

Palladium Extraction Following Metal-Catalyzed Reactions: Recent Advances and Applications in the Pharmaceutical Industry

Marina Economidou,* Nisha Mistry, Katherine M. P. Wheelhouse,* and David M. Lindsay



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ABSTRACT: Palladium-catalyzed cross-coupling reactions are used extensively in the pharmaceutical industry. Therefore, the potential contamination of products with elemental impurities is an issue that any process chemist must consider in the design of a plant process. This is not only to meet regulatory limits, which is unequivocally the primary reason for metal scavenging, but also due to the high cost and limited supply of palladium, driving the need for recovery to recycle. This Review addresses the current approaches for palladium removal from organic solutions, with selected examples of their successful application in industrial-scale processes for pharmaceutical production. Palladium scavengers have been categorized based on their mode of action, i.e., adsorption, extraction/precipitation, and crystallization, to provide a summary of the current state-of-the-art in metal removal. Practical considerations when choosing metal removal methods are briefly discussed, illustrating their intrinsic advantages and drawbacks.

KEYWORDS: *catalysis, scavenging, palladium, extraction*

1. INTRODUCTION

Palladium-catalyzed reactions find great utility in the pharmaceutical industry and the wider synthetic chemistry community, as they offer a facile way of accessing important functional motifs in molecules through the formation of carbon–carbon or carbon–heteroatom bonds.^{1–4} The utility of such reactions is evident in modern drug syntheses, where Buchwald–Hartwig couplings, Negishi couplings, and Suzuki reactions are frequently employed.^{5–10} Paralleling the increasing use of catalysis in synthesis is the demand for efficient methods of metal removal from process streams. Cross-coupling steps are often situated late in the synthetic route, resulting in the potential for contamination of drug products with residual metals.

Metal impurities have, on occasion, been shown to have a detrimental impact on downstream chemistry, but more importantly they are required to be limited below the threshold set by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).^{11,12} Based on ICH guidance Q3D, elemental impurities have no therapeutic effect on patients and need to be controlled to acceptable levels. The guidance includes metal contaminants arising from residual catalysts that were intentionally added in the synthesis, which should not exceed the permitted daily exposure doses established on the basis of safety data. Based on this figure, which is the amount at which no adverse biological effects are observed in target organisms, the permitted concentration of elemental impurities in active pharmaceutical ingredients (APIs) is calculated for commonly used metals (Table 1). Acceptable concentrations vary depending on the metal due to their intrinsic toxicities and likelihood of occurrence in pharmaceutical processes.¹¹

Although the need to meet regulatory criteria is unequivocally the prime driver of the importance for palladium scavenging, the interest in metal extraction can be attributed to a breadth of other reasons. The volatility of palladium supply as a result of geopolitical instabilities has been at the focus of attention recently, with Russia producing up to 30% of the global supply and prices reaching an all-time high of £81,179 per kilogram in February 2022.^{13,14} Although that value has since decreased, palladium costs are still over £30,000 per kilogram. Therefore, there is a pressure to recover metals from waste streams as effectively as possible due to their finite nature and high costs. The sustainability benefits of recovery for circular use generate an additional incentive for an efficient extraction process, as catalysts can be regenerated when the metal waste is returned to suppliers. The increasing demand for greener processes and pledges for more ambitious sustainability goals, such as GSK's environment target of net-zero impact on climate, are additional factors contributing to the need for further refinement of working practices.¹⁵ This is particularly relevant to second and third row metals, whose low abundance results in a high environmental impact from their use. It has been shown that the production of 1 kg of palladium has an estimated global warming potential (GWP) of 3880 kg equiv of carbon dioxide. This value is significantly larger than the corresponding GWP for some of the more abundant first

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Table 1. Permitted Concentrations of Selected Elemental Impurities in Drug Products with Daily Doses of No More Than 10 g/day

metal	oral concentration ($\mu\text{g/g}$)	inhalation concentration ($\mu\text{g/g}$)
Pt, Pd, Ir, Rh, Ru	10	0.1
Ni	20	0.6
Li	55	2.5
Cu	300	3

row metals such as iron, which has a GWP of 1.5 kg equiv of carbon dioxide.¹⁶

Removal of palladium contaminants from reaction products can be achieved through a range of methods. From a process development perspective, a consideration that must be addressed when employing palladium-catalyzed reactions in industry is whether purging of such contaminants can be achieved during the product purification process, which would make the use of additional purification steps redundant. Although this is highly desirable, it is not usually feasible in a pharmaceutical setting, as drug products typically contain a large number of heteroatoms that may act as ligands for metals.¹² Therefore, typical methods of purification, such as crystallization, may be unsuccessful and result in insufficient removal of residual metals.

A range of purification techniques have been thoroughly investigated in attempts to achieve maximal metal removal to the process waste streams, including extraction and adsorption. These have been covered in previous reviews in the literature.^{17–20} The choice of palladium removal technique is very system-dependent; efficiency of removal can be affected by the reaction product, solvent, temperature, and additives.²¹ Simultaneously, metal speciation during the process may give rise to palladium species in multiple oxidation states, which require different approaches for their removal.^{20,22,23} This lack of generality is unfavorable, as process development is necessary for every individual case to ensure that acceptance criteria are met without compromising product yield. The definition of acceptable palladium levels is highly dependent on the location of the metal-catalyzed step in the synthesis. Metal-catalyzed processes located early in the synthesis allow for the opportunity to purge impurities further downstream, if there is the ability to do so, in order to meet the regulatory requirements displayed in Table 1. Therefore, based on the overall process, targets for residual palladium may be variable, something which is also seen in the case studies within this publication.

The following sections describe the strategies available for metal removal, the various approaches within each technique, and how these have been applied in industrial examples to scavenge palladium. This Review focuses on palladium, as it is one of the most commonly used metals used in the manufacture of pharmaceuticals. The majority of case studies selected exemplify large-scale applications of scavenging, with some illustrative examples of the use of novel scavengers that have yet to be utilized on an industrial scale. Certain case studies that have been covered in previous reviews, however, are included herein for completeness.^{17–20} Schemes in each section display the metal-catalyzed reaction, followed by the metal removal protocol, with an indication of the largest scale on which the process has been reported when values have been disclosed by the authors. Parts per million (ppm) values

demonstrating the lowest palladium contents achieved using the removal protocol are also displayed when these values have been disclosed in the publication.

2. ADSORPTION

Adsorption is an interfacial phenomenon and refers to the adhesion of particles onto a surface, the adsorbent, forming a film of adsorbate. It is therefore imperative that, for an efficient sorption process, the adsorbent possesses a large surface area, which will maximize the interfacial interaction with the adsorbate. This is typically achieved by a high surface area to volume ratio and the introduction of porosity that further increases the surface available for sorption. The surface forces involved in the adsorption process can range from weak van der Waals forces to electrostatic attractions and strong covalent bonding. The nature of the interfacial interactions is dependent on the identity of the species involved, which dictates whether physisorption or chemisorption will take place (Figure 1).²⁴ In physisorption, no electronic perturbation is induced upon the adsorption of the atom or molecule onto the surface, and the process is governed by van der Waals forces. On the other hand, chemisorption is a result of strong electrostatic forces between the two components and may be irreversible due to chemical bonding interactions.

In the context of metal extraction, adsorption is the process via which palladium is sorbed onto chemical moieties on a solid scaffold. Treatment of solutions with solid-supported scavengers is highly practical, as the formation of a heterogeneous mixture facilitates the metal removal process. The use of solid adsorbents allows the filtration of the metal from solution to give product-rich liquors, whereas in homogeneous scavenging either phase separation or crystallization is required for physical separation of the product from the metal.

Solid adsorbents exist in the form of simple silica gels or activated carbon, which can be relatively inexpensive.¹⁹ In more challenging metal removal cases, more specialized adsorbents have been developed, such as functionalized resins.²⁵ Treatment with solid adsorbents comes with a number of associated considerations, including the formation of new impurities during treatment, leaching of impurities from the adsorbent, and yield losses due to indiscriminate adsorption of the metal and product.²⁶ Steric hindrance introduced by the solid support may also limit diffusion to the chemical functionalities responsible for removing metals, resulting in the need for a large excess of extractant to be used to ensure maximal metal removal.²⁷

The loose powder form of solid adsorbents also poses issues when applied to an industrial-scale synthesis, with the key challenges arising during filtration and the cleaning of vessels.

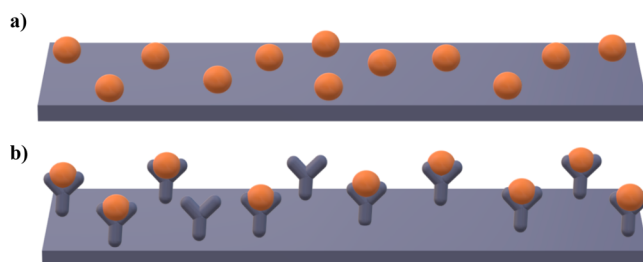


Figure 1. Two adsorption processes are (a) physisorption and (b) chemisorption.

This issue, however, can be addressed through the recirculation of the crude material through an adsorbent-packed bed. Furthermore, highly functionalized adsorbents may be complex to synthesize, making them expensive on a per kilogram basis. To determine the most suitable treatment conditions for a system, it is common practice to screen several adsorbents and determine the selectivity factor, α .^{28,29} This is calculated using the concentrations of the product (x_{prod}) and impurity (x_{imp}) within the liquors according to eq 1.

Calculation of the selectivity factor, α , for a system containing a product and an impurity.

$$\alpha = \frac{\frac{1 - x_{\text{imp}}}{x_{\text{imp}}}}{\frac{1 - x_{\text{prod}}}{x_{\text{prod}}}} \quad (1)$$

The role of the selectivity factor is to quantify how preferential the adsorption of impurity is over the adsorption of product. A high impurity concentration in the liquors would give a smaller value in the numerator, whereas a low product concentration in the liquors results in a large value in the denominator. Consequently, excellent removal of impurities without any product removal would result in a high selectivity value. Use of the selectivity factor gives categorical evidence of the performance of extraction processes, which may otherwise be challenging to assess purely based on the percent material remaining in solution after impurity removal. Calculation of α finds significant utility in the process development of metal extraction processes, as each chemical system is unique and no general prescribed method has been identified to tackle all metal removal problems without the need for optimization. As a result, a systematic approach is required to identify the most appropriate extractant for each individual case, something that is simplified by the comparison of selectivity factors.

With the fundamental principles established, a range of scavengers will now be discussed.

2.1. Silica-Based Scavengers and Resins. Functionalized silicas have numerous operational and performance features that make them favorable for metal removal from larger scale processes, such as compatibility with a range of solvents and excellent stability.^{12,25} Additionally, control over the properties of silica, such as porosity, particle shape, and size, offers additional opportunities for modification of the adsorbent to better suit the process. Silica can be functionalized to incorporate a variety of moieties, with the most frequently used scavengers being sulfur-based due to the element's high affinity for platinum group metals. Examples are shown in Figure 2 and include mercapto-modified silica **1**, aminosulfide-modified silica **2**, (thio)acetic acid-modified silica **3**, and trimercaptotriazine (TMT) modified silica **4**. The

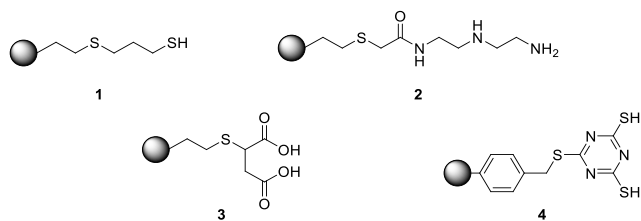


Figure 2. Examples of sulfur-based functionalized silicas. Gray spheres represent the silica support.

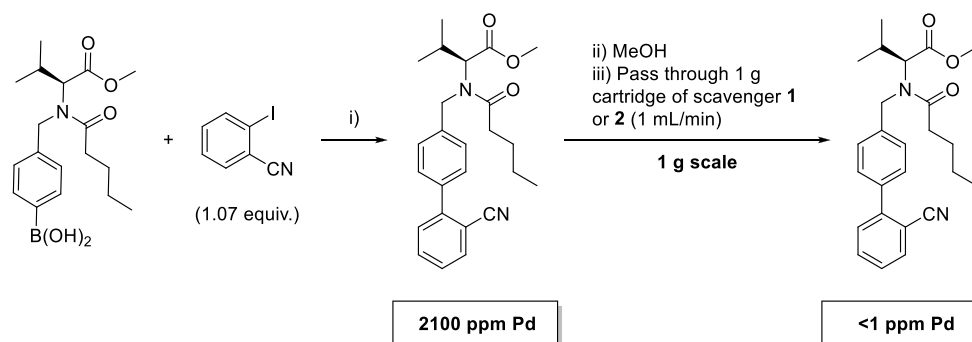
versatility in the design of silica scavengers allows for the presence of multiple functionalities, enabling the use of a single scavenger for the removal of a species in multiple oxidation states. The typically high functional group loading on the silica allows for the removal of high metal contents using a low scavenger mass, while more sophisticated adsorbents are more selective toward metals relative to product, resulting in reduced yield losses. This is achieved through surface modification (end-capping) of the silica to render it non-acidic and unreactive, as well as the refinement of the reactive moieties that will coordinate to the metal.

Functionalized silicas have been applied in metal removal from a variety of coupling reactions commonly used in the synthesis of pharmaceutical molecules.^{30–35} PhosphonicS demonstrated the excellent scavenging ability of their sulfur-based silica scavengers in the literature for a range of case studies. For the Suzuki reaction in Scheme 1, en route to angiotensin II antagonist valsartan, reduction of the palladium content from 2100 ppm to <1 ppm was achieved using scavengers **1** and **2** based on a 1 g input of starting material.²⁵

The metal-removal ability of silica-based scavengers in the presence of a range of functionalized organic molecules was very aptly illustrated in the same study, where the coupling products of Sonogashira, Heck, Suzuki, and Buchwald–Hartwig reactions were analyzed for metal content. Metal extraction was successful for an array of functionally diverse molecules on a 1 g scale, with the products in Figure 3 containing several polar moieties, including amines, amides, and esters.²⁵ Although the extraction conditions described were unoptimized, the authors highlight that the efficiency of metal removal can be fine-tuned using experimental conditions such as temperature, concentration, and contact time with the silica and silica functionalities. The authors acknowledge that the effect changing these conditions has on metal removal is also dependent on the nature of the organic molecule from which the metal is scavenged and suggest that optimization is required on a case-by-case basis.

The use of sulfur-based silica scavengers has been demonstrated on a 20 kg batch scale by AstraZeneca in collaboration with PhosphonicS, where palladium removal from a Buchwald–Hartwig amidation was required.¹² Although palladium removal was successful to relatively low levels (Table 2), the batch cycle time was deemed unsuitable for long-term large-scale operations. Analysis of the data from batch 2 demonstrated that a total of 38 h was required for the scavenger operations, which included a 5 h long filtration and a 10 h vessel clean postscavenging. Simultaneously, the potential health hazards associated with the prescavenging and postscavenging handling of the silica reduced the ease of operability of the process. Overall, the scavenging process with loose functionalized silicas lacks modularity, as there is no dedicated equipment that can be taken out of the equipment chain following the process, which would simultaneously eliminate operator exposure to the material.

Working with PhosphonicS and Amazon Filters Ltd., AstraZeneca prototyped polypropylene cartridges that can be packed with up to 500 g of scavenger and fitted in existing plant equipment. The semicontinuous metal removal process was successfully applied to an α -arylation case study, where the amount of palladium was reduced from 600 to 15 ppm in two 4 kg batches by passing the crude reaction mixture through five silica cartridges containing SPM32 silica in series (Scheme 2). Further scale-up to meet the needs of a 30 kg pilot plant

Scheme 1. Palladium Removal Following a Suzuki Reaction Using Phosphonic Scavengers 1 and 2^a

^a(i) Pd(PPh₃)₄ (1 mol %), DME/EtOH/H₂O (7:3:2), Na₂CO₃ (4.3 equiv), 12 h, reflux.

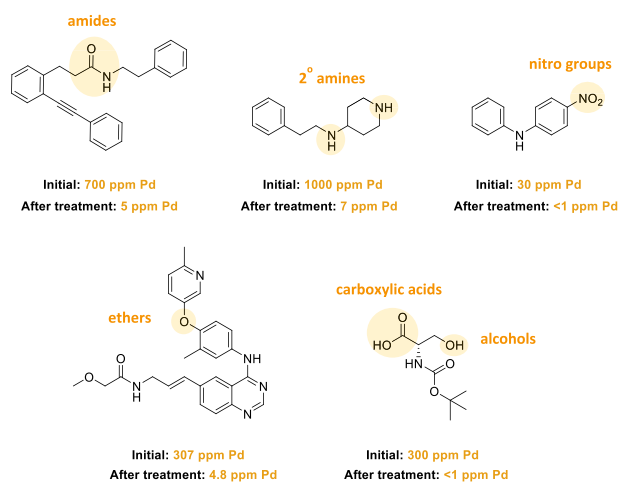


Figure 3. Products of coupling reactions in which functionalized silicas were effective in metal removal on a small scale. The range of functional groups present in the molecules is highlighted in orange.

Table 2. Palladium Removal from Two Batches of a Buchwald–Hartwig Amidation Product^a

batch	initial Pd level (ppm)	final Pd level (ppm)	Pd removed (%)
1 ^b	992.1	190.2	81
2 ^c	455.6	25.4	94

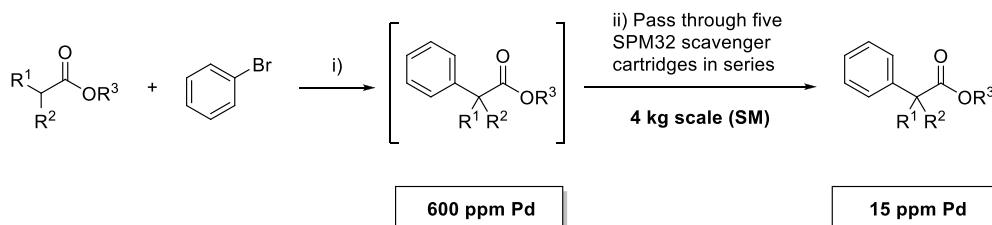
^aConditions: Pd₂dba₃, XPhos, CsCO₃ (equiv not specified). Conditions for Pd removal: SPM36f (0.5 wt), 60 °C, 80 h (batch 1), 18 h (batch 2). ^bThe ratio of scavenger to Pd (kg/kg) was 6.5.

^cThe ratio of scavenger to Pd (kg/kg) was 12.9.

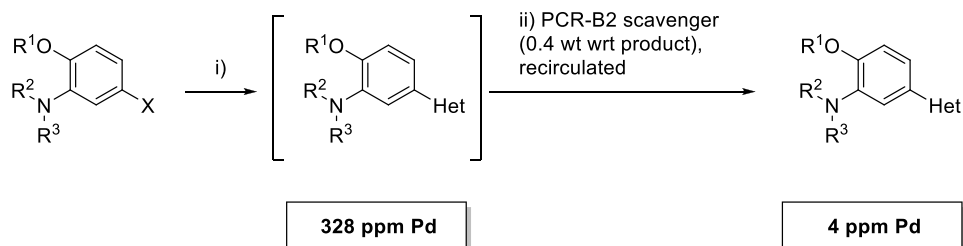
campaign was achieved without the need for further development work, as the purification protocol involved a simple upgrade to a 19-cartridge filter unit. Through this development, the concerns regarding safety and handling issues were alleviated, enabling the facile transfer of the scavenging process to a plant scale.

Recirculation of the solution through cartridges with polychelated resins was also demonstrated to be an effective method for metal removal by pharmaceutical company Teijin Limited.³⁶ In the synthesis of an intermediate using a Negishi C–C bond-forming reaction, the THF and anisole solution of the product contained 328 ppm residual palladium (Scheme 3). Treatment in recirculation mode with PCR-B2, a scavenger whose base is a copolymer of poly(glycidyl methacrylate) and divinylbenzene, at 0.4 wt relative to the intermediate achieved a reduction of palladium down to 4 ppm.

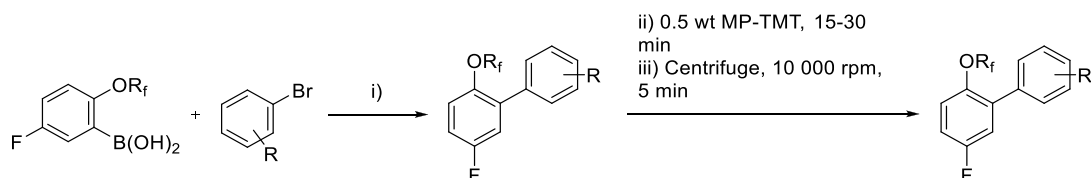
The trimercaptotriazine (TMT) group has also found significant adoption in the field of scavenging, with the moiety being used in both functionalized resins and silicas in a range of examples, including as a candidate in scavenger screening libraries and on a large scale. The selectivity of polystyrene-bound TMT for palladium over organic product was demonstrated in a scavenger screen for a Suzuki–Miyaura biaryl coupling reaction (Scheme 4).²⁸ In an adsorbent screening protocol developed by Merck research scientists, 50 mg of 29 different adsorbents were used in microcentrifuge tubes for the rapid assessment of the scavenging ability of the adsorbents. Microporous polystyrene-bound TMT (MP-TMT) showed superior performance relative to the other 28 resins evaluated, with over 95% of product 7 remaining in the supernatant while over 90% of palladium was extracted out of solution. In relation to the selectivity factor calculation in eq 1, this gave a selectivity of over 190, whereas the second-best-

Scheme 2. α -Arylation Reaction for Which the Semicontinuous Palladium Removal Method Was Used with a Phosphonic Scavenger^a

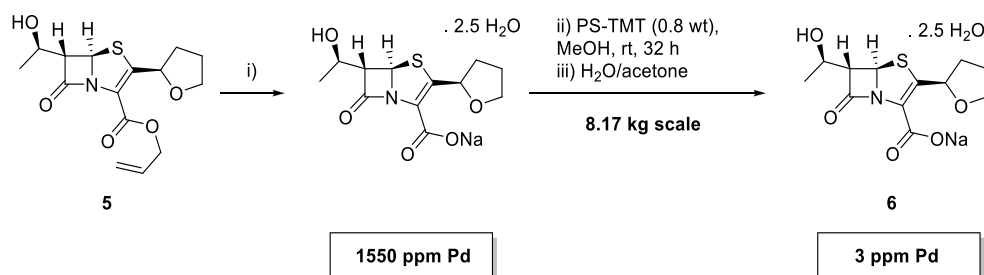
^a(i) [Pd(μ -Br)[P(^tBu)₃]]₂, LDA, toluene (equiv not specified).

Scheme 3. Removal of Palladium from an Intermediate Synthesized Using a Negishi Coupling^a

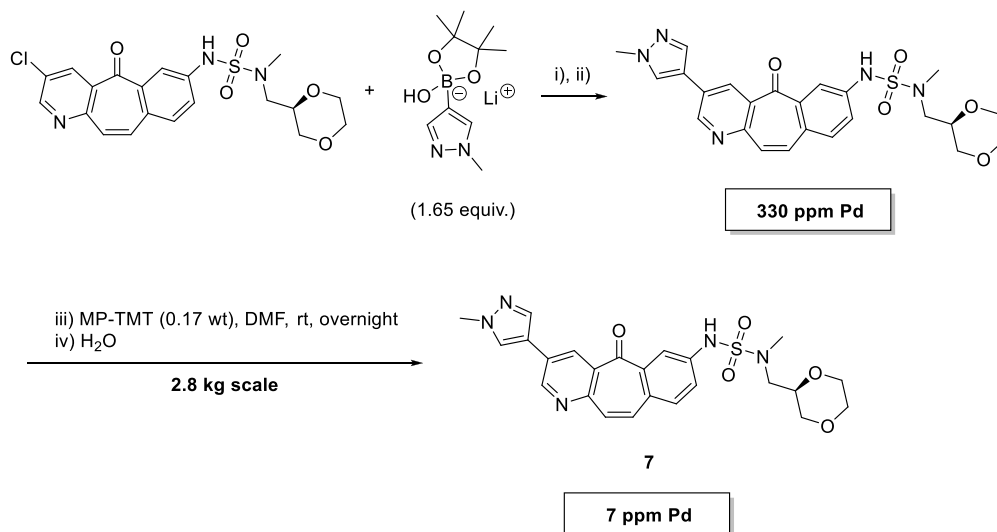
^a(i) Pd catalyst, Zn, THF/anisole (equiv and conditions not specified).

Scheme 4. Suzuki–Miyaura Biaryl Coupling Reaction Used for the Screening of a Large Range of Adsorbents on a Small Scale^a

^a(i) Conditions not specified.

Scheme 5. Palladium Removal Following the Allyl Deprotection of 5 Using MP-TMT^a

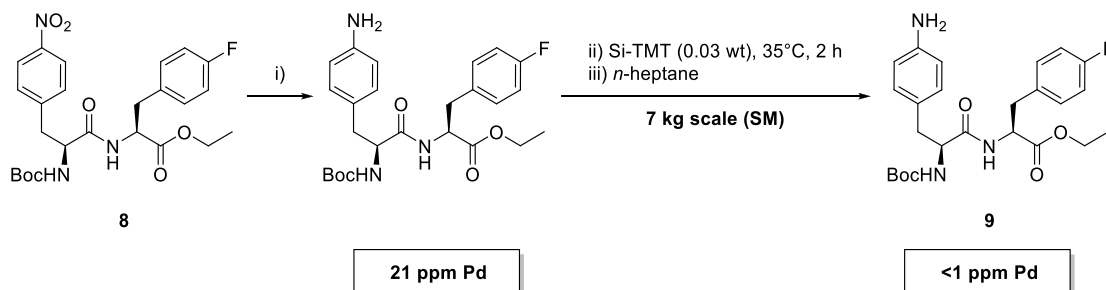
^a(i) Sodium 2-ethylhexanoate (1 equiv), Pd(PPh₃)₂Cl₂ (2.3 mol %), PPh₃ (12 mol %), EtOAc, rt, 5 h.

Scheme 6. Palladium Removal Following a Final-Step Suzuki Reaction Using MP-TMT^a

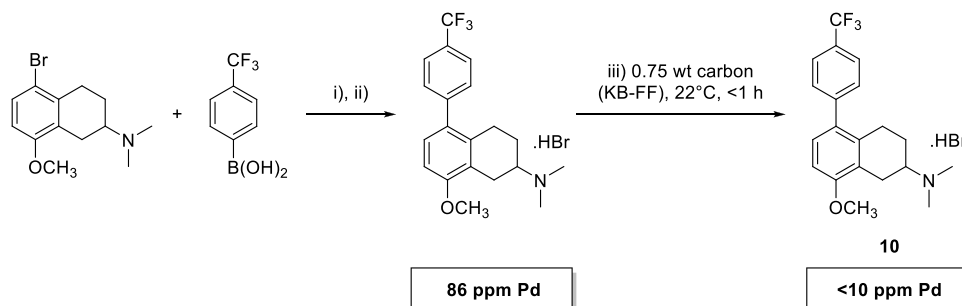
^a(i) Pd(P^tBu₃)₂ (0.6 mol %), DMF, 100 °C, 1 h; (ii) Ecosorb C-941 (0.11 wt), 22 °C, 1.5 h.

performing resin had a selectivity of just under 120. A drawback of these resins, however, is that they do not appear to be amenable to regeneration, even following repeated

washings. The strong association of metal to the adsorbent decreases its overall cost-effectiveness, as the resin cannot be recovered for reuse at the end of the treatment. The higher

Scheme 7. Palladium Removal Following the Hydrogenation of a Nitro Group En Route to Melflufen Using Si-TMT^a

^a(i) Pd/C (5 mol %, 50% moist), H₂ (2 bar), 2-MeTHF, 35 °C, 4 h.

Scheme 8. Palladium Removal from a Suzuki Coupling Reaction Using Activated Carbon (KB-FF)^a

^a(i) Pd(OAc)₂, P(*o*-tolyl)₃ (equiv not specified); (ii) HBr (equiv not specified).

cost of these resins over activated charcoal could be a consideration on a larger scale. However, as the metal can be recovered by incineration of the resin, resulting in significant financial returns, cost calculations of the process may show that the use of these resins is viable at scale. In the case of the Suzuki–Miyaura reaction, silica was found to exhibit satisfactory selectivity for metal removal; hence, its use was preferred over that of the MP-TMT resin, even at 2 wt loading.

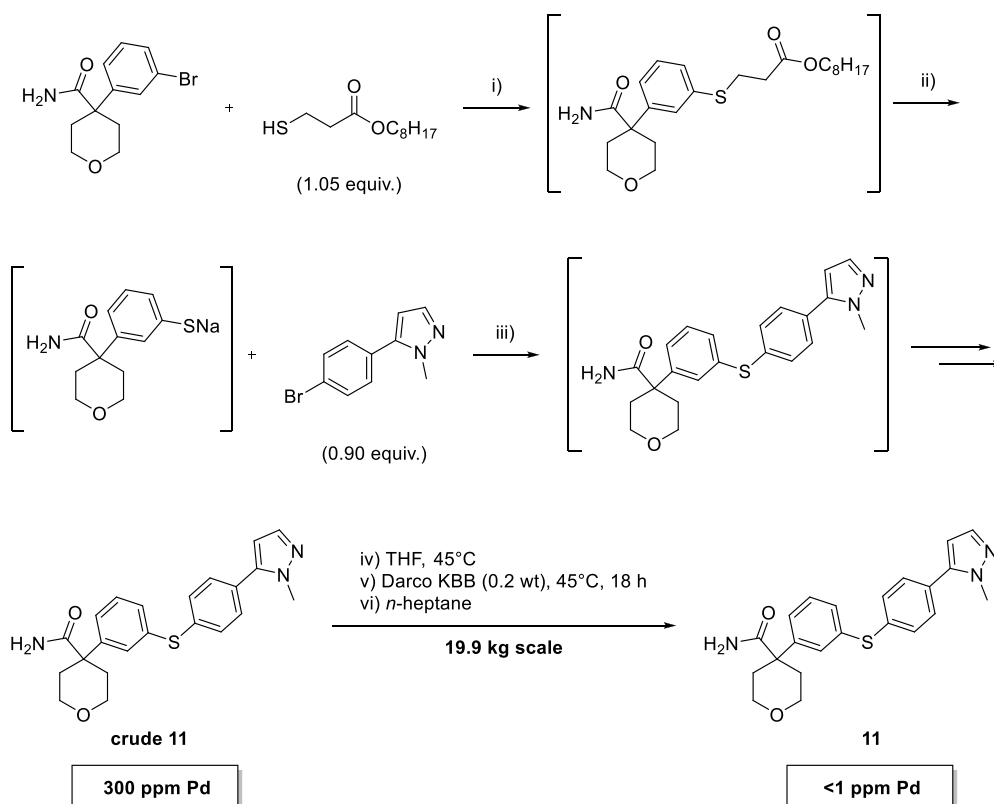
Similarly, polystyrene-bound TMT was used on a multikilogram scale by scientists at Fudan University in China following the allyl deprotection of **5** to produce faropenem sodium salt **6** (Scheme 5).³⁷ Treatment of a methanolic solution of 8.17 kg of faropenem sodium salt with 0.8 wt polystyrene-bound TMT resulted in the removal of palladium down to 3 ppm from an initial content of 1550 ppm. Interestingly, during optimization of the extraction process it was observed that prolonging treatment time or increasing the resin amount did not significantly improve the palladium extraction when the resin itself had a low functional group loading (0.30 mmol TMT/g). However, when the functional group loading on the resin was increased to 0.58 mmol TMT/g, a more noticeable effect was obtained when the scavenging time was extended from 15 to 32 h, with the performance not improving further at 46 h. Similarly, increasing the ratio of the resin to crude from 0.4 to 0.8 g/g also resulted in a significant increase in the scavenging performance.

The use of microporous (MP) polystyrene TMT was demonstrated in the endgame of a c-Met kinase inhibitor **7** by Merck (Scheme 6).³⁸ Following the final Suzuki cross-coupling reaction, overnight aging of the crude API with 0.20 wt MP-TMT was trialed in a range of polar aprotic solvents such as DMF, DMSO, DMAc, and NMP. This resulted in the reduction of palladium levels from 330 ppm to approximately

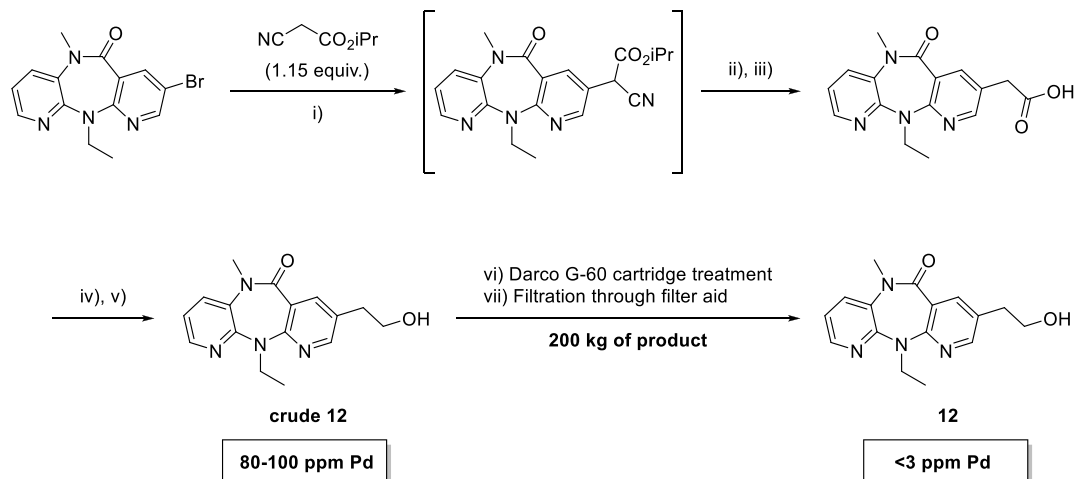
10–30 ppm, with the use of DMF giving the highest removal efficiency and hence being used at scale. The process was demonstrated on a 3.2 kg input of starting material, resulting in 7 ppm palladium in the final product.

The use of silica-supported TMT for palladium removal has also been reported on an industrial scale by Magle Chemoswed and Recipharm, in the process development of Melflufen.³⁹ Following the hydrogenative nitro-reduction of intermediate **8**, palladium levels were higher than the intended target, and a metal removal method was sought (Scheme 7). Treatment with 0.03 wt Si-TMT for 2 h at 35 °C demonstrated the best performance against nine other removal protocols, including thiol- and amine-functionalized silicas, as well as MP-TMT. The chosen treatment achieved the reduction of palladium levels in compound **9** to <1 ppm and was adopted on a 7 kg scale, followed by an antisolvent crystallization.

Several more case studies of the successful use of functionalized silicas and resins have been reported by pharmaceutical companies, demonstrating their utility and applicability on an industrial scale.^{40–46} An additional benefit exhibited by functionalized silica scavengers is the ease of metal recovery via incineration. This is a favorable property, as metal catalysts typically account for approximately 5–20% of total manufacturing costs; hence, recovery and potential recycling of the metal are highly beneficial in making the process as economical as possible.⁴⁷ Solvent extraction methods may require a high number of solvent volumes and repeated washes to achieve sufficient metal removal, which, in turn, results in a large volume of waste. This not only negatively impacts the process mass intensity but also implies that transport and incineration of large volumes of high boiling solvent or water will be required if palladium recovery is desired. The use of solid scavengers circumvents this issue by reducing the bulk of

Scheme 9. Palladium Removal Using Activated Carbon Treatment on Pfizer's Drug Candidate Following the Palladium-Catalyzed Telescope Reaction Sequence^a

^a(i) Pd₂(dba)₃ (1 mol %), Xantphos (2 mol %), DIPEA (2 equiv), toluene, reflux, 2 h; (ii) NaO^tAm, *n*-PrOH, toluene, 80 °C; (iii) Pd₂(dba)₃ (0.5 mol %), Xantphos (1 mol %), NaO^tAm (2.2 equiv), *n*-PrOH, 80 °C, 18 h.

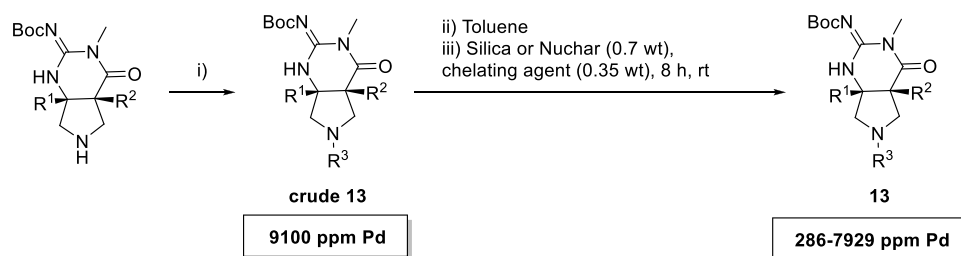
Scheme 10. Use of Activated Carbon for Palladium Removal Following the Arylation/Hydrolysis/Reduction Sequence^a

^a(i) Pd(OAc)₂ (1 mol %), PPh₃ (4 mol %), 60% NaH (2.5 equiv), toluene, 100 °C, 1.5 h; (ii) IPA, 35 °C, 20 min; (iii) 1 M NaOH (aq), 80 °C, 8 h; (iv) HCl (g); THF; (v) NaBH₄, diglyme, 0–22 °C.

material that needs to be transferred for either disposal or metal recovery, as well as the material being in a state that is more easily transported.

2.2. Activated Carbon. Activated carbon is one of the most inexpensive adsorbents used, with the cost of one of the simplest types of activated carbon being less than £87/kg.⁴⁸ Carbon is generated by the pyrolysis of carbon precursors at

high temperatures, followed by either chemical or steam activation to induce further porosity within the carbonized structure.⁴⁹ A wide range of activated carbon adsorbents are available, such as Darco KB-B and Ecosorb C-941, which have been activated using different chemical agents and are affixed onto an inert support, such as polymers, to give them distinct flow characteristics.^{28,50} In the case of Novartis compound 10,

Scheme 11. Palladium Removal from Crude 13 Following a Buchwald–Hartwig Coupling Reaction^a

^a(i) Pd(OAc)₂, R³Cl, phosphine ligand (equiv not specified).

activated carbon demonstrated superior palladium removal compared to specialized scavengers, achieving levels of palladium below the threshold of 10 ppm while being one of the lowest-cost adsorbents trialed (Scheme 8).¹⁷

The use of activated carbon treatment, however, presented some issues, including the adsorption of up to 0.6 g of product 10 per gram of activated carbon. The indiscriminate adsorption of both metal and product is highly undesirable, as it results in a reduction in yield, and further processing is required to ensure maximal recovery of material. This includes the use of large volumes of solvent to attempt product recovery, resulting in the production of large volumes of waste. Partial recovery of the material was achieved using a wash of the adsorbent following filtration; however, palladium was also leached back into the solution as a result of this wash.

In the case of asthma treatment candidate 11 developed by Pfizer (Scheme 9), a three-step one-pot synthesis was employed, which included two palladium-catalyzed reactions in sequence without isolation to construct the molecule.⁵¹ A purity upgrade and polymorph control step did not result in sufficient control of the palladium-related impurities. It was therefore decided to pursue an additional purification step to remove metal impurities. Both activated charcoal and a thiol-3-functionalized silica were effective in achieving the desired palladium levels; however, the lower cost of activated charcoal was more attractive for scale-up. Agitating a THF solution of crude 11 with 0.2 wt Darco KB-B at 45 °C for 18 h, followed by filtration and antisolvent crystallization with heptane, resulted in the decrease of palladium levels from 300 to <1 ppm. The scavenging process was carried out on a 19.9 kg input, with 19.3 kg of purified API being recovered at the end of the process, demonstrating limited loss of product to the activated charcoal treatment with a 97% yield and exhibiting excellent scalability.

Another example of use of activated carbon in the purging of palladium from the process stream can be found in the route toward a nevirapine analog produced for the treatment of HIV by Boehringer Ingelheim (Scheme 10).^{52,53} Typical pilot plant batches of late-stage intermediate 12 contained palladium in the range 80–100 ppm, which was unacceptably high. Through the evaluation of a range of palladium removal methods, it was revealed that metal levels could be controlled via filtration through a 45 μm filter disc or Celite. This demonstrated that the use of a chelator was not necessary, as the palladium was likely present in a macroscopic form. The treatment protocol adopted for manufacturing involved treatment of the material with a charcoal cartridge, followed by filtration through a filter aid, and was used to manufacture 200 kg of alcohol 12.

2.3. Solid Support/Chelating Agent Binary System.

Occasionally, treatment of solutions with functionalized silica resins may result in undesired effects, such as the formation of novel impurities. Researchers from the Merck Research Laboratories encountered this issue during palladium scavenging following the Buchwald–Hartwig coupling reaction in Scheme 11, where treatment with thiol-based scavengers had an undesired effect on the purity of product 13.²⁹ Although a triamine-functionalized silica was initially found to be successful in achieving the target final metal content while generating no novel impurities, pilot plant batches of the API failed to meet the palladium specification, which was set at ≤33 ppm. Due to the relatively high cost of the triamine scavenger, use of this process on a large scale was prohibitive and the focus was shifted to investigating binary metal scavenging systems, where a chelating agent was used in conjunction with a solid support to form an *in situ* scavenger. Different combinations of the solid support and chelating agent resulted in a range of final metal contents, as displayed in Table 3.

Merck researchers theorized that the mechanism of metal scavenging of the binary system could stem from either of the two options demonstrated in Figure 4. In the first scenario, the scavenger–metal chelate is formed in solution, which is then followed by the adsorption of the chelated metal onto the solid support, immobilizing the palladium and enabling removal by

Table 3. Palladium Removal Performance Using Binary Systems vs Solid Support Alone^a

entry	solid support and chelating agent	residual Pd (ppm)	Pd removed (%)
1	Nuchar AquaGuard alone	6450	28
2	Nuchar AquaGuard +1,2-ethanedithiol	<286	>97
3	Nuchar AquaGuard + ethylenediamine	924	90
4	Nuchar AquaGuard +2-mercaptoethanol	1603	82
5	silica gel alone	6097	33
6	silica gel +1,2-ethanedithiol	649	93
7	silica gel + ethylenediamine	2661	71
8	silica gel +2-mercaptoethanol	2421	74

^aConditions: toluene solution of 13 (9100 ppm Pd w.r.t. 13), Nuchar (0.7 wt), chelating agent (0.35 wt), rt, 8 h.

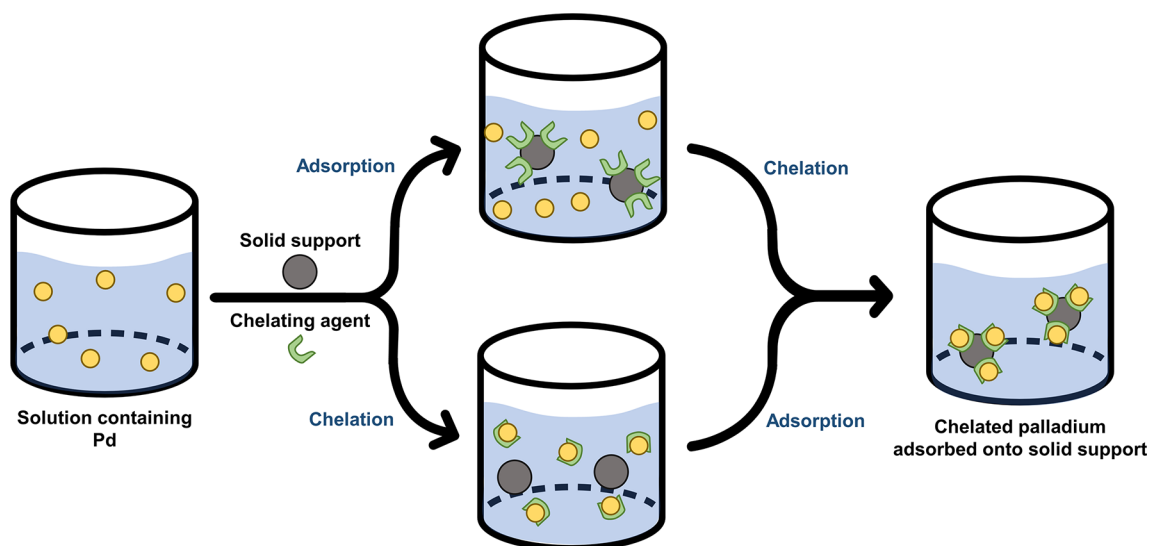
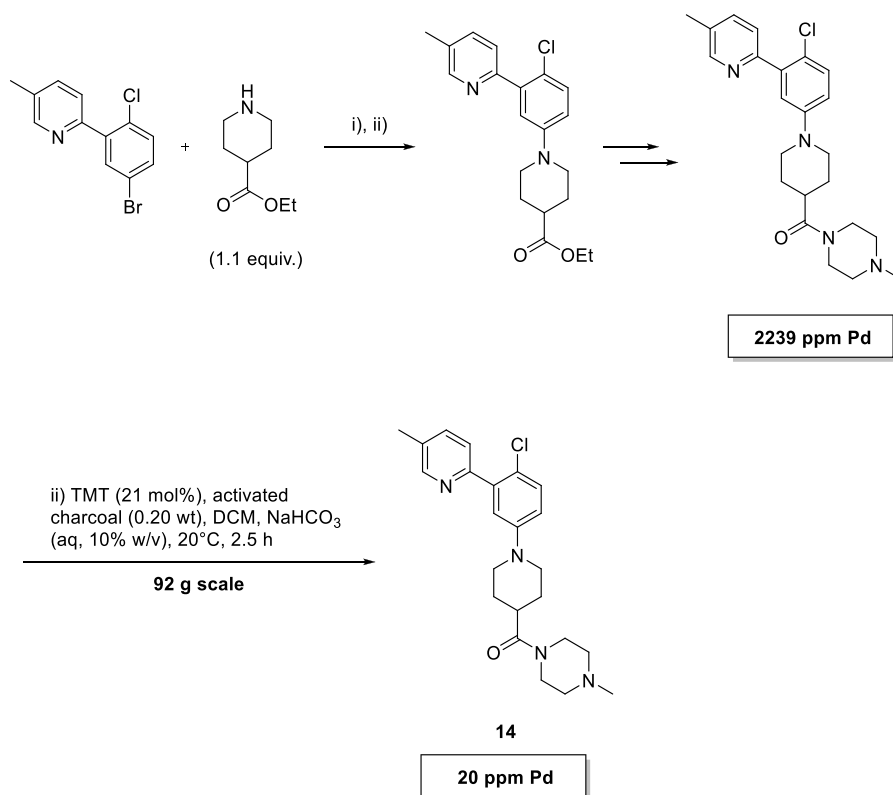


Figure 4. Process of palladium removal using the binary system proposed by Merck. The two potential extraction mechanisms, where chelation and adsorption take place in a different order, are shown. Adapted with permission from ref 29. Copyright 2011 American Chemical Society.

Scheme 12. Palladium Removal Following the Buchwald–Hartwig Amination Reaction En Route to SMO Receptor Agonist 14^a



^a(i) Pd(OAc)₂ (5.9 mol %), BINAP (6.3 mol %), CsCO₃ (3 equiv), toluene, 110 °C, 2 h; (ii) activated charcoal (0.25 wt), 25 °C, 1.5 h.

filtration. Alternatively, the scavenger is immobilized onto the solid support by adsorption first, and the newly functionalized solid support then extracts palladium from the solution, which is removed by filtration.

Combining Nuchar AquaGuard activated carbon at 0.7 wt relative to crude 13 and the chelating agent at 0.35 wt relative to crude 13 gave excellent palladium removal from small-scale solutions, as seen in Table 3. The data demonstrate that the

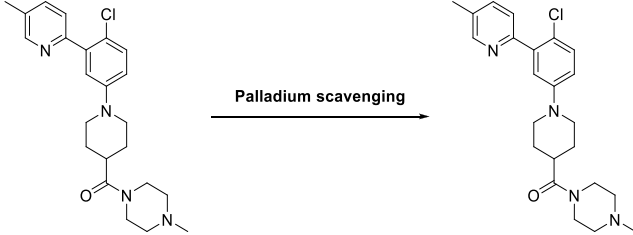
binary systems have a superior performance to simply using Nuchar AquaGuard or silica gel alone. In the case of Nuchar AquaGuard, the metal removal achieved from an initial solution containing 9100 ppm palladium was 28%, while a combination of Nuchar AquaGuard and 1,2-ethanedithiol resulted in >97% metal removal. An improvement of a similar magnitude was observed with 1,2-ethanedithiol and silica gel, where 33% palladium removal was achieved using silica gel

alone, whereas the combination of silica gel and 1,2-ethanedithiol gave 93% removal. The mechanisms proposed in Figure 4 are supported by the fact that all chelating agents in Table 3 are liquid and hence would be unable to extract palladium from the product stream simply through mixing. The mode of action is also supported by the observation that mixing the extractant and solid support from Table 3, entry 3 in solvent resulted in 50% adsorption of the extractant onto the scaffold. This was determined by examination of a solution of the liquid scavenger and the solid support in toluene after the solution was stirred at room temperature for 60 h, proving the formation of an *in situ* scavenger. Changing the addition order of the scavenger and solid support did not produce a difference in scavenging performance, suggesting that both of the mechanisms proposed by Merck researchers in Figure 4 contribute to metal removal.

The synergistic effect of the binary system was demonstrated on a multigram scale by chemists at Siena Biotech during the synthesis of an SMO receptor antagonist 14 (Scheme 12).⁵⁴ As the metal-catalyzed reaction was performed three stages before the final step, development scientists did not include a purification unit operation until after the API was synthesized. This was done because they theorized that intermediate crystallizations would be successful at partly reducing the palladium burden, simplifying the purification process downstream. Indeed, the palladium content was reduced by a factor of 5; however, levels were still outside specifications set by the team.

A range of scavengers were screened, one of them being a combination of trimercaptotriazine (TMT) and activated charcoal. TMT demonstrated a synergistic scavenging effect in the presence of activated charcoal, decreasing palladium levels beyond those achieved when activated charcoal was used on its own. The data are summarized in Table 4, with entries 2 and 4 highlighting the increased scavenging performance of the binary system relative to the single scavenger system, as well as relative to the other scavengers trialed. The scavenging protocol was demonstrated on a 92 g input, with palladium levels in compound 14 being reduced from 2239 to 20 ppm

Table 4. Scavengers Trialed in the Removal of Palladium from the Final Product



entry	scavenger	residual Pd (ppm)
1	no scavenger	1843
2	TMT/activated charcoal ^a	61
3	NaHSO ₃ ^b	190
4	activated charcoal ^c	379
5	polymer-bound tris(aminomethyl)amine ^d	704

^aConditions: TMT (20 mol %), activated charcoal (0.2 wt), DCM, 20 °C, 2 h. ^bConditions: NaHSO₃ (4 equiv), DCM/H₂O (1:1), reflux, 2 h. ^cConditions: activated charcoal (0.1 wt), DCM, 20 °C, 16 h. ^dConditions: polymer-bound tris(aminomethyl)amine (0.5 wt, 3.5–5.0 mmol/g loading), DCM, 20 °C, 16 h.

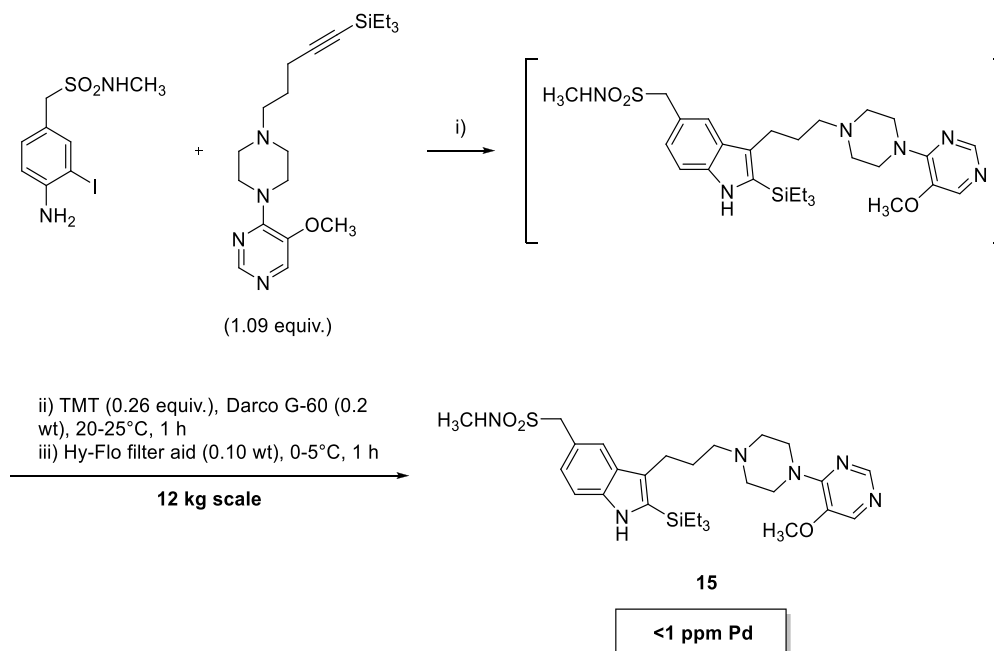
following treatment. The reported yield following treatment was 82%, indicating potential material loss to the scavengers, which has been noted in other case studies using activated charcoal.

The same binary system was used by Bristol-Myers Squibb in the palladium removal following a Larock indolisation reaction to give compound 15 (Scheme 13).⁵⁵ The TMT/charcoal treatment achieved the reduction of palladium without compromising yield and with no detection of residual TMT in the product. Treatments of both the biphasic and the organic phase alone were trialed in the presence and absence of the chelating agent, achieving consistent reduction of the metal content in the final product relative to treatment with Darco G-60 alone. The process was demonstrated to be successful on a 12 kg scale, with palladium levels ranging from 0.1 to 2.2 ppm.

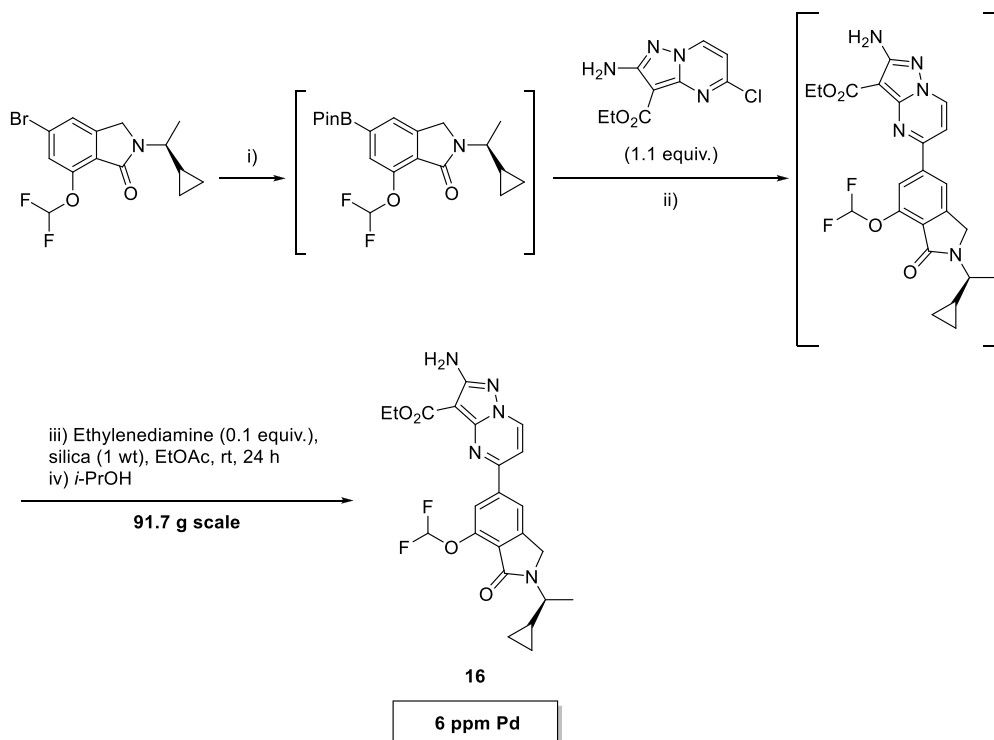
Similarly, a silica/ethylenediamine binary scavenger protocol was used by Arcus Biosciences following a tandem borylation/Suzuki reaction sequence (Scheme 14).⁵⁶ Commercially available activated charcoal treatments were trialed; however, there were practical challenges with these protocols due to clogging of the filter, which did not improve upon the use of a filter aid. Subsequently, palladium scavenging using dithiocarbamates was attempted; however, sufficient metal removal could not be achieved. The use of ammonium pyrrolidine dithiocarbamate (APDTC) and sodium diethyl dithiocarbamate (NaDEDTC) at 20 mol % loading for 1 h at 23 °C only achieved palladium levels of 4437 and 7516 ppm, respectively, on a stream containing an initial 8634 ppm palladium. It was then established that treatment with 1 wt silica and 0.1 wt ethylenediamine followed by filtration and recrystallization from isopropanol resulted in satisfactory palladium levels in intermediate 16, which were further reduced during subsequent synthetic steps.

2.4. Isocyanides. The use of isocyanides as scavengers was first reported for the removal of ruthenium following metathesis reactions; the scavengers operate by the formation of an isocyanide insertion complex of the catalyst.⁵⁷ This complex was determined to be polar and easily removed by silica gel chromatography, giving ruthenium contents down to single-digit parts per million following the use of a range of ruthenium carbene catalysts. Since the initial discovery for their potential use as metal extractants, further refinement of the properties of the isocyanides was carried out, with noncovalently immobilized scavengers on silica gel being reported several years later as a method of semiheterogeneous purification following ring-closing metatheses.²⁷ On the basis of the suitability of isocyanides for the removal of a late transition metal, it was envisaged that similar reactivity could be observed with palladium. Although these scavengers have not been used on scale to date, they are included in this Review for completeness. Silica-supported isocyanide 17, soluble isocyanide 18, and isocyanide 19 (Figure 5) were trialed in the removal of palladium from small-scale reactions by scientists at the University at Buffalo in the United States.⁵⁸ Although the latter two isocyanides do not operate via adsorption of the metal, they are briefly discussed in this section for simplicity.

In the first case, palladium removal was attempted from the Buchwald–Hartwig reaction, as shown in Scheme 15. Where simple purification of the reaction crude by filtration through Celite only achieved a final palladium content of 4146 ppm in compound 20, which corresponded to an 84% reduction in

Scheme 13. Palladium Removal from an Indolisation Reaction Using TMT^a

^a(i) Pd(OAc)₂ (10 mol %), PPh₃ (20 mol %), Na₂CO₃ (3.6 equiv), LiCl (1.3 equiv), MeCN, H₂O, reflux, 6–9 h.

Scheme 14. Removal of Palladium Following the Tandem Borylation/Suzuki Coupling^a

^a(i) (BPin)₂ (1.1 equiv), KOAc (3 equiv), PdCl₂(dppf) (0.25 mol %), dioxane, 90 °C, 1 h; (ii) K₃PO₄ (3 equiv), PdCl₂(dppf) (0.5 mol %), dioxane, 90 °C, 1 h.

metal from the initial content, treatment with 17 and filtration resulted in more than 99% of the metal being removed. In the case of 8 equiv of extractant, the metal content was reduced to 1.52 ppm, whereas a higher loading of 16 equiv of extractant gave a metal content of 2.35 ppm. These are comparably low

levels, demonstrating that the extraction is successful even at the lower end of the isocyanide charge.

An important improvement of this extractant relative to the previous isocyanides used in the ruthenium extraction case studies is that the need for chromatographic purification of the resulting mixture is removed. This was not the case for

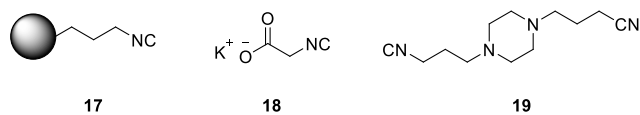


Figure 5. Isocyanide palladium scavengers.

homogeneous extractant **18**, where chromatography was required in conjunction with its use in all cases. This is crucial for the use of this class of extractants in industry, where chromatography is highly disfavored for the purification of large-scale reactions. The success of the heterogeneous isocyanide extractant was also demonstrated comparative to a frequently used silica-based thiol scavenger for the Buchwald–Hartwig reaction displayed in Scheme 16. From an initial palladium content of 221 ppm in the crude, extractant **17** achieved a final metal content of 20.8 ppm in compound **21**, which was slightly better than the performance of a thiol scavenger at a final metal content of 26.1 ppm.

Palladium removal from product **21** was a success for the scavenger, as the diamine moiety in the product had the potential to act as an excellent metal chelator, making the extraction of metals especially challenging. Moreover, the free secondary amine functionalities in the product showed no reactivity with the isocyanide reagent, demonstrating functional group compatibility between the scavenger and amines. Not only was a 10-fold reduction in palladium content achieved but also 96% of the product was also recovered, signifying minimal yield loss to the scavenger.

The versatility in the scavenging capability of isocyanides was tested in the simultaneous removal of palladium and ruthenium following a ring-closing metathesis/Suzuki–Miyaura telescope on a small scale (Scheme 17).⁵⁹ The purification protocol carried out by scientists at the University of Warsaw in Poland included treatment of the crude product **22** with 0.24 equiv of isocyanide **19**, followed by addition of ethanol and 2.5 equiv of citric acid, evaporation of solvents, and filtration through an aluminum oxide cartridge assisted by ethyl acetate. This process resulted in ruthenium and palladium contents of 1.17 and 0.79 ppm, respectively, after evaporation of the filtrate, which further decreased to 0.48 and 0.15 ppm following a recrystallization process. Successful scavenging was demonstrated by comparing the values to a control experiment where the isocyanide was not added, resulting in ruthenium and palladium values of 49 and 467 ppm, respectively.

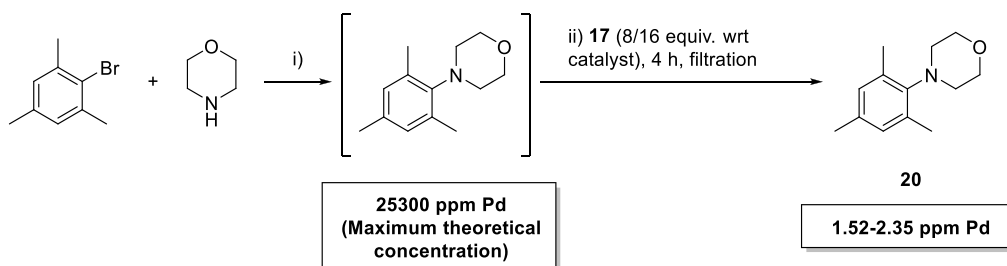
3. EXTRACTION/PRECIPITATION OF METAL COMPLEXES

Extraction is the process in which compounds are separated according to their relative solubilities in two immiscible solvents. This results in the depletion of solute from one solvent and enrichment in the second solvent, in which its solubility is comparatively higher. For a successful extraction, the palladium-related impurity is required to have a significantly different solubility from the drug substance or intermediate so that one can be predominantly found in the aqueous phase while the other is the main component of the organic phase. This would enable the removal of the metal from the phase in which the desired product is most soluble. Extraction in a pharmaceutical setting is typically achieved by chelation of the palladium with a hydrophilic species that allows the transfer of the metal into the aqueous phase while the desired material remains in the organic phase.¹⁷ In the case of precipitation, the impurity becomes insoluble through complexation with an agent, resulting in its facile removal from mixtures through filtration. In the context of palladium removal, the agent typically contains atoms that have a high affinity for palladium, such as sulfur, phosphorus, and nitrogen. The agent may also have multiple atoms able to coordinate the metal, resulting in an entropic benefit arising from the chelate effect.

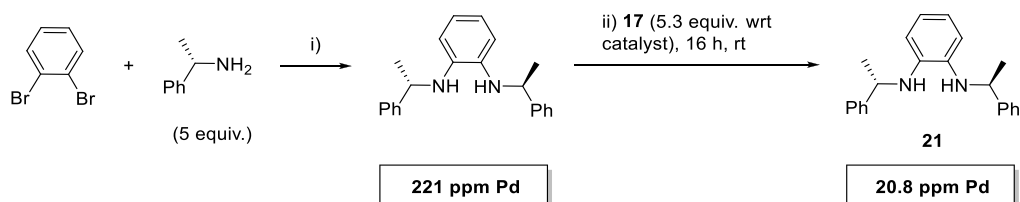
3.1. Sodium Bisulfite. Extraction with sodium bisulfite was identified to operate through the formation of a palladium tetrasulfite complex, Na₆Pd(SO₃)₄·2H₂O, confirming that complexation and formation of an insoluble palladium–extractant species result in the purge of the metal.⁴⁷ Sodium bisulfite as an extractant was found to be the most suitable palladium removal method from a Suzuki–Miyaura coupling employed by GSK for one of their drug discovery programs.⁶⁰ The reaction between indole **23** and boronic acid **24** gave excellent yields of approximately 90% under optimized conditions when product **25** was precipitated with water; however, the palladium content in the product was as high as 12 000 ppm (Scheme 18).

An array of solid scavengers were screened in an attempt to remove the metal via an adsorption or complexation protocol, including Smopex-110, activated carbon, and modified silica and alumina. Only one treatment, a triamine-derived silica, was identified as reducing palladium levels near the target value set by the development team. However, the number of unit operations the solid scavenger would add to the overall process and the relatively high cost were prohibitive in the potential scale up of this workup. The focus was therefore shifted to an extraction/precipitation treatment, where an extractant wash would result in the precipitation of a palladium–extractant

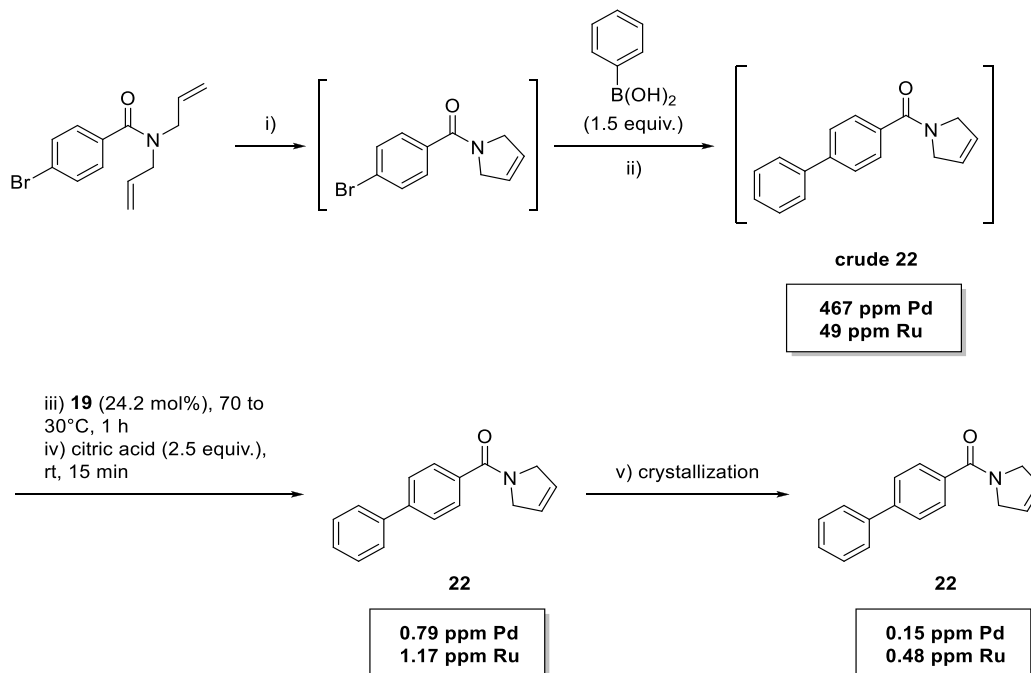
Scheme 15. Palladium Removal from a Buchwald–Hartwig Reaction Using Isocyanide Scavengers^a



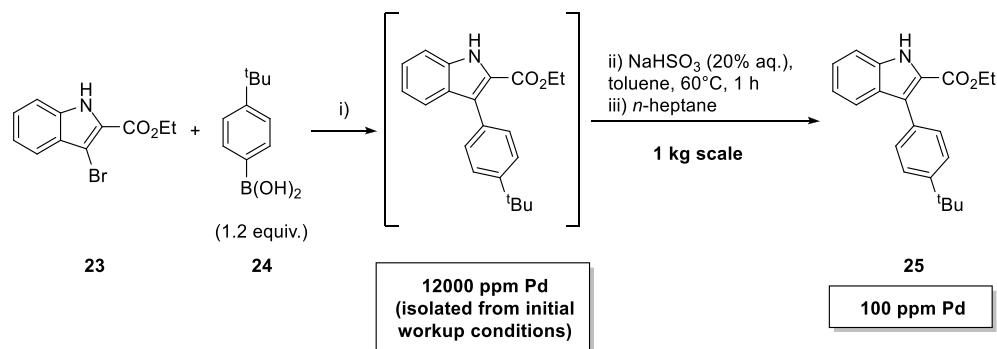
^a(i) Pd₂(dba)₃ (2.5 mol %), (±)-BINAP (7.5 mol %), NaO^tBu (1.2 equiv), toluene, 90 °C, 18 h.

Scheme 16. Palladium Removal from a Chelating Diamine Product Using an Isocyanide Scavenger^a

^a(i) Pd₂(dba)₃ (4 mol %), (±)-BINAP (8 mol %), NaO^tBu (4 equiv), toluene, 130 °C, 1 h.

Scheme 17. Simultaneous Palladium and Ruthenium Removal Following an RCM/Suzuki Telescoped Process Using Isocyanide Scavenger 19^a

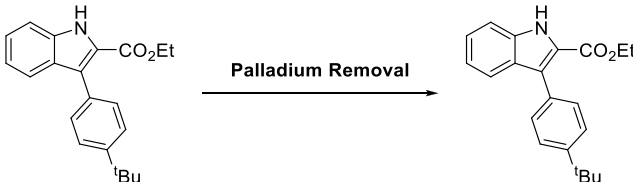
^a(i) Ru cat. (0.5 mol %), EtOAc, rt, 10 min; (ii) Pd(PPh₃)₂Cl₂ (5 mol %), Cs₂CO₃ (1.5 equiv), EtOH, 80 °C, 10 min.

Scheme 18. Optimized Suzuki–Miyaura Coupling from Which Palladium Was Removed Using Sodium Bisulfite^a

^a(i) Pd(OAc)₂ (5 mol %), KHCO₃ (2 equiv), P(*o*-tol)₃ (10 mol %), H₂O/ⁱPrOH (1:4), 60 °C, 2 h.

complex and subsequent filtration of the slurry would remove the metal. Although the initial palladium content determination in the isolated product following NaHSO₃ treatment did not yield promising results, optimization of the workup significantly improved the metal removal (Table 5). It was found that an increase in the concentration of NaHSO₃ improved the metal removal, while a higher temperature

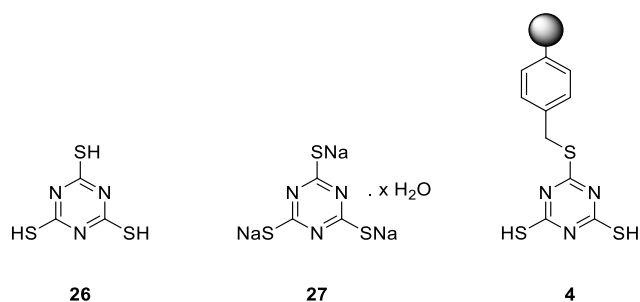
ensured that 25 did not precipitate out during the filtration step. In the subsequent crystallization step following isolation of 25, swapping the solvent system from MTBE/heptane to toluene/heptane gave an increased yield. As a result, to remove the need for a solvent exchange, MTBE was replaced with toluene as the metal extraction solvent, which further reduced the residual palladium levels.

Table 5. Extraction–precipitation Metal Removal Optimization for the Suzuki–Miyaura Coupling


entry	treatment	temperature (°C)	time (min)	solvent	Pd content in product (ppm)
1	10% NaHSO ₃ wash	45	120	MTBE	5134
2	20% NaHSO ₃ wash	60	60	MTBE	193
3	20% NaHSO ₃ wash	45	30	toluene	321
4	20% NaHSO ₃ wash	60	60	toluene	36

From a final metal content of 5134 ppm in the unoptimized trial of NaHSO₃ as a scavenger, a 36 ppm final metal content was achieved in the treatment that was selected as the workup procedure to be scaled up. The identity of the extractant solvent had a significant impact on metal removal, with extraction in toluene exhibiting a more than fivefold lower palladium content in the product compared to extraction in TBME at the same extractant concentration, temperature, and time of treatment (Table 5, entries 2 and 4). Scale up of the optimized palladium technique was carried out on a kilogram scale, achieving a final palladium content of 100 ppm in product **25**, which was well within the 150 ppm threshold set by the team.

3.2. Trimercaptotriazines. Trimercaptotriazine (**26**, Figure 6) is a sulfur-based extractant that has previously found utility in wastewater and flue gas treatment as a reliable method of removing heavy metal contaminants.^{61,62} The low human and animal toxicity of TMT is also a desirable quality that makes it an excellent candidate for use in the pharmaceutical field, as it does not pose a significant risk to health. As previously discussed, solid-supported TMT (**4**) has been used extensively as a scavenger for palladium; however, unbound TMT can also be used for metal removal. The choice of scavenger is highly dependent on the desired properties of the extractant under the solvent and temperature conditions used, with unbound TMT also existing in its trisodium salt

**Figure 6.** Structures of TMT, TMT trisodium salt hydrate, and solid-support-bound TMT.

hydrate form for improved solubility (**27**). Removal of palladium from solution is achieved by the precipitation of the Pd–TMT complex, which can undergo filtration to remove the sequestered metal.⁶⁰

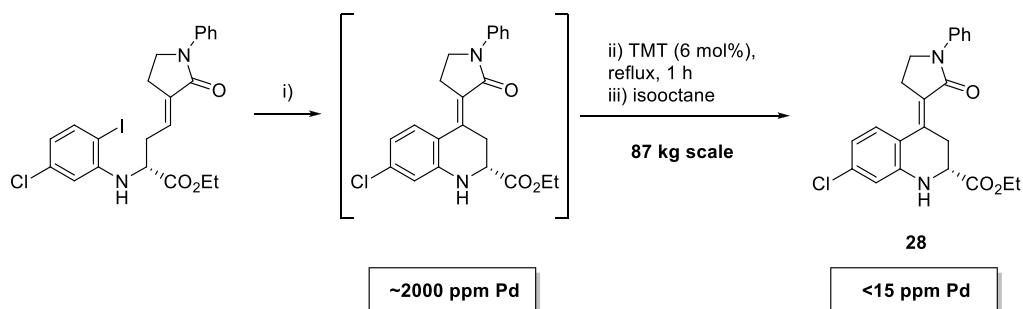
The use of TMT on a multikilogram scale has been reported by GSK. In the case of drug candidate compound **28**, palladium contamination arose by the intramolecular Heck cross coupling reaction en route to the final product (Scheme 19).⁶³ As the palladium content was one of the critical quality attributes directly impacting the quality of the final product, process chemists at GSK were required to find an appropriate control strategy to limit metal levels. Removal of palladium was found to be successful using a TMT treatment protocol, where the TMT–palladium complex as well as residual TMT could be separated from the product stream by filtration. Addition of 6 mol % TMT at the end of the reaction and heating at reflux prior to filtration resulted in the reduction of palladium levels from approximately 2000 to <15 ppm. Ester **28** was then isolated by a controlled crystallization using isooctane as the antisolvent. The scalability of the process was demonstrated on an 87 kg input, yielding excellent intermediate quality and 100% chiral purity.

3.3. L-Cysteine and N-Acetyl Cysteine. L-Cysteine (**29**) and its *N*-acetylated analogue, *N*-acetyl cysteine (**30**), are commercially available and relatively inexpensive amino acids that exhibit metal extractant abilities (Figure 7). *N*-Acetyl cysteine (NAC) has been shown to be an effective treatment against cobalt and chromium systemic toxicity in patients with metal implants, reducing blood metal levels through the chelation of metal ions and excretion through urine, and is also a treatment for acetaminophen toxicity.^{64,65}

The utility of *N*-acetyl cysteine on an industrial scale was demonstrated by Boehringer Ingelheim en route to a compound used as a treatment of type 2 diabetes (Scheme 20).⁶⁶ Following intramolecular C–H arylation and asymmetric hydrogenation, product streams were significantly contaminated with palladium and iridium metallic impurities. Activated carbon treatment with Darco G-60 succeeded in the partial removal of palladium; however, it performed poorly in the removal of iridium. Two treatments with 1 wt Darco G-60 following the asymmetric hydrogenation reaction resulted in 30–110 ppm palladium and 30–73 ppm iridium in **31**, accompanied by a yield loss in the range of 10–15%.

Two treatments of the crude organic layer with aqueous *N*-acetyl-L-cysteine resulted in the reduction of palladium levels from 1600 to 2.8 ppm, with the equivalent iridium values being 670 and 13 ppm. Simultaneously, product loss was significantly limited, with reported values ranging between 2% and 5%. This was demonstrated on an input of 22.2 kg of starting material, resulting in the production of 10.37 kg of intermediate **31**. Metal recovery was also demonstrated by Novartis during palladium removal from fungicidal derivative intermediate, **32**, where activated carbon treatment was insufficient to obtain the desired threshold of <4 ppm palladium, as set by the scientists (Scheme 21).⁶⁷ An L-cysteine wash of the organic phase followed by an L-cysteine/sodium thiosulfate pentahydrate wash achieved a reduction of the metal content to 2 ppm. The metal removal protocol was successfully demonstrated on an input of 14.4 kg of starting material in the pilot plant to give the desired product.

N-Acetyl-L-cysteine was also used in conjunction with silica gel for the purification of product streams. This was incorporated by Astellas Pharma in the route toward an

Scheme 19. Palladium Removal Following the Intramolecular Heck Reaction Using TMT^a

^a(i) PdCl₂ (2 mol %), PPh₃ (5 mol %), NEt₃ (1.33 equiv), toluene, reflux, 4 h.

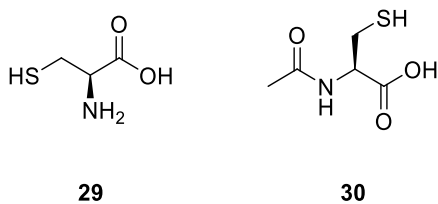


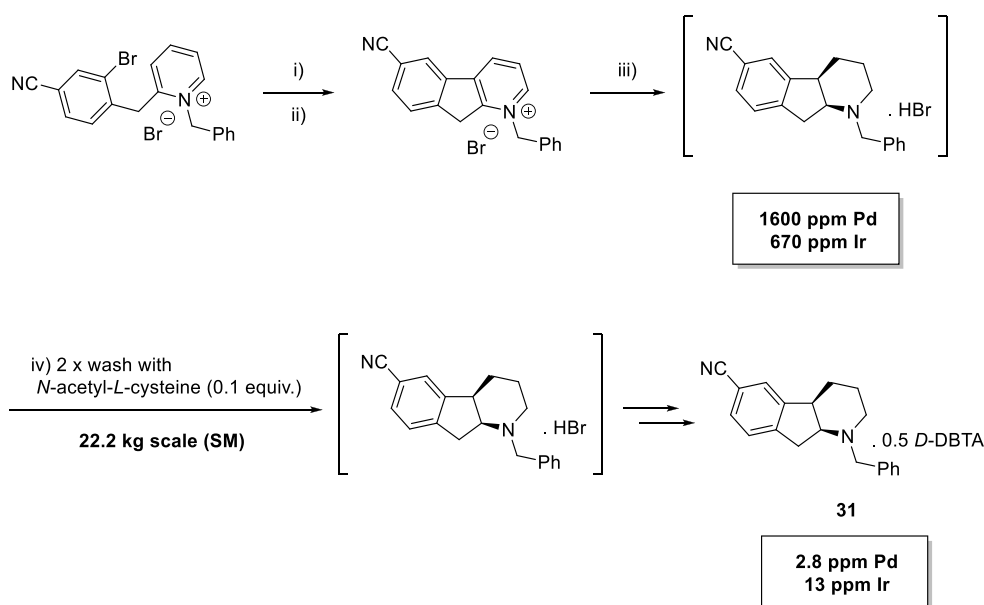
Figure 7. Structures of L-cysteine and N-acetyl-L-cysteine.

adenosine monophosphate-activated protein kinase activator (Scheme 22).⁶⁸ Following a Suzuki–Miyaura cross coupling reaction and a hydrogenation reaction to produce intermediate 33, observed palladium levels were 78.8 ppm. Wanting to reduce the metal content according to regulation, a purification step was incorporated in the amidation stage following the two palladium-catalyzed steps. This involved treatment with 1 equiv of N-acetyl-L-cysteine with respect to the input material before the addition of NaOH and the wash of the organic layer with aqueous NaHCO₃ and brine, followed by treatment with

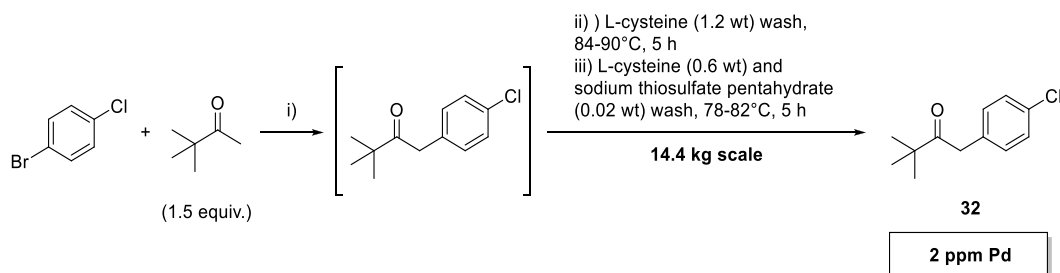
1 wt silica and filtration. This protocol, followed by crystallization from acetonitrile, resulted in a final palladium content of <10 ppm in 34, demonstrating successful scavenging of metal impurities. This process was used to produce 45.9 kg of material, with a product purity of 97.5 by LC area %.

The use of L-cysteine as a scavenger on a large scale was also demonstrated by Astellas Pharma in the palladium-catalyzed debenzoylation reaction shown in Scheme 23 to form an intermediate to a Janus kinase (JAK) inhibitor, 35.⁶⁹ An L-cysteine extraction was adopted on a batch reaction with an input of 39.7 kg of starting material, demonstrating excellent scalability. This protocol was quickly identified following the initial trial of combinations of scavengers on a 0.3 g input of starting material to determine an optimal binary chelating system to remove palladium.

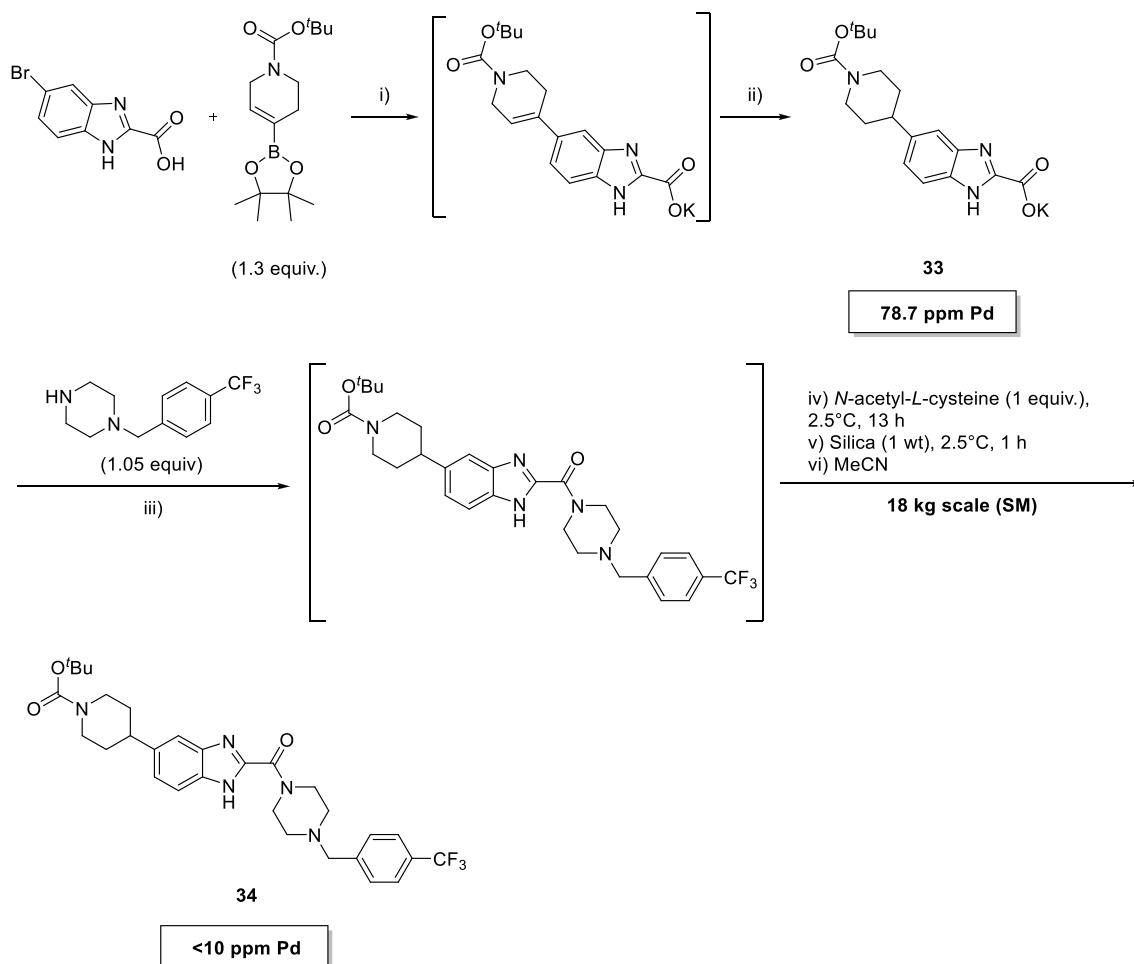
It was demonstrated that the performance of activated carbon as a scavenger was improved by over 20% when used in conjunction with an additional chelating agent such as trimercaptotriazine (TMT) or L-cysteine (Table 6). However,

Scheme 20. Simultaneous Removal of Iridium and Palladium Following a C–H Arylation and Hydrogenation Sequence Using N-Acetyl-L-cysteine^a

^a(i) Pd(dppf)Cl₂·CH₂Cl₂ (1.25 mol %), DBU (3 equiv), DMF, 115 °C, 2 h; (ii) HBr (48%, 1.2 equiv), THF, rt, 1 h; (iii) [Ir(cod)Cl]₂ (0.1 mol %), (S,S)-MeO-BoQPhos (0.3 mol %), I₂, THF/MeOH (1:2.9), H₂ (450 psi), 50 °C, 24 h.

Scheme 21. Palladium Removal Protocol Developed by Novartis^a

^a(i) $\text{Pd}(\text{OAc})_2$ (1 mol %), NaO^tBu (1.6 equiv), toluene, 97 °C, 9 h.

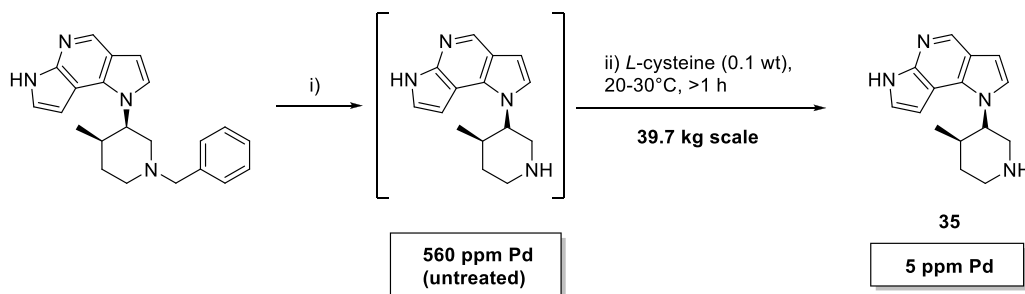
Scheme 22. Sequence of Suzuki–Miyaura Coupling, Hydrogenation and Amidation Reactions Followed by Metal Removal Using *N*-Acetyl-L-cysteine^a

^a(i) $\text{Pd}(\text{dtbpf})\text{Cl}_2$ (5 mol %), K_3PO_4 (3 equiv), 1,4-dioxane, H_2O , 85 °C, 17 h; (ii) H_2 (0.5–0.6 MPa), Pd/C (10%, 52.5% wet), 2-butanol, H_2O , 70 °C, 9 h; (iii) $\text{TsOH}\cdot\text{H}_2\text{O}$ (1 equiv), $\text{HOBT}\cdot\text{H}_2\text{O}$ (1 equiv), $\text{EDCI}\cdot\text{HCl}$ (1.10 equiv), DMF, EtOAc, –10 to 20 °C, 3 h.

the performance of L-cysteine without activated carbon gave comparable metal removal to the binary system while avoiding the use of a filtration step prior to the final crystallization. Due to practical reasons, it was decided to adopt the L-cysteine scavenging method, preventing the additional cleaning of the vessel under good manufacturing practice (GMP) to prevent carbon contamination.

The use of L-cysteine and *N*-acetyl-L-cysteine has also been demonstrated on a multikilogram scale in multiple other industrial case studies in the literature.^{70–73}

3.4. Dithiocarbamates. Dithiocarbamates (DTCs) possess features that are desirable in the removal of metals, as they have the ability to form stable complexes regardless of the oxidation state the metal is in while simultaneously carrying no genotoxic properties themselves.⁷⁴ This is particularly desirable in the pharmaceutical industry, where the toxicity of residual additives could introduce complications further downstream. Bristol-Myers Squibb demonstrated some commercially available DTCs to be excellent extractants, particularly with thiophilic metals such as copper, palladium, and iron.⁷⁵ These

Scheme 23. Metal Removal Using L-Cysteine Following a Debenzylation Reaction^a

^a(i) Pd/C (20%, 0.05 wt dry basis), H₂ (0.15–0.25 MPa), HCl (aq, 2 equiv), EtOH/H₂O (2:3), 30–40°C, 6 h.

Table 6. Scavenger Systems Tried in the Extraction of Palladium Following the Debenzylation Reaction^a

entry	solid support and chelating agent	Pd residue (ppm)	Pd removed (%)
1	activated carbon	160	71
2	activated carbon + TMT	30	95
3	activated carbon + L-cysteine	8.8	98
4	L-cysteine	17	97

^aExtractions were carried out on an input of 0.3 g of crude **35** (initial Pd content of 560 ppm), 0.1 wt of additive and/or 0.1 wt of scavenger, and HCl (6 M aq, 2 equiv) in EtOH/H₂O (3:5) at rt for 1 h, followed by filtration (entries 1–3), neutralization, and crystallization with EtOH (aq).

include sodium dimethyl dithiocarbamate **36** (NaDMDTC), sodium diethyl dithiocarbamate **37** (NaDEDTC), and ammonium pyrrolidine dithiocarbamate **38** (APDTC), as pictured in Figure 8.

This excellent extraction performance is due to the DTCs' ability to act as competitors of the ligands on the catalyst, promoting ligand exchange and the formation of metal(DTC) complexes, which precipitate out of solution and can be removed by filtration. This was clearly demonstrated in the case of PdCl₂(dppf) in THF, where APDTC chelated both the metal and the iron-containing ligand to reduce palladium and iron levels to below 10 ppm. The successful removal of metal from a THF solution crucially demonstrated the excellent extractant properties of APDTC in the presence of ligand competitors, as dppf is known to be an excellent palladium binder. In isolated systems containing 4000 ppm metal, both NaDEDTC and APDTC achieved a final content of <10 ppm for a variety of catalysts in different solvents (Table 7). The

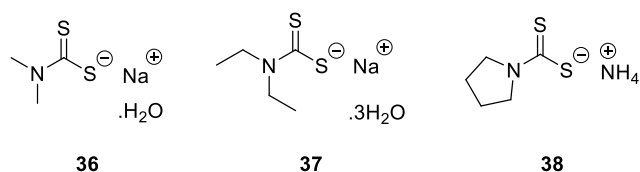


Figure 8. Structures of commercially available dithiocarbamates.

Table 7. Metal Extraction from Different Solutions of Complexes Using APDTC and NaDEDTC^a

catalyst	solvent	final metal content (ppm)
Pd ₂ dba ₃	THF	APDTC, <10; NaDEDTC, <10
	MeCN	APDTC, <10; NaDEDTC, <10
	DMF	APDTC, <10; NaDEDTC, <10
Cu(OAc) ₂	MeCN/MeOH	APDTC, <10; NaDEDTC, <10
	MeCN/MeOH	APDTC, <10; NaDEDTC, <10
Fe(OAc) ₂	NMP	APDTC, <10; NaDEDTC, <10
	MeCN/MeOH	APDTC, <10; NaDEDTC, <10
NiCl ₂ (PPh ₃) ₂	MeCN	APDTC, <10; NaDEDTC, <10
	DMF	APDTC, <10; NaDEDTC, <10

^aConditions: initial metal feed (4000 ppm metal), solid DTC (2.2 equiv w.r.t. metal), water, 20 °C, 1 h.

compatibility of DTCs with a range of metals and solvents is a favorable property, as it gives this class of extractant applicability in a wide scope of organic reactions, and scalability was demonstrated for copper removal following an Ullmann coupling on a 20 kg scale.

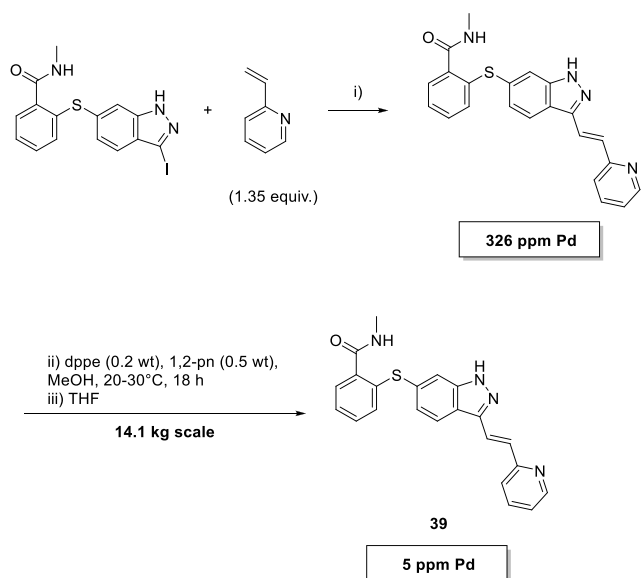
It is, however, important to note that use of these scavengers has to be limited to steps with which the dithiocarbamate moiety is compatible. A safety concern arose during palladium removal in the route of a selective estrogen receptor degrader by Novartis, where acidification of the aqueous layer containing NaDEDTC resulted in the generation of CS₂, a toxic gas with a low ignition temperature.⁷⁶ Although the use of NaDEDTC was successfully demonstrated to produce 75.9 kg of material, the process was further developed in the lab to use an alternative scavenger and alleviate any safety risks.

3.5. Reslurry with Diphosphines and Diamines.

Following a synthetic route change in the manufacturing process of Pfizer's axitinib, **39**, metal removal issues were observed by the Chemical Development team due to the different properties of the drug substance compared to the intermediate from which palladium was previously removed (Scheme 24).²¹ As the final product was relatively insoluble in lower polarity solvents, treatment with the previously developed protocol of 10% cysteine/silica gel was no longer practical. Leaching of the cysteine from the silica gel was observed in polar solvents, and the filterability of the silica was poor, making the step practically challenging. Additionally, only palladium impurities were purged, while chemical impurities were carried further downstream, necessitating an additional purification step for their removal.

Hence, an alternative method was required to meet the palladium specifications. Although recrystallization in the absence of scavenger could achieve up to a 65% reduction in palladium content relative to the feed metal content, this was

Scheme 24. Palladium Removal Using a Chelating Diamine and Diphosphine from Crude Axitinib^a



^a(i) Pd(OAc)₂ (5 mol %), P(*o*-tol)₃ (13 mol %), proton sponge (1.1 equiv), LiBr (6.2 equiv), NMP, 110 °C, 28 h.

insufficient to meet the required regulatory threshold. It was theorized that the insolubility of the API could be taken advantage of in the protocol development, and metal removal could be achieved either by a reslurry process or a recrystallization process. After identification of an appropriate solvent system in which axitinib has limited solubility, an initial scavenger screen was carried out which included simple diamines like 1,2-ethanediamine **40** (1,2-en), 1,2-diaminopropane **41** (1,2-pn), 1,3-propanediamine **42** (1,3-pn), and *N,N,N',N'*-tetramethylenediamine **43** (TMEDA) which are inexpensive. Other scavengers examined were simple diphosphines such as 1,2-bis(diphenylphosphino)ethane (dppe) **44**, 1,3-bis(diphenylphosphino)propane **45** (dppp), and 1,4-bis(diphenylphosphino)butane **46** (dppb), which are significantly more costly (Figure 9). Results demonstrated that dppe and 1,2-pn exhibited a far superior metal removal ability.

Reslurrying crude axitinib with a palladium content of 2807 ppm in a 10:20 v/v NMP/MeOH solvent system and either dppe or 1,2-pn as an additive at room temperature for 12 h, followed by granulation for 12 h and filtration, gave a metal removal greater than 96%, as shown in Table 8. After further refinement, a combination of dppe/1,2-pn was selected for the manufacturing process of palladium removal from crude axitinib on a 14.1 kg scale, achieving a final palladium content of 5 ppm in the product. Relative to the initial cysteine/silica treatment identified in early work, the new system induced a greater than 200× reduction in cost for this step solely based on the scavenger, making the final process financially advantageous.

The axitinib case study is a great example of exploiting compound physical properties in purification processes. By allowing crude axitinib to remain as a solid, the purge of metallic and nonmetallic impurities in a single unit operation could be made possible, something that was not the case with the previously developed cysteine/silica protocol.

3.6. Tri-*n*-butylphosphine. The first use of tri-*n*-butylphosphine as a metal scavenger was reported by Merck,

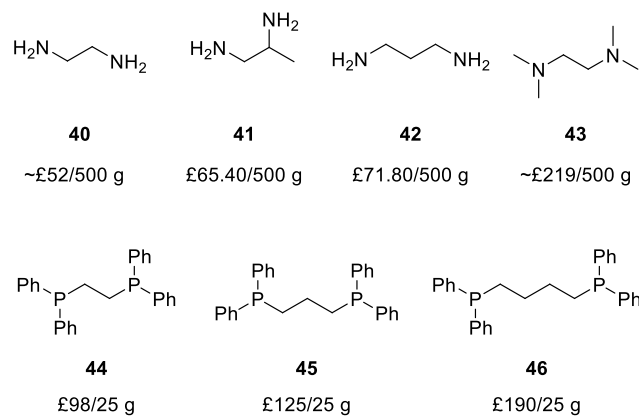


Figure 9. A selection of bidentate phosphine and amine ligands used by Pfizer in the reslurry studies. Prices correct as of June 29, 2023 from the Sigma-Aldrich Web site for amines and Alfa Aesar for phosphines.^{77–83} Prices per 500 g for 1,2-en and TMEDA were calculated based on density and the price of 500 mL of material.

Table 8. Metal Recovery by the Reslurry Process in the Presence of dppe/1,2-pn Scavengers^a

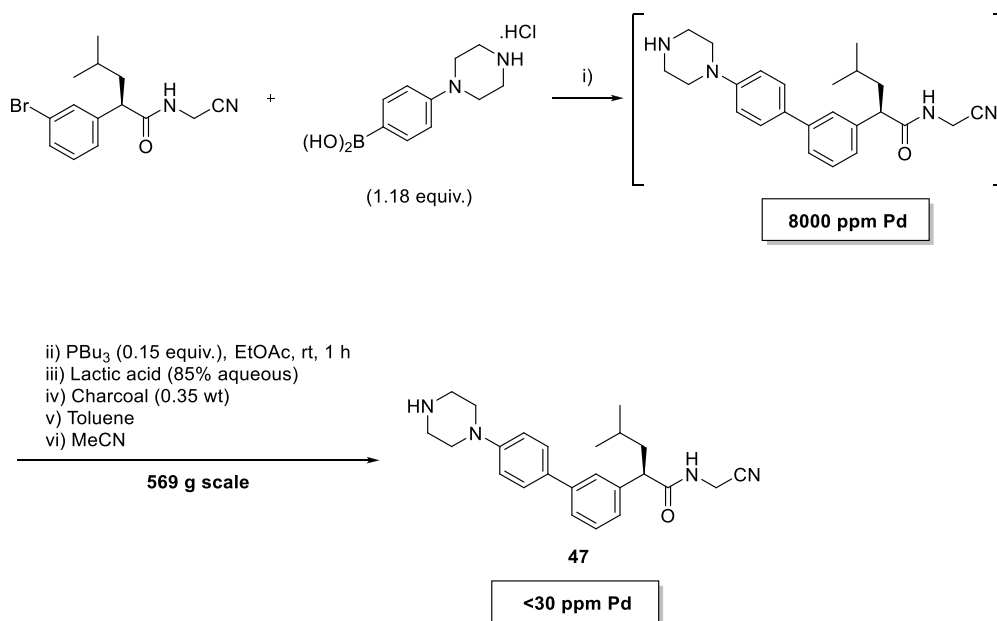
entry	1,2-pn (wt)	dppe (wt)	Pd content (ppm)	% metal removal	recovery (%)
1	1.0		30	99	79
2		1.0	124	96	78
3	0.5	0.5	31	99	78

^aConditions: NMP/MeOH (1:2), rt, 12 h, followed by granulation at rt for 12 h and filtration. The initial Pd content was 2807 ppm.

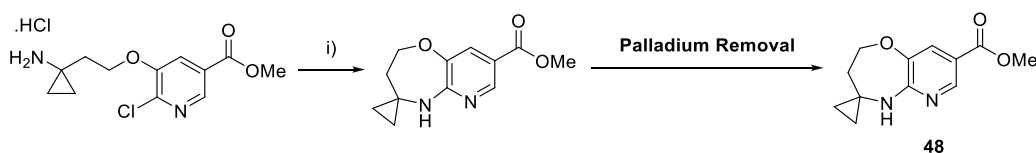
where the phosphine was used as a crystallization additive (*vide infra*). However, an identical crystallization protocol for metal removal could not be successfully applied to reduce metal content during the synthesis of another Merck asset, cathepsin K inhibitor **47** (Scheme 25).⁸⁴ The use of a palladium-catalyzed reaction as the final step toward the API resulted in high metal content in the isolated crude product. The use of strongly acidic extraction conditions was prohibited due to the lability of the nitrile group, which prevented the viable extraction of the product into the aqueous phase. Therefore, researchers at Merck were required to devise alternative workup conditions that would not hydrolyze the moiety. Treatment of crude **47** with 20 mol % tri-*n*-butylphosphine and extraction with aqueous lactic acid, followed by free-basing and subsequent crystallization from toluene, reduced residual palladium levels from 8000 to <30 ppm on a 569 g scale.

4. CRYSTALLIZATION OF PRODUCT

Crystallization is routinely used to control impurities during the manufacture of APIs in industry. It not only improves chemical purity but also provides control over crystal quality attributes, such as particle size distribution, polymorphic form, and morphology.^{85–89} During a typical process, impurity rejection occurs by the crystallization of the desired compound

Scheme 25. Palladium Removal Following a Suzuki–Miyaura Coupling Using Tri-*n*-butylphosphine^a

^a(i) K_2CO_3 (5 equiv), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (3.3 mol %), toluene/DMF/ H_2O (10:1:3), 80–85 °C, 2 h.

Table 9. Palladium Removal from 48 by Recrystallization in the Absence of Additives^a

entry	scale (kg)	initial Pd content (ppm)	final Pd content (ppm)
1	40.05	130–1916	182
2	42.45	1755–1916	75
3	60.76	75–182	131

^aConditions: MeOH, 63–64 °C; (i) $\text{Pd}(\text{OAc})_2$ (0.5 mol %), dppf (0.75 mol %), Cs_2CO_3 (2.2 equiv), MeCN, 82–83 °C.

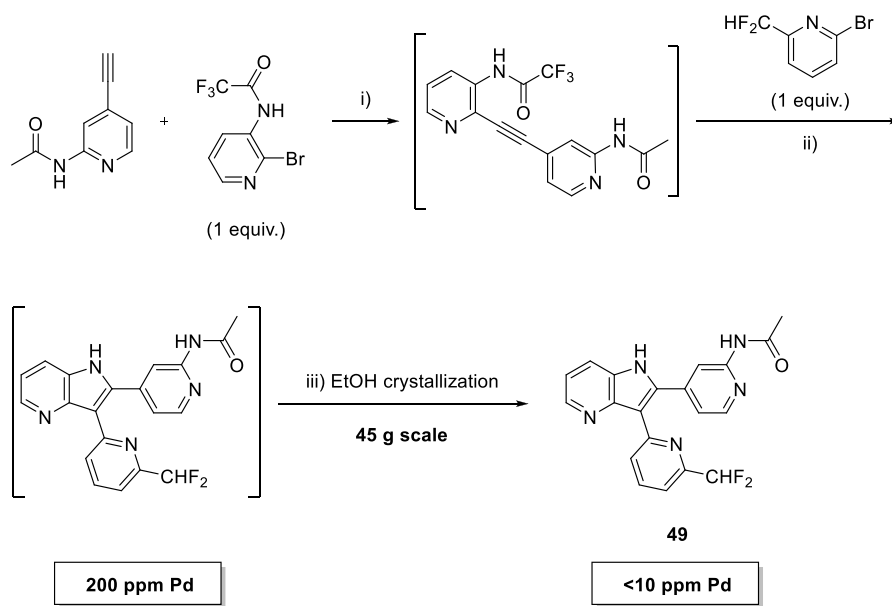
out of solution, leaving behind impurity-rich mother liquors. Often, in the presence of metals, crystallization is not as efficient, particularly for pharmaceutical processes. This can be attributed to the fact that drug-like molecules contain a large number of heteroatoms, which make them structurally similar to ligands and hence able to chelate metals. As a result, crystallization of such molecules may not result in successful purification due to the incorporation of metal atoms within the crystal structure of the product. Modifications are therefore typically required in crystallization processes to overcome this selectivity issue.

4.1. Without Additives. In an early process toward the synthesis of a fused [1,4]-oxazepanopyridine fragment, scientists from Boehringer Ingelheim implemented metal removal during the hydrolysis of intermediate **48** into the corresponding carboxylic acid using CUNO treatment, followed by *N*-acetyl-L-cysteine (Table 9).⁹⁰ However, this combined treatment seemed to be inefficient, which was tentatively attributed to the high polarity of the process solvent, methanol. A recrystallization process was therefore studied as a means of controlling the palladium content prior to the hydrolysis step. Data in Table 9 demonstrate that recrystallization was an effective protocol for the limitation of

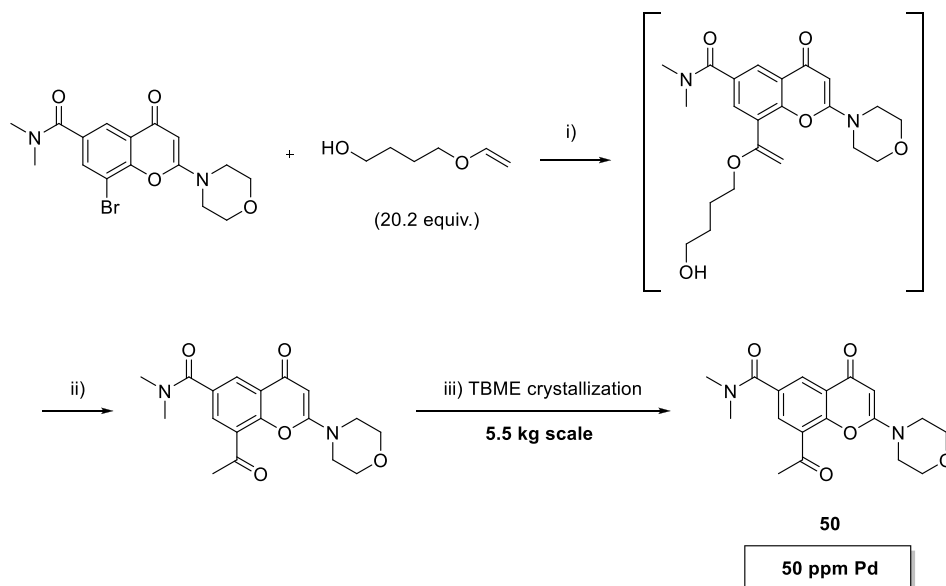
metal content in large batches of material, significantly reducing the metal levels in intermediate **48**. Consequently, CUNO treatment was omitted from the purification protocol of the subsequent step, as *N*-acetyl-L-cysteine addition alone resulted in sufficiently low levels of palladium in the regulatory starting material.

In the case of Bristol-Myers Squibb preclinical candidate **49**, over 150 g of material was required for pharmacological assessment, preclinical toxicology studies, and formulation development (Scheme 26).⁹¹ Compound **49** was synthesized using sequential Sonogashira and Cacchi reactions in a telescoped process using a $\text{Pd}(\text{OAc})_2/\text{BINAP}$ catalytic system. Crystallization in the absence of additives was successful in removing residual palladium from the candidate compound, reducing metal levels from 200 to <10 ppm. The process was used to produce over 160 g of **49**, leading to the successful delivery of the required quality material to support the studies.

Similarly, crystallization was used by AstraZeneca following a Heck cross coupling reaction to give intermediate **50** en route to a compound for treatment of breast and prostate cancer (Scheme 27).⁹² Crystallization from TBME resulted in a final palladium content of 50 ppm in compound **50** and, as the catalytic step was at the early stages of the synthetic route,

Scheme 26. Reduction of Palladium Levels during the One-Pot Preparation of **49** Using Crystallization^a

^a(i) Pd(OAc)₂ (5 mol %), S-BINAP (20 mol %), K₂CO₃ (4 equiv), DMF, 80–83 °C, 16 h; (ii) 90 °C, 2 h.

Scheme 27. Synthesis of **50** via a Heck Reaction and Palladium Removal Using Crystallization^a

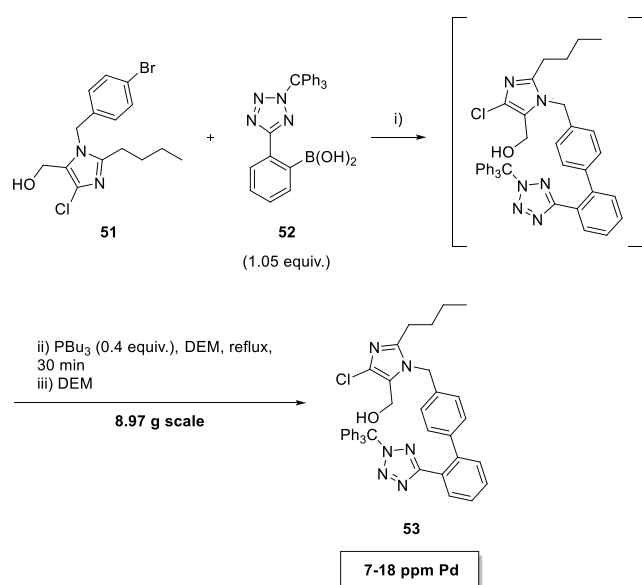
^a(i) Pd(OAc)₂ (10 mol %), dppp (20 mol %), K₂CO₃ (1.5 equiv), H₂O, 80 °C, 3–6 h; (ii) H₃PO₄ (6.8 M, 1.1 equiv), 35 °C.

no additional metal scavenging steps were required. The process was demonstrated on a 5.50 kg scale, enabling the production of >15 kg of intermediate **50**.

4.2. Tri-*n*-butylphosphine. The use of tri-*n*-butylphosphine as a metal scavenger was first reported in 1994 by scientists at Merck following the Suzuki–Miyaura reaction between aryl bromide **51** and boronic acid **52** to give **53**, an intermediate to an angiotensin II receptor agonist (Scheme 28).⁹³ Treatment of the organic layer with tri-*n*-butylphosphine at reflux, followed by crystallization from diethoxymethane (DEM), resulted in palladium levels in the range of 7–18 ppm in isolated product **53**. This protocol was utilized on a multigram scale, demonstrating the successful application of a novel metal removal method.

During the development of a novel pyrimidine-based vanilloid receptor-1 agonist, **54**, the crude drug substance was found to contain high levels of palladium following a late-stage Suzuki–Miyaura coupling reaction (Scheme 29).⁹⁴ As a result, a number of metal scavengers were screened by scientists at Amgen to control the metal content to an acceptable level (Table 10). From the scavenger screen, the best palladium removal was observed using Darco KB-B activated charcoal, which reduced the palladium level to 3.4 ppm.

Although activated charcoal was used during the large-scale campaign, a number of issues were identified with the Suzuki–Miyaura reaction, resulting in the need for postcampaign modifications. One such issue was the fact that 8–10% of

Scheme 28. First Reported Use of PBu_3 as a Metal Removal Method Following a Suzuki–Miyaura Coupling Reaction^a


^a(i) $\text{Pd}(\text{OAc})_2$ (1 mol %), PPh_3 (4 mol %), K_2CO_3 (2.5 equiv), H_2O (2.4 equiv), THF/DEM (1:4), reflux, 3–6 h.

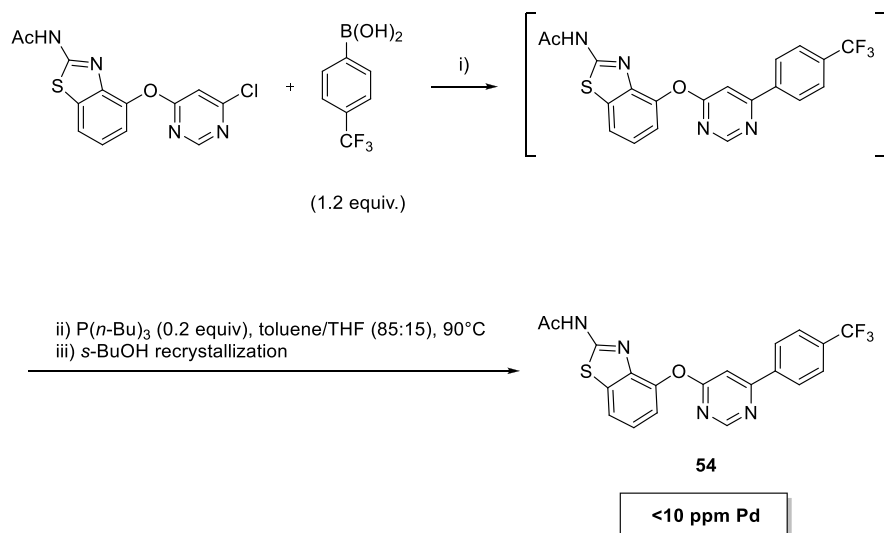
product was lost to the charcoal treatment and mother liquors during the selected isolation protocol, resulting in low yields. As part of the improvements made to the process, treatment with tri-*n*-butylphosphine at reflux (entry 4, Table 10), followed by crystallization from cold toluene, was used as an alternative to the charcoal protocol and was found to reduce palladium levels to 80–150 ppm. Following this treatment, the product was subjected to a discrete recrystallization from *sec*-butanol and dried at 100 °C to give **54** with a final metal content of <10 ppm palladium.

4.3. Xanthates. Xanthates were historically utilized by the mining industry as a means of purifying minerals using froth flotation; more modern applications include their use as

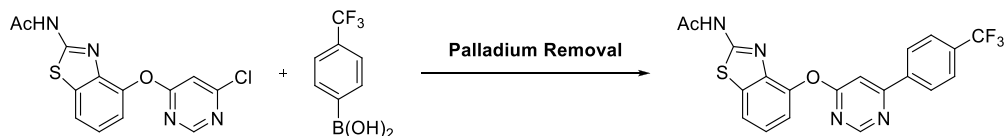
reagents in the manufacture of fungicides, pesticides, and polymers.⁹⁵ Their use as scavengers, however, had not been reported before 2017, where, in the case of the Merck drug product intermediate ceftolozane TFA (**55**, Scheme 30), minimal success was achieved using classical methods of palladium removal.⁹⁶ This was due to the low efficiency of techniques such as adsorption or incompatibility with downstream crystallizations. Therefore, a novel approach was required to attain palladium concentrations below regulatory thresholds for product **56**. It was theorized that the identification of a scavenger able to chelate palladium while remaining in solution would address the issues faced by the other methods. By utilizing this technique, complexation of the palladium with intermediate **55** would be prevented and subsequent crystallization would result in palladium remaining in the liquors rather than being incorporated within the product.

Utilization of DTCs gave excellent palladium rejection; however, the process was poorly reproducible due to the rapid decomposition rate of the scavenger in acidic solutions during the crystallization. The Process Research and Development department at Merck therefore theorized that the decomposition of the scavenger could potentially be prevented by replacing the Lewis basic nitrogen atom in thiocarbamates, which is susceptible to protonation to initiate the decomposition pathway, with an oxygen. Several potential palladium extractants were examined, ranging from short-chain alkyl xanthates such as potassium isopropyl xanthate **57** (PIX), potassium ethyl xanthate **58** (PEX), and potassium *tert*-butyl xanthate **59** (PBX) to long-chain alkyl xanthates like potassium octyl xanthate **60** (POX) (Figure 10).

Stirring the scavengers at a 10 mol % loading in a MeCN/DMAc/ H_2O solvent system for 30 min at room temperature, followed by the addition of ammonium bisulfate and crystallization of **56**, resulted in the successful removal of palladium from the product (Table 11). PIX was identified to be an excellent scavenger for palladium, with successful removal of up to 99.7% of metal from the initial feed of 50 ppm. Combined with its commercial availability relative to

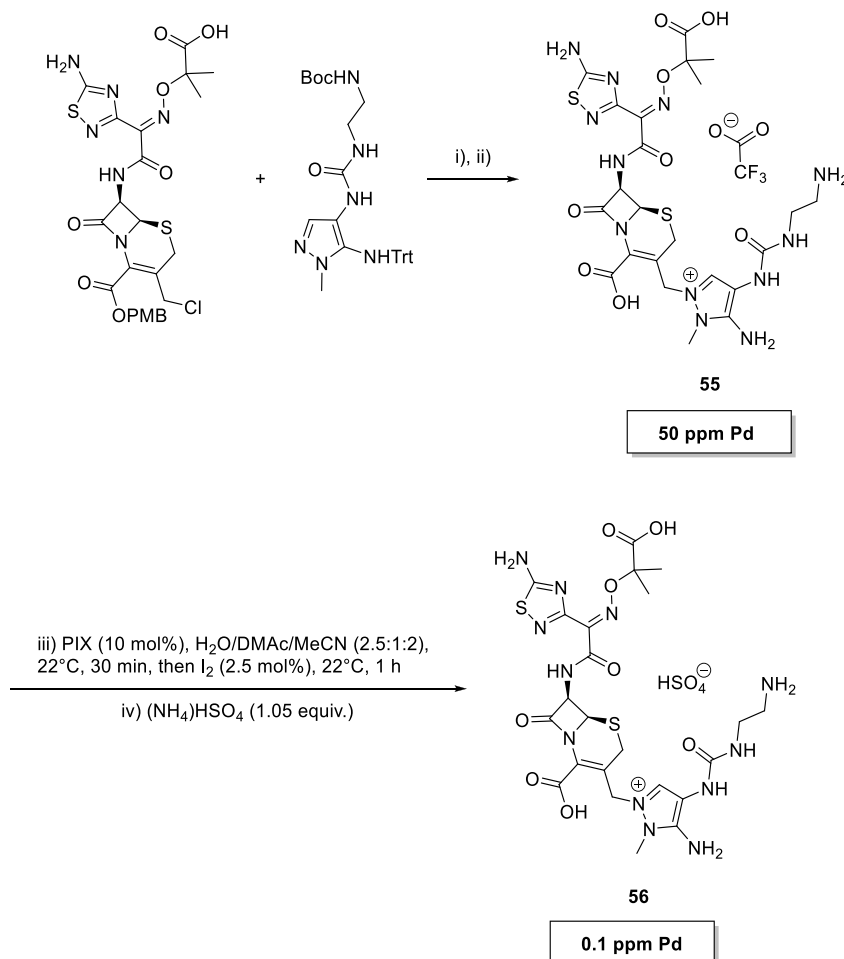
Scheme 29. Use of Tri-*n*-butylphosphine in the Modified Purification Protocol for **54 Postcampaign^a**


^a(i) $\text{PdCl}_2(\text{dtbpf})$ (0.5 mol %), K_2CO_3 (3 equiv), toluene/THF (85:15), 90 °C, 2 h.

Table 10. Metal Scavenging Screen for the Removal of Palladium Following the Late-Stage Suzuki–Miyaura Coupling^a

entry	scavenger	Pd (ppm)
1	none	6100
2	ethanolamine ^b	533
3	TMT ^b	217
4	P(<i>n</i> -Bu) ₃ ^b	156
5	thiourea ^b	98
6	SiliCycle thiol ^c	62
7	SiliCycle thiourea ^c	54
8	Darco G-60 ^d	182
9	Darco KB-B ^d	42
10	Darco KB-B ^e	32
11	Darco KB-B ^{e,f}	3.4

^aCrude was suspended in toluene and refluxed with scavenger for 1–2 h, followed by filtration and crystallization. ^bThe reaction was performed with 16 equiv. ^cThe reaction was performed with 4 equiv. ^dThe reaction was performed with 0.1 wt. ^eThe reaction was performed with 0.4 wt. ^f0.33 wt water was added.

Scheme 30. Removal of Palladium Using a PIX-I₂ Scavenging System^a

^a(i) Pd₂(dba)₃ (1 mol %), ligand (8 mol %), KTFA (1.5 equiv), THF, 15 °C, 14 h; (ii) TFA, DMB, MTBE.

other xanthate derivatives, it was selected as the optimal palladium scavenger.

It was recognized that PIX is an anionic compound, hence it would be a more suitable scavenger for Pd²⁺ species. Speciation of palladium to Pd⁰ during the process is an observed

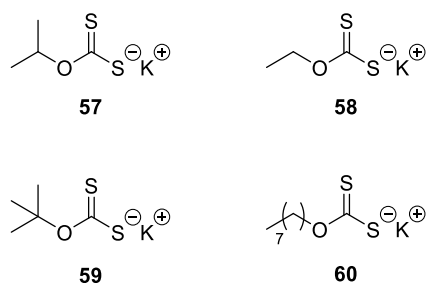


Figure 10. Structures of alkyl xanthates trialed in the palladium extraction from product **55**.

phenomenon; hence, it was theorized that addition of an oxidant to convert trace amounts of Pd⁰ to Pd²⁺ would further improve the scavenging performance. Scavenger (0.05 wt with respect to **55**) was added to compound **55** in MeCN/DMAc/H₂O, and the mixture was stirred for 30 min at room temperature, followed by the addition of 1 equiv of NH₄HSO₄ and MeCN and filtration to collect the product. In the comparative oxidative system, iodine (2.5 mol %) was added along with the scavenger. Iodine was indeed observed to give a threefold reduction in palladium content when used in conjunction with the scavenger while simultaneously being chemically compatible with the compound (Table 12, entry 1).

The scavenger/iodine binary system was also trialed on other scavengers such as NaDEDTC, TMT, and isocyanoacetate. In all cases, use of the scavenger in the presence of elemental iodine gave a superior performance, with further reduction in the metal content being achieved relative to the use of the scavenger alone (Table 12, entries 2–4). This discovery allowed for the development of a binary system for palladium removal that does not introduce additional unit operations to the overall process, as metal scavenging is employed during the crystallization step, which was already in place. Simultaneously, the novel binary system utilizes nonspecialized reagents, making it more amenable to larger scale synthesis. Use of the PIX–I₂ system was successfully demonstrated up to a 30 kg scale input of the starting material.

Table 12. Metal Removal Using a Scavenger/Iodine Binary System Relative to a Scavenger-Only System^a

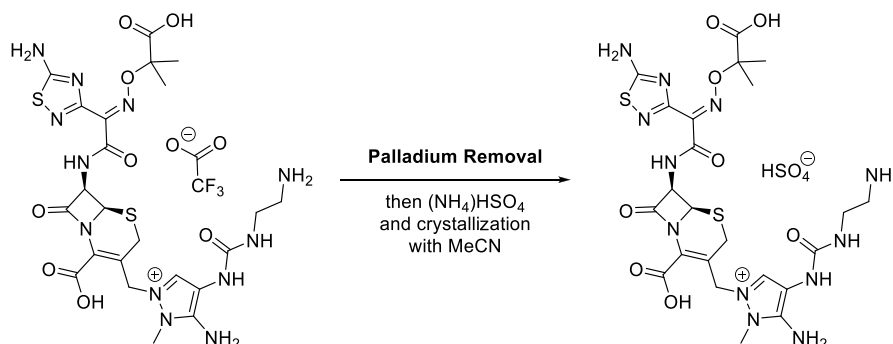
entry	scavenger	feed Pd content (ppm)	Pd content without I ₂ (ppm)	Pd content with I ₂ (ppm)
1	PIX (57)	75	0.9	0.3
2	PEX (58)	42	2.0	0.68
3	NaDEDTC (37)	65	8.5	1.8
4	TMT (26)	25	5.0	2.2
5	isocyanoacetate	25	14	5.5

^aConditions: scavenger (0.05 wt), MeCN/DMAc/H₂O, rt, 30 min, followed by crystallization.

4.4. N-Acetyl Cysteine and Cysteine. In the case of the Novartis antimitotic agent **61**, *N*-acetyl cysteine was utilized as a means of solubilizing palladium following a tandem coupling sequence of two Sonogashira reactions and catalytic reduction of the alkyne (Scheme 31).⁹⁷ Palladium removal using solid adsorbents from a toluene solution of intermediate **62** was unsuccessful; instead, a high-temperature distillation of the crude gave a satisfactory metal content of <3 ppm. Unfortunately, this was deemed to be impractical on the plant scale, which led to the development of the *N*-acetyl cysteine crystallization protocol.

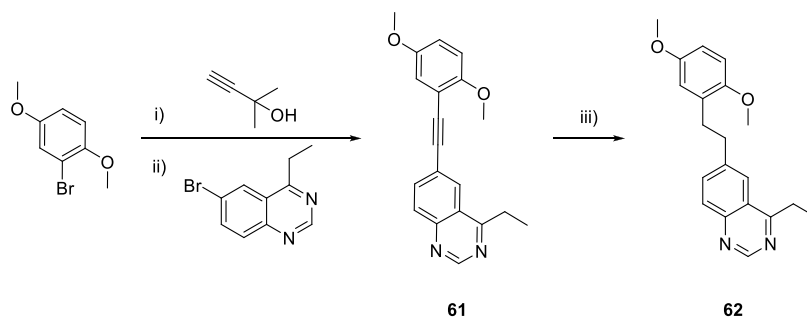
Crystallization of the crude **61** from ethanol with thiourea (1% w/w solution) or *N*-acetyl cysteine (1.1% w/w solution) as additives gave a significant reduction in the product metal content relative to initial metal levels. Palladium contents of 20 and 17 ppm were achieved using thiourea and *N*-acetyl cysteine, respectively, with other process parameters such as yield and product purity also being comparable between the two additives. Consideration of the potential carcinogenicity of thiourea resulted in the decision to use *N*-acetyl cysteine as the additive in the process. Crystallization was also employed in the purification of product **62** following the hydrogenation of alkyne **61**. In feeds of variable initial palladium concentration, crystallization in the presence of *N*-acetyl cysteine resulted in the reduction of palladium to <2 ppm (Table 13, entries 2–4). A reduction in palladium content was also observed in the absence of *N*-acetyl cysteine; however, treatment with the scavenger was necessary to achieve a sub-2 ppm concentration.

Table 11. Metal Removal by the Use of Xanthates as Scavengers from an Initial Metal Feed of 50 ppm^a



entry	scavenger	Pd content (ppm)	% metal removal
1	PIX (57)	0.16	99.7
2	PEX (58)	0.61	98.8
3	PBX (59)	36	28
4	POX (60)	32	36

^aConditions: scavenger (10 mol %), MeCN/DMAc, 30 min, rt, followed by the addition of NH₄HSO₄ and crystallization with MeCN.

Scheme 31. Double Coupling Procedure for the Synthesis of Intermediate 61 for the Antimitotic Agent^a

^a(i) DIPA, Pd(PPh₃)₂Cl₂, CuI, PPh₃, toluene, 78 °C, 13 h; (ii) TBAB, toluene, H₂O, 50% NaOH, reflux, 3 h; (iii) Pd/C (10%, 50% H₂O w/w), H₂ (40 psig), IPA.

Table 13. Palladium Content in Product 62 Following Crystallization in the Presence and Absence of *N*-Acetyl Cysteine

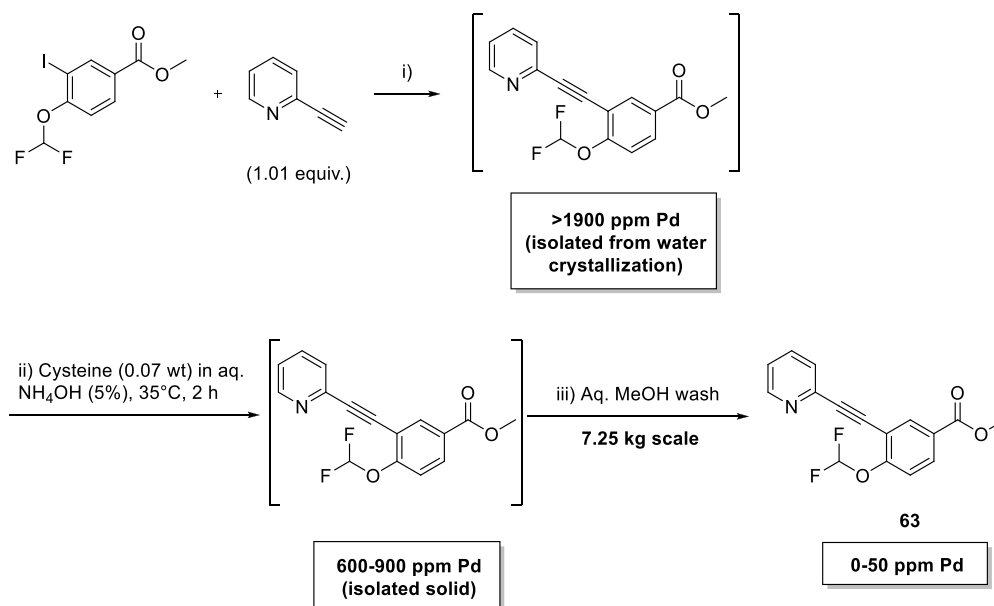
entry	Pd content in product 61 (ppm)	<i>N</i> -acetyl cysteine concentration (g/mL)	Pd content in 62 before crystallization (ppm)	Pd content in 62 after crystallization (ppm)
1	17		10	6
2	17	0.5%	10	1
3	120	1.0%	21	<1
4	30	0.5%	11	<2

In both steps, *N*-acetyl cysteine was used as an additive in the initial controlled crystallization step rather than in a subsequent recrystallization step, removing the need for additional unit operations.

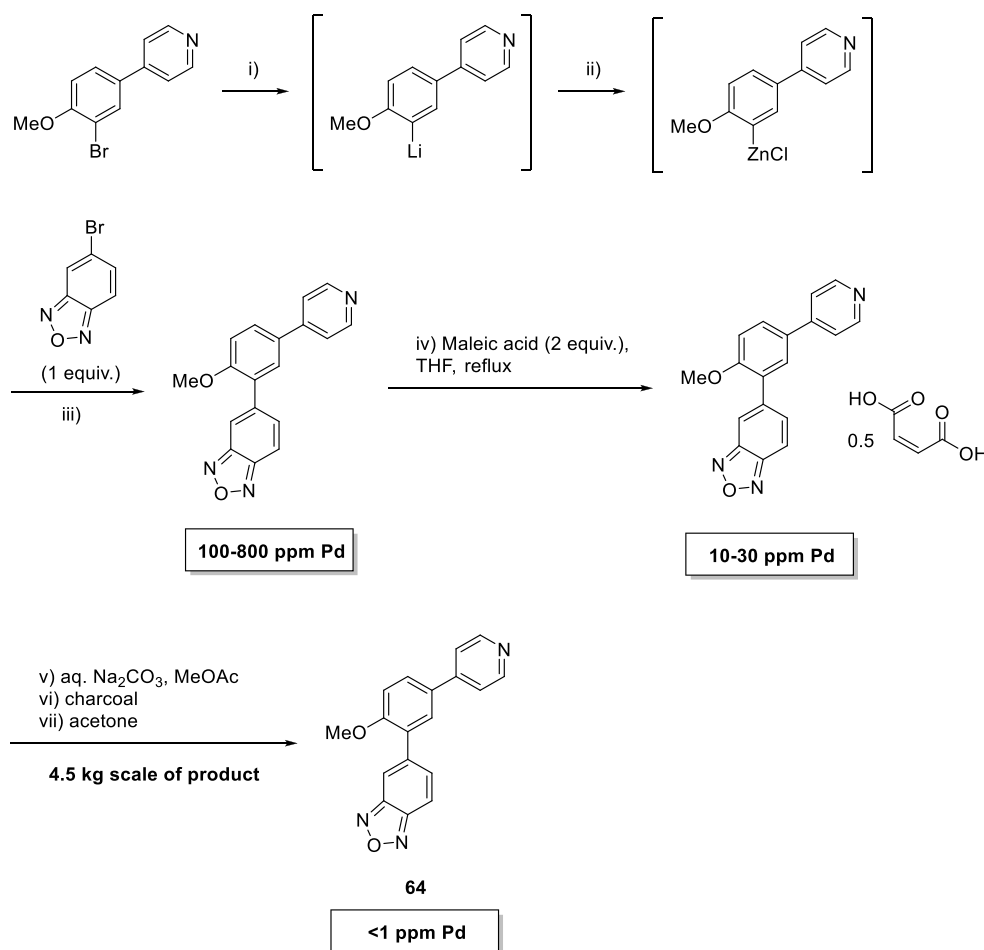
Cysteine as a crystallization additive was also utilized en route to an mGluR5 negative allosteric modulator by Wyeth.^{98,99} Isolation of alkyne 63 following a Sonogashira cross-coupling reaction yielded material containing >1900 ppm

palladium (Scheme 32), with the acceptance criteria for that stage being set to <100 ppm by the development scientists. Addition of a solution of 0.07 wt cysteine in aqueous ammonium hydroxide to the reaction mixture reduced residual palladium levels to 600–900 ppm; however, these levels still exceeded the set threshold. It was discovered that a cake wash of the isolated material with 1.5:1 water/MeOH resulted in palladium levels in the range of 0–50 ppm, achieving the desired control of metal content. It is, however, important to note that the wash incurred an approximately 6% yield loss. Therefore, the authors recommended performing a single wash to avoid the loss of material. This purification method was successfully used to produce 6.34 kg of Sonogashira product 63 on scale.

4.5. Via Intermediate Salt Formation. Palladium levels following a Negishi coupling en route to a drug substance for the treatment of asthma by Novartis were controlled using salt formation (Scheme 33).^{100,101} Several different salts of 64 were trialed, such as the hemi-sulfate, hydrochloride, dihydrogen phosphate, hemi-tartrate, and hemi-fumarate. However, the

Scheme 32. Removal of Palladium Using a Cysteine Crystallization Followed by an Aqueous Methanol Cake Wash Following a Sonogashira Cross-Coupling Reaction^a

^a(i) PdCl₂(PPh₃)₂ (1 mol %), CuI (2 mol %), NH₄OH (8 equiv), NMP, 35–40°C, 1 h.

Scheme 33. Removal of Palladium Following a Negishi Coupling through the Formation of a Hemi-maleate Salt and Subsequent Free-Basing^a

^a(i) *n*-HexLi (1.3 equiv), THF, $-90\text{ }^{\circ}\text{C}$, 15 min; (ii) ZnCl_2 (1.2 equiv), THF, -90 to $0\text{ }^{\circ}\text{C}$; (iii) $\text{Pd}(\text{PPh}_3)_4$ (0.8 mol %), 0 – $22\text{ }^{\circ}\text{C}$.

hemi-maleate salt seemed to yield the highest reduction in palladium content, with typical parts per million values of the salt being within the range of 10–30 ppm compared to 100–800 ppm in the free base. Free-basing of the hemi-maleate salt, followed by treatment with charcoal and crystallization from acetone, gave a final product with <1 ppm palladium. The Negishi reaction was successfully scaled up in the pilot plant to produce 4.5 kg of **64**.

5. SUMMARY OF APPROACHES

This Review describes a range of scavengers reported in the literature for use in both multigram- and kilogram-scale operations. On the basis of the knowledge compiled in this Review, the decision tree diagram in Figure 11 was constructed to guide the selection of a metal removal protocol based on process characteristics.

The presence of scavengers with different modes of action provides an opportunity for targeted metal removal following metal-catalyzed reactions. Although it is acknowledged that each process behaves differently and has its own intricacies, the diagram in Figure 11 can assist with the choice of protocol likely to be appropriate for residual metal removal. In the first decision, the solubility of the product is interrogated as it is the physical property that dictates what type of approach can be adopted. An insoluble product lends itself to a cake wash,

where the residual metal can be removed simply by washing the cake with solvent. Although this has been noted to yield good metal removal in one of the case studies, it also resulted in yield losses. Alternatively, the insoluble product can be slurried with a scavenger that will retain the metal in solution, allowing the product to be filtered off. A range of diamines and diphosphines have been used to achieve the prescribed levels of residual metal in a scavenging screen designed by Pfizer. Although this is the sole literature report of this approach, it benefits from being a facile method of metal removal, as the heterogeneous mixture can be easily separated through filtration at the end of the treatment without adding any further purification steps.

If a reslurry approach is not feasible, then the solubility of the product can be investigated in alternative solvents, enabling the use of metal removal protocols from the left-hand side of the decision tree. If the product is insoluble in alternative solvents, another approach to solubilizing the product may be required, such as investigating salt formation or pH adjustment.

Proceeding to the left-hand side of the tree, a soluble product lends itself to residual metal removal by crystallization. However, this is not always facile, particularly when products contain a large number of heteroatoms that have the potential to act as metal chelators. In such a case, a crystallization with

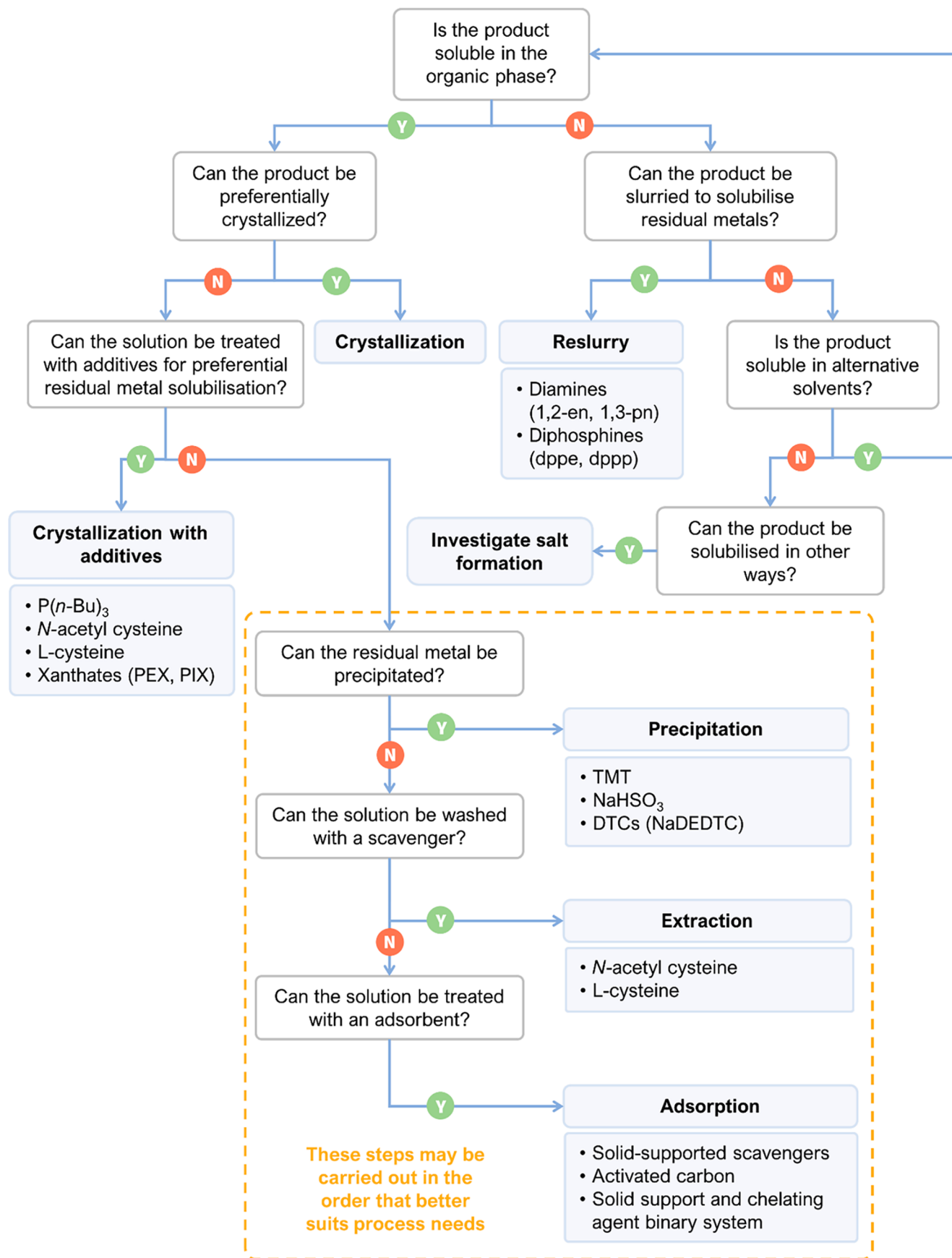


Figure 11. Decision tree diagram to guide the selection of metal extraction conditions.

Table 14. Summary of the Large-Scale Approaches for Metal Removal Reviewed in This Publication

company	year of publication	metal removal protocol	scale (product)	reference
Boehringer Ingelheim	2008	Darco G60 and Hyflo Super-Cel	86 kg	52
GSK	2009	TMT	48.7 kg	63
Astellas Pharma	2021	<i>N</i> -acetyl-L-cysteine	45.9 kg	68
Bristol-Myers Squibb	2017	<i>N</i> -acetyl-L-cysteine	41.4 kg	71
AstraZeneca and PhosphonicS	2011	SPM36f (PhosphonicS)	40 kg ^a	12
GSK	2021	<i>N</i> -acetyl-L-cysteine	36.15 kg	73
AstraZeneca and Asymchem	2021	L-cysteine	32.9 kg	70
Boehringer Ingelheim	2022	recrystallization from MeOH	29.7 kg	90
Astellas Pharma	2019	L-cysteine	27.9 kg	69
Boehringer Ingelheim	2022	<i>N</i> -acetyl-L-cysteine	24.9 kg	90
AstraZeneca and PhosphonicS	2011	SPM36f (PhosphonicS)	20 kg ^a	12
Pfizer	2015	DARCO KB-B	19.3 kg	51
Amgen and Norchim	2015	SiliaMetS thiourea (SiliCycle)	12.1 kg	40
Pfizer	2008	1,2-bis(diphenylphosphino)ethane and 1,2-diaminopropane	10.0 kg	21
Pfizer	2019	Si-thiol (SiliCycle)	7.89 kg	43
Genentech	2016	Si-thiol (SiliCycle)	6.41 kg	31
Pfizer	2013	quadrapure thiourea	6.4 kg	42
Wyeth	2012	L-cysteine, then crystallization and aqueous MeOH cake wash	6.34 kg	99
Fudan University	2010	polystyrene-bound TMT	6.05 kg	37
Magle Chemoswed and Recipharm	2019	Si-TMT	5.5 kg	39
AstraZeneca	2008	Si-thiol (SiliCycle)	5.2 kg	30
AstraZeneca and PhosphonicS	2011	SPM32 (PhosphonicS)	4 kg ^a	12
AstraZeneca	2022	3-mercaptopropyl ethyl sulfide silica	3.96 kg	46
Merck	2010	MP-TMT and filtration through a pad of Solka-Floc	2.71 kg	38
Magle Chemoswed and Recipharm	2018	Hyflo Super-Cel, SEM26, SPM32	2.1 kg	41
Bristol-Myers Squibb	2018	SPM36 (PhosphonicS), siliabond thiol	1.31 kg	45
Bristol-Myers Squibb	2018	activated charcoal, silica gel, and SiliaMetS-thiol	1.2 kg	44
Boehringer Ingelheim	2022	<i>N</i> -acetyl-L-cysteine	1.107 kg	66
GSK	2008	20% NaHSO ₃	983 g	60
Merck	2003	Tri- <i>n</i> -butylphosphine, lactic acid (85%), Darco KB and Solka-Floc 40NF	640 g	84
Teva Pharmaceuticals	2016	SEM26 (PhosphonicS) and filtration through Celite 521	110 g	72
Pfizer	2008	Si-thiol (SiliCycle)	97 g	32
Arcus Biosciences	2022	silica gel, ethylenediamine	94.2 g	56
Teva Pharmaceuticals	2016	L-cysteine	86.2 g	72
Siena Biotech	2012	TMT and activated charcoal, then filtration through a cellulose pad	75 g	54
Janssen Pharmaceuticals	2015	Si-thiol and Si-thiourea (SiliCycle), then filtration through celite	44.4 g	34
Novartis	2003	<i>N</i> -acetyl-L-cysteine, then crystallization	39.5 g	97
Bristol-Myers Squibb	2018	SPM36 (PhosphonicS)	30.01 g	45
Bristol-Myers Squibb	2020	crystallization from EtOH	27.1 g	91
Novartis	2003	intermediate hemi-maleate salt formation	22.0 g	100
Merck	1994	tri- <i>n</i> -butylphosphine	15.5 g	93
Johnson & Johnson	2009	Si-thiol (SiliCycle) and activated carbon (Norit A supra)	14.6 g	35
Abbott Laboratories	2010	3-mercaptopropyl-functionalized silica (SiliCycle)	12.84 g	33

^aRefers to the amount of starting material used in the process.

the use of additives may be explored, to complex the metal and keep it in solution while the product crystallizes. Purification of the product by crystallization has significant process benefits, as no additional vessels are required to carry out downstream unit operations for metal removal. This technique is also typically less solvent-intensive than an extraction approach, allowing for a relatively more sustainable process. Simultaneously, crystal quality attributes such as form can be carefully controlled in the crystallization process, which makes the approach highly desirable. If the crystallization approach fails to give the desired palladium levels, then any of the following three methods can be explored: precipitation, extraction, or adsorption.

There is no prescribed way in which these should be investigated; instead, the process needs should be prioritized,

as each technique has its benefits and drawbacks. For example, if a high molar percent of palladium has been used in the process, it is important to consider that financial returns from recovered metal may offset the cost incurred by the relatively more expensive functionalized resins, making their use viable on a large scale. Scavengers operating through adsorption have the advantage of forming heterogeneous mixtures with the solution being treated, which makes separation facile and is considered to be an advantage of this scavenger class. However, multiple case studies have reported that treatment with adsorbents may incur significant yield losses, resulting in companies searching for alternative metal removal protocols.

Other drawbacks of adsorbent-based protocols include occasionally challenging filtrations for the complete removal of loose adsorbents from large vessels, resulting in longer batch

cycle times. This issue can be circumvented by the use of cartridges in which the adsorbent can be contained, which allow for the crude to be passed through either once or even recirculated through multiple times. The generation of novel impurities during the use of adsorbents has also been reported in the literature, as has the leaching of impurities from scavengers into the crude material. An additional consideration when selecting this class of scavengers is that cost varies according to complexity, with simple activated carbons being significantly less expensive than functionalized resins.

In the case where the use of complex scavengers may not be financially viable, an extraction approach may be more appropriate, with cysteine-based scavengers. Their low cost and commercial availability make them accessible palladium scavengers, and unlike adsorbents, no purity issues have been reported following treatment with these extractants. A drawback of the extractant scavenger class, however, is that removal through extraction can result in large volumes of aqueous waste, particularly if repeated washes of the organic phase are required. Management of such waste with low metal concentrations can incur high costs, particularly due to the transportation and incineration of the material.

If the product is sensitive to pH changes, it may not be appropriate to use an extraction approach, as cysteine and its acylated analog are sparingly soluble in water and require dissolution in basic media. Precipitation can be used in those cases to circumvent the issue of changing the pH. Here, it is important to highlight the case study by Novartis, where use of dithiocarbamate reagent NaDEDTC on scale resulted in the production of CS₂ gas, a significant process safety hazard.⁷⁶

The metal removal protocols from large-scale case studies are summarized in Table 14. These are tabulated with an indication of the scale they have been carried out on, as captured from literature experimental procedures, as well as the year of publication and the name of the company disclosing the protocol. Entries have been sorted in a descending order based on the scale of operation.

The authors of this Review believe that this table provides a useful indication of which scavengers have made it past screening efforts and have been applied on a large scale, allowing for the guided selection of protocols based on their success in past case studies. The table can also act as a guide for the selection of scavengers to include in scavenger screens by development scientists, as the case studies cover a wide range of metal-catalyzed transformations and product physicochemical properties. This will likely help in the identification of at least one successful scavenger during screening, which can then be further optimized.

From Table 14, it is evident that the most frequently used methods of palladium removal are adsorption and extraction. The most frequently encountered adsorbent class in the literature was found to be thiol-functionalized silicas, with their use being successfully demonstrated up to a 40 kg scale process. Activated charcoal has also been used to reduce palladium levels on an industrial scale, with Boehringer Ingelheim using an activated charcoal treatment in the production of 86 kg of material. *N*-Acetyl-L-cysteine and L-cysteine have also found significant use in industrial applications of metal removal, with four out of the seven largest scale case studies in Table 14 utilizing one of these two scavengers. Their utility in industry may also be attributed to their versatility as scavengers, as they can be used both for the aqueous extraction of palladium and as a means of solubilizing

it so that it remains in the mother liquors while the product is crystallized out of solution. It is important to note once again that careful selection of the scavenger is required on a case-by-case basis, as the choice is highly dependent on the physicochemical properties of the product, and it is not possible to recommend one general metal removal approach. Therefore, the screening of multiple scavengers may be necessary to ensure that the optimal protocol has been identified.

The cost and scarcity of precious metal catalysts are both factors prohibiting their one-time use in processes. Understanding how palladium can be extracted in an efficient manner will not only deliver reliable processes able to meet the demands of the market when it comes to the production of goods but also result in economic and environmental benefits, which is what the chemical industry strives for.

AUTHOR INFORMATION

Corresponding Authors

Marina Economidou – Drug Substance Development, GSK, Stevenage SG1 2NY, U.K.; Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, U.K.; orcid.org/0009-0000-3620-429X; Email: marina.x.economidou@gsk.com

Katherine M. P. Wheelhouse – Drug Substance Development, GSK, Stevenage SG1 2NY, U.K.; orcid.org/0000-0002-1963-1465; Email: katherine.m.wheelhouse@gsk.com

Authors

Nisha Mistry – Drug Substance Development, GSK, Stevenage SG1 2NY, U.K.

David M. Lindsay – Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, U.K.; orcid.org/0000-0003-4498-5094

Complete contact information is available at: <https://pubs.acs.org/10.1021/acs.oprd.3c00210>

Author Contributions

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Notes

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