The Actual Active Species of Sulfur-Modified Gold-Supported Palladium as a Highly Effective Palladium Reservoir in the Suzuki–Miyaura Coupling

Naoyuki Hoshiya,^{a,b} Satoshi Shuto,^a and Mitsuhiro Arisawa^{a,*}

^a Faculty of Pharmaceutical Sciences, Hokkaido University, Kita 12, Nishi 6, Kita-ku, Sapporo 060-0812, Japan Fax: (+81)-11-706-3769; e-mail: arisawa@pharm.hokudai.ac.jp

^b Furuya Metal Company Limited, Tokyo 170-0005, Japan Received: October 30, 2010; Revised: January 18, 2011; Published online: March 15, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000820.

Abstract: The actual active species of the recently	an excellent Pd reservoir for liquid-phase combinato-
developed sulfur-modified, gold-supported palladium	rial synthesis.
material, S-modified Au-supported Pd (SAPd), with	
one of the lowest Pd-releasing levels and high recy-	
clability in the Suzuki-Miyaura coupling, was investi-	Keywords: C–C coupling; combinatorial chemistry;
gated. Also, SAPd was found to work repeatedly as	green chemistry; heterogeneous catalysis; palladium

Introduction

Liquid-phase combinatorial parallel synthesis^[1] is an effective method for the generation of a diverse library of small molecules, and it has been used not only in the field of drug discovery^[2] but also in organic materials.^[3]

Palladium-catalyzed reactions allow for the rapid access to a diverse range of compounds, but they also present a problem in that the palladium can often be retained in the product even after the purification steps. For pharmaceutically active ingredients, there are typically strict guidelines to limit the levels of contaminating heavy metals, including palladium, in the drug.^[4]

In an effort to create re-usable, Pd leach-free catalysts, many heterogeneous catalysts have been developed with Pd immobilized on supports such as activated carbon, inorganic solids and polymers.^[5] Yet few of these immobilized Pd catalysts for C–C bond formations can claim both high recyclability (more than 10 cycles) and low Pd leaching (less than 1 ppm). Furthermore, there have been no palladium catalysts, which repeatedly work well in liquid-phase combinatorial synthesis with low Pd leaching.

Most recently, our group has developed a practical Pd material, namely *S*-modified *Au*-supported *Pd*, SAPd [6]. Due to the lowest recorded Pd-releasing levels (less than 1 ppm in 3 mL of solvent, TON up to 2,760,000) and high recyclability (more than 10 cycles)

in the Suzuki–Miyaura coupling, this is one of the best Pd materials developed thus far. Because SAPd leaches extremely low levels of Pd into reaction mixtures, removal of the residual Pd becomes unnecessary, even in the syntheses of pharmaceutical ingredients.

With this background, we continued our chemical experiments to determine how SAPd works in the Suzuki–Miyaura coupling. Thus, the actual active species of SAPd and its application to liquid-phase combinatorial chemistry were investigated. It is noteworthy that SAPd has proven to be a very effective Pd material for liquid-phase combinatorial synthesis and SAPd is repeatedly used for synthesizing structurally diverse molecules by the Suzuki–Miyaura coupling without contamination of substrates or products. Here we report the results of these studies.

Results and Discussion

The Actual Active Species of SAPd

In the development of a novel heterogeneous catalyst, identification of the actual active species is highly important. First, we performed kinetic studies/filtration tests and compared the time conversion plots by following 3 reactions to investigate whether the leached Pd species had catalytic activity for the Suzuki-Miyaura coupling (Figure 1).^[7] A mixture of **1a**



Figure 1. Filtration test.

(0.5 mmol), **2a** (1.5 equiv.), K_2CO_3 (2 equiv.), and SAPd (14 mm × 12 mm), which contained $38 \pm 9 \mu g$ of Pd, was heated at 80 °C in EtOH (3 mL) without stirring for 12 h (reaction a). The coupling proceeded efficiently to give the product **3a** in 92% yield after 12 h. The same reaction was performed for 1.5 h and, after cooling the mixture to room temperature, SAPd was removed from the 'cold' mixture. Then, the resulting solution was heated continuously at 80 °C

without SAPd for 10.5 h (reaction b). Reaction c was carried out in the same manner except that SAPd was removed after 30 min from the start (reaction c). In reaction c, only a trace amount of 3a resulted (less than 3%). On the other hand, in reaction b, the product increased time-dependently, after removal of the catalyst from the reaction mixture, and the yield of 3a reached almost 80% after 12 h. Hence, the yield of 3a continuously increased even in the absence of SAPd. Moreover, a lag time is observed in reactions a and b. Thus, it is conceivable that it takes time for the actual active Pd species to be released to the reaction mixture from SAPd. These results suggest that SAPd might work as an effective Pd reservoir for the following reasons. It is known that Pd is strongly retained in SAPd, and during the Suzuki-Miyaura coupling, a trace of the Pd species is released from SAPd into the reaction mixture. The released Pd species has an extremely high catalytic activity in the Suzuki-Miyaura coupling, since the reaction is complete with only a trace^[8] amount of the Pd species.

Next, we performed a three-phase test^[9] to determine which soluble or insoluble species is the actual active catalyst by carrying out a metal-catalyzed reaction with a substrate immobilized on a polymer. We prepared the immobilized iodobenzene **6** according to the Davies' protocol.^[9a] The immobilized **6** is known to be inactive with the insoluble Pd catalyst but active with the soluble Pd catalyst. Therefore we investigated the Suzuki–Miyaura coupling using **6**. After the reaction, the resulting mixture was treated with an excess of trifluoroacetic acid (TFA) to remove the desired coupling product from the polymer by breaking the amide bond. The Suzuki–Miyaura coupling of **2b** and **6** was performed in the presence of SAPd and K₂CO₃ in EtOH (Figure 2, [case 1] and entry 1). After



Figure 2. Three-phase test.

744 asc.wiley-vch.de

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Figure 3. Plausible mechanism of SAPd.

heating the reaction mixture at 80 °C for 12 h, we then removed the catalyst and filtered the resulting reaction mixture through Celite 545. The resin was treated with TFA at room temperature for 2 h to give only the iodobenzene derivative **7** in 78% yield. As a control, we carried out the Suzuki–Miyaura coupling of **2b** in the presence of two other iodobenzenes, **1b** and **6**, for 12 or 24 h under the same reaction conditions ([case 2] and entries 2 and 3). In both cases, the coupling product **8** was obtained in 6% and 32% yields, respectively. These results are identical with those of the previous filtration tests, namely Pd is strongly retained in SAPd. Furthermore, during the Suzuki–Miyaura coupling, a trace amount of the Pd species was released from SAPd into the reaction mixture. The released Pd species has an extremely high catalytic activity in the Suzuki–Miyaura coupling, since the reaction was completed with only a trace of the Pd species. Furthermore, the three-phase test might suggest that a soluble iodobenzene, such as **1b**, could be a key participant in the mechanism of the Pd release, probably at the oxidative addition step, because **8** was not obtained without **1b** (Figure 2, [case 1]). Soluble boronic acid does not affect the results (Figure 2, [cases 1 and 2]).^[10] Thus, as shown in Figure 3, it is possible that the oxidative addition of **1b** to the Pd supported on SAPd initiates the release of the active Pd species into the reaction mixture. The reaction rate in repeatedly use was also examined (Figure 4).



Figure 4. Reaction rate in repeated use.

Adv. Synth. Catal. 2011, 353, 743-748

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

SAPd as a Pd Reservoir for Liquid-Phase Combinatorial Synthesis

It is widely known that, when polymer-supported Pd is used, the reaction suffers from contamination problems and the catalyst has to be washed very carefully due to the strong absorption of the starting material and/or the product to the polymer. In dramatic contrast, SAPd has a much smaller surface area and could absorb many fewer organic compounds, including starting materials or products, than those of polymer-supported Pd, due to its low affinity for organic molecules. Moreover, the Au mesh, used as the support for Pd in SAPd, is malleable and easy to handle with a pair of tweezers. Combinatorial synthesis is an important technique in medicinal chemistry and is widely used for drug development. However, no practical solid-supported Pd, which can be repeatedly used for different kinds of coupled products synthesis, was known until now.^[11] Considering the above-mentioned advantages, SAPd may indeed be an ideal solid catalyst for combinatorial synthesis. Consequently, we tried liquid-phase combinatorial synthesis with SAPd by changing the iodobenzene derivatives as the substrates.

When SAPd was used in the Suzuki–Miyaura coupling of phenylboronic acid **2b** and ten different iodobenzenes with K_2CO_3 in EtOH, as shown in Table 1, the yields for runs 1 to 10 were excellent to quantitative in all cases (Table 1). In these reactions, products with high purity^[12] were obtained after the usual aqueous work-up. Not only did the aromatic iodide (runs 1–7) react with **2b** to give the coupling products in quantitative yields but also both the heterocyclic iodides (runs 8 and 9) and the styrenyl iodide reacted (run 10). This was likewise the case when the boronic acid derivative was changed (Table 2). Therefore it was found that SAPd was an effective Pd reservoir for this kind of synthesis without any contamination with other products or starting materials.

SAPd was repeatedly used in the above Suzuki-Miyaura couplings. A solution of SAPd (*ca.* 1 cm^2), phenylboronic acid **2b** (1.5 equiv.), an aryl bromide (0.5 mmol), and K₂CO₃ (2 equiv.) was heated in EtOH (3 mL) at 80 °C for 12 h. After the usual aqueous work-up, the corresponding product **3** was obtained in high purity. The SAPd was removed from the reaction mixture and used repeatedly.

Conclusions

In summary, we have demonstrated that SAPd, with the lowest Pd-releasing levels and high recyclability in the Suzuki–Miyaura coupling, works as a Pd reservoir and releases the catalytically active Pd species, which renders it one of the best Pd materials for liquidTable 1. Examples of liquid phase combinatorial chemistry using SAPd.^[a]



^[a] The SAPd was repeatedly used to the above Suzuki-Miyaura couplings. A solution of SAPd (*ca.* 1 cm²), phenylboronic acid **2b** (1.5 equiv.), an aryl iodide (0.5 mmol) and K_2CO_3 (2 equiv.) was heated in EtOH (3 mL) at 80 °C for 12 h. After usual aqueous work-up, the corresponding high quality product **3** was obtained. SAPd was taken out from the reaction mixture and used repeatedly.

phase combinatorial synthesis. One preparation of SAPd can be repeatedly used for different kinds of substrates while furnishing the desired products without any contamination.

Experimental Section

Preparation of SAPd

A $14 \times 12 \text{ mm}^2$ (100 mesh) sample of Au was placed in 35% H₂O₂ aqueous solution (1 mL) and concentrated H₂SO₄ (3 mL) for 3 min and then rinsed in succession with H₂O (3 mL×10) and EtOH (3 mL×5). The sample was placed in a flask and dried for 10 min under reduced pressure (*ca.* 6 mmHg). The resulting sulfur-modified Au [S-Au] was placed in a solution of Pd(OAc)₂ (5.3 mg, 0.023 mmol) in xylene (3 mL) and stirred at 100 °C for 12 h under an argon atmosphere. Then the plate was rinsed with xylene (3 mL×100) and dried under vacuum. The sample was placed in

Table 2. Examples of liquid phase combinatorial chemistry using SAPd.^[a]





^[a] The SAPd was repeatedly used to the above Suzuki-Miyaura couplings. A solution of SAPd (*ca.* 1 cm²), a phenylboronic acid (1.5 equiv.), iodobenzene **1b** (0.5 mmol) and K_2CO_3 (2 equiv.) was heated in EtOH (3 mL) at 80 °C for 12 h. After usual aqueous work-up, the corresponding high quality product **3** was obtained. SAPd was taken out from the reaction mixture and used repeatedly.

xylene (3 mL) and heated at 135 °C for 12 h. The sample was rinsed with xylene (3 mL×50) and dried under vacuum for 10 min to give SAPd (Pd: $38\pm$ 9 µg).

Typical Experimental Procedure of Successively Suzuki–Miyaura Coupling Changed Substrates for Each Reaction [Table 1, 1st Run]

A mixture of iodobenzene (102 mg, 0.5 mmol), phenylboronic acid (91.4 mg, 0.75 mmol), and K_2CO_3 (138 mg, 1.0 mmol) in EtOH (3 mL) was heated in the presence of SAPd (14×12 mm, Pd: 38±9 µg) at 80 °C for 12 h under an argon atmosphere without stirring. After the reaction mixture had been cooled to room temperature, the SAPd plate was removed from the reaction mixture and rinsed several times with EtOH. The reaction mixture was poured into 2M aqueous NaOH and extracted with AcOEt. The organic layer was washed saturated aqueous NH_4Cl , and satuarted aqueous NaCl, dried over anhydrous MgSO₄, concentrated under vacuum to give biphenyl in quantitative yield as a colorless solid.

The recovered SAPd was again subject to the above reaction conditions as a 2nd run. This procedure was repeated a total 10 runs.

Acknowledgements

This research was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and Adaptable and Seamless Technology Transfer Program through target-driven R & D, Japan Science and Technology Agency (JST), Japan.

References

- [1] R. Martínez-Palou, Mol. Diversity 2006, 10, 435.
- [2] S. Fergus, A. Bender, D. R. Spring, Curr. Opin. Chem. Biol. 2005, 9, 304–309. 528.
- [3] C. A. Briehn, M.-S. Schiedel, E. M. Bonsen, W. Schuhmann, P. Bäuerle, *Angew. Chem.* 2001, *113*, 4817–4820; *Angew. Chem. Int. Ed.* 2001, *40*, 4680–4683.
- [4] C. E. Garrett, K. Prasad, Adv. Synth. Catal. 2004, 346, 889–900.
- [5] Reviews: a) N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* 2006, *348*, 609–679; b) L. Yin, J. Liebscher, *Chem. Rev.* 2007, *107*, 133–173; c) M. Lamblin, L. Nassar-Hardy, J.-C. Hierso, E. Fouquet, F.-X. Felpin, *Adv. Synth. Catal.* 2010, *352*, 33–79.
- [6] N. Hoshiya, M. Shimoda, H. Yoshikawa, Y. Yamashita, S. Shuto, M. Arisawa, J. Am. Chem. Soc. 2010, 132, 7270–7272.
- [7] a) J. A. Widegren, R. G. Finke, J. Mol. Catal. A 2003, 198, 317-341; b) J. A. Widegren, M. A. Bennett, R. G. Finke, J. Am. Chem. Soc. 2003, 125, 10301-10310; c) D. A. Conlon, B. Pipik, S. Ferdinand, C. R. LeBlond, J. R. Sowa Jr, B. Izzo, P. Collins, G.-J. Ho, J. M. William, Y.-J. Shi, Y. Sun, Adv. Synth. Catal. 2003, 345, 931-935; d) C. Baleizao, A. Corma, H. Garcia, A. Leyva, J. Org. Chem. 2004, 69, 439-446; e) K. Yu, W. Sommer, J. M. Richardson, M. Weck, C. W. Jones, Adv. Synth. Catal. 2005, 347, 167-171; f) M. Diéguez, O. Pàmies, Y. Mata, E. Teuma, M. Gómez, F. Ribaudo, P. W. N. M. van Leeuwen, Adv. Synth. Catal. 2008, 350, 2583-2598; g) K. Köhler, R. G. Heidenreich, S. S. Soomro, S. S. Pröckl, Adv. Synth. Catal. 2008, 350, 2930-2936; h) L. Huang, P. K. Wong, J. Tan, T. P. Ang, Z. Wang, J. Phys. Chem. C 2009, 113, 10120-10130.
- [8] The Pd leached into the reaction mixture was only 76– 38 ng for a 1 mmol scale preparation (12.7–6.3 ppb in 3 mL of solvent, 0.2–0.1% of Pd from SAPd). See ref.^[6]
- [9] a) J. Rebeck, F. Gavina, J. Am. Chem. Soc. 1974, 96, 7112; b) J. P. Collmann, K. M. Kosydar, M. Bressan, W. Lamanna, T. Garrett, J. Am. Chem. Soc. 1984, 106, 2569; c) I. A. Davies, L. Matty, D. L. Heghes, P. J.

Reider, *J. Am. Chem. Soc.* **2001**, *123*, 10139–10140; d) B. H. Lipshutz, S. Tasler, W. Chrisman, B. Spliethoff, B. Tesche, *J. Org. Chem.* **2003**, *68*, 1177–1189.

- [10] When 5 mol% of Pd(OAc)₂ was used instead of SAPd,
 8 was obtained quantitatively. When the amount of Pd(OAc)₂ was reduced to less than 0.07 mol%, no 8 was obtained.
- [11] Previously reported combinatorial Suzuki-couplings, see: Y. Uozumi, Y. Nakai, Org. Lett. 2002, 4, 2997– 3000.
- [12] The products were pure enough by ¹H NMR spectroscopy. See Supporting Information.