Recovery and recycling of homogeneous catalysts: silica as temporary or permanent support
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Chapter 3


Abstract: Supramolecular strategies, based on hydrogen bonds and ionic interactions, were investigated as tool for the recovery and recycling of homogeneous transition metal catalysts using the Reverse Flow Adsorption (RFA) technology. The association (in solution) and adsorption (on support) of new functionalized host materials and phosphine guest ligands, functionalized with the complementary binding motifs, have been fine-tuned for the application of these materials in a RFA reactor. The RFA technology for the process integrated recycling of homogeneous catalysts using these tailor-made phosphine ligands and silica-supported host materials resulted in a stable catalytic semi-continuous system. Rhodium catalyzed asymmetric hydrogenation of methyl-acetamidoacrylate and asymmetric hydrosilylation of acetophenone were studied as test reactions. Depending on the catalytic process the metal complex could be recycled several times without significant loss.

Fabrizio Marras, Piet W. N. M. van Leeuwen, Joost N. H. Reek, submitted.
3.1 Introduction

The enormous increase in knowledge of organometallic chemistry acquired over the past decades has had a great impact on catalysis, and numerous homogeneous transition metal catalysts for commercially interesting reactions are nowadays available. One of the factors hampering the commercialization of the newly discovered catalytic conversions is the need for an additional separation step, required to remove the homogeneous catalyst from the product mixture. The importance of the separation issue has been acknowledged for more than three decades and intensive research has been devoted to solve this problem.

Reverse Flow Adsorption (RFA) represents a novel concept for the recovery and recycling of homogeneous catalysts (figure 3.1). It combines an adsorptive separation with reverse flow technology to selectively remove the homogeneous catalyst from the reactor effluent and recycle the catalyst to the reactor with its feed. While the reaction takes place homogeneously inside the reactor, the metal complex is adsorbed to one of the adsorption beds from the product flow that leaves the reactor, and simultaneously it is desorbed into the reactor from the other adsorption bed by the substrate flow feeding the reactor.

The first generation of RFA processes relies on a dual adsorption bed that removes the ligand and the metal separately. The potential side-effect obviously is the decomposition of the complexes once the ligands have been stripped from the metal.

![Figure 3.1 The Reverse Flow Adsorption concept.](image-url)
The development of the RFA concept based on a *One Step Adsorption* is here reported. The adsorbent is functionalized with a well-defined binding motif and the complementary motif is covalently attached to the ligand. This supramolecular anchor enables a *one step* simultaneous adsorption of the catalyst (metal-ligand complex) and the excess of ligand onto the adsorbent material (see figure 3.2). In this process the metal complex (*i.e.* the metal ligand coordination complex) remains intact during the adsorption, which is of crucial importance with respect to side-reactions and catalyst stability.

It is absolutely essential that the adsorption is reversible in order to allow desorption of the catalyst system to reintroduce it into the reactor with the reactor feed. To this end, tailor made adsorbent based on a tunable supramolecular interaction would be ideally suited for this purpose.

![Figure 3.2](image.png)

*Figure 3.2* One step adsorption strategy for reversible catalyst adsorption.

In previous work reported in literature on reversibly immobilized catalysts, the use of a non-covalently functionalized dendrimer, as developed by Meijer and coworkers, has shown by NMR studies that the guest ligand is hosted inside the host pocket of the dendrimer by 1) an ionic interaction between the carboxylic group of the guest tail and the tertiary amine of the host, and 2) a hydrogen bond interaction between urea groups on both host and guest molecules (figure 3.3). The binding was sufficiently strong to allow the application of the supramolecular transition metal catalyst system in a continuous-flow membrane reactor.

Subsequently, it was demonstrated that similar host molecules immobilized on silica materials could also be used for non-covalent anchoring of homogeneous catalysts on insoluble supports.
The supramolecular silica-immobilized catalytic system (figure 3.3, right) shows a lower activity, as is commonly observed for heterogenized catalysts. The catalyst is sufficiently strongly bound to the silica-supported host material to enable efficient separation of the catalyst from the reaction mixture by simple filtration. Moreover, the catalyst can be quantitatively removed from the silica material by washing it with methanol. The silica can be reloaded with different transition metal complexes, and these materials used in different reactions.

In this chapter silica materials functionalized with similar binding motifs, based on hydrogen bonds and ionic interactions, were applied as adsorbent for the RFA reactors. Detailed studies show that with the use of the RFA reactor we combine the activity typical of homogeneous transition metal catalysts with an integrated solution for catalyst separation and recovery. Our studies indicate also that improvements of the system should be made in terms of adsorption kinetics before application of this concept comes in sight.

3.2 Results and discussion

Recently, a model for the determination of the binding strength ($K_{ads}$) for a reversible host-guest adsorption process was developed. Modeling of reactor conditions showed that a binding constant, or adsorption constant, around $1 \times 10^3$ M$^{-1}$ of the catalyst to the support is needed for an adsorption process to be reversible, and therefore ideal for the RFA concept.

In the previously developed supramolecular system, the heterogenized homogeneous transition metal complex formed by interaction of the ligand with the solid support showed too strong adsorptions ($K_{ads} \sim 1 \times 10^5$ M$^{-1}$) for the current
project. A weaker interaction between the functionalized transition metal complex and the silica support functionalized with the complementary binding motif is therefore crucial for future applications of the RFA technology.

3.2.1 Synthesis of the Building Blocks

By simple coupling reactions between multidentate amines and various isocyanates, different host materials were prepared with urea-amine and urea-amide binding pockets. It was anticipated that this variation would lead to sufficient ability to tune their interaction with guest molecules (figure 3.4).

![Figure 3.4](image.png)

**Figure 3.4** Host materials used in the current study.

The triethoxy-functionalized compounds 1b and 2b were supported on commercially available silica gel (particle size: 60–200 µm; pore size: 60 Å) following standard supporting strategies (figure 3.5),\(^6\) to obtain the tailor-made adsorbent materials.
Phosphine containing guest molecules, functionalized with various complementary binding motifs, were prepared following published synthetic procedures\textsuperscript{4c} (figure 3.5).

The diphenylphosphine analogue A\textsubscript{3} was prepared by reaction of diphenylphosphine benzylamine A with 1,2-aminoethanol in the presence of CDI (carbonyl-diimidazole) as coupling agent (scheme 3.2).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{monodiphosphine.png}
\caption{Mono- and diphosphine guest ligands.}
\end{figure}
All compounds were characterized by a combination of spectroscopic techniques, mass spectrometry, and elemental analysis.

### 3.2.2 Binding Studies

The host-guest interaction was studied in solution for several combinations of hosts and guests. To this end, $^1$H-NMR titration experiments were carried out to quantitatively evaluate the strength of the host-guest interaction in solution (see chapter 2).

Upon addition of the guest to a host solution, the protons of the urea group of the host, as well as the $\text{CH}_2$ protons next to the tertiary amine, shifted downfield in a fashion similar to that previously observed for the binding into the dendrimers functionalized with the same binding sites.\(^4\)

### Figure 3.6

$^1$H-NMR titration curves obtained for the $1\text{a} \cdot (\text{A1})_2$ host-guest complex in CDCl$_3$ at 298 K. Data points represent the absolute downfield shifts ($\Delta \delta_{\text{1a}}$) of $\text{-CH}_2$- (●) and $\text{-NH}$- (● - ●) protons of $1\text{a} \cdot (\text{A1})_2$ relative to the chemical shift of free $1\text{a}$.

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**Scheme 3.2** Synthesis of guest ligand A3.

\[
\begin{align*}
\text{Ph}_2\text{P} & \quad \text{NH}_2 \quad + \quad \text{H}_2\text{N-} \text{OH} \\
\text{A} & \quad \text{Ph}_2\text{P} \quad \text{NH} \quad \text{OH} \quad \text{N} \quad \text{H} \\
\text{A3} & \quad \text{Ph}_2\text{P} \quad \text{OH} \quad \text{N}\text{H} \\
\end{align*}
\]
The binding constants ($K_{ass}$) were determined by fitting the titration curves using a program developed by Hunter et al.\(^8\) For the binding of two guest molecules in the binding pockets of host 1a (figure 3.6), a binding model was used, assuming that $K_1$ and $K_2$ are independent and not equal. The association constants ($K_{ass}$, table 3.1) obtained from the fit of the titration curves show that, as expected, the strength of the interaction between host and guest varies strongly with the building blocks used.

**Table 3.1** Association constants for the host-guest system in solution.\(^a\)

<table>
<thead>
<tr>
<th>$K_{ass}$ ($\times 10^3$)</th>
<th>A1</th>
<th>A3</th>
<th>B1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a(^b)</td>
<td>80.0(^c)</td>
<td>1.3</td>
<td>3.5</td>
</tr>
<tr>
<td>2a</td>
<td>3.8(^c)</td>
<td>1.1</td>
<td>1.7</td>
</tr>
<tr>
<td>3a</td>
<td>6.8</td>
<td>n.d.(^d)</td>
<td>2.0</td>
</tr>
<tr>
<td>4a</td>
<td>30.0</td>
<td>n.d.(^d)</td>
<td>n.d.(^d)</td>
</tr>
</tbody>
</table>

\(^a\) Association constant in $10^3$ M\(^{-1}\) are measured in CDCl\(_3\) and calculated by using a non-linear curve-fitting program developed by Hunter et al.; \(^b\) $K_1$ and $K_2$ for the first and second association constant between the guest and the two binding pockets of the host; \(^c\) Association constants taken from ref. 6; \(^d\) n.d. = not determined.

When the association to 1a is compared to that to 2a a significant drop (10 times lower in the case of host 2a) is observed. Likely, the pre-organization of the binding sites is much better in 1a, and possibly cooperative effects of the four urea groups in binding the guest molecule play a role. The presence of an amido-group in the pocket of host 4a (instead of tertiary amines, hosts 1a–3a) leads to weaker interaction with the carboxylic acid moiety of the guest ligand, significantly decreasing the association constant (about 40 times). Similar behavior is observed for the association of guest A3 to host 1a. The hydroxy-group has a weak interaction with the amine compared to the carboxylic acid functionality of guest A1, reducing the host-guest association by about 40 times.

The binding strength of B1 in host 2a is slightly lower than A1 in 2a, since A1 has an additional NH involved in the binding process. The association constant of A1 to host 3a is stronger than expected. This has probably to do with the pre-organization of host 3a, and possibly a cooperative effects of various host molecules in binding the guest under these conditions.\(^9\)
The binding of the relevant guest molecules to the soluble urea-based host materials were compared to the adsorption constants (K_{ads}) to silica immobilized analogues measured by means of adsorption titration experiments (see chapter 2). To this end, the concentration of guest molecules in solution in the presence of different amounts of silica supported host material is monitored using UV-vis spectroscopy (figure 3.7).

![Figure 3.7](image)

**Figure 3.7** UV-Vis titration curves obtained for the 1a•(B1)_{2} host-guest complex in CH_{2}Cl_{2} at 298 K. Data points represent the decrease in concentration (M) of guest B1 as the amount of silica host material 1a increases.

From the fit of the titration curves,^{10} we estimated the adsorption constants (K_{ads}) and the number of accessible binding sites for some combinations of host and guest materials (table 3.2). As observed previously for other host-guest systems,^{6} the adsorption constants are slightly higher than the association of the same binding motifs in solution. Similar titration experiments were also performed in tetrahydrofuran, a more polar solvent than dichloromethane (table 3.2). As expected,^{11} the increase in solvent polarity resulted in a decrease in adsorption strength (table 3.2). Remarkably, most of the binding sites present on the support are not accessible to the guest. The number of binding sites calculated from the titration curve is around four times lower than that expected on the basis of the loading (table 3.2). Probably, the host is partly supported in the aggregate state^{12} and therefore does not interact with the guest.
The rate of the adsorption of guest molecules to silica immobilized host materials was also investigated (figure 3.8). In solution the host-guest binding process is very rapid and the host-guest equilibrium measured is not affected by kinetic issues. This may be different for the supported hosts, as the guest molecules need to diffuse to the sites.

In a first experiment, the time necessary to reach equilibrium was determined by monitoring the guest concentration in solution as a function of time after the addition of the silica-supported host. A 5 mL solution (5.4 × 10⁻⁶ mol) of guest B1 in dichloromethane was added to 0.1 g (1.9 × 10⁻⁵ mol of binding sites) of silica supported host 2c. Samples were taken at different time intervals, and the concentration of the guest B1 was determined by UV-vis spectroscopy. From the data collected, it is clear that the thermodynamic equilibrium is reached in about 2 hours (figure 3.8). Starting with 100% of B1 (5.4 × 10⁻⁶ mol) in solution, at the equilibrium 80% (4.3 × 10⁻⁶ mol) of the guest B1 is adsorbed to the support, occupying around 22.5% of the accessible binding sites of the support (around 3.5 times in excess with respect to the amount of guest).

### Table 3.2

Adsorption constants for the host-guest system on support using B1 as guest ligand.

<table>
<thead>
<tr>
<th>SiO₂-Host</th>
<th>K_{ads} (× 10³)ᵃ</th>
<th>N° of binding sitesᵇ</th>
<th>loadingᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>11</td>
<td>0.12</td>
<td>0.25ᵈ</td>
</tr>
<tr>
<td>2c</td>
<td>3.9</td>
<td>0.19</td>
<td>0.50</td>
</tr>
<tr>
<td>2c°</td>
<td>1.8</td>
<td>0.19</td>
<td>0.50</td>
</tr>
</tbody>
</table>

ᵃ) Adsorption constants for the ligand B1 are expressed in 10³ M⁻¹ are measured in CH₂Cl₂, and have been determined by a Langmuir-type fitting procedure;ᵇ) Number of Binding Sites are measured in mmol/g of silica and determined by titration experiments;ᶜ) Loadings are expressed in mmol/g of silica and measured by elemental analysis;ᵈ) Loading for host 1a is measured to be 0.25 mmol of molecules per gram of support, meaning that from elemental analysis 0.50 mmol of binding sites/g of support are present;ᵉ) Measured in THF.
Figure 3.8  Host-guest adsorption monitored in time: 2c (100 mg) and B1 (1mM).

In a second experiment, more relevant for the RFA reactor concept, the adsorption process was investigated under flow conditions. A 1 mM B1 guest solution is pumped through the adsorption bed loaded with silica material 2c (1.9 $\times$ 10$^{-5}$ mol of binding sites in 0.1 g, 0.2 mL volume). The concentration of the guest at the exit of the adsorption bed is monitored by UV-vis spectroscopy (figure 3.9).

Figure 3.9  Adsorption of the ligand B1 (1 mM in CH$_2$Cl$_2$) on 0.1 g of silica supported host 2c at different flow rates (top) and schematic representation of the set-up (bottom).
Assuming that the total amount of accessible binding sites present in the adsorption bed is $1.9 \times 10^{-5}$ mol, the adsorption profiles show that 2% (3.8 $\times$ $10^{-7}$ mol) of the accessible binding sites on support 2c are occupied before the breakthrough of the guest B1 from the adsorption bed is observed (flow rate of 0.2 mL/min). The residence time of the guest in the adsorption bed increases by lowering the flow rate (0.1 mL/min), and then more than 5% (around 1.0 $\times$ $10^{-6}$ mol) of the accessible binding sites on the adsorbent material are occupied before the guest is detected in the bleed stream. This dependency on the flow rate demonstrates that also under flow conditions the adsorption is influenced by the kinetics.

After determining the adsorption behavior of the guest on the functionalized silica, we also studied the desorption. To this end, a 1 mM solution of guest B1 (5.0 $\times$ $10^{-6}$ mol B1 in 5 mL) was pumped through the adsorption bed loaded with 0.5 g (1 mL volume) of silica host 2c with a flow rate of 0.1 mL/min. After 5 mL of guest solution was pumped through the bed, the direction of the flow was reversed, and pure dichloromethane was pumped through the adsorption bed at the same flow rate (0.1 mL/min) to desorb the ligand (figure 3.10). The concentration of B1 at the exit of the bed was monitored by UV-vis spectroscopy.

![Figure 3.10](image)

**Figure 3.10** Adsorption and desorption of the ligand B1 (1 mM) on silica-supported host 2c (0.5 g) (top). Flow rate = 0.1 mL/min. Schematic representation of the set-up (bottom).
The ligand was completely retained on the silica bed in the first 4 mL (1 mL volume of the adsorption bed), and only 2 % of ligand bleeds after 5 mL have been pumped through the adsorption bed. The flow was then reversed and fresh dichloromethane was pumped through the adsorption bed. The concentration of B1 gradually increased up to 65 % of the guest being desorbed by the same amount of fresh solvent (5 mL), showing reversibility of the adsorption process (even though not completely).

This experiment was repeated using the rhodium metal complex based on ligand B1. [Rh(cod)$_2$]BF$_4$ was used as metal precursor and the in situ formation of the diphosphine metal complex [Rh(cod)B1]BF$_4$ was confirmed by $^{31}$P-NMR spectroscopy (figure 3.11). Based on previous studies it was anticipated that this type of ligands, after formation of the metal complex, bind host materials with comparable binding strength as the corresponding functionalized free ligands.$^{13}$

![Figure 3.11](image)

**Figure 3.11** $^{31}$P-NMR spectrum of the metal complex [Rh(cod)(B1)]BF$_4$.

A 1 mM solution of [Rh(cod)B1]BF$_4$ was pumped into the adsorption bed loaded with silica supported 2c (0.5 g) with a flow rate of 0.1 mL/min (adsorption, figure 3.12). Analysis of the solution at the exit of the adsorption bed showed that the metal complex is fully retained up to 3.5 mL of solution, and after 5 mL about 5 % of the complex leached through. When the flow is reversed and fresh dichloromethane is pumped through the adsorption bed, the metal complex gradually desorbs and after 5 mL around 60 % of the metal complex is desorbed from the bed (desorption, figure 3.12).
These results show that the rate of adsorption (and desorption) of the metal complex onto the silica support is slightly lower than that of the functionalized ligand B1. This results in a faster breakthrough of the complex. The difference in adsorption behavior observed for the metal complex and the ligand could be a result of the difference in size or an effect of an additional interaction between the metal site and the support.

It was anticipated that an ideal value of the adsorption constant for the binding of homogeneous catalysts on adsorption beds in RFA reactors should be in the range of \(10^3\) M\(^{-1}\). This range of adsorption values gives the sharpest concentration profile in the adsorption bed for the RFA where a continuous adsorption/desorption process is applied.\(^7\) We carried out an experiment to evaluate the effect of multiple adsorption/desorption using the current system, which has an adsorption constant 4 times higher than ideal.

To this end, a solution of [Rh(cod)(B1)]BF\(_4\) (1 mM) was pumped with a flow rate of 0.1 mL/min from the reactor through the adsorption bed loaded with 2c (0.5 g, 1 mL volume), and collected at the exit of the bed. After 20 minutes (2 mL) the flow was reversed, and fresh solvent was pumped at the same flow rate in the bed from the opposite side to desorb the metal complex into the reactor (figure 3.13). The direction
of the flow was reversed every 20 minutes (2 mL) and the metal complex was adsorbed and desorbed up to 5 times. The rhodium content of the solutions collected at the exit of the bed, and of the samples taken from the reactor after every cycle was measured by means of UV-Vis spectroscopy. Upon multiple adsorption/desorption, the complex only leached from the bed in the last cycle (6 %). After the 5 adsorption/desorption experiments the rhodium complex was distributed over the reactor and the bed, with 40 % of the rhodium in the reactor and the remaining on the silica bed.

The system under investigation, which refers to specific adsorption beds (loading of 0.19 mmol/g and $K_{\text{ads}}$ of $3.9 \times 10^3 \text{ M}^{-1}$) with a volume of 12.5 % of that of the reactor, does not represent the ideal system, which instead has adsorption beds (loading of 1.0 mmol/g and $K_{\text{ads}}$ of $0.8 \times 10^3 \text{ M}^{-1}$) that are only 3 % of the reactor volume. However, the results obtained so far are in line with those previously shown by modeling studies.

![Figure 3.13](image)

**Figure 3.13** Percentage of rhodium in the reactor (●), and its bleeding from the adsorption bed (●) upon consecutive adsorptions and desorptions (top): Flow rate = 0.1 mL/min, [Rh] = 1 mM, adsorption bed volume = 1 mL, 100 % corresponds to the starting amount of rhodium in the reactor. Schematic representation of the set-up (bottom).
3.2.3 Catalysis

A potential drawback of the first generation RFA process, which was based on dual adsorption beds, was anticipated to be the possible decomposition of the metal complex once the ligands have been stripped from the metal. We therefore investigated how the integration with the RFA process influences the catalytic performance by using the *One Step Adsorption* concept based on supramolecular interactions.

To this end, a setup for the RFA process was designed and developed (see experimental section, figure 3.17), following the criteria sketched above (*i.e.*, bed size, flow rate, catalyst concentration, etc.). The asymmetric hydrogenation of methyl-acetamidoacrylate and the asymmetric hydrosilylation of acetophenone (schemes 3.3 and 3.4 respectively) were chosen as catalytic reactions for integration of the RFA technology with homogeneous catalysis, because of their industrial relevance and compatibility with the binding motifs used here.

3.2.3.1 Asymmetric hydrogenation of methyl-acetamidoacrylate

The use of ligand B1 in the Rh-catalyzed asymmetric hydrogenation of methyl-acetamidoacrylate (MAA) (scheme 3.3), and the performance of the functionalized metal complex in catalysis were investigated and compared to the one of the N-Boc-protected analogue BPPM.

![Scheme 3.3](image)

**Scheme 3.3** Rhodium-catalyzed asymmetric hydrogenation of methyl acetoamidoacrylate (MAA).

In a typical RFA experiment, the catalyst is prepared *in situ* by dissolving the rhodium precursor and the chiral ligand in dichloromethane. After formation of the metal complex (stirring the solution for 1 hour), the system is purged with H₂ (1 bar pressure). The substrate is added and the reaction started. After a reaction time of 30
minutes the reaction mixture is pumped (flow rate: 0.1 mL/min) from the reactor into the first adsorption bed and the metal complex adsorbed (figure 3.14). Simultaneously two different dichloromethane solutions, one containing the metal complex and one containing the substrate, are added to the reactor with the same flow rate. After 2 mL of the reactor solution have been collected outside of the first adsorption bed, the direction of the flow is reversed. A substrate solution is pumped into the reactor, passing through the first adsorption bed, desorbing the metal complex into the reactor. At the same time, from the reactor, the reaction mixture is pumped through the second adsorption bed. The flow direction is changed every 20 minutes and the flow interchanged up to 9 times. The product mixture is collected outside the adsorption beds and analyzed by chiral GC.

Figure 3.14  Schematic representation of the RFA set-up.

When used in homogeneous phase both rhodium complexes of ligand B1 and BPPM gave the same results in terms of activity (around 50 % conversion), while an increase in selectivity from 6 % to 28 % in favor of the R product was observed when ligand B1 was used (entries 1 and 2, table 3.3).

Interestingly, the selectivity further increased to 45 % once the system is used in heterogeneous conditions, while the activity decreased, as expected for heterogenized systems (entry 3, table 3.3). The increase in selectivity is likely due to a change in steric properties, which become more pronounced on the support.

Under RFA conditions the selectivity of 20.0 % in the asymmetric hydrogenation of methyl acetamidoacrylate is similar to that of the homogeneous analogue in a batch reactor (28.1 % ee, entries 3 and 4 respectively, table 3.3).
The Reverse Flow Adsorption

Table 3.3 Asymmetric hydrogenation of methyl acetamidoacrylate (MAA) using [Rh(cod)(B1)]BF₄ as catalyst and 2c as silica supported host.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Run</th>
<th>Time (min)</th>
<th>Conv (%)</th>
<th>ee (R) (%)</th>
<th>TOFb</th>
<th>Cumulative TONc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)BPPM]BF₄</td>
<td>60</td>
<td>50.2</td>
<td>5.8</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)B1]BF₄</td>
<td>60</td>
<td>52.6</td>
<td>28.1</td>
<td>105</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(cod)B1]BF₄d</td>
<td>60</td>
<td>28.4</td>
<td>41.9</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>RFA-1</td>
<td>50</td>
<td>55.3</td>
<td>20.0</td>
<td>138</td>
<td>111</td>
</tr>
<tr>
<td>5</td>
<td>RFA-2</td>
<td>50</td>
<td>47.6</td>
<td>16.3</td>
<td>119</td>
<td>206</td>
</tr>
<tr>
<td>6</td>
<td>RFA-3</td>
<td>50</td>
<td>41.8</td>
<td>16.1</td>
<td>105</td>
<td>289</td>
</tr>
<tr>
<td>7</td>
<td>RFA-4</td>
<td>50</td>
<td>38.6</td>
<td>17.4</td>
<td>97</td>
<td>367</td>
</tr>
<tr>
<td>8</td>
<td>RFA-5</td>
<td>50</td>
<td>34.1</td>
<td>18.7</td>
<td>85</td>
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<td>50</td>
<td>29.7</td>
<td>16.1</td>
<td>74</td>
<td>494</td>
</tr>
<tr>
<td>10</td>
<td>RFA-7</td>
<td>50</td>
<td>29.0</td>
<td>13.0</td>
<td>73</td>
<td>552</td>
</tr>
<tr>
<td>11</td>
<td>RFA-8</td>
<td>50</td>
<td>26.2</td>
<td>16.3</td>
<td>66</td>
<td>605</td>
</tr>
</tbody>
</table>

a) [Rh] = 1 mM, Ligand/Rh = 1.1, Sub/Rh = 200, silica bed loaded with 0.5 g of host 2c per bed, Volume reactor = 6 mL, pH₂ = 1 bar, room temperature (the results in RFA conditions derives from samples taken from the reactor mixture); b) Turnover frequencies are calculated as average at the specified time as (mol product)(mol rhodium)⁻¹(time)⁻¹; c) Cumulative turnover numbers calculated as (mol product)(mol rhodium)⁻¹, where the mol of product are calculated as mol of substrate injected x conversion); d) Heterogeneous system using 1c as silica supported host material.

The conversions under these different conditions are hard to compare, but their similarity indicates that the RFA conditions have no negative effect on the activity. This indicates that under RFA conditions the catalysis takes place in the homogeneous phase. The conversion drops significantly from 55.3 % to 26.2 % after 8 consecutive runs, while selectivities remain in the range of 18–16 % (entries 4–11, table 3.3). The decrease in conversion and retention of selectivity after each RFA cycle can largely be explained by the decrease of the catalytic active species inside the reactor, as it was shown to reside on the beds.

To support this the rhodium content was determined after each run with ICP-OES analysis. As can be seen from figure 3.15, the trend in the conversion nicely follows the decrease of rhodium inside the reactor. Importantly, this shows that the catalyst that is fed back into the reactor by desorption is fully active and not decomposed.
In addition, the catalyst leaching at the exit of the adsorption beds was found to be around 15 % of the total amount of rhodium added into the system. This is slightly higher than the 6 % leaching found after multiple adsorption/desorption experiments in pure DCM.

Moreover, under RFA conditions, the amount of rhodium inside the reactor decreased towards a constant value around 60–50 % after the second cycle (in red, figure 3.16), while in pure dichloromethane the amount of rhodium inside the reactor decreased constantly after each cycle (in blue, figure 3.16).

**Figure 3.15** Normalized values for the conversion of 5 RFA cycles (blue) and for the rhodium content in the reactor during 5 RFA cycles (red).

**Figure 3.16** Percentage of rhodium in the reactor upon multiple adsorption/desorption in pure DCM (blue) and in RFA conditions (red).
This indicates that the presence of the substrate and products in solution influence to some extent the adsorption of the rhodium metal complex to the silica support. One should therefore consider the use of non-functionalized substrates, which are hydrogenated usually by iridium-diphosphine catalysts,\textsuperscript{14} to minimize the competition of functionalized metal complex with substrate and products in the binding process once used in RFA reactors, or one should compensate for this in the design of the binding motif, by making the interaction stronger if such competition is expected.

3.2.3.1 Asymmetric hydrosilylation of acetophenone

Asymmetric hydrosilylation of acetophenone\textsuperscript{13,15} catalyzed by $[\text{Rh}(\text{cod})\text{B}]\text{BF}_4$ (scheme 3.4), under homogeneous and heterogeneous conditions, has been carried out in batch reactors (table 3.4 and chapter 2). As for the asymmetric hydrogenation of methyl acetamidoacrylate (\textit{vide supra}), the effect of the binding motif and the support on the catalytic performance was investigated and compared with the N-Boc protected analogue.

![Scheme 3.4](image)

Scheme 3.4 Rhodium-catalyzed asymmetric hydrosilylation of acetophenone.

As previously reported, urea groups of the binding motif influence the catalytic performance of the functionalized rhodium complex. Conversions are reduced from 84 % in the case of the N-Boc protected ligand BPPM to 58 % when the ureido-glycine ester B2 is used (entry 1 and 2, table 3.4).
Table 3.4  Asymmetric hydrosilylation of acetophenone using [Rh(cod)(B1)]BF₄ as catalyst and 2c as silica supported host.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Run</th>
<th>Time (min)</th>
<th>Conv (%)</th>
<th>ee (S) (%)</th>
<th>TOFb</th>
<th>Cumulative TONc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)BPPM]BF₄</td>
<td>60</td>
<td>84.1</td>
<td>29.0</td>
<td>83</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)B1]BF₄</td>
<td>60</td>
<td>57.9</td>
<td>25.5</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(cod)B1]BF₄</td>
<td>30</td>
<td>34.3</td>
<td>33.5</td>
<td>69</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(cod)B1]BF₄</td>
<td>60</td>
<td>45.1</td>
<td>36.1</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(cod)B1]BF₄</td>
<td>90</td>
<td>54.9</td>
<td>28.2</td>
<td>37</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(cod)B1]BF₄</td>
<td>180</td>
<td>58.8</td>
<td>26.3</td>
<td>29</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(cod)B1]BF₄</td>
<td>1080</td>
<td>84.7</td>
<td>22.3</td>
<td>5</td>
<td>-</td>
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<tr>
<td>8</td>
<td>[Rh(cod)B1]BF₄</td>
<td>240</td>
<td>28.7</td>
<td>23.2</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>RFA-1e</td>
<td>50</td>
<td>46.2</td>
<td>37.6</td>
<td>58</td>
<td>46</td>
</tr>
<tr>
<td>10</td>
<td>RFA-2e</td>
<td>50</td>
<td>44.4</td>
<td>32.2</td>
<td>56</td>
<td>91</td>
</tr>
<tr>
<td>11</td>
<td>RFA-3e</td>
<td>50</td>
<td>32.6</td>
<td>32.2</td>
<td>41</td>
<td>123</td>
</tr>
<tr>
<td>12</td>
<td>RFA-4e</td>
<td>50</td>
<td>34.2</td>
<td>34.2</td>
<td>43</td>
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<td>RFA-5e</td>
<td>50</td>
<td>33.1</td>
<td>29.9</td>
<td>41</td>
<td>191</td>
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<tr>
<td>14</td>
<td>RFA-6e</td>
<td>50</td>
<td>36.8</td>
<td>33.0</td>
<td>46</td>
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<tr>
<td>15</td>
<td>RFA-7e</td>
<td>50</td>
<td>33.0</td>
<td>31.3</td>
<td>41</td>
<td>260</td>
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<tr>
<td>16</td>
<td>RFA-8e</td>
<td>50</td>
<td>40.9</td>
<td>34.5</td>
<td>51</td>
<td>301</td>
</tr>
<tr>
<td>17</td>
<td>RFA-9e</td>
<td>50</td>
<td>35.7</td>
<td>32.5</td>
<td>45</td>
<td>337</td>
</tr>
</tbody>
</table>

a) [Rh] = 1 mM, Ligand/Rh = 1.1, Substrate/Rh = 100, Silane = Ph₂SiH₂, Silane/Substrate = 3, Volume reactor = 4 mL, room temperature. b) Turnover frequencies are calculated as average at the specified time as (mol product)(mol rhodium)^–1(time)^–1. c) Cumulative turnover numbers calculated as (mol product)(mol rhodium)^–1, where the moles of product are calculated as injected mol substrate x conversion), d) Heterogeneous system using 1c (0.5 g, see chapter 2) as silica supported host material; e) Each silica bed is loaded with 0.5 g of host 2c.

The conversion decreases further to 45 % when B1, the acid derivative of B2, is used (entry 4). While the conversion changes due to the presence of the binding motif, the selectivity is comparable (30 % in favor of the S enantiomer) in each reaction. The non-covalent anchored catalyst (entry 8, table 3.4) showed lower activity than its homogeneous analogue, as expected for heterogenized systems, with only 29 % conversion after 4 hours. The selectivity obtained with this heterogenized catalyst is similar to that of the homogeneous analogue, indicating no significant influence of the support.

The catalysis experiment was then carried out under R.F.A. conditions (entries 9–17, table 3.4). In a typical RFA experiment [Rh(cod)B1]BF₄ is prepared in situ by dissolving the rhodium precursor and the chiral ligand in dichloromethane. After
formation of the metal complex (stirring the solution for 1 hour), a solution of silane in dichloromethane is added to the reactor. After 30 minutes of incubation, a solution of the substrate in dichloromethane is added and the reaction started. 30 minutes after the reaction started, the reactor mixture is pumped (flow rate: 0.1 mL/min) from the reactor into the first adsorption bed where the metal complex is adsorbed (see figure 3.14). Simultaneously, two different dichloromethane solutions, one containing the metal complex and one containing the substrate and the silane, are added to the reactor with the same flow rate. After 2 mL of the reactor solution have been collected outside of the adsorption bed, the direction of the flow is reversed. A solution containing the substrate and the silane is pumped into the reactor, passing through the first adsorption bed desorbing the metal complex into the reactor. At the same time, from the reactor, the reaction mixture is pumped through the second adsorption bed. After this, the flow direction is changed every 20 minutes and the flow direction was changed up to 9 times. The products collected outside the adsorption beds, are hydrolyzed by MeOH and a 1M HCl(aq) solution, extracted with Et₂O, and subsequently analyzed by chiral GC.

The activity and selectivity obtained under RFA conditions are comparable with the homogeneous catalyst in a batch reactor, with conversions in the range of 46–33 %, and selectivities around 34 % (entries 9–17 and 4 respectively, table 3.4). This shows that the catalysis mostly takes place in the homogeneous phase rather than on the support.

![Figure 3.17](image)

**Figure 3.17** Linear fit of the cumulative turnover numbers.
Moreover, the catalytic performance of [Rh(cod)B1]BF₄ remains stable up to 8 consecutive runs, showing comparable activities and selectivities in each cycle (TOFs around 40 and ee around 30–35 %, entries 1–9, table 3.3). Whereas previous experiments showed a decrease in catalyst concentration inside the reactor as a consequence of the continuous adsorption/desorption experiment (vide supra, figure 3.13), in combination with catalyst leaching (determined by ICP-OES and which showed to be not significant), the current catalytic system showed a linear cumulative turnover number (figure 3.17), suggesting that under these conditions the catalyst concentration in the reactor remains constant.

3.3 Conclusions

In conclusion, we report the application of RFA as a novel technology for the recovery and recycling of homogeneous transition metal catalysts. By combining an adsorptive separation with reverse flow technology we selectively remove the homogeneous catalyst from the reactor effluent and recycle the catalyst to the reactor with the fresh feed. The adsorbents are tailor-made materials based on supramolecular interactions. For this purpose silica materials (host) were functionalized with a well-defined binding motif. The ligands (guest) used for transition metal catalysis have been functionalized with complementary binding motifs. Their interaction is based on hydrogen bonds of urea groups on both host and guest, and an ionic interaction between an amino group on the host and a carboxylic acid group on the guest ligand. Binding studies and adsorption studies showed that the binding between host and guest can be tuned by 1) the number of the interactions (hydrogen bonds) between host and guest, 2) the polarity of the solvent, and 3) changing the acid/base interaction. In this manner the binding strength for integrating these materials with the RFA reactors can be optimized. Adsorption/desorption experiments of functionalized ligand B1 and its rhodium complex [Rh(cod)(B1)]BF₄ on silica-supported host 2c showed that 1) the support is stable upon multiple adsorption-desorption, and that 2) by increasing the residence time of the metal complex on the support (by applying lower flow rates) the leaching from the adsorption bed occurs at a later stage, indicating that the kinetics of the adsorption process play a dominant role.

The catalytic system applied under RFA conditions shows activities and selectivities comparable to its homogeneous batch process. The rhodium complex
could be recycled up to 9 times in the rhodium-catalyzed asymmetric hydrosilylation of acetophenone, showing good retention of both activity and selectivity. In the rhodium-catalyzed hydrogenation of MAA the conversion dropped upon recycling. This drop in activity was attributed to the drop in catalyst concentration. Importantly, the desorbed catalyst was still active and was not decomposed, which is a clear advantage of this one step adsorption strategy.

The RFA is a promising concept for recovery and recycling of homogeneous transition metal catalysts. Further optimization of the process should focus on application of other silica materials to increase the adsorption rates.

3.4 Experimental Section

3.4.1 General Procedure

Unless stated otherwise, reactions were carried out under an atmosphere of argon using standard Schlenk techniques. Solvents were distilled under an atmosphere of nitrogen as follows: THF and EtO₂ from sodium benzophenone ketyl, toluene from sodium, and dichloromethane from CaH₂.

Chemicals were purchased from Sigma-Aldrich and used without further purification. Silica gel (200-400 μm; 60 Å) was purchased from Screening Devices B.V. and pretreated under vacuum at 180 °C for 24 hours prior its use.

NMR spectra (¹H, ³¹P {¹H}, and ¹³C{¹H}) were measured on Varian Mercury 300 MHz, or Varian INOVA 500 MHz spectrometers. Chemical shifts are denoted in ppm, using the solvent itself as internal standard.

High-resolution fast atom bombardment mass spectrometry (HRMS FAB) measurements were carried out on a JEOL IMS-SX/SX 102A spectrometer.

Chiral GC analyses were performed on an Interscience Trace GC Ultra (F.I.D. detector) with a Chirasil Dex CB column (internal diameter 0.1 mm, 5 m column, film thickness 0.1 μm).

Elemental analyses were performed at the H. Kolbe Mikroanalytisches Laboratorium in Mülheim (Germany).
Rhodium analysis were performed on an ICP-OES, PerkinElmer Optima 3000XL with detection limit of 1.4 µg/l (1.4 ppb) and determination limit of 4.2 µg/l (4.2 ppb).

3.4.2 Host Synthesis

\textbf{N,N-bis[(adamantylurea)propyl]-N-methylamine (2a)}

To a stirred solution of 3,3’-diamino-N-methyl-dipropylamine (0.76 mmol) in DCM (6 mL) at room temperature is added adamantylisocyanate (1.53 mmol). The reaction mixture is stirred overnight at room temperature. Then the mixture is concentrated by partially removing the DCM under reduced pressure, and the product is precipitated by addition of Et₂O (30 mL). The product is filtered as white powder in 84 % yield (0.67 mmol). ¹H-NMR (300 MHz, CDCl₃ + CD₃OD, δ): 5.5 (br., 4H), 3.08 (t, J = 7 Hz, 4H), 2.35 (t, J = 7 Hz, 4H), 2.17 (s, 3H), 2.03 (s, 6H), 1.93 (s, 12H), 1.66 (s, 12H), 1.56 (m, 4H); ¹³C{¹H} NMR (75 MHz, CDCl₃, δ): 156.9 (s), 51.8 (s), 50.7 (s), 44.1 (s), 42.6 (s), 36.5 (s), 29.6 (s), 26.8 (s); HRMS (FAB⁺): m/z calcd. for C₂₉H₅₀N₅O₂ ([MH]+): 500.3965; obsd.: 500.3958; Anal. calcd. for C₂₉H₄₉N₅O₂: % C 69.70, % H 9.88, % N 14.01, % O 6.40; found: % C 68.59, % H 9.67, % N 13.88, % O 6.24.

\textbf{N,N-bis[(triethoxysilyl)propylurea]propyl]-N-methylamine (2b)}

To a stirred solution of 3,3’-diamino-N-methyl-dipropylamine (DMDA, 0.76 mmol) in DCM (6 mL) at room temperature is added 3-triethoxysilylpropylisocyanate (1.53 mmol). The reaction mixture is stirred overnight at room temperature. The mixture is concentrated by partially removing the DCM under reduced pressure, and the product is precipitated by addition of Et₂O (30 mL). The product is filtered as white powder in 82 % yield (0.62 mmol). ¹H NMR (500 MHz, CD₂Cl₂, δ): 5.89 (bs, 2H), 5.60 (bs, 2H), 3.80 (q, J = 7 Hz, 12H), 3.23 (q, J = 7 Hz, 4H), 3.11 (q, J = 7 Hz, 4H), 2.34 (dd, J = 5.5 Hz, 4H), 2.10 (s, 3H), 1.63-1.54 (m, 8H), 1.21 (t, J = 7 Hz, 18H), 0.63-0.60 (m,
**N,N-Dimethyl-N-(adamantylurea)propylamine (3a)**

To a stirred solution of N,N-dimethylpropyl-1,3-diamine (0.76 mmol) in DCM (6 mL) at room temperature is added adamantly isocyanate (0.80 mmol). The reaction mixture is stirred overnight at room temperature. The mixture is concentrated by partially removing the DCM under reduced pressure, and the product is precipitated by addition of Et₂O (30 mL). The product is filtered as white powder in 92 % yield (0.70 mmol). ¹H NMR (300 MHz, CDCl₃, δ): 5.33 (bs, 1H), 4.97 (s, 1H), 3.15 (t, J = 5 Hz, 2H), 2.40 (t, J = 6.5 Hz, 2H), 2.25 (s, 6H), 2.05-2.00 (m, 4H), 1.92 (m, 6H), 1.66-1.59 (m, 7H); ¹³C{¹H}-NMR (125 MHz, CD₂Cl₂, δ): 158.42 (s), 57.41 (s), 50.81 (s), 45.30 (s), 42.63 (s), 39.09 (s), 36.68 (s), 29.83 (s), 27.51 (s); HRMS (FAB⁺): m/z calcd. for C₁₆H₃₀N₃O ([MH]⁺): 280.2389; obsd.: 280.2386; Anal. calcd. for C₁₆H₂₉N₃O: % C 68.77, % H 10.46, % N 15.04, % O 5.73; found: % C 68.58, % H 10.39, % N 15.08, % O 5.95.

**N,N-bis[(adamantylurea)propyl]-N’-adamantylurea (4a)**

To a stirred solution of N-(3-aminopropyl)propane-1,3-diamine (ADPA, 0.76 mmol) in DCM (6 mL) at room temperature is added adamantly isocyanate (2.3 mmol). The reaction mixture is stirred overnight at room temperature. The mixture is concentrated partially removing the DCM under reduced pressure, and the product is precipitated by addition of Et₂O (30 mL). The product is filtered as white powder in 88 % yield (0.67 mmol). ¹H NMR (500 MHz, CD₂Cl₂, δ): 5.77 (t, J = 5.2 Hz, 3H), 4.62 (s, 2H), 3.18 (t, J = 6.5 Hz, 4H), 3.04 (q, J = 5.6 Hz, 4H), 2.03 (s, 9H), 1.97 (s, 6H), 1.94 (s, 12H), 1.66 (s, 18H), 1.64-1.61 (m, 4H); ¹³C{¹H}-NMR (125 MHz, CD₂Cl₂, δ): 158.84 (s), 158.81 (s), 158.79 (s), 157.77 (s), 157.74 (s), 66.27 (s), 56.91 (s), 32.27 (s), 29.83 (s), 27.51 (s); HRMS (FAB⁺): m/z calcd. for C₃₃H₇₀N₇O₂ ([MH]⁺): 485.2389; obsd.: 485.2386; Anal. calcd. for C₃₃H₆₉N₇O₂: % C 73.69, % H 10.33, % N 13.98; found: % C 73.64, % H 10.31, % N 13.96.
51.81 (s), 51.70 (s), 50.95 (s), 50.84 (s), 44.58 (s), 43.00 (s), 42.98 (s), 42.84 (s), 42.81 (s), 37.31 (s), 37.20 (s), 37.03 (s), 29.45 (s); HRMS (FAB\(^+\)): m/z calcd. for C\(_{39}\)H\(_{63}\)N\(_6\)O\(_3\) ([MH]\(^+\)): 663.4962; obsd.: 663.4968; Anal. calcd. for C\(_{39}\)H\(_{62}\)N\(_6\)O\(_3\): % C 70.66, % H 9.43, % N 12.68, % O 7.24; found: % C 70.54, % H 9.35, % N 12.83, % O 7.28.

**Immobilization of 1b onto silica gel (1c)**

Synthesis of silica supported G1.0 dendrimer (1c) have been published elsewhere.\(^6\)

**Immobilization of 2b onto silica gel (2c)**

A quantity of 1 g of silica gel is dried under reduced pressure at 180 °C overnight. To a suspension of the silica in toluene (15 mL) is added 2b (1 mmol). The mixture is refluxed for over night. The silica is isolated by filtration, washed with toluene (3 × 10 mL), and dried under reduced pressure. Analysis of the solution showed that 0.50 mmol host material is attached to the silica. Silica modification is performed by refluxing 1 g of the modified silica and 1 mL of dimethoxydimethylsilane in toluene (15 mL) for 24 hours. The resulting silica modified material is isolated by filtration, washed with toluene (3 × 10 mL), dried under reduced pressure, and stored under argon. Anal. found: N 3.49. (loading: 0.498 mmol/g that corresponds to a number of binding sites of 0.498 mmol/g – from titration experiment the number of binding sites is 0.2 mmol/g meaning that only 40 % of the binding sites are accessible to the guest).

3.4.3 Guest synthesis

Synthesis of A1 and A2 is published elsewhere.\(^4c\)

For the synthesis of ligand B1 and B2 see chapter 2.
To a solution of carbonyl diimidazole (CDI, 1.1 mmol) and N-methyl morpholine (0.4 mmol) in 5 mL of DCM a solution of 291 mg (1 mmol) of p-(diphenylphosphino)benzylamine (A) in 25 mL of DCM is added dropwise at room temperature. The mixture is stirred for 16 hours at room temperature. The solution is then concentrated under reduced pressure and a solution of hydroxylamine (1 mmol) in 20 mL of DCM is added dropwise and the mixture is stirred for 16 hours at room temperature. The organic mixture is then washed with degassed water (3 x 40 mL), the organic layer is then dried over MgSO₄. The solvent was partially removed under reduced pressure, and the desired product was precipitated by Et₂O as a white powder. Yield: 95 % (0.95 mmol).

**1H-NMR (500 MHz, CD₂Cl₂, δ):** 7.30 (m, 14H), 5.02 (bs, 1H), 4.91 (bs, 1H), 4.35 (d, J = 5.5 Hz, 2H), 3.64 (t, J = 4.5 Hz, 2H), 3.30 (m, 2H), 2.99 (bs, 1H);

**31P-NMR (202 MHz, CD₂Cl₂, δ):** -5.48;

**13C{¹H}-NMR (125 MHz, CD₂Cl₂, δ):** 159.65 (s), 149.66 (s), 137.93 (d, JCP = 11.5 Hz), 136.72 (d, JCP = 11.5 Hz), 134.62 (s), 134.46 (s), 134.26 (s), 134.11 (s), 129.30 (s), 129.06 (d, JCP = 6.6 Hz), 127.95 (d, JCP = 6.6 Hz), 63.93 (s), 44.62 (s), 44.07 (s); HRMS (FAB⁺): m/z calcd. for C₂₂H₂₄N₂O₂P₂ ([MH⁺]: 379.1575; obsd.: 379.1580; Anal. calcd. for C₂₂H₂₃N₂O₂P₂: % C 68.83, % H 6.13, % N 7.40, % O 8.46, % P 8.19; found: % C 68.96, % H 6.42, % N 7.29, % O 8.19, % P 8.15.

### 3.4.4 ICP-OES Analysis

**Rhodium in the silica support (ICP-OES analysis)**

The silica gel is dissolved in 48 % aqueous HF (1 mL x 50 mg of silica) and heated until all the volatiles are evaporated. The residue is then dissolved by adding fuming nitric acid (2 mL) and warming up the solution to 90 °C for 1 hour. Hydrogen peroxide (few drops) is then added to the warm sample until the solution become colorless. Water is added to bring the total volume up to 10 mL for analysis.
Rhodium in the product mixture (ICP-OES analysis)

5 mL of product solution are evaporated under vacuum at 80 °C. The residue is dissolved by adding fuming nitric acid (2 mL) and warming up the solution to 90 °C for 1 hour. Hydrogen peroxide (few drops) is added to the warm sample until the solution become colorless. Water is added to bring the total volume up to 10 mL for analysis.

3.4.5 The Adsorption-Desorption

The system setup consist of 1) two Bischoff HPLC Compact Pumps 2250 (20 bars, 0–5 mL/min), 2) two Swagelok® crossover 3-way valves (model SS-41XS2), 3) two Supelco SPE Tubes (1 mL volume) equipped with PE frits (20 µm porosity), 4) one Biorad 2110 fraction collector, 5) one glass schlenks as catalyst solution vessel, and 6) Teflon tubings (1 mm diameter).

Conditions: [Rh] = 1 mM (0.006 mmol); Ligand/Rh = 1.1; silica bed is loaded with 0.5 g of silica supported host 2c; volume reactor = 6 mL; room temperature.

3.4.6 The Reverse Flow Adsorption

The setup: The system setup consist of 1) two Bischoff HPLC Compact Pumps 2250 (20 bars, 0–5 mL/min), 2) two Swagelok® crossover 4-way valves (model SS-43YF2), 3) two Supelco SPE Tubes (1 mL volume) equipped with PE frits (20 µm porosity), 4) one Biorad 2110 fraction collector, 5) two glass schlenks as substrate and reactor vessels, and 6) Teflon tubing (1 mm diameter).

1) Asymmetric hydrogenation of MAA:

[Rh] = 1 mM (0.006 mmol); Ligand/Rh = 1.1; Sub/Rh = 200; each silica bed is loaded with 0.5 g of silica supported host 2c; volume reactor = 6 mL; room temperature.

In a typical R.F.A. experiment, the catalyst is prepared in situ by dissolving the rhodium precursor ([Rh(cod)₂BF₄] (0.006 mmol) and the chiral ligand (0.0066
mmol) in dichloromethane (4 mL). After formation of the metal complex (stirring the solution for 1 hour), the system is purged with H\textsubscript{2} (1 bar pressure). The substrate (1.2 mmol) is added and the reaction started. After a reaction time of 30 minutes the reaction mixture is pumped (flow rate: 0.1 mL/min) from the reactor into the \textit{first} adsorption bed (loaded with 0.5 g of silica host \textit{2c}) and the metal complex adsorbed. Simultaneously two different dichloromethane solutions, one containing the metal complex (0.001 mmol in 1 mL of dichloromethane) and one containing the substrate (0.2 mmol in 1 mL of dichloromethane), are added to the reactor with the same flow rate. After 2 mL of the reactor solution have been collected outside of the \textit{first} adsorption bed, the direction of the flow is reversed. A substrate solution (0.2 M) is pumped into the reactor (flow rate: 0.1 mL/min), passing through the \textit{first} adsorption bed, desorbing the metal complex into the reactor. At the same time, from the reactor, the reaction mixture is pumped through the \textit{second} adsorption bed (flow rate: 0.1 mL/min). The flow direction is changed every 20 minutes and the flow interchanged up to 9 times. The product mixture is collected outside the adsorption beds and analyzed by chiral GC.

2) \textit{Asymmetric hydrosilylation of acetophenone}: 

\[ \text{[Rh]} = 1 \text{ mM (0.006 mmol)}; \text{Ligand/Rh} = 1.1; \text{Sub/Rh} = 100; \text{Silane} = \text{Ph}_2\text{SiH}_2; \text{Silane/Sub} = 3; \text{each silica bed is loaded with 0.5 g of silica supported host 2c}; \text{volume reactor} = 6 \text{ mL}; \text{room temperature}. \]

In a typical R.F.A. experiment, the catalyst is prepared \textit{in situ} by dissolving the rhodium precursor ([Rh(cod)\textsubscript{2}BF\textsubscript{4}] (0.006 mmol) and the chiral ligand (0.0066 mmol) in dichloromethane (2 mL). After formation of the metal complex (stirring the solution for 1 hour), a solution of silane (1.8 mmol) in dichloromethane (1 mL) is added to the reactor. After 30 minutes of incubation, a solution of the substrate (0.6 mmol) in dichloromethane (1 mL) is added and the reaction started. 30 minutes after the reaction started, the reactor mixture is pumped (flow rate: 0.1 mL/min) from the reactor into the \textit{first} adsorption bed and the metal complex adsorbed. Simultaneously, two different dichloromethane solutions, one containing the metal complex (0.001 mmol in 1 mL of dichloromethane) and one containing the substrate (0.1 mmol) and the silane (0.3 mmol) in dichloromethane (1 mL), are added to the reactor with the same flow rate. After 2 mL of the reactor solution have been collected outside of the
adsorption bed, the direction of the flow is reversed. A solution containing the substrate (0.1 M) and the silane (0.3 M) is pumped into the reactor (flow rate: 0.1 mL/min), passing through the first adsorption bed desorbing the metal complex into the reactor. At the same time, from the reactor, the reaction mixture is pumped through the second adsorption bed. The flow direction is changed every 20 minutes and the flow interchanged up to 9 times. Samples of the product mixture (2 mL) collected outside the adsorption beds are hydrolyzed by MeOH (1 mL) and a 1M HCl\(_{(aq)}\) solution (1 mL), extracted with Et\(_2\)O (4 mL), and subsequently analyzed by chiral GC.

### 3.5 References


The Reverse Flow Adsorption


13 F. Ribaudo, PhD Thesis: “*Dendrimers and Hyperbranched Polymers as Soluble Supports for Transition Metal Catalysts*”, **2007**.
