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Highly Functionalised Sulfur-Based Silica Scavengers for the Efficient Removal of Palladium Species from Active Pharmaceutical Ingredients

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Abstract:

The use of multidentate sulfur-based silica scavengers 1, 2, and 3 as highly effective adsorbents for the removal of precious metals, specifically palladium residues in this paper, from highly functionalised synthetic intermediates and APIs is described. The synthesis and purification of the polar and electron-rich reaction products, containing multiple functional groups, from palladium-catalysed removals of commonly used protecting groups such as benzyl, benzyloxycarbonyl, and allyloxycarbonyl and Sonogashira, Suzuki, Heck, and Buchwald−Hartwig coupling reactions is reported. The significant levels of residual palladium species, typically associated with these reaction products, are successfully and rapidly removed to below acceptable regulatory levels, of less than 5 ppm, by simple, unoptimised treatment with the designed silica scavengers at room temperature. Performance aspects, including broad solvent compatibility, excellent stability, and high metal affinity, combined with large-scale availability, ease of handling, and minimal loss of API make these silica scavengers particularly useful to process development groups.

Introduction

Precious metal catalysts are extensively used to generate a wide range of products across a variety of industries. Typical precious metal-promoted reactions include carbon−carbon bond formation, carbon−nitrogen bond formation, deprotection reactions, and hydrogenation. In medicinal chemistry, palladium is perhaps the most-widely utilised precious metal, being used for reactions such as Suzuki couplings and Buchwald−Hartwig aminations, which represent key transformations towards the synthesis of new active pharmaceutical ingredients (APIs).[1] This is understandable, given that these reactions provide an easy access, and in high yield, to complex molecules that previously could only be achieved through multistep synthesis. The disadvantage of this metal-catalysed chemistry is that expensive and toxic metal residues are invariably left bound to the desired product. For pharmaceutical intermediates and products there have been a number of reviews on methods for the removal of precious metals from products.[2] These methods include distillation, extraction, adsorption, and crystallisation. However, the most commonly utilised methods for metal removal from APIs often suffer from significant disadvantages; for example the use of either activated carbon or recrystallisation can result in significant product loss, and often with these methodologies very low levels of residual metal content cannot be achieved.

Functionalised materials are an attractive option for scavenging residual metals in products or for capturing catalyst residues from waste streams. One of the key advantages is that the functionality can be designed to have a very high affinity for the residual metal.

The structures of most pharmaceutical intermediates and products contain invariably a number of functional groups in close proximity. These groups or ligands can bind strongly to the precious metal catalyst and its residues. Thus, a key feature in the design of an effective metal scavenger is for the material to possess ligands that have an overall higher affinity for the metal compared to the pharmaceutical product. In addition, given the structural diversity of APIs and related intermediates, a wide range of multifunctional and complex metal scavengers are required.

In this contribution we would like to report the use of a number of multifunctionalised materials for the removal of palladium residues from the products of a selection of reactions widely used in medicinal chemistry. These reactions are commonly used in the synthesis of compounds that contain typical functional groups found in most APIs. Upon completion of a metal-catalysed reaction, the metal residue contained in the reaction product can exist in a variety of oxidation states, such as Pd (0) and Pd (II) in these cases, and to be effective, functionalised materials need the ability and inherent functionality to remove metals in these various oxidation states from the reaction product. The silica scavengers described here are able to achieve this for a wide range of common palladium-catalysed processes.

In this study we have used materials based on a silica framework, which offers both operational and performance advantages, such as no swelling requirement prior to use, broad solvent compatibility, and excellent stability properties (thermal, mechanical, and chemical). The broad solvent compatibility means existing process streams can be directly treated with the supported materials, allowing costly solvent switches to be avoided by process development groups. Customisation of the properties of the silica, including particle size and shape, active site loading, accessible surface area, and pore size, is readily achieved, allowing the silica to be specifically modified for the desired purpose.

* Author to whom correspondence should be addressed. E-mail : jwilson@phosphonics.com.

(1) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(2) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal*. **2004**, *346*, 889; Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev*. **2005**, *9*, 198; Bien, J. T.; Lane, G. C.; Oberholzer, M. R. *Top. Organomet. Chem.* **2004**, *6*, 263.

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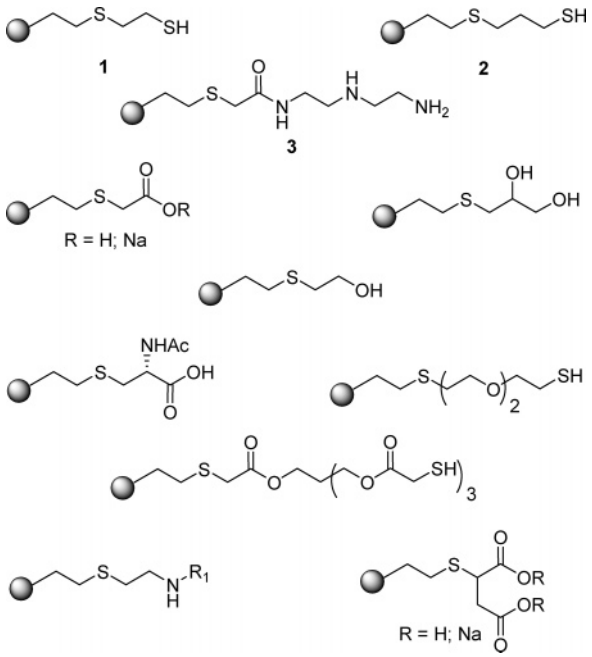


Figure 1. **Multidentate sulfur-based silica scavengers.**

These functionalised silicas have molar loadings of typically 1.0 mmol/g, although the multiple functional groups present within scavengers such as **3** result in higher effective loadings. Whilst scavengers based on alternative materials such as polystyrene (typically 2 to 3 mmol/g) and grafted fibres may have higher nominal molar loadings, the affinity of the functionality, the spacial arrangement of functional groups, and access of the API to the scavenging groups all contribute significantly to the overall effectiveness of the scavenger in use.

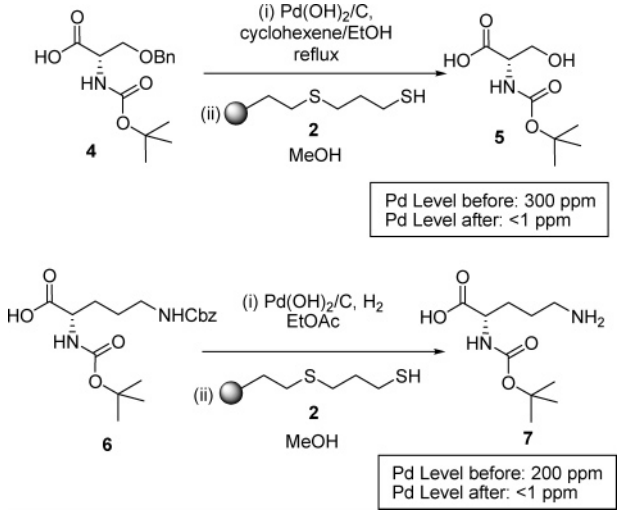
The functionalised silica scavengers are prepared by a highly scaleable process in which a range of trialkoxysilyl compounds are employed as key components, allowing variation of both the spacer to which scavenging functionality is attached and the range and combination of functional groups which can be attached. The inorganic support may also be varied, and alumina and silicones may be employed as well as silica described herein. The use of these materials for process-scale applications has been demonstrated to date by multikilogram slurry batch processing. The development and introduction of large-scale cartridges for use in process development is ongoing.

Sulfur-based ligands are widely known to have a high affinity for precious metals. As part of our investigations into the multidentate mechanism we made a number of functionalised materials, as illustrated in Figure 1. The synthesis of these functionalised materials is reported elsewhere.[3] In this paper we report our results with the functionalised silica scavengers **1**, **2**, and **3**. Future publications will report scavenging progress with the additional materials shown in Figure 1.

Results and Discussion

Recent surveys of the pharmaceutical literature indicate that a very high percentage of small-molecule therapeutics now feature at least one metal-catalysed reaction during their

Scheme 1. **Deprotection of amino acids and scavenging of residual palladium**



synthesis. Among the most commonly used metal catalysts, those based on palladium are routinely employed for the removal of protecting groups and for cross-coupling reactions, as well as having application for a number of other synthetic operations such as carbon monoxide insertions and Wacker-type oxidations.[4]

The effectiveness of the designed multidentate scavenging materials is most challenged, and therefore best demonstrated, by the removal of residual palladium from highly functionalised organic molecules containing a variety of polar moieties, each capable of strongly binding palladium residues and making the metal removal to regulatory-acceptable levels extremely difficult. APIs and their synthetic precursors normally contain such diverse polar functional groups, often imparted as an inherent function of commonly occurring monomers such as amino acids and cyclic secondary amines.

Amino Acid Deprotections. Orthogonally protected amino acids are vital intermediates for the synthesis of complex molecules including many natural products. Selective deprotections of these key amino acid building blocks allow required functionality to be revealed at the appropriate point of a chemical synthesis. Amongst the most common protecting groups for amino and hydroxyl moieties are allyloxycarbonyl (Alloc), benzyloxycarbonyl (Cbz), and benzyl (Bn), which in most cases are all efficiently removed by palladium-catalysed hydrogenation.[5]

Scheme 1 depicts the removal of protecting groups from orthogonally protected serine **4** and lysine **6** derivatives using palladium-catalysed hydrogenations. In both cases the residual level of palladium associated with the deprotected product was analysed after standard reaction work-up, prior to scavenging and after scavenging by passing a methanolic solution of either **5** or **7** through a plug of 3-mercaptopropyl

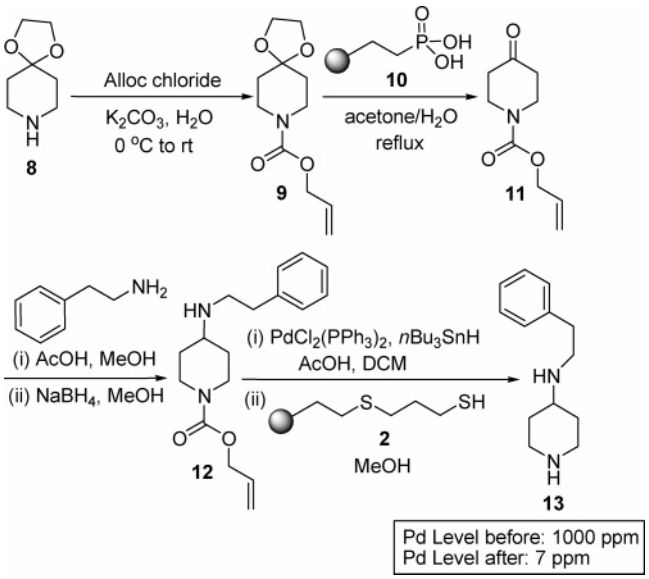
(3) Wilson, J. R. H.; Sullivan, A. C.; Man, S. Substituted Organopolysiloxanes and Use Thereof. WO2006013060, 2006.
(4) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651; Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, 2nd ed.; John Wiley & Sons: New York, 2004.
(5) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley: New York, 2006.

Table 1. **Palladium content of products 5, 7, and 13 before and after scavenging**

	palladium content/ppm	
reaction product	before scavenging	after scavenging with **2**
5	300	<1[a]
7	200	<1[a]
13	1000	7

[a] Indicates palladium content below the detection limits of the instrument (5 ppb).

Scheme 2. **Synthesis of amino-piperidine 13 and scavenging of residual palladium**



ethyl sulfide silica **2** under gravity (over ~5 min). In both cases, the palladium content after scavenging was found to be <1 ppm (Table 1).

Aminopiperidine Deprotections. Piperidine fragments are ubiquitously found in drug molecules, particularly those targeting G-protein-coupled receptors (GPCRs). The synthesis of a protected aminopiperidine was achieved as shown in Scheme 2. *N*-Protection of piperidine derivative **8** was achieved with allyl chloroformate to give **9**.[6] Deprotection of the ketal was achieved very cleanly and in quantitative yield upon treatment of **9** with a slurry suspension of PhosphonicS' heterogeneous phosphonic acid **10**. Reductive amination of the resultant keto-piperidine **11** with phenethylamine gave the *N*1-protected 4-aminopiperidine **12**, which was purified by column chromatography and subsequently treated with bis(triphenylphosphine)palladium (II) dichloride in the presence of tributyltin hydride to furnish the *N*-deprotected aminopiperidine **13**.

Again, the residual level of palladium associated with the deprotected product was analysed after standard reaction work-up prior to and after scavenging by passing a methanolic solution of **13** through a plug of 3-mercaptopropyl ethyl sulfide silica **2** under gravity (over ~5 min). The palladium content of **13** after scavenging was found without optimisation to be just 7 ppm (Table 1). Residual tin levels in **13** after the deprotection reaction were found to be extremely high, as tributyltin hydride was used in large excess. In addition to removal of residual palladium to 7 ppm, scavenging with **2** resulted in removal of >99% of the tin residues present.

The residual palladium content of deprotection reactions of commonly used synthetic intermediates such as amino acids and aminopiperidines, which produce polar, functionalised low-molecular weight molecules, was found to be high (>200 ppm). By use of a simple scavenging protocol employing multidentate scavenger 3-mercaptopropyl ethyl sulfide silica **2** in a cartridge format, levels of palladium were dramatically reduced to <1 ppm for both amino acid derivatives, and to 7 ppm for the aminopiperidine. Additional scavenging efficiency can be obtained by the use of increased contact time, temperature, concentration, and/or equivalents of scavenger, although these factors were not investigated for these examples.

There are many variants of palladium-catalysed carbon−carbon-coupling reactions described in the literature but the Suzuki, Stille, Sonogashira, and Heck reactions have received the most significant synthetic attention. One of the major benefits provided by cross-coupling technologies is the increased convergence when compared to classical methods, as two highly functionalised molecules can be coupled together under relatively mild conditions. As a result, coupling reactions are now likely to feature at any stage in the synthesis of an API, even increasingly as the final synthetic step.

Regardless of the point of use within the synthetic sequence, residual palladium, which can encompass the catalyst itself and associated palladium species generated from the catalyst under the reaction conditions, needs to be minimised in the API. Adherence to the increasingly stringent regulatory requirements for metal content within APIs is highly desirable in order to facilitate progression of the API down the drug development pathway. However, removal of residual palladium from carbon−carbon- and carbon−nitrogen-coupled products can frequently be a complex issue.

Products from a number of the common carbon−carbon coupling reactions were investigated for palladium content before and after treatment with the multidentate scavengers described.

Carbon−Carbon Couplings: Sonogashira Reaction.[7] Compound **17** is related to a calcium entry blocker,[8] which is known to possess a strong ability for chelation of palladium. Formation of the biaryl acetylene by Sonogashira reaction at a late stage of the synthetic sequence towards the drug substance caused significant palladium-removal problems, and the synthetic sequence required reorganisation. We investigated palladium removal from our model com-

(6) Fernández-Forner, D.; Casals, G.; Navarro, E.; Ryder, H.; Albericio, F. *Tetrahedron Lett.* **2001**, *42*, 4471.

(7) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627; Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*, 1st ed.; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; p 203; Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

(8) Maryanoff, C. A.; Mills, J. E.; Stanzione, R. C., Jr.; Hortenstine, J. T. In *Catalysis of Organic Reactions*, 1st ed.; Rylander, P. N., Greenfield, H., Augustine, R. L., Eds.; Marcel Dekker: New York, 1988; Chapter 18, p 368.

Scheme 3. **Sonogashira coupling of 16 with phenylacetylene and scavenging of residual palladium from 17**

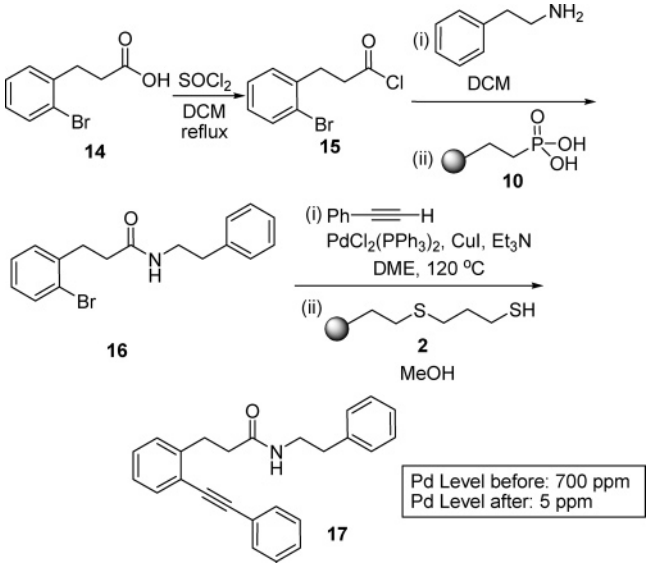


Table 2. **Palladium content of coupling products 17, 21, 31, and 34 before and after scavenging**

type of coupling	product	scavenger	palladium content/ppm before scavenging	palladium content/ppm after scavenging
Sonogashira	**17**	**2**	700	5.0
Suzuki	**21**	**1**	2100	1.6
Suzuki	**21**	**2**	2100	<1[a]
Suzuki	**21**	**3**	2100	<1[a]
Heck	**30**	**1**	307	18.1
Heck	**30**	**2**	307	24.3
Heck	**30**	**3**	307	62.2
Heck	**30**	**1** + **2** + **3**[b]	307	4.8
Buchwald	**33**	**1**	30	<1[a]
Buchwald	**33**	**2**	30	<1[a]
Buchwald	**33**	**3**	30	<1[a]

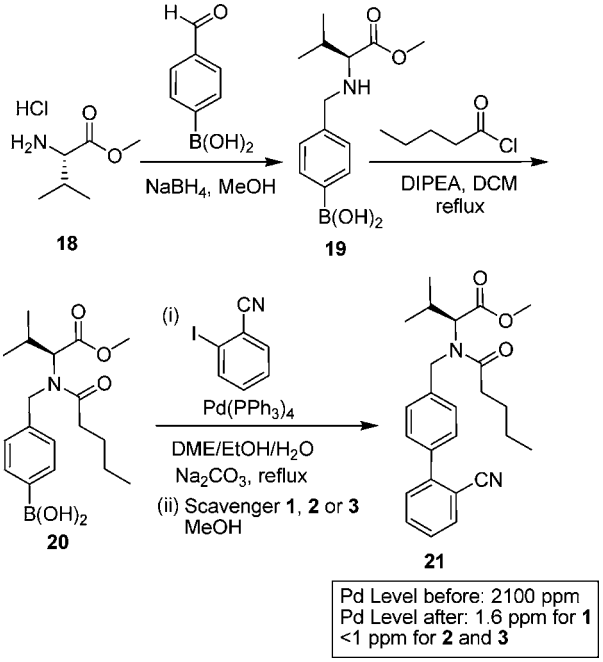
[a] Indicates palladium content below the detection limits of the instrument (5 ppb). [b] Equimolar amounts of **1**, **2**, and **3** were combined.

pound **17**, which employed the key Sonogashira reaction as the final step of the synthesis, Scheme 3.

Compound **16** was readily accessible from commercially available building blocks; however, a highlight of the synthesis was the facile purification of amide **16**, by passing the crude reaction mixture through a cartridge of PhosphonicS' supported phosphonic acid **10**. Amide **16** was successfully coupled with phenylacetylene under Sonogashira conditions to provide the aryl−aryl acetylene **17** in good yield. After standard reaction work-up, the residual level of palladium associated with **17** was analysed both prior to and after scavenging with 3-mercaptopropyl ethyl sulfide silica **2** in methanol. The palladium content of **17** after scavenging was found to be just 5 ppm (Table 2).

Carbon−Carbon Couplings: Suzuki Reaction. The Suzuki reaction[9] is perhaps the most widely utilised of all palladium-catalysed cross-coupling reactions by process development chemistry groups, being routinely performed on multikilogram scale.[10] Valsartan,[11] a potent, orally active angiotensin II antagonist is among a number of marketed

Scheme 4. **Synthesis of Valsartan precursor 21 using a Suzuki coupling**



drugs which contain the privileged biaryl moiety.[12] A potential route into Valsartan precursors involves a key Suzuki coupling, as shown in Scheme 4. Valine methyl ester hydrochloride **18** was reductively alkylated with 4-formylphenylboronic acid. The resultant secondary amine **19** was acylated with valeroyl chloride to give amido aryl boronic acid **20**, which underwent Suzuki coupling under typical literature conditions to give the biaryl amide **21**, a precursor of Valsartan. The residual level of palladium associated with **21** was analysed separately with three different multidentate silica scavengers **1**, **2**, and **3** in methanol both prior to and after scavenging. The palladium content of **21** after scavenging was found to be 1.6 ppm with scavenger **1** and <1 ppm with either scavenger **2** or **3** (Table 2).

Carbon−Carbon Couplings: Heck Reaction. Amongst potential routes to the oncology candidate CP-724,714, a selective ErbB2 angiogenesis inhibitor, routes involving

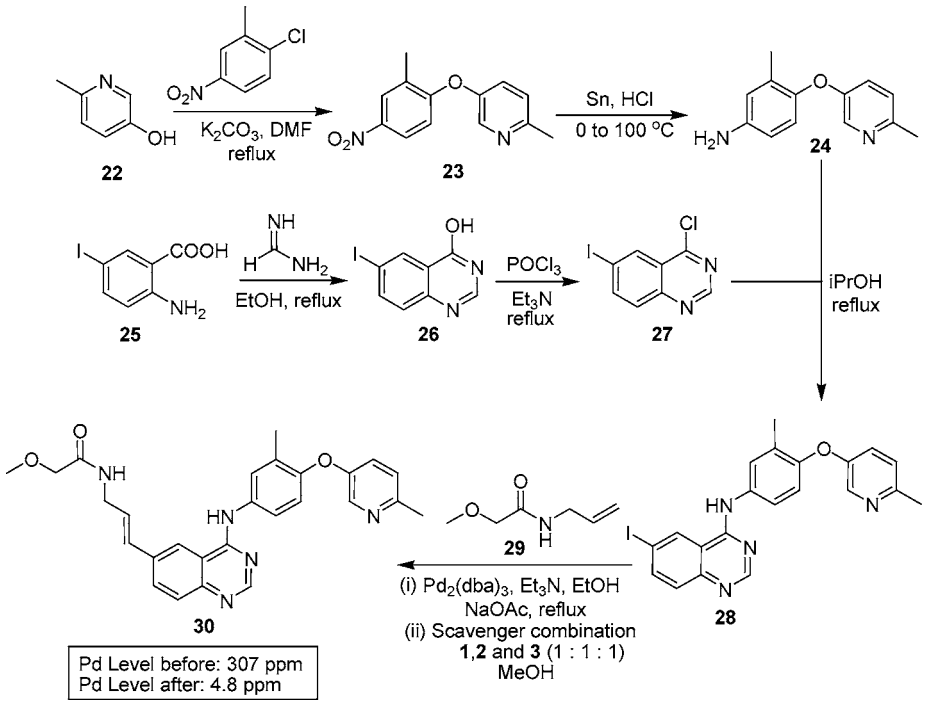
(9) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866; Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419; Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*, 1st ed.; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 3; Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(10) Examples include: Ennis, D.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G.; Carstairs, A. *Org. Process Res. Dev.* **1999**, *3*, 248; Jacks, T. E.; Belmont, D. T.; Briggs, C. A.; Horne, N. M.; Kanter, G. D.; Karrick, G. L.; Krikke, J. J.; McCabe, R. J.; Mustakis, J. G.; Nanninga, T. N.; Risedorph, G. S.; Seamans, R. E.; Skeean, R.; Winkle, D. D.; Zennie, T. M. *Org. Process Res. Dev.* **2004**, *8*, 201; Conlon, D. A.; Drahus-Paone, A.; Ho, G.-J.; Pipik, B.; Helmy, R.; McNamara, J. M.; Shi, Y.-J.; Williams, J. M.; Macdonald, D.; Deschenes, D.; Gallant, M.; Mastracchio, A.; Roy, B.; Scheigetz, J. *Org. Process Res. Dev.* **2006**, *10*, 36; Kerdesky, F. A. J.; Leanna, M. R.; Zhang, J.; Li, W.; Lallaman, J. E.; Ji, J.; Morton, H. E. *Org. Process Res. Dev.* **2006**, *10*, 512.

(11) De Gasparo, M.; Webb, R. L. WO0002543, 2000; Bühlmayer, P.; Furet, P.; Criscione, L.; de Gasparo, M.; Whitebread, S.; Schmidlin, T.; Lattmann, R.; Wood, J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 29.

(12) Evans, B. E.; Rittle, K. E.; Bock, M. G.; Dipardo, R. M.; Freidinger, R. M.; Whiter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235; Patchett, A.; Nargund, R. P. *Annu. Rep. Med. Chem.* **2000**, *35*, 289; Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

Scheme 5. **Heck coupling of iodoquinazoline 28 with *N*-allyl-2-methoxyacetamide 29 and scavenging of residual palladium from 30**



Sonogashira, Suzuki, and Heck couplings were all assessed.[13] A convergent synthesis of CP-724,714 featuring a key Heck[14] coupling as the final step was selected as the process route, as shown in Scheme 5.

S_NAr reaction between pyridinol **22** and 2-chloro-5-nitrotoluene generated biaryl ether **23**, the nitro group of which was reduced using tin in hydrochloric acid. Concurrently, quinazolinol **26** was prepared from iodo-anthranilic acid **25** and formamidine acetate. Chlorination of the resultant quinazolinol was achieved using phosphoroyl chloride. S_N-Ar reaction of chloroquinazoline **27** with aniline **24** proceeded well in isopropanol at reflux to provide anilinoquinazoline biaryl ether **28**, which was coupled with *N*-allyl-2-methoxyacetamide **29** (prepared from allylamine and methoxyacetyl chloride in triethylamine) under typical Heck conditions to give the quinazoline final product CP-724,714, **30.** After work-up, the residual level of palladium associated with **30** was analysed prior to, and after, scavenging.

Scavenging of this Heck-derived product with each of the functionalised scavengers separately, using the method of gravity elution through a cartridge, gave a product **30** with significantly reduced levels of residual palladium (Table 2) but which still exceeded the maximum regulatory-allowed level for palladium content of 5 ppm. Gratifyingly, longer treatment of the Heck reaction product under slurry conditions with a 1:1:1 mixture of the three scavengers **1**, **2**, and **3**, provided product **30** in which the palladium content was reduced to below API acceptable palladium levels.

Even after a number of additional synthetic steps from the point of use, a significant level of tin (1717 ppm) was found to be present in quinazoline **30**. In this case, scavenging of residual tin was again relatively effective, given the scavengers were not optimised; for example, scavenger **3** removed 90% of the residual tin content.

Carbon−Heteroatom Couplings: Buchwald−Hartwig Reaction. Carbon−nitrogen bond formation under palladium-catalysed conditions[15] is one of the most rapidly advancing areas of organic synthesis, and recently these Buchwald−Hartwig reactions have been scaled-up (multikilogram; 250 L).[16] Compound **33** is a precursor of the antioxidant component 4-aminodiphenylamine,[17] which can be prepared by amination reaction between aniline **32** and the aryl chloride **31**, as shown in Scheme 6. After work-up the residual level of palladium associated with **33** was analysed prior to and after scavenging, separately with three different multidentate silica scavengers **1, 2**, and **3** in methanol. The palladium content of **33** after scavenging was found to be <1 ppm, using either scavenger **1**, **2**, or **3** (Table 2).

(13) Brown Ripin, D. H.; Bourassa, D. E.; Brandt, T.; Castaldi, M. J.; Frost, H. N.; Hawkins, J.; Johnson, P. J.; Massett, S. S.; Neumann, K.; Phillips, J.; Raggon, J. W.; Rose, P. R.; Rutherford, J. L.; Sitter, B.; Stewart, A. M., III; Vetelino, M. G.; Wei, L. *Org. Process Res. Dev.* **2005**, *9*, 440.

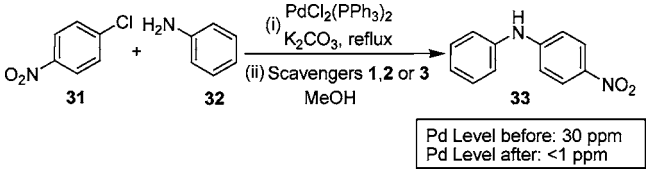
(14) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3; Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 5, page 217; Heck, R. *Org. React.* **1982**, *27*, 345; Chung, J. Y. L.; Cvetovich, R. J.; McLaughlin, M.; Amato, J.; Tsay, F.-R.; Jensen, M.; Weissman, S.; Zewge, D. *J. Org. Chem.* **2006**, *71*, 8602.

(15) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 13, page 699; Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

(16) Mauger, C. C.; Mignani, G. A. *Org. Process Res. Dev.* **2004**, *8*, 1065; Mauger, C. C.; Mignani, G. A. *Aldrichimica Acta* **2006**, *39*, 17; Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23.

(17) Giera, H.; Lange, W.; Pohl, T.; Sicheneder, A.; Schild, C. Patent DE19942394, 2001.

Scheme 6. **Synthesis of antioxidant precursor 33 by Buchwald−Hartwig coupling and scavenging of residual palladium**



The residual palladium content of cross-coupling reaction products was found to be variable but typically high (up to >2000 ppm). Use of one of the multidentate silica scavengers described was typically effective, under simple, nonoptimised conditions, for the reduction of palladium content to well-below acceptable levels for drug submission purposes.[18] The synthesis of tyrosine kinase inhibitor **30** with a Heck coupling as the final step yielded a product containing many hydrogen-bond donors and acceptors. The electron-rich, highly polar properties of **30** were illustrated by its propensity for palladium binding. Scavenging to below regulatory levels proved difficult, even with the efficient multidentate scavengers employed, and necessitated the use of a scavenger mixture and prolonged scavenger−API contact time to achieve the key target palladium content of <5 ppm.

Conclusions

Palladium catalysts have become an indispensable tool to the synthetic organic chemist, being necessary for the performance of a variety of key reactions such as deprotections and cross-couplings en route to APIs. Whilst the use of palladium catalysts allows significantly quicker routes to the desired drug molecule, the downside is the very strong likelihood of high levels of palladium contamination of the molecule, due to the ability of the polar groups usually present within APIs to bind palladium effectively. As with all metals, stringent regulatory guidelines exist for the amount of residual palladium that a drug candidate is allowed to contain.

PhosphonicS has designed a portfolio of functionalised silica scavengers which, amongst other applications, show enhanced efficiency for the removal of a variety of transition, heavy, and precious metals (including palladium) from APIs which themselves contain multiple, diverse polar groups, including hydroxyl, amino, carboxylic acids, nitriles, and amino acids. Scavenger designs incorporate multidentate functional groups, combinations of which provide different scavenging mechanisms and allow different palladium species, in different oxidation states, to be bound with sufficiently high affinity that any binding to the API is effectively overcome. The result is that the final level of palladium associated with the API is removed to below regulatory limits, with minimal loss of the valuable API itself.

These silica scavengers show excellent stability (thermal, physical, chemical, and mechanical), are amenable to a broad range of solvents (avoiding the need for an often time-consuming and costly change of process stream), and display exceptionally fast kinetics even at ambient temperatures. The materials are very easy to use in either cartridge or slurry format. Recovery of the precious metal used, often an economic necessity on process chemistry scales, is also possible by use of a simple scavenger wash protocol, which will be described in due course, or via an incineration process.

The high performance of designed multidentate scavengers and their capability to remove residual palladium to below regulatory-acceptable levels has been demonstrated by the effective removal of residual palladium from druglike products of deprotection, Sonogashira, Suzuki, Heck, and Buchwald−Hartwig reactions.

Experimental Section

Reagents and solvents were purchased from commercial suppliers and used without further purification. LC-ES/MS analyses were carried out on a Shimadzu LC/MS 2010EV system equipped with an Atlantis C18-column 2.1 mm × 50 mm. NMR spectra were recorded on a Bruker 250 MHz DPX NMR running XwinNMR version 3.5 with a 5 mm standard QNP probe spectrometer in the solvents indicated at 298 K. Chemical shifts are reported on the δ scale in ppm and referenced to residual solvent resonances. ICP-OES analyses were conducted using a Spectro Genesis system. Whenever possible, the identity of the products was established by comparison of the spectral data with literature precedents or by direct comparison with commercial samples.

Multidentate Silica Scavengers 1, 2, and 3. See ref 3 for the preparation of a range of multidentate silica scavengers including **1**, **2**, and **3**. The molar loading of the scavengers is typically 1.0 mmol/g.

General Scavenging Procedure for Removal of Palladium Residues from Reaction Products/APIs. The reaction product (typically 1 g) was dissolved in the minimum amount of methanol, and any remaining insoluble particles were removed by filtration. The solution was made up to 100 mL with methanol in a volumetric flask. This standard reaction product/API solution (10 mL, typically containing 100 mg of API) was dropped through a 10 mL cartridge containing 1 g of the appropriate palladium scavenger **1**, **2**, or **3**, which had been preconditioned with 5 mL of methanol, maintaining a flow rate of ∼1 mL per minute. Further portions of methanol (3 × 5 mL) were passed through the cartridge. The organic fractions were combined and evaporated under reduced pressure. A wide variety of other solvents such as ethyl acetate, dichloromethane, toluene, ethers, and water may be used as the scavenging solvents, depending on the solubility of the reaction product to be scavenged.

The scavenging conditions described in this paper are unoptimised. Scavenging efficiency is affected by a number of experimental factors, including contact time, temperature, and concentration, as well as the nature of the structural groups present within the functionalised silica scavenger. The importance of each of these factors is determined by the

(18) See U.S. Food and Drug Administration (www.fda.gov) and European Agency for the Evaluation of Medicinal Products (www.emea.eu.int). At the time of this writing, for the palladium group of metals, the regulatory guidance indicates acceptable residue levels of <5 ppm for oral drug products and <0.5 ppm for parenteral drug products.

nature of the API, and optimisation studies are typically required for each metal removal project.

***N*-Boc-L-serine (5).** *N*-α-Boc-*O*-Benzyl-L-serine **4** (1 g, 3.38 mmol) was dissolved in 9:1 ethanol/cyclohexene (10 mL). Palladium hydroxide on carbon (20 wt %) (0.119 g, 0.17 mmol) was added, and the suspension was refluxed for 16 h. The heterogeneous mixture was filtered and the product solution evaporated under reduced pressure. The residue was purified using silica scavenger **2**. The resultant colourless solution of **5** was evaporated under reduced pressure (quantitative yield). MS (ES^+): $m/z = 206$ $[M + H]^+$.

***N*-Boc-L-lysine (7).** *N*-α-Boc-*N*-ϵ-Cbz-L-lysine **6** (1 g, 2.62 mmol) was dissolved in ethyl acetate (20 mL), and palladium hydroxide on carbon (20 wt %) (0.092 g, 0.131 mmol) was added. The heterogeneous suspension was stirred under a balloon of hydrogen at rt for 2 h, after which time the suspension was filtered and the filtrate evaporated under reduced pressure. The residue was purified using silica scavenger **2**. The resultant colorless solution of **7** was evaporated under reduced pressure (quantitative yield). MS (ES^+): $m/z = 247$ $[M + H]^+$.

***N*-Alloc-4-piperidone Ethylene Acetal (9).** 4-Piperidone ethylene acetal **8** (0.501 g, 3.5 mmol) and potassium carbonate (0.725 g, 5.2 mmol) were dissolved in deionized water (10 mL). Allyl chloroformate (0.632 g, 1.5 mmol) was added dropwise over 15 min at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm slowly to rt, and stirred for a further 2 h. The solution was extracted with ethyl acetate, washed with 2 M aqueous potassium carbonate solution and water, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give **9** (1.2 g, 90%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.96 (tdd, $J =$ 17.2, 10.5, 5.5 Hz, 1H), 5.27 (qdd, $J = 18.1$, 10.4, 1.5 Hz, 2H), 4.61 (td, $J = 5.5$, 1.4 Hz, 2H), 3.99 (s, 4H), 3.63−3.58 (m, 4H), 1.79−1.68 (m, 4H); MS (ES^+): $m/z = 228$ $[M + H]^+$.

***N*-Alloc-4-piperidone (11).** *N*-Alloc-4-piperidone ethylene acetal **9** (0.7 g, 3.3 mmol) was dissolved in acetone (10 mL) and water (0.5 mL). Heterogeneous phosphonic acid **10** was added, and the slurry was stirred at reflux for 6 h. The slurry was filtered through a sintered funnel, and the clear filtrate was evaporated to dryness under reduced pressure to give **11** (0.6 g, quantitative yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.99 (tdd, $J =$ 17.2, 10.4, 5.6, Hz, 1H), 5.31 (qdd, $J =$ 16.2, 10.4, 1.4 Hz, 2H), 4.67 (td, $J = 5.6$, 1.4 Hz, 2H), 3.82 (t, $J = 6.3$ Hz, 4H), 2.50 (t, $J = 6.3$ Hz, 4H); MS (ES^+): $m/z = 184$ $[M + H]^+$.

Allyl 4-(phenethylamino)piperidine-1-carboxylate (12). *N*-Alloc-4-piperidone **11** (0.51 g 2.8 mmol) was dissolved in methanol (5 mL); phenethylamine (0.4 mL, 3 mmol) and glacial acetic acid (5 drops) were added. The reaction mixture was stirred at rt for 1 h. Sodium borohydride (0.113 mg, 3 mmol) dissolved in methanol (5 mL) was added dropwise over 5 min. The reaction mixture was stirred for an additional 2 h at rt, and the solvent was evaporated under reduced pressure. The resultant oil was purified by column chromatography using 20% ethyl acetate/heptane as eluant to give **12** (0.3 g, 40%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25−7.12 (m, 5H), 5.85 (tdd, $J =$ 17.2, 10.4, 5.9 Hz, 1H), 5.21 (qd, $J =$ 17.2, 1.5 Hz, 1H), 5.12 (qd, $J =$ 10.4, 1.4 Hz, 1H), 4.50 (td, $J =$ 5.4, 1.4, 2H), 2.94−2.67 (m, 8H), 2.63−2.50 (m 1H), 1.83−1.73 (m, 2H), 1.27−1.00 (m, 2H); MS (ES^+): $m/z = 289$ $[M + H]^+$.

***N*-Phenethylpiperidin-4-amine (13).** Allyl 4-(phenethylamino)piperidine-1-carboxylate **12** (0.23 g, 0.8 mmol) was dissolved in dichloromethane (5 mL), and $PdCl_2(PPh_3)_2$ (0.02 g, 0.026 mmol) and acetic acid (0.120 g, 2 mmol) were added. The solution was stirred at rt under nitrogen for 5 min and tributyltin hydride (2.4 mL, 8.9 mmol) was added dropwise over 5 min. The reaction mixture was stirred for an additional 2 h at rt. The solution was washed with 2 M aqueous potassium carbonate solution, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified using silica scavenger **2**. The resultant colourless solution of **13** was evaporated under reduced pressure (0.154 g, 75%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.24−7.11 (m, 5H), 3.11−2.44 (m, 9H), 1.89−1.78 (m, 2H), 1.29−1.13 (m, 2H); MS (ES^+): $m/z = 205$ $[M + H]^+$.

3-(2-Bromophenyl)propanoyl Chloride (15). 3-(2-Bromophenyl)propanoic acid **14** (2.29 g, 10 mmol) was dissolved in dichloromethane (5 mL), and thionyl chloride (10 mL, 137 mmol) was added dropwise at rt over 15 min. The mixture was refluxed for 2 h, cooled, and stirred at room temperature for a further 4 h. The excess of thionyl chloride was removed under reduced pressure to give **15** (2.29 g, 99%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45 (d, $J =$ 7.8 Hz, 1H), 7.16 (d, $J =$ 4.3 Hz, 2H), 7.08−6.96 (m, 1H), 3.18−3.11 (m, 2H), 3.05−2.99 (m, 2H).

3-(2-Bromophenyl)-*N*-phenethylpropanamide (16). 3-(2-Bromophenyl)propanoyl chloride **15** (2.28 g, 9.23 mmol), was dissolved in dichloromethane (20 mL), cooled to 0 °C and phenethylamine (5.8 mL, 30 mmol) was added dropwise over 15 min. The reaction mixture was warmed to rt and stirred for an additional 4 h. The solution was passed into a plug of heterogeneous phosphonic acid scavenger **10** (1.5 g) in order to remove the excess amine. The resultant solution was evaporated under reduced pressure to give **16** (2.8 g, 94%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.56 (dd, $J =$ 7.92, 1.05 Hz, 1H), 7.32−7.24 (m, 5H), 7.15−7.09 (m, 3H), 3.55−3.47 (m, 2H), 3.10 (t, $J =$ 7.5 Hz, 2H), 2.77 (t, $J =$ 6.90 Hz, 2H), 2.46 (t, $J =$ 7.5 Hz, 2H); MS (ES^+): $m/z = 332/334$ $[M + H]^+$.

***N*-Phenethyl-3-(2-(phenylethynyl)phenyl)propanamide (17).** 3-(2-Bromophenyl)-*N*-phenethylpropanamide **16** (0.51 g, 1.53 mmol) was dissolved in triethylamine (15 mL) and DME (15 mL). $PdCl_2(PPh_3)_2$ (0.035 g, 0.046 mmol), copper (I) iodide (0.02 g, 0.1 mmol), and phenylacetylene (0.17 mL, 1.5 mmol) were added, and the solution was heated at 120 °C for 16 h with stirring. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate and filtered. The filtrate was washed with saturated aqueous brine solution and dried over $MgSO_4$. The residue was purified using silica scavenger **2**, at which point the palladium content was measured by ICP-OES. Further purification by column chromatography using gradient elution from 0.5% to 60% ethyl acetate/hexane gave

17 (0.53 g, 93%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.48−7.42 (m, 2H), 7.31−7.26 (m, 2H), 7.21−7.11 (m, 7H), 7.03−6.95 (m, 3H), 3.43−3.33 (m, 2H), 3.11 (t, J = 7.11 Hz, 1H), 3.01−2.95 (m, 1H), 2.70−2.58 (m, 2H), 2.49−2.43 (m, 1H), 2.38−2.32 (m, 1H); MS (ES^+): m/z = 354 $[M + H]^+$, m/z = 376 = $[M + Na]^+$.

4-((1-Methoxy-3-methyl-1-oxobutan-2-ylamino)methyl)phenylboronic Acid (19). 4-Formylphenylboronic acid (1.0 g, 6.6 mmol) and valine methyl ester hydrochloride (1.1 g, 7 mmol) were dissolved in methanol (10 mL). Sodium borohydride (0.567 g, 15 mmol) was dissolved in methanol (10 mL) and added dropwise to the reaction mixture over 5 min. The resulting suspension was stirred at rt for 4 h. The solvent was evaporated under reduced pressure, and the resulting white solid was dissolved in water and extracted with ethyl acetate. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography using 40% ethyl acetate/hexane as eluant to give **19** (0.88 g, 54%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.11 (d, J = 7.8 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 3.87 (d, J = 13.6 Hz, 1H), 3.60 (d, J = 13.6 Hz, 1H), 3.67 (s, 3H), 2.97 (d, J = 6.1 Hz, 1H), 1.94−1.81 (m, 1H) 0.92−0.87 (m, 6H); MS (ES^+): m/z = 266 $[M + H]^+$.

4-((*N*-(1-Methoxy-3-methyl-1-oxobutanyl)pentanamido)methyl)phenylboronic Acid (20). 4-((1-Methoxy-3-methyl-1-oxobutan-2-ylamino)methyl)phenylboronic acid **19** (0.634 g, 2.4 mmol) was dissolved in dichloromethane (20 mL). Valeryl chloride (0.6 mL, 4.4 mmol) and DIPEA (0.9 mL, 4.5 mmol) were added dropwise with stirring over 5 min. The reaction mixture was refluxed for 2 h, after which time the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with 2 M aqueous sodium carbonate solution and water and was dried over $MgSO_4$ (0.75 g, 89%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.17 (d, J = 8.5 Hz, 2H), 7.71 (m, 2H), 5.06−4.94 (m, 1H), 4.71 (s, 1H), 4.64 (s, 1H), 3.47 (s, 3H), 3.36−3.32 (m, 1H), 2.42−2.18 (m, 2H), 1.71−1.57 (m, 2H), 1.45−1.20 (m, 2H), 1.03−0.80 (m, 9H); m/z = 350 $[M + H]^+$.

Methyl 2-(*N*-((2′-Cyanobiphenyl-4-yl)methyl)pentanamido)-3-methylbutanoate (21). 4-((*N*-(1-Methoxy-3-methyl-1-oxobutan-2-yl)pentanamido)methyl)phenylboronic acid **20** (0.75 g, 2.2 mmol) and 2-iodobenzonitrile (0.54 g, 2.35 mmol) were dissolved in 7:3:2 DME/ethanol/water. Pd-$(PPh_3)_4$, (0.022 g, 0.02 mmol) and 2 M aqueous sodium carbonate solution (4.7 mL, 9.4 mmol) were added with stirring under nitrogen. The solution was refluxed for 12 h, after which time the solvent was evaporated under reduced pressure (0.82 g, 91%). The residue was purified using silica scavenger **1**, **2**, or **3**. MS (ES^+): m/z = 407 $[M + H]^+$.

2-Methoxy-*N*-(3-{4-[3-methyl-4(6-methyl-pyridin-3-yloxy)phenylamino]quinazolin-6-yl}-*E*-allyl) Acetamide (30). (6-Iodoquinazolin-4-yl)-[3-methyl-4-(6-methyl-pyridine-3-yloxy)phenyl]amine **28** (0.29 g, 0.6 mmol), *N*-allyl-2-methoxyacetamide **29** (0.171 g, 1.3 mmol), $Pd_2(dba)_3$ (0.040 g, 0.04 mmol), sodium acetate (0.15 g, 1.82 mmol), and triethylamine (1.3 mL, 9.3 mmol) were dissolved in ethanol (20 mL) and refluxed for 6 h. The reaction mixture was filtered to remove the solid particles and the product solution evaporated under reduced pressure (0.30 g, quantitative yield). The residue was purified using a 1:1:1 mixture of silica scavengers **1**, **2**, and **3** (0.5 g each). MS (ES^+): m/z = 470 $[M + H]^+$.

4-Nitro-*N*-phenylbenzenamine (33). Aniline **32** (4.0 mL, 42.9 mmol), 4-nitro chlorobenzene (1 mL, 8.22 mmol) **31**, and $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) were stirred at rt for 10 min. Potassium carbonate (1.7 g, 12 mmol) was added, and the solution was refluxed for 16 h. The mixture was cooled to rt, diluted with ethyl acetate (20 mL), washed with water and saturated aqueous brine solution, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give **33** (1.9 g, quantitative yield). The residue was purified using silica scavenger **2**. MS (ES^-): m/z = 213 $[M - H]^-$.

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