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Full Papers

Removal of Heavy Metals from Organic Reaction Mixtures: Preparation and Application of Functionalized Resins[1]

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Abstract:

Using a toolbox, sulfur and amine ligands are attached to a variety of hydrophobic and hydrophilic resins, and the combinations were tested for the removal of heavy metals from a number of products, prepared by metal-catalyzed reactions. As a result, cheap combinations of silica resins and simple polyamines proved to be among the most effective metal scavengers particularly in apolar solvents such as cyclohexane. Expensive cyclic polyamines are not suitable, owing to kinetic retardation of complexation. Functionalized PEG-based polymers, originally designed for solid phase synthesis, show promising performance as metal scavengers. The results are discussed and compared to alternative approaches for purification such as salt-formation and chemical downstream transformation.

Introduction

Metal-organic chemistry is a cornerstone in synthesis. In addition to the stoichiometric use of Mg and Li reagents, the use of heavy metal catalysts is of utmost importance e.g. in *Heck* and cross-coupling reactions whose application has reached industrial scale.[2] The removal of toxic heavy metals needs to be assured for drug substances at the ppm level which has sometimes proved difficult. Several techniques to purge product streams and effluents from metal contamination have been already reviewed[3,4] and have been divided into (1) extraction and precipitation treatments and (2) solid phase treatments;[5] a screening system for the latter method was described recently.[6] Faced with similar problems during drug development, we set up a toolbox of functionalized resins and tested it on a number of heavy metal-contaminated products and reaction mixtures.

Choice and Preparation of Resins

The use of functionalized resins offers a simple suspension−filtration sequence for the purification of metal-contaminated product solutions.[7] The design of such resins has some degree of freedom: (a) the nature of the solid support, (b) the linker or spacer, (c) the complexing agent or ligand, and finally (d) the loading of the resin. All of these factors may contribute to the properties of the final resin. Thus, a toolbox or construction kit was designed as shown in Table 1. We chose silica gel (**S**), cross-linked polystyrene (**P**), and cross-linked polyethyleneglycol (**O**) resins as support; the linkages to the ligands (**a**−**n**) were made direct (**1**) or via methyl-, propyl-, and glycidoxypropyl-spacers (**2**), (**3**), and (**4**), respectively.[8]

For the preparation of silica-based resins, three approaches were applied:

(a) Activation of silica with thionyl chloride to give chloro-silica followed by nucleophilic substitution[9] (Table 2). Whereas polyamines react smoothly to obtain the corresponding silica gels with useful loading (**S1f**, **S1g**, and **S1l**, 0.4−1.0 mmol/g), sulfur nucleophiles lead to resins **S1b** and **S1e** containing less than 0.05 mmol/g of the ligand.

(b) Silanation of (3-bromopropyl)trimethoxysilane or (3-bromopropyl)trichlorosilane[10] followed by nucleophilic substitution (Table 3).

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(1) Part of D.B.'s master thesis at the École Nationale Supérieure de Chimie de Mulhouse, France.

(2) (a) King, A. O.; Yasuda, N. *Top. Organometal. Chem.* **2004**, *6*, 205–245. (b) Blaser, H. U.; Schmidt, E. *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004. (c) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.

(3) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889–900.

(4) Mendonca, A. *Power of Functional Resins in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2008.

(5) Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res. Dev.* **1997**, *1*, 311–314.

(6) 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*, 198–205.

(7) The sometimes low solubility of aromatic compounds makes this approach inefficient. For a recent successful alternative approach based on the reslurry of the metal-contaminated compound in the presence of soluble scavengers, see: Flahive, E. J.; Ewanicki, B. L.; Sach, N. W.; O'Neill-Slawecki, S. A.; Stankovic, N. S.; Yu, S.; Guinness, S. M.; Dunn, J. *Org. Process. Res. Dev.* **2008**, *12*, 637–645.

(8) For details, see the experimental section.

(9) (a) Firouzabadi, H.; Iranpoor, N.; Karimi, B.; Hazarkhani, H. *Synlett* **2000**, 263–265. (b) Zolfigol, M. A.; Madrakian, T.; Ghaemi, E.; Afkhami, A. *Green Chem.* **2002**, *4*, 611–614.

(10) Rosenberg, E. US 5.695.882, 1997.

10.1021/op900102a CCC: $40.75

Table 1. **Construction kit for functionalized resins**

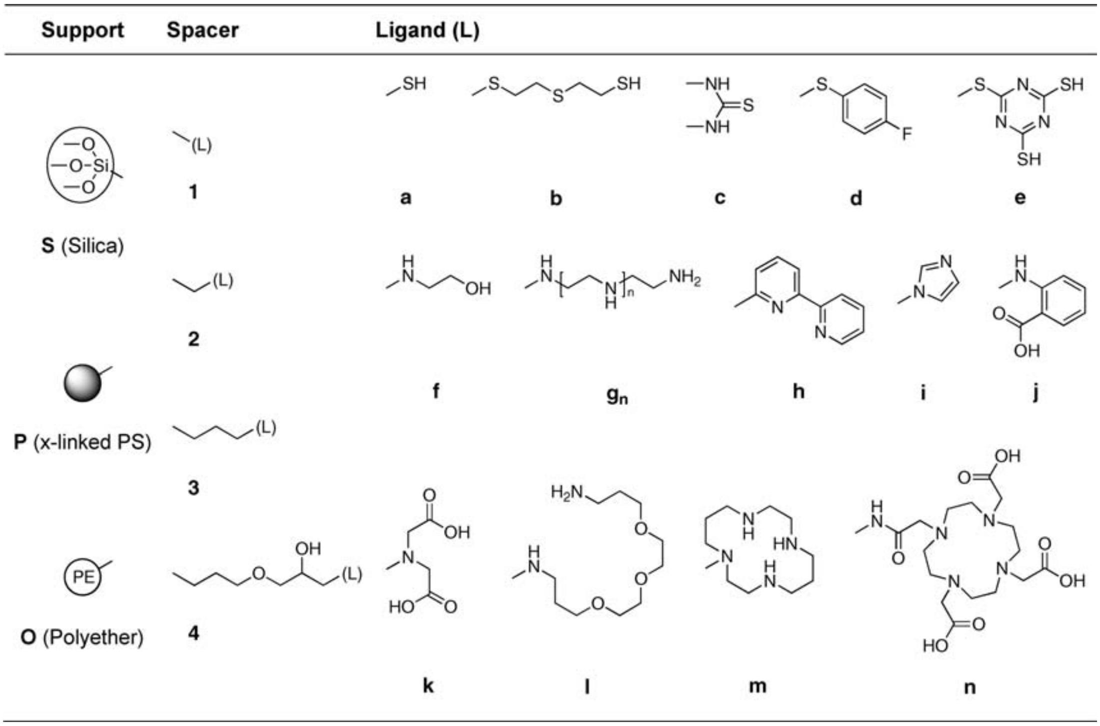
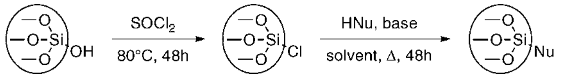


Table 2. **Activation and functionalization of silica to S1x**



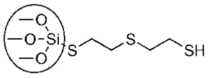
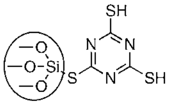
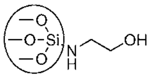
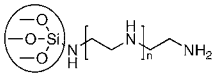
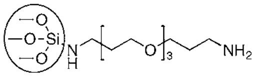
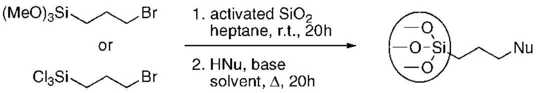
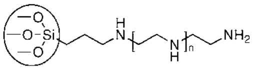
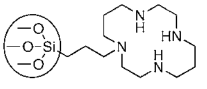
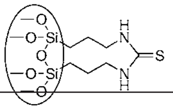
Resin #	Structure	Loading [mmol/g]
S1b		0.04
S1e		0.03
S1f		0.91
S1g$_1$ (n=1)		0.70
S1g$_2$ (n=2)		0.90
S1g$_3$ (n=3)		0.66
S1g$_4$ (n=4)		0.57
S1l		0.40

Table 3. **Silanation and nucleophilic substitution of (3-bromopropyl)trimethoxysilane or (3-bromopropyl)-trichlorosilane to S3x**



Resin #	Structure	Loading [mmol/g]
S3g$_2$ (n=2)		0.89
S3m		0.26
Deloxan® THP II «S3c»		0.30-0.50

(c) Nucleophilic epoxide opening of (3-glycidoxypropyl)-trimethoxysilane[11] followed by silanation onto silica gel (Table 4). The latter two methods also make sulfur-based scavengers such as **S4b**, **S4d**, **S4e** easily accessible.

Polysiloxane-based resins functionalized with thiourea are commercially available as Deloxan THP II (loading: $\geq$0.3−0.5 mmol/g) from Evonik−Degussa[12] and can be numbered in our system as **S3c** (see Table 3, last entry).

A great variety of functionalized polystyrenes are already commercially available; e.g. Matrix Innovation[13] offer a metal scavenger kit containing resins carrying thiol, diethylenetriamine, phenanthrene, imidazole, and anthranilic acid as ligands (see Table 5, **P2a**, **P2g$_1$**, **P1h**, **P2i**, **P2j**), and, of course, the well-known Amberlite resins are designed for various extraction purposes.[14] Two more resins have also been prepared (Table

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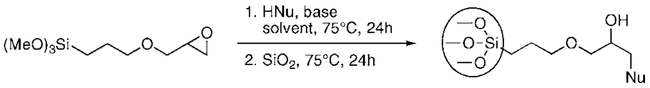
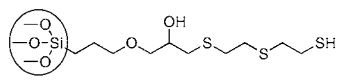
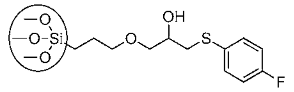
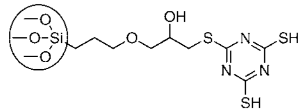
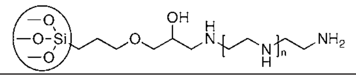
(11) Bruening, R. L.; Tarbet, B. J.; Izatt, R. M.; Bradshaw, J. S. U.S. Patent 5.190.661, 1993.

(12) (a) Woods, J. B.; Spears, R.; Krauter, J.; McCarthy, T.; Murphy, M.; Hord, L.; Doorley, P.; Chen, B. *Chem. Ind. (Boca Raton, FL, U.S.)* **2007**, *115*, 493–499. (b) See entries for "Deloxan" at http://www.finechemicals.de.

(13) Matrix innovation: http://www.matrix-innovation.com; other companies now offer similar kits, see: http://www.silicycle.com; http://www.reaxa.com; http://www.jmcatalysts.com/pharma/index.asp (Smopex); http://www.phosphonics.com; http://www.polymerlabs.com.

Table 4. **Nucleophilic epoxide opening and silanation of (3-glycidoxypropyl)trimethoxysilane to S4x**



Resin #	Structure	Loading [mmol/g]
S4b		0.46
S4d		0.68
S4e		0.67
S4g$_1$ (n=1)		1.07
S4g$_2$ (n=2)		0.78

5): The known polystyrene-bound trimercapto-triazine (PS-TMT: **P2e**) is accessible from Merrifield resin (chloromethyl polystyrene) by means of nucleophilic substitution.[15] The expensive DOTA (1,4,7,10-tetraazacyclododecan-*N*,*N′*,*N″*,*N‴*-tetra-acetic acid), as another example of a macrocyclic polyamine, was attached to aminomethyl polystyrene by means of a peptide coupling reaction[16] to form **P2n**.

Highly hydrophilic polyether resins were introduced by Meldal for solid phase synthesis.[17] These super permeable organic combinatorial chemistry (SPOCC) resins (marketed as Versabeads O) were further functionalized to resin **O3g$_1$** (Scheme 1). Furthermore, because of their high N content, polyvinyl amines cross-linked with PEG-diglycidyl-ethers appeared very interesting.[18] For test purposes a sample of (**5**), V-LE400 PG2229, was included in a preliminary study.

Test Cases

To test the resin−spacer−ligand combinations described above we used real products and reaction mixtures from metal-catalyzed reactions. Table 6 summarizes these test cases. Entries 1 and 2 depict reactions in the synthesis of SPP100 (Aliskiren),[19] a renin inhibitor recently launched for the treatment of hypertension.[20] The *Kumada* coupling (entry 1) to form **T1** uses nickel catalysts; nickel salts end up in the aqueous waste after workup. The drug substance base **T2** of Aliskiren is formed by catalyzed hydrogenation of an azide (entry 2) and may sometimes be contaminated with up to 20 ppm of Pd due to the so-called leaching. *Sonogashira* coupling uses a combination of Pd and Cu catalysts, as in the effective synthesis of terbinafine **T3**,[21] an antimycotic drug (entry 3). The crude product contains 50−200 ppm Pd and 10−20 ppm Cu which are usually removed by short-path distillation.[22] *Suzuki* coupling is amongst the widely used reaction to couple aryl-moieties. Using soluble Pd catalysts, the heavy metal remains entirely in the crude product; **T4** shows an example (entry 4). *Buchwald−Hartwig* coupling is a viable method to prepare diarylamines. **T5** and **T6** (intermediates for COX-2 inhibitors) represent examples of such a transformation.[23]

Results and Discussion

For the target **T2**—Aliskiren free base, as a solution in ethanol, obtained after hydrogenation of the precursor azide (Table 6)—not many methods for the removal of heavy metals are feasible: Aqueous extraction is impossible, and crystallization to the later drug substance salt does not alter the metal content significantly. Thus, a broad screening of scavengers for the ethanolic solution was performed. A simple set up[24] was applied: 4 mL of the metal-contaminated solutions (10% **T2** in ethanol) were treated with functionalized resins (100−300 mg), and the mixtures were shaken in screw cap vials for 20 h at room temperature. The samples were filtered, the filtrates were evaporated to dryness, and the residues were analyzed for the metals. Table 7 shows the result for all available and synthesized resins.

In general most polystyrene-based resins (Table 5 for structures) proved to be unsuccessful (Table 7, entries 18−28) along with most Matrix Innovation resins, PS-TMT (**P2e**), PS-DOTA (**P2n**) resins, and some Amberlite resins. Only PS-diethylenetriamine (**P2g$_1$**, entry 20) as well as Amberlite GT73 (entry 26) were capable of reducing the Pd content from 14 ppm to 3 ppm and 2 ppm, respectively.

Silica-based resins show a much better performance (Table 7, entries 1−16). Most of the resins depicted in Tables 2−4 fulfilled the requirement for test case **T2** (14 ppm → $\leq$2 ppm) regardless of the nature of the ligand (S- or N-based); exceptions were low-loaded S-resins (**S1b** and **S1e**, Table 7, entries 1 and 2), the macrocyclic **S3m**, and the arylthioether **S4d**[25] (Table 7, entries 11 and 13). For a limited kinetic study, 100 mL of the ethanolic solution of **T2** was stirred with 7.5 g of resin **S4g$_2$**, and samples of the supernatant were drawn each hour and analyzed for the Pd content of their evaporation residue. After 4 h, a steady state was achieved at 6−7 ppm, and it took 20 and 90 more hours to lower the Pd content to 6 and 4 ppm, respectively (Figure 1). These results indicate that complexation is not at all an instantaneous process. For macrocyclic polyamines, complexation with Pd is known to be even more kinetically hindered[26] which is the explanation for the temperature effect of the experiment using resin **S3m** in which 1,4,8,11-tetraazacyclotetradecane (cyclam) is attached on propyl-silica (Table 7, entries 11 and 12).

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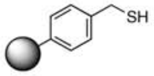
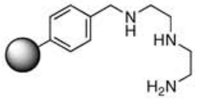
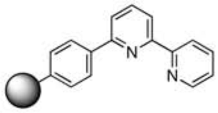
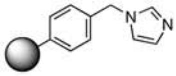
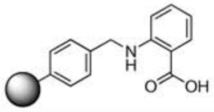
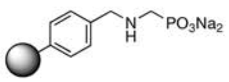
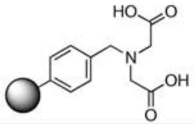
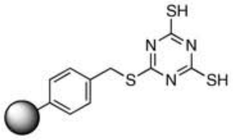
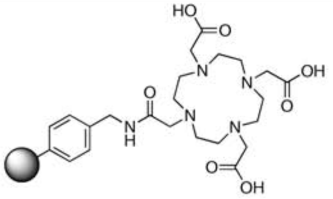
(14) Rohm & Haas: http://www.amberlyst.com/literature/us/IRC748.pdf.
(15) For the preparation of PS-TMT, see: Ishihara, K.; Nakayama, M.; Kurihara, H.; Haraguchi, H. *Chem. Lett.* **2000**, *10*, 1218–1219.
(16) Böhnke, H. *Novartis Pharma AG*, Process Research and Development Report, 1996.
(17) Grøtli, M.; Gotfredsen, C. H.; Rademann, J.; Buchardt, J.; Clark, A. J.; Duus, J. Ø.; Meldal, M. *J. Comb. Chem.* **2000**, *2*, 108–119.
(18) Gavelin, P.; Rehnberg, P. N.; Johannsen, I. WO 2006015594 A1 2006/0216, 2006.
(19) Herold, P.; Stutz, S.; Spindler, F. WO 2002002508 A1 20020110, 2002.
(20) (a) Anderson, D. L. *Drugs Today* **2007**, *43*, 849–855. (b) Siragy, H. M.; Kar, S.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2007**, *6*, 779–780.
(21) Beutler, U.; Fleury, C.; Penn, G.; Ryser, T.; Schenkel, B. *Surf. Sci. Catal.* **1997**, *108*, 31–35.
(22) Beutler, U.; Penn, G. WO 2005021483 A2 20050310, 2005.
(23) Acemoglu, M.; Allmendinger, T.; Calienni, J.; Cercus, J.; Loiseleur, O.; Sedelmeier, G. H.; Xu, D. *Tetrahedron* **2004**, *60*, 11571–11586.
(24) For details, see the Experimental Section.
(25) This was described in a patent to be an efficient scavenger, see reference 11.
(26) Kaden, T. University of Basel, personal communication.

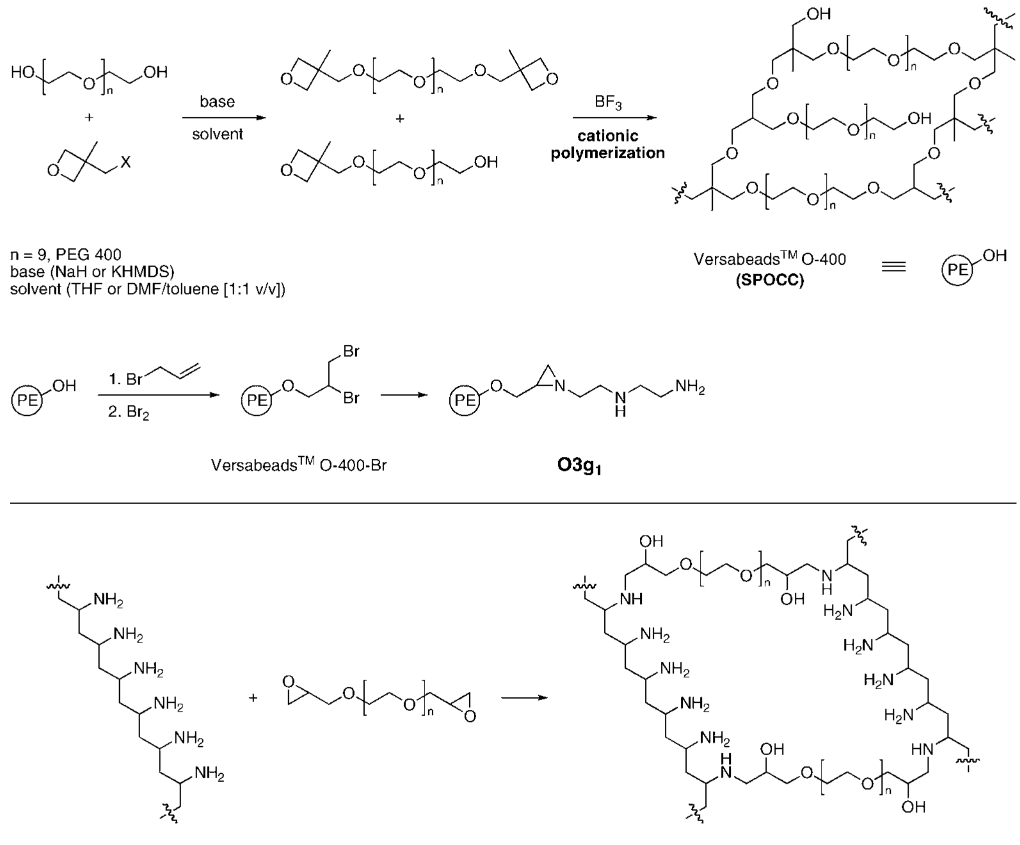
Table 5. **Functionalized polystyrenes P2x**

	Resin #	Structure	Loading [mmol/g]
Matrix Innovation Resins	P2a		2.20
	P2g$_1$		2.30
	P1h		1.70
	P2i		1.80
	P2j		2.00
Rohm & Haas Resins	Amberlite® GT73	Thiol-functionalized styrene divinylstyrene copolymer	≥1.20
	Amberlite® IRC747		≥1.75
	Amberlite® IRC748 « P2k »		≥1.35
PS-TMT	P2e		0.93
PS-DOTA	P2n		0.54

To compare the resins and the conditions a simple calculation is helpful. Taking the amount of resin applied (g), considering its individual loading (mmol/g), and calculating the amount of Pd removed from the solution ($\text{mmol}_{\text{before treatment}} - \text{mmol}_{\text{after treatment}}$) an efficiency ratio R_E of mmol ligand/mmol Pd can be calculated[27] which is depicted in Tables 7−12. It is worth noting that for the ethanolic solution of **T2** containing 14 ppm of Pd (based on solvent-free substance) a ligand/Pd ratio of >800 is needed to achieve the goal (<2 ppm Pd). The sulfur-functionalized resins **S1b** and **S1e** were inefficient because of their very low loading, but the low ratio R_E indicates the high complexing power of bis(2-mercaptoethyl) sulfide (**b**) and of 2,4,6-trimercapto-[1,3,5]-triazine (**e**).

The most effective resins were found to be **S4g$_1$** < **S4b** ≈ **S3c** < **GT73** < **S1gn** ≈ **S3g$_2$** ≈ **S4e** (Table 7). For these resins the experiments were repeated, using gradually lower amounts down to 10 mg; the results are summarized in Table 8 and reveal **S1g$_2$** and Amberlite GT73 to be the best (25 mg are sufficient). The performance of Amberlite GT73, a commercial thiol-functionalized polystyrene-based resin, appears to be astonishing, as a similar resin (**P2a**) from Matrix Innovation proved to be ineffective. This is common to most other polystyrene-based resins applied for **T2** (see above) and can be explained by the swelling characteristics of cross-linked polystyrene being not sufficient in ethanol, making the binding sites not well accessible. It is most likely that Amberlite GT73 has another open-pore core structure to explain its properties.[28,29]

Scheme 1. **Preparation of polyether-functionalized resins $O3g_1$ and 5**



5

For terbinafine **T3**, containing 10 ppm Cu and 58 ppm Pd, the resin screening was restricted to the best resins found for **T2**: **S1g$_2$**, **S3g$_2$**, **S4e**, **S4g$_2$**, **O3g$_1$**, and **GT73**. Additionally the effect of the solvent on the metal extraction process was evaluated. Thus, 10% solutions of **T3** in cyclohexane, dichloromethane, and ethanol were prepared, and 4 mL of each solution was tested against 300 mg of the chosen resins. The results are summarized in Table 9. Whereas the copper content of terbinafine **T3** was reduced in each case from 10 to <2 ppm, the scavenging efficiency for Pd showed a strong solvent effect. In dichloromethane most resins exhibited the worst performance, which was somewhat better in ethanol. In cyclohexane even silica had some effect, and all the resins used removed Pd to <2 ppm. For this solvent the screening was extended to lower amounts of resin (Table 10), and R_E values were calculated. Compared to ethanol (where the resins show R_E values of ~1000 or larger), good resins now show R_E ratios of <50 and can be ordered as **S4e** > **S1g$_2$** > **S4g$_2$** > **S3g$_2$** > **GT73**.

Products derived from *Suzuki* and *Buchwald−Hartwig* coupling reactions usually contain much more Pd than the examples **T2** and **T3** just discussed.[30] For instance crude and even recrystallized **T4** has a content of 9000 and 3350 ppm, respectively. The latter material was subjected to metal scavenging in isopropanol, using a subset of resins and applying the standard protocol (100 and 300 mg resin); the results are summarized in Table 11. A small number of resins were used for the metal removal from xylene solutions of Pd-contaminated biaryl amines **T5** and **T6**, obtained from *Buchwald−Hartwig* coupling reactions (Table 12). For **T4** and **T6** resins **S4e**, **S3g$_2$**, and **S4g$_2$** were found to be effective to lower the target's high Pd-load considerably (3350 → <10 ppm, 1800 → <40 ppm, Tables 11 and 12). Again, **P2g$_1$** is less efficient in protic isopropanol (Table 11, entry 5).

As a test case we also examined aqueous effluents stemming from the Ni-catalyzed *Kumada* coupling to **T1** which contain >200 ppm Ni. We used a classical ion-exchange resin and compared it with modern polyamines. Thus, the aqueous phase from the workup of **T1** was neutralized[31] and treated with Amberlite IRC748, a polystyrene resin functionalized with an imino-diacetic acid group. The results, which are summarized

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(27) The calculation is done according to the formula:

$$R_E = \frac{n_R}{\Delta n_{Pd}} = \frac{M_R \times L_R \times M_{Pd}}{m_T \times (c^0_{Pd} - c^{aT}_{Pd})}$$

where n_R is the molar amount of ligand bound to resin used for one scavenging experiment; Δn_{Pd} is the molar amount of Pd removed from the sample, m_R is the mass of resin used, L_R is its loading with the ligand, m_T is the mass of the target sample (evaporation residue or mass of solution × its concentration), c_{Pd} is the concentration of Pd in the sample before (0) and after treatment (aT) in ppm or mg/kg; M_{Pd} is the molecular weight of Pd (106.4). The higher the value of R_E the less efficient is the resin.

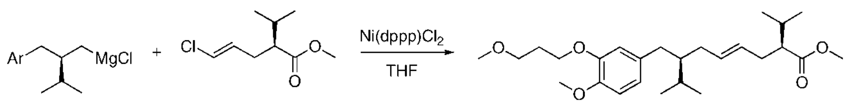
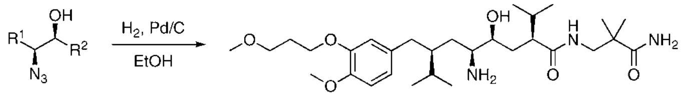
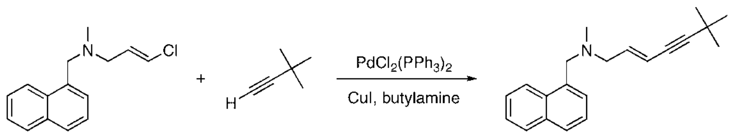
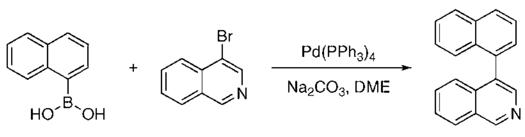
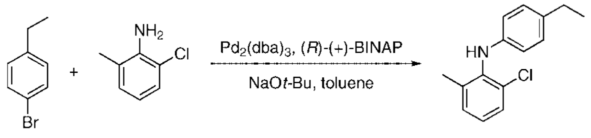
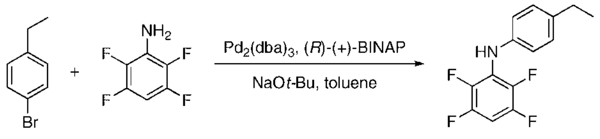
(28) Rohm & Haas did not disclose the details for Amberlite GT73 which is now replaced by the commercial Amberlite GT74.

(29) Thiol-modified scavengers such as Smopex 234 from Johnson Matthey (fibres, surface modified with−CO−O−CH_2−CH_2−SH) proved to be efficient in certain other cases tested by Markus Bänziger (personal communication).

(30) One target of catalyst optimization is, of course, to increase the turnover number and thus to decrease the amount of precious metal needed.

(31) The reaction mixture for the preparation of **T1** is worked up with aqueous HCl or H_2SO_4 solution. For details, see reference 19.

Table 6. **Contaminated products from metal-catalyzed reactions as test cases for functionalized resins**[a]

#	Reaction and product		Metal content [ppm]
1	Ni-catalyzed Kumada-coupling 	T1	Ni: 200
2	Pd/C-catalyzed hydrogenation of the azide-precursor to Aliskiren base 	T2	Pd: 14*
3	Pd/Cu-catalyzed Sonogashira-coupling to Terbinafine 	T3	Pd: 58* Cu: 10*
4	Pd-catalyzed Suzuki-coupling 	T4	Pd: 9300* (crude) Pd: 3350* (recryst.)
5	Pd-catalyzed Buchwald-Hartwig coupling 	T5	Pd: 9300*
6	Pd-catalyzed Buchwald-Hartwig coupling 	T6	Pd: 1280*

* Relative to dry substance

[a] Relative to dry substance.

in Table 13, show the feasibility of this approach. Similar results can be obtained with the highly amino functionalized polyether-resin **5**. Less than 1% of the resin is sufficient to remove the nickel completely. Not unexpectedly, resin **5** appears blue when loaded with nickel, resembling the properties of the Ni(en)$_2$Cl$_2$ complexe[32] (Figure 2).

Summary and Outlook

The most efficient resins found in our study are summarized in Table 14; the majority of them are based on silica gel carrying polyamine functionalities. The spacer obviously does not play a major role as direct linkage (**S1g**), propyl-spacers (**S3g**) and glycidoxypropyl anchors (**S4g**) are equivalent. To choose for a particular application, their accessibility and cost need to be considered. Activation of silica to obtain (**S1x**) resins is a laborious and hazardous process since excess of thionyl chloride needs to be used and (even worse) then removed by either distillation (similar to the literature[9]) or filtration. On the other hand, silanation of organosilanes is much simpler. The differences to prepare (**S3g*n***) and (**S4g*n***) resins culminate in the price of the linkers: (3-bromopropyl)trimethoxysilane being about 30 times more expensive than (3-glycidoxypropyl)trimethoxysilane.[33] Polyamines themselves such as triethylenetetramine (in

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(32) Sullivan, J. K.; Fanning, J. C. *J. Inorg. Nucl. Chem.* **1969**, *31*, 49–57.

Table 7. **Pd content of T2 after treatment of 4 g of 10% solution in ethanol with 100 or 300 mg resin at room temperature for 20 h (initial content 14 ppm Pd)**

			Pd level [ppm] of **T2** after treatment with		
entry	resin #	loading [mmol/g]	100 mg	300 mg	R_E
1	**S1b**	0.04	9	11	210
2	**S1e**	0.03	11	13	270
3	**S1g$_1$**	0.70	**2**	**2**	1600
4	**S1g$_2$**	0.90	**1**	**<1**	1800
5	**S1g$_3$**	0.66	**1**	**<1**	1400
6	**S1g$_4$**	0.57	**1**	**<1**	1200
7	**S1f**	0.91	10	9	>6000
8	**S1l**	0.40	6	**3**	>1300
9	**S3c**	0.50	**3**	**2**	3300
10	**S3g$_2$**	0.89	**2**	**1**	2000
11	**S3m**	0.26	12	9	>4000
12	**S3m** (40 °C)	0.26	13	5	>2000
13	**S4d**	0.68	13	12	>27000
14	**S4b**	0.46	**3**	**2**	1100
15	**S4e**	0.67	**2**	**<1**	1500
16	**S4g$_1$**	1.07	**3**	**3**	>2500
17	**Silica**	1.00	14	14	∞
18	**P2a**	2.20	13	12	>87000
19	**P2e**	0.62	12	11	>16000
20	**P2g$_1$**	2.30	4	**3**	>6000
21	**P1h**	1.70	14	14	∞
22	**P2i**	1.80	9	6	18000
23	**P2j**	2.00	14	14	∞
24	**P2n**	0.26	14	14	∞
25	**P2n** (40 °C)	0.26	14	14	∞
26	**GT73**	1.20	**2**	**2**	2700
27	IRC747	1.75	13	13	>46000
28	IRC748	1.35	13	13	>35000

particular the technical grade composed of mixtures) are bulk chemicals and very cheap (compare Table 15). The more expensive 2,4,6-trimercapto-[1,3,5]-triazine (TMT) is well perceived as a metal scavenger.[5,15] The present study revealed its advantage when linked to silica **S4e** in contrast to the polystyrene analogue **P2e**.[34] Silica is not combustible which might serve as a disadvantage compared to polystyrene when it comes to the need for resin disposal.[35] Here functionalized polyether resins may play a role as they combine the hydrophilic properties with combustibility. **O3g$_1$**—the only prepared sample yet—proved to have efficiency comparable to that of **S1g$_2$**, and further elaboration will bring about better polyether-based resins.

As scavenging would add as an additional process step, it has to be compared to possible alternatives.

- First of all, the heavy metal load could be reduced by optimizing the catalysis step, but also leaching from solid supported catalysts has to be suppressed by other means.
- For terbinafine **T3** a short-path distillation was established to reduce the heavy metal content.[22]
- As salt formation of basic products is a viable method to reduce their metal content,[36] this was verified for **T4**, too. After screening of some acids,[37] the naphthalene-2-sulfonic acid salt of **T4** was prepared, exhibiting a Pd content of only 13 ppm (Scheme 2).
- As **T5** and **T6** are intermediates in the synthesis of COX-2 inhibitors,[23] it is worthwhile checking for the depletion of the Pd level further along the syntheses. Thus, **T6** was transformed into its chloroacetyl derivative **T6-CA** (a precursor towards the preparation of the final drug candidate, Robenacoxib)[38] which was free of Pd after crystallization (Scheme 3). In addition, chromatography on silica gel was efficient to remove Pd to <1 ppm for **T5** and **T6**.

Experimental Section

General Methods. Reactions were carried out using oven-dried glassware under an atmosphere of dry argon or nitrogen and magnetically or mechanically stirred, unless noted otherwise. Reagents were purchased from commercial suppliers (Acros, Aldrich, Fluka, Lancaster) and used without further purification, unless noted otherwise. Analytical grade solvents (*n*-butanol, ethanol, ethyl acetate, isopropanol, methanol, methylene chloride, *tert*-butylmethylether) were used as received for reactions, for extractions, and chromatographic purifications, unless otherwise stated. *N*,*N*-dimethylacetamide, 1,2-dimethoxyethane, *N*,*N*-dimethylformamide, dimethylsulfoxide, *n*-heptane, tetrahydrofuran, and toluene were stored over molecular sieves. Deuterated solvents were obtained from Armar Chemicals, Switzerland. Thin layer chromatography (TLC) was used for monitoring reactions, carried out using Merck silica gel 60 F_{254} plates, and visualized with UV light, except as indicated otherwise. Flash chromatography (FC) was performed using Merck silica gel 60 (230−400 mesh) at a pressure of ~0.3 bar.[39] Eluents and R_f are indicated. Concentration under reduced pressure was performed at 40 °C. Yields refer to chromatographically purified or recrystallized, spectroscopically pure compounds. Melting points were measured on a Büchi SMP-20 apparatus in open glass capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Bruker DPX 300 MHz or on Bruker DMX 500 MHz spectrometer at 298 K in the indicated deuterated solvent, unless otherwise stated. Data are reported as follow: chemical shift (δ, ppm), integration, multiplicity (s, singulet; d, doublet; t, triplet; q, quartet; m, multiplet or not resolved signal; br, broad signal), coupling constant(s) (J, Hz). All signals were referenced to the internal solvent signal as standard ($CDCl_3$, δ 7.26; CD_3OD, δ 3.31; DMSO, δ 2.50). ^{13}C NMR spectra were recorded with ^{1}H-decoupling on Bruker DPX 75 MHz or on Bruker DMX 125 MHz spectrometer at 298 K in the indicated deuterated solvent, unless otherwise stated. All signals were referenced to the internal solvent signal as standard ($CDCl_3$, δ 77.0; CD_3OD, δ 49.0; DMSO, δ 39.5). Mass spectra were obtained from the Mass Spectroscopy

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(33) See Table 15; 30 CHF/g compared to 1 CHF/g (Sigma-Aldrich prices for 25 and 250 mL quantities, respectively).

(34) Similar resins are now commercially available: Isolute Si-TMT by Biotage (http://www.biotage.com) and SiliaBond DMT by Silicycle (http://www.silicycle.com) which could be enumerated in our system as **S3e**.

(35) For cost reasons, reuse of the resin needs to be considered; during regeneration the precious metal may be recovered as well.

(36) Manley, P. W.; Acemoglu, M.; Marterer, W.; Pachinger, W. *Org. Process Res. Dev.* **2003**, *7*, 436–445.

(37) Naphthalene-1-carboxylic acid, sulfuric acid, benzene−sulfonic acid, and naphthalene-2-sulfonic acid were used.

(38) Acemoglu, M.; Allmendinger, T.; Calienni, J. V.; Cercus, J.; Loiseleur, O.; Sedelmeier, G. H.; Xu, D. WO 2001023346, A2 20010405,2001.

(39) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

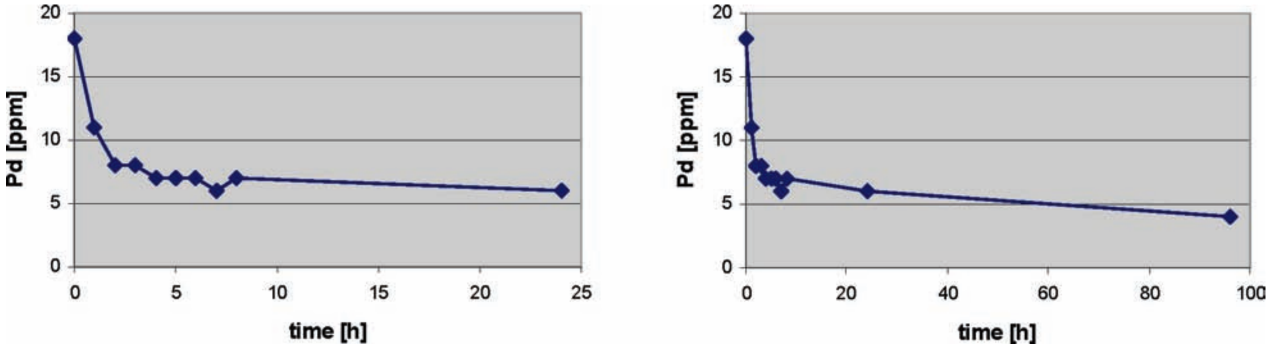


Figure 1. **Time dependence for the removal of Pd from ethanolic T2 solution using resin S3g$_2$.**

Table 8. **Pd content of T2 after treatment of 4 g of 10% solution in ethanol with 10−50 mg resin at room temperature for 20 h (initial content 14 ppm Pd)**

entry	resin no.	loading [mmol/g]	Pd level [ppm] of **T2** after treatment with 10 mg	25 mg	50 mg	R_E (50 mg resin)
1	**S1g$_2$**	0.90	4	**3**	**2**	1000
2	**S3c**	0.50	10	6	4	700
3	**S3g$_2$**	0.89	11	8	6	1500
4	**S4e**	0.67	7	5	4	900
5	**S4g$_2$**	0.71	4	4	4	950
6	**GT73**	1.20	5	**3**	**2**	1300

Service of Novartis Pharma AG, Basel (Switzerland). Elemental analyses and loading of all functionalized resins were obtained from the Analytical Service of Solvias AG, Basel (Switzerland). For the determination of heavy metals, inductively coupled plasma-optical emission spectrometry (ICP-OES) measurement after a wet decomposition step was used which corresponds to the method described in European Pharmacopoeia, 6th ed., 2008 <2.2.57>. The limit of quantification for each analyte is 1 mg/kg with a relative standard deviation of not more than 10%.

General Procedure for the Chlorination of Silica Gel (Table 2). Silica gel (20.0 g) and $SOCl_2$ (80 mL) were introduced in a 250 mL double-wall filter reactor equipped with a mechanical stirrer and a condenser. The reaction mixture was vigorously stirred and heated at 80 °C for 48 h. The unreacted $SOCl_2$ was filtered, and the chloride silica gel was dried under vacuum at 40 °C for 48 h.

Procedure for the Preparation of Resin S1b. Chloride silica gel (5.0 g, 6.50 mmol Cl, 1 equiv) and anhydrous DMF (50 mL) were introduced in a 200 mL three-necked reactor equipped with a mechanical stirrer and a condenser. A solution of bis-(2-mercaptoethyl)sulfide (10.03 g, 65.0 mmol, 10 equiv) and DIPEA (5.4 mL, 32.50 mmol, 5 equiv) in anhydrous DMF (40 mL) was slowly added to the beige-yellow mixture. The reaction mixture was vigorously stirred and heated at 40 °C for 48 h. The functionalized silica resin was isolated by filtration, washed with DMF (2 × 50 mL), EtOH (3 × 50 mL), and dried under vacuum at 40 °C for 12 h.

Procedure for the Preparation of Resin S1e. Chloride silica gel (5.0 g, 6.50 mmol Cl, 1 equiv) and anhydrous DMAc (50 mL) were introduced in a 200 mL three-necked reactor equipped with a mechanical stirrer and a condenser. Et_3N (9.0 mL, 65 mmol, 10 equiv) and 2,4,6-trimercapto-[1,3,5]-triazine (TMT) (5.76 g, 32.5 mmol, 5 equiv) were added to the brown solution. The reaction mixture was vigorously stirred and heated at 50 °C for 48 h. The functionalized silica resin was isolated by filtration, washed with DMAc (2 × 50 mL), 2 M HCl (2 × 50 mL), H_2O (2 × 50 mL), EtOH (2 × 50 mL), and dried under vacuum at 40 °C for 12 h.

General Procedure for the Preparation of Resins S1f, S1g$_{1-4}$, and S1l. Chloride silica gel (5.0 g, 6.50 mmol Cl, 1 equiv) and anhydrous THF (50 mL) were introduced in a 100 mL three-necked reactor equipped with a mechanical stirrer and a condenser. The desired mono- or polyamine (10 equiv) was slowly added to the solution. The reaction mixture was vigorously stirred and heated at 40 °C for 48 h. The functionalized silica resin was isolated by filtration, washed with THF (2 × 50 mL), EtOH (3 × 50 mL), and dried under vacuum at 40 °C for 12 h.

General Procedure for the Activation of Silica Gel (Table 3). Nitric acid solution (1 N, 40 mL) was slowly added to a 100 mL three-necked reactor containing silica gel (10.0 g) and equipped with a mechanical stirrer, a reflux condenser and a thermometer. The mixture was degassed, stirred, and heated at reflux for 6 h. The activated silica gel was isolated by filtration, washed with H_2O (3 × 50 mL), MeOH (3 × 50 mL), and dried under vacuum at 40 °C for 48 h. The oven-dried gel was then placed in a 200 mL sintered glass funnel. Moisturized air generated from a saturated solution of sodium bromide was passed through the gel for 12 h.

General Procedure for the Silanation Reaction (Table 3). Dried-activated silica gel (10.0 g) was introduced in a 100 mL three-necked reactor equipped with a mechanical stirrer and a reflux condenser. A solution of (3-bromopropyl)trimethoxysilane (36.5 mL, 150 mmol) in *n*-heptane (40 mL) was slowly added, and the reaction mixture was stirred at r.t. for 48 h. The functionalized silica resin was isolated by filtration, washed with heptane (3 × 50 mL), MeOH (3 × 50 mL), H_2O (3 × 50 mL), MeOH (3 × 50 mL), and dried under vacuum at 100 °C for 2 h.

Procedure for the Preparation of Resin S3g$_2$. 3-Bromopropyl-functionalized silica resin (6.0 g, 14.5 mmol Br, 1 equiv) and *N*-methylpyrrolidone (25 mL) were introduced in a 100 mL three-necked reactor equipped with a mechanical stirrer and a condenser. Triethylenetetramine (21.6 mL, 145.0 mmol, 10 equiv) was slowly added, and the reaction mixture was vigorously stirred and heated at 80 °C for 20 h. The functionalized silica resin was isolated by filtration, washed with H_2O (3 × 20 mL), 1 M aqueous H_2SO_4 solution (20 mL), H_2O (3 × 20 mL), 1 M aqueous ammonium hydroxide solution (20

Table 9. **Pd content of T3 after treatment of 4 g of 10% solution in cyclohexane, dichloromethane, or ethanol with 300 mg resin at room temperature for 20 h (initial content 59 ppm Pd)**

			Pd level [ppm] of **T3** after treatment in			R_E		
entry	resin #	loading [mmol/g]	cC_6H_{12}	CH_2Cl_2	EtOH	cC_6H_{12}	CH_2Cl_2	EtOH
1	**S1g$_2$**	0.90	**<2**	3	6	1300	1300	1400
2	**S3g$_2$**	0.89	**2**	24	14	1300	2100	1600
3	**S4e**	0.67	**<2**	**<2**	**<2**	900	900	900
4	**S4g$_2$**	0.71	**2**	18	10	1000	1400	1200
5	**O3g$_1$**	0.52	**2**	8	3	700	800	800
6	**GT73**	1.20	**<2**	16	**<2**	1700	2300	1700
7	**silica**	1.00	6	50	12	–	–	–

Table 10. **Pd content of T3 after treatment of 4 g of 10% solution in cyclohexane with 10−100 mg resin at room temperature for 20 h (initial content 59 ppm Pd)**

			Pd level [ppm] of **T3** after treatment in cC_6H_{12} with				
entry	resin #	loading [mmol/g]	10 mg	20 mg	50 mg	100 mg	R_E
1	**S1g$_2$**	0.90	**1**	**<1**	**<1**	**<1**	40
2	**S3g$_2$**	0.89	14	5	**2**	**1**	200
3	**S4e**	0.67	**<1**	**<1**	**<1**	**<1**	<30
4	**S4g$_2$**	0.71	7	**2**	**1**	**<1**	70
5	**GT73**	1.20	27	6	**2**	**<1**	290
6	**silica**	1.00	41	23	14	10	–

Table 11. **Pd content of T4 after treatment of 4 g of 10% solution in isopropanol with 100 or 300 mg resin at room temperature for 20 h (initial content 3350 ppm Pd)**

			Pd level [ppm] of **T4** after treatment with		
entry	resin #	loading [mmol/g]	100 mg	300 mg	R_E
1	**S1g$_2$**	0.90	603	50	22
2	**S3g$_2$**	0.89	950	8	21
3	**S4e**	0.67	904	5	16
4	**S4g$_2$**	0.71	790	6	17
5	**P2g$_1$**	2.30	930	750	71
6	**O3g$_1$**	0.52	530	99	13
7	**GT73**	1.20	2940	1980	70

Table 12. **Pd content of T5 and T6 before and after treatment of 4 g of 2.5% solution in xylene with 300 mg resin at room temperature for 20 h**

				Pd level [ppm] after treatment with	
target	resin #	loading [mmol/g]	Pd content [ppm]	300 mg	R_E
T5	**S4e**	0.67	9300	5000	50
T6	**S1g$_2$**	0.90	1800	320	190
	S3g$_2$	0.89		<40	<160
	S4e	0.67		<40	<120
	S4g$_1$	0.71		600	190

mL), H_2O (3 × 20 mL), MeOH (3 × 20 mL), and dried under vacuum at 40 °C for 12 h.

Procedure for the Preparation of Resin S3m. 3-Bromopropyl-functionalized silica resin (6.0 g, 14.5 mmol Br, 1 equiv) and methanol (90 mL) were introduced in a 200 mL three-necked reactor equipped with a mechanical stirrer and a condenser. 1,4,8,11-Tetraazacyclotetradecane (14.52 g, 72.5 mmol, 5 equiv) was slowly added, and the reaction mixture was vigorously stirred and heated at 40 °C for 20 h. The functionalized silica resin was isolated by filtration, washed with H_2O (3 × 20 mL), 1 M aqueous H_2SO_4 solution (20 mL), H_2O (3 × 20 mL), 1 M aqueous ammonium hydroxide solution (20 mL), H_2O (3 × 20 mL), MeOH (3 × 20 mL), and dried under vacuum at 40 °C for 12 h.

General Procedure for the Preparation of Resins S4b, S4d, and S4e (Table 4). (3-Glycidoxypropyl)trimethoxysilane (4.73 g, 20.0 mmol, 1 equiv) and anhydrous toluene (30 mL) were introduced in a 100 mL three-necked reactor equipped with a mechanical stirrer and a condenser. A solution of the desired mono- or polythiol (1 equiv) in toluene (25 mL) and a sodium methylate solution in MeOH (5.4 M, 3.7 mL, 20.0 mmol, 1 equiv) were slowly added to the colorless solution under an atmosphere of N_2. The yellow mixture was vigorously stirred and heated at 75 °C for 24 h. Silica gel (10.0 g) was added to the yellow intermediate, and the mixture was heated at 75 °C for 24 h. The functionalized silica resin was isolated by filtration, washed with toluene (2 × 50 mL), EtOH (2 × 50 mL), and dried under vacuum at 40 °C for 12 h.

General Procedure for the Preparation of Resins S4g$_1$ and S4g$_2$. (3-Glycidoxypropyl)trimethoxysilane (4.73 g, 20.0 mmol, 1 equiv) and anhydrous toluene (30 mL) were introduced in a 100 mL three-necked reactor equipped with a mechanical stirrer and a condenser. A solution of the desired polyamine (20.0 mmol, 1 equiv) in MeOH (20 mL) was slowly added to the colorless solution under an atmosphere of N_2. The yellow mixture was vigorously stirred and heated at 75 °C for 24 h. Silica gel (10.0 g) was added to the yellow intermediate, and the mixture was heated at 75 °C for 24 h. The functionalized silica resin was isolated by filtration, washed with toluene (2 × 50 mL), EtOH (2 × 50 mL), and dried under vacuum at 40 °C for 12 h.

Procedure for the Preparation of Resin P2e (Table 5). Merrifield resin (7.0 g, 1.0 mmol/g, 1 equiv) and MeOH (35 mL) were introduced in a 100 mL three-necked reactor equipped with a mechanical stirrer and a condenser. TMT (2.50 g, 14.0 mmol, 2 equiv), potassium iodide (1.20 g, 7.0 mmol, 1 equiv), and Et_3N (35 mL, 42.0 mmol, 6 equiv) were successively added to the solution. The reaction mixture was vigorously stirred and heated at reflux for 24 h. The polystyrene-bound TMT resin was isolated by filtration, washed with 2 m aqueous HCl solution (50 mL), DMSO (2 × 50 mL), 2 M aqueous HCl solution (50 mL), THF (100 mL), and dried under vacuum at 100 °C for 12 h.

Procedure for the Preparation of Resin P2n. 1,4,7,10-Tetraazacyclododecan-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (DOTA) (2.51 g, 6.2 mmol, 1 equiv), 1*H*-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) (3.22 g, 6.2 mmol, 1 equiv), *N*-methylmorpholine (4.1 mL, 37.2 mmol, 6 equiv), and anhydrous DMF (30 mL) were introduced in a 200 mL three-necked reactor equipped with a mechanical stirrer and a condenser. The white mixture was vigorously stirred at r.t.

Table 13. **Ni content of the aqueous phase (work-up of T1) before and after treatment with resin at room temperature for 20 h**

aqueous solution		resin				
Ni [ppm]	amount [mL]	no.	[g]	g resin/g aq soln [%]	Ni level after treatment [ppm]	Ni removed [%]
240	10	IRC748	8	80	<1	>99
240	10	IRC748	0.8	8	<1	>99
12	100	IRC748	0.05	0.05	10	17
12	100	IRC748	0.5	0.5	<1	>92
7	10	IRC748	0.03	0.3	<1	>85
7	10	IRC748	0.01	0.1	4	43
270	10	IRC748	0.1	1	<43	>85
121	13	**5**	0.808	6.5	<10	>92
121	12	**5**	0.11	0.9	<10	>92
127	101	**5**	0.13	0.13	18	86
127	200	**5**	0.087	0.04	83	35

for 30 min. Amino-methyl-polystyrene (PS-CH_2-NH_2) (5.60 g, 1.1 mmol/g, 1 equiv) was added to the solution, and the reaction mixture was stirred for 8 h at r.t. The yellow reaction mixture was quenched by the careful addition of ice (10.0 g). The polystyrene-bound DOTA was isolated by filtration, washed with H_2O (3 × 50 mL), DMF (3 × 50 mL), TBME (3 × 50 mL), and dried under vacuum at 40 °C for 12 h.

Procedure for the Preparation of Resin O3g$_1$. (Scheme 1) Versabeads O 400-Br resin (3.80 g, 5.32 mmol Br, 1 equiv) and *n*-BuOH (10 mL) were introduced in a 50 mL three-necked reactor equipped with a mechanical stirrer and a condenser. Diethylenetriamine (11.4 mL, 106.4 mmol, 20 equiv) was slowly added to the solution. The brown reaction mixture was vigorously stirred and heated at 120 °C for 48 h. The functionalized polyether resin was isolated by filtration, washed with *n*-BuOH (3 × 30 mL), EtOH (3 × 30 mL), and dried under vacuum at 40 °C for 12 h.

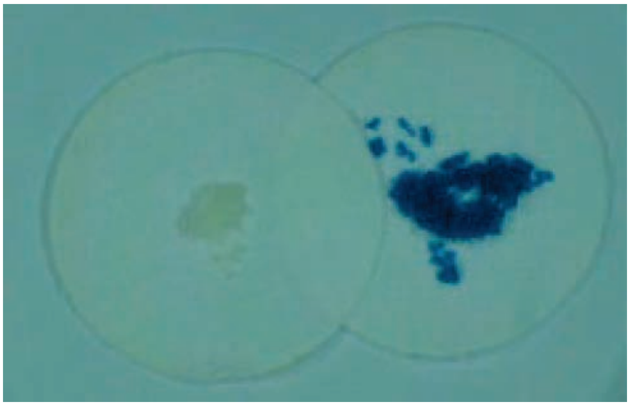
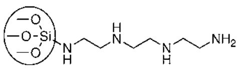
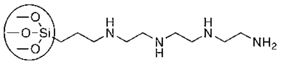
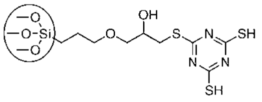
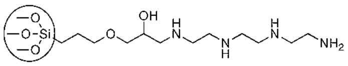


Figure 2. **Picture of resin 5 before and after chelating Ni^{2+} ions from aqueous solutions.**

Table 14. **Most effective scavengers in our study**

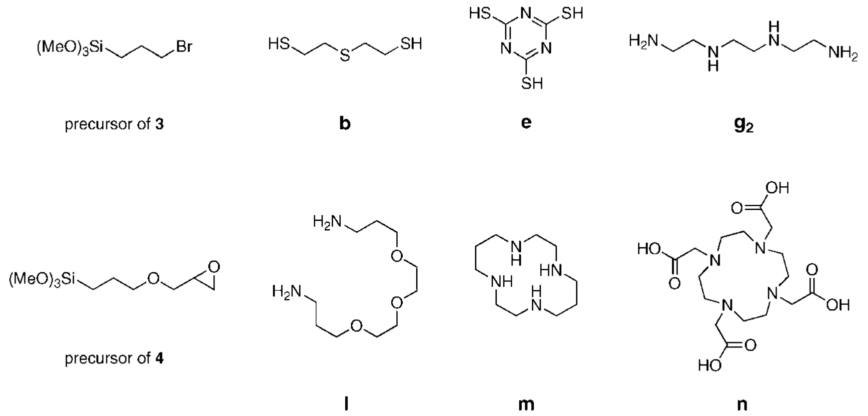
Resin #	Structure	Loading [mmol/g]
S1g$_2$		0.90
S3g$_2$		0.89
S4e		0.67
S4g$_2$		0.71
Amberlite® GT73	Thiol-functionalized styrene-divinylstyrene copolymer	≥1.20

4-Naphthalen-1-yl-isoquinoline (T4). To a solution of 4-bromoisoquinoline (19.00 g, 91.3 mmol, 1 equiv) in anhydrous DME (150 mL) in a 500 mL three-necked round-bottom flask equipped with a condenser were successively added naphthalene-1-boronic acid (17.28 g, 100.5 mmol, 1.1 equiv) and an aqueous sodium carbonate solution (2 M, 100 mL, 182.6 mmol, 2 equiv). The reaction mixture was magnetically stirred and heated at 80 °C for 10 min under an atmosphere of N_2. Tetrakis(triphenylphosphine)palladium (3.16 g, 2.74 mmol, 3 mol %) was added to the orange solution. The resulting brown reaction mixture was vigorously stirred and heated at 80 °C for 20 h. The black solution was allowed to cool to r.t., and then toluene (100 mL) and H_2O (100 mL) were added. The suspension was filtered through Celite. The organic layer was washed with an aqueous saturated NaCl solution (3 × 100 mL), H_2O (2 × 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Recrystallization from *i*-PrOH gave 4-naphthalen-1-yl-isoquinoline **T4** as brown powder (21.45 g, 84 mmol, 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.22 (d, $J = 8.5$ Hz, 1H, H$-$C$_{9'}$), 7.24 (d, $J = 8.5$ Hz, 1H, H$-$C$_6$), 7.36 (t, $J = 7.0$ Hz, $J = 8.5$ Hz, 1H, H$-$C$_{8'}$), 7.54 (t, $J = 7.0$ Hz, $J = 8.3$ Hz, 1H, H$-$C$_{7'}$), 7.56 (d, $J = 7.0$ Hz, 1H, H$-$C$_{2'}$), 7.63 (t, $J = 7.0$ Hz, $J = 8.5$ Hz, 1H, H$-$C$_7$), 7.68 (t, $J = 7.0$ Hz, $J = 8.0$ Hz, 1H, H$-$C$_{3'}$), 7.71 (t, $J = 7.0$ Hz, $J = 8.3$ Hz, 1H, H$-$C$_8$), 8.06 (d, $J = 8.3$ Hz, 1H, H$-$C$_{6'}$), 8.09 (d, $J = 8.0$ Hz, 1H, H$-$C$_{4'}$), 8.26 (d, $J = 8.3$ Hz, 1H, H$-$C$_9$), 8.49 (s, 1H, H$-$C$_3$), 9.46 (s, 1H, H$-$C$_1$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 124.91 (C$_6$), 125.81 (C$_{9'}$), 126.07 (C$_{3'}$), 126.58 (C$_{7'}$), 127.02 (C$_{8'}$), 128.02 (C$_8$), 128.26 (C$_{10}$), 128.49 (C$_9$), 128.69 (C$_{2'}$), 128.86 (C$_{6'}$), 129.03 (C$_{4'}$), 131.39 (C$_4$), 131.43 (C$_7$), 132.56 (C$_{10'}$), 133.62 (C$_{5'}$), 134.42 (C$_{1'}$), 135.01 (C$_5$), 143.60 (C$_3$), 152.90 (C$_1$). Anal. Calc. for $C_{19}H_{13}N$ (255.32): C 89.38, H 5.13, N 5.49; found: C 88.09, H 5.34, N 5.17. EI-MS calc. for $C_{19}H_{13}N$: [M]$^+$ 255; found: 255 (100%, [M]$^+$), 254 (96%, [M $-$ H]$^+$), 127 (15%, [M $-$ $C_{10}H_7$ + H]$^+$).

4-Naphthalen-1-yl-isoquinolinium Naphthalene-2-sulfonic Acid Salt (T4*NSA). 4-Naphthalen-1-yl-isoquinoline **T4** (1.00 g, 7.83 mmol, 1 equiv) and naphthalene-2-sulfonic dihydrate (1.91 g, 7.83 mmol, 1 equiv) were dissolved in toluene (10 mL)

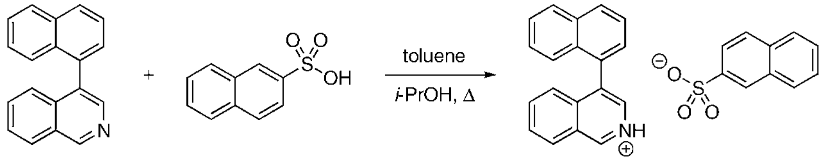
Table 15. Lab-scale prices of selected reagents and precursors of resin-based scavengers[a]

Reagent	# (see table 1)	mL or g	CHF	CHF/kg or L
Triethylenetetramine technical grade	**g2**	1000	79.5	80
O,O'-Bis-(3-aminopropyl)diethyleneglycol	**l**	500	141.5	283
Glycidyloxytrimethoxysilane	precursor of **4**	250	246	984
2,2'-Thiodiethanethiol	**b**	50	324	6'480
Triethylenetetramine purum	**g2**	50	404	8'080
2,4,6-trimercapto-[1,3,5]-triazine	**e**	25	262	10'480
(3-Bromopropyl)trimethoxysilane	precursor of **3**	25	779	31'160
1,4,8,11-Tetraaza-cyclotetradecane	**m**	5	265	53'000
1,4,7,10-Tetraazacyclododecan-tetraacetic acid	**n**	0.25	318	1'272'000



[a] CHF = Swiss francs.

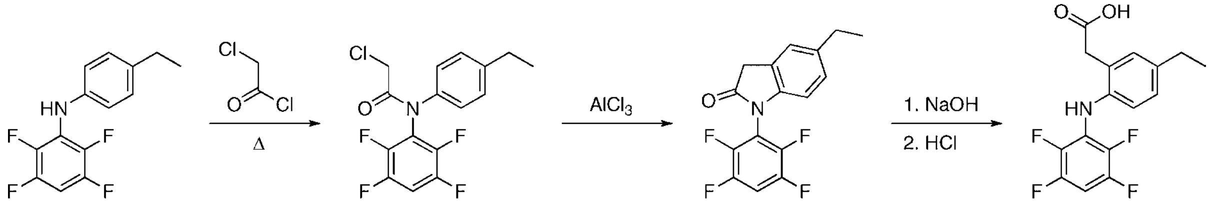
Scheme 2. Reduction of Pd content by salt formation



T4
Pd: 3350 ppm

T4*NSA
Pd: 13 ppm

Scheme 3. Acylation of diarylamine T6 (down to the final compound) as a means to reduce the Pd content



T6
Pd: 1280 ppm

T6-CA
Pd: < 1 ppm
(after crystallization)

Robenacoxib

in a 50 mL round-bottom flask equipped with a condenser. The reaction mixture was heated at 40 °C for 10 min. In order to facilitate the formation of the salt, *i*-PrOH (2 × 2 mL) was added, and the homogeneous beige mixture was heated at 40 °C for 20 min. The solution was allowed to cool to r.t. The precipitate was filtered, washed with ice-cold toluene (5 × 20 mL), and dried under reduced pressure at 40 °C overnight. 4-Naphthalen-1-yl-isoquinolinium naphthalene-2-sulfonic acid salt **T4*NSA** was isolated as white powder (3.01 g, 6.50 mmol, 83%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.18 (d, J = 8.3 Hz, 1H, H$-$C$_{9'}$), 7.29 (t, J = 7.0 Hz, J = 8.3 Hz, 1H, H$-$C$_{8'}$), 7.30 (d, J = 8.3 Hz, 1H, H$-$C$_6$), 7.38 (t, J = 7.0 Hz, J = 8.1 Hz, 1H, H$-$C$_{7''}$), 7.39 (t, J = 7.0 Hz, J = 8.1 Hz, 1H, H$-$C$_{6''}$), 7.47 (t, J = 7.0 Hz, J = 8.1 Hz, 1H, H- C$_{7'}$), 7.51 (d, J = 7.5 Hz, 1H, H$-$C$_{2'}$), 7.59 (d, J = 8.2 Hz, 1H, H$-$C$_{2''}$), 7.61 (t, J = 7.5 Hz, J = 7.7 Hz, 1H, H$-$C$_{3'}$), 7.71 (d, J = 8.2 Hz, 1H, H$-$C$_{3''}$), 7.77 (d, J = 8.1 Hz, 1H, H$-$C$_{5''}$), 7.84 (d, J = 8.1 Hz, 1H, H$-$C$_{8''}$), 7.85 (t, J = 7.0 Hz, J = 8.3 Hz, 1H, H$-$C$_7$), 7.86 (t, $J = 7.0$ Hz, $J = 8.2$ Hz, 1H, H$-$C$_{8}$), 7.98 (d, $J = 8.1$ Hz, 1H, H$-$C$_{6'}$), 8.01 (s, 1H, H$-$C$_{10''}$), 8.05 (d, $J = 7.7$ Hz, 1H, H$-$C$_{4'}$), 8.48 (d, $J = 8.2$ Hz, $J = 0.3$ Hz, 1H, H$-$C$_{9}$), 8.63 (d, $J = 0.8$ Hz, 1H, H$-$C$_{3}$), 9.81 (t, $J = 0.3$ Hz, $J = 0.8$ Hz, 1H, H$-$C$_{1}$), 13.10 (br, s, 1H, NH^{+}). ^{13}C NMR (125 MHz, DMSO-d_6) δ 124.03 (C$_{2''}$), 124.13 (C$_{10''}$), 125.31 (C$_{9'}$), 125.35 (C$_{6}$), 125.69 (C$_{3'}$), 126.35 (C$_{7'''}$), 126.49 (C$_{6'}$), 126.59 (C$_{7'}$), 127.12 (C$_{8'}$), 127.33 (C$_{10}$), 127.38 (C$_{3''}$), 127.50 (C$_{5''}$), 128.50 (C$_{8''}$), 128.75 (C$_{2'}$), 129.77 (C$_{4'}$), 130.46 (C$_{8}$), 130.98 (C$_{9}$), 131.15 (C$_{1'}$), 131.74 (C$_{10'}$), 132.20 (C$_{9''}$), 132.78 (C$_{4''}$), 132.99 (C$_{3}$), 133.21 (C$_{5'}$), 135.50 (C$_{4}$), 136.46 (C$_{7}$), 137.64 (C$_{5}$), 145.60 (C$_{1''}$), 148.00 (C$_{1}$). Anal. Calcd for $C_{29}H_{21}NO_3S$ (463.55): C 75.14, H 4.57, N 3.02, S 6.92; found: C 73.07, H 4.58, N 3.02, S 7.01. IT-MS calcd for $C_{19}H_{14}N^{+}$: [M^{+}] 256; found: 256 (100%, [M]$^{+}$). IT-MS calcd for $C_{10}H_8O_3S$: [M $-$ H]$^{+}$ 207; found: 207 (100%, [M $-$ H]$^{+}$).

Screening Experiments for the Removal of Heavy Metals Using Functionalized Resins. The appropriate quantity (in mg) of a functionalized resin and 4 mL of a metal-contaminated solution were introduced in a 5 mL Supelco vial. The mixture was agitated at room temperature for 20 h on a shaker. The solution was filtered through a 1.20 μm single-use Supelco filter, transferred in a 5 mL Supelco vial that was closed with a semipermeable septum, and finally concentrated under reduced pressure at r.t. Heavy metal contents were determined by elemental analysis.

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Supporting Information Available

Copies of ^{1}H and ^{13}C NMR spectra of new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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