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Technical Notes

Pd−Smopex-111: A New Catalyst for Heck and Suzuki Cross-Coupling Reactions

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Abstract:

Smopex-111, a commercially available metal-scavenging styryl thiol-grafted polyolefin fiber was treated with palladium acetate giving a reagent with a palladium loading of 4.4−4.7 (wt %). The Pd−Smopex-111 thus generated was found to be a highly active catalyst for Heck and Suzuki coupling reactions and was found to be reusable with negligible leaching of palladium.

Introduction

Palladium-catalyzed cross-coupling reactions such as Suzuki and Heck have been demonstrated to be some of the most powerful methods for constructing carbon−carbon bonds.[1−3] In general, a homogeneous palladium catalyst and ligand are required for these reactions. However, cross-coupling reactions with homogeneous palladium have several shortcomings such as limited reusability, which impacts cost and palladium contamination in the product. Removal of residual palladium[4] provides a challenging task for chemists in the pharmaceutical industry to reduce the palladium to a level that satisfies specifications required by regulators.

Many methods have been introduced recently to address the palladium contamination issue, which include palladium-containing perovskites,[5] palladium supported on various materials such as carbon,[6] zeolites,[7] silica,[8] sepiolites,[9,10] polyionic gels,[11] hydrotalcite,[12] core−shell block copolymers,[13] and triphenylphosphinated polystyrene beads.[14] The palladium level in the product was lower in these systems when compared to homogeneous palladium catalysts; however, in many cases, it was still above the limit set for active pharmaceutical ingredients. With our recent successful experience in using the Smopex family[15] of absorbents for removing residual palladium from products derived from palladium-catalyzed reactions, we were intrigued by the possibility of using the complex formed between Pd and Smopex-111 in organic reactions.

Smopex-111, commercially available from Johnson Matthey, is a styryl thiol-grafted polyolefin fiber. It is a new metal-scavenging system for the recovery of low levels of precious metals from catalytic reactions. Binding to palladium is very efficient due to active groups located almost exclusively on the surface of the fiber, making this material very attractive for removing palladium from processes. In keeping with our ongoing objectives to develop practical and economical processes for industrial applications, we sought to use palladium adsorbed on Smopex-111 (Pd−Smopex-111) as a catalyst in Suzuki and Heck cross-coupling reactions.

Table 1. **Palladium loading on Smopex-111 in different solvents**

solvent(s)	Pd−Smopex-111 Pd loading (wt %)
THF	0.75
toluene	4.4 to 4.7
EtOH	2.4
EtOH (70 °C)	3

(1) For leading references, see: (a) Suzuki, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002. (b) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(2) For recent reviews, see: (a) Prashad, M. *Top. Organomet. Chem.* (Organometallics in Process Chemistry) **2004**, *6*, 181−203 and references therein. (b) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917−1927. (c) Albrecht, M.; van Koten, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 3750−3781. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (e) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553−1582.

(3) (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146−151. (b) de Vries, J. G. *Dalton Trans.* **2006**, 421−429.

(4) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.

(5) (a) Smith, M. D.; Stephan, A. F.; Ramarao, C.; Brennan, P. E.; Ley, S. V. *Chem. Commun.* **2003**, 2652−2653. (b) Andrews, S. P.; Stephan, A. F.; Tanaka, H.; Ley, S. V.; Smith, M. D. *Adv. Synth. Catal.* **2005**, *347*, 647−654.

(6) Dantas Ramos, A. L.; da Silva Alves, P.; Aranda, D. A. G.; Schmal, M. *Appl. Catal., A* **2004**, *277*, 71.

(7) Okumura, K.; Nota, K.; Yoshida, K.; Niwa, M. *J. Catal.* **2005**, *231*, 245.

(8) (a) Crudden, C. M.; Sateesh, M.; Lewis, R. *J. Am. Chem. Soc.* **2005**, *127*, 10045−10050 and references therein. (b) Papp, A.; Galbacs, G.; Molnar, A. *Tetrahedron Lett.* **2005**, *46*, 7725−7728.

(9) Corma, A.; Garcia, H.; Leyva, A.; Primo, A. *Appl. Catal., A* **2004**, *257*, 77−83.

(10) Shimizu, K.; Maruyama, R.; Komai, S.; Kodama, T.; Kitayama, Y. *J. Catal.* **2004**, *227*, 202−209.

(11) Thiot, C.; Schmutz, M.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2868−2871.

(12) Ruiz, J. R.; Jimenez-Sanchidrian, C.; Mora, M. *Tetrahedron* **2006**, *62*, 2922−2926.

(13) Okamoto, K.; Akiyama, R.; Kobayashi, S. *Org. Lett.* **2004**, *6*, 1987.

(14) Shieh, W.-S.; Shekhar, R.; Blacklock, T.; Tedesco, A. *Synth. Commun.* **2002**, *32*, 1059−1067.

(15) Johnson Matthey Catalysts, *The Catalyst Technical Handbook*; Johnson Matthey Co.: London, UK, 2005; p 20.

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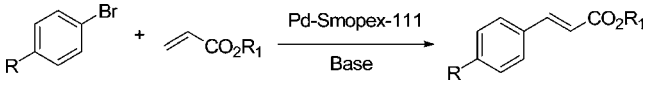
Scheme 1. **Heck reaction of Ar-Br with alkyl acrylate**



Preparation of Pd−Smopex-111

Palladium can be easily loaded onto Smopex-111 by stirring a prefiltered solution of palladium acetate and Smopex-111 at elevated temperature. After filtration and washing, the complex was dried and the content of palladium confirmed by weight and analysis. As demonstrated in Table 1, palladium content depended on the solvent system used. For example, palladium loading on Smopex-111 was 0.75% (by weight) using THF, while a range of 4.4−4.7% palladium loading was obtained when toluene was used as the solvent. More polar solvents such as ethanol and *N*-methylpyrrolidinone (NMP) afforded 1.53 and 2.4% palladium loading, respectively. On the basis of the amount of palladium loaded on Smopex-111, the complex obtained from toluene was selected for further use.

Heck Reaction

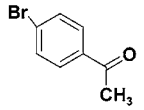
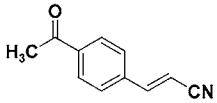
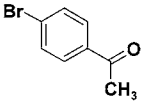
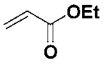
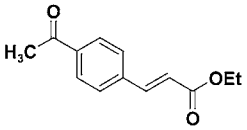
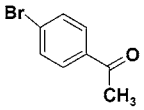
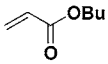
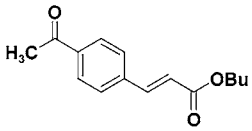
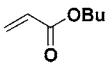
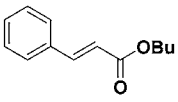
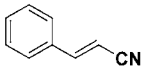
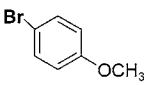
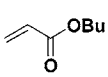
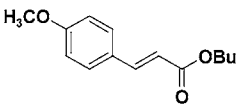
The Heck reaction shown in Scheme 1, was conducted by reaction of aryl bromide with alkyl acrylate (1.3 equiv) and a base (1.3 equiv) in the presence of Pd−Smopex-111 catalyst (2.5% by weight) in NMP. After heating the reaction mixture at 120 °C for 20−24 h, the reaction mixture was cooled, and the catalyst was filtered. The filtrate was extracted with ethyl acetate and washed with water. The crude product was obtained by evaporation of ethyl acetate to dryness. The palladium content of this crude mixture was analyzed before further purification by column chromatography on silica gel.

As depicted in Table 2, the catalyst demonstrated good activity. All substrates either with electron-donating or electron-withdrawing functional groups afforded good yields. In entry 2, hydrolysis of the ethyl ester was observed under the basic condition, and 13% of the corresponding acid was isolated. The treatment of bromobenzene with acrylonitrile (entry 5) also gave a low conversion due to the low boiling point of the reaction mixture containing acrylonitrile. The palladium content of the reaction mixture after filtration of the catalyst, as demonstrated in Table 2, was below 10 ppm, which indicated that the Smopex-111 has a strong affinity for palladium even under harsh reaction conditions. The results clearly demonstrate this catalyst may have practical utility.

Suzuki Reaction

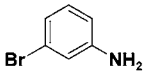
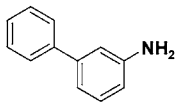
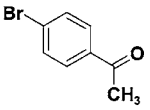
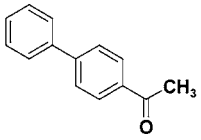
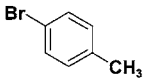
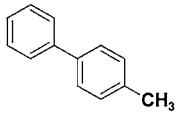
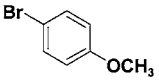
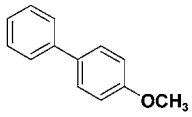
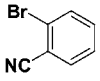
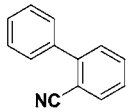
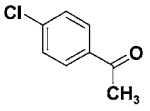
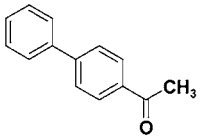
The Pd−Smopex-111 complex was also successful when employed in Suzuki couplings. Coupling of aryl bromides with phenylboronic acid occurred readily with Pd−Smopex-

Table 2. **Heck reaction[a] using Pd−Smopex-111**

Entry	Substrate	Heck Acceptor	Product	Yield	Leached Pd
1				80%	4.0 ppm
2				77%	5.8 ppm
3				87%	8.7 ppm
4				83%	6.0 ppm
5				70%	4.8 ppm
6				80%	4.9 ppm

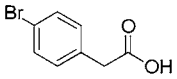
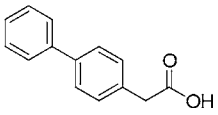
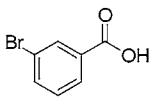
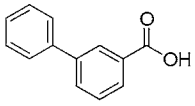
[a] Reaction conditions: 10 mmol of substrate, 13 mmol of Heck acceptor, 0.8 g of Pd−Smopex (2.5 wt % of Pd with respect to the substrate), 10 mL of NMP, 118 °C, 16−24 h.

Table 3. **Suzuki coupling reactions using phenylboronic acid and Pd−Smopex-111**

Entry	Substrate	Pd[a]	Time	Product	Yield	Leached Pd
1		2.5%	2.5 h		92%	8.0 ppm
2		2.5%	2.5 h		97%	<1.0 ppm
3		2.5%	4 h		80%	2.0 ppm
4		5.0%	3 h		79%	<1.0 ppm
5		2.5%	2 h		81%	< 1.0 ppm
6		5.0%[b]	7 h		75%	8.7 ppm

[a] wt % of Pd with respect to the substrate. [b] 5% 2-(di-*tert*-butylphosphino)biphenyl added.

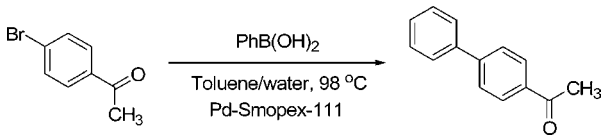
Table 4. **Suzuki reactions with phenylboronic acid using water as a solvent**

Entry	Substrate	Pd	Time	Product	Yield)	Leached Pd
1		2.5%	2 h		91%	3.0 ppm
2		1%	2 h		67%	20 ppm

111 using K_3PO_4 as the base and a water/toluene mixture (Table 3). Only in the case of chloroacetophenone (entry 6**)** was a ligand required for coupling to occur. No coupling was observed in the absence of ligand. Interestingly, even in this case, leaching was minimal. Substrates containing electron-donating groups (entry 4) required twice the amount of catalyst typically employed.

We also explored water alone as a solvent for water-soluble substrates. We were pleased to find that the palladium leaching was not significant (Table 4, entry 1) under these conditions. It is unclear why the 3-bromobenzoic acid derivative experienced higher Pd contamination.

Scheme 2. **Recycling of the catalyst**



Recycling of the Catalyst

Recycling of the Pd−Smopex-111 was also explored (Scheme 2). In each iteration, the catalyst from the reaction was filtered off, washed, and reused without concern for exposure to air. As is evident from the data (Table 5), palladium leaching from the catalyst is negligible with each cycle. No noticeable loss of activity was observed as noted

Table 5

cycle	1	2	3	4
Pd leaching (ppm)	<1.0	1.4	1.7	4.1
conversion (%)	100	100	100	100

by reproducible reaction times for each cycle. In all of the four cycles, the reaction was complete in 2.5 h.

In conclusion, Pd−Smopex-111 was found to be an interesting catalyst for both Suzuki and Heck cross-coupling reactions. The catalyst system is recyclable with no noticeable change in activity. Isolation of the catalyst involves simple filtration of the solid-supported Pd. In cases were the substrate was soluble, water was used as the solvent. Both electron-donating and electron-withdrawing groups on the bromo-arene are tolerated.

Experimental Section

All chemicals were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 500 or 300 and at 125 or 75 MHz respectively, in $CDCl_3$ unless otherwise noted. Proton and carbon chemical shifts are expressed in ppm relative to internal tetramethylsilane; coupling constants (*J*) are expressed in Hertz. Melting points were measured on a Büchi 535 melting point apparatus. Pd contents were measured by ICP analysis method at Novartis or in Robertson Microlit Lab after the reaction mixture was filtered, then extracted with ethyl acetate, washed with water, dried, and concentrated to dryness.

General Procedure for the Preparation of Pd−Smopex-111. To a N_2-purged three-necked round-bottomed flask fitted with an overhead stirrer and an internal thermometer were added $Pd(OAc)_2$ (2.0 g, 8.92 mmol) and toluene (100 mL). The mixture was heated to 70 °C internally for 15 min to give a solution with traces of suspended particles present. The insoluble material was filtered off using a syringe filter, and the resulting solution was placed in a clean, inerted three-necked, round-bottomed flask fitted with an overhead stirrer and an internal thermometer. To the palladium acetate solution was added Smopex-111 (18.0 g) and the mixture heated to 70 °C internally for 5 h. After heating, the mixture was stirred at 17 °C for 12 h. The mixture was filtered, and the solids were washed twice with 100 mL of toluene. The isolated solid was placed in a vacuum oven (50 mbar, 40 °C) for 12 h. The resulting brown solid weighed 19.92 g and contained 4.32% Pd by weight based on the ICP analysis of the digested complex.

General Procedure for Heck Couplings with Pd−Smopex-111 in *N*-Methyl-2-pyrrolidione (NMP). To a N_2-purged 50-mL round-bottomed flask were added 4-bromoacetophenone (2.0 g, 10 mmol), butyl acrylate (1.68 g, 13 mmol), *N*,*N*-diisopropylethylamine (1.68 g, 13 mmol), Pd−Smopex-111 (0.8 g , 2.5%), and *N*-methyl-2-pyrrolidinone (NMP, 10 mL). The resulting mixture was heated at 118 °C for 16 h, and the reaction was monitored by HPLC. After the completion of the reaction, the mixture was cooled to room temperature and filtered through Celite. The filtrate was diluted with 50 mL of ethyl acetate and washed with two 10-mL portions of water. The organic layer was dried over $MgSO_4$ and concentrated to dryness under pressure.

General Procedure for Suzuki Couplings with Pd−Smopex-111 in Toluene. To a N_2-purged 25-mL round-bottomed flask were added 4-bromoacetophenone (500 mg, 2.51 mmol), phenyl boronic acid (389 mg, 3.19 mmol), $K_3PO_4 \cdot H_2O$ (1.15 g, 5.0 mmol), Pd−Smopex-111 (140 mg, 2.5%), toluene (4 mL). and water (1 mL). The mixture was heated to 95 °C for 2.5 h. Upon completion of the reaction, the mixture was filtered through Celite, and the filtered solids were washed with 40 mL of toluene in two portions followed by 40 mL of water in two portions. The aqueous layer was discarded, and the organic layer was dried with Mg_2SO_4. The organic layer was concentrated and placed in a vacuum oven (50 mbar, 40 °C) for 12 h to give a white solid (475 mg, 97%) which was examined for Pd. The resulting solid was found to be pure by HPLC and NMR.

General Procedure for Suzuki Couplings with Pd−Smopex-111 in Water. To a N_2-purged 25-mL round-bottomed flask were added 4-bromophenylacetic acid (1.0 g, 4.64 mmol), phenyl boronic acid (0.74 g, 6.07 mmol), K_2CO_3 (1.92 g, 13.9 mmol), Pd−Smopex-111 (280 mg, 2.5%), and water (9.3 mL). The mixture was heated at 98 °C for 2.5 h. Upon completion of the reaction, the mixture was filtered through Celite, and the filtered cake was washed with 40 mL of water in two portions. The aqueous layer was extracted with 40 mL of ethyl acetate in two portions. The aqueous layer was acidified by adding 30 mL of 1 N HCl to give a white precipitate. The solid was collected by vacuum filtration, washed with 10 mL of water, and placed in a vacuum oven (50 mbar, 40 °C) for 12 h. The resulting white solid (928 mg, 91%) was examined for Pd. The resulting solid was pure by HPLC and NMR.

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