The Art of Meeting Palladium Specifications in Active Pharmaceutical Ingredients Produced by Pd-Catalyzed Reactions

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Abstract: The use of palladium-derived catalysts in the synthesis of fine chemicals, pharmaceutical intermediates and active pharmaceutical ingredients (APIs) has become quite common in the last few decades. The number of palladium-catalyzed synthetic reactions (both achiral and chiral) available to chemists has provided access to more complex structures in fewer steps and with less waste, due to the catalytic nature of many of the methods. An unfortunate side effect of using palladium is the potential for palladium-containing impurities to remain in the desired compound after isolation. This is an especially significant problem for the pharmaceutical industry since there is a low limit for heavy metal impurities allowed in the drug substance. Therefore, various methods of removing palladium impurities from organic compounds of pharmaceutical interest have been developed. This review will provide a survey of the published methods but is not meant to be inclusive of all published material in this area of research.

Keywords: active pharmaceutical ingredients; heavy-metal impurities; homogeneous catalysis; palladium; purification; separation science

1 Introduction

Palladium was discovered by W. H. Wollaston in 1803. It is known for its ability to absorb large amounts of hydrogen gas (up to 900 times its own volume of H_2 at room temperature), which led to one of its earliest chemical uses as a hydrogenation catalyst (typically using a solid support to make removal easier). In recent years, many new synthetic transformations have been developed that use palladium compounds, such as the catalysis of carbon-carbon and carbon-heteroatom coupling reactions (e.g., by Buchwald–Hartwig, Heck, Kumada, Negishi, Nozaki–Hiyama, Sonogashira, Stille, Suzuki–Miyaura, and Tsuji–Trost).[1] These reactions have found increased popularity amongst pharmaceutical chemists as they are generally tolerant of a wide-range of functional groups and can therefore be used on complicated molecules.

Whereas palladium-catalyzed reactions allow for rapid access to a diverse range of compounds, they also present a problem in that the palladium can often be retained in the isolated product. For pharmaceutically active ingredients there are typically strict guidelines to limit the levels of heavy metals, including palladium, in the drug substance. These limits may vary depending on which phase of development the compound is in and the type of metal. With homogeneous palladium-catalyzed reactions this is especially important as all of the palladium has the potential to remain in the product after isolation. With heterogeneous catalysts, such as Pd on charcoal and Pd bound to polymeric supports, the Pd load is often greatly reduced in the active pharmaceutical ingredient (API), as most of the Pd remains bound to the support, which is removed by filtration. Unfortunately, solubilization and leaching of the Pd from the support is still possible (depending on the reaction conditions and the catalyst being used), so removal of residual palladium from products generated *via* heterogeneous catalysis can still be an issue.

The low levels of palladium allowed in an API likely result from the fact that palladium has no known biological role. Since there are only limited data on environmental contact with palladium, the proposed value for dietary intake (as a crude estimate) is $< 1.5-15$ μg/day per person. Due to its ability to coordinate with amino acids, proteins, DNA, and other macromolecules (e.g.,

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vitamin B_6) palladium is potentially capable of inhibiting many cellular functions. Its absorption, though, is highly dependent on its chemical form and the route of administration. The LD_{50} values determined in rats, mice, or rabbits ranged from 3 mg/kg body weight ($PdCl_2$, *i.v.* administration) to > 4900 mg/kg body weight (PdO, oral administration).[2]

The recommendations[3] from the European Agency for the Evaluation of Medicinal Products (EMEA) for the allowable level of metals in drug substances account for a number of criteria. First, the permitted daily exposure (PDE) for each metal is estimated. This is the daily exposure that is determined to be unlikely to produce adverse health affects in humans. This number can be highly dependent on the specific metal as some metals have known, positive biological roles, while others (e.g., palladium) have no known beneficial role. For the platinoid group in particular (Pt, Pd, Ir, Rh, Ru, Os) there are very little data in this regard, and only platinum has sufficient toxicological data to make a good assessment of an appropriate limit. This limit is used as a specification for the sum of the entire platinoid group.

Bioavailability of the metal (in its many forms) is taken into account as well as whether there are other logical sources of the metal in the human diet (thereby reducing the maximum amount allowable in the drug substance). A ppm limit for the metal can be calculated using these pieces of data. The calculation [see Eq. (1)] gives the ppm limit for oral dosages, while the parenteral dosage is considered (in the case of the platinoid group) to be 1/10 of the oral limit. For the sake of this calculation, the dose is considered to be 10 g/day and the body weight is assumed to be 60 kg.

$$\text{Concentration (ppm)} = \frac{(y/100) \times \text{PDE} \times \text{Body weight}}{\text{Dose}} \quad (1)$$

y = % of PDE apportioned to drug substance
PDE = permitted daily exposure (μg/kg/day)
Dose = daily intake of the drug substance in g/day
Body weight = body weight in kg

Based on this calculation, limits were calculated for a variety of heavy metals typically used in synthetic sequences, including palladium (see Table 1). If two or more heavy metals are present in a sample, the limit for oral dosage forms should be $\leq$ 20 ppm, while the total parenteral concentration should be $\leq$ 2 ppm. For the platinoid metals group, the sum of the metals must be below the limit suggested (for oral dosage forms, 5 ppm). For dosages greater than 10 g/day, the values in Table 1 can be pro-rated.

2 Medicinal Uses of Pd and Side-Effects

There are a few known therapeutic uses of palladium-based compounds. The use of ^{103}Pd needles in radiotherapy treatment for prostrate cancer showed some side-ef-

Table 1.

Element	Oral Concentration Limit [ppm]	Parenteral Concentration Limit [ppm]
Pt, Pd, Ir, Rh, Ru, Os	5 (group)	0.5 (group)
Mo, V, Ni, Cr	10	1.0
Cu, Mn	15	1.5
Zn, Fe	20	2.0

fects, but they were representative of the typical side-effects of radiation therapy. Colloidal palladium hydroxide (administered by repeated subcutaneous injections) was used for treating obesity in the early 1900 s, with side-effects of fever, euphoria, long-lasting discoloration and/or necrosis at the injection site. Oral doses of 65 mg/day of $PdCl_2$ were used, ineffectively, to treat tuberculosis in the 1940 s. There were no apparent adverse effects in the tuberculosis patients.[1] Looking at these data as a whole, palladium does not appear to be highly toxic in all forms, but the cautious approach has been taken and palladium limits were set at low values for all pharmaceutical drug substances.

3 Analysis of Pd

Analysis of palladium (and other metals) at such low levels can be a challenge. A variety of acceptable methods exist including the USP metals test (which tests for total heavy metals at the ppm level, but not levels of specific metals), and several methods which can detect specific metals at low limits. The USP metals test is a visual comparison test in which the scientist treats a prepared solution of the drug substance (or pharmaceutical intermediate) with H_2S or thioacetamide.[4] The reaction of H_2S with various metals (i.e., Pb, Hg, Bi, As, Sb, Sn, Cd, Ag, Cu, and Mo) will result in the colored insoluble sulfides of these metals. The color of the resulting solution is compared to a standard and the presence or absence of metals is confirmed.[5]

The methods which are specific for certain metals include atomic absorption, X-ray fluorescence, and plasma emission methods. The methods need to be capable of detecting as little as 1–2 ppm of the metals to meet the specified limits. Atomic absorption spectroscopy (AAS) is commonly used for detection of small amounts of various metals. The limit of detection for this method is dependent on the preparation method, but the lower limits of detection for palladium appear to be in the ng/g range. X-ray fluorescence is used somewhat less frequently and can detect Pd as low as $\mu g/m^3$. Plasma emission methods (e.g., ICP-MS and ICP-AES) are frequently used[1] and can have detection limits as low as $\mu g/m^3$. While ICP and X-ray fluorescence can be used for the determination of multiple metals in one analysis, AAS is used to analyze one metal at a time. AAS on the other hand is typically more sensitive and uses equipment which is less expensive and simpler to own and operate.[6]

4 Survey of Palladium Removal Methods

In general, once palladium is indicated for a synthetic step there are two options that can be evaluated to produce an API with low palladium content: 1) use a heterogeneous palladium catalyst to reduce the amount of soluble palladium which can be retained in the organic compound, 2) use homogeneous catalysis and a purification method to reduce the Pd load in the product. Each of these options will be discussed.

4.1 Heterogeneous Catalysts

In addition to standard Pd on charcoal (and other supports) for use in hydrogenation reactions, a number of heterogeneous catalysts have been developed recently to allow for efficient cross-coupling reactions. The use of these catalysts tends to significantly reduce the Pd load in the isolated product, due to the ease with which the catalyst can be removed by filtration. It has been noted, though, that significant solubilization and leaching of Pd from the support is possible[7] depending on the reaction conditions and the compound being synthesized. A recent review of the latest advances in the area of heterogeneous catalysts for use in the Heck reaction provides a good overview of the current trends in supported palladium catalysts.[8] A review of heterogeneous catalysts will therefore not be presented here. Any of the techniques described below can be utilized to remove residual palladium from organic compounds prepared by heterogeneous catalysis, if needed.

4.2 Purification Methods

The purification method which is applied to the organic substance will vary greatly depending on the state of palladium to be removed [typically Pd(0), Pd(II), or colloidal Pd]. The compound from which Pd is being removed and the reaction conditions that are being utilized also have a great effect on how effective the purification method is. Ultimately, this means that the purification technique for each compound may be slightly different, and fine-tuning of the method will be needed to provide suitable results. Several general techniques for reducing the level of Pd to acceptable levels are distillation, adsorption, crystallization and extraction. Each will be covered with illustrative example(s) from the chemical literature.

4.2.1 Distillation

As palladium and other heavy metals are not significantly volatile at "normal" laboratory distillation temperatures ($< 250\ ^\circ C$) and pressures it is sometimes possible to distill out the desired organic product, leaving the heavy metals in the residue. This approach was used by Beutler[9] in the preparation of a key intermediate of terbinafine hydrochloride (**4**; the active ingredient in Lamisil®). A Pd-catalyzed coupling reaction of **1**

and **2** (Scheme 1) resulted in product **3**, which was purified by an aqueous, extractive work-up. This crude product contained 177 ppm Pd and 19 ppm Cu (most of the Cu was removed by the extractive work-up). Distillation of this material resulted in a 92.2% yield of **3** (based on **1**) which was 99% pure and contained only 1 ppm Pd and <1 ppm Cu. The distillation residue of **3** contained almost all Pd and Cu. Synthesis of the HCl salt of **3** resulted in API **4**, which easily met the heavy metals specifications.

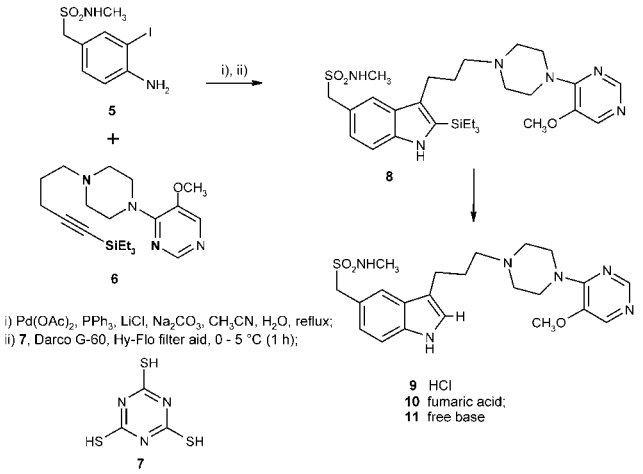
4.2.2 Adsorption

The process of adsorbing or complexing palladium to different chemical moieties will necessarily change the physical properties of the palladium. By adsorbing the palladium to a solid scaffold, the palladium complex can typically be filtered from the reaction medium (assuming a solvent was used in which the scaffold is not soluble). Many examples of this type of purification exist. The resulting palladium complexes can also be rendered more soluble in the solvent system being used. Therefore, purifications using this technique can also result in crystallization of the desired compound, leaving the palladium complex in the mother liquor.

4.2.2.1 Solid TMT

A method employed at Bristol–Myers Squibb involved complexing the palladium with trimercaptotriazine (**7**; TMT).[10] This treatment resulted in insoluble complexes of TMT and Pd which could be filtered out of the product solution.[11] The original synthesis called for the drug substance to be prepared by a palladium-catalyzed indolization. Filtration of the crude solution removed some palladium which had precipitated at this stage. Isolation of an HCl salt, which contained 600–650 ppm Pd, followed by a salt exchange and multiple recrystallizations reduced the Pd level to 25–30 ppm. The goal was to isolate drug substance with ≤ 5 ppm of residual palladium, so alternative methods were explored. The most effective method found was to utilize a TMT treatment prior to desilylation of **8** (Scheme 2).

The palladium-catalyzed indolization generates a solution of **8** in aqueous acetonitrile. To optimize the removal of palladium solids from this step, the mixture was stirred with TMT, charcoal, and diatomaceous earth. The slurry was cooled to 0–5 °C and filtered. The remaining steps were performed as before and **11** was isolated containing 1–4 ppm Pd. The yield of **11** was not affected by the TMT treatment, nor was TMT noted as an impurity in **10** or **11**. This procedure was scaled to 12 kg which effectively reduced the Pd levels to the same extent as in the laboratory process.

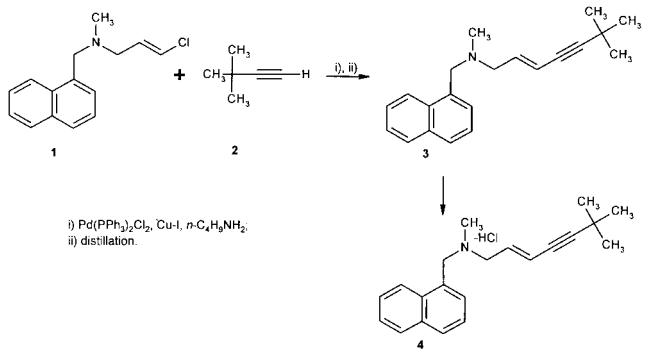


Scheme 2. TMT treatment to remove palladium.

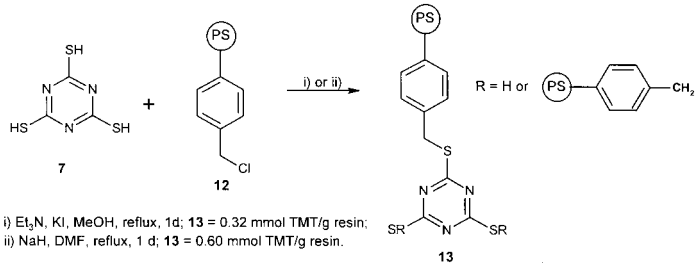
4.2.2.2 Polystyrene-Bound TMT

Polystyrene-bound TMT has also been used to remove palladium from aqueous and organic solutions.[12] This particular polymeric scaffold should have a low solubility in many organic solvents thereby increasing the ease with which the complexed palladium can be removed without leaving the resin or palladium as an impurity in the product.

The resin was prepared by reacting the Merrifield resin with TMT (**7**, Scheme 3). Resin containing 0.32 mmol TMT/g resin was used for all of the experiments descri-



Scheme 1. Synthesis and purification of a key intermediate in the terbinafine hydrochloride synthesis.



Scheme 3. Preparation of polystyrene-bound TMT.

bed below.[11] The resulting TMT-loaded resin **13** was used to purify a number of solutions containing $Pd(II)Cl_2$. After stirring the solution in the presence of **13** [3.8 equivs. of resin per Pd(II)] at room temperature for 1 day, the slurries were filtered, and the palladium content of the filtrate was determined. The resin was effective at removing palladium at or below pH 2.2 (see Table 2, entries 1–4). Increasing the amount of **13**/Pd(II) [to 11.5 equivs. **13**/Pd(II)] helped remove palladium even at higher pH (Table 2, entries 5 and 6). An organic solution of $Pd(OAc)_2$ was also able to be purified using **13** (Table 2, entries 7 and 8). Once palladium was bound to the resin it could not be easily dissociated, despite repeated washings. Therefore, the resin does not appear to be reusable.

4.2.2.3 MP-TMT

MP-TMT[13] is a highly cross-linked macro-porous polystyrene-bound trimercaptotriazine resin recently introduced by Argonaut for scavenging residual palladium, and it is analogous to the one described above. This resin has a TMT loading of 0.7–1.1 mmol/g, is effective in both organic and aqueous solvents and is not dependent on solvent swelling. Typical conditions for palladium scavenging require 2–5 equivs. of resin relative to the palladium content for a period of 16–24 h. Reaction time appears to be the most important factor in effective scavenging.

4.2.2.4 Polystyrene-Bound Ethylenediamine

The synthesis of the pharmaceutical intermediate **16** was achieved *via* the Suzuki–Miyaura coupling reaction at Eisai Co. (Scheme 4).[14] Upon isolation, it was found to contain from 2000–3000 ppm Pd, and the API (**17**, E2040) did not meet the required purity target (< 10 ppm Pd). Purification of the intermediate **16** was therefore attempted. It was found that the addition of ethylenediamine to the toluene reaction solution effec-

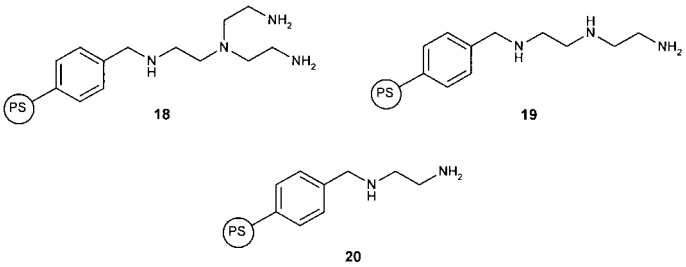


Figure 1. Several polymer-bound amines useful for metal scavenging.

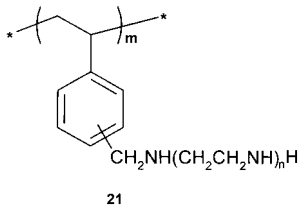
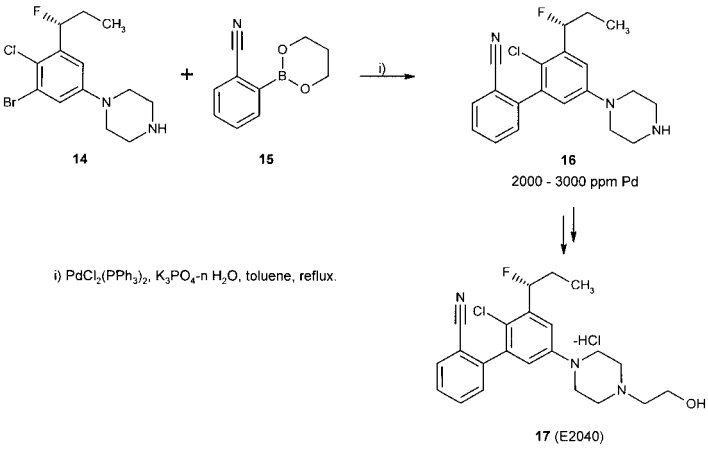


Figure 2. DIAION CR20, a polymeric palladium scavenger.



Scheme 4. Use of the Suzuki–Miyaura coupling for preparation of an API.

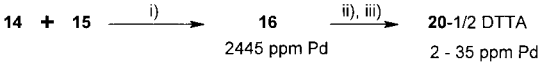
Table 2. Removal of palladium using polystyrene-bound TMT.

Entry	Solvent	Solution pH	Residual Pd [ppm]	Adsorption [%]
1[a]	1 M HCl (aq.)	0.1	0.061[b]	99.9
2[a]	1 M CH_3CO_2H (aq.)	2.2	0.110[b]	99.8
3[a]	5 wt % NH_4Cl (aq.)	3.8	19.0[b]	68.3
4[a]	5 wt % NH_4OAc (aq.)	6.9	33.0[b]	45.0
5[c]	5 wt % NH_4Cl (aq.)	3.8	0.180[b]	99.7
6[c]	5 wt % NH_4OAc (aq.)	6.9	2.0[b]	96.7
7[a]	1 M CH_3CO_2H in THF	---	0.045[d]	99.91
8[a]	THF	---	0.002[e]	99.99

[a] 3.8 equivs. **13**/Pd(II) was used.
[b] Each solution contained ~ 60.0 ppm Pd originally.
[c] 11.5 equivs. of **13**/Pd(II) was used.
[d] The solution originally contained 47.4 ppm Pd(II).
[e] The solution originally contained 23.7 ppm Pd(II).

tively complexed the Pd, but the resulting insoluble oil was difficult to separate from the product. Therefore, polymer-supported ethylenediamines were used as scavengers for the palladium. Several versions of these polymer-bound amines are available commercially (Figure 1) and are stable in organic solvents. The ability of each resin to remove Pd from the reaction solution was investigated in several organic solvents (acetone, toluene, or methanol) with stirring for 65 h. DIAION CR20 (**21**), also available commercially, was investigated as well (Figure 2). The best option for removal of palladium was found to be the use of **21**.

The Suzuki–Miyaura reaction was run, and the reaction solution was washed with water. To the organic layer was added **21** (~ 2:1 w/w of **21** to crude product), and the slurry was stirred for 17 h at 60 ^{0}C. The resin was removed by filtration and the solution was concentrated to yield **16** as a yellow oil (typical residual palladium was about 6–10% of the original amount). This yellow oil was dissolved in acetone and treated with (+)-di-*p*-toluoyl-D-tartaric acid (DTTA) and water. A crystallization of the resulting solution followed by filtration and washing gave the product salt which contained 2–35 ppm Pd (**20**·1/2-DTTA, see Scheme 5). This material was carried on to the drug substance **17** which contained acceptable levels of Pd.

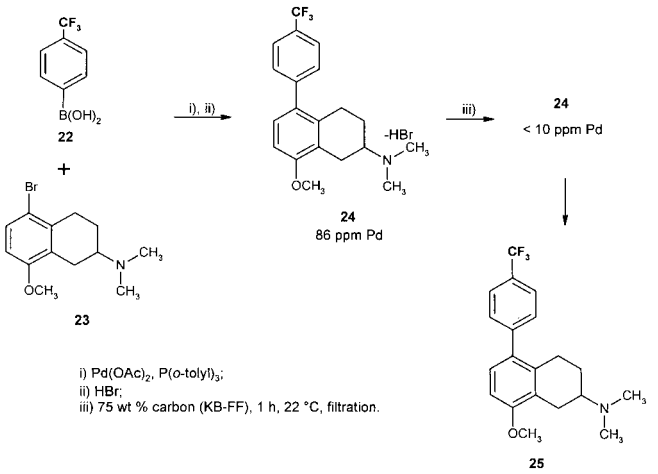


i) $PdCl_2(PPh_3)_2$, K_3PO_4-nH_2O, toluene, reflux, 1h.
ii) **21**, 60 °C, 17 h; filtration; evaporation;
iii) DTTA, acetone/water, 60 °C, 2.5 - 5 h; r.t (crystallization), 1.3 - 16 h; filter

Scheme 5. Purification of **16** *via* treatment with DIAION CR20 (**21**).

4.2.2.5 Activated Carbon

Preparation of a compound (**25**) for the treatment of head trauma, also involved a Pd-catalyzed Suzuki coupling to generate the drug substance (Scheme 6), first as the HBr salt **24**, and then as the free base **25**.[15] Several key points were examined during this work, which included reducing the levels of Pd to acceptable levels, for providing a cost-effective work-up, and ensuring that any filtration utilized was fast and efficient. To this end, several different adsorbents were evaluated, including chelating resins, cation exchange resins, and activated carbon. It was found that purification of **24** was most effective with activated carbon (KB-FF). This specific type of carbon has a "reduced fines content" and therefore filters much faster than many other types of carbon. Treatment of **24** (6.5 wt % in heptane) with *ca.* 75 wt % carbon for <1 h at 22 °C reduced the Pd from 86 ± 8 ppm to <10 ppm. In addition to having the best result for removal of palladium, this type of carbon



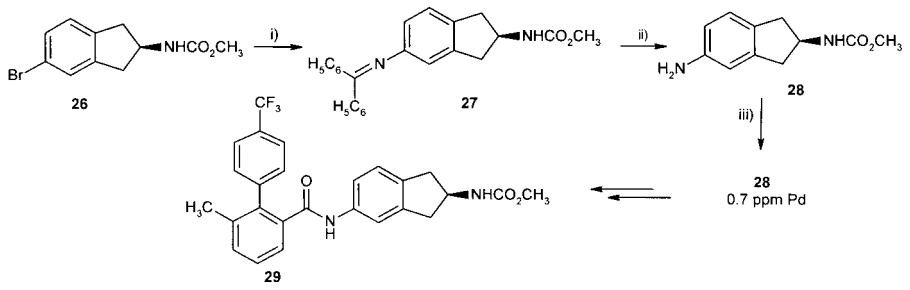
Scheme 6. Palladium removal using carbon (KB-FF) in **25**.

was one of the lowest-cost alternatives tried in this study. It was found, though, that a significant amount of the product (~0.5 to 0.6 g/ g carbon) was adsorbed to the carbon after filtration. When the carbon was washed with heptane, the drug substance was significantly recovered, but the adsorbed palladium could also be partially washed off the carbon, so care was taken to limit the washing of the carbon bed following filtration.

Whereas the carbon treatment was found to be effective in the laboratory, it was decided that adding carbon directly to the batch reactor was not a suitable option in the plant, so a carbon-bed treatment was investigated. While the palladium was still removed efficiently (depending on the flow rate through the column), it was found that compression of the bed resulted in very large pressure differentials so this option was not used in the pilot plant. The option ultimately used in the plant involved filtration through several types of filters in series, with at least one containing Celite to aid in filtration of fine particles. The use of the carbon bed was kept as an option to be used after further development work was performed.

In another example (**29**, an inhibitor of microsomal triglyceride transfer protein), Prashad and co-workers[16] successfully used activated carbon (PICA P1400) for reducing palladium. Here the compound **28** was prepared from **26** (Scheme 7) using palladium-catalyzed amination conditions [benzophenone imine, BINAP, $Pd_2(dba)_3$ and sodium methoxide] followed by hydrolysis. The crude **28** containing palladium was treated with activated carbon in refluxing methanol followed by filtration and recrystallization to reduce the palladium content to 0.7 ppm.

Several suppliers offer carbon cartridges, which can be used for palladium removal. These cartridges take advantage of the adsorbent properties of activated carbon, but contain the carbon in a disposable cartridge. Use of the cartridges avoids the need to add carbon powder or



i) $(C_6H_5)_2C{=}NH$, BINAP, $Pd_2(dba)_3$, $NaOCH_3$, toluene; ii) a. 2 N HCl; b. NaOH;
iii) 100% wt % carbon (PICA P1400), MeOH, 63 - 67 °C, 5 h; filtration.

Scheme 7. Palladium removal using carbon (PICA-1400).

granules to a batch reactor, which often results in carbon contamination of the vessel.[17]

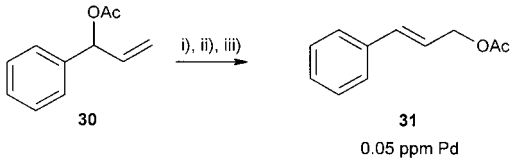
4.2.2.6 Glass Bead Sponges

The methods used to make supported palladium catalysts, by default, should also be able to make supported compounds that can adsorb residual palladium from reaction solutions. This approach has been taken by Williams and co-workers in a collaboration between the former Glaxo Wellcome R&D group and the Department of Chemistry at the University of Bath.[18] The original approach from these groups was to perform catalysis using transition metals supported on glass beads. This was quite successful, but in the interests of extending the utility of the glass beads, palladium removal was also attempted.

The glass beads were therefore prepared without the palladium for use as a palladium "sponge". The beads were synthesized by mixing an appropriate polar ligand [e.g., *m*-$(NaO_3SC_6H_4)_3P$] and 500 Å Davisil beads in a small amount of ethylene glycol. The resulting beads can be handled as a free-flowing powder which could be easily added and removed from reaction mixtures. These beads were utilized for the removal of palladium from several solutions including that of the allylic rearrangement (Scheme 8) in THF. The residual palladium was reduced to 0.05 ppm by stirring the product in the presence of 1 weight equivalent of beads for 10 min. Palladium levels in a product prepared by a Heck reaction were also reduced significantly by the same treatment (Scheme 9). In addition, the beads were used as a bed to purify a solution of palladium acetate in toluene [50 mg $Pd(OAc)_2$ in 10 mL of toluene]. One pass through 1 g of the glass beads reduced the Pd level to only 0.4 wt % of the original concentration. Increasing the amount of glass beads provided even better results (0.1 wt % of the original palladium was found in the filtrate).

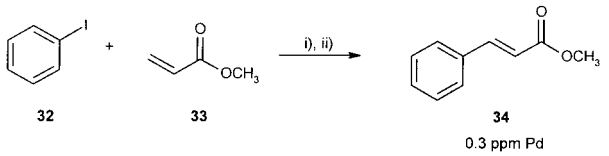
4.2.2.7 Smopex™

Smopex ™ fibers from Johnson Matthey have also proven effective at removing residual palladium from both aqueous and organic reaction solutions.[19] These fibers



i) $PdCl_2(CH_3CN)_2$, THF, r.t., 24 h; ii) remove THF, add hexane:diethyl ether (2:1);
iii) Pd sponge beads, 10 min, r.t., filter.

Scheme 8. Removal of palladium from a [3,3] sigmatropic allylic rearrangement reaction with glass bead sponges.

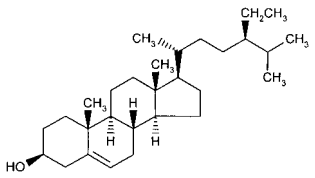


i) $PdCl_2$, PPh_3, Et_3N, toluene, reflux, 3 h;
ii) Pd sponge beads, r.t. 10 min, filter.

Scheme 9. Removal of palladium from a Heck coupling reaction mixture with glass bead sponges.

are either polyethylene or cellulose based and contain grafted side chains with appropriate functional groups for the complexation of metals. Both sets of fibers are mechanically and chemically stable and can be used in many solvent systems. The fibers can be used in batch or column mode, depending on the application. Unlike ion exchange resins (IERs), these fibers have mobile side chains which allow for easy diffusion of solution into all portions of the side chains. Also, the fibers do not have the tendency to break, as IERs are sometimes prone to do, and they do not swell as significantly as ion exchange resins. Like IERs, Smopex™ fibers are available with a wide range of functional groups (e.g., strong and weak acid cation exchangers, strong and weak base anion exchangers, mixed strong and weak cation exchangers, chelation anion exchangers, and chelating and reducing exchanger) to allow for a variety of metals (and different oxidation states of those metals) to be removed efficiently. As with all the other methods, optimization of the type of fiber(s) used and of purification conditions is necessary for best results. Some examples of the use of Smopex™ fibers are shown below.

A mother liquor solution from a coupling reaction contained 70–75% DMF, 10–15% water, 5–10 wt % triethylamine, 5–10 wt % iodine plus starting materials, triphenylphosphine, and 395 ppm Pd. This solution was treated with ~ 1.1 wt % of Smopex-110 overnight with stirring at room temperature. The solution was filtered and the resulting mother liquor contained only 3 ppm of Pd. A methanol solution containing 10 wt % nitroaromatics and 23 ppm of Pd, which was the product of a heterogeneous Pd/C hydrogenation reaction, was also purified. This purification used a mixture of Smopex-101 and -105 (0.005 g/mL of each fiber) and stirring for 30 min at room temperature to reduce the palladium concentration in the solution to <1 ppm. Colloidal palladium was also easily removed from a 25 wt % solution of sitosterol (**35**) in *n*-propanol, which contained 30 ppm of Pd fines from the preceding hydrogenation. Smopex-102 (0.005 g/mL) was added to the solution and the resulting slurry was stirred for 30 min at 80 °C. Filtration of the mixture provided a clear filtrate which contained <0.2 ppm Pd.



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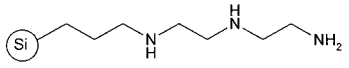
4.2.2.8 Silica-Bound Scavengers

The use of silica-bound scavengers has also been demonstrated using materials available commercially from SiliCycle.[20] Silica-based scavengers have several advantages over polymer-based ion exchange resins, the most important of which is that they do not swell and their particle size can be strictly controlled. Several different side chains are available on silica supports for metal scavenging, including ethylenediamine and thiol side chains (Figure 3), for which examples are give below.[21] Two solutions of $Pd(OAc)_2$ in THF were prepared at a concentration of 1000 ppm Pd. With stirring at room temperature, these solutions were each treated with 4 equivs. of a silica-based scavenger. After stirring for 1 h, the scavengers were removed and the filtrate analyzed for residual Pd. The ethylenediamine scavenger **36** reduced the Pd to about 40–50 ppm, while the mercapto-functionalized resin **37** reduced the palladium level to <10 ppm.

4.2.3 Crystallization

The concept of removing/crystallizing the desired product from the reaction mixture while keeping the palladium in solution with other impurities is an interesting one, and it has a better chance for reproducibility on scale-up as experimental conditions are homogeneous.



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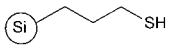

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Figure 3. Silica-supported metal scavengers.

4.2.3.1 **N-*Acetylcysteine***

Crystallization of the desired compound while keeping the residual palladium in the mother liquor with the help of palladium complexing additives was recently demonstrated by us.[22] An intermediate for the compound of interest was synthesized by a Sonogashira coupling and contained residual palladium at varying levels, all above the 4 ppm limit set for the drug substance. Treatment of **40** (Scheme 10) with various adsorbents (e.g., activated carbon and IERs) resulted in a decrease in the palladium load, but palladium levels were still between 70–150 ppm. The solution came in using an additive to complex with the palladium and solubilize the complex in the crystallization solution. This approach was successful with *N*-acetylcysteine (1.1 wt %) added to the crystallization solution. The palladium in **40** was reduced from 400 ppm to $\leq$ 30 ppm. While this did not meet our 4 ppm Pd limit, the same approach repeated in the crystallization of **41** resulted in a product containing only 1–2 ppm of Pd. This procedure was scaled up on a multikilo-scale in the pilot plant.

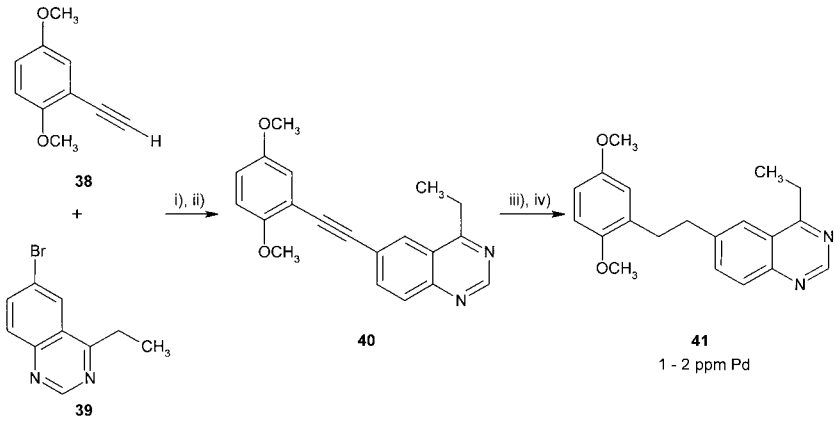
In developing a practical synthesis for compound **44**, Slade and Liu[23] used a Heck reaction starting from 4-bromobenzaldehyde (**42**), methyl acrylate (**43**), and $Pd(OAc)_2/(o\text{-}Tol)_3P$ (Scheme 11). The crude product contained ~1400 ppm of palladium. To remove palladium, *N*-acetyl-L-cysteine (2% by weight) was added to a crystallization medium of acetonitrile/water. The product was isolated in 77% yield with a palladium content of <1 ppm.

4.2.3.2 Thiourea

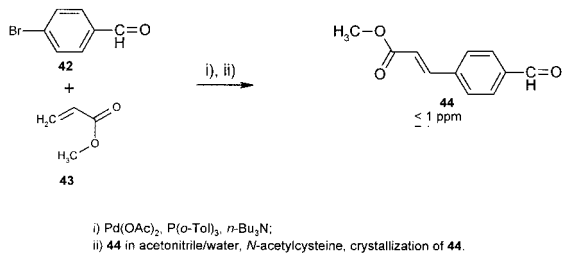
With **40**, thiourea was shown[21] to be as efficient as *N*-acetylcysteine for scavenging palladium into the mother liquor. As thiourea is a suspected carcinogen no further work was done with this reagent.

4.2.3.3 Hemi-Maleate Salt

A process for the development of **47**, a selective inhibitor of the phosphodiesterase PDE4D iosenzyme and a potential treatment for asthma, involved a Negishi coupling in the final step, which left the isolated drug substance contaminated with significant amounts of palladium (300–800 ppm), even after chromatography and crystallization. The difficulty in removing Pd from **47** (Scheme 12) could be attributed to **47** being a reasonable ligand for palladium. It was desired to develop a scale-up procedure that could be effectively run in the pilot plant and would result in product with <2 ppm



Scheme 10. Removal of palladium from an intermediate and drug substance synthesized by a Sonogashira coupling.



Scheme 11. Removal of palladium from a Heck-reaction product.

of Pd. To achieve this result, Manley and Acemoglu[24] examined a number of crystalline salts with the hope that the differing physical characteristics of the salt would enable efficient removal of palladium from the API. While several salts were tried, the hemi-maleate salt was the most successful. It was prepared in 97% yield and had a low palladium content (10–50 ppm) compared with the crude **47** (100–800 ppm). To further reduce the level of palladium, the hemi-maleate salt was converted back to the free base with aqueous sodium carbonate (5%) in methyl acetate. The organic phase containing the drug substance was then treated with activated charcoal, filtered, and recrystallized from acetone. This resulted in **47** with 94% recovery and containing <0.5 ppm of Pd.

4.2.3.4 n-*Bu$_3$P*

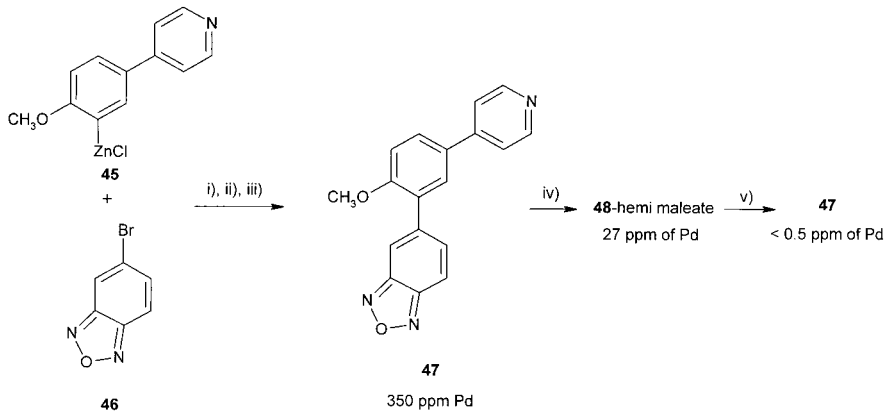
One method utilized at Merck/DuPont Merck was to solubilize the palladium such that the drug substance could be crystallized free of palladium. This method was used in the synthesis of Losartan (**51**, Scheme 13).[25] The penultimate intermediate **50** was generated by a palladium-catalyzed coupling of **48** and **49**. After the reaction was complete, the reaction solution was washed with water. *n*-Bu_3P [40 equivs. *vs.* $Pd(OAc)_2$] was added to the organic layer and the mixture was filtered and concentrated. Recrystallization of the crude intermediate resulted in a 93% recovery of **50**, which contained only 7–18 ppm of Pd.

4.2.4 Extraction

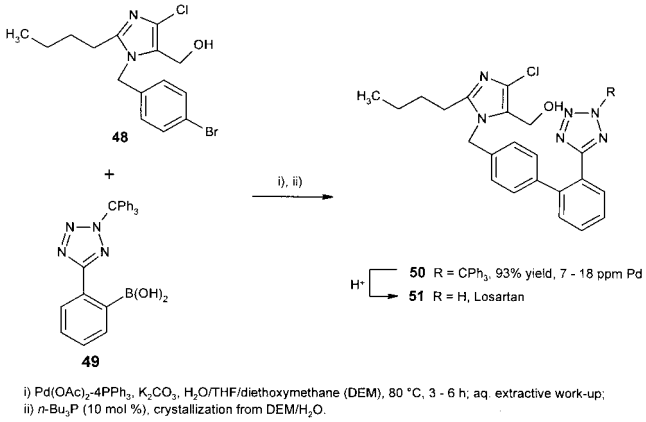
Extraction of Pd from a solution of drug substance requires that there be a significant solubility difference between the palladium compound and the drug substance (i.e., one should be mostly soluble in water and the other mostly soluble in the organic solvent). This allows for extraction of the palladium from the layer in which the drug substance is soluble.

4.2.4.1 N-*Acetylcysteine*

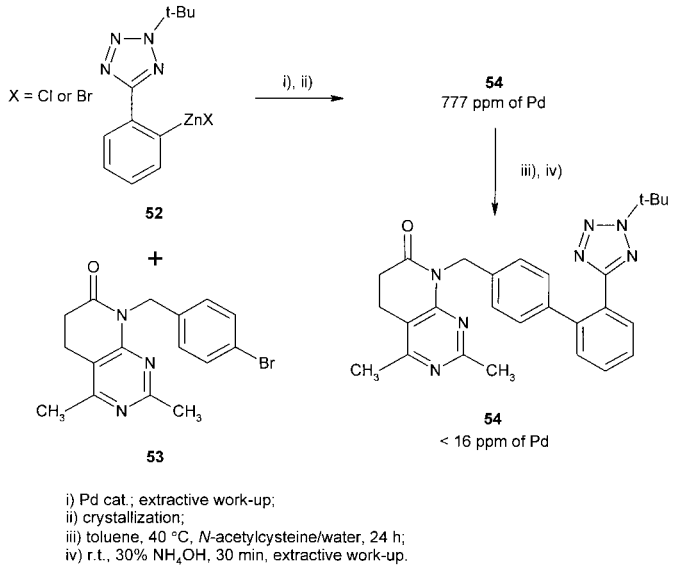
An interesting use of extractive purification was described by Villa and coworkers.[26] Compound **54** is the direct precursor to an antihypertensive agent described by American Home Products.[27] Compound **54** is prepared in one instance by a Pd-catalyzed coupling reaction (see Scheme 14) of **52** and **53**. The isolated product contained 777 ppm of Pd after an extractive work-up and crystallization. This product was dissolved in toluene and warmed to 40 °C. A solution of *N*-acetylcysteine in water[28] was added and the reaction mixture stirred for 24 h at 40 °C. The biphasic solution was cooled to room temperature, and 30% ammonia was added. This mixture was stirred for 30 min and the layers separated, resulting in an organic layer containing the drug substance precursor and <16 ppm of Pd. The *N*-acetylcysteine likely forms a complex with the palladium rendering it more soluble in the water phase than in the organic



Scheme 12. Use of crystallization to remove palladium from an API (**47**).



Scheme 13. Synthesis of Losartan (**51**).

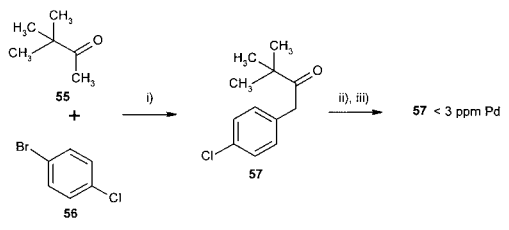


Scheme 14. Purification of a pharmaceutical intermediate (**54**) by extraction with *N*-acetylcysteine.

phase. Compound **54** was taken on to the drug substance, which contained acceptable levels of Pd.

4.2.4.2 L-Cysteine

Compound **57** is an intermediate in the synthesis of fungicidal derivatives, and an efficient synthesis was needed for making this compound. This was achieved by Prashad and coworkers[29] through α-arylation of ketone **55** with **56** using *t*-BuONa, $Pd(OAc)_2$, and toluene under ligand-free conditions (Scheme 15). Initial attempts to remove the residual palladium using activated carbon (PICA P1400) resulted in the product containing 32 ppm which was not acceptable. After an extensive study they found that the palladium could be reduced to <3 ppm by washing the crude toluene layer with an aqueous solution of L-cysteine at 85–90 °C, followed by washing with a solution of L-cysteine and sodium thiosulfate at 78–82 °C.



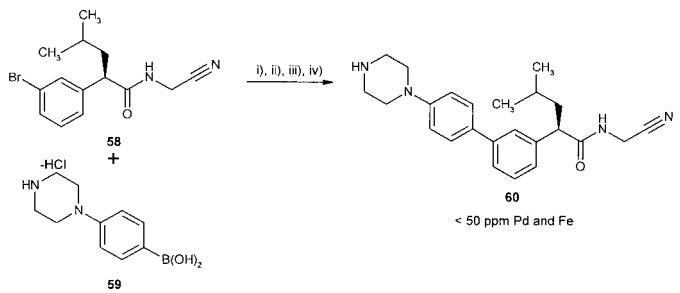
Scheme 15. Removal of palladium by extraction with L-cysteine.

4.2.4.3 n-*Bu_3P/Lactic Acid*

Drug substance **60** was prepared by a Suzuki coupling of **58** and **59** (see Scheme 16).[30] O'Shea and co-workers found that the initial levels of Pd and Fe in this crude drug substance were ~8000 ppm. The techniques attempted (chromatography and the use of *n*-Bu_3P to solubilize the Pd) were not effective at removing the Pd to an appropriate level. Therefore a new purification technique was developed, which utilized the tendency of **60** to form a water-soluble salt when reacted with lactic acid. The crude API was dissolved in ethyl acetate and treated with *n*-Bu_3P to complex and solubilize the Pd in the organic phase, then the mixture was extracted with aqueous lactic acid, thereby forming the salt of **60** and transferring this salt to the aqueous layer. The organic layer, which contained the Pd-phosphine complex was removed, and after another organic wash of the aqueous layer, a significantly purer drug substance solution was obtained. The free base of the drug substance was regenerated by treatment of the aqueous layer with sodium carbonate and extraction of the free base into ethyl acetate. The ethyl acetate layer was treated with Darko KB® and Solka Floc 40NF, filtered, concentrated, and a crystallization from toluene resulted in **61** with <50 ppm of Pd and Fe.

5 Reorganized Synthesis

When the API is a good chelator for Pd, Pd is naturally hard to remove from the compound. Reorganization of the synthesis is perhaps a better approach, as described by Maryanoff and coworkers.[31] The drug substance that they were producing was **66**, a calcium entry blocker originally generated by a Pd-catalyzed coupling reaction in the final step. A high level of palladium was found in the crude drug substance, and a number of work-up techniques were employed (e.g., treatment with $NaBH_4$, hydrogenation, chelation with dimethylglyoxime, treatment with Amborane resin, etc.). Depending on the treatment conditions, the product was still contaminated with 100–900 ppm of Pd. The target level for this compound was <20 ppm. Since it was thought that the chelation ability of **66** for Pd (see Figure 4) was part of the problem with the purification, the synthesis scheme was reorganized such that the palladium-catalyzed reaction was positioned where the product should not chelate palladium as well. This new synthesis was undertaken with the palladium-catalyzed reaction performed followed by reductive amination (Scheme 17). The palladium levels in the resulting amine **65** were typically <5 ppm. This intermediate was carried on to generate **66** with acceptable levels of residual palladium.



Scheme 16. Synthesis of API by a Suzuki coupling, and purification *via* lactic acid salt formation and extraction.

6 Conclusions

The development of palladium-catalyzed reactions for organic synthesis has allowed numerous new chemical entities to be produced efficiently and in many cases elegantly. The use of these reactions in the synthesis of active pharmaceutical ingredients (APIs), though, has also resulted in the problem that products are often contami-

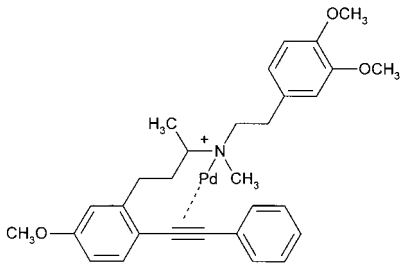
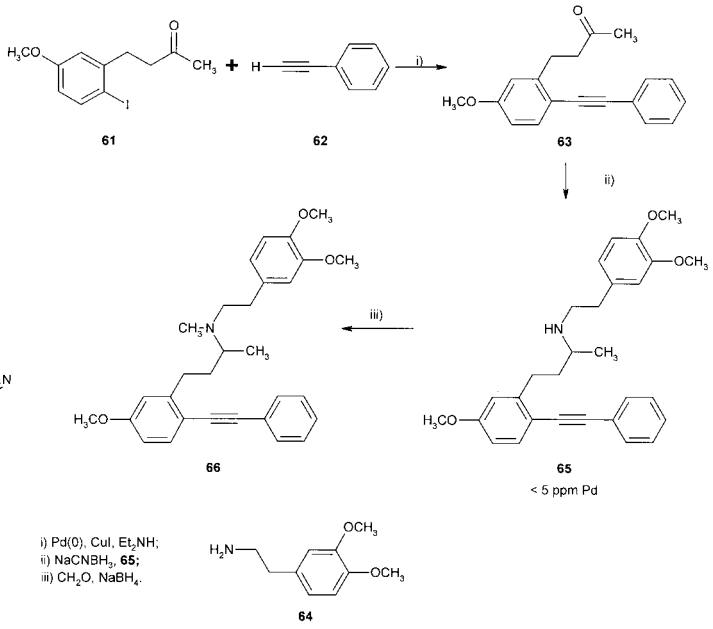


Figure 4. Potential chelation site for palladium in **66**.



Scheme 17. Reorganized synthetic scheme for the preparation of **66** with reduced palladium load.

nated with the metal. The levels of palladium in APIs must be kept very low (typically 2–20 ppm) for the compound to be used for testing and ultimate medicinal use. There are many methods which have been utilized for the removal of palladium from pharmaceutical intermediates as well as APIs. These methods typically fall into four categories: distillation, adsorption, extraction, and crystallization.

Distillation involves collection of the pure API as a distillate and leaving the non-volatile palladium compounds in the distillation residue. Adsorption is the most commonly used technique. A variety of methods have been developed including using supported chelating agents to adsorb the palladium and render it insoluble in the reaction mixture as well as complexing the palladium and rendering it more soluble in the non-drug substance phase. Crystallization can be used where the product is insoluble in the solvent, while the palladium is still soluble and is retained in the mother liquor. Finally, extraction can be used, which also involves rendering the palladium more soluble in the non-drug substance phase. These four basic methods have been examined and examples given for pharmaceutically relevant compounds, where possible. Trial and error seems to be the norm when determining the optimal conditions for removal of palladium. Most of the methods described are very specific with respect to the physical characteristics of both the compound being purified and the form of palladium to be removed. The solvent conditions and intended work-up also play a large part in determining the most effective purification method.

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