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COMMUNICATION

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Screening Binary Systems of Chelating Agents Combined with Carbon or Silica Gel Adsorbents: The Development of a Cost-Effective Method to Remove Palladium from Pharmaceutical Intermediates and APIs

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ABSTRACT: The increasing use of palladium catalysts in the synthesis of pharmaceutical intermediates and active pharmaceutical ingredients (APIs) has created the rising need for cost-effective ways to remove the resulting metal contaminants. A simple binary palladium scavenging system was developed using a chelating agent in combination with either activated carbon or silica gel adsorbents. Successful palladium removal was demonstrated on several reaction streams after treating contaminated solutions with the binary system followed by filtration. The binary system is proposed to effectively provide an in situ generated metal scavenger, but typically costs much less than corresponding commercial solid-supported scavengers.

INTRODUCTION

Palladium-catalyzed reactions are widely used in pharmaceutical industry to construct carbon—carbon bonds and carbon—heteroatom bonds. Application of reactions such as the Buchwald—Hartwig coupling, Heck reaction, Negishi coupling, and Suzuki reaction can be found in numerous drug syntheses.[1] A general SciFinder search using the keyword "palladium-catalyzed" gave more than 1500 results for the year 2010, which is a significant increase from the 854 hits in the year 2000 and 289 hits in the year 1990. While palladium-catalyzed reactions are undoubtedly very powerful, they also oftentimes lead to the undesired outcome of contamination of reaction products by palladium. The acceptable limits for residual palladium are quite stringent, with an oral permitted daily exposure (PDE) of 100 μg/day (2 μg/kg/day in a 50 kg person) based on EMEA guidelines.[2]

A variety of methods have been developed to remove palladium and other residual heavy metal contaminants from reaction products.[2−5] In the ideal scenario, palladium contaminants are removed in the product purification processes along with other impurities. In pharmaceutical development, crystallization is the most commonly used technique for product purification and is often very effective in rejecting palladium contaminants.[3] However, when the substrate itself has multiple heteroatoms and resembles a metal ligand, crystallization can become ineffective for palladium removal. In these instances, improved palladium rejection can sometimes be achieved by adding metal chelating agents to increase the solubility of palladium in the mother liquors.[4] Additionally, some compounds are not crystalline, making the use of crystallization to remove palladium contaminants impractical.

Extraction is another commonly used purification technique that is often useful for removal of palladium impurities, particularly when combined with soluble chelating agents capable of metal sequestration.[5] Many nitrogen- or sulfur-containing molecules and polyacids (e.g., cysteine, EDTA, citric acid, lactic acid, and thiourea) have been employed for this purpose.[6]

When crystallization or extraction approaches are ineffective, treatments using solid-phase adsorbents are often employed to remove palladium. Simple and inexpensive silica gel or activated carbon is the ideal adsorbent to be used to remove palladium contaminants. In cases where palladium removal is more difficult, a variety of commercially available specialty scavengers either in loose or column format have been successfully used.[7] The disadvantage of the use of solid adsorbents includes potential product losses during the treatment, leaching of impurities from the adsorbent, and in some cases, formation of new impurities. It should be noted that, while the use of loose adsorbents represents a simple and effective approach at smaller scale, significant problems with this approach may be encountered during filtration and cleaning at larger scale, with the use of columns and cartridges often being preferred.

In recent years, the use of scavengers that contain metal-chelating agents covalently bound to inorganic or polymer supports has become more popular because of their effectiveness, ease of use, broad applicability, and the availability of a variety of different scavenger types. However, the price of these materials is often very high, limiting their application on large scale. Leaching of the functionalizing agents from the scavengers, some of which may be genotoxic or potentially genotoxic (e.g., thiourea), can generate concern. In this contribution, we report the development of a cost-effective method for removing residual palladium contaminants using a binary system that contains a chelating agent along with an activated carbon or silica gel adsorbent. In this system, the chelating agent binds to palladium, and carbon or silica gel then helps to remove the resulting complex from the reaction stream. Alternatively, the chelating agent may first be adsorbed on the solid phase, followed by capture of palladium from solution. The system performs like an in situ generated metal scavenger but is much less expensive than the corresponding commercial solid-supported scavengers.

BACKGROUND

In a recent program, pyrrolidine **1** was synthesized using a Buchwald—Hartwig coupling reaction catalyzed by $Pd(OAc)_2$.[8]

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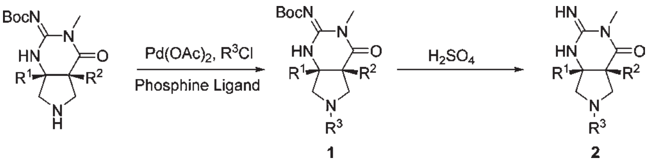
Scheme 1. Synthesis of 1 using a Buchwald−Hartwig coupling



Residual palladium in the solution of **1** was found to be very difficult to remove, presumably owing to the ligand-like structure of the product. Moreover, pyrrolidine **1** is amorphous and cannot be crystallized. After aqueous citric acid washes, the solution of **1** still had over 6000 ppm of palladium (relative to **1**). Furthermore, downstream steps (including aqueous extractions and crystallization) did not promote sufficient palladium removal, making the production of API meeting the required low palladium limits very challenging.

Due to the tight timeline to deliver API for preclinical studies, we screened 30 solid-phase metal scavengers[7a] to examine their ability to remove palladium from a solution of **1**. Thiol-based scavengers, such as Si-thiol and macroporous polystyrene-bound 2,4,6-trimercaptotriazine (MP-TMT) from Biotage[9] and Thiol SAMMS from Steward[10] were found to provide the most efficient palladium removal, but they also led to the formation of a new impurity. Activated carbons alone provided only moderate palladium rejection, often with poor recovery of **1**. Eventually, an immobilized triamine resin (Silicycle *Si*-triamine)[11] was selected because it effectively removed palladium (by ∼98%) with 1.5 weight equivalent of loading and did not cause the formation of any new impurities. *Si*-Triamine was used in a pilot-plant batch on 20-kg scale (based on the starting material in Scheme 1) that produced API with acceptable palladium content (≤33 ppm).

In a subsequent campaign, however, poor performance of palladium removal using *Si*-triamine was observed. Even though the same lot of *Si*-triamine as for previous batch was used, the palladium content in the solution of **1** was only reduced by 88%. Additional treatments with fresh *Si*-triamine or extended treatment time did not reduce the palladium content further. The exact reason for the different performances is unknown; however, this inconsistent performance, along with the price of *Si*-triamine ($1250/kg), prompted us to search for a more effective and inexpensive way to remove palladium in the downstream steps.

Removal of the Boc group on the guanidine moiety of **1** using sulfuric acid provided amine **2** (Scheme 1). Amine **2** forms a salt with sulfuric acid and remains in the aqueous layer. The aqueous solution of **2** was subjected to another round of scavenger screening. From this screening, we found that MP-TMT effectively removed >98% of the palladium in the solution of **2**. However, MP-TMT is too expensive ($11,890/kg)[12] to be used for large-scale production.

Researchers at Bristol-Myers Squibb have demonstrated the use of a combination of 2,4,6-trimercapto-*s*-triazine (TMT), carbon, and diatomaceous earth to effectively remove palladium in a reaction stream.[13] Residual TMT was easily tracked in the process, and no TMT contamination was detected in the product. This precedent, along with the lead results of MP-TMT, prompted us to test the combination of TMT and various activated carbons to remove palladium in the solution of **2**.

Table 1. TMT and carbon treatment to remove palladium from 2[a]

$Pd_{\text{before treatment}}$ (ppm)	Pd_{residual} (ppm)	Pd removed (%)
905	20	98.6
893	25	98.6
2990	33	99.6

[a] Solutions of **2** were stirred with TMT and Nuchar AquaGuard (15 wt % each) at 25 °C for 8 h and then filtered. The filtrate was tested for palladium content.

To our delight, the first experiment showed that treating an aqueous solution of **2** with TMT and the activated carbon, Ecosorb C-941[14] (20 wt % each relative to **1**) for 24 h at rt followed by filtration removed 98.6% of palladium in the solution. After a quick screening of several carbons (Norit, Darco, decolorizing charcoal, and Nuchar) in combination with TMT, we found that they all performed similarly, but Nuchar AquaGuard[15] removed slightly more palladium than other carbons. Stirring a solution of **2** with TMT and Nuchar AquaGuard (15 wt % each) at 25 °C for 8 h followed by filtration consistently removed palladium by ∼99% (Table 1). TMT was not detected in the isolated product (detection limit 0.03 wt % by HPLC). These conditions performed successfully and consistently in the pilot-plant productions without operational issues. The use of TMT (∼$200/kg) and Nuchar ($20-$50/kg) at 0.15 wt equiv loading each created significant savings compared to using *Si*-triamine ($1,250/kg at 1.5 wt equiv loading).

Interestingly, using carbon or TMT alone to treat a solution of **2** did not effectively remove palladium. The use of carbon (Ecosorb C-941) alone only removed 54% of palladium from the solution, and the use of TMT alone only removed 63% of palladium. However, the use of carbon and TMT together afforded 98.6% Pd removal, suggesting a synergistic effect worthy of further study.

■ RESULTS AND DISCUSSIONS

Inspired by the above results, we investigated the possibility of a simple binary metal scavenging system using a chelating agent in combination with either activated carbon or silica gel. Two possible scenarios can be proposed to account for the effectiveness of this approach as depicted in Figure 1. In the first, the chelating agent is adsorbed onto the surface of carbon or silica gel, effectively generating a solid-supported metal scavenger which can then capture palladium from solution. An alternative scenario involves the initial formation of a complex between the chelating agent and palladium, followed by adsorption of the complex by carbon or silica gel. In either case simple filtration allows for effective removal of palladium or other heavy metals from the reaction stream, affording a simple and inexpensive system that greatly reduces the cost associated with the use of commercial solid-supported specialty scavengers.

We selected a few ligands, shown in the following graphic, that are known to be excellent chelating agents for palladium or metals, including thiols, amines, acids, and phosphines.[4c] Several of the selected agents contain multiple functional groups, which may further improve their chelating ability. Most of these chelating agents are quite inexpensive,[16] as compared to specialty solid-supported scavengers that are mostly in the range of several

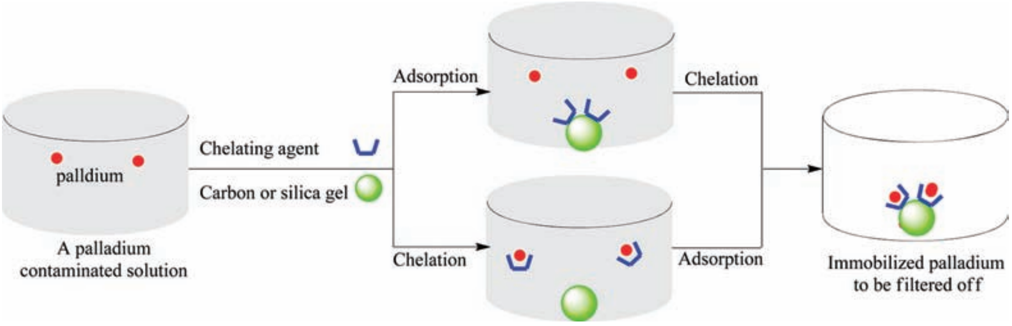


Figure 1. Proposed metal scavenging mechanism of the binary system.

Table 2. Palladium removal from 1 with Nuchar AquaGuard and chelating agents[a]

entry	chelating agent	$Pd_{residual}$ (ppm)	Pd removed (%)
1	Nuchar AquaGuard alone	6450	28
2[b,c]	1,2-ethanedithiol	<286	>97
3[b,c]	ethylenediamine	924	90
4[c]	DPPE	1496	84
5[c]	2-mercaptoethanol	1603	82
6[c]	tris-(2-aminoethyl)amine	1623	82
7[c]	L-cysteine	2013	78
8[c]	2-(dimethylamino)ethanethiol hydrochloride	7929	13

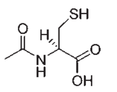
[a] A toluene solution of **1** with 9100 ppm of palladium (relative to **1**) was stirred with Nuchar (70 wt % relative to **1**) in combination with a chelating agent (35 wt % relative to **1**) for 8 h at rt. The resulting mixture was filtered and the filtrate was tested for palladium content. [b] Tested recovery of **1** after the treatment: 94% for entries 2 and 3. [c] At rt, chelating agents in entries 2, 3, 5, and 6 are well soluble in toluene, 7 and 8 are insoluble in toluene, and DPPE has a solubility of about 10 mg/mL in toluene.

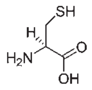
Table 3. Palladium removal from 1 with several solid chelating agents[a]

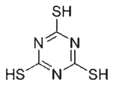
chelating agent	$Pd_{residual}$ (ppm)	Pd removed (%)
N-acetyl cysteine	286	>97
thiosalicyclic acid	328	96
TMT	494	95

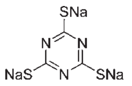
[a] A toluene solution of **1** with 9100 ppm of palladium (relative to **1**) was stirred with a solid chelating agent (35 wt % relative to **1**) for 8 h at rt. The resulting mixture was filtered, and the filtrate was tested for palladium content.

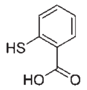
thousand dollars per kilogram. Additionally, most types of silica gel and carbon are inexpensive as well (<\$50/kg).

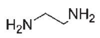

N-acetyl cysteine
\$250/kg

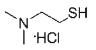

L-cysteine
\$200/kg

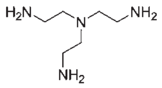

2,4,6-Trimercapto-s-triazine (TMT) \$200/kg

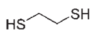

2,4,6-Trimercapto-s-triazine Sodium Salt (TMT-Na)
\$740/kg

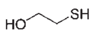

Thiosalicyclic acid
\$200/kg

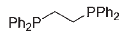

Ethylenediamine
\$20/kg


2-(Dimethylamino)ethanethiol hydrochloride
\$475/kg


Tris(2-aminoethyl)amine
\$900/kg


1,2-Ethanedithiol
\$180/kg


2-Mercaptoethanol
\$50/kg


1,2-bis(diphenylphosphino) ethane (DPPE) \$1,150/kg

We first revisited the palladium removal from pyrrolidine **1**. A toluene solution of **1** with 9100 ppm of palladium (relative to **1**) was stirred with Nuchar AquaGuard in combination with a chelating agent for 8 h at rt. The resulting mixture was filtered, and the filtrate was analyzed for palladium content. The first-round screening results demonstrated that several of the combinations provided significantly better palladium removal than did Nuchar AquaGuard alone (Table 2). Using Nuchar alone (entry 1), palladium in the solution was only removed by 28%, down to 6450 ppm. However, with the addition of 1,2-ethanedithiol, >97% of the palladium was removed from the solution (entry 2). Ethylenediamine combined with Nuchar removed 90% of palladium (entry 3), also significantly better than Nuchar alone. Using 2-mercaptoethanol and Nuchar (entry 5), 82% of palladium was removed from the solution. These chelating agents are liquid and will not provide palladium removal on their own, which suggests that there is an interaction between Nuchar and the chelating agent that significantly improves the efficiency of palladium adsorption onto carbon, possibly by the proposed mechanism discussed earlier. Examination of a solution of ethylenediamine (125 mg) in toluene (10 mL) stirred with Nuchar (500 mg) for 60 h at rt showed that 50% of ethylenediamine was adsorbed onto Nuchar, supporting the proposed in situ scavenger formation. Furthermore, addition order (add Nuchar last or add substrate last) does not generate a performance difference, suggesting both proposed scenarios may contribute to palladium removal. Phosphine ligand DPPE and several other amines showed only a moderate ability to enhance palladium removal in this case (entries 4, 6–8).

The combination of *N*-acetyl cysteine and Nuchar provided >97% palladium removal. However, to our surprise, another separate experiment showed that *N*-acetyl cysteine alone also generated >97% palladium removal under the same conditions (Table 3). Thiosalicyclic acid and TMT performed similarly to *N*-acetyl cysteine and provided 95–96% palladium removal with or without combined with Nuchar. The reason appears to be that these solid chelating agents have very low solubility in toluene and can thus serve as effective solid-phase metal scavengers on their own.[17] This provides another potential way to remove heavy metals when a solid chelating agent has low solubility in the target substrate solution.

After treatment with a chelating agent and carbon followed by filtration, the resulting filtrate will likely contain some chelating agent not completely adsorbed onto carbon. Clearly, a heavy metal removal protocol that introduces a new impurity would be undesirable and would require tracking and removing the residual chelating agent. However, in most cases, removing the residual chelating agent is much less challenging compared to the task of removing residual heavy metals. The chelating agent impurity is well-defined, easily monitored, and removable by crystallization or aqueous washes. For instance, the residual ethylenediamine in the solution of **1** was reduced to very low levels (<0.005 wt % relative to **1**) after water washes.

We also tested the combination of silica gel and chelating agents to remove palladium from the solution of **1**.[18] Using silica gel alone, only 33% of palladium in the solution was removed (Table 4). With the addition of tris(2-aminoethyl)amine, however, the removal of palladium was dramatically improved to >97%. 2-(Dimethylamino)ethanethiol hydrochloride and 1,2-ethanedithiol also significantly increased the efficiency of palladium removal compared to silica gel alone, indicating a synergetic effect when silica gel and a chelating agent are used together. L-cysteine, DPPE, 2-mercaptoethanol, and ethylenediamine showed moderate improvement compared to silica gel alone.

The first round of screening demonstrated that many chelating agents can synergize with carbon or silica gel and provide significantly improved palladium removal, including the combination of ethylenediamine with Nuchar, tris-(2-aminoethyl)-amine with silica gel, etc. We further tested our method on several other projects where palladium removal was challenging.

In Scheme 2, removal of two different palladium catalysts, $Pd(OAc)_2$ and $PdCl_2(dppf)_2$ from a solution of pyridine **3** was required. The solution of **3** in ethyl acetate (EtOAc) contained about 1000 ppm of palladium (relative to **3**), which was not easily rejected by crystallization. When using Nuchar AquaGuard alone (10 wt % relative to **3**) to treat the solution of **3**, palladium was only removed by 78% (down to 220 ppm). However, Nuchar combined with ethylenediamine (10 wt % each) removed 98.4% of palladium from the solution (down to 16 ppm), which is a significant improvement over Nuchar alone.

We also compared the above conditions to washing a solution of **3** with 5% ethylenediamine aqueous solution. After two equal-volume ethylenediamine aqueous washes, only 20% of the palladium was removed from the solution of **3**, which was far less efficient than using Nuchar and ethylenediamine. In this example, the synergistic effect between Nuchar and ethylenediamine in palladium removal is not achievable by ethylenediamine aqueous solution.

Using silica gel and chelating agents, several effective combinations were identified. Silica gel alone only removed 63% of the palladium from the solution of **3** (Table 5). When combining silica gel with chelating agents, such as DPPE or tris-(2-aminoethyl)amine, 99% palladium removal was achieved. Ethylenediamine is similarly effective. TMT-Na, L-cysteine, etc. provided good to moderate enhancement to palladium removal. In this case, TMT was ineffectual.

In another program, aniline **4** was synthesized using Buchwald-Hartwig C−O and C−N bond formation reactions catalyzed by $Pd_2(dba)_3$ (Scheme 3). The solution of aniline **4** in toluene contained 150 ppm of palladium (relative to **4**) and was tested with six sets of conditions that were effective in previous screenings. Using 10 wt % of Nuchar alone, palladium in a solution of aniline **4** was reduced to 94 ppm (a reduction of 37%, Table 6). However, when 10 wt % of ethylenediamine was used along with Nuchar, 95% of palladium in the solution was removed (down to 8 ppm). For this substrate, TMT, TMT-Na, thiosalicyclic acid, or DPPE were not as effective as ethylenediamine.

Table 4. Palladium removal from 1 with silica gel and chelating agents[a]

chelating agent	$Pd_{residual}$ (ppm)	Pd removed (%)
silica gel alone	6097	33
tris(2-aminoethyl)amine[b]	<286	>97
2-(dimethylamino)ethanethiol hydrochloride[b]	495	95
1,2-ethanedithiol[b]	649	93
L-cysteine[b]	1192	87
DPPE	2209	76
2-mercaptoethanol	2421	74
ethylenediamine	2661	71

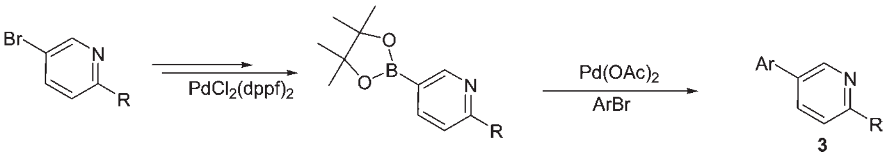
[a] A toluene solution of **1** with 9100 ppm of palladium (relative to **1**) was stirred with silica gel (70 wt % relative to **1**) in combination with a chelating agent (35 wt % relative to **1**) for 8 h at rt. The resulting mixture was filtered, and the filtrate was tested for palladium content. [b] Greater than 98% of **1** was recovered in entries 2−5 after treatment.

Table 5. Removal of palladium from 3 with silica gel and chelating agents[a]

chelating agent	$Pd_{residual}$ (ppm)	Pd removed (%)
silica gel alone	369	63
DPPE	10	99
tris(2-aminoethyl)amine	14	99
ethylenediamine	18	98
TMT-Na	50	95
L-cysteine	76	92
2-(dimethylamino)ethanethiol hydrochloride	88	91
thiosalicyclic acid	122	88
TMT	480	51

[a] An EtOAc solution of **3** with 998 ppm of palladium (relative to **3**) was stirred with silica gel (80 wt % relative to **3**) in combination with a chelating agent (80 wt % relative to **3**) for 8 h at rt. The resulting mixture was filtered, and the filtrate was tested for palladium content.

Scheme 2. Synthesis of 3 using a Suzuki reaction



Scheme 3. Synthesis of 4 using Buchwald−Hartwig reactions

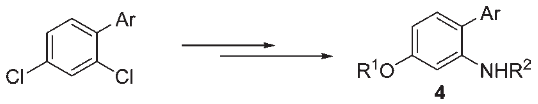


Table 6. Palladium removal from 4 with Nuchar and chelating agents[a]

chelating agent	$Pd_{residual}$ (ppm)	Pd removed (%)
Nuchar AquaGuard alone	94	37
ethylenediamine	8	95
TMT	32	79
TMT-Na	32	79
DPPE	36	76
thiosalicyclic acid	114	24

[a] A toluene solution of **4** with 150 ppm of palladium (relative to **4**) was stirred with Nuchar (10 wt % relative to **4**) in combination with a chelating agent (10 wt % relative to **4**) for 8 h at rt. The resulting mixture was filtered, and the filtrate was tested for palladium content.

Table 7. Removal of palladium from 4 using silica gel and chelating agents[a]

chelating agent	$Pd_{residual}$ (ppm)	Pd removed (%)
silica gel alone	142	5
TMT Na	56	63
L-cysteine	56	63
DPPE	100	33
TAEA	100	33
thiosalicyclic acid	140	7

[a] A toluene solution of **4** with 150 ppm of palladium (relative to **4**) was stirred with silica gel (10 wt % relative to **4**) in combination with a chelating agent (10 wt % relative to **4**) for 8 h at rt. The resulting mixture was filtered, and the filtrate was tested for palladium content.

For aniline **4**, the combination of silica gel and a chelating agent only provided moderate improvement over silica gel alone. Using silica gel alone, 5% of palladium was removed from the solution (Table 7). Adding TMT-Na or L-cysteine improved the rejection of palladium to 63%. DPPE, TAEA, and thiosalicyclic acid were not effective.

As with any other heavy metal removal technique, the performance of the binary system described is highly dependent on the substrate structure, metal species, solvent, etc. An optimal system for a specific metal contaminant cannot be predicted easily, and initial screening experiments will most likely be required to identify the most effective chelating agent and carbon or silica gel adsorbent. Once an optimal system is identified, further studies can be carried out to fine-tune the conditions such as loading, chelating agent/adsorbent ratio, treatment time, and temperature.

CONCLUSIONS

With the increasing use of homogeneous palladium-catalyzed reactions in the pharmaceutical industry, the need for developing cost-effective ways to remove palladium contamination is rising as well. Here we describe our results in the development of a cost-effective method to remove palladium using a binary system containing a chelating agent in combination with either activated carbon or silica gel adsorbents. The binary system performs in the same way as an in situ generated metal scavenger. This method has shown effectiveness on several reaction streams to remove palladium. We expect that in many cases this method has the potential to replace expensive commercial solid-supported scavengers in the removal of palladium and other heavy metals.

EXPERIMENTAL SECTION

HPLC analysis was carried out using an Agilent 1100 system (Agilent, Santa Clara, CA, U.S.A.) with diode array UV−visible detection, YMC C-18 column, and water/ACN (0.01% trifluoroacetic acid) as mobile phases. GC analysis was carried out using an Agilent 6850 GC system with FID detection and Resteck RTX-35 amine column. Palladium concentrations of samples were tested using either the Perkin-Elmer Elan 6100 quadrupole ICP-MS (inductively coupled plasma mass spectroscopy) spectrometer (Perkin-Elmer, Norwalk, CT, U.S.A.) or the Thermo Finnigan Element 2 high-resolution ICP-MS spectrometer (Finnigan, Bremen, Germany). Samples were either diluted directly in concentrated nitric acid or rotovap-evaporated first and then redissolved in concentrated nitric for ICP-MS analysis.

General Procedure for Palladium Removal Screening. Nuchar AquaGuard (50 mg) or silica gel (Fisher, 230−400 mesh, grade 60, 50 mg) and a chelating agent (25 mg) were placed in a vial equipped with a magnetic stirrer bar. A substrate solution (1 mL, containing ∼50 mg of substrate) was added to the vial. (Note: (1) The order of addition did not appear to be important. (2) When the initial palladium content is relatively low, the loading of carbon or silica gel and chelating agent can be reduced.) The vial was capped tightly and left stirring at rt for 8 h. The resulting mixture was filtered through a Gelman Acrodisc CR PTFE 0.45 μm filter into a clean vial for palladium testing and HPLC analysis.

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(17) Solubility of TMT in toluene: 0.02 mg/mL, see reference 11. Solubility of thiosalicyclic acid or *N*-acetyl cysteine in toluene is <1 mg/mL.

(18) Flahive and colleagues have demonstrated the use of 10% cysteine saturated on silica gel to remove palladium. See reference 4b.