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Ligand-Free Buchwald–Hartwig Aromatic Aminations of Aryl Halides Catalyzed by Low-Leaching and Highly Recyclable Sulfur-Modified Gold-Supported Palladium Material

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Abstract: A stable heterogeneous catalyst precursor, sulfur-modified gold-supported palladium material (SAPd), has proved to be an excellent source of leached, ligand-free, Pd for the amination of aryl bromides and chlorides. The reaction-enabling catalyst is provided *in situ* as leached Pd in low catalyst loading (0.21 ± 0.02 mol%). This allows the precatalyst (SAPd) to be filtered off and used for a minimum of ten reaction cycles without loss of catalytic activity. SAPd released only trace amounts, less than 0.6 ppm, of highly active Pd during the reaction without any aggregation.

Keywords: amination; cross-coupling; gold; ligand effects; palladium; supported catalysts

Introduction

Arylamines are widely used in the synthesis of pharmaceutical intermediates, natural products, dyes, agrochemicals and polymers in both academic and industrial laboratories.[1] Arylamines have also been shown to be useful as ligands for transition metal catalysis.[2]

The palladium-catalyzed cross-coupling of aryl halides and tin amides to generate arylamines in homogeneous systems was first studied by Migita et al.[3] Using Pd-methodology, an almost simultaneous landmark development was carried out by the Buchwald and Hartwig groups under relatively mild conditions.[4] Shortly thereafter, a variety of effective ligands were reported for the development of Pd-catalyzed aromatic aminations.[1,5] Even though various transition metals, such as Fe,[6] Cu,[7] Ni[8] and Cd,[9] have been employed in combination with certain ligands for arylamine synthesis, the Pd methodology is still of great interest because of its better functional group compatibility, one-step reaction and mild reaction conditions.[10]

Although Pd-catalyzed reactions are an important method for rapidly accessing arylamines, the previously reported Pd-catalyzed aromatic aminations all rely on various sophisticated ligands. These ligands are designed to accelerate oxidative addition, to enhance reductive elimination and sometimes to prevent β-hydride elimination.[5e,11] A more important function of the ligands is to stabilize the highly active Pd(0) species by preventing them from aggregating in the reaction mixture.[5e,11] Nevertheless the use of ligands has some obvious disadvantages, such as toxicity and often water- and/or air-sensitivity. Ligands can hamper the isolation and purification of the desired products, i.e., they can make it difficult to remove them from the final products. Furthermore, the multistep synthesis and their high cost also restrict ligand application. In order to overcome these issues and meet environmental, safety, and economical standards, ligand-free Pd-catalyzed aromatic aminations would offer a viable, alternative.

We recently discovered the ***S***-modified ***A***u-supported ***Pd***-material (SAPd) to be an excellent immobilized Pd catalyst for the ligand-free Suzuki–Miyaura coupling reaction with low leaching and highly recyclable characteristics.[12] SAPd released only trace amounts of highly active Pd during the reaction without any aggregation. Although, to the best of our knowledge, there is no example of ligand-free Pd-catalyzed aromatic amination, we thought that aromatic amination might proceed without a ligand by using SAPd, in which a very low concentration of active Pd(0) species would not aggregate in order to be available for the catalytic cycle. Thus, we decided to employ the SAPd catalyst for ligand-free catalytic aromatic amination.

Here, we report that SAPd is an excellent catalyst for ligand-free aromatic aminations of various aryl halides, including a chloride, with a variety of amines. Moreover, after reuse for more than ten cycles, clean SAPd was easily recovered merely by washing with solvent.

Results and Discussion

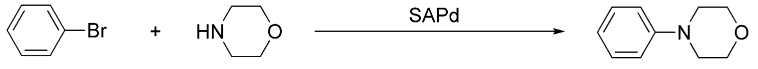
Optimization of the Reaction Conditions

Initially, we examined a model reaction with bromobenzene **1a** and morpholine **2a** to set up the appropriate reaction conditions for the cross-coupling in the presence of SAPd to yield the desired coupled product arylamine **3a** (Table 1). First, the screening of bases was carried out in toluene at 100 °C for 24 h using Cs_2CO_3, K_3PO_4, K_2CO_3 and KOH, in which only a trace of the product **3a** was isolated (entries 1–4). However, we found that by using NaO-*t*-Bu, the yield of the desired coupled product for the 1st cycle was increased to 28%, and for additional cycles, the yield gradually decreased (entry 5). These results showed that the ligand-free aromatic amination actually proceeded with SAPd. When the base was changed to KO-*t*-Bu, the yield of **3a** was improved to 62% for the 1st cycle, while for the additional cycles, the yield slightly decreased (entry 6). Although we tried to find a suitable solvent for the model reaction and tested alcoholic solvents like *t*-BuOH and *n*-PrOH, in accordance with Novak's work,[13] none of the product **3a** was detected (data not shown). We found that when the amount of toluene was decreased, the yield of product **3a** increased (entries 7–10). The reaction at higher temperature also increased the yield of the product **3a** (entry 11). Furthermore, when the reaction was performed at 120 °C or 130 °C in xylene, the yield of the product **3a** also increased (entries 12 and 13). Finally, by setting the exact completion of the reaction time to 7 h, a high yield of the product **3a** was repeatedly obtained from the 1st to the 10th cycles (entry 14).[14] Thus the optimization of the ligand-free SAPd-catalyzed coupling of **1a** (1.0 equiv.) and **2a** (1.4 equiv.) succeeded by the use of KO-*t*-Bu (1.4 equiv.) as the base in xylene (1.0 mL) at 130 °C for 7 h.

Time Course Experiments

We next studied the reaction time course of the SAPd-catalyzed aromatic amination between **1a** and **2a** in repeated use according to the best reaction conditions (Table 1, entry 14, reaction of 0.7 mmol of bro-

Table 1. Optimization of the SAPd-catalyzed amination reaction.[a]



1a **2a** **3a**

Entry	Base	Solvent (mL)	Temperature [°C][b]	Time [h]	**3a** (Yield [%])[c]									
					1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
1	Cs_2CO_3	toluene (3.0)	100	24	trace									
2	K_3PO_4	toluene (3.0)	100	24	trace									
3	K_2CO_3	toluene (3.0)	100	24	trace									
4	KOH	toluene (3.0)	100	24	trace									
5	NaO-*t*-Bu	toluene (3.0)	100	24	28	17	16	20	15					
6	KO-*t*-Bu	toluene (3.0)	100	24	62	61	57	58	54	58	58	53	53	53
7	KO-*t*-Bu	toluene (2.0)	100	24	68	68	66	67	35	31				
8	KO-*t*-Bu	toluene (1.5)	100	24	74	70	72	71	37	35				
9	KO-*t*-Bu	toluene (1.0)	100	24	82	81	82	49	49					
10	KO-*t*-Bu	toluene (1.0)	100	12	74	73	75	73	53	48	43	43	42	36
11	KO-*t*-Bu	toluene (1.0)	110	12	87	87	79	80	82	76	77	76	73	71
12	KO-*t*-Bu	xylene (1.0)	120	12	88	86	87	86	85	81	74	76	75	79
13	KO-*t*-Bu	xylene (1.0)	130	12	90	88	88	95	89	84	84	77	78	82
14	KO-*t*-Bu	xylene (1.0)	130	7	93	93	92	93	92	92	92	92	91	91

[a] *Reaction conditions:* bromobenzene (0.70 mmol, 1.0 equiv.), morpholine (1.2 equiv.), KO-*t*-Bu (1.4 equiv.).

[b] Bath temperature.

[c] Isolated yield.

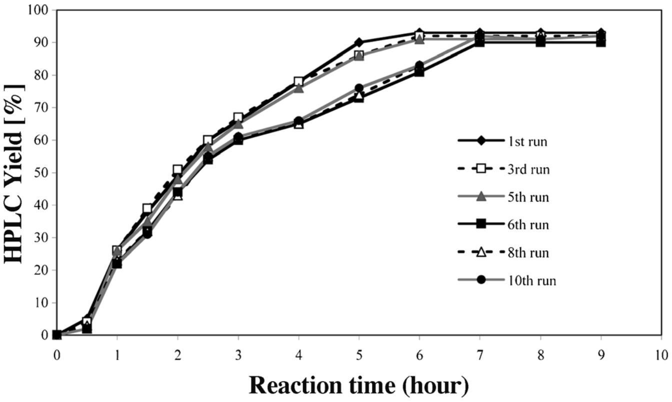


Figure 1. Time course experiments for the coupling of **1a** and **2a**

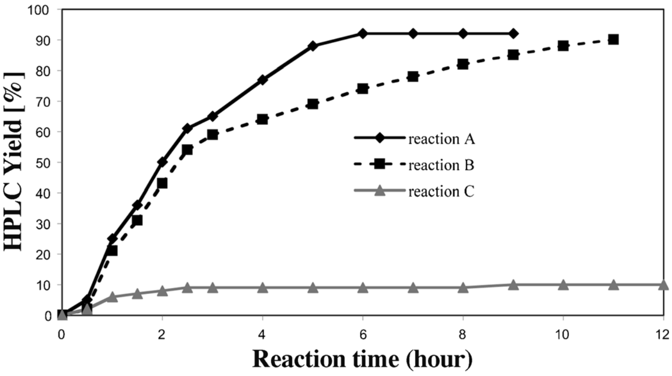


Figure 2. Filtration test for the coupling of **1a** and **2a**

mobenzene). The time course experiments were carried out by monitoring the reactions of the 1st, 3rd, 5th, 6th, 8th and 10th cycles (Figure 1). As shown in Figure 1, 7 h was needed to complete the reaction. These results clearly indicated that, when the reaction time was 7 h, the coupling was complete and the catalytic activity of SAPd was maintained in repeated experiments.

Kinetic Studies/Filtration Test

Since the identification of the actual catalytic species from the immobilized catalyst is very important, we therefore performed kinetic studies/filtration tests and compared the time conversion plots of the following three reactions (A, B and C). These investigations were carried out to confirm whether the leached Pd species possessed catalytic activity for the aromatic amination (Figure 2). Reaction A was performed according to the optimized conditions (Table 1, entry 14) and the reaction proceeded efficiently to give the coupled product **3a** in 93% yield after 7 h. Reactions B and C were also performed under the same conditions with one exception, namely SAPd was removed from the mixture after 2 h or 30 min from the start of the reaction, respectively. Reaction B yielded 90% of the product **3a** after 11 h, whereas, in reaction C, only 10% of the product **3a** was detected after 12 h. Thus, it is likely that the active Pd species are indeed released from SAPd and that it takes some time for release of the active Pd species from SAPd.

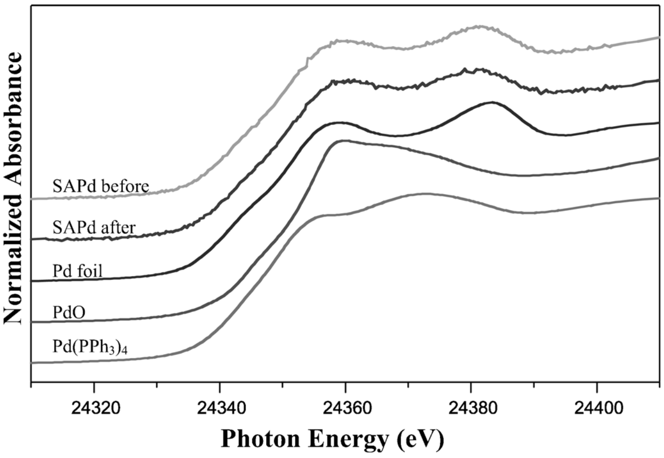


Figure 3. Pd K-edge XANES spectra: SAPd before and SAPd after mean SAPds before and after the 10th cycle of amination reaction.

X-Ray Absorbtion Fine Structure (XAFS) Measurement

In order to obtain information on the properties of Pd in SAPd, we measured the XAFS.[15] Figure 3 shows the Pd K-edge X-ray absorption near edge structure (XANES) spectra of Pd foil, PdO, $Pd(PPh_3)_4$ and SAPds before and after the 10th cycle of the optimized amination reactions (Table 1, entry 14). The Pd K-edge XANES spectra of the SAPds before and after the 10th cycle are the same and are analogous to that of the Pd foil. These results indicate that the Pd species of SAPds before and after use for the 10th cycle of the amination reactions are the same, and the Pd on SAPd seems to be zero valent Pd or metallic Pd.

Measurement of the Pd Amount in SAPd and in the Reaction Mixture

We next measured the amount of immobilized Pd in SAPd and also the leached Pd in the reaction mixture by inductively coupled plasma mass spectroscopy (ICP-MS). The immobilized Pd in SAPd was measured before and after the 10th cycle of the optimized reactions (Table 1, entry 14). As shown in Table 2, the

Table 2. Amount of Pd in the reaction mixture of **1a** with **2a**[a] and on SAPd itself.

Amount of leached Pd (ng) in the reaction mixture[b,c,d]											Immobilized Pd on SAPd itself (µg)[c]	
1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Total	before use	after use
588±494 (0.6)	359±204 (0.4)	61±25 (0.06)	231±64 (0.2)	202±51 (0.2)	419±152 (0.4)	294±94 (0.3)	205±47 (0.2)	339±85 (0.3)	320±65 (0.3)	3063±1248	79±11[20]	68±18[21]

[a] *Reaction conditions:* **1a** (0.32 mmol), **2a** (1.2 equiv.), KO-*t*-Bu (1.4 equiv.), xylene (1.0 mL), 130 °C, 7 h.

[b] The entire reaction mixture was acidified and subjected directly to ICP-MS measurement.

[c] The standard deviation was calculated from 2 sets of samples.

[d] Numbers in parentheses indicate the amount of leached Pd in ppm.[22]

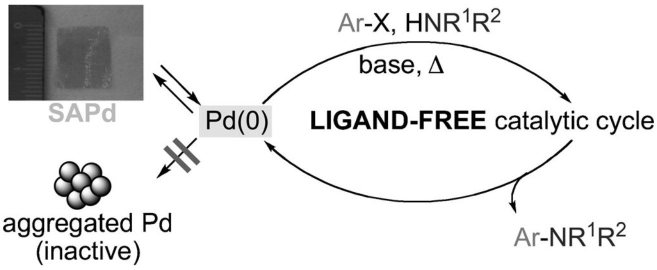


Figure 4. General scheme for ligand-free aromatic aminations catalyzed by SAPd without aggregation.

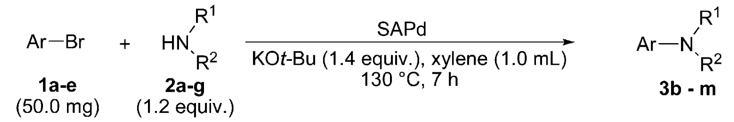
amounts of immobilized Pd in SAPd before and after the reactions were 79±11 µg and 68±18 µg, respectively. The amount of released Pd after cooling in each cycle was extremely low [61–588 ng (0.06–0.6 ppm) for a 0.32 mmol scale reaction][16] and the amount of Pd is far lower than the U.S. government-required value of residual metal in the product streams.[17] Moreover, SAPd is highly recyclable (more than 10 cycles). Thus, to the best of our knowledge, as a Pd-catalyzed aromatic amination, this is not only the first ligand-free example but also the best example of a low leaching (less than 0.6 ppm) and highly recyclable (more than 10 cycles) catalyst using immobilized Pd.[18,19]

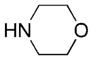
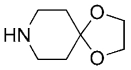
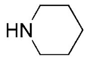
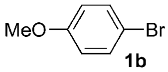
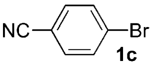
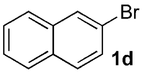
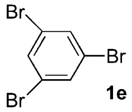
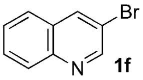
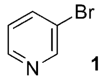
The results of the above experiments show that the SAPd is an excellent Pd reservoir during the amination reaction to release traces of highly reactive Pd (less than 0.6 ppm) in the reaction mixture.[14] Therefore, the low Pd concentrations suppress the aggregation of Pd and allow the reaction to be effectively catalyzed. Thus, a general scheme for the SAPd-catalyzed ligand-free Buchwald–Hartwig amination can be postulated as shown in Figure 4.

Scope and Limitations

Our first aim was to generalize the reaction by using bromobenzene **1a** as a substrate with a variety of secondary amines. It is noteworthy that SAPd catalyzed the aromatic amination of **1a** with various amines without losing catalytic activity from the 1st to 10th cycles (Table 3). For instance, when **1a** was coupled with cyclic amines, i.e., morpholine **2a**, 1,4-dioxa-8-azaspiro[4.5]decane **2b** and piperidine **2c**, the average yields of products **3a**, **3b** and **3c** were 92%, 91% and 96%, respectively (entries 1–3). The reactions of an acyclic secondary amine, *n*-dibutylamine **2d** and an aromatic secondary amine, *N*-methylaniline **2e** with **1a** yielded the corresponding coupling products **3d** and **3e** in 97% and 92% average yield, respectively (entries 4 and 5). We then explored the reaction of **1a** with primary amines, such as benzylamine **2f** and cyclohexylamine **2g**, in which the corresponding mono-

Table 3. Aromatic aminations of various aryl bromides with a variety of amines using SAPd.



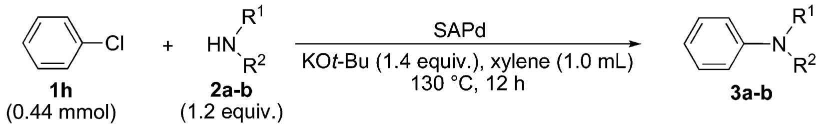
Entry	Ar—Br	HNR^1R^2	Yields (%)[a] 1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Average yields (%)
1[b]	PhBr **1a**	 **2a**	93	93	92	93	92	92	92	92	91	91	**92**
2	**1a**	 **2b**	93	92	92	94	92	93	92	91	92	92	**92**
3	**1a**	 **2c**	97	97	97	95	96	96	95	96	96	95	**96**
4	**1a**	$n\text{Bu}_2\text{NH}$ **2d**	98	97	99	97	97	96	96	96	96	96	**97**
5	**1a**	PhNHMe **2e**	93	91	92	93	92	92	91	92	92	91	**92**
6[c]	**1a**	BnNH_2 **2f**	89	89	88	89	88	89	88	88	88	88	**88**
7[c]	**1a**	$c\text{HexNH}_2$ **2g**	92	92	92	92	89	88	92	92	89	91	**91**
8	 **1b**	**2a**	92	92	91	92	91	92	91	91	92	90	**91**
9	 **1c**	**2a**	89	88	89	88	88	87	89	88	88	87	**88**
10	 **1d**	**2a**	92	92	91	90	91	92	91	91	91	91	**91**
11[d]	 **1e**	**2a**	86	86	85	85	85	85	86	85	85	85	**85**
12	 **1f**	**2a**	89	91	91	90	90	90	90	90	90	90	**90**
13[e]	 **1g**	**2a**	86	87	87	88	87	87	87	86	87	87	**87**

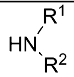
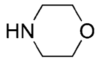
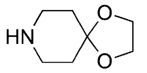
[a] Isolated yields.
[b] The results described in Table 1, entry 14.
[c] Monoarylated product was isolated.
[d] 3.6 equiv. of amine and 4.0 equiv. of KO-*t*-Bu were used to give the corresponding triaminated product.
[e] The reaction was carried out at 120 °C.

arylated products **3f** and **3g** were obtained in average yields of 88% and 91%, respectively (entries 6 and 7). However, the reaction of biphenylamine was not successful because biphenylamine was decomposed under our optimized conditions.

We next examined the coupling reactions among a variety of aryl bromides with **2a**. Thus, when 4-bromoanisole **1b**, having an electron-donating methoxy group, was treated with **2a**, the corresponding product **3h** was obtained in an average yield of 92% (entry 8). 4-Bromobenzonitrile **1c**, with an electron-withdrawing cyano group, also coupled successfully with **2a**, where the average yield of the product **3i** was 88% (entry 9). In the reaction of a fused aryl bromide, 2-bromonaph-

Table 4. Aromatic aminations of chlorobenzene **1h** with amines, **2a** and **2b** using SAPd.



Entry		Yields (%)[a]										Average yields (%)
		1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	
1	 **2a**	89	89	89	88	88	89	89	88	88	87	**88**
2	 **2b**	94	94	94	92	93	93	92	92	91	91	**93**

[a] Isolated yields.

thalene **1d** and **2a**, the coupled product **3j** was obtained in 91% average yield (entry 10). Interestingly, the aryl tribromide, 1,3,5-tribromobenzene **1e** underwent the coupling reaction with **2a** to give the triaminated product **3k** in an average yield of 85% (entry 11). Heterocyclic bromides also coupled with amine to give the corresponding products in excellent yields (entries 12 and 13). The reaction of aryl iodides under our reaction conditions afforded the corresponding product in lower chemical yield than that of aryl bromide.

Aminations of Aryl Chloride

Although a few immobilized Pd-catalyzed aminations of aryl chlorides as the substrate have been reported,[13,18,23] these reactions are not ligand-free, and the catalysts used are not low leaching (<1 ppm) nor are they highly recyclable (>10 times). Thus, we next examined the ligand-free cross-coupling of the less reactive chlorobenzene **4** using SAPd repetitively for 10 cycles (Table 4). Thus when **4** was treated with **2a** or **2b**, according to the optimized conditions (Table 1, entry 14), after 12 h, the corresponding coupling products **3a** and **3b** were successfully obtained with average yields of 88% and 93%, respectively (entries 1 and 2).

SAPd has a much smaller surface area and could absorb many fewer organic compounds, including starting materials or products, than that 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. Considering the above-mentioned advantages, we tried liquid-phase combinatorial synthesis with SAPd by changing the aromatic chloride derivatives or the amines as the substrates.

When SAPd was used in the Buchwald–Hartwig reaction of phenyl chlorides **1** and theree different amines **2** with *t*-BuOK in xylene, as shown in Table 5, the yields for runs 1 to 7 were excellent to quantitative in all cases. In these reactions, products with high purity were obtained after the usual aqueous work-up. 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.

Conclusions

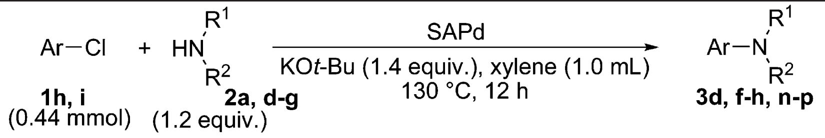
In summary, we have presented a new, efficient method for ligand-free aromatic aminations catalyzed by SAPd, an excellent reservoir of Pd, where various aryl bromides and chlorides were effectively coupled with a variety of amines. In the reactions, only a trace of the active Pd species (less than 0.6 ppm for a 0.32 mmol scale reaction, one of the lowest recorded in the literature) was released from SAPd. Moreover, the low leaching property of SAPd makes it recyclable for more than 10 cycles without loss of catalytic activity. Efforts to clarify details of the physical and chemical properties of SAPd and its applications to other ligand-free cross-coupling reactions are currently in progress.

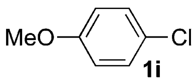
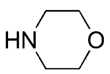
Experimental Section

Preparation of Sulfur-Modified Gold-Supported Palledium Material (SAPd)[12]

The Au (100 mesh – 14×12 mm^2, 100.7 mg) was placed in the piranha solution [prepared *in situ* by 35% H_2O_2 aqueous solution (1.0 mL) and concentrated H_2SO_4 (3.0 mL)] for 5 min and then washed first by H_2O (3.0 mL×10) and then

Table 5. Example of liquid-phase combinatorial chemistry; aomatic aminations of chlorobenzenes **1** with amines **2** using SAPd.



Entry	Ar—Cl	HNR¹R²	Yields (%)[a]
1	PhCl **1h**	*n*Bu$_2$NH **2d**	96
2	**1h**	BnNH$_2$ **2f**	89
3	**1h**	*c*HexNH$_2$ **2g**	93
4	 **1i**	 **2a**	93
5	**1i**	**2d**	91
6	**1i**	**2f**	91
7	**1i**	**2g**	94

[a] Isolated yields.

with EtOH (3.0 mL×6). The Au mesh was placed in a round-bottom flask and dried for 10 min under reduced pressure (*ca.* 6 mm Hg). The resulting sulfur-modified Au was placed in a solution of Pd(OAc)$_2$ (5.3 mg, 0.023 mmol) in xylene (3.0 mL) and stirred at 100 °C for 12 h under an argon atmosphere. Then it was rinsed with xylene (3.0 mL × 50) and, after vacuum drying, it was placed in xylene (3.0 mL) and heated at 135 °C for 12 h. Finally, it was rinsed with xylene (3.0 mL×50) and dried under vacuum for 10 min to give sulfur-modified Au-supported Pd material (SAPd, 100.8 mg) and only this SAPd was used throughout this research. As shown in Table 2, the immobilized Pd in SAPd was 79±11 μg.

Typical Experimental Procedure for Buchwald–Hartwig Coupling Reaction using Aryl Bromide Catalyzed by SAPd (Table 3, entry 1)

A mixture of bromobenzene (**1a**, 50.0 mg, 0.32 mmol), morpholine (**2a**, 33.3 mg, 0.38 mmol) and KO-*t*-Bu (50.3 mg, 0.45 mmol) in xylene (1.0 mL) was heated in the presence of SAPd ín a glove box at 130 °C for 7 h. The reaction mixture was cooled to room temperature and SAPd was recovered from the cold reaction mixture and washed several times with xylene. The reaction mixture was poured into water (5.0 mL) and the organic layer was extracted with AcOEt (3×10 mL). The combined organic extracts were washed with brine (3×10 mL) and dried over Na$_2$SO$_4$. Concentration at reduced pressure gave a yellowish oil, which was chromatographed on silica gel with hexane-AcOEt (90:10 v/v) as eluent to give 4-phenylmorpholine (**3a**) as a white solid; yield: 47.1 mg (93%). The recovered SAPd catalyst was again subjected to the above reaction condition as for 2nd cycle and this procedure was repeated for a total 10 cycles.

Typical Experimental Procedure for Buchwald–Hartwig Coupling Reaction using Aryl Chloride Catalyzed by SAPd (Table 4, entry 1)

A mixture of chlorobenzene (**1h**, 50.0 mg, 0.44 mmol), morpholine (**2a**, 46.0 mg, 0.53 mmol) and KO-*t*-Bu (69.0 mg, 0.62 mmol) in xylene (1.0 mL) was heated in the presence of SAPd on glove box at 130 °C for 12 h. The reaction mixture was cooled to room temperature and SAPd was recovered from the cold reaction mixture and washed several times with xylene. The reaction mixture was poured into water (5.0 mL) and the organic layer was extracted with AcOEt (3×10 mL). The combined organic extracts were washed with brine (3×10 mL) and dried over Na$_2$SO$_4$. Concentration at reduced pressure gave a yellowish oil, which was chromatographed on silica gel with hexane-AcOEt (90:10 v/v) as eluent to give the 4-phenylmorpholine (**3a**) as a white solid; yield: 64.6 mg (89%). The recovered SAPd catalyst was again subjected to the above reaction condition as for 2nd cycle and this procedure was repeated for a total 10 cycles.

Supporting Information

Detailed experimental procedures and full characterization data of the compounds are available in the Supporting Information.

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