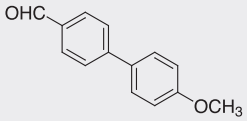
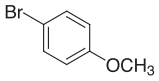
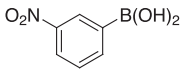
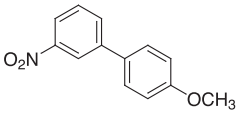
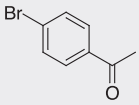
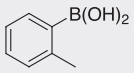
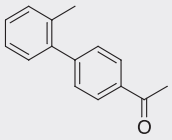
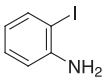
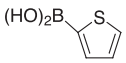
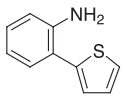
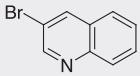
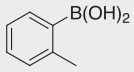
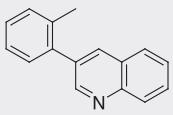
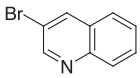
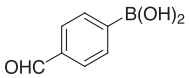
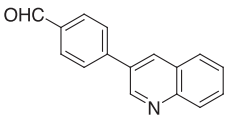
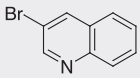
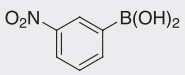
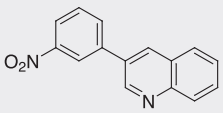
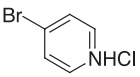
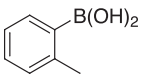
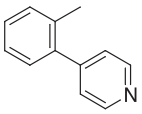
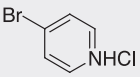
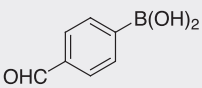
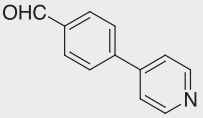
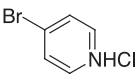
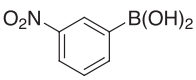
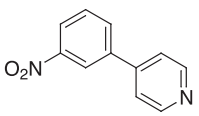
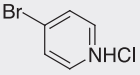
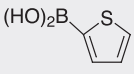
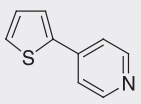
Entry	Aryl Halide	Boronic Acid	Product	PS-PPh3-Pd Conversion (Purity) % Pd(Ph3P)4	Conversion (Purity) %
1				97 (97)	100 (94)
2				98 (87)	97 (87)
3				98 (85)	99 (90)
4				100 (95)	ND
5				51 (36)	100 (93)
6				98 (98)	76 (79)
7				89 (85)	93 (73)
8				93 (69)	99 (76)
9				99 (97)	99 (89)
10				99 (94)	99 (96)
11				99 (90)	99 (92)
12				99 (99)	99(95)

Table 1. Suzuki coupling of aryl boronic acids with aryl halides.

Suzuki Reaction Reacivity

To evaluate the scope and reactivity of PS-PPh_3-Pd resin, a series of Suzuki coupling reactions was 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 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.

The range of aryl bromides, including the heterocyclic bromides, underwent high conversion to product with the series of boronic acids studied. In most cases the results for the solid-supported 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 (Table 1, Entry 5) where $Pd(Ph_3P)_4$ provided products in higher yield and purity than PS-PPh_3-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. 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).

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.

Representative Procedures

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

4-bromoanisole (0.187 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 passed through a silica SPE cartridge (500 mg), 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.

Ordering Information

Part Number	Quantity
800473	3g
800474	10 g
800475	25 g
800476	100 g

bsi. ISO 9001 Quality Management FM 31206 ISO 14001 Environmental Management EMS 640981

Biotage holds certification for both ISO9001 Quality Management and ISO14001 Environmental Management.

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