500 μm diameter beads as single reactors to screen organometallic catalysts: discovery of a new supported catalyst for the hydrosilylation of ketones

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A library of aminophosphine-phosphinite ligands was prepared in the form of 500 μm beads, each single cross-linked polystyrene bead supporting only one type of ligand. After reaction with a rhodium complex, the library was evaluated for the hydrosilylation of acetophenone. This study demonstrated that results obtained by the standard Schlenck technique are reproducible at the single 500 μm diameter bead level. Moreover, the screening of this "catalysts on beads" library led to discovery of a new supported and easily recoverable catalyst, derived from the amino alcohol $H_2NCH_2CH_2OCH_2CH_2OH$.

Anchoring catalysts on insoluble supports provides an efficient way to recover the catalyst after a reaction.[1] This approach is used extensively for the recovery of expensive ligands and noble metals since the catalyst-supported species can be easily separated from the products in solution by a simple filtration. While this operation has economic importance as it allows for recycling of valuable material, it also has an obvious attraction in the field of pharmaceutical research where traces of metal residues cannot be tolerated in drug applications. Following the pioneering work of Merrifield,[2] several supports have been developed for such use,[3] including a recent innovation that uses fluorous phases to recover catalysts.[4]

Resins containing reactive groups are also used for "chemistry on beads" techniques[5] such as the *split and pool* method,[6] which have become particularly useful in pharmaceutical research to generate, with a minimum of operations, large libraries of molecules. Other applications of functionalised beads were recently reported, such as in HPLC[7] and catalyst discovery.[8]

Recently, combinatorial concepts were applied to generate and to screen large collections of organometallic catalysts in solution phase.[9] The principle of combinatorial catalysis is to create a large number of organometallic complexes within a short period of time and to evaluate them with a specific screening test in order to extract the best catalysts for a given reaction. Then only these detected catalysts are re-synthesised and investigated in detail. We have begun to examine the utility of "chemistry on beads" strategy for the detection of new supported catalysts since it allows rapid creation of chemical diversity and also provides recyclable supported catalysts as described above. The key point was to prepare and to screen catalysts linked to single 500 μm diameter beads, which could be described as individual miniaturised reactors.

We report here our initial *proof of concept* investigation related to catalytic hydrosilylation of ketones. This reaction is of interest for the generation of secondary alcohols.[10] Innovation in this specific field of organometallic catalysis concerns both the modification of the metal centre[11] and of the ligand.[12] We have selected aminophosphine-phosphinite ligands for this study because they were reported to give efficient catalytic systems for hydrosilylation reactions when they were associated to rhodium precursors[13] and also because of their modular preparation from amino alcohols.

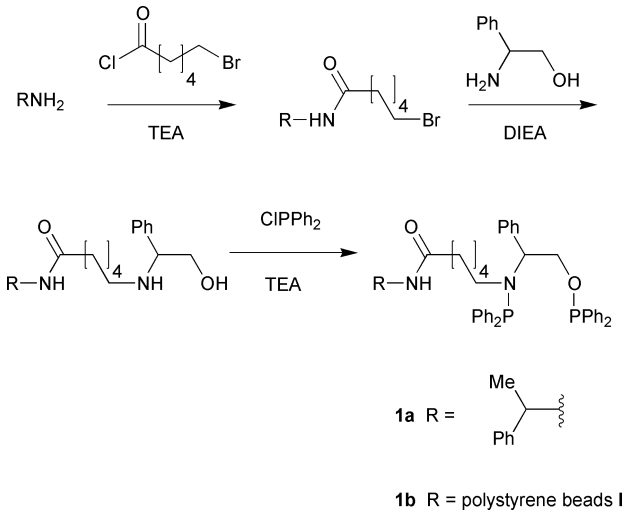
Results and discussion

This study was divided into four steps: (i) the study of a homogeneous model, (ii) the evaluation of the "single bead" catalytic activity of the corresponding supported catalyst, (iii) the preparation and screening of a 40-member library of catalysts for the hydrosilylation of acetophenone and (iv) the synthesis and recovery experiments of a new supported catalyst based on the $H_2NCH_2CH_2OCH_2CH_2OH$ amino alcohol.

(i) Study of a homogeneous model

Before the preparation of a catalyst library on beads, we investigated a homogeneous model (Scheme 1) in order to select the optimum experimental conditions for the synthesis of the aminophosphine–phosphinite complex **1a**.

The organic "arm" connected to the amino alcohol nitrogen atom in **1a** was selected to simulate the future linker between the heterogeneous support and the catalyst. Acylation of 1-phenylethylamine with 6-bromohexanoyl chloride in the presence of triethylamine, TEA (yield: 94%) was followed by nucleophilic displacement of the bromide with 2-phenylglycinol in the presence of *N*,*N*-diisopropylamine, DIEA (yield: 94%). Then a treatment with chlorodiphenylphosphine at 80 °C in toluene in the presence of TEA led to the complete consumption of PPh_2Cl and to the formation of the aminophosphine-phosphinite chelating ligand **1a**, whose ^{31}P NMR spectra was consistent with literature values (δ NP and OP vs. H_3PO_4: 63 and 114 ppm).[14] The synthetic sequence therefore validated the proposed solid-phase ligand synthesis described below.

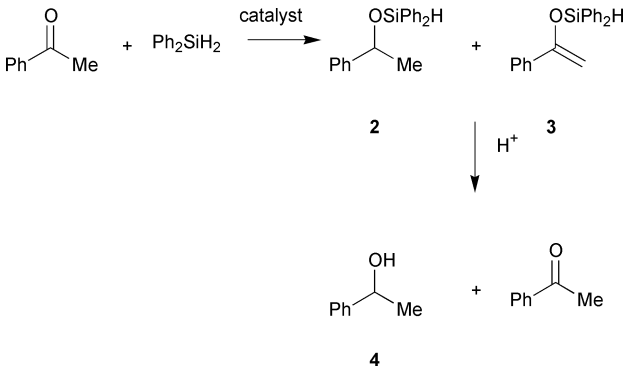


Scheme 1 Synthesis of homogeneous and supported models.

(ii) Evaluation of the "one bead" catalytic activity of the corresponding supported catalyst model

The same experimental conditions were applied to a heterogeneous system to generate the supported catalytic model **1b**. Commercially available polystyrene beads functionalised with primary amine groups were transformed using the synthetic sequence described above (Scheme 1). It should be noted that possible over-alkylation of the amino alcohol was highly unlikely because a large excess (10 equiv) of amino alcohol was reacted with the bromo functions supported on beads. The ^{31}P NMR spectrum of the beads **1b** (solvent swollen resin) indicated comparable results between the supported system **1b** (δ OP: 108 ppm; NP: 51 ppm) and the model **1a**. While the synthetic sequence was successful when employing chlorodiphenylphosphine, it was unsatisfactory with chlorodialkylphosphines PR_2Cl (R: methyl and cyclohexyl), which therefore led us discontinue further use of these two phosphines in order to assure the quality of the final library. The addition of the dimer $[Rh(cod)Cl]_2$ to the pale yellow beads **1b** generated orange beads **1b-Rh** after 2 h at room temperature. The ^{31}P NMR spectrum showed the absence of any free phosphorus ligand, indicating a quantitative reaction, but broad signals prevented us from determining the exact supported organometallic structure.

The catalytic activity of catalyst **1b-Rh** was examined in the context of the hydrosilylation of acetophenone (Scheme 2). Thirty beads of **1b-Rh** were introduced into an NMR tube containing 35 μl (0.3 mmol) of $PhCOCH_3$, 56 μl (0.3 mmol) of Ph_2SiH_2 and 0.5 ml of C_6D_6. The progress of the reaction at 50 °C was monitored by the relative integration of the methyl or methylene groups of compounds **2**, **3** and acetophenone



Scheme 2 Catalytic hydrosilylation of acetophenone.

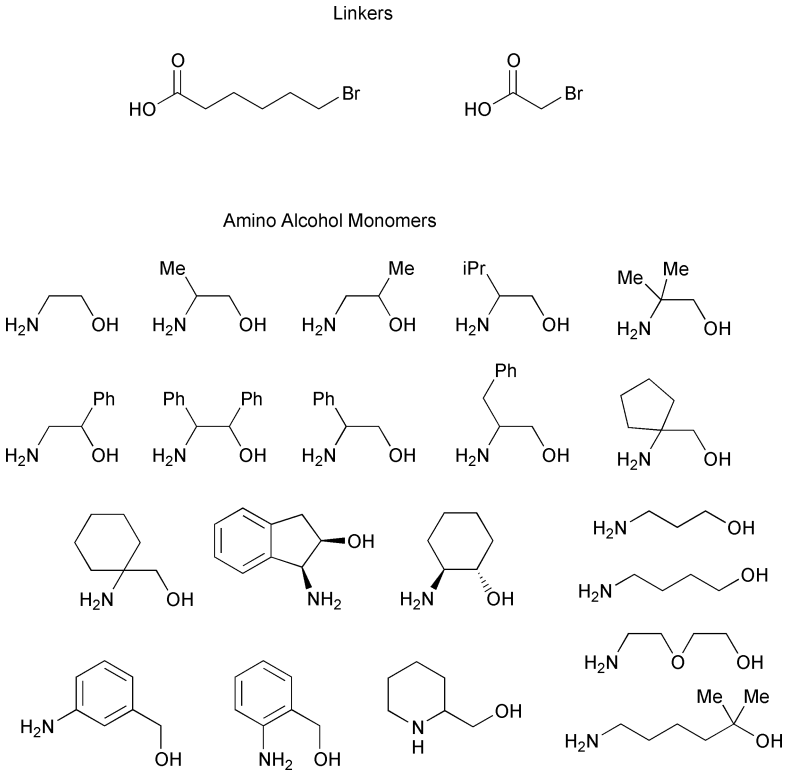
using ^1H NMR.[15] After 0.5 h at 50 °C the conversion was 55% and the ratio **2** : **3** was 74 : 26. After 1.5 h, the reaction was practically complete without modification of the ratio 2 : 3. No remaining starting acetophenone was detected after 2.5 h and the ratio 2 : 3 was unchanged. Continuous heating for 20 h did not significantly change the ratio of 2 : 3 (79 : 21), indicating that the presence of **3** came from a side reaction and not from a transformation of **2** into **3**. Treatment of the reaction mixture with acid generated the secondary alcohol **4** and, as expected, acetophenone from deprotection of enol **3**. Gas chromatography of the treated mixture showed the presence of 74% of the secondary alcohol **4** and 26% of acetophenone, which closely matched conclusions obtained from ^1H NMR analysis. From this first investigation we can conclude that the supported catalyst **1b-Rh** possesses similar catalytic properties as the previously reported homogeneous catalysts derived from an aminophosphine-phosphinite chelating ligand.[13] Moreover, the regeneration of acetophenone from the side-product **3** led us to use the formation of **4** as a measure of the efficiency of catalysts, and not the consumption of the starting material.

To determine the optimum solvent for reaction and to determine whether catalyst activity could be assessed from a single bead, stock solutions of substrates (0.5 M) were prepared in methylene chloride, toluene and THF. Twenty microliters of these solutions were dispatched in three vessels, each containing *one bead* of **1b-Rh** (0.9% catalyst). After 14 h at room temperature, acidic treatment followed by GC analysis indicated that the reaction was faster in CH_2Cl_2 (44%) than in toluene (28%) or THF (28%). The same difference was observed with a lower catalyst : substrate ratio (0.2% catalyst), although it was necessary to heat at 50 °C to maintain comparable catalyst activity (CH_2Cl_2: 42%, toluene: 33%, THF: 20%) for the same period of time (14 h). Thus, methylene dichloride solvent was selected for the following step.

(iii) Preparation and screening of a 40-member library of catalysts for the hydrosilylation of acetophenone

In order to quickly generate a diverse collection of supported catalysts, our approach to create a catalyst library was based on the split and pool strategy.[6] The library of potential catalysts was prepared on polystyrene macrobeads in a manner analogous to that described above for the model system and using the monomer sets depicted in Scheme 3.

With two different linkers and 20 amino alcohols, a total of 40 library members were prepared by split and pool synthesis, using photocleavable tags as described by Still and co-workers.[16] With this method, even if all beads are mixed together, the structure of the ligand supported on each bead could be obtained by the "reading" of the specific tags linked to each bead. After split and pool synthesis, the collected beads were treated together in one vessel with diphenylchlorophosphine and the rhodium dimer, similarly to the procedure described above. In order to promote the dissociation of the chloro group and to generate active cationic species,[17] MeOH was added and the beads were reacted for an additional hour. All the beads presented a more or less intense orange colour. For the parallel evaluation of several catalytic reactions, we have used a home-made 76-well plate connected to a vortex type stirrer in order to assure an efficient stirring. Seventy-six beads were selected randomly and introduced into individual vessels with the same amount (400 μl) of a stock solution of 0.5 M acetophenone and Ph_2SiH_2 in CH_2Cl_2 (0.05% catalyst). After 40 h at room temperature all reactions were quenched with 10% HCl (20 μl) in acetone (150 μl) and the aqueous phases were extracted with diethyl ether (500 μl). This long reaction time was selected in order to take into account the slower kinetics due to the diffusion control induced by the polymeric matrix and also to avoid the non-detection of catalysts needing a long activation period.



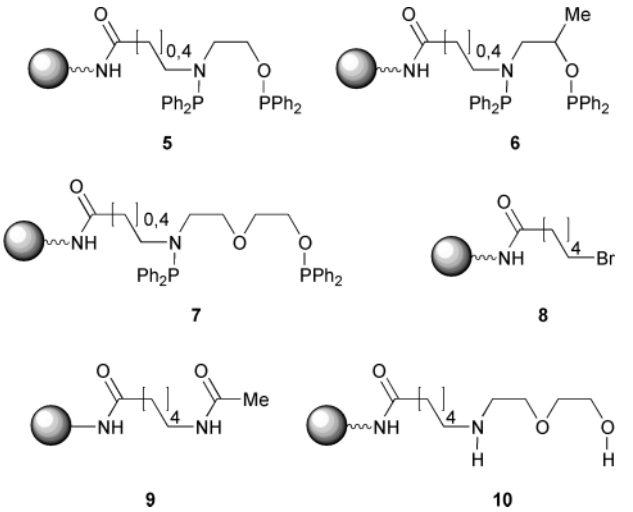
Scheme 3 Different linkers and amino alcohols involved in the library preparation.

All organic phases were then analysed by gas chromatography in order to measure the formation of the secondary alcohol **4**. All beads showed some catalytic activity (varying from 0 to 31%) as expected for this type of ligand associated with a rhodium moiety. This allowed to classify beads into three groups according to their relative activity: beads showing the lowest activity, moderate activity and the highest activity.

Upon decoding, it was found that beads showing the lowest relative activity (<10%) were derived from the secondary amino alcohol. This amino alcohol would provide a monocoordinating amino-phosphinite ligand instead of a bis-chelating aminophosphine-phosphinite ligand. The goal of this study was to develop a simple approach to extract the more interesting candidates from a large number of catalysts, thus beads showing moderate relative activity were not analysed. Only the beads that showed the relative highest activity (> 85%) were decoded. The results of the decoding indicated that the most efficient catalysts were derived from either the structurally simple ethanolamine **5** or 1-methylethanolamine **6** (Scheme 4).

Aminophosphine-phosphinite ligands with a two-carbon bridge between the nitrogen and the oxygen atoms have been previously described for the hydrosilylation reaction,[13] indicating that results observed on the Schlenk tube scale reaction are reproducible at the one bead scale. In addition to these ligands **5** and **6**, it was also found that the ligand **7**, derived from 2-(2-aminoethoxy)ethanol, generated an active catalyst. To our knowledge, this is the first example of a catalyst derived from an amino alcohol containing a long spacer between the nitrogen and the oxygen atoms. The central oxygen seems to play a key role because none of the amino alcohol ligands containing 3-, 4- or 5-carbon bridges were present in the beads showing the highest activity.

As the molecule loading of individual beads obtained by the split and pool strategy cannot be determined, we assumed that the metal loading was homogeneous over the whole library. The quantitative coordination reaction observed with the model **1b-Rh** and the fact that all the beads were treated in similar conditions militates for this assumption. It should be added that a ligand inducing a too low coordination reaction yield, due to any electronic or steric hindrance effects, could be undetected. Thus, this approach could be also useful to avoid catalysts showing a potential problematic synthesis.



Scheme 4 Efficient catalyst precursors: **5**, **6** and **7**. Supported species showing no catalytic activity: **8**, **9** and **10**.

(iv) Synthesis and recovery experiments of a new supported catalyst based on the $H_2NCH_2CH_2OCH_2CH_2OH$ amino alcohol

To confirm the results above, we have prepared the supported catalyst on beads, **7-Rh**, by using the same methodology as described in Scheme 1 but with the amino alcohol $H_2NCH_2CH_2OCH_2CH_2OH$. The ^{31}P NMR of the

corresponding free aminophosphine-phosphinite ligand gave two signals at 114 ppm (PO) and 63 ppm (PN), respectively. After reaction with the rhodium precursor the complete disappearance of these two peaks and the presence of a large signal at 120 ppm indicated a quantitative coordination of the metal. This is in accordance with previously reported homogeneous catalysts, which in ^{31}P NMR present two peaks at 121 ppm (PO) and 120 ppm (PN), respectively.[17] The broad signal could be explained by the presence of the solid support and also by the coupling between the two phosphorous centres (average coupling $J_{PP} = 40$ Hz) and the rhodium isotope ^{103}Rh (average coupling $J_{PRh} = 170$ Hz).[13,17]

Finally, we have checked the recycling of this new catalyst **7-Rh** for the hydrosilylation of acetophenone. Thirty beads of catalyst **7-Rh** (3×10^{-6} mmol) were introduced in a vessel containing 35 μl (3×10^{-4} mmol) of acetophenone, 56 μl (3×10^{-4} mmol) of Ph_2SiH_2 and 500 μl of CH_2Cl_2. After 16 h at room temperature the solution was drained from the beads with a pipette and treated with HCl in acetone. GC analysis indicated the presence of 85% secondary alcohol and 15% $PhCOCH_3$. The 30 beads were again treated with the substrates in CH_2Cl_2. The solution was drained after 5 h at room temperature, then evaporated to remove the solvent. The NMR (in C_6D_6) of the resulting liquid showed a complete conversion with 75% yield of $PhCH(CH_3)OSiR_3$, **2**. The remaining beads were put in the presence of the two substrates for the third time. After 3 h at room temperature and evaporation of solvent the ^1H NMR indicated that the conversion was complete. These three experiments indicated clearly that the catalyst **7-Rh** could be reused several times. Furthermore, by reducing the reaction time for the second and the third reactions we have found that the catalytic reaction was complete in only 3 h, indicating a high efficiency for the catalyst **7-Rh**. In the first experiment, the reaction was certainly complete in less than 16 h, however conversion was not complete below 3 h of reaction time. As control reactions, beads containing respectively terminal bromide (**8**), amide (**9**), and amino alcohol (**10**) functions were prepared and reacted with the rhodium precursor. No catalytic activity for the hydrosilylation reaction was detected with the corresponding complexes, indicating clearly that the catalytic property of the supported catalyst **7-Rh** comes from the chelating ligand and not from a possible interaction of the rhodium moiety with a part of the organic linker or the potential presence of unreacted bromo or amino alcohol groups at the surface of the beads.

Conclusions

In summary, we report that the solid phase organometallic chemistry strategy applied to 500 μm diameter beads offers the opportunity to generate and evaluate a diversity of supported catalysts in the form of miniaturised reactors. The catalytic activity evaluation of only one bead was demonstrated and validated for the comparative screening of an aminophosphine-phosphinite ligand library. This led us to detect a new catalytic system showing an unusual long bridge between the two phosphido groups. The recovery experiments were successfully performed by simply draining the solution from the beads. This study, in addition to the pioneering results for the evaluation of catalysts supported on single beads,[8b–d] indicates that this "one bead-one catalyst" approach may represent a general alternative to the standard method based on Schlenck tubes. This approach could be generalised to a large panel of organometallic catalysis, providing that efficient strategies for the synthesis of organometallic supported catalysts are available. Further investigations in this area are in progress.

Experimental

General methods

NMR spectra were recorded at 25 °C with a 400 MHz spectrometer (Bruker) for ^1H NMR and a 121.5 MHz one for ^{31}P NMR (Varian Unity 300). Polystyrene Macrobead AM-NH_2 resins (size 400–450 μm; 1% DVB crosslinked; capacity: 0.8–1.2 mmol g^{-1}) were purchased from Rapp Polymere GmbH. HATU [2-(1*H*-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] and Fmoc caproic acid (Fmoc: 9-fluorenylmethoxycarbonyl) were purchased from Novabiochem. Other reagents were purchased from Aldrich and were used without further purification. Solvents were dried and distilled prior to use. All reactions involving sensitive compounds were performed in a glove box. Gas chromatography was performed with an HP 5890 with an Ultra 1 column and with an ECD for the halogen-containing tag detection. For classical solid phase organic chemistry procedures see ref. 18.

Kaiser test

The three following solutions were prepared: A: 5 g of ninhydrin in 100 ml of ethanol. B: 80 g of phenol in 20 ml of ethanol. C: 2 ml of 0.001 M KCN in water in 98 ml of pyridine.

Take a few resin beads, add 2 drops of each solution A, B and C. Heat to 100 °C for 5 min. The presence of residual primary amino group is detected by blue resin beads.

Preparation of the supported model 1b

Polystyrene beads containing amino groups (1 g, 1 mmol –NH_2) were reacted with Fmoc caproic acid (1.35 g, 4.4 mmol), HATU (1.14 g, 3 mmol) and diisopropylamine, DIEA (0.87 ml, 5 mmol) in DMF (6 mL) at room temperature for 16.5 h. After draining and careful washing with CH_2Cl_2, DMF and MeOH, beads gave no blue colour with the Kaiser test.[18]

The previous Fmoc protected beads were treated with 20% piperidine in DMF for 10 min. After draining, the treatment was repeated. After draining the beads were carefully washed by DMF (30 ml, 2 h) and CH_2Cl_2 (30 ml, 2 h) to generate the beads **I**.

The beads **I** were reacted in CH_2Cl_2 (25 mL) with NEt_3 (2.15 mL, 24 mmol) and 6-bromohexanoylchloride (1.44 mL, 9.9 mmol) for 2 h at room temperature. Beads were drained and carefully washed by DMF (20 mL for 2 h) and CH_2Cl_2 (20 mL for 1 h). This procedure was repeated twice to obtain a negative Kaiser test (no blue colour). The beads were then reacted in CH_2Cl_2 (30 mL) with 2-phenylglycinol (1.37 g, 10 mmol) in the presence of DIEA (2.6 mL, 15 mmol) for 14 h at room temperature. After draining and washing twice with CH_2Cl_2, the beads were carefully purified by washing with DMF (30 mL for 1 h) and CH_2Cl_2 (30 mL for 1 h). These beads were reacted in toluene (4 mL) with diphenylchlorophosphine (0.65 mL, 3.6 mmol) in the presence of NEt_3 (0.84 mL, 6 mmol) for 20 h at room temperature to give pale yellow beads after washing with toluene and CH_3CN. After drying in vacuum for 16 h beads **1b** were swollen in C_6D_6 to obtain the corresponding ^{31}P NMR spectrum: δ: 108 (OP); 51 (NP).

Preparation of the model supported Rh catalyst 1b-Rh

Beads **1b** were reacted in toluene with an excess of the dimer $[Rh(cod)Cl]_2$ for 1 h, then MeOH was added and the mixture was stirred for an additional hour to give orange beads.

Preparation of the catalyst library

Equivalents amounts of beads **I** (0.33 g, 0.33 mmol) were introduced in two vessels. A specific tag was applied to both of them according to the classical tagging procedure.[16] The first

vessel received a CH_2Cl_2 (3 mL) solution of 2-bromoacetic acid (0.57 g, 4 mmol) and diisopropylcarbodiimide, DIC (0.75 mL, 4.6 mmol), maintained at 0 °C for 20 min. After 1 h of stirring at room temperature, the beads were washed several time with DMF and CH_2Cl_2. The second vessel received NEt_3 (0.8 mL, 5 mmol) and CH_2Cl_2 (6 ml), then 6-bromohexanoylchloride (0.6 mL, 4 mmol) was slowly added to control the temperature rise. After 2 h of stirring at room temperature the beads were drained and washed with DMF and CH_2Cl_2. For both vessels the Kaiser test was negative.

All beads were mixed together and divided into 20 equivalent portions (0.033 g, 0.033 mmol). Each vessel received CH_2Cl_2 (1 mL), a specific amino alcohol (0.33 mmol) and DIEA (0.5 mmol). After 15 h, the beads were drained and were carefully washed with DMF and CH_2Cl_2. Then a specific tagging procedure was applied to each vessel. All the beads were then mixed. The same experimental protocol used for the synthesis of **1b-Rh** was applied to these beads to generate the forty member library.

Preparation of the supported catalyst 7-Rh

2-Bromoacetic acid (0.117 g, 0.8 mmol) was reacted with DIC (309 μL, 1.9 mmol) in CH_2Cl_2 at 0 °C for 20 min. This solution was added to beads **I** (0.138 mmol of $-NH_2$ groups). After 1 h at room temperature, the solution was drained and the beads were carefully washed with DMF (2×30 min) then CH_2Cl_2 (2×10 min). The Kaiser test was negative. These beads were reacted with $H_2NCH_2CH_2OCH_2CH_2NH_2$ (0.138 mL, 1.38 mmol) in the presence of DIEA (0.360 mL, 2.07 mmol) in CH_2Cl_2 at room temperature for 16 h. The beads were carefully washed with DMF (1 h) then with CH_2Cl_2. In a glove box, PPh_2Cl (80 μL, 0.44 mmol) in 3 mL of toluene was added to these beads in the presence of triethylamine (190 μL, 1.24 mmol). After 4 h at room temperature, the solution was drained and the beads were washed with toluene (1 h) and CH_3CN (15 min), then dried. ^{31}P NMR of **7** (C_6D_6): δ: 114 (OP); 63 (NP). $[Rh(cod)Cl]_2$ (100 mg, 0.2 mmol) was reacted with beads **7** in toluene (3 mL) for 4.5 h at room temperature, then 1 ml of MeOH was added. After 1 h the solution was drained and the orange beads **7-Rh** were washed with toluene ^{31}P NMR of **7-Rh** (C_6D_6): δ: 120 (br signal).

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