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A Phosphorous-Rich Polymer as a Homogeneous Catalyst Scavenger

T.J. Cuthbert, E. Evoy, J. P. J. Bow, R. Guterman, J.M. Stubbs, E.R. Gilles, P.J. Ragogna* and J.M. Blacquiere*

A soft polymer network prepared through a phosphane-ene reaction successfully sequestered Rh and Ru from hydrogenation and ring closing metathesis reactions, respectively. Scavenging effectively quenches catalytic activity and ultimately removes >98% of the metal.

Homogeneous catalysis enables many difficult bond transformations and significantly reduces the need for stoichiometric reagents and waste.[1] These are highly desirable properties for the industrial synthesis of high-value compounds (i.e. pharmaceuticals),[2] yet homogeneous catalysis is used in a minority of steps in the pharmaceutical industry.[3, 4] A challenge to increasing catalysis uptake is the required removal of spent catalyst (i.e. the metal) from the organic product.[5, 6] While the optimal catalytic scenario involves a catalyst with very high TON, so that metal removal is precluded,[7, 8] this is not always attainable. The residual metal is problematic in downstream reactions whereby it can promote undesired reactivity.[9, 10] Additionally, strict toxicity guidelines for pharmaceutical products set very low limits of <10 ppm for Pt group metal contaminants.[11] While the heavier metals are most often cited for their toxicity, the abundant first-row metals may also have cause for concern.[12] Traditional metal removal methods are a challenge on large scale, which has led to the development and commercialization of scavenger materials.[13, 14] Many of the available scavengers are efficient, appropriate for a broad range of metal complexes and are easy to use. The desire for scavenger materials with lower required loadings, short incubation times, improved reusability and lower cost continues to motivate research in this area.

Recently, phosphorous-rich polymer networks were prepared through a step-growth polymerization, involving phosphane-ene reactions of primary bis-phosphines and terminal diolefins.[15, 16] The polymers are soft or rigid in nature depending on the flexibility of the monomers. The soft polymer network (**SPN**) exhibits appreciable swelling in organic solvents and are capable of coordinating simple metal salts.[16] Therefore the polymer networks could act as a ligand for metals of homogeneous catalysts and effectively scavenge them from catalytic reaction mixtures. The Lewis basic sites of the polymer networks are part of the polymer structure and are present in high concentrations. This is distinct from most scavenger materials that typically contain a Lewis basic functional group that is appended to a resin bead (i.e. polystyrene).[14] Herein, we demonstrate that the phosphorous-rich **SPN** is an excellent catalyst scavenger. This represents a new, modular and easily prepared architecture for metal scavenging materials that are competitive with current systems.

The soft polymer network **SPN** was prepared following reported procedures.[15] All primary and secondary phosphine sites were converted to tertiary phosphines by reaction of the network with excess 1-hexene. To establish the affinity of metals to the polymer network, **SPN** was stirred at room temperature for 24 h with excess Wilkinson's catalyst (**WI**; Scheme 1). The solution changes colour from dark red to orange and isolation of the solid reveals that the polymer has changed from white to orange. Incorporation of **WI** into the polymer product (**Rh-SPN**) was confirmed by ICP-MS analysis that gave a metal loading of 0.389 Rh/S (mol/mol). This loading corresponds to nearly one rhodium centre (0.778) per unit of diphosphine in the network.
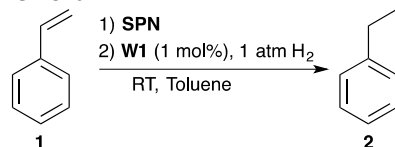
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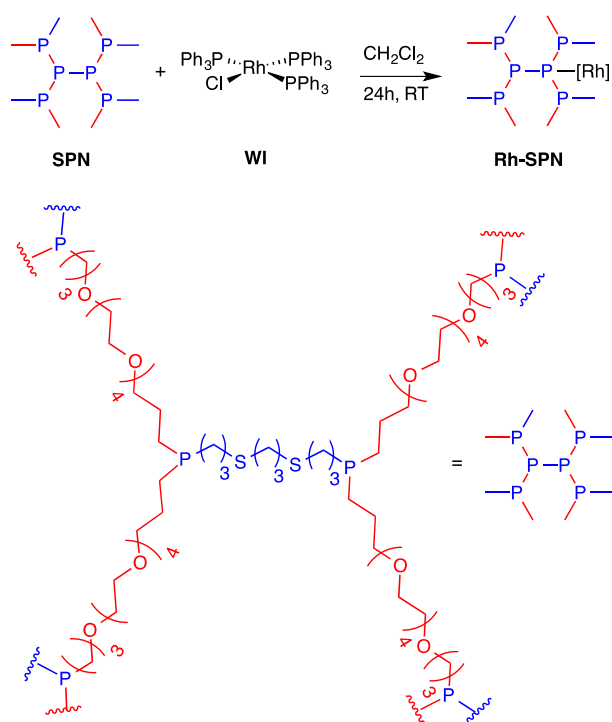
Scheme 1. Loading the Soft-Polymer Network (**SPN**) with Wilkinson's catalyst (**WI**) to give **Rh-SPN.**

Figure 1. Consumption of styrene (**1**) by hydrogenation with **WI** without additive (×) and with **SPN** (16 g/mmol Rh) added at the outset of reaction (■). Conversion values were determined by calibrated GC-FID analysis of reaction aliquots with integration relative to an internal standard.

The efficacy of **SPN** toward metal removal from a catalytic reaction was evaluated in the proof-of-principle reaction of the hydrogenation of styrene with 1 mol% **WI** (4747 ppm Rh; Scheme 2). In the absence of **SPN** hydrogenation is complete within 1.5 h under 1 atm of H_2 at room temperature (Figure 1). Pre-treatment of the hydrogenation reaction with **SPN** (16 mg/μmol Rh) at the outset of reaction, gives only a 20% conversion of styrene over 1.5 h (Figure 1). Indeed, catalytic turnover is arrested completely within 10 minutes as the catalyst was rapidly and efficiently sequestered from solution. This effective suppression of catalyst activity is an additional application for **SPN**, which prevents undesired side reactions mediated by altered catalyst structures formed *in situ.* This is in contrast to other metal-loaded phosphine polymers that are active as solid supported catalysts.[17-19] Incubation of **SPN** with the reaction for 24 h was followed by a facile filtration step. ICP-MS analysis of the soluble organic residues revealed that only 11 ppm of Rh remained, which equals 99.8% rhodium removal.

Scheme 2. Hydrogenation of styrene (**1**) with Wilkinson's catalyst (**W1**) and with scavenger **SPN** added at the outset of reaction.
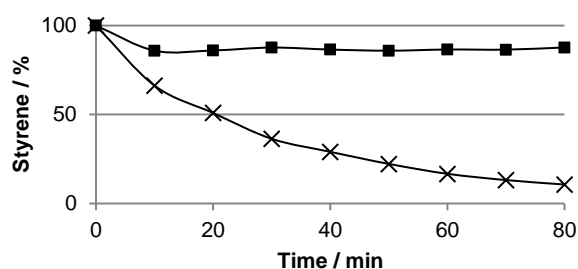
A broadly applicable metal scavenger material should efficiently sequester a range of homogeneous catalysts that have diverse structures. The Grubbs catalyst (**GI**) was selected as a second proof-of-principle system due to the synthetic utility of olefin metathesis[20-22] and since this is a common test system for catalyst sequestration strategies.[23] Ring closing metathesis (RCM) of the benchmark substrate diethyldiallylmalonate (**3**) was conducted under standard[24] conditions with 1 mol% **GI** in CH_2Cl_2 at room temperature (Scheme 3). After 1 h maximum conversion to RCM product **4** was achieved. Reaction samples were stirred with **SPN** (10 mg **SPN**/μmol **GI**) for a range of incubation times (0.3, 12, 24 and 48 h) prior to filtration (Table 1, Entries 1-5). Within 20 min 30% of the metal is removed and by 12 h removal reaches ca. 94%. Prolonged incubation (72 h) gave a maximum removal of nearly 99%. A similar trend was found with a lower **SPN** loading of 5 mg **SPN**/μmol **GI** (Table 1, Entries 6-8), albeit with a slightly lower maximum metal removal (ca. 98% after 72 h). The **SPN** scavenger outcompetes solid-supported ligands, such as phosphines and isocyanates (Table 1, Entries 9 and 10).[25, 26] While the scavenging efficiency of **SPN** is lower than the reported protocol involving a silica gel and activated charcoal incubation, followed by column chromatography (Entry 11),[27] the **SPN** protocol is significantly more user friendly. Oxidation of **GI** with a very large excess of H_2O_2 followed by extraction is convenient and removes >99% of Ru (Entry 12).[28] However, the incompatibility of the oxidant with many functional groups, is a severe practical limitation. Overall, **SPN** is easy to use and it removes a maximum of 98.8% Ru, which is similar to known scavengers of **GI**.
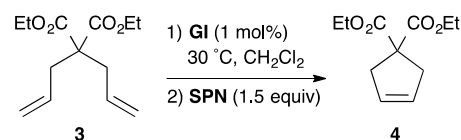
Scheme 3. RCM of **3** with **GI** followed by sequestration of the catalyst with **SPN**.

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Table 1. Sequestration of **GI** from RCM of **3**.[a]

Entry	Removal method (equiv scavenger)	GI mol% (ppm)	Incubation time (h)[b]	Residual Ru (ppm)	Ru Removed (%)[c]	Ref
1	**SPN**/filtration (10 mg/μmol Ru)	1 (4755)	0.3	3319	30.2	[d]
2	**SPN**/filtration (10 mg/μmol Ru)	1 (4755)	12	307	93.5	[d]
3	**SPN**/filtration (10 mg/μmol Ru)	1 (4755)	24	140	97.1	[d]
4	**SPN**/filtration (10 mg/μmol Ru)	1 (4755)	48	78	98.4	[d]
5	**SPN**/filtration (10 mg/μmol Ru)	1 (4755)	72	59	98.8	[d]
6	**SPN**/filtration (5 mg/μmol Ru)	1 (4755)	24	253	94.7	[d]
7	**SPN**/filtration (5 mg/μmol Ru)	1 (4755)	48	139	97.1	[d]
8	**SPN**/filtration (5 mg/μmol Ru)	1 (4755)	72	111	97.7	[d]
9[e]	Resin-bound phosphine (5 equiv) /charcoal	5 (23775)	17[f]	1120	95.3	[25]
10	SiO$_2$-bound isocyanide (60 equiv)	2.5 (11888)	0.5	468	95.6	[26]
11[e]	SiO$_2$/activated carbon (100 equiv wt rel to GI)/SiO$_2$	10 (47550)	12[g]	60	99.9	[27]
12	H$_2$O$_2$/extraction (5000 equiv)	5 (23775)	0.3	15.10	99.45	[28]

[a] Conditions: **3** (106 mM) in CH$_2$Cl$_2$ at 30 ˚C. [b] Time scavenger is exposed to the reaction solution prior to filtration/extraction. [c] %Ru removed = [(loading Ru − residual Ru)/(loading Ru)]*100. [d] This work. [e] RCM conducted at RT. [f] Time resin exposed to reaction solution. [g] Time activated carbon is exposed to the reaction solution.

The prevalence of Pd catalysis in the pharmaceutical industry[4, 29] prompted evaluation of metal scavenging from a Suzuki coupling reaction of bromobenzene and 4-methylboronic acid catalyzed by Pd(OAc)$_2$/PCy$_3$ (see S.I.). Incubation of the reaction solution with **SPN** followed by filtration resulted in the removal of >94% Pd. As a caveat, simple filtration without **SPN** incubation leads to removal of 67% Pd. This may be a consequence of the formation of Pd black and larger nanoparticles that are acknowledged species in Pd catalysis.[30] Element mapping of the incubated **SPN**, using SEM/EDX, confirms Pd incorporation in low levels throughout the polymer network. Very little evidence for nanoparticulate Pd was observed, which suggests the network predominantly scavenges molecular Pd species.

A sample of metal-loaded polymer (**Ru-SPN**) was prepared by stirring **GI** with the polymer network. Metal loading was confirmed by ICP-MS analysis and solid-state ^{31}P{^{1}H} NMR spectroscopy. The latter revealed broad signals in the range of

0-40 ppm that are consistent with metal-bound tertiary phosphine sites. The nature of the metal species may be molecular, which would be consistent with the SEM analysis of the Pd-loaded polymer, however we cannot conclusively exclude sequestration of the metal as clusters or small nanoparticles. A signal for metal-free phosphine is observed (− 32 ppm) and this may reflect the incomplete loading of Ru due to the limited accessibility of **GI** to the interior of the network. The thioether moieties are likely also involved in metal sequestration and this would go unobserved by ^{31}P NMR spectroscopy. To attempt scavenger regeneration the metal loaded polymer (**Ru-SPN**) was stirred in neat PEt$_3$ or TMEDA (*N,N,N',N'*-tetramethylethane-1,2-diamine) for 24 h (Table 2). At room temperature both the phosphine and amine reagents displaced ruthenium, albeit in low amounts (ca. 20 and 30%, respectively). Scavenger regeneration at elevated temperature is more effective with a maximum removal of 42.6% achieved in PEt$_3$ at 80 ˚C. Successful metal removal supports the hypothesis that metal sequestration involves reversible adduct formation between the metal and Lewis basic sites of the polymer network.

Table 2. Regeneration of metal free **SPN** from **Ru-SPN**.[a]

Entry	Regeneration method	Temp. (˚C)	Residual Ru (ppm)	Ru Removed (%)[b]
1[c]	Neat PEt$_3$	23	17020	20.4
2[c]	Neat TMEDA	23	14286	33.2
3[c]	Neat PEt$_3$	80	12274	42.6
4[d]	Neat TMEDA	80	2575.4	39.1

[a] Conditions: Ruthenium-loaded **SPN** (**Ru-SPN**) in neat reagent for 24 h. [b] %Ru removed = [(initial Ru) − (residual Ru)/(initial Ru)]*100. [c] Initial Ru on **Ru-SPN** = 21393 ppm. [d] Initial Ru on **Ru-SPN** = 4230.7 ppm.

The phosphorous-rich soft polymer network (**SPN**) effectively scavenges homogenous catalysts from reaction mixtures. Hydrogenation and ring closing metathesis were used as proof-of-principle reactions where 99.9 and 98.8% Rh (**WI**) and Ru (**GI**) were sequestered, respectively. Promising Pd removal was also found, but further studies are warranted to evaluate the scope of applicability in Pd catalysis given the complexity of speciation (i.e. molecular vs. nanoparticulate material) in these systems. Scavenger regeneration by removal of the loaded metal from the polymer network is possible. The facile methodology for polymer network preparation is sure to lead to improved formulations and next generation polymers with superior rate of scavenging, metal removal efficiency and regeneration protocols.

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