Tailor-made Catalysts Immobilised on Silica.
Sandee, A.J.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Solid phase synthesis of homogeneous ruthenium catalysts on silica for the continuous asymmetric transfer hydrogenation reaction*

Abstract

The solid phase synthesis of new asymmetric transfer hydrogenation catalysts and the use of these silica supported systems in batch and flow reactors is reported. The ruthenium complex of NH-benzyl-(1R,2S)-(-)-norephedrine covalently tethered to silica showed a high activity and enantioselectivity in the reduction of acetophenone. In a continuous flow reactor a very constant catalytic activity was observed; no catalyst deactivation occurred during 1 week. This has been ascribed to successful site isolation. Using optimised conditions in this flow reactor the ee was as high as 90% at 95% conversion. The use of silica as a support in the solid phase preparation of asymmetric transfer hydrogenation catalysts and the application of a small series of these catalysts was demonstrated. The supported catalysts generally show the same trend in catalyst performance as in solution.

7.1 Introduction

Chiral alcohols form an important class of intermediates for the pharmaceutical, agrochemical, flavor and fragrance industry. The enantioselective synthesis of chiral secondary alcohols by catalytic reduction of the corresponding ketone is therefore an important transformation in organic synthesis. One of the most attractive methods for this reaction is asymmetric transfer hydrogenation since it can give a high product yield in high enantiomeric excess at relatively mild conditions.

\[
\text{[Ru]*/base} \quad \text{[Ru]*/base} \quad \text{[Ru]*/base}
\]

Much effort has been devoted to the development of new chiral catalysts resulting in a rapid progress in the area. The insight in the mechanism is increasing rapidly and the rational design of catalysts led to several efficient systems. The best catalysts reported so far, are ruthenium(n) complexes with chiral diamine and aminoalcohol ligands. In previous studies, the ruthenium complex of NH-benzyl-(1R,2S)-(-)-norephedrine proved to be an excellent catalyst for the reduction of acetophenone showing up to 95% ee at a high conversion.

The utilisation of immobilised catalysts in the asymmetric transfer hydrogenation can provide a significant improvement over the homogeneous process. It enables the long term use of expensive catalyst and provides a clean and straightforward separation of the product. More importantly, the transfer hydrogenation reaction in isopropanol benefits from being performed in a continuous process as it requires a low substrate concentration to obtain high enantioselectivity. Hence, the space-time-yield can be increased on using a continuous flow reactor. Examples of immobilised asymmetric transfer hydrogenation catalysts, however, are still rare. Recently a few interesting approaches were reported concerning the anchoring of transfer hydrogenation catalysts onto organic supports. Although high ee’s were obtained, the applicability of these immobilised systems is limited due to swelling of the support which resulted in a low activity and a poor recyclability. The immobilisation onto inorganic supports could improve the catalyst performance in this respect. To the best of our knowledge only two examples have been reported in literature so far concerning a silica immobilised asymmetric transfer hydrogenation catalyst. Lemaire et al. reported a catalyst “non-covalently” linked to the silica support showing a good initial performance in a continuous flow reactor. This system suffered from deactivation of the catalyst due to catalyst destruction or leaching of catalytically active material. A covalently anchored catalyst based on a rhodium complex of gamma-silylated amines was reported by Moreau et al. This system was found to be extremely slow and the ee’s ranged from 25 to 80%. The recovery or recycling of this catalyst was not reported. Here we report the synthesis of asymmetric transfer hydrogenation catalysts.
on silica and the use of these systems in batch and flow reactors. Furthermore we recognised that one of our synthetic strategies towards immobilised transfer hydrogenation catalysts could be applied expeditiously in the solid phase synthesis of novel transfer hydrogenation catalysts. This is shown by the synthesis and subsequent testing of a small series of new asymmetric transfer hydrogenation catalysts on silica. We will show that silica is a valuable support for solid phase synthesis, catalysis and catalyst recycling.

7.2 Results and discussion

7.2.1 Ligand immobilisation
A novel ligand, NH-3-(trimethoxysilyl)benzyl-(1R,2S)-norephedrine (3), was synthesised via an N-alkylation of (1R,2S)-norephedrine (1) (Chart 7.1) by p-(chloromethyl)phenyltrimethoxysilane using Na₂CO₃ as a base (Scheme 7.1-A). This ligand is the trialkoxyfunctionalised analogue of the N-benzylated-norephedrine ligand (2) that gave high ee's in our previous studies in the homogeneously catalysed reaction. Ru(3) in solution also gave high ee's at a high conversion (see section 7.2.2). Ligand 3 was immobilised on silica by refluxing a toluene suspension of silica and 3 for 18 hours followed by several washings with toluene to obtain 4. The support was modified by reacting 4 with a large excess of dimethyldimethoxysilane to form 4a. As a result the silanol sites of the silica support are transformed into alkylsilyl sites.

Chart 7.1
Alternatively, the solid phase synthesis route was investigated (Scheme 7.1-B). Via this method, the silica support was first functionalized with para-benzyl chloride sites. In the next step the silanol sites were modified to alkylsilanes using an excess of dichlorodimethylsilane in the presence of triethylamine. In the final step the ligand synthesis of 4b was completed by coupling of the aminoalcohol to the para-benzyl chloride sites.

Catalytic experiments were performed with freshly in-situ prepared ruthenium-amino alcohol complexes using [{RuCl₂(η⁶-p-cymene)}] as the Ruᴵᴵ precursor.


### 7.2.2 Catalyst studies

The catalytic performance of the silica immobilised systems were initially examined in batch experiments using suspensions containing 400 mg silica loaded with 0.06 mmol NH-3-(trimethoxysilyl)benzyl-(1R,2S)-norephedrine and 0.006 mmol (p-cymene)ruthenium(II)
chloride dimer in 10 ml dry propan-2-ol containing 0.01 mmol tBuOK and 1 mmol acetophenone.\textsuperscript{10} The ruthenium catalysed asymmetric transfer hydrogenation of acetophenone (Table 7.1, entry 3) resulted in ee’s up to 88% at 95% conversion.

\textit{Table 7.1: Results from the transfer hydrogenation of acetophenone in a batch slurry reaction}\textsuperscript{a}

| Entry | Catalyst & \(
\text{cycle}\) | Conversion\textsuperscript{b} (%) | Ee alcohol\textsuperscript{c} (%) | Ru-leaching\textsuperscript{d} (%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ru(2)</td>
<td>88\textsuperscript{c}</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ru(3) homogeneous</td>
<td>81</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ru(4)</td>
<td>95\textsuperscript{a}</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ru(silica)</td>
<td>0.2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ru(1)/silica</td>
<td>4</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ru(4) {1}</td>
<td>38</td>
<td>88</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>Ru(4) {2}</td>
<td>33</td>
<td>88</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Ru(4) {3}</td>
<td>27</td>
<td>88</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>Ru(4a) {1}</td>
<td>25</td>
<td>88</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>Ru(4a) {2}</td>
<td>27</td>
<td>88</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>Ru(4a) {3}</td>
<td>20</td>
<td>87</td>
<td>&lt;1</td>
</tr>
<tr>
<td>12</td>
<td>Ru(4b) {1}</td>
<td>51</td>
<td>85</td>
<td>11</td>
</tr>
<tr>
<td>13</td>
<td>Ru(4b) {2}</td>
<td>43</td>
<td>86</td>
<td>6</td>
</tr>
<tr>
<td>14</td>
<td>Ru(4b) {3}</td>
<td>34</td>
<td>92</td>
<td>3</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The reaction was carried out with \(6\times10^{-6}\) mol \([\text{RuCl}_2(\text{p-cymene})]_2\) and 400 mg silica, containing \(6\times10^{-4}\) mol ligand at room temperature in 10 ml isopropanol containing 0.1 M acetophenone and 0.01 M tBuOK. \textsuperscript{b} Conversions after 2 hours, determined by means of GLC analysis. \textsuperscript{c} Determined by means of GLC analysis using a chiral cycloSil-B column. \textsuperscript{d} Determined by means of Atomic Emission Spectroscopy, percentage of the total amount of Ru charged. \textsuperscript{e} Data taken from ref.5. \textsuperscript{f} Conversion after 1 hour. \textsuperscript{g} Conversion after 24 hours.

The catalyst is remarkably fast; a conversion of 20% was obtained after 1 hour, which is only 2 to 3 times as slow as the homogeneous analogue under the same conditions. Monitoring the reaction showed that initially the reaction rate is almost independent of the substrate concentration (Figure 7.1). At higher conversions the rate becomes dependent of the substrate concentration which was also observed for the homogeneously catalysed analogue.\textsuperscript{5} A blank reaction, in the absence of amino-alcohol ligand, was performed to investigate the effect of the inorganic support on the catalytic reaction. On mixing \([\{\text{RuCl}_2(\text{n}^6-\text{p-cymene})]\) and silica without any ligand the Ru\textsuperscript{II} precursor adsorbs on the silica as was concluded from the color change of the silica from white to orange. The reactivity of these Ru-species, however, is negligible (Table 7.1, entry 4). The influence of acidic silanol sites of the support on the catalysis was further investigated by comparing the result of Ru(4) with that of Ru(4a).
It was found that these sites did not influence the stereoselectivity of the catalytic reaction (Table 7.1, entry 6 and 9). This again shows that the reaction is not catalysed by unligated Ru\textsuperscript{II} species, adsorbed or ionically bonded to the silica. The catalytic activity was found to be somewhat lower for Ru(4a) than for Ru(4). We ascribe this to the poisoning of part of the immobilised aminoalcohol sites during the pre-modification procedure. Using the alternatively prepared Ru(4b) this is effectively circumvented since the aminoalcohol ligand is introduced after the modification procedure. We indeed found that the activity of Ru(4b) is higher than that of Ru(4a) (Table 7.1, entries 9 and 12). The conversion after 2 hours increases from 25% for Ru(4a) to 51% for Ru(4b). More importantly, Ru(4b) was also more active than the catalyst anchored on the unmodified silica Ru(4). The results indicate that non-modified silica does affect the catalyst by adsorbing part of the Ru\textsuperscript{II}, hence disturbing the formation of catalytically active sites. This is effectively suppressed by pre-modification of the silica with alkylsilane groups via method B.

To show the importance of the benzyl chloride linker in tethering the amino-alcohol to the surface, a catalytic experiment was performed using a mixture of 1, [{RuCl\textsubscript{2}(\textcyr{6}cymene)}] and silica. After thoroughly washing the reaction mixture it showed a poor catalytic activity (Table 7.1, entry 5). From this experiment it was concluded that immobilisation is not effective without benzylechloide linker.

### 7.2.3 Catalyst recovery

The recoverability of the catalyst was investigated by performing subsequent batch-wise experiments (Table 7.1). In three consecutive catalytic runs the enantioselectivity remained the same (88%) or even increased (from 85 to 92%). By means of Atomic Emission Spectroscopy it was found that in the first catalytic runs ruthenium leached from the catalyst system more (5 to 10 percent) than in subsequent runs (1 or 2 percent).
The catalyst showed a very constant, steady performance within a catalytic run up to high conversions (Figure 7.1). A small decrease in catalyst activity was found in successive runs. This is probably due to slow decomposition of the catalyst caused by the recycling routine, since color changes (from purple-red to orange-yellow) were observed upon the addition of a fresh batch of reaction mixture. This can also account for the observed ruthenium leaching.  

The performance of Ru(4b) in a continuous flow reactor was investigated in order to obtain a more robust system for the asymmetric reduction of ketones with an immediate and straightforward separation of the product from the catalyst. To this end a small column equipped with a glass-filter was charged with freshly prepared Ru(4b) (1 g catalyst containing 10-20 mg ruthenium precursor). A homogeneous isopropanol solution containing 0.01 M potassium-tert-butoxyde (tBuOK) and 0.1 M acetophenone was allowed to pass through the catalyst bed. The catalyst performance was investigated at flow-rates in the range of 120-1400 μl/h (Figure 7.2 and Table 7.2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow-rate (μl/h)</th>
<th>Conversion (%)</th>
<th>Ee alcohol (%)</th>
<th>Ru-leaching (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>95</td>
<td>63</td>
<td>Nd</td>
</tr>
<tr>
<td>2</td>
<td>240</td>
<td>95</td>
<td>77</td>
<td>Nd</td>
</tr>
<tr>
<td>3</td>
<td>350</td>
<td>95</td>
<td>83</td>
<td>Nd</td>
</tr>
<tr>
<td>4</td>
<td>700</td>
<td>95</td>
<td>89</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>1400</td>
<td>81</td>
<td>90</td>
<td>&lt;1</td>
</tr>
<tr>
<td>6</td>
<td>1400</td>
<td>95</td>
<td>89</td>
<td>&lt;1</td>
</tr>
<tr>
<td>7</td>
<td>1400</td>
<td>95</td>
<td>89</td>
<td>&lt;1</td>
</tr>
<tr>
<td>8</td>
<td>1400</td>
<td>95</td>
<td>90</td>
<td>&lt;1</td>
</tr>
<tr>
<td>9</td>
<td>1400</td>
<td>53</td>
<td>88</td>
<td>&lt;1</td>
</tr>
<tr>
<td>10</td>
<td>1400</td>
<td>29</td>
<td>88</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

The reactions were carried out at room temperature using 1 g silica, containing ~ 0.35 mmol ligand and 0.0143 mmol [RuCl₂(p-cymene)]₂ and an eluent of isopropanol, containing 0.01 M tBuOK and 0.1 M acetophenone. Conversions are average numbers of 2-11 hours continuous product stream, determined each 30 or 60 minutes by means of GLC analysis. Average numbers of 2-11 hours stabilised product stream determined by means of GLC analysis using a chiral cycloSil-B column. Determined by means of Atomic Emission Spectroscopy, percentage of the total amount of Ru per h. [RuCl₂(p-cymene)]₂ charging = 0.0324 mmol. As entry 6 but c[tBuOK] = 0.005 M. As entry 6 but in the absence of tBuOK. As entry 8 but [acetophenone] = 0.4 M. As entry 8 but [acetophenone] = 0.8 M. As entry 8 but [acetophenone] = 0.8 M.

As expected, the catalyst performance is strongly dependent on the flow-rate. At a flow-rate of 120 μl/h the observed ee of the product is 63% at 95% conversion, whereas at flow-rates higher than 700 μl/h the product is formed in 89% ee. At a lower flow-rate and...
hence a longer residence time of the product, the equilibration becomes significant. This results in a decrease in the ee because the reverse reaction is faster for the product formed in enantiomeric excess in the reduction reaction. Under the reaction conditions used, the catalyst performed best at a flow-rate of 700 μl/h (89% ee at 95% conversion).

The influence of the base concentration was found to be small. On reducing the amount of tBuOK in the substrate mixture to 0.005 M there was no change in catalyst performance (Table 7.2, entry 7). In the complete absence of base it was found that the catalyst performed optimally, with 90% ee at 95% conversion (Table 7.2, entry 8). The results clearly show, in accordance to Noyori’s work on ruthenium diamine catalysts, that the base is only required for the formation of the active transfer hydrogenation complex. This feature is particularly interesting in the use of our continuous flow system since the chiral product is immediately obtained free from base and catalyst.

The influence of the substrate concentration on the ee was investigated using acetophenone concentrations ranging from 0.1 to 0.8 M (Table 7.2, entry 6, 9 and 10). The enantioselectivity remained unchanged in this range (89 ± 1%) and the conversion at 0.8 M acetophenone is still 29%. The application of the immobilised catalyst in a continuous set up resulted in interestingly high space-time-yields. Depending on the acetophenone concentration it was between 15 (entry 8) and 39 g/l/h (entry 10) whereas for the homogeneous analogue it was estimated at 5.7 g/l/h.
Solid phase synthesis of homogeneous ruthenium catalysts...

The immobilised ruthenium catalyst applied in the continuous flow system is remarkably stable. In order to study the difference in stability we performed several experiments to compare the flow system with the homogeneously catalyzed reaction. At 0.1 M acetophenone it was found that the homogeneous system Ru(2) was deactivated after 95 percent conversion of the first batch of substrate (Figure 7.3). In a second experiment at a higher concentration (0.8 M) we observed complete catalyst deactivation at 33 percent conversion. Typically catalyst deactivation occurred after 20 hours reaction time.

In the continuous flow reactor the catalyst is surprisingly more stable; both conversion and enantioselectivity remained the same for days (Figure 7.4). The reaction was monitored at 1 hour intervals over a period of 11 hours and the product yield was found to be stable with a constant enantiomeric excess of 90% (Figure 7.4-A). In order to study the catalyst stability the reaction was monitored for a longer period (Figure 7.4-B). A small decrease in activity of the catalyst was observed after 1 week only. Within 7 days no notable changes were observed in both product yield and enantioselectivity of the catalyst, while the catalyst was still active after three weeks of continuous use. The chiral product was obtained free from polluting base and ruthenium, which was substantiated by AES experiments (leaching less then 1% of the ruthenium charged during 3-11 hours of catalysis). The remarkable difference in catalyst stability between Ru(2) in solution and the silica immobilised analogue is suggested to be an effect of site isolation.\textsuperscript{18,19,20} Clear evidence supporting the view that the polymer matrix

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7_3.png}
\caption{Catalyst performance of Ru(2) in the homogeneous transfer hydrogenation of two subsequent batches of acetophenone (The reaction was carried out at 20 °C using 0.01225 mmol [RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}, 0.0313 mmol 2, 0.075 mmol tBuOK and 5 mmol acetophenone in 50 ml propane-2-ol).}
\end{figure}
maintains the isolation of active catalytic sites has been reported in the reduction of olefins using polymer anchored titanocene catalysts.\textsuperscript{21} Also in the enantioselective hydrogenation using immobilised rhodium and iridium catalysts, site isolation was shown to play an important role.\textsuperscript{22} It was evidenced that, via immobilisation, the catalytic sites were prevented from irreversible clustering towards catalytically inactive species. In the enantioselective reduction of 3-oxobutanoate using [RuCl((S)-binap)(arene)]Cl the formation of ruthenium trimers were reported to give complete catalyst deactivation.\textsuperscript{23,24}

![Catalyst performance of Ru(4b) in a continuous flow reactor for the hydrogen transfer reduction of acetophenone. A: Detailed monitoring of the product yield per hour and enantiomeric excess of the product flow. B: Study of the long term catalyst stability (details in experimental section).](image)

Since the Ru(2) catalysed reduction proceeds under comparable conditions we suggest that ruthenium clustering is also responsible for the observed catalyst deactivation in our case. The
difference in catalyst stability between Ru(2) and the immobilised analogue is therefore likely to be a results of an effective site isolation.

7.2.4 Catalyst screening
Although some excellent catalysts for the transfer hydrogenation of acetophenone have been reported, there is still a challenge to find selective catalysts for functionalized substrates of industrial interest. Solid phase synthesis and rapid screening techniques25 are being applied increasingly to speed up the search for novel catalysts.26 Silica has not been reported as a support for solid phase synthesis of homogeneous catalysts thus far, whereas inorganic materials already have proven to be very useful in libraries of heterogeneous catalysis and in combinatorial material science.27

Table 7.3: Results from the screening of catalysts Ru(4b) to Ru(9) in the transfer hydrogenation of acetophenone in a batch slurry reactor

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion (%)</th>
<th>Ee alcohol (%)</th>
<th>Config</th>
</tr>
</thead>
<tbody>
<tr>
<td>1{1}</td>
<td>Ru(4b)</td>
<td>51</td>
<td>85 (R)</td>
<td></td>
</tr>
<tr>
<td>2{2}</td>
<td>Ru(4b)</td>
<td>43</td>
<td>86 (R)</td>
<td></td>
</tr>
<tr>
<td>3{1}</td>
<td>Ru(5)</td>
<td>9</td>
<td>58 (S)</td>
<td></td>
</tr>
<tr>
<td>4{2}</td>
<td>Ru(5)</td>
<td>5</td>
<td>49 (S)</td>
<td></td>
</tr>
<tr>
<td>5{1}</td>
<td>Ru(6)</td>
<td>48</td>
<td>27 (R)</td>
<td></td>
</tr>
<tr>
<td>6{2}</td>
<td>Ru(6)</td>
<td>30</td>
<td>27 (R)</td>
<td></td>
</tr>
<tr>
<td>7{1}</td>
<td>Ru(7)</td>
<td>49</td>
<td>32 (S)</td>
<td></td>
</tr>
<tr>
<td>8{2}</td>
<td>Ru(7)</td>
<td>73</td>
<td>29 (S)</td>
<td></td>
</tr>
<tr>
<td>9{1}</td>
<td>Ru(8)</td>
<td>8</td>
<td>5 (R)</td>
<td></td>
</tr>
<tr>
<td>10{2}</td>
<td>Ru(8)</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>11{1}</td>
<td>Ru(9)</td>
<td>83</td>
<td>13 (R)</td>
<td></td>
</tr>
<tr>
<td>12{2}</td>
<td>Ru(9)</td>
<td>52</td>
<td>19 (R)</td>
<td></td>
</tr>
</tbody>
</table>

Table 7.3: Results from the screening of catalysts Ru(4b) to Ru(9) in the transfer hydrogenation of acetophenone in a batch slurry reactor

Table 7.3: Results from the screening of catalysts Ru(4b) to Ru(9) in the transfer hydrogenation of acetophenone in a batch slurry reactor

a The reaction was carried out with $4 \times 10^{-5}$ mol [RuCl$_2$(p-cymene)]$_2$ and 250 mg silica, containing $3.5 \times 10^{-5}$ mol ligand at room temperature in 10 ml isopropanol containing 0.1 M acetophenone and 0.01 M tBuOK. b Conversions after 2 hours, determined by means of GLC analysis. c Determined by means of GLC analysis using a chiral cycloSil-B column.

The solid phase synthesis strategy B (Scheme 7.1), which proved to be a viable procedure towards Ru(4b), facilitates the development of series of potentially interesting silica immobilised catalysts. This is demonstrated by the straightforward synthesis (and screening) of a small series of immobilised chiral ruthenium complexes. The immobilised NH-benzylated ligands were derived from five different aminoalcohols: (1R,2S)-
norephedrine, (1S,2R)-(+) 2 amino-1,2-diphenyl ethanol, (R)-(−)-2- amino-2-phenyl ethanol, (S)-(−)-2- amino-3-methyl-1-butanol, (R)-(−)-2- amino-3-phenyl-1-propanol and a diamine: (1R,2R)-(−)-1,2-diphenylethylenediamine (Chart 7.1). These systems were (simultaneously) prepared in separate vials and applied in combination with ruthenium in the transfer hydrogenation of acetophenone using a batch-wise process.

All ruthenium-aminoalcohol complexes showed a good activity and significant enantioselectivity in the transfer-hydrogenation of acetophenone whereas the diamine 8 hardly induced any ee (Table 7.3). Surprisingly, catalyst Ru(5), giving 58% ee, was far more selective than the homogeneous analogue for which an ee of 20% was reported. We suggest that a higher catalyst stability due to immobilisation can give rise to an improvement in catalyst selectivity, especially for complexes that are intrinsically less stable due to steric restrictions. The other catalysts performed as expected, based on previous detailed studies on substituent effects of homogeneous systems. All Ru(n)aminoalcohol containing catalysts could be used in a second catalyst run generally showing approximately the same ee (Table 7.3) at lower conversions.

7.3 Conclusion

We have shown that silica is a valuable support for enantioselective transfer hydrogenation catalysts. Owing to the properties (chemical and physical) of the support, the immobilised catalysts are only slightly less active than the homogeneous analogue. The silica surface was found to influence the catalyst efficiency as it adsorbs inactive ruthenium-species. This was effectively suppressed by modifying the silica with alkylsilane groups.

The silica-immobilised ruthenium-complex of NH-3-(trimethoxysilyl)benzyl-(1S,2S)-norephedrine complex showed a good performance in successive runs in the asymmetric transfer hydrogenation of acetophenone. An even better performance was found for this catalyst in a continuous flow reactor. Under optimised conditions this process converts a constant flow of acetophenone into phenylethanol in a 95% yield and 90% ee. The performance of this system is virtually unaltered for 1 week showing no significant ruthenium leaching. The high stability of this system is in contrast with that of the homogeneous analogue. In this respect effective site isolation due to the immobilisation of the ruthenium catalyst was found to be of great importance.

The flow system is potentially interesting for applications in the synthesis of fine chemicals; the facile and immediate separation of the catalyst from the product, which is obtained free from polluting ruthenium and base, is more convenient than conventional separation methods. It also requires much smaller equipment than the homogeneous analogue since the reaction is concentration restricted.
The solid phase synthesis strategy, in which the amino-alcohol ligand is introduced in the final step of the synthesis, enables the unique integration of a rapid catalyst synthesis method with the application of these systems in subsequent batch reactions or a continuous flow reactor. Any successful “hit” in the screening experiment can subsequently be tested in a continuous flow reactor on a range of different substrates. In view of the rapid development in combinatorial approaches in catalysis we believe that the strategy to use silica supports for solid phase synthesis in combination with catalyst immobilisation is very promising.

7.4 Experimental section

General information
All reactions and manipulations were routinely performed under an argon or nitrogen atmosphere using standard Schlenk techniques. Acetonitrile, propan-2-ol, methanol and triethylamine were distilled from CaH₂, THF and toluene were distilled from Na prior to use. Acetophenone was degassed and stored over molisieves. All other reagents and chemicals were reagent grade and were used as received from commercial suppliers. Column chromatography was performed using silica 60, 70-230 mesh ASTM (Merck). ¹H NMR spectra were recorded on a Varian AMX 300 spectrometer and ¹³C NMR spectra were recorded on a Varian Inova 500 spectrometer. Chemical shifts are in ppm relative to TMS. Mass spectra were recorded on a JEOL JMS SX/SX102A four section mass spectrometer, coupled to a JEOL MS-MP7000 data system. Micro analyses (C, H, N) were performed on an Elementar Vario EL apparatus (Foss Electric). Gas chromatography was performed using a Carlo Erba GC Vega 2 instrument, 25 m column: CycloSil-B (chiral) and a Carlo Erba HRGC Mega 2 instrument, 25 m column: BPX 35 (SGE) (nonchiral).

Synthesis of NH-3-(trimethoxysilyl)benzyl-(1R,2S)-norephedrine (3)
At 0°C, (448 mg, 1.85 mmol) p-(chloromethyl)phenyl-trimethoxysilane was added to a suspension of (250 mg, 1.65 mmol) norephedrine and (192 mg, 1.85 mmol) Na₂CO₃ in acetonitril (20 ml). The white turbid suspension was slowly heated and stirrer for 18 h at 60°C. The reaction mixture was filtered of over a path of Celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica 60, eluent: ethyl acetate) and obtained as a colorless oil. Yield 19% (113 mg). (The ligand was stored under an inert atmosphere at -20°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.63 + 7.34 (ab, ³J = 8.1 Hz, 4H; ArH), 7.29-7.24 (m, 5H; ArH), 4.80 (d, ³J = 3.0 Hz, 1H; CHOH), 3.89 (s, 2H; CH₂), 3.61 (s, 9H; OCH₃), 2.99 (dq, ³J = 3.9 Hz, ²J = 2.7 Hz, 1H; CHNH), 0.85 (d, ³J = 6.6 Hz, 3H; CH₃). ¹³C NMR (500 MHz, CDCl₃): δ = 142.85 (Ç-ÇH₂), 141.34 (Ç-CHOH), 135.20 (SiC-ÇH), 128.24 (SiC), 128.20 (CHOH-Ç-ÇH), 127.82 (CHOH-Ç-ÇH), 127.23 (CH-Ç-ÇH), 126.23 (CH₂-Ç-ÇH), 73.26 (CHOH), 57.89 (Ç-CH₂), 51.34 (ÇH₂), 93
Chapter 7

51.00 (OCH$_3$), 14.86 (CH$_3$). Exact Mass (FAB): 362.1787 (calcd. C$_{10}$H$_{25}$O$_4$NSi: 362.1787). C$_{10}$H$_{27}$O$_4$NSi: calcd. C 63.13, H 7.53, N 3.87; found C 62.83, H 7.11, N 3.73.

Immobilisation procedures

(4) (1 g) Degassed and predried silica gel 60 was slurried in a solution of (50 mg, 0.14 mmol) NH-3-(trimethoxysilyl)benzyl-(1R,2S)-norephedrine (3) in toluene (20 ml). The suspension was stirred for 18 h at 100°C. The silica was washed with 3 portions of toluene and dried at reduced pressure.

(4a) Dimethyldimethoxysilane (1 ml) was added to a suspension of 4 (500 mg) in toluene (10 ml). The suspension was stirred for 18 h at 100°C and the silica was washed with 3 portions of toluene and dried at reduced pressure.

(4b) Degassed silica 60 (4 g) was suspended to a solution of (350 mg, 1.42 mmol)/p-(chloromethyl)phenyl-trimethoxysilane in toluene (20 ml). After the slurry was stirrer for 2.5 h at 80°C the toluene was removed and the silica was subsequently washed with 3 portions of toluene. Then toluene (30 ml), triethylamine (10 ml) were added followed by the dropwise addition of dichlorodimethylsilane (5 ml). A white precipitate was immediately formed. After the reaction mixture was stirred for 18 h at room temperature the crude product was collected on a filter and subsequently washed with 3 portions of THF (10 ml), 3 portions of MeOH (10 ml) and with 3 portions of THF (10 ml) and finally dried under reduced pressure.

The above described benzylchloride functionalized silica (2 g) was suspended in a mixture of norephedrine (200 mg, 1.32 mmol) and triethylamine (2 ml) in acetonitriil (30 ml). The slurry was stirrer for 18 h at 70°C. After the liquids were removed from the reaction mixture, 4b was washed with 2 portions of MeOH (10 ml) and 2 portions of THF (10 ml). 4b was dried under reduced pressure and was stored at -20°C under an inert atmosphere.

Catalysis procedure

In a typical catalysis experiment a suspension of (p-cymene)ruthenium(ii) chloride dimer (3.5 mg, 0.006 mmol) and silica (400 mg) containing NH-3-(trimethoxysilyl)benzyl-(1R,2S)-norephedrine (0.06 mmol) in dry propan-2-ol (7 ml) was heated at 60°C for 30 min. After cooling the deep red reaction mixture to 0°C, 0.1M tBuOK in propan-2-ol (3 ml) and acetophenone (0.1 ml) were added. The resulting purple-red suspension was stirrer for 2 hours at room temperature. The liquids were subsequently removed from the catalyst by means of a syringe. Then propan-2-ol (9 ml), 0.1M tBuOK (1 ml) and acetophenone (0.1 ml) were added to the catalyst. Catalytic reactions were typically run for 2 h and recycled two times.

Continuous flow reactor

a mixture of (20 mg, 0.033 mmol) [{RuCl$_2$(η$^6$-p-cymene)}] and 4b (1 g, containing ~0.35 mmol NH-benzylated ligand) were slurried in propan-2-ol (20 ml) and heated at 60°C for 30
Solid phase synthesis of homogeneous ruthenium catalysts...

After the resulting red mixture was cooled down to 0°C, 0.1M tBuOK in propan-2-ol (4 ml) and acetophenone (0.3 ml) were added. The resulting purple-red mixture was stirred at room temperature until a deep red silica in a light-yellow solution was obtained (approximately 20 min). The flow reactor (having a diameter of 0.7 cm) was loaded with the reaction mixture using a glass elbow (forming a catalyst bed of ~1.5 cm high). The catalyst bed was allowed to settle and the reaction mixture on top was gently forced through the bed using a small over-pressure of argon or nitrogen. A fresh reaction mixture of propan-2-ol (50 ml) containing 0.1 M acetophenone and 0.01 M tBuOK was allowed to pass the catalyst bed. Samples were taken each 30 or 60 minutes and analyzed on GC. Experiments were started when product streams were stabilised after the initiation period (approximately 1 hour). The flow-rate of the reactor was adjusted with the over-pressure of argon or nitrogen. Overnight standing was applied by maintaining a very small argon overpressure and a low flow-rate.

Catalyst screening

The series of catalysts in the screening experiment were synthesised in a procedure similar to the synthesis of 4b. 5 To 9 were prepared on stirring slurries of p-benzylchloride on silica (250 mg), aminoalcohol or diamine (25 mg), triethylamine (250 µl) in acetonitrile (5 ml) for 18 h at 60°C. After removal of the solvent all samples were washed with successively: 2 portions of methanol (4 ml), 2 portions of THF (4 ml) and propan-2-ol (4 ml). The samples were charged with (2.5 mg, 4*10⁻⁶ mol) [{RuCl₂(η⁶-p-cymene)}] and propan-2-ol (8 ml) and stirrer for 30 min at 60°C. After cooling to room temperature 1 ml of a mixture containing 0.1M tBuOK and 0.1 ml acetophenone were added. All reactions were sampled after 2 h and fresh substrate solutions were added after removal of the liquid layer.

7.5 References and notes

Chapter 7


10 At a ligand to metal ratio close to 1 the catalyst becomes slightly less efficient.

11 Small amounts of water also don’t effect the catalyst performance.

12 This poisoning was clearly observed by means of NMR and TLC techniques. A slow decomposition takes place of NH-benzylated norephedrine on refluxing in toluene in the presence of dimethyldimethoxysilane.


14 Contact with air is avoided accurately as it gives rise to a rapid decomposition of the catalyst.


17 Flowreactor: \( \frac{1400 \, \mu L/h \times 0.8 \, (mol/l) \times 0.29 \times 120 \, (Fw) / 1 \times 10^7 \, (l) = 38976 \, mg/l/h. \) Homogeneous: \( \{0.1 \, (mol/l) \times 120 \, (g/mol) \times 1000\} / 2 \, (h) = 5700 \, mg/l/h. \)


29 A comparable effect was previously reported in ref 9. In this reference, however, a comparison was made between the homogeneous catalyzed reaction at 95 percent conversion (after 5 days reaction time) and the heterogenised analogue at lower conversion. At 95 percent conversion the reverse reaction becomes significant and will be favored for the enantiomer formed in excess, hereby decreasing the overall ee.