Asymmetric transfer hydrogenation of ketones
Petra, D.G.I.

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.
Chapter 6

IR spectroscopy as a high throughput screening technique in the enantioselective transfer hydrogenation of ketones

Daniëlle G.I. Petra, Joost N.H. Reek, Paul C.J. Kamer, Hans E. Schoemaker, Piet W.N.M. van Leeuwen

Institute of Molecular Chemistry, University of Amsterdam, Amsterdam, The Netherlands
Abstract

A new high throughput screening technique was developed for the ruthenium(II)-amino alcohol catalysed asymmetric transfer hydrogenation of ketones. The reverse reaction was used in order to determine the difference in dehydrogenation rate between both (R)- and (S)-phenyl ethanol and (R)- and (S)-2-hexanol, which were applied separately as hydrogen donors. The difference in de-hydrogenation rate was used to determine the enantioselectivity of the reaction. The performance of transfer hydrogenation catalysts was determined by monitoring the reaction rate of the reduction of various ketones and the simultaneous oxidation of (R)- versus (S)-secondary alcohol. Infrared spectroscopy was used as a rapid screening technique which will allow the determination of the enantioselectivity of at least 120 samples per hour.
6.1 Introduction

Asymmetric catalysis started to develop in the early sixties and has become a useful method for the synthesis of enantiopure compounds. Transition metal catalysis is one important route to obtain asymmetric products of high purity.\(^1\) Much effort has been devoted to asymmetric synthesis catalysed by transition metals. In asymmetric homogeneous catalysis the metal ion is stabilised by an organic ligand bearing the chiral information and creating a chiral environment in close proximity to the active site of the catalyst. Hundreds of ligands have been prepared giving rise to enantioselectivities in the range of 90-99%.\(^1,\)\(^2\) In spite of such impressive advances the reaction conditions, the chemoselectivity and enantioselectivity of an asymmetric reaction performed on functionalised substrates can still be improved. In order to realise such goals it is necessary to develop new chiral ligands. Therefore ligand tuning has become a very important tool in catalysis. Ligand synthesis is a very time consuming process, since generally many ligands have to be synthesised before the catalyst performance meets the demands. The principles of combinatorial chemistry can be applied to the synthesis of modified analogues of chiral auxiliaries.\(^3\) However, it is necessary to separate the chiral ligands before using them, since a reaction performed with a mixture of homogeneous does not generate information about the individual catalyst. Therefore, the strategy of parallel screening is necessary.

So far the application of combinatorial chemistry in asymmetric metal catalysis has mainly focussed on the high throughput screening aspects.\(^4\) Recently, Reetz \textit{et al.} reported the development of new screening methods for enantioselective catalysis, based on UV/VIS spectroscopy, IR-thermography and electrospray ionisation mass spectrometry (ESI-MS), respectively.\(^5\)\(^-\)\(^8\) Using the latter technique, the enantiomeric excess of up to 1000 isotopically labelled reaction mixtures could be determined per day. Here, a different technique for the enantioselective transfer hydrogenation of ketones based on IR-spectroscopy is presented.

Asymmetric transfer hydrogenation has been applied successfully to aryl-alkyl ketones.\(^9\) However, substrates of industrial interest carry functional groups that, in general, can have a dramatic effect on both the activity and the selectivity of the...
Chapter 6

catalyst. Only a few examples are known of the enantioselective transfer hydrogenation of functionalised ketones, dialkyl ketones and imines that may lead to useful intermediates for the fine-chemical industries. It is necessary to tune catalysts to the transfer hydrogenation of these substrates. In this view a rapid screening method would be very useful. Furthermore, unlike asymmetric hydrogenation, the reaction does not require high-pressure equipment, since an organic hydrogen donor, often 2-propanol, is used as the reducing agent. Therefore, the reaction is very suitable for high throughput screening techniques.

An inherent problem of this potentially useful asymmetric catalytic reaction is the reversibility of the reaction, owing to the structural similarities between 2-propanol and the product alcohol. Even if the reaction proceeds with excellent enantiofacial differentiation, the equilibration often reduces the enantiomeric purity of the alcoholic products. When the reduction of acetophenone occurs with an enantiofacial differentiation of $k_{R} / k_{S} \approx 100$, the dehydrogenation of (R)-phenyl ethanol is ca. 100 times faster than that of (S)-phenyl ethanol. To minimise this unfavourable reaction in 2-propanol, the transfer hydrogenation reaction must be performed with a substrate concentration of up to 0.3 M, in order to slow down the reverse process.

The reverse reaction can also be used in a beneficial way, since the difference in dehydrogenation rate between the (R)- and the (S)-alcohol is a measure of the enantioselectivity of the reaction. By monitoring the reaction rate of the reduction of ketone and the oxidation of secondary alcohol, using (R)-alcohol and (S)-alcohol separately as hydrogen donors, the performance of transfer hydrogenation catalysts can be determined. So far, the catalyst performance and enantiomeric excesses of the product alcohols have almost always been determined using chiral HPLC or chiral GLC techniques. These methods are limited in the amount of samples that can be measured per hour, since the retention times of the products are around 15 minutes or more. In view of this, new techniques in rapid screening of the generated samples would be very useful.

The reduction of e.g. acetone and the simultaneous oxidation of acetophenone can easily be monitored in time by infrared spectroscopy. Using an infrared
spectrophotometer equipped with an autosampler, at least 120 samples per hour can be screened in a 96-well titreplate via reflection techniques.\(^\text{16}\)

### 6.2 Results and Discussion

Ruthenium(II) catalysed transfer hydrogenation reactions were carried out using amino alcohols as the ligands. Reactions were studied using the \((p\text{-cymene)})\text{ruthenium(II)}\ chloride dimer as a catalyst precursor and two different amino alcohols as the ligands, \(i.e\). (\(1R, 2S\))-ephedrine (1) and (\(R\))-phenylglycinol (2). In a typical catalysis experiment a reaction mixture of ketone (0.1M in alcohol), a stock solution of the \textit{in situ} generated catalyst from \([\text{RuCl}_2(p\text{-cymene})]_2\) (0.5 mol\%) and the amino alcohol ligand (1 mol\%) in dichloromethane, and \(t\text{BuOK}\) (2.5 mol\%) was run at room temperature under argon in the alcoholic solution. The conversions and enantioselectivities were monitored in time by infrared spectroscopy and/or GLC analysis. When the former technique was used the reaction was run in an IR cell under argon.

![Chemical structures](image)

The reduction of acetophenone (3) in 2-propanol was chosen as the model reaction (see Scheme 6.1, Table 6.1). The use of (\(1R, 2S\))-ephedrine and (\(R\))-phenylglycinol has been investigated previously in the ruthenium(II) catalysed transfer hydrogenation of acetophenone and the results are depicted in Table 6.1.\(^\text{17-19}\) The use of (\(1R, 2S\))-ephedrine gives rise to an enantioselectivity of 89\%, whereas the use of (\(R\)-
phenylglycinol as the amino alcohol ligand results in an enantioselectivity of 24% (entries 1 and 2).

\[ \text{Scheme 6.1} \]

Figure 6.1 shows the typical IR spectra of the reaction (entry 1, Table 6.1) monitored in time. The carbonyl absorptions of the aryl-alkyl ketones are observed at a different wavenumber (cm\(^{-1}\)) than the absorptions of the dialkyl ketones. Reduction of acetophenone is observed by the decreasing carbonyl signal at 1682 cm\(^{-1}\). Formation of acetone, via oxidation of the hydrogen donor, is shown by the increasing carbonyl signal at 1707 cm\(^{-1}\). The conversions proved to be consistent using either gas chromatography or infrared spectroscopy as technique to analyse the reaction mixture (see Figure 6.2).
Table 6.1 Ru(II)-amino alcohol catalysed Transfer Hydrogenation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Ketone</th>
<th>H-donor</th>
<th>Conv of ketone [%]</th>
<th>Ee [%]</th>
<th>(k_{Si}/k_{Re})</th>
<th>(k_R/k_S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2-propanol</td>
<td>96</td>
<td>89</td>
<td>17</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2-propanol</td>
<td>94</td>
<td>24</td>
<td>1.6</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>4</td>
<td>(R)-phenylethanol</td>
<td>95</td>
<td>-</td>
<td>-</td>
<td>} (15^g)</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>4</td>
<td>(S)-phenylethanol</td>
<td>15</td>
<td>-</td>
<td>-</td>
<td>} (2^g)</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>4</td>
<td>(R)-phenylethanol</td>
<td>93</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>4</td>
<td>(S)-phenylethanol</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>3</td>
<td>(R)-2-hexanol</td>
<td>91</td>
<td>86</td>
<td>13</td>
<td>} (2^h)</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>3</td>
<td>(S)-2-hexanol</td>
<td>62</td>
<td>88</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>3</td>
<td>(R)-2-hexanol</td>
<td>89</td>
<td>22</td>
<td>1.6</td>
<td>} (1^h)</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>3</td>
<td>(S)-2-hexanol</td>
<td>70</td>
<td>23</td>
<td>1.6</td>
<td>} (2^h)</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>5</td>
<td>(R)-2-hexanol</td>
<td>76</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>5</td>
<td>(S)-2-hexanol</td>
<td>45</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)The reaction was carried out at room temperature using a 0.1 M solution (5 mmol) in alcohol. Substrate : [RuCl₂(p-cymene)]₂ : ligand : iBuOK = 400 : 1 : 5 : 12.5. \(^b\)Conversions were determined after 40 min by GLC analysis and/or IR spectroscopy. \(^c\)Determined by capillary GLC analysis using a chiral cycloSil-B column. \(^d\)The product configurations are (R). \(^e\)\(k_S / k_{Re} = (100-x) / x; x = (100-ee) / 2\). \(^f\)Determined by IR spectroscopy after ca. 50% conversion. \(^g\)The \(k_R / k_S\) corresponds to acetophenone reduction. \(^h\)The \(k_R / k_S\) corresponds to 2-hexanone reduction.

The reverse reaction can be used to determine the difference in dehydrogenation rate between (R)- and the (S)-phenylethanol which can serve as an method to determine the enantioselectivity of the reaction (see Scheme 6.2).

Hence, by monitoring the reaction rate of the reduction of acetone (4) using (R)-phenylethanol and (S)-phenylethanol as separate hydrogen donors the performance of transfer hydrogenation catalysts is elucidated.

Table 6.1 shows the performance of the ruthenium(II)-amino alcohol catalysts, containing 1 and 2, for the dehydrogenation of (R)- and the (S)-phenylethanol, respectively (entries 3-6). The reaction rate was followed by IR spectroscopy.
Figure 6.3 shows the IR spectra of the reactions described in entries 3 and 5, Table 6.1, monitored in time, using (1R, 2S)-ephedrine as the amino alcohol ligand.

As can be seen from Figure 6.3 the reaction rate for the dehydrogenation of the (R)-phenylethanol is much faster than the dehydrogenation of the (S)-phenylethanol. The initial reaction rate is ca. 15 times faster for the (R)-phenylethanol than for the (S)-phenylethanol. This is in agreement with the $k_{Si} / k_{Re}$ ratio of 17, which is calculated from the enantioselectivity.

Table 6.1 and Figure 6.3 show that a smaller difference in dehydrogenation rate is observed for the Ru(II)-phenylglycinol catalyst (entries 4 and 6). The conversion of acetone to 2-propanol using (S)-phenylethanol as a hydrogen source is much higher.
using ligand 2 than the use of 1. The smaller difference in dehydrogenation rate using ligand 2 implies a lower enantioselectivity, which is indeed the case (cf. entries 1 and 2).

Dehydrogenation of \((R)\)-phenylethanol using ligand 2

Dehydrogenation of \((S)\)-phenylethanol using ligand 2

Figure 6.4

Similar differences in dehydrogenation rate were obtained in the dehydrogenation of \((R)\)- and \((S)\)-2-hexanol (Scheme 6.3).

\[
\text{OH} \quad \begin{array}{c}
\text{CH}_3 \\
\text{Ph}
\end{array} \quad \text{Ru(II), ligand} \quad \begin{array}{c}
\text{CH}_3 \\
\text{Ph}
\end{array} \\
3: R = \text{CH}_3 \\
5: R = \text{Ph}
\]

Scheme 6.3

Since acetone and 2-hexanone are both dialkyl ketones their signals overlap in the IR spectrum. For this reason acetophenone (3) and benzophenone (5) were used as
The difference in dehydrogenation rate between (R)- and (S)-2-hexanol was found to be in the same order of magnitude as the difference in dehydrogenation rates between (R)- and (S)-phenylethanol (entries 7-10, Table 6.1). Using benzophenone (5) as a substrate the observed reaction rates were lower for both the dehydrogenation of (R)- and (S)-2-hexanol (entries 11 and 12, Table 6.1). The bulky phenyl groups on both sides of the carbonyl group of the hydrogen acceptor most likely slow down the reaction. The difference in dehydrogenation rates between (R)- and (S)-2-hexanol was found to be similar to the reduction rate of acetophenone.

For a rapid screening of the samples generated by catalysis experiments a single sample per reaction mixture suffices for determination of an approximate ee value. The difference in dehydrogenation rate between (R)-phenyl ethanol and (S)-phenyl ethanol after 30 minutes using either ligand 1 or ligand 2 in the ruthenium(II) catalysed transfer hydrogenation of acetone is visualised in Figure 6.5.

Subtraction of the IR-spectra as in Figure 6.5 clearly shows that the difference in reaction rate between the oxidation of (R)-phenyl ethanol and (S)-phenyl ethanol is much larger when Ru(II)-ligand 1 is used than when Ru(II)-ligand 2 is used as a catalyst.

Thus, IR spectroscopy is a very useful technique to measure the difference in
dehydrogenation rate between (R)-phenylethanol and (S)-phenylethanol in order to determine the enantioselectivity of the transfer hydrogenation of acetophenone in 2-propanol, using the same catalyst.

6.3 Concluding remarks

Infrared spectroscopy proved to be a very useful technique to determine the performance of enantioselective transfer hydrogenation catalysts. The difference in dehydrogenation rate between the (R)- and the (S)-alcohol, i.e. the $k_R / k_S$ ratio, served as a reliable indication for the enantioselectivity of the transfer hydrogenation of ketones. On using this technique rapid screening of the generated samples can be achieved.

6.4 Acknowledgements

The Innovation Oriented Research Programme (IOP-Katalyse) is gratefuly acknowledged for their financial support of this research.

6.5 Experimental Section

**General Remarks**

Reactions were run under an atmosphere of argon in flame dried Schlenk flasks, using anhydrous solvents. Propan-2-ol was freshly distilled from CaH$_2$ prior to use. IR spectra were recorded on a BioRad FTS-60A spectrophotometer. Gas chromatography was performed using a Carlo Erba GC 6000 Vega 2 instrument, 25 m column: CycloSil-B (chiral) and a Carlo Erba HRGC Mega 2 instrument, 25 m column: BPX 35 (SGE) (achiral).
Enantioselective reduction of ketones

A solution of (p-cymene)ruthenium(II) chloride dimer (0.05 mg, 0.083 μmol) and the amino alcohol as a ligand (0.33 μmol) in dichloromethane (0.1 ml) was added to the chiral alcohol (4.3 mmol) at room temperature under argon. After stirring the mixture for 5 min the ketone (33.3 μmol) was added followed by iBuOK (0.09 mg, 0.83 μmol). The reaction was run at room temperature under argon for the time indicated and monitored by IR and/or GC. The IR cell was flushed with argon for 2 min prior to use.

6.6 References
