Doctoral Thesis

Catalytic diastereoselective hydrogenation of substituted aromatic compounds

Author(s):
Ranade, Vidyadhar Sudhir

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_Catalytic Diastereoselective Hydrogenation of Substituted Aromatic Compounds_

A dissertation submitted to the _Swiss Federal Institute of Technology Zurich_

For the degree of _Doctor of Technical Sciences_

Presented by

_Vidyadhar Sudhir Ranade_
B. Chem. Engg., University of Bombay, India
Ingenieur, University of Twente, The Netherlands
born on 16 September 1973
citizen of India

Accepted on the recommendation of

Prof. Dr. Roel Prins, examiner
Prof. Dr. Giambattista Consiglio, co-examiner
Prof. Dr. Antonio Togni, co-examiner

_Zurich, 2000_
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Following publications are based on the contents of this dissertation

*Catalytic Diastereoselective Hydrogenation of (S)-Proline-Modified Anthranilic Acid*

V.S. Ranade, G. Consiglio and R. Prins

*Diastereoselective Hydrogenation of (S)-Proline-2-Methylanilide*

V.S. Ranade and R. Prins

*Functional-Group-Directed Diastereoselective Hydrogenation of Aromatic Compounds. 1*

V.S. Ranade, G. Consiglio and R. Prins

*Hydrogenolysis of Benzylic Alcohols on Rhodium Catalysts*

V.S. Ranade and R. Prins

*Functional-Group-Directed Diastereoselective Hydrogenation of Aromatic Compounds. 2*

V.S. Ranade, G. Consiglio and R. Prins
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Curriculum Vitae
Summary

This thesis focuses on the liquid-phase diastereoselective hydrogenation of model disubstituted aromatic compounds on heterogeneous rhodium catalysts. o-Toluidine was modified by coupling its amino group to the carboxylic acid group of (S)-proline through an amide bond. Hydrogenation under 50 bar hydrogen pressure and at 70°C of the resulting (S)-proline-2-methylanilide in ethanol gave primarily the cis diastereomers (~80%) of (S)-proline-2-methylcyclohexylamide and a diastereomeric excess of about 50% between the two cis diastereomers. Amongst the noble metal catalysts investigated (palladium, platinum, ruthenium and rhodium), rhodium gave the highest activity and diastereoselectivity. Hydrogenation over catalysts with different rhodium dispersions, different supports and different solvents did not alter the diastereoselectivity to a significant extent.

It was hypothesized that a rigid auxiliary-aromatic compound moiety would hydrogenate with a higher diastereoselectivity. Accordingly, (S)-proline was bonded via two amide bonds to anthranilic acid and the resulting adduct was hydrogenated in water or ethanol under 50 bar hydrogen and at 50°C over rhodium and ruthenium catalysts supported on carbon and alumina. Hydrogenation over all catalysts gave the two cis product diastereomers with a moderate chemoselectivity (20-35%), the principle by-product being the partially hydrogenated aromatic substrate (65-80%). High diastereoselectivity was obtained in reactions conducted in ethanol over the alumina-supported ruthenium and rhodium catalysts. The diastereoselectivity on carbon-supported catalysts was diminished, especially with water solvent because the cyclohexene by-product hydrogenated further with an opposing selectivity than the parent aromatic substrate.

The selectivity in diastereoselective hydrogenation arises because of preferred hydrogenation of one of the two diastereotopic faces of the aromatic substrate. Thus, to obtain high selectivity, the aromatic substrate should preferably adopt only one conformation on the surface, in which only one of the two diastereotopic faces is adsorbed on the catalyst surface. The adsorption mode of the substrate on a catalyst
surface is determined by interactions of individual functional groups of the substrate with the catalyst surface, the nature of the catalyst surface, and the substrate structure in the unadsorbed state. Results of hydrogenation of (S)-proline-modified o-toluidine and anthranilic acid as well as those obtained for other substrates by other investigators indicate that the selectivities obtained in direct hydrogenation are not strongly correlated to the nature of the catalyst surface. Therefore, the conformation of the aromatic substrate in the unadsorbed state and its interactions with the catalyst surface are regarded as the two important factors determining selectivity. To estimate the interaction of each functional group individually, while keeping the conformation of the substrate constant, the diastereoselective hydrogenation of 1-substituted indanes was studied. Only the amino group was found to have a strong attractive electronic interaction with the catalyst surface. The hydroxyl group has a moderate interaction with the catalyst surface, whereas the carboxyl groups (acid, ester and amide) like the alkoxy and the alkyl groups have a relatively strong repulsive steric repulsion to the catalyst surface. Since most of the functional groups show a steric interaction with the catalyst surface, high selectivity in diastereoselective hydrogenation can only be achieved when the steric properties of the auxiliary prevent the adsorption of one of the two diastereotopic faces of the aromatic substrate-auxiliary moiety. This condition is, however, by itself not sufficient. To get a high diastereoselectivity, in addition, it is very important to ensure that rotations around single bonds connecting the auxiliary to the aromatic compound are prevented. A rigid molecule with a unique conformation thus has a higher chance to become selectively hydrogenated. The formation of cyclohexene intermediates was identified as one of the major factors which is detrimental to the diastereoselectivity.

In diastereoselective hydrogenation of 1-substituted indanes, 1-indanol and 1-alkoxyindanes underwent considerable hydrogenolysis on carbon-supported rhodium catalysts but very little on alumina-supported rhodium catalysts. The mechanism of hydrogenolysis, as well as the large differences in hydrogenolysis activity of the two rhodium catalysts were investigated by $^2$D coupled $^{13}$C NMR spectroscopy and mass spectrometry experiments. The mechanism of hydrogenolysis was ascertained to be a single step process occurring on the carbon support with spillover hydrogen.
Zusammenfassung


Chance, selektiv hydriert zu werden. Die Bildung von Cyclohexen-Zwischenstufen wurde als einer der Hauptfaktoren identifiziert, die sich nachteilig auf die Diastereoselektivität auswirken.

In der diastereoselektiven Hydrierung von 1-substituierten Indanen, fand eine Hydrogenolyse des 1-Indanols und 1-Alkoxyindans über Rhodiumkatalysatoren auf Aktivkohle in hohem Ausmasse, aber nur wenig über Rhodiumkatalysatoren auf Aluminiumoxid statt. Sowohl der Mechanismus der Hydrogenolyse, als auch die grossen Unterschiede in der Aktivität der Hydrogenolyse der zwei Rhodiumkatalysatoren wurden durch 2D/13C gekoppelte NMR-Spektroskopie und massenspektroskopische Experimente auf deren Reaktionsprodukte hin untersucht. Es wurde festgestellt, dass der Mechanismus der Hydrogenolyse ein Einschritt-Prozess ist, der auf der Aktivkohle als Trägermaterial durch "spillover" von Wasserstoff stattfindet.
1. Introduction

1.1 Motivation

Molecules of many natural products like alkaloids, steroids and terpenoids have six-membered alicyclic and/or heterocyclic components [1] (see examples in Fig. 1.1). Preparation of these components is therefore of interest to the pharmaceutical and the agrochemical industry.

![Figure 1.1 Examples of alkaloids, steroids and terpenoids](image)

Multiply substituted cyclic rings exist in different stereoisomeric forms. For instance, a non-identically disubstituted cyclohexyl ring can exist in four different forms (Fig. 1.2). The enantiomeric pair in which the two substituents lie on the same side of the carbon skeleton of the six-membered ring has the cis configuration, whereas the other enantiomeric pair in which the two substituents lie on the opposite side of the skeleton has the trans configuration. The relation between the cis and the trans isomers is diastereomeric. Since almost all biologically active compounds are enantiopure, only
one of the isomers is of interest. Therefore, either it has to be synthesized selectively or it has to be separated from the other isomers after a synthesis of a mixture of the isomers. Clearly, the former method involving selective synthesis of one enantiomer (also known as asymmetric synthesis) is favoured because it uses reagents and reactants more efficiently.

\[ \text{cis} \quad \text{trans} \]

**Figure 1.2** Isomers of 1,2-disubstituted cyclohexane

For a reaction to take place stereoselectively, the presence of an element of chirality during the reaction is necessary. This chirality element can be incorporated either in a catalytic system directing the change or it can be incorporated in one of the reactants. The former technique is termed enantioselective and it uses a non-stoichiometric amount of the chiral entity while the latter technique is termed diastereoselective and it uses a stoichiometric amount of the chiral entity. The enantioselective technique produces many moles of chiral product per mole of the catalyst. The diastereoselective technique besides requiring a stoichiometric quantity of the chiral entity requires additional synthetic steps to incorporate and later remove the chiral entity. These two factors make the enantioselective technique much more attractive than the diastereoselective one, although it is more difficult in practice. The diastereoselective technique becomes more attractive, of course, when the target molecule has more than
one element of chirality and if the element(s) of chirality already present can be used to leverage selectivity during the formation of an additional element(s) of chirality.

A useful example of the above strategy is illustrated in Scheme 1.1 and is used in the synthesis of a new HIV protease inhibitor Saquinavir (4) by F. Hoffman La Roche [2]. In the example shown, one of the two cis isomers of the decahydroisoquinoline derivative (3) is stereoselectively (selectivity = 94%) manufactured by using the directing effect of the amide group present at a stereogenic center in the catalytic hydrogenation of the tetrahydroisoquinoline derivative 1.

\[
\text{CONHf-Bu} \quad \xrightarrow{\text{catalyst}} \quad \text{CONHf-Bu}
\]

\[
\text{cis-cis diastereomer 3}
\]

\[
\text{catalyst}
\]

\[
\text{CONHf-Bu}
\]

\[
\text{cis-trans diastereomer 2}
\]

\[
\text{Saquinavir 4}
\]

Scheme 1.1 Synthesis of a key intermediate en route to HIV protease inhibitor Saquinavir

This thesis does not demonstrate the application of the catalytic diastereoselective hydrogenation technique to the synthesis of biologically active compounds such as 4. It, however, seeks to demonstrate the viability of this technique, ascertain its limits in terms of diastereoselectivities, and gain an insight into the mechanism of diastereoselection by studying hydrogenation of simple chiral aromatic substrates. Details of the contents of the thesis are provided in Section 1.5. Section 1.2 summarizes
briefly alternative methods to construct substituted alicyclic molecules stereoselectively. Sections 1.3 and 1.4 provide a brief introduction to stereoselective hydrogenation in general and a survey of literature published related to the core topic of catalytic diastereoselective aromatic hydrogenation respectively.

1.2 Synthesis Methods

Diels-Alder condensation, Birch reduction and catalytic hydrogenation are the three principle methods of constructing saturated cyclic compounds. Not all these methods are equal in the sense that they have different chemoselectivity and stereoselectivity. For instance, catalytic hydrogenation yields predominantly the cis diastereomers whereas Diels-Alder condensation can lead to the formation of the cis or the trans isomers depending on the reactants. Condensation of two functional groups via a nucleophilic attack in the same molecule, involving for example, an amine and an aldehyde, or an alcohol and an acid, can also lead to heterocyclic compounds, namely, piperidone and pyrone. These methods are, however, special to specific classes of heterocyclic substrates and hence are not discussed here.

The Diels-Alder reaction is a very useful [4 + 2] cycloaddition reaction in which a dienophile and a diene add to form a cyclic six-membered olefinic molecule. Thus in a single concerted step up to four new asymmetric centers can be generated. This reaction is extremely useful not only because it leads to a formation of a cyclic structure from acyclic components but also because it can be applied to a wide variety of reactants. Advances have been made in conducting the Diels-Alder reaction asymmetrically using both enantioselective and diastereoselective approaches. In the enantioselective approach, usually, a chiral metal complex with Lewis acidity is employed. In the diastereoselective approach, reactions of a variety of dienes as well as dienophiles modified by chiral auxiliaries have been successfully accomplished. A brief summary of asymmetric Diels-Alder reactions conducted in the diastereoselective and the enantioselective techniques for a variety of substrates including those with heteroatoms is given by Whiting [3] and by Oppolzer [4].
An application of the Diels-Alder reaction to the synthesis of pumiliotoxin C (9) [5] is shown in the Scheme 1.2. Addition of the chiral dienophile 6 to the diene 5 generates simultaneously three chiral centers in 7, the diastereoselectivity being directed by the chiral carbon atom bearing the t-Bu group. After the generation of the six-membered ring, this chiral center is removed in the second step giving 8, which is converted further to the desired product 9.

Birch reduction has been gainfully employed in reduction of a wide variety of aromatic ethers, amines, esters, ketones and amides. Birch reduction involves formation of a radical anion by addition of an electron to an aromatic ring followed by protonation. The radical anion is generated using a mixture of a Group I or II metal and anhydrous ammonia. In general, reaction conditions are rather stringent, requiring very low temperatures (< -50°C) and rigorous exclusion of water and oxygen. Birch reduction reduces the aromatic ring incompletely in that either a cyclohexadiene or cyclohexene derivative is obtained as the final product depending on the substrate reduced and the reaction conditions. Therein also lies its advantage if the unsaturated product is desired.
Another advantage is the ability to reduce and alkylate simultaneously if an alkyl halide is added to the reaction mixture after generation of the radical anion. Enantioselective synthesis is of course not possible in Birch reduction but diastereoselective synthesis of a multitude of compounds has been performed. A comprehensive review by Hook and Mander [6] describes several applications of stereoselective Birch reduction of aromatic compounds to the synthesis of natural products. More recent applications of diastereoselective Birch reduction, particularly those starting from proline-modified aromatic carboxylic acids, are reviewed by Schultz [7].

Scheme 1.3 Example of an application of stereoselective Birch reduction

An application of Birch reduction to the synthesis of pumiliotoxin C starting from (S)-proline-modified methyl anthranilic acid 10 [8] is shown in Scheme 1.3. The cyclohexene generated through Birch reduction (11) is hydrogenated with a homogeneous iridium catalyst to yield the substituted cyclohexyl derivative 12 with the required configuration and is further converted to the desired product 9.
Catalytic hydrogenation of unsaturated compounds with molecular hydrogen is one of the most widely practiced steps in organic synthesis. Hydrogenation is conducted over supported or unsupported heterogeneous catalysts or with homogeneous soluble metal complexes. Heterogenized homogeneous catalysts have also been exploited increasingly. The difference between such a catalyst and a homogeneous catalyst is primarily the ease of engineering in using these catalysts but the mechanism of stereodifferentiation of the parent homogeneous catalyst is retained. Both enantioselective and diastereoselective hydrogenation techniques have been used over the years with heterogeneous as well as homogeneous catalysts for the reduction of a very wide variety of unsaturated substrates. However, the stereoselective reduction of aromatic compounds has received less attention probably because of the difficulty in hydrogenating the rather stable aromatic ring. In fact, aromatic hydrogenation under mild reaction conditions has been possible only relatively recently in the history of catalytic hydrogenation, especially after the discovery of heterogeneous rhodium [9] and ruthenium [10] catalysts for aromatic hydrogenation. To the best of our knowledge, there are no reports of either enantioselective or diastereoselective hydrogenation with homogeneous catalysts and enantioselective hydrogenation with heterogeneous catalysts of aromatic compounds. Even though stereoselective hydrogenation of aromatic compounds to the corresponding saturated cyclic compounds is of prime interest for the current study, in the following section, stereoselective hydrogenation of other substrates is briefly summarized.
1.3 Stereoselective Catalytic Hydrogenation

1.3.1 Homogeneous Catalysts

In general, application of homogeneous catalysts in arene reduction has been quite limited [11] probably because of their low activity. A few examples of successful applications to aromatic reduction exist [11-14], however, these have not been investigated beyond simple substrates like fused aromatics, alkylbenzenes, and aromatic amines and ketones. The following two subsections discuss briefly, enantioselective and diastereoselective hydrogenation of olefinic and other double bonds involving heteroatoms, which has been overwhelmingly successful and a subject of great interest in the field of homogeneous catalysis.

![Chiral ligands used in homogeneous catalysts](image)

**Figure 1.3** Chiral ligands used in homogeneous catalysts
Enantioselective Hydrogenation

Enantioselective hydrogenation is conducted with transition metal complexes, by binding chiral ligands to the metal, usually through phosphorous and/or nitrogen atoms. Typically bidentate ligands are used because they are rigid and stay firmly bonded to the metal [15]. Although, a wide variety of combinations of bidentate ligands and metals have been used, only a handful of ligands give high selectivity and these have been used extensively. Some of them are indicated in Fig. 1.3.

Table 1.1 Examples of enantioselective hydrogenation of different substrates with homogeneous catalysts

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Catalyst</th>
<th>ee</th>
<th>Reference</th>
<th>Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-\text{COOH})</td>
<td>(-\text{COOH})</td>
<td>Rh[(S)-BINAP]</td>
<td>98</td>
<td>[17]</td>
<td>A</td>
</tr>
<tr>
<td>(\text{Ph})</td>
<td>(\text{Ph})</td>
<td>Rh-(S,S)</td>
<td>68</td>
<td>[18]</td>
<td>B</td>
</tr>
<tr>
<td>(\text{Me})</td>
<td>(\text{COOH})</td>
<td>Ru[[(R)-BINAP]</td>
<td>85</td>
<td>[19]</td>
<td>C</td>
</tr>
<tr>
<td>(\text{Me})</td>
<td>(\text{NMe}_2)</td>
<td>Ru[(S)-BINAP]</td>
<td>96</td>
<td>[20]</td>
<td>D</td>
</tr>
<tr>
<td>(\text{Me})</td>
<td>(\text{NMe}_2)</td>
<td>Rh-(S,S)</td>
<td>86</td>
<td>[21]</td>
<td>E</td>
</tr>
<tr>
<td>(\text{Me})</td>
<td>(\text{OH})</td>
<td>Ru-(R,R)</td>
<td>87</td>
<td>[22]</td>
<td>F</td>
</tr>
<tr>
<td>(\text{Me})</td>
<td>(\text{OH})</td>
<td>Ru[(R)-BINAP]</td>
<td>99</td>
<td>[23]</td>
<td>G</td>
</tr>
</tbody>
</table>

The performance of rhodium or ruthenium catalysts coordinated to these ligands in the hydrogenation of a variety of double bonds is superior in terms of enantioselectivities, reaction conditions and reaction rates. A few representative examples of hydrogenation
reactions of prochiral dehydroamino acids (A), enamides (B), \( \alpha,\beta \)-unsaturated acids (C), ketones (D), \( \alpha \) and \( \beta \)-keto esters (E,F) and imines (G) on homogeneous catalysts coordinated to ligands shown in Fig. 1.3 are presented in Table 1.1. While the most successful applications of chiral homogeneous catalysts are in the reduction of C=C bonds, the reduction of C=O bonds has been difficult to achieve and that of C=N bond has not been investigated in details [16]. Although high enantioselectivities have been achieved with a large variety of substrates, typically, enantioselectivity is excellent in the hydrogenation reactions only when a neighbouring polar group (very often a substituent at the \( \alpha \)-carbon atom) can complex with the catalyst in addition to the double bond undergoing reduction. Since the presence of these polar groups leads to a high discrimination of the enantiotopic faces of the molecule, electronic interactions between these groups and the metal center of the catalyst must be important.

**Diastereoselective Hydrogenation**

![Diastereoselective Hydrogenation](image)

*Figure 1.4 Homogeneous catalysts used in diastereoselective hydrogenation (The methyl group of 4-methylcyclohex-3-enol in structure III is not shown for clarity)*

Directed hydrogenation of olefinic compounds, particularly with rhodium and iridium cationic complexes (I and II in Fig. 1.4) has been investigated to a great extent [24, 25]. Using the complexation abilities of a neighbouring polar functional group, excellent stereocontrol has been achieved. For example, structure III in Fig. 1.4 illustrates the
complexation of the homoallylic alcohol, 4-methylcyclohex-3-enol through its hydroxyl group in addition to the olefinic bond. Thus, the hydroxyl group, by virtue of its electronic affinity to the Rh complex I, is able to direct hydrogenation of the double bond from its side.

A few examples of successful applications of Rh and Ir catalysts to the diastereoselective hydrogenation of a variety of substrates are presented in Table 1.2. From the results reported, it is clear that excellent directing effects can be achieved with many polar groups such as hydroxyl (A, C, E, G), keto (F), ester (D,H) and amide (I,J) groups, including the less polar methoxy group (B). Not only substituents at a position α to the double bond (A-D), but also those at the β position (E-I) and even at the γ position (J) have been successfully exploited for directing hydrogenation of cyclic olefinic substrates. In addition, directing effects have been exploited usefully in the hydrogenation of acyclic olefinic substrates (K,L) wherein the performance of heterogeneous catalysts is very poor.

Surprisingly, reactions exemplifying the directing effect of the amino group are absent and there is even one report of failure of the amino group to direct the hydrogenation of an acyclic olefinic substrate [32]. Amino groups have also seldom been used for assisting the coordination of prochiral substrates in enantioselective hydrogenation reactions with chiral homogeneous catalysts [20]. Examples of catalytic diastereoselective reductions of C=N and C=O bonds using homogeneous catalysts are also very rare.
Table 1.2 Examples of diastereoselective hydrogenation of different substrates with homogeneous catalysts

<table>
<thead>
<tr>
<th>Substrate, G =</th>
<th>Product</th>
<th>Catalyst</th>
<th>d.r.(a)</th>
<th>Reference(s)</th>
<th>Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>Ir, Rh</td>
<td>74, 290</td>
<td>[26, 27]</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>Ir</td>
<td>&gt;99</td>
<td>[28]</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>CH(_2)OH</td>
<td>Ir</td>
<td>9</td>
<td>[26]</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>CO(_2)Me</td>
<td>Ir, Rh</td>
<td>&gt;99, 32</td>
<td>[29]</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>OH</td>
<td>Ir, Rh</td>
<td>33, 64</td>
<td>[26, 27]</td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>COMe</td>
<td>Ir</td>
<td>99</td>
<td>[28]</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>CH(_2)OH</td>
<td>Ir, Rh</td>
<td>25, 19</td>
<td>[27]</td>
<td>G</td>
<td></td>
</tr>
<tr>
<td>CO(_2)Me</td>
<td>Ir, Rh</td>
<td>46, 7</td>
<td>[28, 29]</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>O(^{\text{N}})N</td>
<td>Ir</td>
<td>130</td>
<td>[30]</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>O(^{\text{N}})N</td>
<td>Ir</td>
<td>&gt;100</td>
<td>[30]</td>
<td>J</td>
<td></td>
</tr>
<tr>
<td>Rh</td>
<td>32</td>
<td>[31]</td>
<td>K</td>
<td></td>
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<tr>
<td>Rh</td>
<td>99</td>
<td>[25]</td>
<td>L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(a\) trans / cis
1.3.2 Heterogeneous Catalysts

In general, heterogeneous catalysts have lagged behind their homogeneous counterparts in stereospecific hydrogenation reactions and instances where the selectivity of heterogeneous catalysts has exceeded that of homogeneous catalysts are rare. Nevertheless, some of the most successful stereoselective hydrogenation reactions of C=C, C=O and C=N bonds, enantioselective as well as diastereoselective, are summarized briefly in the following two subsections. Diastereoselective hydrogenation of aromatic compounds, which is the topic of primary interest for the present study is summarized to a greater detail in Section 1.4.

**Enantioselective Hydrogenation**

While enantioselective hydrogenation has been very successful with soluble metal complexes modified with chiral ligands, this approach has met with limited success with heterogeneous catalysts. The initial approach in conducting enantioselective reactions was to support the metal on naturally occurring chiral supports like silk, polysaccharides and cellulose. This approach, however, was not very successful and gave way to the idea of modifying the metal particles on a commonly used support with chiral modifiers. Pioneering efforts by Japanese researchers led to the discovery of two new systems (Scheme 1.4) namely, the hydrogenation of α-keto compounds on cinchona-modified platinum catalysts, and the hydrogenation of β-keto compounds on tartaric acid-modified nickel catalysts to the corresponding alcohols [33]. However, high ee values are obtained for the two systems only with a very small number of substrates even in their respective classes.
A compilation of some of the best results in terms of enantioselectivity for the platinum-cinchonidine system is given in Table 1.3 (substrates A-D). In spite of intense efforts, the mechanism of enantioselection remains unclarified and, therefore, efforts to extend the versatility of these systems to the hydrogenation of other substrates and to identify new catalyst-modifier systems have met limited success [34]. Amongst many intriguing characteristics of this system, a small difference in the structure of the substrate may result in an unexpected change in the selectivity. For instance, substrates A, E and F are very similar but high selectivity is obtained only with A.

Nothing has been published on enantioselective hydrogenation of aromatic rings using heterogeneous catalysts. This is not surprising, however, since the problem of reduction of aromatic substrates is complicated further in that the aromatic substrates would adsorb much stronger than the typically employed olefinic substrates and would require higher temperature (and/or hydrogen pressure) during hydrogenation.
Table 1.3 Examples of enantioselective hydrogenation of different substrates over heterogeneous platinum catalysts modified by cinchonidine or its derivatives

<table>
<thead>
<tr>
<th>Substrate</th>
<th>ee</th>
<th>Reference(s)</th>
<th>Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Substrate" /></td>
<td>96</td>
<td>[35, 36]</td>
<td>A</td>
</tr>
<tr>
<td><img src="image2.png" alt="Substrate" /></td>
<td>95</td>
<td>[37]</td>
<td>B</td>
</tr>
<tr>
<td><img src="image3.png" alt="Substrate" /></td>
<td>79</td>
<td>[38]</td>
<td>C</td>
</tr>
<tr>
<td><img src="image4.png" alt="Substrate" /></td>
<td>82</td>
<td>[39]</td>
<td>D</td>
</tr>
<tr>
<td><img src="image5.png" alt="Substrate" /></td>
<td>12</td>
<td>[40]</td>
<td>E</td>
</tr>
<tr>
<td><img src="image6.png" alt="Substrate" /></td>
<td>&lt;10</td>
<td>[36]</td>
<td>F</td>
</tr>
</tbody>
</table>

**Diastereoselective Hydrogenation**

There is an enormous amount of literature about stereoselective hydrogenation over supported metal catalysts of chiral as well as pro-chiral unsaturated substrates giving racemic chiral products. In fact, a book devoted to these reactions has been published and it provides a comprehensive summary of these investigations [41]. Applications of the diastereoselective technique for asymmetric synthesis are, however, harder to find. The hydrogenation of C=C, C=O and C=N bonds leading to amino acids or amine products especially starting from α-keto acids and their derivatives has been studied extensively. A recent review by Besson and Pinel [42], and earlier reviews by Tungler and Fodor [43] and Harada [44] summarize asymmetric diastereoselective hydrogenations over heterogeneous catalysts. In the majority of the hydrogenation
reactions, palladium catalysts, and chiral amino acids, alcohols and amines as chiral auxiliaries have been employed.

Scheme 1.5 Diastereoselective hydrogenation of dehydro-amino acids

With a very few exceptions, the hydrogenation reactions of acyclic amino acid derivatives of dehydro-amino acids has not been very selective [44]. A more successful approach involves the modification of dehydro-amino acids by a natural amino acid giving a rigid cyclic diketopiperazine structure (13, Scheme 1.5). After hydrogenation over a heterogeneous palladium or platinum catalyst, the auxiliary (15) is recovered together with the newly formed amino acid (16) by acidic hydrolysis of the hydrogenated diketopiperazine (14). Diastereoselectivities in the excess of 90% were obtained using this technique [45-47].

Mitsui et al. studied the diastereoselective hydrogenation of the C=O bond in a-keto acids after converting the acid to an ester using an optically active alcohol (route I, Scheme 1.6) [44]. In a similar study, Harada and Munegumi coupled the acid to an optically active amine [48] or an amino acid derivative [49] (route II, Scheme 1.6). The auxiliaries were cleaved after hydrogenation over palladium, either by acidic hydrolysis or catalytic hydrogenolysis. Using this technique, 75% diastereoselectivity was obtained in the hydrogenation of pyruvic acid with a prolinamide auxiliary [50].
Diastereoselective hydrogenation of the C=N bond formed by condensing amines with the C=O bond of α-keto acids has been widely studied. Although there are several possibilities to diastereoselectively hydrogenate such a C=N bond, the transamination technique has found widespread use. In this technique, the α-keto acid (17, Scheme 1.7) is derivatized with an optically active primary benzylic amine. The imine is then hydrogenated over a heterogeneous catalyst and subsequently the benzylic group is hydrogenolyzed over a palladium catalyst to give the amino acid product (19).

In this self-immolation type method, the original chiral center on the benzylic amine is lost and the amino group is transferred to the new amino acid product. Using this method, Hiskey and Northrop obtained a high diastereoselectivity (70-90%) for many α-keto acids with 1-phenylethylamine as the auxiliary [51]. This method has been more successful for the synthesis of chiral amines (20) from the corresponding ketones (18). Using 1-phenylethylamine as the transamination agent, excellent diastereoselectivities (>95%) were reported by Frahm and co-workers in the preparation of alicyclic primary amines from the corresponding alkanones [52, 53]. In their work, reduction of the imine was conducted with a Raney nickel catalyst instead of a palladium catalyst since it afforded high selectivities. Bringmann and Geisler extended this method successfully to the preparation of other 1-phenylethylamines substituted at the aromatic ring [54].

Scheme 1.6 Diastereoselective hydrogenation of α-keto acids using chiral amine (or amino acid derivative) and alcohol auxiliaries
A variation of the transamination method, in which an optically active amino acid was condensed with an α-keto acid or a ketone to give imines of type 21 and 22 (Scheme 1.8), was used by Yamada and co-workers [55, 56]. On hydrogenation of these imines over a palladium catalyst and removal of the auxiliary, amino acids and amines were obtained with moderate diastereoselectivities (50-85%) and a low chemical yield.

\[
\begin{align*}
\text{R}^1\text{C}^\text{HR}^2\text{NH}_2 & \quad \text{PhC}^*\text{HR}^2\text{NH}_2 \\
\text{H}_2, \text{solv.} & \quad \text{PhC}^*\text{HR}^2\text{NH}_2 \\
\text{Pd cat.} & \quad \text{PhC}^*\text{HR}^2\text{NH}_2 \\
\text{PhCH}_2\text{R}^2 & + \quad \text{PhCH}_2\text{R}^2 \\
\text{NH}_2 & \quad \text{NH}_2
\end{align*}
\]

\[X = \text{COOH}, \quad \text{alkyl or aryl}, \]

Scheme 1.7 Diastereoselective hydrogenation of α-keto acids and ketones using the transamination method

In addition to studying hydrogenation of imines similar to those prepared by Hiskey and Northrop, Harada and Matsumoto studied the hydrogenation of other imino derivatives of α-keto acids (23 and 24, Scheme 1.9) using amino acid ester auxiliaries (R^2*NH₂) [57-59]. With a few exceptions, this approach gave diastereoselectivities below 50%, probably because the center of chirality in the auxiliary was at a greater distance from the double bond undergoing hydrogenation than in the previous cases.
Scheme 1.8 Diastereoselective hydrogenation of α-keto acids and ketones using amino-acid auxiliaries

Scheme 1.9 Diastereoselective hydrogenation of α-keto acids investigated by Harada and Matsumoto
1.4 Catalytic Diastereoselective Aromatic Hydrogenation

It is known for many decades, that hydrogenation over heterogeneous catalysts in the majority of disubstituted aromatic compounds under relatively mild reaction conditions in the liquid phase yields the corresponding disubstituted cyclohexanes primarily with the cis configuration. However, to synthesize selectively one of the two cis isomers by using a chiral auxiliary is much more difficult [60]. Efforts to hydrogenate the aromatic ring diastereoselectively using heterogeneous catalysts gained momentum only recently and examples are summarized in the following paragraphs. Almost all investigations have been conducted with ruthenium and rhodium catalysts because they excel in their ability to hydrogenate aromatic rings under mild reaction conditions and generally leave the non-reducible functional groups intact during the reaction [61-63].

Gallezot and co-workers attempted the hydrogenation of 2-methylanisole over colloidal rhodium modified by a chiral amine but a very low (~1%) enantioselectivity was obtained [64]. Due to the poor selectivity of this system, they focussed their attention on diastereoselective hydrogenation. Thus, o-cresol was coupled to menthoxycetic acid (25) and camphanic acid (26). Hydrogenation of these derivatives gave up to 10% d.e. Hönig and co-workers coupled vanillic acid to either (S)-proline or menthol at the carboxyl group (27,28), and to acetyl-(S)-proline at the hydroxyl group (29). Hydrogenation of these derivatives gave a maximum d.e. of about 6% [65].
Gallezot and co-workers studied exhaustively the diastereoselective hydrogenation of o-toluic acid coupled to many different proline-type auxiliaries. Hydrogenation reactions were conducted at room temperature in alcoholic solvents and under 50 bar hydrogen pressure over either carbon- or alumina-supported rhodium catalysts. With all catalysts and almost all substrates the yield of cis diastereomers exceeded 90%. They found that addition of an amine modifier during the reaction changes the extent of diastereoselectivity. Table 1.4 summarizes the results obtained for a variety of substrates (30-33) hydrogenated with and without the addition of an amine.
Scheme 1.10 Substrates investigated by Gallezot and co-workers

Table 1.4 Results obtained in diastereoselective hydrogenation reactions investigated by Gallezot and co-workers

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Modifier</th>
<th>d.e.</th>
<th>Reference</th>
<th>Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>30, X = CH₂, G = COOMe</td>
<td>Rh/C</td>
<td>EtOH</td>
<td>-</td>
<td>-17</td>
<td>[66]</td>
<td>A</td>
</tr>
<tr>
<td>32, X = CH₂, G = CONHᵢ-Pr</td>
<td>Rh/C</td>
<td>MeOH</td>
<td>-</td>
<td>-13</td>
<td>[68]</td>
<td>J</td>
</tr>
<tr>
<td>33, X = CO</td>
<td>Rh/C</td>
<td>EtOH</td>
<td>-</td>
<td>35</td>
<td>[69]</td>
<td>L</td>
</tr>
<tr>
<td>31, X = CH₂, G = COOᵢ-Pr</td>
<td>Rh/C</td>
<td>EtOH</td>
<td>EDCA</td>
<td>48</td>
<td>[66]</td>
<td>I</td>
</tr>
<tr>
<td>33, X = CO</td>
<td>Rh/C</td>
<td>EtOH</td>
<td>EDCA</td>
<td>90</td>
<td>[69]</td>
<td>M</td>
</tr>
<tr>
<td>33, X = CO</td>
<td>Rh/C</td>
<td>EtOH</td>
<td>EDCA</td>
<td>95</td>
<td>[69]</td>
<td>O</td>
</tr>
<tr>
<td>32, X = CH₂, G = CONHᵢ-Pr</td>
<td>Rh/C</td>
<td>MeOH</td>
<td>DOCEA</td>
<td>16</td>
<td>[68]</td>
<td>K</td>
</tr>
</tbody>
</table>

EDCA = N-ethyl-N,N-dicyclohexylamine; DOCEA = (-) N,N-dioctyl-N-cyclohexylamine
With Rh/C catalysts a low selectivity to 34 was obtained on hydrogenation without addition of the amine (A,C,D,H,J). Addition of increasing concentrations of the amine EDCA resulted in a steady increase in the selectivity to the other diastereomer 35 and a steady decrease in the reaction rate. The increase in selectivity was not specific to the amine used; a variety of amines including primary and tertiary and even chiral amines, gave a very similar increase in the selectivity. The effect of increasing concentration of amine to rhodium ratio was studied with a couple of amine additives and it was found that the selectivity to 35 stabilizes at an amine to rhodium molar ratio of 3.5. This was considered as the optimum amine to rhodium ratio, since the addition of amine was detrimental to the activity of the catalyst. Thus a significant enhancement could be achieved in the diastereoselectivity on hydrogenation over the Rh/C catalyst of a reaction mixture with amine additive with all substrates investigated (for e.g. H to I). Contrarily, the alumina-supported rhodium catalyst was moderately selective to 35 even without the addition of the amine (F). The selectivity to 35 increased further with this catalyst on the addition of the amine (F to G). Changing the auxiliary from methyl ester (30) to isopropyl ester (31) did not result in a significant change in the selectivity. However, changing the solvent from ethanol to isopropanol resulted in a significant reduction of the diastereoselectivity for 30, but changing the solvent to methanol had almost no effect. A change in the auxiliary to an amide (32) instead of an ester (31) gave lower selectivities.

A change in hydrogen pressure during the reaction or a change in the dispersion of the catalyst had no effect on the diastereoselectivity obtained in the hydrogenation of 30 [70]. A detailed investigation with 30 indicated that an incompletely hydrogenated cyclohexene intermediate is formed during hydrogenation of 30 with all catalysts. The intermediate hydrogenated with a different diastereoselectivity to 34/35 than the parent aromatic substrate [66]. The formation of the intermediate complicated the interpretation of the variation of selectivity on the addition of amine or on changing the solvent. Further complications were introduced because the substrate 30 existed in two atropisomeric forms which may hydrogenate with different diastereoselectivities [70]. On the contrary, 33 could be prepared selectively in one of its atropisomeric form [69]. The excellent diastereoselectivity obtained in the hydrogenation of 33 over the alumina-
supported catalyst (N) was attributed to a stronger interaction of the substrate to incompletely reduced rhodium, higher sterical constraints due to the flat morphology of rhodium particles, and the interaction of the substrate with alumina on adsorption [71].

Hydrogenation of 30 was conducted on ruthenium, palladium and platinum catalysts in addition to rhodium, but the performance of these catalysts was much poorer than that of rhodium catalysts [70]. In the case of 33, the selectivity obtained with the ruthenium catalyst was high and only slightly lower than that obtained with the rhodium catalysts [69].

Hydrogenation of other aromatic compound - auxiliary moieties investigated by Neto [71] are shown in Fig. 1.6. The methoxy group in 36 was partly hydrogenolysed during hydrogenation of the aromatic ring over the rhodium catalysts and a d.e. up to 30% was obtained in the hydrogenated product. The hydrogenation did not proceed at room temperature over rhodium catalysts in the case of 37 probably because of the inhibiting effect of the amine and hence no further investigations were conducted. Using pantolactone as the chiral auxiliary (38), a diastereoselectivity of 20% was obtained on hydrogenation over a alumina-supported rhodium catalyst. Hydrogenation of m-toluic acid using the same auxiliary as in 30 (39) gave a diastereoselectivity of 35% with a Rh/C catalyst on addition of amine. A high yield of the trans products (cis:trans = 80:20) was obtained in this reaction.
1.5 Scope of the Thesis

The investigations in the enantioselective and diastereoselective hydrogenation of carbon-carbon as well as carbon-heteroatom double bonds, and the investigations of Gallezot and co-workers in diastereoselective hydrogenation of aromatic compounds provided us with some "starting points" in our research work. Gallezot and co-workers had successfully used the proline/pyroglutamic acid auxiliary for the stereoselective hydrogenation of o-toluic acid. Our early investigations were focussed on extending the diastereoselective approach to the stereoselective hydrogenation of other aromatic compounds. These investigations are reported in Chapters 2 and 3. In Chapter 2, the stereoselective hydrogenation of o-toluidine modified by (S)-proline is reported. The auxiliary was not changed from the one used by Gallezot and co-workers because of its very rigid structure amongst all proteinogenic amino acids. Literature on hydrogenation
had already pointed out that amines adsorb strongly on noble metal catalysts. The use of the amino group of (S)-proline in directing the adsorption of the substrate to yield a moderate diastereoselectivity (up to 50%) is demonstrated in this chapter. In addition, the dependence of activity on the nature of support and precursors of the catalyst and the reaction conditions is demonstrated. The independence of diastereoselectivity on these factors except the nature of noble metal is also shown. These investigations enabled us to identify rhodium as the most selective and active catalyst and hence it was used extensively in further investigations.

Thus, from early on, the results of our investigations corroborated the intuitive thinking that the selectivity is largely dependent on the structure of the chirally modified aromatic compound. This is demonstrated in Chapter 3 with the investigation of the diastereoselective hydrogenation of (S)-proline-modified anthranilic acid. The rigidity with which the (S)-proline auxiliary was bound by two covalent bonds to anthranilic acid enabled us to obtain very high diastereoselectivities (up to 95%). In this chapter, it is shown that a good selectivity is obtained, again, irrespective of the reaction conditions, except when the catalyst is able to reduce a olefinic by-product selectively to the isomer opposite of that produced by direct hydrogenation. These results enable us to demonstrate the importance of conformational rigidity of the aromatic compound-auxiliary adduct, for attaining high stereoselectivity during its hydrogenation.

Understanding the mechanism of diastereoselection is the subject of Chapters 4 and 5. The two cis diastereomeric products are formed in the hydrogenation of the chirally modified substrate from its two diastereotopic faces. The selectivity is thus determined by the preference (dictated by the auxiliary) to one of the two faces during adsorption of the modified substrate. It is of great interest, therefore, to find out the magnitude and direction (attractive or repulsive) of the forces between the modified substrate and metal surface of the catalyst. The attractive forces are of the electronic type, while the repulsive forces are of the steric type. This investigation would reveal whether one can influence the adsorption of the modified substrate by using electronic interaction of some functional group substituents, as has been exploited in the stereoselective hydrogenation with homogeneous catalysts. We simplified the problem by investigating
the interaction of individual functional groups. This was done by determining selectivities in the hydrogenation of indane mono-substituted with functional groups. It is demonstrated that unlike with homogeneous catalysts, the steric interaction is of prime importance in the case of heterogeneous catalysts and it is probably this interaction which directs the face-selectivity and thus the hydrogenation diastereoselectivity.

The important aspect of thermodynamic or steric control in stereoselective hydrogenation reactions reported in this thesis is dealt with in the first section of Chapter 6. In addition, in this chapter, the importance of rigidity and conformational homogeneity of the modified substrate is pointed out. It is also shown how information can be obtained regarding rigidity of the conformation of the modified substrate using simple molecular modelling techniques. Also, attempts are made to explain the difference in selectivities obtained in hydrogenation of different aromatic compound-auxiliary systems investigated to date by using two important criteria, namely, their rigidity and their steric interaction with the catalyst surface. Some concluding remarks on diastereoselective hydrogenation of aromatics over heterogeneous catalysts are included in the final section.

During our investigations into hydrogenation of 1-methoxyindane and 1-indanol conducted in the context of Chapters 4 and 5, we found that the carbon-supported catalysts caused considerably more hydrogenolysis than alumina-supported catalysts. To explain the big difference in chemoselectivities of the two types of catalyst, we undertook a detailed investigation into the mechanism of hydrogenolysis of the carbon-supported catalysts. These are reported in Chapter 7. Of the two possibilities for hydrogenolysis, namely, direct C-O bond scission and dehydration followed by hydrogenation, it is demonstrated that the former is the predominant route.

References


2. Diastereoselective Hydrogenation of (S)-Proline-modified o-Toluidine

2.1 Introduction

One of the first successful application of the diastereoselective hydrogenation of aromatic compounds was reported by Besson et al. [1-3]. They bonded o-toluic acid covalently to the chiral amino acid (S)-proline through an amide linkage. Hydrogenation over supported rhodium catalysts of the resulting o-toluoyl-(S)-proline gave a moderate to high diastereoselectivity (up to 70%) and a good cis to trans selectivity. The reaction system investigated by Besson et al. had many interesting characteristics; the presence of substrate (o-toluoyl-(S)-proline) in two atropisomeric forms, the increase in stereoselectivity on addition of an amine to the reaction system, the dependence of stereoselectivity on the nature of the catalyst support, and the hydrogenation of cyclohexene intermediate and the parent substrate with different stereoselectivities. Naturally, we were interested to know whether these properties were peculiar to the system they had investigated or if they were displayed by a variety of different substrates. We started our investigations, therefore, with the diastereoselective hydrogenation of o-toluidine with (S)-proline as the chiral auxiliary, with an aim to gather more data for the elucidation of the mechanism of diastereoselection and for the identification of the various factors that influence it. All hydrogenation reactions were run in the liquid phase under hydrogen pressure over noble metal catalysts. The use of rhodium was investigated in great detail because of its unique ability to hydrogenate aromatic rings under relatively mild reaction conditions. We found that although supported noble metal catalysts are frequently employed in hydrogenation reactions in organic syntheses, very little data are available regarding the nature of the active site in these kind of reactions. We also attempted, therefore, to delineate the changes in the rhodium catalyst during the hydrogenation reaction.
2.2 Experimental

2.2.1 Synthesis of Substrate and Reference Compounds

All organic chemicals, except 2-methylcyclohexylamine (Aldrich), were supplied by Fluka. (S)-Proline-2-methylanilide was synthesized by coupling the carboxylic acid group of a butyloxy carbonyl (BOC)-protected (S)-proline molecule with the amine group of o-toluidine, according to the following procedure. 20 g (93 mmol) of BOC-(S)-proline was dissolved in 150 ml THF and 13.0 ml (93 mmol) of triethylamine was added to the solution. The mixture was cooled to -15°C and 13.3 ml (102 mmol) of isobutyl chloroformate was added dropwise with stirring followed by 20 ml (187 mmol) of o-toluidine after 5 min. The mixture was allowed to reach room temperature and stirred for a couple of hours. The solution was concentrated in vacuo to about 50 ml and then poured into 300 ml of a 1 N HCl solution. This solution was extracted twice with 300 ml diethyl ether. The diethyl ether extracts were pooled together and washed twice each with a sodium bicarbonate solution and water and then dried over sodium sulfate. The solvent was removed in vacuo to give 22.5 g of solid BOC-(S)-proline-2-methylanilide (yield = 80%), which was purified by re-crystallization from hexane. Analytical data of BOC-(S)-proline-2-methylanilide:-

EI-MS: 304 (M⁺, 6), 248 (5), 231 (4), 203 (1), 170 (12), 114 (79), 70 (100), 57 (63), 41 (31);

1H NMR (CDCl₃, 300 MHz, r.t.) δ: 8.00 (br, 1H), 7.27-6.93 (m, 3H), 4.51 (br, 1H), 3.46 (br, 2H), 2.50 (br, 1H), 2.29 (s, 3H), 2.03 (m, 3H), 1.51 (s, 9H);

13C NMR (CDCl₃, 125 MHz, r.t.) δ: 170.0, 156.4, 136.4, 130.4, 128.2, 126.6, 124.4, 121.9, 80.8, 60.6, 47.3, 28.5 (3C), 27.3, 24.6, 17.9.

De-protection of proline was achieved by adding the purified BOC-(S)-proline-2-methylanilide to pure trifluoroacetic acid at 0°C, with stirring. The stirring was then continued for a couple of hours at room temperature. The excess of trifluoroacetic acid was removed in vacuo and sodium hydroxide solution was added till the pH was 13. The aqueous solution was extracted twice with diethyl ether and the extracts were treated as in the previous case. Re-crystallization from hexane afforded 6 g pure (>98%) (S)-proline-2-methylanilide (yield = 40%). Analytical data of (S)-proline-2-methylanilide:-

EI-MS: 204 (M⁺, 1), 107 (6), 91 (2), 77(4), 71 (5), 70 (100), 68 (5), 43
Diastereoselective hydrogenation of o-toluidine

(10), 39 (5); \(^1\)H NMR (CDCl\(_3\), 500 MHz, r.t.) \(\delta: 9.83\) (br, 1H), 8.12 (d, 1H, \(J = 7.8\)), 7.20 (t, 1H, \(J = 7.7\)), 7.15 (d, 1H, \(J = 7.4\)), 7.02 (td, 1H, \(J = 7.5, 1.1\)), 3.90 (dd, 1H, \(J = 9.2, 4.9\)), 3.10 (m, 1H), 3.00 (m, 1H), 2.29 (s, 3H), 2.19 (m, 1H), 2.07 (m, 1H), 1.78 (m, 2H); \(^1\)C NMR (CDCl\(_3\), 125 MHz, r.t.) \(\delta: 173.1, 136.0, 130.2, 127.4, 126.8, 124.1, 120.8, 61.3, 47.4, 30.8, 26.3, 17.6\). The scheme of the preparation of the substrate is shown in Scheme 2.1. See Appendix 2 for further details on amino acid coupling techniques.

[Diagram of synthesis of (S)-proline-2-methylanilide]

Scheme 2.1 Synthesis of (S)-proline-2-methylanilide

Identification of the absolute configuration of the isomeric products of hydrogenation of (S)-proline-2-methylanilide was done by preparing a reference racemic mixture and the \(\text{R},\text{S}^\text{eis}\) isomer (through a synthetic route) in an optically pure form as described in the following paragraphs.

Preparation of Racemic Cis and Racemic Trans Reference Mixture of (S)-Proline-2-Methylcyclohexylamide

A small amount of BOC-(S)-proline was dissolved in 40 ml chloroform and the solution cooled to 0°C under nitrogen. 3 equivalents of triethylamine, 1.2 equivalent of hydroxybenzotriazole, 1 equivalent 2-methylcyclohexylamine (cis:trans = 1:3) and 1.2 eq. \(N\)-(3-dimethylaminopropyl)-\(N\)'-ethyl-carbodiimide hydrochloride were added to the
cooled solution in succession. The solution was allowed to warm to room temperature and was stirred overnight under nitrogen. After washing the solution three times with 1 N HCl and twice with saturated sodium bicarbonate solution and finally with brine, the solvent was removed in vacuo to yield racemic cis and racemic trans BOC-(S)-proline-2-methylcyclohexylamide with a cis-trans ratio of 1:3. Analytical data of the racemic cis and racemic trans mixture:- EI-MS: 310 (M+ 2), 254 (2), 209 (5), 170 (21), 114 (100), 97 (18), 70 (98), 57 (59), 41 (36); 1H NMR (CDCl3, 200 MHz, r.t.) δ: 4.26 (br, 1H), 4.02 and 3.43 (br, 3H), 2.17-0.79 (m, 25H) including a singlet (9H) at 1.47 and four doublets (3H) at 0.93 (J = 6.1, trans), 0.88 (J = 7.0, cis), 0.87 (J = 6.1, trans), 0.81 (J = 6.9, cis).

De-protection of the amides was carried out in autoclavable sample bottles using a solution of dry HCl in dioxane. Thus, racemic cis- and racemic trans- (S)-proline-2-methylcyclohexylamide with a cis to trans ratio of 1:3 were obtained. Analytical data of the racemic cis and racemic trans mixture:- EI-MS: 210 (M+, 0.1), 168 (0.2), 137 (0.1), 112 (0.5), 97 (0.4), 70 (100), 68 (4), 55 (4), 43 (7); 1H NMR (CDCl3, 300 MHz, r.t.) δ: 4.24-2.85 (m, 4H), 2.20-0.82 (m, 16H) including four doublets (3H) at 0.89 (J = 6.5, trans), 0.88 (J = 6.5, trans), 0.85 (J = 6.9, cis), 0.84 (J = 6.9, cis). The dioxane was then evaporated in a stream of air and about 0.5 ml of dichloromethane and 0.05 ml of perfluoropropionic anhydride was added. The mixture was heated to 110°C for 5 min after sealing the sample bottle. The excess anhydride was evaporated in a stream of air along with dichloromethane and the contents of the sample bottle were dissolved in fresh dichloromethane. The perfluoropropionic acid derivative of the racemic cis- and trans- (S)-proline-2-methylcyclohexylamide were then injected in a GC equipped with a RTX-200 capillary column. The isolated product of catalytic hydrogenation was derivatised similarly. Comparison of the chromatogram of the derivatised racemic mixture to that of the derivatised product of catalytic hydrogenation, confirmed that the cis products were obtained in excess during catalytic hydrogenation.

Preparation of (S)-Proline-(1R,2S)-2-Methylcyclohexylamide (as Reference Compound)
The optically active cis-BOC-(S)-proline-(1R,2S)-2-methylcyclohexylamide isomer was synthesised as described above except that optically active (1R,2S)-2-methylcyclohexylamine hydrochloride was used instead of racemic 2-methylcyclohexylamine. Analytical data of cis-BOC-(S)-proline-(1R,2S)-2-methylcyclohexylamide: $^1$H NMR (CDCl$_3$, 200 MHz, r.t.) $\delta$: 4.30 (br, 1H), 4.03 (br, 1H), 3.4 (br, 2H), 2.42-1.12 (m, 22H) including a singlet (9H) at 1.47, 0.81 (d, 3H, $J = 6.9$); $^{13}$C NMR (DMSO, 75 MHz, 100 °C) $\delta$: 171.8, 154.6, 79.3, 60.4, 49.5, 47.2, 33.8, 30.4, 30.2, 29.7, 28.7, 23.9, 23.7, 22.2, 16.5. The optically active amine hydrochloride was synthesised from 2-methylcyclohexanone and 1-phenylethylamine using the transamination procedure (see Scheme 1.7) as reported by Knupp and Frahm [4]. Analytical data of 1R,2S-2-methylcyclohexyl amine hydrochloride: $^1$H NMR (CDCl$_3$, 200 MHz, r.t.) $\delta$: 8.36 (br, 3H), 3.37 (m, 1H), 2.07-1.21 (m, 9H), 1.11 (d, 3H, $J = 7.1$); $^{13}$C NMR (CDCl$_3$, 125 MHz, r.t.) $\delta$: 53.2, 32.4, 29.5, 27.6, 22.3, 21.7, 15.7. Deprotection of BOC-(S)-proline-(1R,2S)-2-methylcyclohexylamide and subsequent derivatisation of the optically pure (S)-proline-(1R,2S)-2-methylcyclohexylamide isomer was carried out as reported above for the racemic product. Comparison of the chromatogram of the derivatised optically pure product to that of derivatised product of catalytic hydrogenation, as for the racemic mixture, revealed the absolute configuration of the cis products.

2.2.2 Catalyst Preparation and Characterization

5 wt% Rh/C (Aldrich, 20,616-4), 5 wt% Ru/C (Fluka, 84031) and 10 wt% Pd/C (Fluka, 75990) were used as supplied. Several other catalysts were made by the incipient wetness technique using various supports (Al$_2$O$_3$, TiO$_2$ and ZrO$_2$) and precursors as shown in Table 2.1. TiO$_2$ (anatase, BET area = 54 m$^2$/g) and ZrO$_2$ (BET area = 54 m$^2$/g) were used as obtained from Degussa. Al$_2$O$_3$ granules from Condea were crushed to particles smaller than 60 μm (BET area = 230 m$^2$/g). All rhodium salt precursors were supplied by Johnson Matthey and the platinum salt was supplied by Fluka. The catalysts were prepared with a metal loading of 5 wt% and were dried in an oven at 120°C and then calcined in air at 350°C for 3 h after impregnation. These calcined catalysts were used for the hydrogenation experiments in the autoclave. In order to quantify the active
surface area of the catalyst, hydrogen chemisorption was used (for a brief description of the chemisorption apparatus and its application, see the dissertation of Gotti [5]). The catalysts were first reduced at 300°C for 1 h in hydrogen and outgassed under vacuum at the same temperature for the same period of time. The desorption isotherms were measured at 20°C and the H/M value [5] was determined by extrapolating the part of the isotherm between 10 and 50 kPa to zero hydrogen pressure. Table 2.1 lists the H/M values for various rhodium catalysts. In the case of the Rh/Al₂O₃ III catalyst, three batches of catalyst were prepared with dispersions ranging from 0.67 to 0.70.

Table 2.1 Catalyst precursors and solvents used in the preparation of rhodium and platinum catalysts by the incipient wetness technique

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Precursor</th>
<th>Solvent</th>
<th>H/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/C</td>
<td>Not available</td>
<td>-</td>
<td>0.29</td>
</tr>
<tr>
<td>Rh/Al₂O₃ I</td>
<td>Rh(acac)₃</td>
<td>Acetone</td>
<td>0.27</td>
</tr>
<tr>
<td>Rh/Al₂O₃ II</td>
<td>Rh(NO₃)₃.2H₂O</td>
<td>Water</td>
<td>0.74</td>
</tr>
<tr>
<td>Rh/Al₂O₃ III</td>
<td>RhCl₃.3H₂O</td>
<td>Water</td>
<td>0.67-0.70</td>
</tr>
<tr>
<td>Rh/TiO₂</td>
<td>Rh(acac)₃</td>
<td>Acetone</td>
<td>0.27</td>
</tr>
<tr>
<td>Rh/ZrO₂</td>
<td>Rh(acac)₃</td>
<td>Acetone</td>
<td>0.19</td>
</tr>
<tr>
<td>Pt/Al₂O₃</td>
<td>PtCl₄</td>
<td>Water</td>
<td>Not determined</td>
</tr>
</tbody>
</table>

2.2.3 Catalytic Hydrogenation

Experiments were conducted in a 200 ml stainless steel autoclave at a total pressure of 40 bar and a temperature of 70°C. In a typical experiment 400 mg of (S)-proline-2-methylanilide was dissolved in 60 ml ethanol. To this solution, 200 mg of supported metal catalyst was added in the oxidic form and the slurry was transferred to the autoclave. The autoclave was closed and flushed three times with nitrogen and subsequently three times with hydrogen. The hydrogen pressure was then increased to 37 bar and stirring (1000 rpm) was started. The subsequent heating of the autoclave to 70°C resulted in a total pressure of about 40 ± 2 bar. Changing the stirring speed to 800
and 1200 rpm did not change the rate of the reaction, establishing the absence of diffusion limitations. All subsequent reactions were conducted with a stirring speed of 1000 rpm. Since the autoclave was being heated to 70°C during the first few minutes of reaction, it was not possible to obtain reliable initial reaction rate values. The activities (ACT) are therefore reported as reciprocal of the time required for 50% conversion of the substrate (ACT = 1/t₅₀%).

The autoclave was equipped with a sampling tube, enabling periodic sampling of the liquid phase (sample volume, 0.5-1 ml). The samples were analyzed using a GC equipped with a γ-cyclodextrin column and a FID detector. The relative response factors of the reactant, intermediate and the products were assumed to be 1. In a typical chromatogram all the diastereomers of (S)-proline-2-methylcyclohexylamide were separated from each other as well as from the intermediate cyclohexene derivative (identified by GC-MS) and the reactant. The position of the double bond in the cyclohexene intermediate could not be identified.

2.2.4 X-ray Absorption Experiments

X-ray absorption spectra of the catalysts at the Rh-K edge were measured in the transmission mode at the synchrotron facility at the Swiss-Norwegian Beamline (SNBL) at ESRF, Grenoble. The catalyst samples were prepared by reduction and/or reaction in the autoclave at 40 bar hydrogen pressure and 70°C. After reduction and/or reaction and after filtering off the solvent, the catalysts were transferred to the sample cells in a nitrogen environment. The sample cell was then closed and the measurements were performed at room temperature without exposure to the atmosphere. Reference measurements were made on the calcined catalyst and a rhodium foil.

2.3 Results

Two cis and two trans hydrogenated products as well as a cyclohexene intermediate were obtained in the hydrogenation of (S)-proline-2-methylanilide (Scheme 2.2). The cis to trans ratio was between 4 and 5 for all experiments. The two trans isomers were
formed in almost equal amounts without any diastereoselectivity. In the case of the cis isomers, the 1R,2S isomer was always obtained in excess when (S)-proline was used as the chiral auxiliary. The selectivity between the cis isomers is reported as the d.e. Kinetic data of the reaction (cf. Fig. 2.1) indicated that the cyclohexene intermediate was hydrogenated simultaneously with the substrate and, in a standard experiment, it reached a maximum concentration up to 8% of the initial reactant concentration. The d.e. increased gradually with the conversion of the substrate and typically reached a value of 45% for rhodium catalysts. The reproducibility of the d.e. was about ±2%. Hydrogenation of BOC-(S)-proline-2-methylanilide was also conducted, but since the diastereoselectivity between the resulting fully hydrogenated cis products was very low (up to 10%), its hydrogenation was not investigated further.

**Scheme 2.2** Hydrogenation of (S)-proline-2-methylanilide (*the position of the double bond in the cyclohexene intermediate is not known*)
2.3.1 Comparison of Different Catalysts

The results of the hydrogenation reaction with various noble metal catalysts are summarized in Table 2.2. All reactions were conducted at 70°C and 40 bar, using ethanol as the solvent. At higher conversion considerable amounts of side products were obtained over the ruthenium catalyst.

Table 2.2 Activity (1/t50%) and selectivity of noble metal catalysts in the hydrogenation of (S)-proline-2-methylanilide at 70°C and 40 bar in ethanol

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>ACT (h⁻¹)</th>
<th>d.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/Al₂O₃</td>
<td>0.50</td>
<td>55</td>
</tr>
<tr>
<td>Rh/C</td>
<td>0.75</td>
<td>41</td>
</tr>
<tr>
<td>Ru/C</td>
<td>0.47</td>
<td>11</td>
</tr>
<tr>
<td>Pt/Al₂O₃</td>
<td>Negligible</td>
<td></td>
</tr>
<tr>
<td>Pd/C</td>
<td>Negligible</td>
<td></td>
</tr>
</tbody>
</table>

* of 1R,2S diastereomer
Table 2.3 Activity and selectivity of different rhodium catalysts in hydrogenation of (S)-proline-2-methylanilide at 70°C and 40 bar in ethanol

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>BET area (m²/g)</th>
<th>H/M</th>
<th>ACT (h⁻¹)</th>
<th>d.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/TiO₂</td>
<td>54</td>
<td>0.27</td>
<td>0.75</td>
<td>56</td>
</tr>
<tr>
<td>Rh/C</td>
<td>944</td>
<td>0.29</td>
<td>0.75</td>
<td>41</td>
</tr>
<tr>
<td>Rh/ZrO₂</td>
<td>54</td>
<td>0.19</td>
<td>0.27</td>
<td>57</td>
</tr>
<tr>
<td>Rh/Al₂O₃ I</td>
<td>227</td>
<td>0.27</td>
<td>0.50</td>
<td>55</td>
</tr>
<tr>
<td>Rh/Al₂O₃ II</td>
<td>227</td>
<td>0.74</td>
<td>1.20</td>
<td>49</td>
</tr>
<tr>
<td>Rh/Al₂O₃ III</td>
<td>227</td>
<td>0.67</td>
<td>1.50</td>
<td>46</td>
</tr>
</tbody>
</table>

* of 1R,2S diastereomer

Because of the low activity of the palladium and platinum catalysts and the low selectivity of the ruthenium catalyst, rhodium metal catalysts were chosen for further studies. With rhodium acetylacetonate (acac) as the precursor, a series of rhodium catalysts were prepared on different supports (namely, Rh/TiO₂, Rh/ZrO₂ and Rh/Al₂O₃ I). The activities of these catalysts differed widely (Table 2.3) but they had an identical diastereoselectivity. With the same Al₂O₃ as support, three rhodium catalysts were prepared using different metal precursors, as indicated in Table 2.1. The activity and to some extent the diastereoselectivity of these catalyst depended on the rhodium salt used in their preparation (Table 2.3).

2.3.2 Influence of Process Conditions: Temperature, Pressure and Solvent

The reaction temperature had a considerable influence on the activity of the catalyst. Thus, after about 500 min, only 40% conversion of the reactant was obtained when the reaction was carried out at 50°C with the Rh/Al₂O₃ III catalyst, while at 70°C complete conversion was obtained. With the Rh/Al₂O₃ III catalyst, the reaction rate as well as the selectivity remained almost unaffected on increasing the hydrogen pressure from 40 to 60 bar. Solvents are known to play a significant role in determining the stereoselectivity in hydrogenation reactions. Besides using ethanol as the standard solvent, therefore, the
use of tetrahydrofuran, ethyl acetate and chloroform was investigated. In the case of chloroform, the reactant was slowly converted to an unidentified product without any selectivity towards the ring hydrogenation product. The activity in tetrahydrofuran and ethyl acetate was much lower than that in ethanol but a slightly higher diastereoselectivity was obtained (Table 2.4).

Table 2.4 Effect of solvent on the activity and selectivity in the hydrogenation of (S)-proline-2-methylanilide with Rh/Al₂O₃ III catalyst at 70°C and 40 bar

<table>
<thead>
<tr>
<th>Solvent</th>
<th>ACT (h⁻¹)</th>
<th>d.e. (%)ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>1.50</td>
<td>46</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>0.50</td>
<td>56</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>0.11</td>
<td>52</td>
</tr>
<tr>
<td>Chloroform</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

ᵃ of 1R,2S diastereomer

2.3.3 Influence of Pre-reduction, Reuse of Catalyst and Addition of Diethylamine

As described in the experimental section, the catalyst was introduced in the oxidic form in the autoclave along with the substrate and the solvent. Reduction of the catalyst took place on introducing hydrogen and subsequent heating of the autoclave to 70°C. This procedure gave relatively good activities for the rhodium catalysts. Pre-reduction of the Rh/C catalyst under hydrogen at 100°C (before or after introduction into the autoclave in the absence of ethanol) led to a drastic reduction in the rate of the reaction. Pre-reduction of the catalyst in the solvent under hydrogen pressure led to an even lower rate and d.e. Similar results were obtained with the Rh/Al₂O₃ III catalyst.

After a standard experiment with the Rh/Al₂O₃ III catalyst, the reaction mixture was decanted to remove most of the solvent and substrate and the catalyst was repeatedly washed with ethanol, until the ethanol was almost free of product (as detected by GC analysis). The catalyst was then used again for another hydrogenation reaction. This
reused catalyst exhibited a much lower activity and the reaction almost stopped at about 50% conversion of the substrate. In a separate experiment, one equivalent of diethylamine was added to the reaction mixture before it was pressurized under hydrogen. Diethylamine was used as the additive because its basicity is comparable to that of the secondary amine group present in the substrate. The addition of diethylamine resulted in a marginal increase in the diastereoselectivity, but in a large reduction in the reaction rate.

2.3.4 EXAFS and XANES Studies on the Catalyst

| Table 2.5 EXAFS and XANES results for the Rh/Al₂O₃ III catalyst |
|---------------------------------|-----------------|-----------------|
|                                 | Co-ordination number | Percentage of |
|                                 | Rh-Rh | Rh-O | Rh(0) |
| Catalyst after reduction in EtOH | 6.1   | 1.2  | 69    |
| Catalyst after reaction in EtOH  | 5.3   | 1.4  | 53    |
| Catalyst as calcined            | 0.0   | 5.3  | 0     |

* Obtained from EXAFS;  † Obtained from XANES

EXAFS measurements and analyses were performed on the Rh/Al₂O₃ III catalyst to obtain information about the change in the oxidation state of rhodium during reaction. The EXAFS data were fitted using the \( k^4 \) weighted Fourier transformed \( \chi(k) \) function. Details of the analysis and interpretation of such spectra can be found elsewhere [6]. The co-ordination numbers obtained from the EXAFS analysis and the percentage of reduced rhodium obtained from the XANES data are reported for various samples in Table 2.5. The data indicate that the reduction of rhodium metal is incomplete during either reduction or reaction, under the typical process conditions. The catalyst is reduced to a lesser extent during reaction (53%) than during reduction (69%).
2.4 Discussion

![Chemical structures](image)

**Figure 2.2** Top views of the structures of proline-2-methylanilide adsorbed on a metal surface. From top, clockwise, formation of $R',1S,2R$; $S',1R,2S$; $S',1S,2R$, and $R',1R,2S$ product isomers.

The $1R,2S$ cis diastereomer was formed in excess when $(S)$-proline was used as the chiral auxiliary, while on hydrogenating a substrate made by coupling of $\alpha$-toluidine with $(R)$-proline instead of $(S)$-proline, the $1S,2R$ diastereomer was formed in excess.
This demonstrates that the proline auxiliary is responsible for the chiral induction in the hydrogenation reaction. The d.e. values obtained with (S)-proline and (R)-proline were equal but opposite in sign. Thus it looks as if the top two (R)-proline-2-methylanilide and (S)-proline-2-methylanilide structures adsorbed on the rhodium surface shown in Fig. 2.2 result in the formation of the $R',1S,2R$ and the $S',1R,2S$ diastereomers respectively on addition of hydrogen from the metal face of the rhodium catalyst. In these two structures, the nitrogen atom of the proline ring and the aromatic ring lie in the same plane on the catalyst surface and the amide bond is approximately parallel to the surface of the catalyst. The other cis diastereomers, namely $S',1S,2R$ and $R',1R,2S$, are formed when the adsorption through the benzene ring takes place by its opposite face (bottom two structures in Fig. 2.2). However, these configurations lead to more steric crowding because of the interaction of the methyl group with the carbonyl group and hence are the less preferred structures.
Partial hydrogenation of a substituted aromatic ring leads to the formation of cyclohexene and cyclohexadiene derivatives. Intermediate cyclohexadiene species have rarely been observed in hydrogenation of aromatic compounds [7], but cyclohexene species have often been detected. Hydrogenation of these cyclohexene species is responsible for the formation of trans isomers. Although many different cyclohexene intermediates can be formed, only the five species shown in Scheme 2.3 are relevant in the present reaction for the formation of trans isomers. In the case of intermediate I, trans formation can result only if the addition of the two hydrogen atoms takes place from the opposite faces on the aromatic ring. This is possible if the catalyst has a stepped surface or if the hydrogen atom comes from the solvent (in the case of protic solvents or acidic conditions) [8]. Since the cis to trans ratio was independent of the solvent and the metal dispersion, these possibilities do not seem likely.

The maximum concentration of the intermediate detected in the solution phase (~6%) cannot be correlated with the amount of trans products (20%) because the intermediate...
and the reactant are hydrogenated simultaneously. Thus the formation of trans isomers exclusively from the intermediate I via its conversion on the surface of the catalyst, by a \( \pi \)-allyl mechanism or intramolecular hydrogen transfer as shown in Scheme 2.4 to the intermediates II and III is a possibility. In addition, the trans products could be formed directly through the hydrogenation of intermediates II and III, or by intramolecular hydrogen transfer followed by hydrogenation [9, 10]. The slow hydrogenation of the substrate probably allows equilibrium to be reached between various hydrogenation and isomerisation processes of the intermediate(s). This accounts for the independence of the cis to trans ratio from either the process parameters or the catalyst preparation. The d.e. is strongly dependent only on the nature of the noble metal and fairly independent of the process conditions. A relatively small dependence of the diastereoselectivity on the process parameters but a strong dependence on the molecular structure has been observed in other (non-aromatic) diastereoselective hydrogenations [11]. As has been reported earlier for different kinds of aromatic substrates [12], ruthenium and rhodium were the most active catalysts for the present hydrogenation reaction. The platinum and palladium catalysts were almost inactive probably because of strong adsorption of the amine group on those catalysts [13]. All catalysts prepared from the same rhodium precursor but with different oxide supports gave similar results in terms of diastereoselectivity (namely, Rh/TiO\(_2\), Rh/ZrO\(_2\) and Rh/Al\(_2\)O\(_3\) I, Table 2.3). The difference in diastereoselectivity between the oxide-supported catalysts and carbon-supported catalyst could be due to the difference in the nature of the surface of the two supports. However, this difference in selectivity may also be due to the different precursor, which has been used in the preparation of the catalysts. (Since the Rh/C catalyst was purchased from Aldrich, the rhodium precursor is not known for this catalyst). For the three catalysts prepared on the same Al\(_2\)O\(_3\) support but from different precursors (namely, Rh/Al\(_2\)O\(_3\) I, Rh/Al\(_2\)O\(_3\) II and Rh/Al\(_2\)O\(_3\) III) no clear correlation is observed between the activity of the catalysts and their dispersion (Table 2.3). In general a higher activity is obtained at higher dispersion. The EXAFS data on the calcined Rh/Al\(_2\)O\(_3\) III catalyst indicated that the chlorine originating from the rhodium chloride precursor was probably not completely removed during the calcination step. Thus the possibility of residual chlorine influencing the activity of this catalyst cannot
be excluded. The Rh/Al₂O₃ II catalyst was, however, free of nitrate as confirmed by FT-IR measurements on the impregnated and the calcined catalyst samples.

Rhodium is a very good catalyst for hydrogenation of aromatic compounds since it can catalyze these reactions under relatively mild process conditions as compared to other catalysts. However, the present substrate hydrogenated very slowly at room temperature. Hence, the reaction was conducted at 70°C in order to get a reasonable activity. The relatively strong dependence of the rate of reaction on temperature is indicative of a strong adsorption of the substrate on the catalyst. The substrate molecule is most probably preferentially adsorbed through the secondary amine group on the proline ring as is evident from the experiments in which diethylamine was added to the reaction mixture. The product of the hydrogenation reaction is also an amine and hence the total concentration of amine groups remains constant in the reaction mixture. A negligible effect of the hydrogen pressure on the reaction rate suggests that the reaction is product-desorption controlled. In the diastereoselective hydrogenation of (S)-proline modified o-toluic acid, Besson et al. [2] have reported enhancement of the diastereoselectivity and a decrease in the reaction rate on the addition of an amine. In the present case no big enhancement in the diastereoselectivity was observed because the reaction mixture already contained a high concentration of amine groups.

Use of aprotic solvents like tetrahydrofuran and ethyl acetate resulted in a marginally higher d.e. (Table 2.4). As observed before in the hydrogenation of other aromatic substrates [14], the rate was fastest in the alcoholic solvent. The reason for a fourteen fold higher activity in ethanol than in ethyl acetate is unclear. The hydrogenation failed when chloroform was used as the solvent, probably because of poisoning of the active sites by chloride resulting from chloroform [13].

The catalyst is not reduced completely during either pre-reduction or reaction as indicated in Table 2.5. When the catalyst is reduced in hydrogen gas at a moderate temperature, it has a lower activity, as shown by experiments in which the catalyst is pre-reduced. Also a re-used catalyst exhibits a lower activity than a fresh one. The loss in activity occurs irrespective of the fact whether carbon or alumina is used as the
support. The EXAFS data reported for catalyst Rh/Al2O3 III in Table 2.5 indicate that the particle size remains unchanged during the reduction of the catalyst. Therefore sintering of small metal particles during reaction can be excluded as an explanation for the loss in catalyst activity. The loss in activity is therefore probably due to loss of the active sites, either due to a change in the morphology of the rhodium particles or a change in the oxidation state of the rhodium or due to strong adsorption of organic species formed during the reaction. See Appendix 1 for a further discussion about deactivation.

2.5 Conclusions

Ruthenium and rhodium are the most active metal catalysts for the hydrogenation of the (S)-proline-2-methylanilide amongst the noble metal catalysts investigated. The stereoselectivity seems to be strongly dependent on the substrate and weakly on other factors since relatively small differences are observed between the rhodium catalysts prepared from different precursors, on different supports, and under different reaction conditions. This has also been observed in other diastereoselective heterogeneous catalytic hydrogenations. The hydrogenation activity, however, is dependent on the temperature, the catalyst precursor and support and the solvent. The substrate adsorbs preferentially through the amine group and the diastereoselectivity arises from adsorption of the substrate on a rhodium surface preferentially through one of the two diastereotopic faces of the aromatic ring. The catalyst deactivates as it is reduced during the reaction. EXAFS and XANES experiments indicate that only a part of the rhodium in the catalyst is reduced under reaction conditions. A partly reduced catalyst is thus more active than a fully reduced catalyst.

References


3. Diastereoselective Hydrogenation of (S)-Proline-modified Anthranilic acid

3.1 Introduction

In catalytic hydrogenation of unsaturated compounds, hydrogen is very likely added to the stereotopic face with which the unsaturated compound adsorbs or complexes with the catalyst. Thus the problem of achieving high selectivity reduces essentially to constraining the molecule to adsorb from only one of the two stereotopic faces. This was shown in the hydrogenation of (S)-proline-2-methylanilide in Fig. 2.1 in the previous chapter; the two cis diastereomeric products result from the adsorption and subsequent hydrogenation of the molecule in the two configurations it adopts on the catalyst surface. Thus, ideally, a molecule, which adsors only in one configuration on the surface of the catalyst should be hydrogenated with a high selectivity. The number of configurations a molecule can adopt on the catalyst surface is dependent on the strength of interactions of the different functional groups in the molecule with the catalyst and the flexibility of the molecule. The stronger the interaction (either attractive or repulsive) and the lower the flexibility, the greater the chance that the molecule adsorbs only in one configuration on the metal surface. The discussion pertaining to the strength of interaction of the molecule with the catalyst will be deferred till the next chapter. The flexibility of the molecule is inversely dependent on the degree of rotation around every single bond in the molecule. By preventing rotation along single bonds, therefore, one should be able to increase the hydrogenation selectivity. Specifically, rotation should be hindered along those single bonds which determine the spatial relationship between the two faces of the aromatic ring and the centre of chirality of the auxiliary. This relationship is primarily determined by the single bonds connecting the aromatic ring to the auxiliary. For example, the two structures of (S)-proline-2-methylanilide shown in Fig 2.2 can be inter-converted by rotation around a-b and c-d chemical bonds as shown in structure I in Fig. 3.1 Therefore, if rotation around these
bonds is hindered high stereoselectivities should be attainable. To test this hypothesis, we studied the hydrogenation of anthranilic acid modified with (S)-proline. The ability of anthranilic acid to form two covalent bonds with the amino acid auxiliary (structure

\[
\text{II in Fig. 3.1)} \text{ was exploited to give extra rigidity to the aromatic compound-auxiliary system as compared to the o-toluidine-(S)-proline system. Reduction of the anthranilic acid-(S)-proline adduct, using the non-catalytic Birch technique, was successfully implemented by Schultz et al. [1]. In the present chapter, the use of heterogeneous and homogeneous catalysts for the reduction of the adduct is reported. Catalytic reduction of the adduct, if it proceeds with a good selectivity, would be a viable alternative to the Birch reduction, which requires rather demanding reaction conditions.}

3.2 Experimental

3.2.1 Catalytic Hydrogenation

The commercially available anthranilic acid-(S)-proline adduct, (11aS)-2,3-dihydro-1H-pyrrolo[2,1c][1,4]benzodiazepine-5,11-dione (Aldrich), was used without further purification. The catalysts investigated were Rh/C (Aldrich), Rh/Al₂O₃, Ru/charcoal and Ru/Al₂O₃ (all Fluka). Reactions were conducted in a 60 ml stainless steel autoclave equipped with a sampling tube at 50°C and 50 bar hydrogen pressure. In a typical experiment, 100 mg of substrate was dissolved in 30 ml solvent and 50 mg of the supported catalyst was added (substrate to metal ratio ~19). In the reactions with homogeneous catalysts, deoxygenated solvents were used. In some solvents the
substrate was insoluble at room temperature hence a suspension was used. The slurry was transferred to the autoclave and flushed successively with nitrogen and hydrogen. The autoclave was pressurised to 50 bar with hydrogen, stirring at 1100 rpm using a gas inducing impeller was started and the autoclave was heated to the final temperature. As reported in Chapter 2, it was difficult to obtain reliable initial reaction rate values because of the initial heating period. The activities are therefore reported as the reciprocal of time required for 50% conversion of the substrate \((ACT = 1/t_{50\%})\).

Samples (~0.2 ml) were taken through the sample tube to study the kinetics of the reaction and were analysed using a GC equipped with a FID detector. The conversion was determined using a 5 m γ-DEX capillary column and the diastereoselectivity was determined with a 30 m RTX capillary column. In addition to the fully hydrogenated products a cyclohexene by-product was obtained (Scheme 3.2). The relative response factors of all products and the substrate were assumed to be 1.

### 3.2.2 Synthesis of the Reference Compounds

Reference *cis* and *trans* compounds were synthesized starting from the corresponding racemic hexahydrophthalic anhydride in a three-step procedure (Scheme 3.1). The first two steps were conducted exactly as reported by Kircheldorf [2]. In the first step, the hexahydrophthalic anhydride was converted to the trimethylsilyl ester-isocyanate by treatment with trimethylsilyl-azide. The solvent and excess trimethylsilyl-azide were distilled off to isolate the isocyanate. Hydrolysis of the isolated isocyanate with water in ether gave the corresponding racemic hexahydro-isatoic anhydride as a white powder in an analytically pure form. The *cis* and *trans* hexahydro-isatoic anhydrides were identified by comparison of their NMR spectra with those reported in the literature [2]. Analytical data of racemic *cis* hexahydro-isatoic anhydride (*cis* hexahydro-benzo[1,3]oxazine-2,4-dione): - **EI-MS**: 169 (M⁺, 0.4), 141 (8), 123 (18), 96 (30), 82 (100), 69 (26), 54 (45), 44 (46); **¹H NMR** (CDCl₃, 500 MHz, r.t.) \(\delta\): 7.05 (br, 1H), 3.57 (m, 1H), 2.94 (dt, 1H, \(J=5.1, 5.0\)), 2.23 (m, 1H), 1.89 (m, 1H), 1.65 (m, 1H), 1.58-1.44 (m, 3H), 1.4-1.25 (m, 1H); **¹³C NMR** (CDCl₃, 125 MHz, r.t.) \(\delta\): 167.1, 150.6, 47.9, 39.8, 30.7, 24.2, 22.5, 21.7. Analytical data of racemic *trans* hexahydro-isatoic
anhydride (*trans* hexahydro-benzo[1,3]oxazine-2,4-dione):- \textbf{EI-MS}: 169(M^+, 0.2), 141 (26), 123 (71), 100 (24), 82 (100), 67 (55), 55 (42), 41 (39); \textbf{H NMR} (CDCl$_3$, 500 MHz, r.t.) $\delta$: 6.87 (br, 1H), 3.26 (m, 1H), 2.30-2.24 (m, 2H), 2.11 (m, 1H), 1.91-1.83 (m, 2H), 1.44-1.25 (m, 4H); \textbf{C NMR} (CDCl$_3$, 125 MHz, r.t.) $\delta$: 167.1, 150.4, 50.7, 43.8, 31.4, 24.6, 24.2, 23.4.

![Scheme 3.1 Preparation of reference compounds](image)

In the third step, the hexahydro-isatoic anhydrides were converted to the reference mixtures by refluxing overnight in pyridine with an equimolar amount of pyridine hydrochloride and a slight excess of (S)-proline, as reported by Schultz et al. [1]. The reaction gave low isolated yields (~30%) unlike the high yield obtained with aromatic anhydrides used by Schultz. The reaction also proceeded diastereoselectively and unequal amounts of the *cis* (and *trans*) isomers were obtained from the racemic *cis* (and *trans*) isatoic anhydrides. Subsequent purification of the *cis* and *trans* reference mixture was done by flash chromatography on silica gel (EtOAc:MeOH = 19:1) to give analytically pure reference compounds. The ratio of diastereomeric products in the *cis* and *trans* reference mixtures in the analytically pure samples was 1.8 (5aR,9aS:5aS,9aR)
Diastereoselective hydrogenation of anthranilic acid

and 1.4 (5aR,9aR:5aS,9aS) respectively. Analytical data of the cis reference mixture (5aR,9aS and 5aS,9aR diastereomers): - EI-MS: 222 (M⁺, 33), 194 (11), 167 (6), 126 (7), 82 (12), 70 (100), 55 (9), 41 (15). (5aR,9aS,11aS)-Perhydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione: - ¹H NMR (CDCl₃, 500 MHz, r.t.) δ: 5.80 (br, 1 H), 4.49 (t, 1 H, J = 7 Hz), 4.09 (br, 1 H), 3.67 (m, 1 H), 3.54 (m, 1 H), 2.71 (m, 1 H), 2.15-2.26 (m, 1 H), 2.05-2.11 (m, 1 H), 1.38-2.00 (m, 10 H); ¹³C NMR (CDCl₃, 125 MHz, r.t.) δ: 171.1, 170.9, 57.4, 48.5, 48.4, 46.8, 30.1, 28.5, 25.7, 24.7, 22.4, 20.9. (5aS,9aR,11aS)-Perhydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione: - ¹H NMR (CDCl₃, 500 MHz, r.t.) δ: 5.62 (br, 1 H), 4.46 (t, 1 H, J = 7.8 Hz), 3.92 (br, 1 H), 3.78 (m, 1 H), 3.49 (m, 1 H), 2.85 (m, 1 H), 2.37-2.50 (m, 2 H), 1.38-2.00 (m, 10 H); ¹³C NMR (CDCl₃, 125 MHz, r.t.) δ: 172.5, 171.3, 59.4, 50.1, 49.8, 48.9, 33.1, 31.5, 25.3, 22.2, 21.8, 19.8.

The identification of the absolute configuration of the cis diastereomers was done using two dimensional ¹H NMR NOE spectroscopy. Since proline used in the preparation of the reference mixture was enantiomerically pure, the determination of orientation of the two junction protons on the cyclohexyl ring (namely those at 5a and 9a) with respect to the proton at 11a, gave us the absolute configurations of the 5a and 9a carbon atoms. A NOE was observed between protons at 5a, 9a and 11a for the 5aR,9aS diastereomer because they lie on the same side of the molecular plane in this isomer (Fig. A3.1 in Appendix 3). For the other cis diastereomer (5aS,9aR) a NOE was observed only between protons at 5a and 9a but not between 11a and these two protons. The 5aS,9aS trans diastereomer in the mixture of the two trans isomers was identified by comparison of the NMR spectra of the mixture to the NMR spectra reported by Schultz and Alva [3] for this diastereomer. The other trans diastereomer in the reference mixture was assigned the 5aR,9aR configuration.

The cyclohexene by-product of the reaction was isolated by repeated crystallisation of a mixture of reaction products containing the by-product and the fully hydrogenated products using a hexane-dichloromethane solvent mixture. It was characterised by elemental analysis, mass spectrometry and NMR. The position of the C=C double bond in the six-membered ring of the cyclohexene by-product was identified by a ¹³C NMR
DEPT analysis. It was found to be located between the two junction carbon atoms.
Analytical data of the cyclohexene by-product ((11aS)-1,2,3,6,7,8,9,10,11,11a-decahydro-5H-pyrrolo[2,1-c] [1,4]benzodiazepine-5,11-dione):- **EI-MS**: 220 (M^+, 78), 191 (21), 164 (20), 150 (7), 123 (13), 95 (35), 70 (100), 41 (17); **^1H NMR** (CDCl₃, 500 MHz, r.t.) δ: 7.57 (br, 1 H), 4.05 (dd, 1 H, J = 2.3, 8.0 Hz), 3.64 (m, 1 H), 3.49 (m, 1 H), 2.67-2.76 (m, 2 H), 2.17-2.31 (m, 3 H), 1.91-2.04 (m, 3 H), 1.79-1.90 (m, 2 H), 1.64 (m, 1 H), 1.47-1.60 (m, 1 H); **^13C NMR** (CDCl₃, 125 MHz, r.t.) δ: 170.1, 166.7, 135.8, 119.1, 57.2, 46.5, 30.2, 25.8, 25.4, 23.3, 22.1, 21.8; **^13C DEPT NMR** (CDCl₃, 125 MHz, r.t.) δ: 57.2 (CH), 46.5, 30.2, 25.8, 25.4, 23.3, 22.1, 21.8 (all CH₂).

### 3.3 Results and Discussion

![Scheme 3.2 Hydrogenation products of (S)-proline-modified anthranilic acid](image)
Hydrogenation of the adduct led to the simultaneous formation of the fully hydrogenated cis products and of a cyclohexene by-product (see kinetics in Fig. 3.2 and Scheme 3.2). The fully hydrogenated trans products were also obtained in very small amounts. Typically the yield of cis diastereomers together was 30-40% and that of the cyclohexene by-product was 60-70%. Samples were taken during the reaction to monitor the selectivity and the activity of the catalyst. Accurate determination of the concentration of one of the two trans isomers was not possible and therefore a good estimation of the d.e. between the two trans isomers cannot be given. However, a very high cis to trans ratio was obtained (typically 15-30). The formation of the trans diastereomers is not shown in Fig. 3.2 for clarity. The 5aR,9aS diastereomer was always obtained in excess upon direct hydrogenation of the adduct. The chemoselectivity is reported as the selectivity to the two cis diastereomers, while the diastereoselectivity is reported as the diastereomeric excess between the cis diastereomers. The chemoselectivity and the diastereoselectivity (cf. Fig. 3.2) varied only slightly with the conversion of the adduct for the alumina-supported catalysts. For the carbon-supported catalysts, the chemoselectivity increased but the diastereoselectivity decreased with conversion.
Preliminary experiments with Pt/Al2O3 and Pd/C catalysts revealed that they were not effective and, hence, they were excluded from further studies. Results of the hydrogenation reaction with the Rh and Ru catalysts are reported in Table 3.1. The chemoselectivity and the diastereoselectivity are reported at 100% conversion of the adduct. The activity and selectivity of the catalysts varied widely depending on the catalyst and the solvent. In general, all the catalysts exhibited a low activity. The carbon-supported catalysts were more active than those supported on alumina. The activity was higher when water was used as the solvent and increased as expected with increasing hydrogen pressure and temperature. Ru-based catalysts gave a higher yield of cis products than Rh catalysts but exhibited a lower diastereoselectivity. When water was used as the solvent with carbon-supported catalysts, the chemoselectivity increased, but the diastereoselectivity decreased. The alumina-supported Rh catalysts yielded more cis products than the carbon-supported ones. In the case of Ru catalysts, it is difficult to draw any conclusions about the dependence of chemoselectivity on the nature of the support because of the subsequent reduction of the cyclohexene by-product, as will be discussed later. Use of alumina as the support resulted in a high diastereoselectivity with both Rh and Ru catalysts, as observed for other aromatic substrates with Rh catalysts [4,

### Table 3.1 Hydrogenation of the adduct using heterogeneous Rh and Ru catalysts

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>ACT (h⁻¹)</th>
<th>Chemoselectivity (%)</th>
<th>d.e. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/Al2O3</td>
<td>EtOH</td>
<td>0.92</td>
<td>31</td>
<td>94</td>
</tr>
<tr>
<td>Rh/Al2O3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>EtOH</td>
<td>0.83</td>
<td>30</td>
<td>96</td>
</tr>
<tr>
<td>Rh/Al2O3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>EtOH</td>
<td>0.67</td>
<td>26</td>
<td>91</td>
</tr>
<tr>
<td>Rh/C</td>
<td>EtOH</td>
<td>0.67</td>
<td>22</td>
<td>76</td>
</tr>
<tr>
<td>Ru/Al2O3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>EtOH</td>
<td>0.20</td>
<td>26</td>
<td>83</td>
</tr>
<tr>
<td>Ru/charcoal</td>
<td>EtOH</td>
<td>2.00</td>
<td>36</td>
<td>73</td>
</tr>
<tr>
<td>Rh/Al2O3</td>
<td>H2O</td>
<td>5.00</td>
<td>38</td>
<td>94</td>
</tr>
<tr>
<td>Rh/C</td>
<td>H2O</td>
<td>6.67</td>
<td>32</td>
<td>60</td>
</tr>
<tr>
<td>Ru/Al2O3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>H2O</td>
<td>0.83</td>
<td>33</td>
<td>82</td>
</tr>
<tr>
<td>Ru/charcoal</td>
<td>H2O</td>
<td>6.00</td>
<td>53</td>
<td>52</td>
</tr>
</tbody>
</table>

<sup>a</sup> of 5αR, 9αS diastereomer; <sup>b</sup> Reaction conducted under 80 bar hydrogen pressure; <sup>c</sup> Reaction conducted at 80°C; <sup>d</sup> Due to low reactivity of the catalyst, reaction was conducted at 80°C and stopped at a conversion of 59%
With the Rh/Al₂O₃ catalyst, the diastereoselectivity varied between 85-95% on changing solvent to t-butanol, methanol, isopropanol and ethyl acetate whereas the chemoselectivity remained unaltered. Various alumina-supported rhodium catalysts having varying dispersions prepared using different rhodium salt precursors (see Chapter 2) gave similar stereo and chemoselectivities as the commercial Rh/Al₂O₃ catalyst. As reported earlier by Besson et al. for the hydrogenation of N-(2-methylbenzoyl)-(S)-proline esters [6], we also found that the addition of triethylamine to the present reaction mixture, with Rh/C as the catalyst, resulted in an improved diastereoselectivity but in a concomitant reduction in the rate.

To compare the performance of heterogeneous and homogeneous catalysts, we hydrogenated the substrate using two homogeneous catalysts namely [Rh(C₅Me₅)Cl₂]₂ [7] and [(η⁶-C₆H₆)RuCl₂]₂ [8, 9] which have been used successfully in the hydrogenation of a wide variety of substituted aromatic compounds. The reaction conditions and the results of hydrogenation with homogeneous catalysts are reported in Table 3.2. In the case of the homogeneous Ru catalyst, colloidal metal particles were detected in the solution at the end of the reaction. The two homogeneous catalysts used in our investigation hydrogenate the substrate with a lower activity but a comparable selectivity as their heterogeneous counterparts.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>ACT (h⁻¹)</th>
<th>Chemoselectivity (%)</th>
<th>d.e. (%)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Rh(C₅Me₅)Cl₂]₂</td>
<td>i-PrOH</td>
<td>0.33</td>
<td>26</td>
<td>92</td>
</tr>
<tr>
<td>[Ru(C₆H₆)Cl₂]₂</td>
<td>EtOH-H₂O</td>
<td>0.43</td>
<td>32</td>
<td>74</td>
</tr>
</tbody>
</table>

³ of 5aR, 9aS diastereomer; ⁴ Reaction conditions: 70°C and 50 bar hydrogen pressure with 200 mg substrate (substrate to metal molar ratio of 41) in 20 ml IPA and 20 equivalents of triethylamine; ⁵ Reaction conditions: 90°C and 60 bar hydrogen pressure with 430 mg substrate (substrate to metal molar ratio of 21) in 30 ml 1:1 EtOH-H₂O mixture

The cyclohexene by-product (isolated with > 96% purity) was further hydrogenated with the Rh/C, Rh/Al₂O₃ and Ru/charcoal catalysts under the same reaction conditions as those for the hydrogenation of adduct but with a lower substrate to catalyst ratio of 9.
The hydrogenation of the cyclohexene by-product occurred at a much slower rate than that of the adduct on all catalysts. In the case of the Rh/Al₂O₃ catalyst, the activity was negligible, while in the case of Ru/charcoal, hydrogenation proceeded at a moderate rate but not to completion, probably because of deactivation. The activity of Rh/C was low but detectable. Hydrogenation of the cyclohexene by-product yielded predominantly the cis diastereomers with carbon-supported catalysts. However, there was an inversion in the diastereoselectivity, and the 5aS,9aR cis diastereomer was obtained as the major product with a d.e. of about 30% for Ru/charcoal and about 40% for the Rh/C catalyst. Thus, the subsequent hydrogenation of the cyclohexene by-product on carbon-supported catalysts accounts for their low overall d.e. Hydrogenation of the cyclohexene by-product was facilitated when water was used as the solvent. This explains the low overall d.e. and the high yield of cis products obtained when water is used as the solvent as opposed to ethanol, especially with carbon-supported catalysts. The reason for the very slow hydrogenation of the by-product, even when a powerful hydrogenating catalyst such as Rh is employed, is unclear. Hydrogenation may be difficult because of the inability of the olefinic carbons to coordinate with the metal surface, due to either electronic or steric reasons. In the case of alumina-supported catalysts, preferential adsorption of the by-product on the alumina surface via the polar amide groups can account for their inactivity. The alumina-supported catalysts exhibit a lower activity than the carbon-supported catalysts in the hydrogenation of the adduct, probably due to a similar preferential adsorption on the alumina support. We also attempted the hydrogenation of the by-product using [Ir(cod)py(PCy₃)]PF₆ in CH₂Cl₂ [10]. Under the typical reaction conditions employed, no activity was detected.

The diastereoselectivity obtained in the hydrogenation of the adduct is a result of the preferential reactivity of one of its two diastereotopic faces on the surface of the catalyst. Surprisingly, if only steric factors are considered to be important in determining the face with which the adduct adsorbs on the surface of the catalyst, molecular modelling (using the MM2 force-field in MacroModel) suggests that the 5aS,9aR diastereomer is likely to be the major product. The structure of the adduct molecule was also confirmed using the program Cerius² [11] and is similar to its crystal structure determined by Feigel et al. [12]. The NMR spectrum of the adduct remains
unchanged between -100°C and 120°C, suggesting its conformational homogeneity in the CDCl₃ solution. The diastereoselectivity in hydrogenation of the adduct seems to be the result of electronic interactions of its amide bonds with the surface of the catalyst. These electronic interactions are probably weaker with Ru than those with Rh, causing Ru catalysts to be less selective. The diastereoselectivity obtained in the hydrogenation of the adduct is very high as compared to those obtained in the hydrogenation of other substrates [13]. The better performance of this system is attributed to the greater rigidity with which the chiral auxiliary is bound to the aromatic compound. This facilitates good differentiation between the two diastereotopic faces of the aromatic compound on the metal surface of a heterogeneous catalyst or at a homogeneous catalyst. This result is comparable to the high selectivities achieved in the hydrogenation of the C=O bond in dehydro-amino acids by construction of a rigid diketopiperazine structure with an amino-acid auxiliary (see Scheme 1.5). In addition, in our system the amino acid (S)-proline imparts additional rigidity to its structure, favouring high stereocontrol during hydrogenation. Besson et al. reported a high diastereoselectivity in the hydrogenation of o-toluic acid using (S)-pyroglutamic acid as the chiral auxiliary [14]. Also in that case, the high stereoinduction is probably due to the rigidity of the aromatic compound-auxiliary system because of hindered rotation around the C(O)-N amide bonds.

3.4 Conclusions

Hydrogenation of (S)-proline-modified anthranilic acid occurs with a high diastereoselectivity but low chemoselectivity on Rh and Ru catalysts. The low chemoselectivity precludes its use as an alternative to Birch reduction. The high diastereoselectivity is attributed to the rigidity of the anthranilic acid-proline moiety. The diastereoselectivity seems to be independent of the nature of the solvent (except water) or the catalyst precursor and dispersion. The carbon-supported catalysts hydrogenate with a lower diastereoselectivity than the alumina-supported catalysts. The lower diastereoselectivity is due to the ability of the carbon-supported catalysts, especially when water is used as the solvent, to hydrogenate the cyclohexene by-product. All catalysts exhibit a higher activity when water is used as the solvent. Rh and
Ru based homogeneous catalysts are as selective but less active than their heterogeneous counterparts.

References

4. Diastereoselective Hydrogenation of 1-Substituted Indanes (Part I)

4.1 Introduction

In Chapter 3 it was proposed that the diastereoselectivity obtained in the hydrogenation of an auxiliary-modified aromatic compound is dependent on its rigidity and its strength of interaction with the metal surface. The former hypothesis was substantiated by hydrogenating the (S)-proline-anthranilic acid adduct with a high stereoselectivity. Although high selectivity was obtained, it was not possible to know a priori from the structure of molecule as to which of the two cis diastereomers would be obtained on hydrogenation. To allow such a prediction, the interaction of this molecule with the catalyst surface has to be understood. The face with which the molecule adsorbs preferentially will be hydrogenated. Thus the strength of interaction of the molecule through one of its two faces must exceed that through the other face considerably. In order to rationalize the strength of interaction of the faces of a molecule with the catalyst, one has to understand the interaction of every functional group of the molecule with the catalyst. A literature survey revealed that interactions of individual functional groups had been determined for cyclic olefinic substrates during their hydrogenation over palladium catalysts [1-4]. A comparable study of hydrogenation of aromatics was, however, lacking.

We, therefore, studied the hydrogenation of a series of disubstituted aromatic compounds, differing only in the functional group attached to a carbon atom near the aromatic ring. Thus a series of indanes, substituted at a carbon atom in the saturated ring, were hydrogenated. The present chapter elucidates the results of hydrogenation of such substrates bearing the hydroxyl, amino and alkyl functional groups (Fig. 4.1). Results pertaining to the hydrogenation of substrates bearing the carboxylic acid, amide, ester and alkoxy groups will be presented in Chapter 5. To understand the influence of the size of the ring bearing the functional group, 1- and 2-tetralol were hydrogenated as
well. The molecules shown in Fig. 4.1 can adopt only two conformations on the surface of the noble metal, depending on which face of the aromatic ring they adsorb. Since the chosen substrates can be considered approximately planar, the induction obtained in their hydrogenation is directed by the functional group substituent present on the saturated ring. Also, since rotation of the bonds connecting the carbon atom bearing the functional group to the aromatic ring is impossible, an unambiguous and direct correlation can be established between a functional group of a substrate and the configuration of its hydrogenation product.

![Figure 4.1 Aromatic substrates hydrogenated](image)

As mentioned in Section 1.3, directing effects of a substituent have been used effectively in the diastereoselective hydrogenation of olefinic substrates, catalyzed particularly by homogeneous rhodium and iridium complexes [5, 6]. Co-ordination of a neighboring polar functional group has also been exploited in distinguishing the enantiotopic faces of a C=C bond in the enantioselective hydrogenation of olefinic substrates with chiral homogeneous catalysts. However, since homogeneous catalysts often show a low activity in aromatic hydrogenation, studies pertaining to directing effects in these hydrogenation reactions have not been conducted. Our aim was to investigate if directing effects of some functional groups can be utilized, similar to those
exploited in homogeneous catalysis, during hydrogenation of these relatively simple aromatic compounds over heterogeneous rhodium catalysts.

In addition, we investigated the hydrogenation of these substrates to understand the intriguing effect of the addition of organic bases on stereoselectivity, reported in earlier diastereoselective aromatic hydrogenation reactions \[7, 8\]. A complementary study investigating the influence of the addition of inorganic bases on the stereoselectivity was also conducted. The present chapter focuses on stereoselectivity rather than activity obtained in the hydrogenation of various aromatic substrates under different process conditions.

### 4.2 Experimental

#### 4.2.1 Hydrogenation Experiments

Hydrogenation reactions were conducted under efficient mass-transport conditions in a 60 ml stainless steel autoclave equipped with a gas-inducing impeller at a stirring speed of 1100 rpm. In a typical experiment, a solution of 0.5 g substrate in 15 ml ethanol or hexane (and basic additive, if any) was added to 50 mg catalyst in the autoclave. Pt/Al$_2$O$_3$, Rh/Al$_2$O$_3$ (Fluka) and Rh/C (Aldrich) catalysts (metal loading 5 wt\%) were used as supplied. The autoclave was closed, flushed three times successively with nitrogen and hydrogen and then pressurized to 50 bar with hydrogen. Hydrogenation of 1-aminoindane on the rhodium catalysts and that of 2-tetralol on the platinum catalyst was conducted at 70°C. All other reactions were conducted at room temperature. Samples could be taken with a sample tube during the reaction to detect the completion of the reaction (typically less than 12 h in experiments without base addition), but no kinetic measurements were done because of unpredictable deactivation of the catalysts (Appendix 1). Analysis of samples for the determination of conversion and selectivity was done using a GC equipped with a FID detector and various capillary columns depending on the substrate hydrogenated. Although the diastereomeric products in most cases could be separated on a non-chiral HP-1 column, chiral columns were also used for GC analyses. In the case of 1-aminoindane, the reaction samples were dried free of
ethanol, derivatized with N-methyl-bis-trifluoroacetamide (MBTFA) overnight at room temperature and then injected in a RTX-200 capillary column after redissolving the sample in dichloromethane. Some hydrogenation experiments were continued overnight, even after complete conversion of the substrate and the intermediate. The diastereoselectivity remained unchanged over this additional period indicating that no epimerisation occurs under reaction conditions.

### 4.2.2 Preparation of 1-Indanylmethanol and 1-Methylindane

Racemic 1-indanol, 1-tetralol, 1-aminoindane (all Fluka) and 2-tetralol (Acros) were used as obtained. Racemic 1-indanylmethanol was prepared in two steps from racemic 3-oxoindan-1-carboxylic acid (Aldrich). In the first step the keto group was hydrogenolyzed over 10 wt% Pd/C catalyst (Fluka). In the second step the carboxylic acid group was hydrogenated to the hydroxymethylene group using LiAlH₄. The product of synthesis was identified as 1-indanylmethanol by comparison of its NMR data with those reported in the literature [9]. Hydrogenolysis of racemic 3-methyl-1-oxoindanone (Aldrich) over Pd/C catalyst in ethanol under 3 bar hydrogen yielded racemic 1-methylindane quantitatively. It was identified by comparison of MS data with that reported in the literature [10]. The catalyst was filtered off and the solution of racemic 1-methylindane in ethanol was used in its hydrogenation. The purity of all substrates exceeded 97% as determined by GC analysis.

### 4.2.3 Identification of Cis-cis and Cis-trans Product Isomers

The relative configurations of the cis product isomers (cis-cis and cis-trans, Scheme 4.2) of some substrates were identified by preparing reference mixtures. The relative configurations of trans product isomers (trans-cis and trans-trans) were not identified. Isomers of perhydro-1-indanol were identified by comparison of a 13C NMR spectrum of the product mixture with their spectra reported in the literature [11]. Isomers of perhydro-1-tetralol were identified by comparison of a 1H NMR spectrum of the product mixture to their spectra reported in the literature [12]. The cis-cis perhydro-2-tetralol (2-decalol) isomer was identified by comparison of a 13C NMR spectrum of the
product mixture to the spectrum reported in the literature. The identification of the other isomeric product was difficult, however, because of conflicting $^{13}$C NMR data in the literature for the cis-trans isomer [13,14]. The product mixture was therefore oxidized to 2-decalone using chromic acid as reported by Brown and Garg [15]. $^{13}$C NMR of the 2-decalone product showed only one C=O group, indicating that the hydrogenation product consisted of cis-cis and cis-trans isomers. The cis configuration of 2-decalone was also confirmed by comparison of its $^{13}$C NMR spectrum with that reported in the literature [16].

\[
\begin{align*}
\text{COOH} & \xrightarrow{\text{LiAlH}_4, \text{Et}_2\text{O}} \text{CH}_2\text{OH} \\
& \xrightarrow{\text{r.t., 3 h}} \\
\text{CH}_3 & \xrightarrow{T\text{sCl, Py}} \text{CH}_2\text{OTs} \\
& \xrightarrow{0^\circ \text{C, 1 h} \text{ r.t., 12 h}} \\
& \xrightarrow{\text{reflux., 12 h}} \\
\end{align*}
\]

**Scheme 4.1 Preparation of the reference perhydro-1-methylindane mixture**

Identification of the absolute configuration of the perhydro-1-methylindane product posed considerable difficulty because no separate spectral data of the isomers were available in the literature. Therefore a reference mixture of cis-cis and cis-trans diastereomers was synthesized starting from perhydroindan-1-carboxylic acid (cis-cis to cis-trans ratio of 3:1) using the route reported by Brewster and Buta [17]. The mixture of perhydroindan-1-carboxylic acid was obtained by hydrogenation of indan-1-carboxylic acid on Rh/C catalyst as indicated in Chapter 5. Comparison of the gas chromatograms of the reaction product obtained using a $\alpha$-DEX capillary column and
that of the synthesized reference sample enabled identification of the relative configuration. As shown in Scheme 4.1, the synthesis of the reference sample involved reduction of the mixture of cis-cis and cis-trans diastereomers of perhydroindan-1-carboxylic acid to the corresponding perhydro-1-indanylmethanol isomers using LiAlH₄. The isomeric mixture of alcohols was converted into their tosyl derivatives. These tosyl derivatives were then reduced using LiAlH₄ to give a mixture of cis-cis and cis-trans perhydro-1-methylindane in approximately the same ratio as the diastereomeric mixture of the starting acid. Analytical data of cis-cis and cis-trans diastereomers of perhydro-1-methylindane:

- **EI-MS**: 138 (M⁺, 15), 96 (34), 81 (83), 67 (71), 53 (49), 41 (100), 39 (86), 27 (49). Cis-cis isomer:
  - ¹H NMR (CDCl₃, 500 MHz, r.t.) δ: 2.09-0.85 (m, 18H) including a doublet at 0.89 (J = 4.3) corresponding to the methyl group;
  - ¹³C NMR (CDCl₃, 125 MHz, r.t.) δ: 43.7, 39.7, 38.7, 30.6, 27.3, 26.2, 25.6, 22.2, 21.1, 15.4. Cis-trans isomer:
  - ¹H NMR (CDCl₃, 500 MHz, r.t.) δ: 2.09-0.85 (m, 18H) including a doublet at 0.93 (J = 6.6) corresponding to the methyl group;
  - ¹³C NMR (CDCl₃, 125 MHz, r.t.) δ: 47.0, 39.3, 34.5, 32.0, 29.8, 29.0, 26.2, 24.9, 22.4, 20.3.

The intermediate mixture of perhydro-1-indanylmethanol isomers was used as a reference for identification of the product isomers obtained in the hydrogenation of 1-indanylmethanol. Analytical data of cis-cis and cis-trans diastereomers of perhydro-1-indanylmethanol:

- **EI-MS**: 136 (11), 121 (20), 94 (34), 81 (45), 67 (49), 53 (23), 41 (54), 31 (100). Cis-cis isomer:
  - ¹H NMR (DMSO, 500 MHz, r.t.) δ: 4.22 (t, 1H, J = 5.0 Hz), 3.39-3.25 (m, 2H), 2.05-0.86 (m, 15H); ¹³C NMR (CDCl₃, 75 MHz, r.t.) δ: 64.1, 47.0, 40.5, 39.4, 27.0, 25.4, 25.2, 25.2, 22.1, 20.9. Cis-trans isomer:
  - ¹H NMR (DMSO, 500 MHz, r.t.) δ: 4.35 (t, 1H, J = 5.2 Hz), 3.39-3.25 (m, 1H), 3.22-3.17 (m, 1H) 2.05-0.86 (m, 15H); ¹³C NMR (CDCl₃, 75 MHz, r.t.) δ: 67.2, 44.0, 41.4, 39.1, 29.4, 27.8, 27.4, 26.6, 23.9, 23.1.

Hydrogenation of 1-aminoindane gave two products, which were identified as the cis-cis and cis-trans diastereomers (vide infra). Analytical data of cis-cis and cis-trans diastereomers of perhydro-1-aminoindane:

- **EI-MS**: 139 (M⁺, 21), 122 (18), 110 (57), 93 (20), 79 (22), 67 (23), 56 (100), 43 (66). Cis-trans isomer:
  - ¹H NMR (CDCl₃, 500 MHz, r.t.) δ: 3.15 (m, 1H), 2.16-2.04 (m, 2H), 1.81-1.74 (m, 1H), 1.55-1.21 (m, 11H);
**Diastereoselective hydrogenation of indanes. I**

$^{13}$C NMR (CDCl$_3$, 125 MHz, r.t.) $\delta$: 54.7, 48.9, 37.8, 33.6, 28.8, 28.2, 25.5, 24.1, 22.8.

Cis-cis isomer: $^1$H NMR (CDCl$_3$, 500 MHz, r.t.) $\delta$: 3.28 (m, 1H), 2.16-0.95 (m, 14H);
$^{13}$C NMR (CDCl$_3$, 125 MHz, r.t.) $\delta$: 56.9, 44.0, 37.4, 32.2, 27.2, 25.1, 24.8, 21.1, 21.0.

The relative configuration of perhydro-1-aminoindane (major product) was identified by converting it to the $N$-benzoyl derivative, by treatment of the isolated product with benzoyl chloride in a dilute NaOH solution. A two dimensional $^1$H NOE NMR spectrum of the resulting amide enabled us to determine that the proton at the carbon atom bearing the amide group was *trans* to the protons attached to both junction carbon atoms. Analytical data of cis-trans $N$-benzoyl-perhydro-1-aminoindane:-

- EI-MS: 243 (M$^+$, 4), 148 (7), 134 (6), 122 (100), 105 (83), 93 (8), 77 (52), 51 (11);
- $^1$H NMR (CDCl$_3$-DMSO, 500 MHz, r.t.) $\delta$: 7.86-7.83 (m, 2H), 7.48-7.39 (m, 4H), 4.37 (m, 1H), 2.26 (m, 1H), 2.06 (br, 1H), 1.93 (br, 1H), 1.84 (m, 1H), 1.60-1.23 (m, 10H);
- $^{13}$C NMR (CDCl$_3$, 75 MHz, r.t.) $\delta$: 167.4, 135.0, 131.3, 128.5, 128.5, 126.9, 126.9, 52.9, 46.4, 37.8, 31.0, 28.4, 28.4, 25.2, 24.0, 22.4.

Further proof of the structure was obtained by X-ray crystallography on a monoclinic crystal of the $N$-benzoyl derivative [18], obtained by crystallization from a diisopropyl ether-hexane solvent mixture. A summary of the crystal structure data (Table A3.1) and a graphical display of the crystal structure (Fig. A3.2) of the $N$-benzoyl derivative are included in Appendix 3. For detailed information of the crystal structure of the $N$-benzoyl derivative see the Supporting Information to the article by Ranade et al. [19]. The minor product of hydrogenation was assumed to have the cis-cis configuration in analogy to the results of other hydrogenation reactions.

### 4.3 Results

Hydrogenation of all the substrates yielded predominantly *cis* diastereomers (usually *cis* to *trans* ratio $> 10$) with respect to the substituents on the six membered ring (for example see Scheme 4.2 for hydrogenation of 1-indanol). Different methods were employed for the identification of the relative configurations of the *cis* diastereomers (cis-cis and cis-trans), depending upon the substrate hydrogenated as described in Section 4.2. The chemoselectivity to the hydrogenated *cis* products is defined as the
fractional yield of the two cis isomers at 100% conversion of the substrate. The selectivity between the two cis isomers is reported as the diastereomeric ratio (d.r.) at 100% conversion of the substrate and hydrogenation intermediates. For presentation of the diastereomeric ratio, the sum of the yield of the two diastereomers is normalized to 100. In the case of alcoholic substrates a significant amount of hydrogenolysis-hydrogenation by-products (cis and trans) was obtained. The fractional yield of the hydrogenolysis-hydrogenation products of these substrates is reported at 100% conversion of the substrates as well.

Scheme 4.2 Products of hydrogenation of 1-indanol over rhodium catalysts
Small to significant amounts (up to 10%) of cyclohexene intermediates were observed (and identified by GC-MS analysis) depending on the substrate hydrogenated and the reaction conditions. In most of the substrates the hydrogenation of the cyclohexene intermediate proceeded much slower than that of the substrate and it caused a change in the diastereoselectivity, the magnitude of which depended on the substrate hydrogenated. The cyclohexene intermediate hydrogenated slower than the corresponding aromatic substrate probably because of its higher steric hindrance (attributed to its non-planar structure) during its adsorption on the catalyst. The position of the double bond in the cyclohexene intermediates was not identified rigorously. However, from steric considerations it is likely that the double bond is situated between the two junction carbon atoms.

Hydrogenation of 1-indanol gave cis and trans isomers of the hydrogenation product perhydro-1-indanol and of the hydrogenolysis-hydrogenation product perhydroindane (Scheme 4.2). We confirmed that perhydroindane was formed directly from 1-indanol and not by hydrogenolysis of perhydro-1-indanol. The results of the hydrogenation in ethanol and hexane using the Rh/C and Rh/Al₂O₃ catalysts are presented in Table 4.1. With ethanol as the solvent, the Rh/C catalyst yielded predominantly perhydroindane while the Rh/Al₂O₃ catalyst yielded predominantly perhydro-1-indanol. With hexane as the solvent, the yield of perhydroindane was lowered with both catalysts. Low d.r. values were obtained for both catalysts, and the value was lower in hexane than in ethanol. Halving the substrate to metal ratio in the case of Rh/Al₂O₃ had a negligible influence on the d.r. and the chemoselectivity.

The results obtained in the hydrogenation of 1-tetralol are reported in Table 4.2. The yield of the two cis perhydro-1-tetralol (1-decalol) isomers as well as the d.r. of the two cis isomers depended on the catalyst support. As for 1-indanol, severe hydrogenolysis was observed on Rh/C in ethanol. The d.r. as well as the yield of 1-decalol was higher on Rh/Al₂O₃ than Rh/C. With the Rh/Al₂O₃ and Rh/C catalysts, changing the solvent from ethanol to hexane increased the yield to 1-decalol but decreased the d.r.
Table 4.1 Hydrogenation of 1-indanol

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield of cis &amp; trans perhydroindane&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield of cis perhydro-1-indanol isomers&lt;sup&gt;b&lt;/sup&gt;</th>
<th>d.r.&lt;sup&gt;ab&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/C&lt;sup&gt;c&lt;/sup&gt;</td>
<td>EtOH</td>
<td>77</td>
<td>19</td>
<td>59:41</td>
</tr>
<tr>
<td>Rh/C&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hexane</td>
<td>42</td>
<td>55</td>
<td>47:53</td>
</tr>
<tr>
<td>Rh/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>EtOH</td>
<td>10</td>
<td>88</td>
<td>65:35</td>
</tr>
<tr>
<td>Rh/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;d&lt;/sup&gt;</td>
<td>EtOH</td>
<td>6</td>
<td>93</td>
<td>67:33</td>
</tr>
<tr>
<td>Rh/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hexane</td>
<td>3</td>
<td>96</td>
<td>57:43</td>
</tr>
</tbody>
</table>

<sup>a</sup> cis-cis: cis-trans; <sup>b</sup> Determined by GC (HP-1 and α-DEX capillary columns); <sup>c</sup> Substrate to rhodium molar ratio = 154; <sup>d</sup> Substrate to rhodium molar ratio = 72

Table 4.2 Hydrogenation of 1-tetralol

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield of cis &amp; trans decalin&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield of cis 1-decalol isomers&lt;sup&gt;b&lt;/sup&gt;</th>
<th>d.r.&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/C</td>
<td>EtOH</td>
<td>76</td>
<td>16</td>
<td>53:47</td>
</tr>
<tr>
<td>Rh/C</td>
<td>Hexane</td>
<td>53</td>
<td>43</td>
<td>45:55</td>
</tr>
<tr>
<td>Rh/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>EtOH</td>
<td>12</td>
<td>81</td>
<td>69:31</td>
</tr>
<tr>
<td>Rh/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Hexane</td>
<td>3</td>
<td>91</td>
<td>55:45</td>
</tr>
</tbody>
</table>

<sup>a</sup> Substrate to rhodium molar ratio = 139; <sup>b</sup> Determined by GC (HP-1 and α-DEX capillary columns); <sup>c</sup> cis-cis: cis-trans

Table 4.3 Hydrogenation of 1-indanylmethanol

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield of cis &amp; trans perhydro-1-methylindane&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield of cis perhydro-1-indanylmethanol isomers&lt;sup&gt;b&lt;/sup&gt;</th>
<th>d.r.&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/C</td>
<td>EtOH</td>
<td>30</td>
<td>70</td>
<td>45:55</td>
</tr>
<tr>
<td>Rh/C</td>
<td>Hexane</td>
<td>16</td>
<td>82</td>
<td>47:53</td>
</tr>
<tr>
<td>Rh/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>EtOH</td>
<td>5</td>
<td>92</td>
<td>52:48</td>
</tr>
<tr>
<td>Rh/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Hexane</td>
<td>1</td>
<td>97</td>
<td>47:53</td>
</tr>
</tbody>
</table>

<sup>a</sup> Substrate to metal molar ratio = 139; <sup>b</sup> Determined by GC (HP-1 and α-DEX capillary columns); <sup>c</sup> cis-cis: cis-trans
Results of hydrogenation of **1-indanylmethanol** on carbon and alumina supported rhodium catalysts in ethanol and hexane are shown in Table 4.3. Significant hydrogenolysis was observed on the Rh/C catalyst. The d.r. value was almost unity and changed only slightly with either the catalyst support or the solvent.

The results obtained in the hydrogenation of **2-tetralol** are shown in Table 4.4. Like in the above cases, significant hydrogenolysis was observed on the Rh/C catalyst. Reactions with the Pt/Al₂O₃ catalyst were conducted at 70°C because of lower activity. As observed for 1-indanol and 1-tetralol, using hexane as the solvent instead of ethanol lowered the d.r. for Rh/Al₂O₃ as well as Pt/Al₂O₃ catalysts.

| Catalyst | Solvent | Yield of cis & trans decalin | Yield of cis 2-decalol isomers | d.r.  
|----------|---------|------------------------------|-----------------------------|--
| Rh/C     | EtOH    | 25                           | 68                          | 63:37  
| Rh/Al₂O₃ | EtOH    | 8                            | 85                          | 76:24  
| Rh/Al₂O₃ | Hexane  | 3                            | 89                          | 64:36  
| Pt/Al₂O₃ | EtOH    | 5d                           | 83d                         | 65:35d 
| Pt/Al₂O₃ | Hexane  | 1                            | 95                          | 49:51  

* Reaction conducted at 70°C with Pt/Al₂O₃, Substrate to metal molar ratio = 139; 
Determined by GC (HP-1 and β-DEX capillary columns); 
* cis-cis:cis-trans; 
* at 85% conversion of 2-tetralol

**1-Methylindane** was prepared in ethanol by hydrogenolysis of 3-methyl-1-oxoindane and was contaminated with the water formed during its preparation. The separation of 1-methylindane from ethanol and water was difficult because of its low boiling point and azeotrope formation with ethanol. Hence, its solution in the ethanol-water mixture was directly used in the hydrogenation experiments. Table 4.5 reports the results obtained at different process conditions on the Rh/C catalyst and at one condition on the Rh/Al₂O₃ catalyst. The difference in the performance of Rh/C and Rh/Al₂O₃ is negligible. The yield to the cis isomers and the d.r. were almost unaffected by a change in the hydrogen pressure and the substrate to rhodium molar ratio.
Table 4.5 Hydrogenation of 1-methylindane

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield of cis perhydro-1-methylindane isomers</th>
<th>d.r.(^{a,b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/Al(_2)O(_3)(^c)</td>
<td>EtOH</td>
<td>92</td>
<td>64:36</td>
</tr>
<tr>
<td>Rh/C(^c)</td>
<td>EtOH</td>
<td>93</td>
<td>63:37</td>
</tr>
<tr>
<td>Rh/C(^d)</td>
<td>EtOH</td>
<td>92</td>
<td>62:38</td>
</tr>
<tr>
<td>Rh/C(^c,e)</td>
<td>EtOH</td>
<td>92</td>
<td>64:36</td>
</tr>
</tbody>
</table>

\(^{a}\) Determined by GC (HP-1 and \(\alpha\)-DEX capillary columns); \(^{b}\) cis-cis:cis-trans; \(^{c}\) Substrate to metal molar ratio = 156; \(^{d}\) Substrate to metal molar ratio = 312; \(^{e}\) H\(_2\) pressure = 15 bar

The hydrogenation of 1-aminoindane proceeded very slowly at room temperature and hence was conducted at 70°C and with approximately half the normal substrate to rhodium molar ratio (~77). Irrespective of the catalyst support, a very low d.r. (i.e. a high selectivity to the cis-trans diastereomer of perhydro-1-aminoindane) was obtained (Table 4.6). A small amount of 1-aminoindane was converted to 1-aminoindane hydrochloride in a diethyl ether solution by bubbling dry hydrogen chloride gas. After isolation of the salt, 0.5 g of it was hydrogenated at the standard temperature and pressure on the Rh/Al\(_2\)O\(_3\) catalyst in ethanol. The yield of the cis-trans isomer decreased and the d.r. increased to 32:68. As stated in Section 4.2, the relative configuration of the other diastereomer formed was not identified rigorously but in analogy to the results of hydrogenation of all other substrates was assumed to be cis-cis.

Table 4.6 Hydrogenation of 1-aminoindane

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield to cis perhydro-1-aminoindane isomers</th>
<th>d.r.(^{a,b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/C(^c)</td>
<td>EtOH</td>
<td>100</td>
<td>2:98</td>
</tr>
<tr>
<td>Rh/Al(_2)O(_3)(^c)</td>
<td>EtOH</td>
<td>100</td>
<td>1.5:98.5</td>
</tr>
<tr>
<td>Rh/Al(_2)O(_3)(^d)</td>
<td>EtOH</td>
<td>90</td>
<td>32:68</td>
</tr>
</tbody>
</table>

\(^{a}\) Determined by GC using a RTX-200 capillary column after derivatization of the product with MBTFA; \(^{b}\) cis-cis:cis-trans; \(^{c}\) Reaction conducted at 70°C with substrate to metal molar ratio = 77; \(^{d}\) Hydrogenation of 1-aminoindane hydrochloride at room temperature with a substrate to metal molar ratio = 122
Addition of amines has been used before to influence the diastereoselectivity in aromatic hydrogenation reactions [7, 8]. We studied the effect of the addition of triethylamine to reaction mixtures of the different substrates before their hydrogenation in ethanol. The results of the experiments are reported in Table 4.7. Addition of amine resulted in a substantial decrease in the activity of the rhodium catalysts for all substrates. Very little activity was detected for hydrogenation of 1-tetralol and 1-indanylmethanol. The hydrogenolysis activity of Rh/C catalyst in hydrogenation of 1-indanol was almost completely suppressed, thus increasing the yield of the cis perhydro-1-indanol isomers. The value of d.r. decreased on addition of amine for both 1-indanol and 1-methylindane.

Table 4.7 Hydrogenation in ethanol with triethylamine additive

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Substrate to rhodium molar ratio</th>
<th>Yield of cis isomers</th>
<th>d.r.$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-indanol</td>
<td>Rh/C</td>
<td>154</td>
<td>97</td>
<td>50:50</td>
</tr>
<tr>
<td>1-methylindane</td>
<td>Rh/C</td>
<td>156</td>
<td>86</td>
<td>56:44</td>
</tr>
<tr>
<td>1-methylindane</td>
<td>Rh/Al$_2$O$_3$</td>
<td>156</td>
<td>90</td>
<td>59:41</td>
</tr>
</tbody>
</table>

$^a$ triethylamine to rhodium molar ratio = 10; $^b$ cis-cis:cis-trans

Addition of an aqueous solution (0.3 ml of 0.5 N) of inorganic bases to the reaction mixture with ethanol and Rh/C resulted in a decrease in the activity of the catalyst by an order of magnitude. The activity decreased with increasing concentration of the base and with increasing size of the cation. The results are shown in Table 4.8. A drastic suppression of hydrogenolysis activity was observed on the addition of inorganic bases, as observed with triethylamine. In the case of 1-indanol and 1-tetralol, the cis-trans diastereomer was the major product. The d.r. depended on the base added and increased with the size of the cation in the case of alkaline hydroxide additives. On increasing the amount of NaOH solution from 0.3 to 1 ml in the hydrogenation of 1-indanol, the d.r. decreased further from 19:81 to 12:88 and was accompanied by a further decrease in the activity.
Table 4.8 Hydrogenation over Rh/C in ethanol with inorganic base additives

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Substrate to rhodium molar ratio</th>
<th>Base (^a)</th>
<th>Time (days)</th>
<th>Conversion</th>
<th>Yield of cis isomers (^b)</th>
<th>d.r. (^{b,c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-indanol</td>
<td>154</td>
<td>LiOH</td>
<td>1</td>
<td>100</td>
<td>96</td>
<td>41:59</td>
</tr>
<tr>
<td>1-indanol</td>
<td>154</td>
<td>NaOH</td>
<td>1</td>
<td>91</td>
<td>95</td>
<td>19:81</td>
</tr>
<tr>
<td>1-indanol</td>
<td>154</td>
<td>Na(_2)CO(_3)</td>
<td>1</td>
<td>92</td>
<td>96</td>
<td>31:69</td>
</tr>
<tr>
<td>1-indanol</td>
<td>154</td>
<td>KOH</td>
<td>4</td>
<td>81</td>
<td>89</td>
<td>15:85</td>
</tr>
<tr>
<td>1-tetralol</td>
<td>139</td>
<td>NaOH</td>
<td>3</td>
<td>100</td>
<td>84</td>
<td>28:72</td>
</tr>
<tr>
<td>1-methylindane</td>
<td>156</td>
<td>NaOH</td>
<td>-</td>
<td>-</td>
<td>88</td>
<td>53:47</td>
</tr>
</tbody>
</table>

\(^a\) alkali metal to rhodium molar ratio = 6; \(^b\) at 81% conversion of 1-indanol in the experiment with the KOH additive and at 100% conversion of substrates in all other experiments; \(^c\) cis-cis:cis-trans

4.4 Discussion

The aromatic substrates undergoing hydrogenation can adsorb in two ways on the catalyst surface depending on the interaction of the functional group present on the neighboring saturated ring. The interaction of a functional group with the catalyst surface depends on steric and electronic factors. When the electronic interaction dominates, hydrogenation of the aromatic ring takes place from the side of the substituent leading to the cis-trans diastereomer. Contrarily, when the steric repulsion dominates, hydrogenation occurs from the side opposite to the substituent leading to the cis-cis diastereomer. Similar studies were done by Thompson et al. [1-3] in the hydrogenation of cyclic olefinic substrates over heterogeneous palladium catalyst. They showed that some functional groups had a strong affinity (also termed as haptophilicity) for the catalyst, resulting in hydrogenation products with a configuration opposite to that expected when considering only steric repulsion of the functional group. While their study was conducted on the hydrogenation of olefinic substrates over platinum and palladium-based catalysts, we studied the hydrogenation of aromatic substrates over rhodium-based catalysts.
In the hydrogenation of the aromatic substrates, cyclohexene intermediates were often observed. The cyclohexene intermediates hydrogenated further only after complete conversion of the substrate or when the substrate concentration was very low. The diastereoselectivity obtained in their hydrogenation was different from that obtained in the direct hydrogenation of the parent aromatic substrate. A rigorous examination of the diastereoselectivity-functional group relationship of the aromatic substrates should include a separate investigation of a similar relationship of the corresponding cyclohexene intermediates. Since the latter investigation was not done, we are unable to separate the directing effect of the functional group in the aromatic compound from that in the corresponding cyclohexene intermediates. However, the influence on the final diastereoselectivity is relatively small since only a small percentage of the aromatic compound desorbs as cyclohexene intermediate after its partial hydrogenation. For example, in the hydrogenation of 1-tetralol in hexane over the Rh/Al₂O₃ catalyst, the d.r. changed from 56:44 at 12% conversion to 55:45 at 100% conversion.

Results shown in Table 4.1 indicate that the haptophilicity of the hydroxyl group to the rhodium catalyst, if at all present, is definitely not high, since the cis-cis instead of the cis-trans isomer is obtained in excess with Rh/C and Rh/Al₂O₃ catalysts. The Rh/C catalyst showed considerably more hydrogenolysis selectivity than the Rh/Al₂O₃ catalyst. Labeling experiments indicated that hydrogenolysis on Rh/C occurs by elimination of the protonated hydroxyl group by spillover hydrogen on the mildly acidic carbon support (Chapter 7). Hydrogenation was also investigated in hexane because the ethanol hydroxyl groups could compete with and/or solvate the 1-indanol hydroxyl groups, thus masking its haptophilicity. The selectivity to perhydroindane is lower in hexane than in ethanol, because of lower stability of the intermediate in the hydrogenolysis reaction. In hexane the selectivity to the cis-cis isomer is reduced indicating that the hydroxyl group in 1-indanol probably interacts mildly with the catalyst surface. Results of hydrogenation of 1-tetralol are qualitatively similar to those obtained with 1-indanol (Table 4.2). The influence of the nature of the catalyst support on the diastereoselectivity could be due to the difference in the magnitude of interaction of the hydroxyl group of the substrate with the catalyst support and/or a contribution of hydrogenation with spillover hydrogen in some supports. Since the adsorption of an
aromatic ring is much stronger than that of a double bond on rhodium [20], the difference in energy between the two adsorbed structures leading to the two different cis diastereomers is probably smaller than that between the highly hindered olefinic substrates investigated by Thompson and co-workers [1-3]. This can explain why the interaction of the hydroxyl group with the rhodium catalyst is much weaker than that in their investigation. We were unable to study hydrogenation of the benzylic aromatic substrates with platinum or palladium catalysts, because of even more hydrogenolysis than with rhodium.

In 1-indanol and 1-tetralol the hydroxyl group is attached to a carbon at the α position with respect to the aromatic ring. The effect on the selectivities of shifting the location of the hydroxyl group to the β carbon was studied by hydrogenating 1-indanylmethanol and 2-tetralol (Tables 4.3 and 4.4). The values of d.r. as well as the variation of the d.r. with catalyst support and solvent are considerably different in 1-indanylmethanol and 2-tetralol. In the case of 1-indanylmethanol the haptophilic effect is stronger than in 1-indanol or 1-tetralol since the value of d.r. is almost unity, and it does not vary with catalyst support or the solvent. In contrast, the results of the hydrogenation of 2-tetralol indicate the presence of a mild haptophilic effect the magnitude of which changes with the solvent as in the cases of 1-indanol and 1-tetralol. The difference in the diastereoselectivities of hydrogenation of 2-tetralol and 1-indanylmethanol is probably due to the orientation of the hydroxyl group when these molecules adsorb on the catalyst surface. Hydrogenation of 2-tetralol was conducted on Pt/Al₂O₃ catalyst to compare the haptophilicity of the hydroxyl group to platinum with that to rhodium. Although a quantitative comparison between platinum and rhodium catalysts is not possible because the hydrogenation reactions were conducted at different temperatures, a similar trend is observed on changing the solvent from ethanol to hexane with platinum as with rhodium.

1-Methylindane can interact only sterically with the surface of the catalyst and hence both the Rh/C and the Rh/Al₂O₃ catalysts give the same results (Table 4.5). Since each substrate molecule bears the chiral element necessary for stereoselective hydrogenation, we do not expect a big effect on diastereoselectivity of the substrate to rhodium ratio
and hydrogen pressure, as observed in hydrogenation of 1-methylindane. This is confirmed also in the case of 1-indanol where a change in the substrate to catalyst ratio by a factor of two resulted in hardly any change in the d.r. The purely steric interaction of the methyl group is unable to prevent the adsorption of the aromatic substrate from the methyl-group side and only a small preference to the cis-cis isomer is observed. The reason for the low selectivity must be the small size of the methyl group. The magnitude of the steric hindrance of the hydroxyl group in 1-indanol is comparable to that of the methyl group in 1-methylindane in ethanol.

It is a well known that amines adsorb strongly on noble metal catalysts [21, 22]. In some of the diastereoselective hydrogenation reactions reported earlier, amine additives were used. These additives decreased the rate of reaction by strongly adsorbing on the metal and modified the selectivity. Thus, as expected, strong adsorption of 1-aminindane during reaction resulted in a very low hydrogenation activity at room temperature and hence the reactions had to be conducted at 70°C. The amino group showed a strong haptophilic effect giving an almost quantitative yield of the cis-trans isomer. The effect is irrespective of whether Rh/C or Rh/Al₂O₃ is used as the catalyst because the substrate interacts primarily with the rhodium metal during hydrogenation. On neutralizing the basicity of the amino group by converting 1-aminindane to its hydrochloric acid salt before hydrogenation, the selectivity to the cis-trans isomer was drastically reduced clearly demonstrating the haptophilicity of the amino group.

Addition of triethylamine reduces the activity of the catalyst due to strong adsorption. The d.r. decreases on addition of amine in the hydrogenation of 1-indanol over Rh/C and somewhat surprisingly also in the hydrogenation of 1-methylindane. The decrease in diastereoselectivity of 1-methylindane indicates that the amine modifies the stereoselectivity not only by an electronic mechanism but also by a steric mechanism.

The influence of inorganic base additives on stereoselectivity in the hydrogenation of substituted phenolic aromatic compounds on rhodium catalysts has been reported before [23]. The results in Table 4.8 show that the addition of inorganic bases induces a substantial change in diastereoselectivity of the benzylic aromatic substrates.
investigated. The addition of alkali hydroxides in the hydrogenation of benzylic alcohols, not only reduced the value of the d.r. below unity but even produced the cis-trans diastereomer with a moderately high selectivity. This could be due to the interaction of the hydroxyl group of the substrate with the alkali metal cations on the surface of the catalyst. The activity decreases with an increase in the size of cation, probably because a bigger cation blocks more surface rhodium atoms than a smaller cation. The higher d.r. obtained for Na\textsubscript{2}CO\textsubscript{3} than NaOH is probably due to a lower extent of dissociation in the ethanol-water mixture. Addition of NaOH in the hydrogenation of 1-methylindane also reduced the d.r. Reduction in the d.r. in hydrogenation of 1-methylindane by organic as well as inorganic bases indicates that the decrease is primarily a result of steric constraints imposed on its adsorption on the surface of the catalyst by the adsorbed bases. Studies by Norcross et al. of platinum catalysts modified by alkaline hydroxides reveal that platinum remains electronically unmodified after the adsorption of Na\textsuperscript{+} ion on its surface [24]. Hence, it seems likely that the addition of inorganic bases in the present study does not cause an electronic modification of the rhodium atoms at the surface.

4.5 Conclusions

The aromatic substrates investigated give very different stereoselectivities depending on the functional group substituent. The hydroxyl group in most of the alcoholic substrates has a mild haptophilic effect, which becomes evident on conducting the reaction in hexane. The d.r. obtained in the hydrogenation of these substrates depends on the exact location and orientation of the hydroxyl group and is influenced by the nature of the catalyst support. Aromatic substrates with hydroxyl group at the \( \beta \) position are also significantly hydrogenolyzed on Rh/C catalyst in ethanol. The methyl group in 1-methylindane, because of its relatively small steric repulsion, leads to only a small preference for the cis-cis isomer. Since it interacts exclusively sterically with the catalyst surface, the diastereoselectivity is independent of the catalyst support. The amino group in 1-aminoindane interacts very strongly (high haptophilicity) with the catalyst and the cis-trans isomer is obtained almost exclusively. The haptophilicity of the amino group is diminished considerably on converting it to its salt. The addition of
organic and inorganic bases results in a reduction of the diastereoselectivity to the cis-cis diastereomer in the case of 1-methylindane, primarily by constraining its adsorption on the surface of the catalyst. In the case of benzylic alcohols, the magnitude of the d.r. decreases to a value significantly below unity, on addition of inorganic bases because of the interaction of the hydroxyl group with the alkali metal cations. From a synthetic point of view, the high haptophilicity of the amino group and, the ability of the inorganic basic additives to influence the selectivity in the hydrogenation of benzylic alcohols should be of interest.

References


18. Crystals of the N-benzoyl derivative showed polymorphism. The needle-shaped crystals in the diisopropyl ether-hexane solvent mixture were slowly converted to block shape with time. Benzamide was amongst the first compounds discovered to exhibit polymorphism [25].


5. Diastereoselective Hydrogenation of 1-Substituted Indanes (Part II)

5.1 Introduction

Thompson and co-workers hydrogenated a series of substituted tetrahydrofluorenes [1] (I, Fig. 5.1) and 2-exo-substituted 7-methylenenorbornanes [2] (II, Fig. 5.1), differing only in the functional group substituent at one stereocenter, over supported palladium catalysts. Since the two faces of the olefinic substrates are not identical, hydrogenation from either of the two faces results in different products. Assuming that hydrogenation

\[
\begin{align*}
\text{distofacial} & \quad \rightarrow \\
\text{proximofacial} & \quad \leftarrow
\end{align*}
\]

Figure 5.1 Substrates investigated by Thompson and co-workers (I and II) [1, 2] and substituted indane substrates (III) investigated in Chapters 4 and 5
proceeds mainly from the side of the functional group (proximofacial) if the electronic interaction between this group and the metal surface dominates, whereas it proceeds predominantly from the side opposite to the functional group (distofacial) if the steric repulsion dominates. The relative magnitude of repulsion and attraction of the substituents with a particular catalyst was gauged by hydrogenating under identical conditions a series of olefinic compounds differing only in the substituent. In Chapter 4, we conducted a similar study involving hydrogenation of substituted indanes substituted at the benzylic position by hydroxyl, amino and alkyl groups (Fig. 4.1). The present chapter reports the results of hydrogenation of indane substrates having alkoxy and carboxyl groups at the benzylic position. We also continued our investigations into the influence of the addition of inorganic and organic bases during reaction on the diastereoselectivity as in the previous chapter.

5.2 Experimental

5.2.1 Hydrogenation Experiments

Hydrogenation reactions were conducted in a 60 ml stainless steel autoclave equipped with a gas-inducing impeller at a stirring speed of 1100 rpm under efficient mass transport conditions. In a typical experiment, a solution of 0.5 g substrate in 15 ml ethanol or hexane (and basic additive, if any) was added to 50 mg catalyst in the autoclave. Rh/Al₂O₃ (Fluka) and Rh/C (Aldrich) catalysts (metal loading 5 wt%) were used as supplied. The autoclave was closed, flushed three times successively with nitrogen and hydrogen and then pressurized to 50 bar with hydrogen. All reactions were conducted at room temperature. Samples could be taken with a sample tube during the reaction to detect the completion of the reaction (typically less than 48 h in experiments without base addition). Analyses of samples for determination of conversion and selectivity was done using a GC equipped with a FID detector and various capillary columns depending on the substrate hydrogenated.
5.2.2 Preparation of the Substrates

Racemic 1-methoxyindane was prepared from racemic 1-indanol. To a solution of 1-indanol in dry tetrahydrofuran, NaN3 was added and the mixture was heated to 60°C and maintained under argon for 30 min at the same temperature. Methyl iodide was added to the mixture and it was maintained at 60°C for 4 h. Excess NaN3 was hydrolyzed with water and the mixture was extracted twice with ether. The ether extracts were pooled together and washed with water. The ether was removed in vacuo and the yellowish liquid product was purified by kugelrohr distillation. The resulting colorless distillate of 1-methoxyindane was stored under argon, since it was air-sensitive, and directly used in the hydrogenation experiments. Racemic 1-propoxyindane was prepared in exactly the same way with propyl iodide instead of methyl iodide. The yellowish liquid product contained the product as well as the unconverted adduct in a ratio of about 1:3. Separation was affected by column chromatography (hexane:ethyl acetate 19:1) to yield pure (>99%) 1-propoxyindane as a colorless liquid. The identity of 1-methoxyindane was established by comparing its NMR spectrum to that reported in the literature [3]. The identity of 1-propoxyindane was established from its NMR and MS analyses.

Analytical data of 1-propoxyindane: - EI-MS: 176 (M+ , 3), 175 (4), 133 (20), 117 (100), 115 (75), 91 (23), 77 (13), 41 (13); 1H NMR (CDCl3, 300 MHz, r.t.) δ: 7.39-7.37 (m, 1H), 7.23-7.15 (m, 3H), 3.49 (td, 1H, J= 1.5, 6.7 Hz), 3.05 (m, 1H), 2.78 (m, 1H), 2.33 (m, 1H), 2.06 (m, 1H), 1.62 (m, 1H), 0.94 (t, 1H, J= 7.4 Hz); 13C NMR (CDCl3, 75 MHz, r.t.) δ: 143.9, 143.3, 128.2, 126.3, 125.1, 124.9, 83.2, 70.5, 32.5, 30.2, 23.4, 10.8.

Racemic indan-1-carboxylic acid was prepared by reduction of racemic 3-oxoindan-1-carboxylic acid over 10wt% Pd/C catalyst (Fluka) in ethanol under 3 bar hydrogen pressure (Scheme 5.1). The resulting product was isolated by removal of the solvent in vacuo after filtering off the catalyst. A quantitative yield of indan-1-carboxylic acid (white solid) was obtained. The air-sensitive acid was stored under argon and was used directly without any purification in further reactions/hydrogenations. The racemic methyl ester of indan-1-carboxylic acid was prepared by refluxing a solution of the acid in methanol after addition of an excess of thionyl chloride for 2 h (Scheme 5.1). The solvent was removed in vacuo and the yellowish liquid product was distilled under
vacuum in a kugelrohr distillation apparatus. The resulting colorless liquid was used in the hydrogenation experiments.

Scheme 5.1 Preparation of the carboxyl substrates

Racemic indan-1-carboxamide was prepared by two methods (Scheme 5.1). In one method, a suspension of the methyl ester of indan-1-carboxylic acid was stirred vigorously in an aqueous ammonia solution, giving a slightly greenish white precipitate, which was isolated by filtration and washed successively with water. In the second method, indan-1-carboxylic acid was converted to the acid chloride by heating with
thionyl chloride for 20 min at about 40°C. The acid chloride was isolated by removing the excess thionyl chloride in vacuo. It was dissolved in tetrahydrofuran and anhydrous ammonia gas was bubbled through to get a slightly greenish white precipitate. The solvent was removed in vacuo and the resulting solid washed with water. The crude indan-1-carboxamide was recrystallized from water.

\[
\begin{align*}
\text{Pd/C, EtOH} & \quad \text{Rh catalyst, EtOH} \\
10 \text{ bar H}_2, \text{ r.t.} & \quad 50 \text{ bar H}_2, \text{ r.t.}
\end{align*}
\]

\[\text{cis-trans} \quad \text{cis-cis}\]

Scheme 5.2 Preparation and hydrogenation of 3-propyl-3H-isobenzofuran-1-one

Commercially available propyldene phthalide (Lancaster: cis:trans = 6.7, total purity = 96.6%) was hydrogenated on the Pd/C catalyst at ambient temperature and 10 bar hydrogen pressure in ethanol (Scheme 5.2). The catalyst hydrogenated exclusively the olefinic bond and a quantitative yield of pure racemic 3-propyl-3H-isobenzofuran-1-one (>99.6% pure, identified by NMR [4]) was obtained as a colorless liquid after removal.
of the solvent in vacuo. This was used further in hydrogenation experiments. Analytical data of 3-propyl-3H-isobenzofuran-1-one: EI-MS: 176 (M+, 20), 134 (25), 133 (100), 105 (68), 91 (5), 77 (36), 51 (17), 39 (5); $^1$H NMR (CDCl$_3$, 500 MHz, r.t.) δ: 7.89 (d, 1H, $J = 7.7$ Hz), 7.67 (dt, $J = 1.0, 7.5$ Hz), 7.52 (t, 1H, $J = 7.4$ Hz), 7.45 (dd, $J = 0.8, 7.7$ Hz), 5.48 (dd, 1H, $J = 4.1, 8.0$ Hz), 2.02 (m, 1H), 1.75 (m, 1H), 1.53 (m, 2H), 0.99 (t, 3H, $J = 7.3$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz, r.t.) δ: 170.7, 150.2, 134.0, 129.0, 126.2, 125.7, 121.8, 81.3, 36.8, 18.2, 13.8.

### 5.2.3 Identification of Cis-cis and Cis-trans Product Diastereomers

**Perhydro-1-methoxyindane and Perhydro-1-propoxyindane**

A reference mixture of the cis-cis and cis-trans diastereomers was prepared starting from perhydro-1-indanol using the same method as used in the preparation of 1-methoxyindane [5]. The $^1$H and $^{13}$C NMR spectra of the reference mixture were used to identify the relative configurations of the products of hydrogenation. Analytical data of cis-cis and cis-trans diastereomers of perhydro-1-methoxyindane: EI-MS: 154 (M+, 5), 122 (51), 94 (24), 79 (45), 71 (54), 58 (17), 53 (32), 41 (100). Cis-cis isomer: $^1$H NMR (CDCl$_3$, 300 MHz, r.t.) δ: 3.73 (m, 1H), 3H (s, 3.30), 2.15-1.05 (m, 14H); $^{13}$C NMR (CDCl$_3$, 75 MHz, r.t.) δ: 85.3, 57.3, 40.8, 35.7, 28.2, 27.1, 24.9, 23.7, 21.1, 21.1. Cis-trans isomer: $^1$H NMR (CDCl$_3$, 300 MHz, r.t.) δ: 3.49 (m, 1H), 3.27 (s, 3H), 2.15-1.05 (m, 14H); $^{13}$C NMR (CDCl$_3$, 75 MHz, r.t.) δ: 86.8, 56.6, 44.5, 36.7, 29.6, 27.3, 27.0, 25.7, 24.1, 22.5. For 1-propoxyindane it was assumed that the major product had the cis-cis configuration, in analogy to the results of 1-methoxyindane. Analytical data of cis-cis and cis-trans diastereomers of perhydro-1-propoxyindane: EI-MS: 182 (M+, 4), 153 (10), 122 (35), 99 (23), 81 (40), 67 (47), 57 (30), 41 (100). Cis-cis isomer: $^1$H NMR (CDCl$_3$, 300 MHz, r.t.) δ: 3.79 (m, 1H), 3.36 (dt, 1H, $J = 9.1, 6.8$ Hz), 3.31 (dt, 1H, $J = 9.0, 6.7$ Hz), 2.13-1.09 (m, 16H), 0.91 (t, 3H, $J = 7.4$ Hz); $^{13}$C NMR (CDCl$_3$, 75 MHz, r.t.) δ: 83.5, 71.2, 41.1, 35.8, 28.5, 27.3, 24.9, 23.8, 23.3, 21.3, 21.3, 10.7. Cis-trans isomer: $^1$H NMR (CDCl$_3$, 300 MHz, r.t.) δ: 3.59 (m, 1H), 3.40-3.26 (m, 2H), 2.14-1.04 (m, 16H), 0.90 (t, 3H, $J = 7.4$ Hz); $^{13}$C NMR (CDCl$_3$, 75 MHz, r.t.) δ: 84.8, 70.9, 44.8, 36.8, 30.1, 27.6, 27.2, 25.7, 24.1, 23.4, 22.8, 10.7.
Perhydroindan-1-carboxylic acid and Perhydroindan-1-carboxylic acid, Methyl Ester

The product of hydrogenation of indan-1-carboxylic acid consisted primarily of two diastereomers as observed by NMR analysis. The $^1$H and $^{13}$C NMR spectral data of the product mixture did not fit the NMR spectral data reported for the trans isomers by Galteri et al. [6]. Analytical data of cis-cis and cis-trans diastereomers of perhydroindan-1-carboxylic acid:- EI-MS: 168 (M⁺, 6), 150 (43), 108 (34), 81 (63), 67 (64), 55 (43), 45 (100), 39 (88). Cis-cis isomer:- $^1$H NMR (CDCl₃, 500 MHz, r.t.) δ: 2.91 (td, 1H, J = 6.1, 9.3), 2.24-1.02 (m, 14H); $^{13}$C NMR (CDCl₃, 125 MHz, r.t.) δ: 181.2, 49.0, 42.7, 39.6, 26.7, 25.4, 25.2, 23.7, 23.0, 20.5. Cis-trans isomer:- $^1$H NMR (CDCl₃, 500 MHz, r.t.) δ: 2.71 (m, 1H), 2.24-1.02 (m, 14H); $^{13}$C NMR (CDCl₃, 125 MHz, r.t.) δ: 183.9, 45.9, 43.9, 39.6, 30.1, 27.8, 27.0, 26.7, 24.1, 22.3. For the identification of the relative configuration of the cis diastereomers, the hydrogenated carboxylic acid was converted to its methyl ester by treatment with diazomethane in ether (prepared using the method of Black [7]). The mixture of hydrogenated indan-1-carboxylic acid methyl esters was then injected into a GC equipped with a HP-1 capillary column. Comparison of the order of elution of the two diastereomers to that reported by Granger et al. [8] was used to identify the absolute configuration. The cis-trans diastereomer elutes before the cis-cis diastereomer. Analytical data of cis-cis and cis-trans diastereomers of perhydroindan-1-carboxylic acid, methyl ester:- EI-MS: 182 (M⁺, 13), 150 (90), 108 (27), 96 (46), 87 (100), 81 (60), 67 (65), 55 (60). Cis-cis isomer:- $^1$H NMR (CDCl₃, 500 MHz, r.t.) δ: 3.66 (s, 3H), 2.87 (dt, J = 6.0, 9.3 Hz, 1H), 2.25-0.92 (m, 14H); $^{13}$C NMR (CDCl₃, 125 MHz, r.t.) δ: 174.9, 51.3, 48.9, 42.7, 39.5, 26.7, 25.4, 25.2, 24.0, 23.2, 20.5. Cis-trans isomer:- $^1$H NMR (CDCl₃, 500 MHz, r.t.) δ: 3.67 (s, 3H), 2.69 (m, 1H), 2.25-0.92 (m, 14H); $^{13}$C NMR (CDCl₃, 125 MHz, r.t.) δ: 177.6, 51.5, 45.7, 43.8, 39.5, 30.0, 27.8, 27.1, 26.7, 24.1, 22.4.

Perhydroindan-1-carboxamide

For identification of the cis diastereomeric products obtained in the hydrogenation of indan-1-carboxamide a reference mixture was prepared from perhydroindan-1-
carboxylic acid in a two step procedure via the acid chloride as reported for indan-1-carboxamide. The reference products were isolated and comparison of their $^1$H and $^{13}$C NMR spectra and chromatogram in an RTX-200 column with the products of hydrogenation enabled the assignment of the cis-cis and cis-trans configurations to the major and the minor products respectively. Analytical data of cis-cis and cis-trans diastereomers of perhydroidan-1-carboxamide:- **EI-MS:** 167 (M+, 4), 150 (14), 108 (7), 72 (46), 67 (33), 55 (26), 44 (100), 39 (43). **Cis-cis isomer:** $^1$H NMR (CDCl$_3$, 300 MHz, r.t.) $\delta$: 5.4 (br, 2H), 2.76 (dt, 1H, $J$ = 6.2, 9.3 Hz), 2.24-1.08 (m, 14H); $^{13}$C NMR (CDCl$_3$, 75 MHz, r.t.) $\delta$: 175.5, 50.2, 43.0, 39.8, 26.8, 25.5, 25.2, 24.0, 22.7, 20.5. **Cis-trans isomer:** $^1$H NMR (CDCl$_3$, 300 MHz, r.t.) $\delta$: 5.4 (br, 2H), 2.52 (m, 1H), 3H (s, 3.27), 2.24-1.08 (m, 14H); $^{13}$C NMR (CDCl$_3$, 75 MHz, r.t.) $\delta$: 178.7, 47.4, 43.8, 39.5, 30.2, 28.0, 27.8, 26.9, 24.1, 22.4.

3-Propyl-3H-hexahydroisobenzofuran-1-one

The relative configuration of 3-propyl-3H-hexahydroisobenzofuran-1-one was identified by a two dimensional NOESY analysis of the isolated product mixture (see Fig. A3.3 in Appendix 3). In the two-dimensional $^1$H NMR spectrum of the product mixture a NOE was observed between the protons at the 3a and 7a positions on the cyclohexanediyl ring for both the major and the minor diastereomer, indicating that the cis diastereomers were formed exclusively. A NOE was observed between the proton at position 3a and the protons at positions 3 and 7a, however, only for the major diastereomer. Thus the cis-cis and cis-trans configurations were assigned to the major and minor product respectively. Analytical data of cis-cis and cis-trans diastereomers of 3-propyl-3H-hexahydroisobenzofuran-1-one:- **EI-MS:** 182 (M$,^+$, 0.5), 139 (21), 109 (24), 96 (79), 82 (97), 81 (94), 67 (100), 55 (30). **Cis-cis isomer:** $^1$H NMR (DMSO, 500 MHz, r.t.) $\delta$: 4.30 (m, 1H), 2.86 (t, 1H, $J$ = 5.9 Hz), 2.33 (m, 1H), 1.92 (m, 1H), 1.62-0.84 (m, 14H); $^{13}$C NMR (CDCl$_3$, 75 MHz, r.t.) $\delta$: 178.2, 81.8, 42.1, 39.0, 31.3, 23.6, 22.9, 22.7, 22.5, 19.2, 14.0. **Cis-trans isomer:** $^1$H NMR (DMSO, 500 MHz, r.t.) $\delta$: 4.09 (td, 1H, $J$ = 2.8, 6.7 Hz), 2.80 (m, 1H), 2.20 (m, 1H), 1.83-0.84 (m, 15H).
5.3 Results

Hydrogenation of all substrates yielded predominantly cis \((\text{cis-cis} + \text{cis-trans})\) diastereomers (usually cis to trans ratio > 10) with respect to the two substituents on the six membered ring (Scheme 5.3). Different methods were employed for the identification of the relative configuration of the cis-cis and cis-trans diastereomers, depending upon the substrate hydrogenated as described in Section 5.2. The diastereoselectivity to the two cis isomers is expressed as the diastereomeric ratio (d.r.) at 100% conversion of the substrate and intermediates as in the previous Chapter. For clarity, the d.r. is presented as a ratio in which the sum of the yields of the two
diastereomers is normalized to 100. To demonstrate the variation of diastereoselectivity with reaction time, selectivity and incremental selectivity to the *cis-cis* diastereomer are presented for a few experiments. For definition of selectivity and incremental selectivity see the Glossary of Terms at the end of the thesis.

Small to significant amounts of cyclohexene intermediates were observed (identified by GC-MS analysis) depending on the substrate hydrogenated and the reaction conditions. For most substrates the hydrogenation of the cyclohexene intermediate proceeded slower than that of the substrate and it caused a change in the diastereoselectivity, the magnitude of which depended on the parent aromatic substrate. The position of the double bond in the cyclohexene intermediates was identified by NMR analysis to be between the junction carbon atoms, only in the case of the ester. Analytical data of the cyclohexene intermediate (2,3,4,5,6,7-hexahydro-1H-indene-1-carboxylic acid, methyl ester): - **EI-MS**: 180 (M⁺, 15), 150 (4), 121 (100), 91 (44), 79 (43), 67 (15), 59 (12), 51 (8); **¹³C NMR** (CDCl₃, 75 MHz, r.t.) δ: 175.9, 138.6, 131.9, 53.6, 51.5, 35.4, 26.4, 25.9, 24.5, 22.9, 22.7; **¹³C DEPT NMR** (CDCl₃, 75 MHz, r.t.) δ: 53.6 & 51.5 (CH & CH₃), 35.4, 26.4, 25.9, 24.5, 22.9, 22.7 (CH₂).

Results of the hydrogenation of 1-methoxyindane are reported in Table 5.1. Substantial amounts of the hydrogenolysis-hydrogenation by-products *cis* and *trans* perhydroindane were obtained in addition to the fully hydrogenated products on the Rh/C catalyst, especially in ethanol. The fractional yield of these products is also reported in Table 5.1 at 100 % conversion of the substrates. Less hydrogenolysis occurred on the Rh/C catalyst in hexane and very little on the Rh/Al₂O₃ catalyst. In general, a high diastereoselectivity to the *cis-cis* isomer was obtained over both catalysts, Rh/Al₂O₃ being more stereoselective than Rh/C, and reactions in ethanol being more stereoselective than those in hexane. Hydrogenation of 1-propoxyindane in ethanol was studied to investigate the effect of the size of the alkoxy substituent on the diastereoselectivity. Like in the case of 1-methoxyindane, the Rh/C catalyst showed a lower chemoselectivity as well as diastereoselectivity than the Rh/Al₂O₃ catalyst (Table 5.1). The diastereoselectivity in the hydrogenation of 1-propoxyindane was slightly higher than in that of 1-methoxyindane.
Diastereoselective hydrogenation of substituted indanes. II

Table 5.1 Hydrogenation of 1-alkoxyindanes

<table>
<thead>
<tr>
<th>III, G =</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield of cis &amp; trans perhydroindane</th>
<th>Yield of cis perhydro products</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>Rh/C</td>
<td>EtOH</td>
<td>74</td>
<td>21</td>
<td>79:21</td>
</tr>
<tr>
<td>OMe</td>
<td>Rh/C</td>
<td>Hexane</td>
<td>36</td>
<td>60</td>
<td>75:25</td>
</tr>
<tr>
<td>OMe</td>
<td>Rh/Al₂O₃</td>
<td>EtOH</td>
<td>4</td>
<td>91</td>
<td>88:12</td>
</tr>
<tr>
<td>OMe</td>
<td>Rh/Al₂O₃</td>
<td>Hexane</td>
<td>5</td>
<td>85</td>
<td>82:18</td>
</tr>
<tr>
<td>OPr</td>
<td>Rh/C</td>
<td>EtOH</td>
<td>78</td>
<td>19</td>
<td>81:19</td>
</tr>
<tr>
<td>OPr</td>
<td>Rh/Al₂O₃</td>
<td>EtOH</td>
<td>7</td>
<td>88</td>
<td>92:8</td>
</tr>
</tbody>
</table>

* Substrate to metal molar ratio for 1-methoxyindane = 128 and for 1-propoxyindane = 117; b Determined by GC (HP-1 capillary column); c cis-cis: cis-trans

In 1-methoxyindane as well as 1-propoxyindane the diastereoselectivity to the cis-cis isomer decreased as the reaction proceeded to completion. The decrease in selectivity and the incremental selectivity to the cis-cis diastereomer with conversion in the hydrogenation of 1-methoxyindane (and its intermediate) in hexane over the Rh/Al₂O₃ catalyst are shown in Fig. 5.2. The d.r. values corresponding to the initial and final selectivity and incremental selectivity are also indicated in the figure. The substrate concentration decreases continuously whereas the concentration of the intermediate goes through a maximum. Towards the end of the reaction the fully hydrogenated cis products are formed primarily by the hydrogenation of the intermediate and not of the substrate. The selectivity and incremental selectivity stay constant during the initial period, in which the cyclohexene intermediate is being formed, and decrease with the conversion of the intermediate to the products. This indicates that the decrease in the selectivity to the cis-cis diastereomer and hence the d.r. with time is primarily due to the fact that the cyclohexene intermediate hydrogenates with a much lower selectivity to the cis-cis diastereomer than 1-methoxyindane [9].
Results of hydrogenation of the carboxyl substrates, namely, indan-1-carboxylic acid, the methyl ester of indan-1-carboxylic acid and indan-1-carboxamide are presented in Table 5.2. All substrates yielded predominantly (92-95%) the cis-cis and cis-trans diastereomers, with a comparable and relatively high selectivity to the cis-cis diastereomer. The selectivity is higher with Rh/Al₂O₃ than with Rh/C. For the ester, the selectivity is hardly affected by the change in the solvent from ethanol to hexane. Reactions of the other substrates were conducted only in ethanol because of their limited solubility in hexane. The diastereoselectivity of all substrates was unaffected by changing the substrate to catalyst ratio. The diastereoselectivity to the cis-cis diastereomer decreased significantly, however, in the ester hydrogenation especially towards the end of the reaction. For example, in the hydrogenation of the ester over the Rh/Al₂O₃ catalyst in ethanol, the d.r. decreased from 89:11 at the beginning to 83:17 at the end of the reaction.

![Figure 5.2](image_url)

**Figure 5.2** Kinetics of the hydrogenation of 1-methoxyindane in hexane over Rh/Al₂O₃ under standard reaction conditions; concentration of 1-methoxyindane ■ and its cyclohexene intermediate ●, selectivity ▲ and incremental selectivity ▼ to the cis-cis diastereomer
Diastereoselective hydrogenation of substituted indanes. II

Table 5.2 Hydrogenation of carboxyl substrates

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOH</td>
<td>Rh/C</td>
<td>EtOH</td>
<td>77:23</td>
</tr>
<tr>
<td>CONH₂</td>
<td>Rh/C</td>
<td>EtOH</td>
<td>71:28</td>
</tr>
<tr>
<td>COOMe</td>
<td>Rh/C</td>
<td>EtOH</td>
<td>80:20</td>
</tr>
<tr>
<td>COOMe</td>
<td>Rh/C</td>
<td>Hexane</td>
<td>80:20</td>
</tr>
<tr>
<td>COOH</td>
<td>Rh/Al₂O₃</td>
<td>EtOH</td>
<td>84:16</td>
</tr>
<tr>
<td>CONH₂</td>
<td>Rh/Al₂O₃</td>
<td>EtOH</td>
<td>81:19</td>
</tr>
<tr>
<td>COOMe</td>
<td>Rh/Al₂O₃</td>
<td>EtOH</td>
<td>85:15</td>
</tr>
<tr>
<td>COOMe</td>
<td>Rh/Al₂O₃</td>
<td>Hexane</td>
<td>82:18</td>
</tr>
</tbody>
</table>

*Substrate to metal molar ratio for acid and amide = 127, for ester = 117; * Yield to the cis diastereomers (>92%) and d.r. determined by GC (RTX-200 capillary column); c cis-cis: cis-trans

In one experiment, the hydrogenation of the ester was interrupted at an intermediate conversion and a mixture of the unconverted substrate, its cyclohexene intermediate and fully hydrogenated products was isolated by removing the catalyst and the solvent. Column chromatography over silica gel (hexane:ethyl acetate 9:1) enabled separation of a mixture of the cyclohexene intermediate and the fully hydrogenated products from the unconverted substrate. This mixture contained 21% cyclohexene intermediate, 73% cis diastereomers (with d.r. = 86:14), and 5% trans diastereomers. The cyclohexene intermediate in this mixture was hydrogenated further over the Rh/Al₂O₃ catalyst in ethanol under standard reaction conditions. A d.r. value of 71:29 was obtained in this experiment (after discounting the initial d.r. due to the cis products in the starting reaction mixture) and the value changed very little with increasing conversion of the cyclohexene intermediate. Thus, hydrogenation of the cyclohexene intermediate occurred with a constant but different selectivity than the parent aromatic substrate. The change in diastereoselectivity during the reaction could not be determined in the case of the acid substrate because of insufficient chromatographic resolution and in the case of the amide substrate because of the precipitation of the cis-cis diastereomer.

Results of hydrogenation of 3-propyl-3H-isobenzofuran-1-one (Scheme 5.2) in ethanol are shown in Table 5.3. In all experiments, a very high chemoselectivity (~
99%) towards the fully hydrogenated cis products (Scheme 5.2) and a very high diastereoselectivity towards the cis-cis diastereomer were obtained. Rh/C and Rh/Al₂O₃ were equally selective. A cyclohexene intermediate was formed during the hydrogenation and its maximum concentration reached exceptionally high values of 20 to 40% of the initial substrate concentration, depending on the reaction conditions. The diastereoselectivity to the cis-cis isomer increased very slightly as the reaction proceeded to completion implying that the intermediate was hydrogenated with a greater selectivity to the cis-cis isomer than the parent substrate. Changing the reaction temperature from ambient to 50°C, the pressure from 50 to 10 bar, and halving the substrate to rhodium ratio had a small effect on the d.r. with the Rh/C catalyst.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Hydrogen pressure</th>
<th>d.r. a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/C c</td>
<td>50</td>
<td>94:6</td>
</tr>
<tr>
<td>Rh/C cc</td>
<td>50</td>
<td>92:8</td>
</tr>
<tr>
<td>Rh/C c</td>
<td>20</td>
<td>95:5</td>
</tr>
<tr>
<td>Rh/C d</td>
<td>10</td>
<td>95:5</td>
</tr>
<tr>
<td>Rh/Al₂O₃ c</td>
<td>50</td>
<td>94:6</td>
</tr>
</tbody>
</table>

a cis-cis:cis-trans; b Yield of the cis diastereomers (~99%) and d.r. determined by ¹H NMR analyses and GC (γ-DEX capillary column); c Substrate to metal molar ratio = 115; d Catalyst to substrate molar ratio 60; e reaction conducted at 50°C.

The influence of the addition of triethylamine during hydrogenation was investigated for all substrates. In line with previous observations [10], the addition of amine decreased the activity in all reactions and led to almost complete suppression of the hydrogenolysis of the 1-alkoxyindane substrates. With all substrates but for 1-methoxyindane and 3-propyl-3H-isobenzofuran-1-one, the triethylamine to Rh and substrate to catalyst ratios were halved (by doubling the catalyst amount) because of very low activity. Results in Tables 5.4 show that the diastereoselectivity increased in the case of 1-propoxyindane from 81:19 to 93:7 and in the case of indan-1-carboxamide from 71:28 to 82:18, whereas in all other substrates it remained almost unaffected. Typically the initial d.r. values were higher than the corresponding values in the
Table 5.4 Hydrogenation in ethanol over Rh/C with triethylamine and NaOH additives

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Substrate to rhodium molar ratio</th>
<th>d.r. (^a) with additive</th>
<th>d.r. (^a) without additive</th>
<th>d.r. (^a) triethylamine additive</th>
<th>d.r. (^a) NaOH additive</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-OMe (^b)</td>
<td>128</td>
<td>81:19</td>
<td>79:21</td>
<td>49:51</td>
<td></td>
</tr>
<tr>
<td>III-OMe (^c)</td>
<td>64</td>
<td>93:7</td>
<td>81:19</td>
<td>67:33</td>
<td></td>
</tr>
<tr>
<td>III-OPr (^c)</td>
<td>59</td>
<td>79:21</td>
<td>80:20</td>
<td>61:39</td>
<td></td>
</tr>
<tr>
<td>III-COOME (^c)</td>
<td>59</td>
<td>82:18</td>
<td>71:28</td>
<td>59:41</td>
<td></td>
</tr>
<tr>
<td>III-CONH(_2)(^c)</td>
<td>64</td>
<td>95:5</td>
<td>94:6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3-propyl-3(H)-isobenzofuran-1-one (^b)</td>
<td>115</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) cis-cis: cis-trans; \(^b\) Triethylamine to rhodium molar ratio = 10 and Na to rhodium molar ratio = 6; \(^c\) Triethylamine to rhodium molar ratio = 5 and Na to rhodium molar ratio = 3

As in the case of triethylamine, addition of an aqueous solution of NaOH (0.3 ml of 0.5 N) resulted in a decrease in the activity accompanied by almost complete suppression of hydrogenolysis of the alkoxyindane substrates. Because of the low activity, the substrate to catalyst and Na to Rh ratios were halved by doubling the amount of the catalyst. The d.r. was significantly reduced in all cases (Table 5.4). In the case of 1-methoxyindane, a substantial reduction is obtained in the value of d.r. and it reached unity in the experiment with a higher Na to Rh ratio. For all substrates the d.r. value decreased as the reaction proceeded probably because of the hydrogenation of the cyclohexene intermediate. The decrease in d.r. during reaction was largest for 1-methoxyindane. Fig. 5.3 shows the kinetics of hydrogenation of 1-methoxyindane in ethanol with NaOH additive over the Rh/C catalyst. Analogous to Fig. 5.2, the selectivity and incremental selectivity to the cis-cis diastereomer are plotted as a function of reaction time along with the concentrations of 1-methoxyindane and its intermediate, and the initial and final d.r. values are also indicated. As in the case of reactions without additives, towards the end of the reaction, the fully hydrogenated cis products are formed predominantly by the hydrogenation of the intermediate and not of the substrate. It is evident from
Figs. 5.2 and 5.3 that the addition of NaOH leads to a lower activity and a substantial reduction in the initial as well as the final d.r. value. The drop in incremental d.r. is substantial especially during the hydrogenation of the intermediate indicating that the cyclohexene intermediate is much less hydrogenated in a distofacial fashion than the parent substrate.

Figure 5.3 Kinetics of the hydrogenation of 1-methoxyindane in ethanol over Rh/C with NaOH additive, under standard reaction conditions; concentration of 1-methoxyindane ■ and its cyclohexene intermediate ●, selectivity ▲ and incremental selectivity ▼ to the cis-cis diastereomer

5.4 Discussion

The substrates are hydrogenated distofacially when the steric repulsion of the substituent dominates yielding predominantly the cis-cis diastereomer, whereas they are hydrogenated proximofacially when the electronic attraction dominates yielding predominantly the cis-trans diastereomer (Scheme 5.3). The ratio of the cis-cis to cis-
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Trans diastereomers gives an estimate of the relative repulsive and attractive interactions between substituent and rhodium surface. The results in the previous chapter indicated that only the amino group in 1-aminoindane interacted very strongly with the catalyst surface, giving almost exclusively the cis-trans diastereomeric product. The yield to the cis-trans diastereomer is thus a measure of attraction of the functional group in the aromatic substrate to the catalyst, also called as the haptophilicity of the functional group. The hydroxyl group had a very small haptophilic effect, if at all, because the cis-cis diastereomer was obtained as the major product. The methyl group by virtue of its small size produced the cis-cis diastereomer in moderate excess. We expected the alkoxy group to have little or no interaction with the metal surface because of its low polarity. However, the carboxyl group can in principle interact with the metal surface on account of its high polarity. This interaction has often been successfully exploited in homogeneous catalysis to obtain high selectivities to the proximofacial products in olefin hydrogenations [11, 12].

The results of the hydrogenation of 1-methoxyindane (Table 5.1) indicate that the cis-cis diastereomer is obtained with a high selectivity. As observed in the case of indanol (Chapter 4), substantial hydrogenolysis takes place over the Rh/C catalyst with spillover hydrogen, as will be proved in Chapter 7. The extent of hydrogenolysis is smaller with hexane as the solvent for both catalysts. 1-Propoxyindane shows the same trends as 1-methoxyindane. The Rh/Al2O3 catalyst gives a slightly higher selectivity to the cis-cis isomer with 1-propoxyindane than with 1-methoxyindane in line with the larger steric hindrance of the propyl group than the methyl group.

The results for the substrates with carboxylic acid and ester substituents (Table 5.2) indicate that these groups show little attraction to the catalyst surface since the cis-cis diastereomer is produced with a relatively high selectivity. Indan-1-carboxamide is also hydrogenated with a moderately high selectivity to the cis-cis diastereomer. The low electronic interaction exhibited by the relatively polar carboxyl groups is surprising. For all substrates, higher selectivity is obtained over the Rh/Al2O3 catalyst than over Rh/C, in line with the results for the other substrates. Hydrogenation of 3-propyl-3H-isobenzofuran-1-one proceeds with a very high selectivity as expected due to the
substantial steric hindrance of the propyl group (Table 5.3). The selectivity is comparable to the one obtained in the hydrogenation of 1-propoxyindane. As expected in the hydrogenation of all substrates a change in the process conditions or in the metal to substrate ratio has a very small influence on the selectivity because the directing information is carried individually by each molecule.

Cyclohexene intermediates were observed in the hydrogenation of all substrates over the rhodium catalysts. These intermediates underwent hydrogenation when the concentration of the parent aromatic substrate had become sufficiently low. The position of the double bond in the cyclohexene intermediate was identified as between the junction carbon atoms only for the ester. It is likely, however, that the double bond is located between the two junction carbon atoms for the other substrates as well. This position is favored from a steric point of view since the junction carbon atoms of the aromatic substrate stay farther away from the surface during adsorption than the other carbon atoms in the six membered ring. This position of the double bond is also likely from a thermodynamic point of view (Zaitsev's rule). In addition, chromatographic analyses during the reaction always showed only one peak for the intermediate on achiral as well as chiral columns. The intermediates were hydrogenated with a lower selectivity to the cis-cis diastereomer than the parent aromatic substrate in all substrates (except for 3-propyl-3H-isobenzofuran-1-one) where the cyclohexene intermediate concentration was followed as a function of time, as can be seen in the kinetics of the hydrogenation of 1-methoxyindane in Fig. 5.2. The diastereoselectivity values reported for different substrates are thus contaminated by the results of hydrogenation of the corresponding cyclohexene intermediates. Separating the two effects would be possible if an independent study of the hydrogenation of the cyclohexene intermediates is conducted. This is of little practical interest, however, considering that the formation of the intermediates seems unavoidable during aromatic hydrogenation. Nevertheless, the hydrogenation of the cyclohexene intermediate of the ester substrate was studied to clarify the role of the cyclohexene intermediates in the hydrogenation of the aromatic substrates. This study enabled us to calculate the d.r. values of 89:11 and 71:29 in the direct hydrogenation of the aromatic ring and the hydrogenation of the cyclohexene intermediate in the case of the ester. Also, from the first and last points in the kinetic
analysis in Fig. 5.2, the d.r. values of 88:12 and 59:41 were obtained in the direct hydrogenation of the aromatic ring and the hydrogenation of the cyclohexene intermediate respectively in the case of 1-methoxyindane. Unfortunately, the d.r. values for the cyclohexene intermediates in the hydrogenation of other aromatic substrates could not be similarly calculated because the intermediates underwent hydrogenation together with the substrate when the concentration of the substrate was sufficiently low. The lower d.r. obtained in the hydrogenation of the cyclohexene intermediate could be due to the spatial arrangement of the adsorbed cyclohexene intermediate resulting in a weaker expression of the steric influence of the functional group. However, it might also be due to the weaker adsorption of the olefinic bond as compared to an aromatic ring resulting in a stronger expression of the electronic influence of the group.

Addition of triethylamine increased the yield to the cis-cis isomer in some substrates whereas in other substrates it had no effect on the selectivity (Table 5.4). The aromatic molecules undergoing hydrogenation occupy more space on the metal surface when they are adsorbed in the proximofacial fashion than in the distofacial fashion. Addition of amine increases the crowding even more thus favoring the formation of the cis-cis isomer. This is not observed for all substrates, probably because of an opposing selectivity obtained in the hydrogenation of the corresponding cyclohexene intermediates. On addition of NaOH the d.r. reduces drastically for the alkoxyindane substrates and approaches unity especially for 1-methoxyindane (Table 5.4) suggesting that an interaction of the etheric oxygen with the Na cations adsorbed on the rhodium surface exists. The reduction in d.r. is accentuated by the fact that the cyclohexene intermediates produce the cis-trans diastereomer with a much higher selectivity than the parent benzylic ether as shown in Fig. 5.3. The d.r. values obtained in the direct hydrogenation of the aromatic ring and the hydrogenation of the cyclohexene intermediate were 67:33 and 10:90 respectively. The selectivity is also reduced in the carboxyl substrates probably because of similar interactions of the carbonyl oxygen in the carboxyl substrates and their intermediates with the Na cations. Thus, results of addition of bases suggest that the amine influences the facial selectivity by a steric mechanism while NaOH acts primarily by an electronic mechanism.
Table 5.5 Comparison of haptophilicities (expressed as the selectivity to the proximofacial diastereomer in the hydrogenation product) of various functional groups in substrates I, II and III (cf. Fig. 5.1)

<table>
<thead>
<tr>
<th>G</th>
<th>Substrate</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH₂</td>
<td></td>
<td>98</td>
<td>63</td>
<td>98</td>
</tr>
<tr>
<td>CH₂NH₂</td>
<td></td>
<td>63</td>
<td>63</td>
<td>63</td>
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<tr>
<td>CH₂OH</td>
<td></td>
<td>95</td>
<td>19</td>
<td>55</td>
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<tr>
<td>OH</td>
<td></td>
<td>18</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>Me</td>
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<td>10</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>CONH₂</td>
<td></td>
<td>15</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>COOH</td>
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<td>15</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>OMe</td>
<td></td>
<td>18</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>COOMe</td>
<td></td>
<td>28</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>OPr</td>
<td></td>
<td>19</td>
<td>0</td>
<td>19</td>
</tr>
</tbody>
</table>

*a* After Thompson and Naipawer [1], Pd/C catalyst, solvent 2-methoxyethanol; *b* After Thompson and Wong [2], Pd/C catalyst, solvent ethanol; *c* Chapter 4, Rh/C catalyst, solvent ethanol; *d* present study, Rh/C catalyst, solvent ethanol

The results presented in part 1 (Chapter 4) and in this chapter encompass directing effects of several non-reducible substituents encountered in aromatic hydrogenation. Table 5.5 summarizes the haptophilicity of substituents expressed in terms of the selectivity to the proximofacial product. For comparison we have included the selectivities to proximofacial products reported by Thompson and co-workers for substrates I and II obtained over a Pd/C catalyst. It is seen that in spite of differences in substrates, reaction conditions and catalysts, the trends in the haptophilicity are the same. The amino group, the hydroxymethylene group and the carboxyl groups exhibit a high, moderate and a low haptophilicity respectively. In addition, in our investigations, the haptophilicities of the hydroxyl and methyl groups lie between those of the hydroxymethylene and carboxyl groups, whereas the haptophilicities of the methoxy and propoxy groups are comparable to those of the carboxyl groups.

It is noteworthy that the directing effects of the hydroxyl and carboxyl substituents influence the stereoselectivity in the hydrogenation of olefinic substrates with
homogeneous catalysts strongly (cf. Section 1.3.1). The results presented in Chapter 4 and here show that these effects are much weaker (especially for the carboxyl substituents) in the case of heterogeneous catalysts. In fact, in complete contrast to the results with homogeneous catalysts, the distofacial product is obtained predominantly in the hydrogenation of the aromatic compounds directed by carboxyl substituents. Comparative data available for the application of heterogeneous and homogeneous catalysts in directed hydrogenation reactions of olefinic substrates [13-15] also indicate that in general heterogeneous catalysts lag well behind their homogeneous counterparts in terms of selectivities, even under comparable reaction conditions.

The superior abilities of homogeneous catalysts in directed hydrogenation by means of co-ordination to neighboring polar groups can be explained in terms of their higher Lewis acidity [16] and the lower steric hindrance around the metal center as compared to their heterogeneous counterparts. The coordination sphere of a metal atom embedded in a surface in heterogeneous catalysts is less flexible than that of a metal center in homogeneous catalysts. Therefore, unlike in the case of homogeneous catalysts, an increase in electronic attraction due to a substituent is accompanied by an increase in steric hindrance in the case of heterogeneous catalysts.

5.5 Conclusions

The alkoxy groups in benzylic ethers do not interact significantly with the surface of the catalyst. The interaction is low irrespective of the catalyst support or the solvent. The same result holds true for all carboxyl (acid, ester and amide) substrates, contrary to the intuitive expectation that these polar groups would interact with the rhodium surface. The diastereoselectivity is slightly affected by changing either the substrate to catalyst ratio or the reaction conditions.

The benzylic ethers undergo severe hydrogenolysis over Rh/C catalysts as observed for 1-indanol, especially in ethanol. Hydrogenolysis is retarded on the addition of organic or inorganic bases. The addition of triethylamine has a relatively small influence on the diastereoselectivity obtained in substrates with either the alkoxy or the carboxyl
substituent. Addition of NaOH reduces the diastereoselectivity to the cis-cis isomer drastically for the alkoxy substrates due to interaction of the etheric oxygen with Na cations on the rhodium surface. The diastereoselectivity to the cis-cis isomer also reduces significantly in the case of carboxyl substrates presumably due to the interaction of the carbonyl oxygen with the Na cations.

The main implication of the results presented in Chapters 4 and 5 is that the facial selection in diastereoselective hydrogenation of aromatics on heterogeneous catalysts is primarily determined by the sterical requirements of the molecule. The electronic interaction plays an important role only when the molecule bears an amino group or when the hydrogenation is conducted in the presence of inorganic basic additives.

References

9. It could be argued that the change in diastereoselectivity is related to a change in the catalyst with time. We have eliminated this possibility, at least in the case of 1-methoxyindane, by conducting an experiment in which a fresh batch of catalyst was added, after removal of the original catalyst, to a half converted reaction mixture. The diastereoselectivity obtained in this experiment was the same as that obtained in the normal experiment.
6. Rationalization of the Stereoselectivity

6.1 Introduction

As stated in section 1.1, one of the objectives of this work was to demonstrate the feasibility of the diastereoselective hydrogenation technique for the preparation of disubstituted saturated alicyclic compounds, beyond the single example of o-toluic acid reported earlier by Gallezot et al. [1]. In Chapters 2 and 3 investigations were directed to broaden the scope of this technique to the diastereoselective hydrogenation to o-toluidine and anthranilic acid. The other objective of this study was to gain an insight into the mechanism of diastereoselection. Detailed investigation with various catalysts revealed that the selectivity depended more on the structure of the aromatic compound-auxiliary moiety than on the properties of the supported catalyst (except the nature of the noble metal). Hence the emphasis of the investigations in Chapters 4 and 5 was directed towards establishing a correlation between the structure of the substrates and the diastereoselectivity obtained in their hydrogenation. Investigations in Chapters 4 and 5 revealed the preponderance of steric interactions over electronic interactions in directing the selectivity of the reaction. In light of these findings, the mechanism of diastereoselection is more closely scrutinized in Section 6.2. In Section 6.3, some guidelines are provided to enable the construction of aromatic compound-auxiliary systems which could give a high diastereoselectivity. All auxiliary aided hydrogenations conducted previously have used an amino acid auxiliary. The results of these hydrogenations are rationalized based on conformational studies of peptides in Section 6.4. In Section 6.5, the most important conclusions pertaining to diastereoselective hydrogenation are summarized.
6.2 Kinetic or Thermodynamic control?

Scheme 6.1 Distofacial and proximofacial hydrogenation of 1-methylindane
As mentioned in Chapter 1 and demonstrated in our investigations, the hydrogenation of 1,2-disubstituted aromatic compounds on metal catalysts leads predominantly to the two *cis* cyclohexandi-1,2-yl products. In all investigations described in Chapters 2-5, selectivity towards one of the two *cis* cyclohexandi-1,2-yl isomers was leveraged by an asymmetric carbon atom, bonded to the aromatic ring. The two *cis* diastereomers are formed by the hydrogenation of the aromatic ring from its two faces. Hydrogenation of one of the two diastereotopic faces of a chirally modified aromatic compound may occur preferentially, either because of thermodynamic (relative stability of adsorbed species) or kinetic reasons. Thermodynamic control (vide infra) was assumed to prevail in the discussions in earlier chapters. We will now explore if this assumption is reasonable.

Let us consider the diastereoselective hydrogenation of 1-methylindane (Scheme 6.1). The *cis-cis* and *cis-trans* diastereomers of perhydro-1-methylindane are formed due to hydrogenation of 1-methylindane from the opposite side and the same side of the methyl substituent respectively. Assuming the addition of six hydrogen atoms to occur in a single step, the overall process of hydrogenation requires three steps. They are the adsorption of the aromatic substrate on the surface of rhodium, the addition of hydrogen atoms to the aromatic ring, and the desorption of the hydrogenated products from the rhodium surface. The step involving the addition of hydrogen atoms to the aromatic ring is essentially irreversible under the mild reaction conditions employed in our investigations. In principle, the selectivity between the two fully hydrogenated *cis* products may be determined by one (or more) of these three steps. However, since the π-electron rich aromatic ring will interact more strongly with the metal atoms of the catalyst than the saturated product, the last step can be discounted as the one controlling the final outcome of the process. The selectivity is then controlled either by the adsorption step and/or the addition of hydrogen atoms (reaction) step.

We can think of two extreme cases; one in which exclusively the adsorption step is controlling and the other in which exclusively the reaction step is controlling. The adsorption step controls the overall reaction when it is much slower than the reaction step (i.e., $k_{cc-a}, k'_{cc-a}, k_{ct-a}, k'_{ct-a} \ll k_{cc-r}, k_{ct-r}$). In this case the difference in the adsorption
constants of the two diastereotopic faces determines the product selectivity. It is to be noted that in all the investigations reported in this thesis no epimerisation of the product isomers was possible under the reaction conditions employed. Therefore, the product composition does not change to the thermodynamic value once the products are formed. The reaction step controls the overall reaction when the adsorption step is much faster than the reaction step (i.e., \( k_{cc-a} \), \( k'_{cc-a} \), \( k_{ct-a} \), \( k'_{ct-a} \gg k_{cc-r} \), \( k_{ct-r} \)). In this case the difference in the reaction rate constants of the two diastereotopic faces determines the product selectivity. Kinetic control thus implies rapid equilibrium at the adsorption stage via desorption. Although in principle, equilibration can occur either via complete or via partial desorption, it is not clear whether the partial desorption mechanism operates in the present case.

Table 6.1 Possible situations in diastereoselective hydrogenation

<table>
<thead>
<tr>
<th>Adsorption</th>
<th>Reaction</th>
<th>Thermodynamic control</th>
<th>Major product</th>
<th>Kinetic control</th>
<th>Situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K_{cc-a} &gt; K_{ct-a} )</td>
<td>( k_{cc-r} &gt; k_{ct-r} )</td>
<td>Cis-cis</td>
<td>At</td>
<td>Cis-cis</td>
<td>Ak</td>
</tr>
<tr>
<td>( K_{cc-a} &gt; K_{ct-a} )</td>
<td>( k_{cc-r} \sim k_{ct-r} )</td>
<td>Cis-cis</td>
<td>Bt</td>
<td>None</td>
<td>Bk</td>
</tr>
<tr>
<td>( K_{cc-a} &gt; K_{ct-a} )</td>
<td>( k_{cc-r} &lt; k_{ct-r} )</td>
<td>Cis-cis</td>
<td>Ct</td>
<td>Cis-trans</td>
<td>Ck</td>
</tr>
<tr>
<td>( K_{cc-a} &lt; K_{ct-a} )</td>
<td>( k_{cc-r} &gt; k_{ct-r} )</td>
<td>Cis-trans</td>
<td>Dt</td>
<td>Cis-cis</td>
<td>Dk</td>
</tr>
<tr>
<td>( K_{cc-a} &lt; K_{ct-a} )</td>
<td>( k_{cc-r} \sim k_{ct-r} )</td>
<td>Cis-trans</td>
<td>Et</td>
<td>None</td>
<td>Ek</td>
</tr>
<tr>
<td>( K_{cc-a} &lt; K_{ct-a} )</td>
<td>( k_{cc-r} &lt; k_{ct-r} )</td>
<td>Cis-trans</td>
<td>Ft</td>
<td>Cis-trans</td>
<td>Fk</td>
</tr>
<tr>
<td>( K_{cc-a} \sim K_{ct-a} )</td>
<td>( k_{cc-r} &gt; k_{ct-r} )</td>
<td>None</td>
<td>Gt</td>
<td>Cis-cis</td>
<td>Gk</td>
</tr>
<tr>
<td>( K_{cc-a} \sim K_{ct-a} )</td>
<td>( k_{cc-r} \sim k_{ct-r} )</td>
<td>None</td>
<td>Ht</td>
<td>None</td>
<td>Hk</td>
</tr>
<tr>
<td>( K_{cc-a} \sim K_{ct-a} )</td>
<td>( k_{cc-r} &lt; k_{ct-r} )</td>
<td>None</td>
<td>It</td>
<td>Cis-trans</td>
<td>Ik</td>
</tr>
</tbody>
</table>

*In thermodynamic control the relative magnitude of adsorption constants (\( K_{cc-a} \) and \( K_{ct-a} \)) determines the major product; *b In kinetic control the relative magnitude of reaction rate constants (\( k_{cc-r} \) and \( k_{ct-r} \)) determines the product selectivity

To ascertain whether a reaction takes place with thermodynamic or kinetic control, it is necessary to know the values of all the rate constants in the adsorption as well as the reaction step. Once the type of control is determined, the product selectivity is easily predicted from the relative values of rate and adsorption constants as indicated in Table
6.1. Even after considering only the extremes of thermodynamic or kinetic control for the hydrogenation of 1-methylindane 18 different situations can exist, as shown in Table 6.1. The problem at hand is thus extremely complicated and without concrete data one cannot expect to make much headway in a priori prediction of either the type of control or the product selectivity. Although measurement of all relevant rate constants is probably an impossible task, especially in liquid phase reactions with heterogeneous catalyst, some information about the relative magnitudes of rate and adsorption constants is accessible for alkyl aromatics from the literature as will be described in the following paragraph. Using this information, we will attempt to narrow the number of situations to a few for hydrogenation of all classes of 1-substituted indanes investigated in Chapters 4 and 5.

Competitive hydrogenation of alkyl aromatics in the liquid phase on noble metal catalysts has been investigated extensively by many workers [2-4]. The investigation of Rader and Smith using platinum oxide catalyst revealed that the rate constants as well as adsorption constants decrease on increasing the nuclear substitution of the aromatic ring [2]. Thus, assuming a Langmuir-Hinshelwood mechanism [5], they found the following order for the rate constants as well as adsorption constants: benzene > toluene > xylenes > trimethylbenzenes. They also found that in case of multiply substituted benzenes, the rate as well as the adsorption constant was dependent on the symmetry of substitution. In the case of trimethylbenzenes and tetramethylbenzenes the strength of adsorption decreased but the rate constants increased with increasing symmetry of substitution. A similar investigation by Siegel et al. [3] on an alumina-supported rhodium catalyst involving t-butylbenzenes showed that adsorption constants decreased with increasing substitution (and increasing symmetry of substitution) in the order: t-butylbenzene > 4-t-butyltoluene > 1,3-di-t-butylbenzene > 1,4-di-t-butylbenzene. The rate constants, however, did not follow a trend similar to the adsorption constants probably due to the symmetry differences between the different substituted aromatics hydrogenated. The values of the adsorption constants and the rate constants of substituted aromatics decrease with increasing substitution very likely because of the steric interaction of the alkyl group with the surface of the catalyst and, the steric interactions between the alkyl substitutents in the adsorbed substrate.
Let us now consider in detail the directing effect of the methyl group in the diastereoselective hydrogenation of 1-methylindane. The adsorption of 1-methylindane on the rhodium surface through its diastereotopic faces is unequal in that in the situation leading to the cis-cis product the methyl group points away from the metal surface, whereas in the situation leading to the cis-trans product the methyl group points towards the metal surface. The adsorption structures of 1-methylindane in distofacial and proximofacial fashions can be compared to the adsorption structures of 2-isopropyltoluene and 2-t-butyltoluene respectively (cf. Scheme 6.1). Symmetry-wise 2-isopropyltoluene and 2-t-butyltoluene are equivalent in that they are both 1,2-disubstituted aromatics. Since the t-butyl group is bigger than the isopropyl group, it can be extrapolated from the results of Rader and Smith that the rate constant as well as the adsorption constant of 2-isopropyltoluene are greater than the corresponding constants of 2-t-butyltoluene. This implies that the hydrogenation of the distofacial face is favored both thermodynamically and kinetically. The product selectivity (d.e. ~ 30% to the cis-cis diastereomer), however, reflects that the differences in the values of the constants are not big enough to substantially bias the selectivity towards the cis-cis diastereomer. The bias towards distofacial addition is much stronger in the case of 3-propyl-3H-isobenzofuran-1-one (Chapter 5) wherein the propyl group offers substantially more steric hindrance than the methyl group in 1-methylindane (d.e. ~ 90% to the cis-cis diastereomer). The important question as to whether thermodynamic control prevailed during the hydrogenation of 1-methylindane cannot be addressed, however, since the values of individual rate constants are not known. Luckily, in this case, however, the thermodynamic control and the kinetic control dictate the selectivity in the same direction, namely, towards the cis-cis isomer. Thus the situation in the hydrogenation of 1-methylindane can be compared to At or Ak. The assumption of thermodynamic control is not valid if situation Ak prevails, nevertheless, the cis-cis isomer is predicted as the major product irrespective of the control.

Table 6.2 categorizes the diastereoselective hydrogenation reactions reported for 1-substituted indanes in Chapters 4 and 5 into the likely situations reported in Table 6.1. The relatively non-polar alkoxy group is expected to have very little interaction with the
Rationalization of the stereoselectivity

surface of the catalyst and hence is treated at par with the alkyl group. All carboxy substrates (acid, ester and amide) give a high selectivity to the cis-cis diastereomer. From Table 6.1 it is seen that the cis-cis diastereomer is obtained as the major product in the situations At, Bt, Ct, Ak, Dk and Gk. In situations At, Bt and Ct, thermodynamic control prevails. In situation Ak, although kinetic control prevails, thermodynamic and kinetic control do not predict opposite selectivity. Thermodynamic control can be assumed to predict the correct selectivity in these four situations. It would be interesting to see whether situations Dk and Gk can occur in the case at hand.

In these situations the adsorption via the proximofacial face is favored either equally or more over the adsorption via the distofacial face due to additional stabilization arising from the interaction of the carboxy group with the surface of the catalyst. This does not seem likely, however, since a similar diastereoselectivity is obtained with the acid, ester and amide substrates although the groups differ electronically substantially. Hence it seems likely that the assumption of thermodynamic control correctly predicts the product selectivity in the carboxy substrates too. In the case of 1-aminoindane, the rate of the reaction is considerably retarded due to the strong adsorption of the amino group. It is very probably that in this case the reaction rate is slower than the adsorption, allowing pre-equilibrium of the adsorbed state. Thermodynamic control is thus likely in this circumstance too and, since the cis-trans diasteromer is obtained very selectively, the situation is probably one amongst Dt, Et or Ft. In the case of hydroxy substrates the hydrogenation is not selective either to the cis-cis or the cis-trans diastereomer. Therefore, it is very hard to make a reasonable guess about the type of control, hence the situation could correspond to many possibilities listed in Table 6.1.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>% Proximofacial product</th>
<th>Likely situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe, OPr</td>
<td>21, 19</td>
<td>At / Ak</td>
</tr>
<tr>
<td>COOH, CONH₂, COOme</td>
<td>23, 28, 20</td>
<td>At / Bt / Ct / Ak</td>
</tr>
<tr>
<td>Me, Pr</td>
<td>37, 5</td>
<td>At / Ak</td>
</tr>
<tr>
<td>OH, CH₂OH</td>
<td>41, 55</td>
<td>Many possibilities</td>
</tr>
<tr>
<td>NH₂</td>
<td>98</td>
<td>Dt / Et / Ft</td>
</tr>
</tbody>
</table>
The arguments presented in the previous paragraphs, show that it is not possible to pinpoint whether kinetic or thermodynamic control prevails in each of the hydrogenation conducted in Chapters 4 and 5. It is possible, nevertheless, to make a knowledgeable guess about the likely situation prevailing during hydrogenation. For most of the 1-substituted indanes the assumption of thermodynamic control seems to be reasonable for the prediction of the configuration of the major product. Although this analysis is done for simple substrates, it can be readily extended to other diastereoselective aromatic hydrogenations, thanks to the strong correlation between the steric effects of the majority of the functional groups and the product selectivity. It can be predicted with reasonable confidence, therefore, that the hydrogenation of a large number of chirally-modified aromatic substrates will take place from the diastereotopic face which has lower steric hindrance.

### 6.3 Steric Requirements for High Diastereoselectivity

We have seen in the previous section that, although one cannot predict whether thermodynamic or kinetic control prevails during the diastereoselective hydrogenation of aromatic compounds over heterogeneous catalysts, one can conclude from the product selectivity that the steric effects are strongly expressed. We can hope to achieve high diastereoselectivity, therefore, if the adsorption of one of the two diastereotopic faces of the aromatic compound is sterically hindered, after modification with an auxiliary. Based on this idea, some strategies for modification are suggested in this section in order to obtain high selectivity. In Scheme 6.2, it is illustrated that chiral auxiliary 2 can be bonded to the disubstituted aromatic compound 1 in two modes giving the two structures 3A and 3B. An auxiliary with a cyclic structure was chosen because it can impart more rigidity to the aromatic compound-auxiliary system than an acyclic one. 3A and 3B would be hydrogenated preferably from the face opposite to the auxiliary (as shown by the bold arrows) because of steric reasons. The two structures are non-equivalent in the present context if the modified aromatic compound has these two distinct and stable conformations under reaction conditions. Stable conformations of 3 will exist (in the present context) provided the rotation of the single bond connecting the auxiliary to the substituent on the aromatic ring (i.e., Cl-R in Scheme
6.2) is hindered. Rotation of this bond can be prevented by constructing aromatic compound-auxiliary motifs shown in Fig. 6.1.

Scheme 6.2 Bonding of a chiral auxiliary to a disubstituted aromatic compound (bold arrows indicate the preferred direction of hydrogen addition)

Rotation around the Cl-R bond is prevented in 4A and 4B because of steric interaction of the auxiliary with the substituent Q at the ortho position of the aromatic ring. Thus 4A and 4B are atropisomers of each other. It is to be noted that 4A and 4B are diasteromeric atropisomers, possessing an identical center of chirality on the auxiliary but a non-identical axis of chirality between the auxiliary and the aromatic compound.

Rotation in structure 5 is prevented by doubly binding the auxiliary to the dissubstituted aromatic compound, while in structures 6A and 6B it is achieved by connecting the two substituents by covalent bonds. 5 can exist only in one form and has only one center of chirality element on the auxiliary. 6A and 6B are diastereomers of each other having an
identical center of chirality element on the auxiliary but a non-identical center of chirality element at the atom at the junction between the auxiliary and the aromatic compound.

Figure 6.1 Different motifs to prevent rotation of bonds connecting the auxiliary to the aromatic compound (bold arrows indicate the preferred direction of hydrogen addition)

During synthesis of molecules with structures 4 and 6, an additional element of chirality, namely a chirality axis in 4 and a chirality center in 6 is generated. It is this element of chirality, which is responsible for restriction of rotation around the covalent bond, connecting the chiral auxiliary to the aromatic compound, and, therefore, it would
be desirable to control completely the stereochemical outcome of the modification reaction. In other words, it would be beneficial to synthesize only one of the two possible diastereomers A or B. Thus, a diastereoselective synthesis would be an essential pre-requisite for good selectivity in the subsequent hydrogenation step. Interestingly, after selective synthesis of either A or B it is unimportant whether the original center of chirality on the auxiliary is retained or not. It is conceivable, however, that this original center of chirality on the auxiliary is essential during the stereoselective formation of the important chirality element during modification. Alternatively, introduction of the necessary element of chirality (either a center or an axis) via an enantioselective synthesis using an achiral auxiliary can also be envisaged. Motif 5 is advantageous from this point of view since only one conformation can be obtained by default.

To enable diastereoselective hydrogenation of a multisubstituted aromatic compound, at least one of the substituents should be easily modifiable by chemical bonding of the auxiliary. The modification techniques leading to structures 5 and 6 require that the second substituent also be amenable to chemical bonding. This, however, greatly limits the scope of the application of diastereoselective hydrogenation to different aromatic compounds. From this point of view motif 4 seems to be more useful than 5 or 6. In addition, from the point of view of cleaving the auxiliary to get the hydrogenated cyclohexanediyl product, techniques involving structures 5 and 6 are cumbersome, because of the rigidity with which the auxiliary will be bonded to the product. Hence considering pros and cons of all three motifs, it seems that the motif 4 is perhaps the most convenient one.

All three motifs have been already exploited for obtaining good selectivity in diastereoselective hydrogenation. The examples are shown in Fig. 6.2. Gallezot and co-workers succeeded in synthesizing only one of the two possible atropisomers of (S)-pyroglutamic acid-modified o-toluic acid (7A). Hydrogenation of the resulting adduct gave a very high diastereoselectivity (>90%) and a good chemoselectivity. In Chapter 3, the hydrogenation of adduct 8, obtained by the modification of anthranilic acid by (S)-proline was investigated. In this case, a rigid aromatic compound-auxiliary structure
was constructed by doubly bonding the auxiliary to the aromatic compound. Once again a high diastereoselectivity was obtained (~95%), unfortunately, accompanied by a low chemoselectivity. In this case, however, the major product had a configuration opposite to the one expected if the steric hindrance had dominated. An explanation for this observation is provided in the following section. Finally, an example of the realization of high diastereoselectivity, by bonding the two substituents, was provided in Chapter 5. In the hydrogenation of 3-propyl-3H-isobenzofuran-1-one (9), the achiral propyl group acted as the auxiliary.

**Figure 6.2** Examples of different motifs for binding auxiliary to the aromatic compound (bold arrows indicate the preferred direction of hydrogen addition)
6.4 Diastereoselective Hydrogenation using Amino Acid Auxiliaries

Figure 6.3 Rotation along single bonds in a peptide/protein backbone

In all diastereoselective hydrogenation reactions investigated in the present work and in the works by Gallezot and co-workers, amino acid auxiliaries were employed. The amino acid auxiliaries were bonded through an amide bond to the aromatic substrate. The importance of conformational homogeneity was pointed out in the preceding section, especially for the structural motif 4. The structure of aromatic compound-auxiliary system can be compared with that of a dipeptide in which two different units are connected by a peptide bond. The conformation of peptides and proteins is a subject of great interest and an in-depth understanding of its relation to free (or hindered) rotation along single bonds in the protein/peptide backbone has evolved. We will discuss this aspect briefly before we attempt to clarify the relation between diastereoselectivity and substrate structure in amino acid auxiliary aided diastereoselective hydrogenation reactions.

A small part of the amino acid chain of a protein/peptide is shown in Fig. 6.3. There are three types of bonds in the protein backbone, namely, \( N_i-C_{\alpha}, C_{\alpha}-C_i(O) \) and \( C_i(O)-N_{i+1} \). The corresponding torsion or dihedral angles are denoted by \( \phi, \psi \) and \( \omega \) respectively. The last angle has typically a value of 180° (or 0°) because of the double bond character of the amide bond [6]. Since rotation is possible along the single bonds \( N_i-C_{\alpha} \) and \( C_{\alpha}-C_i(O) \), the structure of the protein/peptide is determined by the values of the angles \( \phi \) and \( \psi \) of all amino acid units. Many combinations of \( \phi \) and \( \psi \) are not allowed, however,
because of steric interactions. If the allowed values of $\psi$ are plotted against those of $\phi$, a so-called two-dimensional Ramachandran map is generated [7]. Depending on the secondary structure of a protein, these angles fall within a range of values. The conformational flexibility of the peptide/protein backbone can be reduced further by either making cyclic peptides, or forming bridges between amino acids, or within an amino acid by cyclization [8]. The last is accomplished by using an amino acid like proline, wherein the angle $\phi$ is restricted to $-65 \pm 15^\circ$ because of its five-membered ring structure. Because of this unique characteristic of proline (or pyroglutamic acid), it was employed in all successful diastereoselective hydrogenations investigated by us (Chapters 3 and 4) and Gallezot and co-workers [9, 10].

![Chemical structures](image)

**Figure 6.4** Amino acid auxiliary modified disubstituted aromatic compounds

Fig. 6.4 shows the structures of the four aromatic compound-auxiliary systems investigated to date using proline-type auxiliaries. The important dihedral angles are also shown. Clearly, in the cyclic peptide formed by doubly bonding anthranilic acid (which in fact is a $\beta$ amino acid) to proline (8), no free rotation is possible around any of the bonds and the molecule exists in only one conformation. The restriction of the value
Rationalization of the stereoselectivity

of $\omega$ to 180° (or 0°) is applicable to amino acids which are part of a protein or peptide, and it would be interesting to see if this value is maintained in molecules 7, 10 and 11. Molecular mechanics techniques offer a simple and quick way for conformational analysis of a molecule. Hence, using the MM2 forcefield with the MacroModel package, we made a Ramachandran-type analysis of molecule 7 by variation of angles $\psi$ and $\omega$ systematically over an entire range from 0° to 360°. The resulting two-dimensional conformation map is shown in Fig. 6.5. In the map, the isoenergetic points are connected by lines. There are two energy minima enclosed by contours with minimum energy. Both minima (M1 and M2 in Fig. 6.5) are at $\omega = 180°$, indicating that the amide bond maintains its planarity. The structures corresponding to the two minima are shown in Fig. 6.6. The difference in the two structures is the position of the pyroglutamic auxiliary with respect to the aromatic ring. In both conformations, the plane of the trigonal carbonyl-carbon, connecting the auxiliary to the aromatic ring, makes an angle to the aromatic ring. There are two additional minima at $\omega = 0°$, but these minima have a higher energy than those at $\omega = 180°$ [6]. The angle $\omega$ is thus not free to assume any value because of the double bond character of the amide bond.

There are clearly two relatively broad regions for the angle $\psi$ containing M1 and M2. Inter-conversion between the conformations M1 and M2 along the $\psi$ axis is hindered by a relatively high-energy barrier because of the steric interaction of the carbonyl oxygen of the amide bond with the proton and the methyl group at the ortho positions on the aromatic ring [11]. A similar result is obtained in the conformational analysis of 11. 7 could be hydrogenated with a high diastereoselectivity (>90%) because, fortunately, Gallezot and co-workers could synthesize it in only one of the four possible conformations, namely the M2 conformation in Fig. 6.6. The fact that 11 could not be synthesized selectively in one of its two conformations explains the low diastereoselectivity (<60%) obtained in its hydrogenation. One can see in Fig. 6.4 that in 10, in addition to angle $\psi$, angle $\phi'$ is also free to assume any value, unlike in the case of 7. Thus 10 is more flexible than 7 and consequently is hydrogenated with a lower diastereoselectivity. The most important reason for the low diastereoselectivity (<50%) obtained in the hydrogenation of 10 is perhaps the relatively unhindered rotation of the angle $\phi'$, because of the inability of the N-H bond (in the amide group) to sterically
interact with the proton and the methyl group at the ortho positions on the aromatic ring. We attempted to hinder the free rotation of the angle \( \varphi' \) by replacing the H atom in the N-H bond (in the amide group) by an ethyl or an acetyl group as shown in Fig. 6.7. Again, using a Ramachandran-type analysis, we were able to confirm hindrance of the rotation of the angle \( \varphi' \) on such a replacement [12]. Although we succeeded in the synthesis of the molecules shown in Fig. 6.7, unfortunately, the products obtained were not atropisomerically pure. Attempts to separate the diastereomeric atropisomers by chromatographic techniques failed and hence we did not investigate in this direction further.

Figure 6.5 Two dimensional Ramachandran-type map for 7. (X-axis: \( \omega \), Y-axis: \( \psi \)). Numbers indicate energy values in kJ/mol. Contours with darker lines connect points with higher energies.
Hydrogenation of 8 occurred from a face opposite to that expected from a steric point of view. The structure of 8 was optimized using molecular modeling (MM2 force field). As shown in Fig. 6.8, the proline ring should hinder adsorption of the aromatic ring from its top face. The hydrogenation should thus proceed from the bottom face (in Fig. 6.8) which is the face on the opposite side of the proton at the stereogenic center. The carbonyl group connected to the aromatic carbon 5a, however, introduces a steric hindrance to the adsorption of the bottom face of the aromatic ring. It seems that the hindrance offered by this carbonyl group exceeds that provided by the proline ring, thus, preventing a planar adsorption of the aromatic ring. Thus the aromatic ring gets only partially hydrogenated to the cyclohexene intermediate, if it adsorbs through the bottom
face. It seems that the adsorption from the top face, although hindered by the proline ring, occurs to a small extent i.e. with a low chemoselectivity. Further analysis by molecular modeling revealed that once the carbon atom 5a becomes sp$^3$ hybridized on addition of an hydrogen atom, the carbonyl group at 5 very effectively blocks the face of the six membered ring from its side. As a result of this, the subsequent hydrogenation can take place only from the side opposite to the carbonyl group. This can account for the high diastereoselectivity obtained in the hydrogenation of 8.

Figure 6.7 Synthesis of (S)-proline modified o-toluidine derivatives with hindered rotation around the C-N bond at the aromatic ring.
6.5 Concluding Remarks on Diastereoselective Hydrogenation

The discussion in previous sections shows that high selectivity is obtainable in the diastereoselective hydrogenation of aromatic compounds only if the adsorption of one of the two aromatic faces of the molecule is made sterically unfavorable. The question is whether this is the necessary and also the sufficient condition for high selectivity. In Chapter 5, the selectivity in the hydrogenation of cyclohexene intermediates was shown to occur with a lower selectivity than that of the parent aromatic substrate. In our opinion, this problem is more general, because of the fact that cyclohexene intermediates have four sp$^3$ hybridized carbon atoms (and 4 single bonds) as against none in the case of the parent aromatic substrate, thus, offering a scope for increased flexibility and consequently lower selectivity. Hence, there is a good possibility that the cyclohexene intermediates, if they are formed with a good chemoselectivity would decrease the diastereoselectivity. The other factor reducing the diastereoselectivity could be the chemoselectivity. It was seen in the case of (S)-proline-modified anthranilic acid, how a strong steric interaction of the molecule from one of its two faces resulted in incomplete hydrogenation of the aromatic ring. Increased rigidity, thus could be bad for obtaining a good selectivity. In conclusion, sterically hindering one of the two faces of the aromatic ring is only a necessary but may not be a sufficient condition for obtaining a high diastereoselectivity.
If diastereoselective hydrogenation is attempted using motifs similar to 4 and 6, it must be remembered that only one of the possible two diastereomers A or B should be synthesized selectively. To the best of our knowledge, there is no reaction yet which enables complete control of atropisomeric selectivity (for non-biaryl atropisomers) and hence it is a matter of chance if one of the two atropisomeric diastereomers of 4 is obtained. The possibility of existence of atropisomeric conformations can, however, be predicted a priori by using molecular modeling techniques. Again, it is emphasized that synthesizing one of the two diastereomers A and B in the case of 4 or 6, may not be sufficient to get high diastereoselectivity in hydrogenation as pointed out in the preceding paragraph.

In summary, the requirements for good selectivity in diastereoselective hydrogenation of substituted aromatic compounds over heterogeneous catalysts are quite stringent. Molecular mechanics can be applied to check if a certain auxiliary results in an aromatic compound-auxiliary system that is rigid enough, and if the two faces of aromatic ring are well differentiated with respect to their adsorption ability. This prediction is obviously of little use, unless a method to synthesize selectively either the A or B diastereomer selectively, in the case of motifs 4 or 6 can be found. Having said this, it must be emphasized that there seems to be no alternative to conduct the hydrogenation reaction itself to check whether one can obtain high diastereoselectivity, because of the uncertainties associated with the formation and the subsequent hydrogenation of the cyclohexene intermediate, and the chemoselectivity. With a rather long list of requirements for attaining good selectivity, the diastereoselective hydrogenation of aromatic compounds using chiral auxiliaries seems to be a formidable task. Nevertheless, it should be a rather rewarding proposition, considering that only very few catalytic systems are active for stereoselective hydrogenation of aromatic rings. Although even the best selectivities obtained in diastereoselective hydrogenation over heterogeneous catalysts may not rival the best homogeneous catalytic systems, the overwhelming domination of steric factors gives it a degree of predictability, rivaled only by a handful of other stereoselective hydrogenation systems. Notwithstanding this advantage, it seems that the best applications of diastereoselective hydrogenation will be
Rationalization of the stereoselectivity

in situations where the element of chirality used for leveraging selectivity is also a part of the final target molecule.

References

5. Direct measurement of the absolute values of reaction constant (k) and adsorption constant (K) is extremely difficult for supported heterogeneous catalysts. Their values can be derived, however, by fitting kinetic data using the Langmuir-Hinshelwood model.
6. Because of its hindered rotation, the amide bond can have two coformations. In the case of peptides these conformations are commonly referred to as *cis* (φ = 0°) and *trans* (φ = 180°). Normally the *trans* conformation of the amide bond is favored energetically in peptides for steric reasons. Although the present case conforms to this rule, it should be noted that proline is known to favor *cis* conformation in proteins and peptides at a higher frequency than other amino acids due to its unique cyclic structure [13].
11. Hindered rotation around the C-C(O) bond in aryl carbonyls is a well known phenomenon [14]. Some attempts to resolve atropisomers of aryl carbonyl amides have been made [15].
12. Some atropisomeric derivatives of substituted anilines have been exploited as reactants in diastereoselective reactions [16].
7. Hydrogenolysis of Benzylic Alcohols and Ethers

7.1 Introduction

In the liquid phase hydrogenation of 1-indanol and 1-alkoxyindanes over rhodium catalysts, large differences in the chemoselectivity of carbon-supported and alumina-supported catalysts were observed (Chapters 4 and 5). Additional investigations revealed that various commercially produced carbon-supported catalysts predominantly yielded perhydroindane, while alumina-supported catalysts predominantly yielded perhydroindanol (see Scheme 7.1). Similar results were obtained for 1-tetralol and 1-phenylethanol. To the best of our knowledge such a big difference in the chemoselectivity of rhodium catalysts on these two common catalyst supports has never been described. It is widely known that aromatic substrates with a benzylic hydroxyl or a benzylic alkoxy group are prone to scission of the C-O bond [1] during hydrogenation on noble metal catalysts [2]. It is also known that the extent of bond scission depends on the nature of the noble metal used as the catalyst [3]. The high C-O bond scission capability of carbon-supported rhodium was surprising, however, since rhodium is known to leave non-reducible groups intact during hydrogenation of aromatic substrates [4]. We, therefore, conducted experiments to study the mechanism of C-O bond scission in 1-indanol on carbon-supported rhodium catalysts, focussing for the most part on deuterium experiments. The average incorporation of deuterium in the C-O bond scission product, perhydroindane, was measured by mass spectrometry. This value exceeded the expected values when the incorporation took place exclusively by saturation of the C-C double bonds and C-O bond scission and thus it was necessary to determine the isotopic composition at each carbon atom in the product. $^2$D coupled $^{13}$C NMR spectroscopy was used for this purpose, because $^2$D NMR spectroscopy had insufficient resolution.
Scheme 7.1 Hydrogenation and hydrogenolysis of 1-indanol

7.2 Experimental

Rh/C (Fluka, Aldrich, PCC), Rh/Al₂O₃ (Fluka) and Rh black (Johnson Matthey, >99.9% pure on a metal basis) catalysts were used. The PCC catalyst contained 54% water and was not dried before use. Activated carbon-supported (Fluka) and graphite-supported (Lonza) catalysts were made by impregnating the respective supports with an aqueous rhodium nitrate solution. After drying (120°C) the impregnated catalysts overnight in air, they were calcined (350°C for 3 h) in nitrogen. A series of Rh/Al₂O₃ catalysts was prepared by impregnation of solutions of different rhodium salt precursors on Al₂O₃ (Condea) as described in Chapter 2. The alumina catalysts were treated like the carbon and graphite catalysts, with the exception that the final calcination was done in air. The salt precursors were supplied by Johnson Matthey. A list of all the catalysts used is given in Table 7.1. The metal surface area of some of the catalysts was quantified by hydrogen chemisorption measurements as stated in Chapter 2. Zeolite beta was used as an additive in the proton form, obtained by pretreating the supplied material (CU Chemie Uetikon, Si/Al = 9.1, Na form) with ammonium nitrate followed by calcination.
Table 7.1 Different catalysts used for the hydrogenation of 1-indanol

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Source</th>
<th>Precursora</th>
<th>Dispersion (H/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh black</td>
<td>Johnson Matthey</td>
<td>n.a.</td>
<td>not applicable</td>
</tr>
<tr>
<td>Rh/Al₂O₃ I</td>
<td>Condea alumina</td>
<td>Rh(acac)₃</td>
<td>0.27</td>
</tr>
<tr>
<td>Rh/Al₂O₃ II</td>
<td>Condea alumina</td>
<td>Rh(NO₃)₃·2H₂O</td>
<td>0.74</td>
</tr>
<tr>
<td>1.25Rh/Al₂O₃ I</td>
<td>Condea alumina</td>
<td>Rh(NO₃)₃·2H₂O</td>
<td>1.22</td>
</tr>
<tr>
<td>Rh/Al₂O₃ (F)</td>
<td>Fluka</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Rh/C (A)</td>
<td>Aldrich</td>
<td>n.a.</td>
<td>0.29</td>
</tr>
<tr>
<td>Rh/C (F)</td>
<td>Fluka carbon</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Rh/C (P)</td>
<td>PCC</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Rh/G</td>
<td>Lonza graphite</td>
<td>Rh(NO₃)₃·2H₂O</td>
<td></td>
</tr>
</tbody>
</table>

a n.a. = not available

Hydrogenation experiments were conducted at room temperature in a 60 ml stainless steel autoclave, stirred with a gas-inducing impeller. In a typical experiment, 1-indanol (0.5 g, Fluka) was dissolved in the solvent (15 ml) in the autoclave and supported catalyst (50 mg and additives, if used) were added to this solution. The autoclave was closed, flushed with nitrogen and hydrogen, and pressurized to about 50 bar with hydrogen. Samples were taken through a sample tube to determine the completion of the reaction (reaction time was usually less than 4 hrs), but thorough kinetic measurements were not made. Samples were analyzed using an HP 5890 GC equipped with an HP-1 capillary column and a FID detector.

Deuteration experiments [5] were conducted with the Rh/C (A) catalyst under the same process conditions as the hydrogenation experiments. In addition to deuteration of 1-indanol, deuteration of indane and indene (both Aldrich) were studied to help us understand the mechanism of the C-O bond cleavage. To compare the performance of carbon-supported and alumina-supported catalysts, indane deuteration was carried out in cyclohexane on the Rh/Al₂O₃ (F) catalyst. The substrate to catalyst molar ratio and the reaction conditions were kept constant in all deuterium experiments. The isotopic purity of deuterium (Sauerstoffwerke Lenzburg) was 99.8%. C₂H₅OD (Fluka, isotopic purity >99.5%) was used as the solvent instead of ethanol in the deuterium experiments, while
cyclohexane was used in its undeuterated form. Mass spectra of the gas phase in the autoclave (measured on a quadrupolar Balzer QME Prisma 200 instrument) after the deuteration experiments with 1-indanol in C₂H₅OD and cyclohexane indicated that the concentration of deuterium in the gas phase was higher than 85%, the other main components being HD and H₂. This indicates that deuterium rather than hydrogen was predominantly added to the substrate during the deuteration experiments. GC-MS analysis was used to quantify total deuterium incorporation in the perhydroindane product. The reaction mixture was analyzed directly by injecting a sample (after dilution) at the end of the reaction, i.e., at 100% conversion of 1-indanol. Injection of the gas phase in equilibrium with the liquid sample enabled us to measure the mass spectrum of the solvent. More than 95% of the molecules of C₂H₅OD and cyclohexane did not incorporate a deuterium atom during the reaction. MS analyses were done in the EI mode on a HP 6890 GC coupled to an HP 5973 MS at an ionization energy of 70 eV. Deuterium incorporation was calculated on the basis of molecular peaks of perhydroindane isotopomers in the mass spectrum. Since the mass spectrum varied according to the point on the perhydroindane peak at which it was measured, the average mass spectrum of the entire peak was used for calculations. In calculating the percentage of each isotopomer of perhydroindane, the isotopomers with concentrations lower than 5% of the main isotopomer (as calculated from the molecular peak intensities) were omitted. For the NMR analyses, the perhydroindane product was separated from the other products and from the solvent after separating the reaction mixture by filtering the solid catalyst [6]. ¹³C NMR spectra and ¹³C NMR DEPT spectra were then measured on the isolated samples with a Bruker AVANCE DPX 300 instrument to determine the degree of deuteration at individual carbon atoms [7]. The resonance frequency of the instrument was 75 MHz.
7.3 Results

Hydrogenolysis of benzylic alcohols and ethers

Figure 7.1 Kinetics of hydrogenation of 1-indanol on Rh/C (A) catalyst in hexane.

Hydrogenation of 1-indanol resulted in the formation of the C-O bond scission-hydrogenation product perhydroindane and the hydrogenation product perhydro-1-indanol (Scheme 7.1). Although the cis as well as the trans isomers of both perhydro-1-indanol and perhydroindane were obtained, the cis:trans ratio was very high (usually above 20). Both the cis-cis and cis-trans products of perhydro-1-indanol were obtained. The cis-cis isomer was always obtained in excess, and the magnitude of the diastereoselectivity depended on the catalyst employed as described in Chapter 4. The yield of the products varied with the catalyst used. The C-O bond scission product indane, an intermediate between 1-indanol and perhydroindane, was found with some catalysts, and small amounts (up to 5%) of partly hydrogenated cyclohexene intermediates between 1-indanol and perhydro-1-indanol were found with all catalysts. Table 7.2 lists the selectivity to the C-O bond scission-hydrogenation products (cis and trans perhydroindane) and the hydrogenation products (cis-cis and cis-trans perhydro-1-indanol) obtained with various catalysts at 100% conversion of 1-indanol and all the intermediates. The data in Table 7.2 show that carbon-supported catalysts result in
extensive C-O bond breaking. The selectivity to perhydroindane on alumina-supported catalysts varied with the catalyst used but was never above 10%. Rhodium black gave a small but significant selectivity to perhydroindane. With hexane as the solvent, the extent of C-O bond scission was reduced for both the alumina-supported and the carbon-supported catalysts. The reaction of 1-indanol was faster over carbon-supported catalysts than over alumina-supported catalysts (not indicated in Table 7.2). The rate of reaction depended on the solvent and was higher in hexane than in ethanol. In the case of ethanol, the reaction was slowed down considerably towards the end. It was verified that perhydro-1-indanol does not hydrogenolyse to perhydroindane under reaction conditions, by running the reaction over all the catalysts for a few more hours after the complete conversion of 1-indanol and the intermediates. Fig. 7.1 shows the consumption of 1-indanol, and the formation of perhydro-1-indanol and perhydroindane as a function of time in a reaction over the Rh/C (A) catalyst in hexane. From Fig. 7.1 it is clear that the pathway perhydro-1-indanol to perhydroindane is not possible under the present reaction conditions since their concentrations remain unaltered with time after complete consumption of 1-indanol. The formation and the consumption of the intermediate indane (Scheme 7.2) is also shown in the figure. The cyclohexene intermediates between 1-indanol and perhydro-1-indanol are not shown in the figure for clarity.

The effect of the addition of various reagents to the reaction mixture on the final selectivity was also studied (Table 7.3). The selectivity to perhydroindane with the water-saturated Rh/C (P) catalyst was comparable to the Rh/C (A) catalyst (Table 7.2). A separate experiment was conducted with the Rh/C (A) catalyst in which 0.3 ml of water was added to the reaction mixture. The selectivity to perhydroindane in this experiment was 79%, comparable to that obtained with Rh/C (A) in ethanol. In an experiment with the Rh/Al₂O₃ II catalyst, 150 mg of extra alumina support were added to the reaction mixture; the selectivity to perhydroindane remained unchanged at 4%. In another experiment, activated carbon (Fluka, 50 mg) was added to the reaction mixture in an experiment with the Rh/Al₂O₃ (F) catalyst in ethanol. The selectivity to perhydroindane was 33%. In a reverse experiment, in which alumina support (Condea, 50 mg) were added to the reaction mixture in an experiment with the Rh/C (A) catalyst,
the performance of the Rh/C (A) catalyst remained the same. Adding zeolite beta (50 mg) to the reaction mixture in an experiment with the Rh/Al₂O₃ (F) catalyst in ethanol resulted in 24% selectivity to perhydroindane. Addition of a small amount of concentrated hydrochloric acid (0.1 ml) instead of the zeolite beta resulted in a 96% selectivity to perhydroindane. Conducting the reaction in acetic acid instead of ethanol with the Rh/Al₂O₃ (F) catalyst gave 82% selectivity to perhydroindane.

Table 7.2 Selectivity to the C-O bond scission-hydrogenation products and hydrogenation products at 100% conversion of 1-indanol with various solvents and catalysts

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Selectivity to perhydroindane (%)</th>
<th>Selectivity to perhydro-1-indanol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh black</td>
<td>EtOH</td>
<td>3</td>
<td>96</td>
</tr>
<tr>
<td>Rh/Al₂O₃ I</td>
<td>EtOH</td>
<td>9</td>
<td>91</td>
</tr>
<tr>
<td>Rh/Al₂O₃ II</td>
<td>EtOH</td>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>1.25Rh/Al₂O₃ II</td>
<td>EtOH</td>
<td>10</td>
<td>89</td>
</tr>
<tr>
<td>Rh/Al₂O₃ (F)</td>
<td>Hexane</td>
<td>3</td>
<td>96</td>
</tr>
<tr>
<td>Rh/Al₂O₃ (F)</td>
<td>EtOH</td>
<td>7</td>
<td>93</td>
</tr>
<tr>
<td>Rh/C (A)</td>
<td>Hexane</td>
<td>32</td>
<td>60</td>
</tr>
<tr>
<td>Rh/C (A)</td>
<td>EtOH</td>
<td>77</td>
<td>19</td>
</tr>
<tr>
<td>Rh/C (F)</td>
<td>EtOH</td>
<td>74</td>
<td>19</td>
</tr>
<tr>
<td>Rh/C (P)</td>
<td>EtOH</td>
<td>79</td>
<td>18</td>
</tr>
<tr>
<td>Rh/C</td>
<td>EtOH</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Rh/G</td>
<td>EtOH</td>
<td>95</td>
<td>3</td>
</tr>
</tbody>
</table>

*200 mg of 1.25Rh/Al₂O₃ II, 25 mg of Rh black and 50 mg of all other rhodium catalysts were used.

Table 7.4 lists the selectivity to the fully hydrogenated C-O bond scission products obtained in the hydrogenation of other benzylic alcohols when hydrogenated in ethanol under the same reaction conditions as for 1-indanol. The carbon-supported catalyst shows a substantially higher C-O bond scission activity than the alumina-supported catalyst with all the substrates. The difference in the selectivity to C-O bond scission products between the carbon-supported and the alumina-supported catalyst is lowest in the case of benzyl alcohol. The difference in selectivity is not limited to alcohols but is
also observed in the case of benzylic 1-alkoxyindane ethers as illustrated by results in Table 5.1.

### Table 7.3 Influence of additives on hydrogenolysis

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Additive</th>
<th>Selectivity to perhydroindane (%)</th>
<th>Selectivity to perhydro-1-indanol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/C (A)</td>
<td>EtOH</td>
<td>0.3 ml H₂O</td>
<td>79</td>
<td>18</td>
</tr>
<tr>
<td>Rh/C (A)</td>
<td>EtOH</td>
<td>50 mg Al₂O₃</td>
<td>79</td>
<td>17</td>
</tr>
<tr>
<td>Rh/Al₂O₃ II</td>
<td>EtOH</td>
<td>150 mg Al₂O₃</td>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>Rh/Al₂O₃ (F)</td>
<td>EtOH</td>
<td>50 mg C</td>
<td>33</td>
<td>64ᵇ</td>
</tr>
<tr>
<td>Rh/Al₂O₃ (F)</td>
<td>EtOH</td>
<td>50 mg zeolite</td>
<td>24</td>
<td>76ᵇ</td>
</tr>
<tr>
<td>Rh/Al₂O₃ (F)</td>
<td>EtOH</td>
<td>0.1 ml HCl</td>
<td>96</td>
<td>2</td>
</tr>
<tr>
<td>Rh/C (A)</td>
<td>AcOH</td>
<td>-</td>
<td>82</td>
<td>17</td>
</tr>
</tbody>
</table>

* 50 mg of rhodium catalyst were used;ᵇ selectivity to perhydro-1-indanol and its ether with ethanol

### Table 7.4 Selectivity to the fully hydrogenated C-O bond scission products at 100% conversion of various benzylic alcohols

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Substrate to rhodium molar ratio</th>
<th>Selectivity to fully hydrogenated C-O bond scission product(s) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Tetralol</td>
<td>139</td>
<td>Rh/Al₂O₃ (F) 82ᵃ</td>
</tr>
<tr>
<td>1-Phenylethanol</td>
<td>169</td>
<td>Rh/C (A) 68</td>
</tr>
<tr>
<td>Benzylalcohol</td>
<td>191</td>
<td>Rh/Al₂O₃ (F) 49ᵇ</td>
</tr>
</tbody>
</table>

ᵃ Selectivity to cis + trans decalin;ᵇ Selectivity to methylcyclohexane + toluene (the catalyst was deactivated before complete conversion of toluene to methylcyclohexane)

We also added bases to the reaction mixture in the hydrogenation with Rh/C (A), because they are known to suppress C-O bond scission [8, 9]. When an aqueous solution (0.3 ml of 0.5 N) of the inorganic bases LiOH, KOH, NaOH and Na₂CO₃ was added to the reaction mixture containing either a benzylic alcohol or a benzylic ether, the C-O bond scission was suppressed completely. This was accompanied by a decrease in the activity of hydrogenation by an order of magnitude. Adding the organic base
triethylamine to the reaction mixture also suppressed C-O bond scission in both ethers and alcohols, and only 2% perhydroindane was obtained in the hydrogenation of 1-indanol at an amine to rhodium molar ratio of 10:1. As in the case of inorganic bases, there was a simultaneous reduction in activity.

Figure 7.2 Deuterium incorporation in the perhydroindane product of the deuteration of 1-indanol in C$_2$H$_5$OD and cyclohexane on Rh/C (A) catalyst

MS analyses of the perhydroindane product of the deuteration of 1-indanol in C$_2$H$_5$OD and cyclohexane indicated a distribution of deuterium incorporation. Fig. 7.2 gives the percentage of each isotopomer of perhydroindane corresponding to the number of deuterium atoms incorporated as obtained with the Rh/C (A) catalyst. The incorporation of deuterium in perhydroindane in the C$_2$H$_5$OD and cyclohexane experiments was very similar. The number of deuterium atoms incorporated in the majority of the isotopomers exceeds the number required for complete saturation of the aromatic ring and a direct cleavage of the C-O bond (i.e., 6 + 1 = 7).
Fig. 7.3 $^{13}$C NMR spectra

**A.** $^2$D coupled spectrum (solvent: C$_6$H$_6$-C$_6$D$_6$ mixture) of the perhydroindane product obtained in the deuteration of 1-indanol in C$_2$H$_5$OD

**B.** $^2$D coupled DEPT spectrum (solvent: C$_6$H$_6$-C$_6$D$_6$ mixture) of the perhydroindane product obtained in the deuteration of 1-indanol in C$_2$H$_5$OD

**C.** DEPT spectrum of undeuterated perhydroindane (solvent: C$_6$D$_6$)

Fig. 7.3 shows a the $^{13}$C NMR spectrum (A) of the reaction product perhydroindane obtained in the deuteration of 1-indanol in C$_2$H$_5$OD. In addition, the corresponding $^{13}$C NMR DEPT spectrum (B), and a $^{13}$C NMR DEPT spectrum (C) of an undeuterated perhydroindane sample are shown. The peaks in spectrum C have been numbered according to their position on the ring in perhydroindane. The assignment of the $^{13}$C NMR peaks to the carbon atoms in perhydroindane was confirmed by a 2D INADEQUATE NMR experiment [10] with an undeuterated perhydroindane sample. The peaks of the carbon atoms in spectra A and B are shifted to high field compared to the peaks in spectrum C because of the replacement of protons by deuterium atoms [11]. The order of the peaks, however, remains unchanged. Spectrum B in Fig. 7.3 shows that all the carbon atoms in the six-membered ring have predominantly incorporated one deuterium atom. The peaks corresponding to the carbon atoms 4 to 7 are of the CHD
type, because they are triplets in the normal as well as in the DEPT spectrum, while those corresponding to 3a and 7a are of the CD type since they do not appear in the DEPT spectrum. Spectrum B shows that the carbon atoms at the positions 1 and 3 are partly deuterated. The carbon atom at position 2 is predominantly undeuterated and is of the CH₂ type. Several CH₂ peaks are observed because of the difference in the chemical shift of the isotopomers of perhydroindane. These isotopomers differ in deuterium substitution patterns on the carbon atoms at the 1 and 3 positions. The higher the degree of deuteration at the carbon atoms at positions 1 and 3, the greater the magnitude of the high field shift of the CH₂ peak of the carbon atom at position 2 [11]. It is clear that the carbon atoms at positions 1 and 3 are of both CH₂ and CHD types in spectrum B; as expected, the CHD peak is high field shifted compared to the CH₂ peak. The NMR spectra of the reaction product perhydroindane obtained in the deuteration of 1-indanol in cyclohexane (not presented) were similar to those obtained in the deuteration of 1-indanol in C₂H₅OD.

Fig. 7.4 shows deuterium incorporation in experiments with indane in C₂H₅OD and cyclohexane. The number of deuterium atoms incorporated exceeds the number required for complete saturation of the aromatic ring (i.e., 6) in the majority of the isotopomers. The pattern of deuterium incorporation in the perhydroindane products obtained in the 1-indanol and indane deuteration experiments is comparable but has shifted to lower deuterium incorporation in the case of indane. The NMR spectra of these samples (not presented) are also comparable to those obtained in the 1-indanol deuteration experiments. NMR analyses of these samples show that the carbon atoms at positions 1 and 3 are partly deuterated, while the carbon atom at 2 is largely undeuterated. The ratio of intensities of peaks corresponding to the CH₂ and the CHD type of carbon atoms at positions 1 and 3 is higher in perhydroindane obtained in indane deuteration than the ratio obtained in 1-indanol deuteration. The carbon atoms in the six-membered ring generally bear one deuterium atom. Fig. 7.5 compares the incorporation of deuterium in the deuteration of indane in cyclohexane on Rh/C (A) and Rh/Al₂O₃ (F). The concentrations of different isotopomers of perhydroindane obtained with both catalysts are similar. This was also confirmed by the ¹³C NMR spectra of the product perhydroindane obtained in both experiments.
Figure 7.4 Deuterium incorporation in the perhydroindane product of the deuteration of indane in C₂H₅OD and cyclohexane on Rh/C (A) catalyst

Figure 7.5 Deuterium incorporation in the perhydroindane product of the deuteration of indane in cyclohexane on Rh/C (A) and Rh/Al₂O₃ (F) catalysts
Fig. 7.6 shows deuterium incorporation in perhydroindane in the deuteration of indene in C₂H₅OD. The distribution of deuterium is narrower and shifted towards a higher deuterium incorporation than the distribution obtained with 1-indanol and indane, as would be expected from a parent substrate with a higher degree of unsaturation. Fig. 7.7 shows the normal ¹³C NMR spectrum (A) and the ¹³C NMR DEPT spectrum (B) of the isolated sample obtained in this experiment. After deuteration, all carbon atoms in the six-membered ring of indene have one deuterium atom as in the case of 1-indanol and indane. The spectra indicate deuterium incorporation at the carbon atoms at positions 1, 2 and 3.

![Figure 7.6 Deuterium incorporation in the perhydroindane product of the deuteration of indene in C₂H₅OD on Rh/C (A) catalyst](image)

The average incorporation of deuterium in perhydroindane and the theoretical incorporation expected in these experiments are shown in Fig. 7.8. The degree of incorporation of deuterium in 1-indanol and indane is slightly higher in C₂H₅OD than in cyclohexane. The theoretical value of deuterium incorporation was calculated by assuming that the incorporation in perhydroindane occurs only when deuterium is added to the aromatic ring and to the C-C double bond. Fig. 7.8 shows that the theoretical values of deuterium incorporation are 6 and 8 for indane and indene respectively. The actual incorporation of deuterium in indane and indene always exceeds the theoretical
value by 1.5 to 2. The average incorporation of deuterium in the case of 1-indanol is between that for indene and indane. The theoretical value of deuterium incorporation in perhydroindane during deuteration of 1-indanol is 7 or 8, depending on the mechanism by which C-O bond scission takes place (vide infra). However, only the value 7 has been considered in Fig. 7.8.

**Figure 7.7** $^{13}$C NMR spectra of the perhydroindane product of the deuteration of indene in C$_2$H$_5$OD

**A.** $^2$D coupled spectrum (solvent: C$_6$H$_6$-C$_6$D$_6$ mixture)

**B.** $^2$D coupled DEPT spectrum (solvent: C$_6$H$_6$-C$_6$D$_6$ mixture)
7.4 Discussion

Data presented in Table 7.4 show that the big difference in the chemoselectivity of the carbon-supported and the alumina-supported catalysts is not restricted to 1-indanol but is also observed for other benzylic alcohols. Moreover, it occurs also with 1-alkoxyindanes. Data in Table 7.2 indicate that the carbon-supported catalysts, obtained from different sources, exhibit a higher activity of C-O bond scission than the alumina-supported catalysts with widely different dispersions, a different salt precursor, and obtained from different sources. Thus, differences in salt precursors and dispersion cannot explain the higher C-O bond scission capability of carbon-supported catalysts.

C-O bond scission can proceed via two routes (Scheme 7.2): dehydration followed by hydrogenation of the resulting olefin on rhodium (I followed by II) and the direct hydrogenolysis of the C-O bond (III). The former route involves elimination of water and formation of indene, followed by hydrogenation to indane. The latter route involves
direct scission of the C-O bond. Hydrogenation in steps II and III requires hydrogen from the metal (either on the metal or spillover hydrogen). The dehydration step I requires acid sites which, in a reducing atmosphere, are present only on the support. The carbon support can have acidic sites, depending on the preparation procedure [12]. Different carbon supports have been reported to catalyze etherification, albeit at a higher temperature of 150°C [13], and etherification is known to be catalyzed by acids. Manninger et al. [14] have reported that a charcoal type carbon support catalyzed the dehydration of cyclohexanol to cyclohexene at 300°C. Alumina is also known to be a good dehydration catalyst at higher temperature. However, very little C-O bond scission is observed on the alumina catalysts under the process conditions employed in the current hydrogenation. An experiment in which extra alumina was added to the reaction mixture with the Rh/Al₂O₃ II catalyst proves that alumina is not involved in the overall C-O bond scission reaction. In addition, Rh black is also active for C-O bond scission, though to a very small extent.

The questions to be addressed are: Does C-O bond scission on the carbon-supported catalysts proceed via steps I and II or via III? and if it proceeds simultaneously via both routes, which of the two routes is faster? The most obvious answer is that acid sites on
Hydrogenolysis of benzylic alcohols and ethers

the carbon catalyze the dehydration and that the subsequent hydrogenation takes place on the rhodium catalyst. In that case, indene would not be observed, because the activated double bond would be rapidly hydrogenated. This agrees with the facts that C-O bond scission is completely suppressed when inorganic and organic bases (which neutralize the acid sites) are added and that scission occurs to a lower extent in apolar solvents such as hexane. However, bases have been added to suppress hydrogenolysis catalysed by palladium and rhodium catalysts [15, 16]. Moreover, it is well known that alkali and alkaline earth metal additives suppress hydrogenolysis in the hydrogenation of carbon monoxide on palladium and rhodium catalysts to methanol [17]. Acidity of the carbon support cannot, therefore, be deemed responsible for the observed C-O bond scission, based solely on the results of experiments in which a base was added.

Deuterium experiments offer a possibility to distinguish between the two pathways of C-O bond scission. If C-O bond scission proceeds through step I followed by step II, deuterium incorporation should be observed at carbon 2. If the pathway is direct hydrogenolysis then no deuterium is expected at this carbon. Thus, in the absence of deuterium-proton exchange, 8 deuterium atoms should be incorporated into the product perhydroindane if I followed by II is the main pathway and 7 deuterium atoms if III is the main pathway. Fig. 7.2 shows that, on deuteration of 1-indanol, a relatively wide distribution of deuterium incorporation in perhydroindane is obtained. The distribution is similar for the solvents C₂H₅OD and cyclohexane, although it is slightly shifted to higher deuterium incorporation for C₂H₅OD (as seen too in the average degree of deuterium incorporation in Fig. 7.8). Moreover, the average deuterium incorporation exceeds the theoretically expected values (Fig. 7.8), implying that some proton-deuterium exchange occurs. The exchange is not restricted to the deuteration of 1-indanol, it also occurs in the deuteration of indane and indene (Figs. 7.4 and 7.6). Furthermore, the exchange must take place before (or during) the saturation of the aromatic ring, since it was observed that further exchange does not take place once the completely hydrogenated products are formed.

There are three types of carbon atoms on which proton-deuterium exchange can take place. The aromatic carbons (4-7), the benzylic carbons (1 and 3), and the carbon at
position 2. The $^2$D coupled $^{13}$C NMR DEPT spectrum enabled us to identify the carbon atoms to which deuterium is bonded. From the spectra A and B in Fig. 7.3, it is concluded that deuterium exchange occurs at the carbon atoms at positions 1 and 3 but not at position 2. Each carbon atom in the six-membered ring bears a single deuterium atom, indicating that the aromatic protons do not undergo exchange under the present experimental conditions. This is also clear from Fig. 7.7, in which the carbon atoms in the six-membered ring of deuterated indene bear one deuterium each after deuteration. Only the benzylic C-H bond undergoes scission during the hydrogenation of 1-indanol, indane and indene because of its lower strength as compared to the other C-H bonds.

In light of the above results, the theoretical values for the incorporation of deuterium can be modified to include the incorporation as a result of proton-deuterium exchange at the benzylic position. Thus, depending on the extent of proton deuteration exchange in the deuteration of indane, 1-indanol, and indene, the theoretical values for the incorporation of deuterium should lie between 6 and 10, 7 and 10 (or 11), and 8 and 11 respectively for these substrates. Results in Figs 7.2, 7.4, and 7.6 indicate deuterium incorporation to be broader than the theoretical range of deuterium incorporation for the three substrates. Deuterium incorporation values lower than the theoretical range of values indicate that, in some perhydroindane isotopomers, hydrogen rather than deuterium has been added during deuteration. The source of hydrogen may be the catalyst support, the substrate, or the solvent. Deuterium incorporation values higher than the theoretical range of values in some perhydroindane isotopomers are possible because of the incorporation of two deuterium atoms at the carbon atoms at positions 4 to 7 and the incorporation of one or even two deuterium atoms at the carbon atoms at position 2. In the spectra shown in Figs 7.2 and 7.6, it appears as if none of the carbon atoms, including those at positions 1 and 3, is of the CD$_2$ type. From the distribution of deuterium shown in Figs. 7.2, 7.4, 7.5 and 7.6, it is clear that the perhydroindane isotopomers, doubly deuterated at positions 1 and 3, are present in significant concentrations. The absence of the CD$_2$ type of carbon atoms at positions 1 and 3 in the NMR spectra is attributed to the longer relaxation time of a carbon nucleus coupled with a deuterium nucleus. It is even more difficult to detect the CD$_2$ type of carbon atoms at
the other positions in the perhydroindane molecule, because the concentrations of such perhydroindane isotopomers are very low.

Fortunately, the total number of deuterium atoms on the neighbouring carbon atoms can be determined from the chemical shifts of a carbon peak in the $^{13}$C NMR spectrum [11]. In this way, the presence of CD$_2$ type carbon atoms at positions 1 and 3 could be verified by chemical shifts induced in the peaks of carbon atoms at positions 2, 3a and 7a. Furthermore, the chemical shifts of the carbon atoms at positions 1 and 3 enabled us to confirm that a CD$_2$ type carbon atom was not present at position 2.

Absence of deuterium at position 2 in spectra A and B (Fig. 7.3) indicates that direct hydrogenolysis (III) is the dominant pathway. This is confirmed by the deuteration experiments with indene under similar conditions. In Fig. 7.7, spectra A and B indicate that the carbon atom at position 2 is predominantly of the CHD type. Further proof of C-O bond scission via pathway III is provided by the average values of deuterium incorporation presented in Fig. 7.8. III is the only pathway allowing an average deuteration incorporation value in perhydroindane, obtained in the deuteration of 1-indanol, between those found in the indane and indene deuteration experiments.

Although the pathway of C-O bond scission is, without a doubt, direct hydrogenolysis, a fundamental question still remains to be answered, why is carbon-supported rhodium much more active for hydrogenolysis than alumina-supported rhodium? There are two possible explanations for the high hydrogenolysis capability of the carbon-supported rhodium catalysts. One is that the rhodium particles on carbon and alumina supports differ in morphology and/or oxidation state, and the other is that carbon facilitates the formation of a better leaving group (i.e., water) from the alcohol functional group and that the resulting OH$_2^{+}$ group is replaced by spillover hydrogen (or deuterium). From the deuterium distribution in the perhydroindane product obtained in the deuteration experiments with indane in cyclohexane on carbon-supported and alumina-supported rhodium catalysts (Fig. 7.5), it is concluded that the proton-deuterium exchange is similar for both catalysts. This implies that the rhodium particles on both supports have similar capabilities of scission of the benzylic C-H bond. In the experiment in which
activated carbon was added to a reaction mixture with a Rh/Al₂O₃ catalyst, considerably more hydrogenolysis is obtained when carbon is added to the reaction mixture. A similar increase in selectivity to perhydroindane is observed in the experiment with the zeolite beta additive. This suggests that the hydrogenolysis step occurs on the extra support with the help of spillover hydrogen that is transferred from the supported catalyst. The proton on carbon or on the zeolite thus facilitates the formation of a better leaving group. Although alumina has Lewis acid sites, they are covered with water and are unable to protonate the hydroxyl group unless catalytic amounts of a protic acid are present. Accordingly, extensive hydrogenolysis was observed in the experiments in which acetic acid was used as the solvent instead of ethanol or concentrated hydrochloric acid was added. Thus, hydrogenolysis proceeds readily under the present reaction conditions on the carbon-supported catalysts but not on the alumina-supported catalysts. Although the pathway of hydrogenolysis was proved by deuterium experiments rigorously for 1-indanol only, this pathway is the most obvious for the hydrogenolysis of 1-alkoxyindanes as well.

7.5 Conclusions

Carbon-supported rhodium catalysts are much more active for C-O bond scission of benzylic alcohols and ethers than their alumina-supported counterparts. C-O bond scission of the carbon-supported catalysts can be suppressed by adding organic and inorganic bases during the reaction. Different isotopomers with varying degrees of deuterium incorporation of the C-O bond scission-hydrogenation product perhydroindane were obtained in deuteration experiments with 1-indanol, indane, and indene. ²D coupled ¹³C NMR experiments revealed the degree of deuteration at each carbon atom in the perhydroindane product. It was found that, under the present experimental conditions, proton-deuterium exchange occurs only at the benzylic carbon atoms. In addition, absence of deuterium at carbon atom at position 2 enabled us to distinguish between the two C-O bond scission pathways. C-O bond scission occurs through the direct hydrogenolysis route and not through the dehydration route. The greater hydrogenolysis activity of the carbon-supported catalysts is due to the formation of a better leaving group from the benzyl hydroxyl group on the carbon support.
followed by the cleavage of the C-O bond with spillover hydrogen on these catalysts. A more interesting implication of the present results is perhaps in the use of carbon-supported palladium catalysts which are used extensively for de-protection of benzylic group-protected amines and alcohols. Depending on the carbon used as the support, a part of de-protection with these catalysts might well be occurring on the support rather than the metal.

References

1. Although both routes of C-O bond cleavage (Scheme 7.2), namely, dehydration-hydrogenation (I + II) and direct hydrogenolysis (III) are empirically referred to as hydrogenolysis, we have used the term hydrogenolysis in its strictest sense, i.e., cleavage of the C-O bond accompanied by the addition of hydrogen. Thus, only route III involves hydrogenolysis, while routes I followed by II and route III are collectively referred to as C-O bond scission routes.


5. The term deuteration implies the addition of deuterium to a C-C double bond and not H-D exchange

6. Different techniques were used to isolate perhydroindane, depending on the solvent and the substrate used in the reaction. After the deuteration of 1-indanol in C$_2$H$_5$OD, the perhydroindane-C$_2$H$_5$OD azeotrope (b.p. ~78°C) was distilled from a mixture of perhydroindane, perhydro-1-indanol and C$_2$H$_5$OD. Benzene was then added to this azeotropic mixture and a benzene-C$_2$H$_5$OD azeotrope (b.p. ~68°C) was distilled. After distillation of excess benzene, a concentrated mixture of perhydroindane in benzene was obtained and was used directly in NMR analyses. In the case of deuteration of indane and indene in C$_2$H$_5$OD, the first distillation step was omitted. When the deuteration of 1-indanol was
conducted in cyclohexane, the reaction mixture consisting of perhydroindane, perhydroindanol, and cyclohexane was passed over a silica gel column to remove the alcohol product. The remaining perhydroindane solution in cyclohexane was concentrated by distilling off excess cyclohexane. The concentrated solution was then used directly in NMR analyses. Again, in the case of deuteration of indane in cyclohexane the silica gel step was omitted. In some cases the sample was concentrated further by removing some of the cyclohexane by azeotropic distillation with benzene (b.p. ~77°C).

7. The degree of deuteration at a carbon atom is determined by the multiplicity of the carbon peak in a normal $^{13}$C NMR spectrum and a $^{13}$C NMR DEPT spectrum and its direction in the $^{13}$C NMR DEPT spectrum. Carbon atoms with no deuterium bonded to them appear as singlets in the normal as well as the DEPT spectrum because the carbon nucleus is decoupled from the hydrogen nucleus. Multiplicity arises because of the coupling of a carbon nucleus with a deuterium attached to it. Thus, a monodeuterated carbon appears as a triplet, while a bideuterated carbon appears as a quintuplet in the normal spectrum. In the DEPT spectrum, peaks corresponding to carbon atoms with no proton attached to them (CD and CD$_2$ type carbon atoms in the case of perhydroindane) disappear. In this spectrum the peaks corresponding to the CHD type carbon atoms point upwards while those corresponding to the CH$_2$ type carbon atoms point downwards.

11. Replacing a proton attached to a carbon atom by a deuterium atom results in a high field shift of the carbon atom peak in a $^{13}$C NMR spectrum ($\alpha$-effect). A similar replacement on the neighbouring carbon atom also induces a high field shift, albeit of a smaller magnitude ($\beta$-effect). The magnitude of this isotope-induced chemical shift increases as more protons are replaced by deuterium atoms, and decreases with increasing distance from the substituted carbon atom. The magnitude of the isotopic chemical shift in alkanes is well documented and is listed in Table 7.5 [18].
Table 7.5 Isotopic chemical shifts

<table>
<thead>
<tr>
<th>Substituent(s)</th>
<th>α shift (ppm)</th>
<th>β shift (ppm)</th>
<th>γ shift (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>-0.4</td>
<td>-0.12</td>
<td>-0.02</td>
</tr>
<tr>
<td>D₂</td>
<td>-0.7</td>
<td>-0.24</td>
<td>-0.08</td>
</tr>
<tr>
<td>D₃</td>
<td>-0.9</td>
<td>-0.36</td>
<td>-0.16</td>
</tr>
</tbody>
</table>

The total degree of deuteration at the neighbouring carbon atoms can be obtained by fitting the shifts observed in the $^{13}$C NMR spectrum of a deuterated sample as compared to the $^{13}$C NMR spectrum of an undeuterated sample with the values shown in the above table.

Appendix 1

Deactivation of Rhodium Catalysts

In all hydrogenation experiments, commercial rhodium catalysts were used directly in reactions without any further treatment, while the catalysts we made were used directly after calcination. Thus, in all experiments the catalysts were used in their oxidic form. Pre-reduction of the catalysts was detrimental to the activity in the hydrogenation of (S)-proline-2-methylanilide. In all hydrogenation experiments, the rhodium catalysts deactivated as the reaction proceeded to completion, irrespective of the nature of the support of the catalysts (including the unsupported rhodium black) or the type of the substrate. The catalyst was not completely deactivated after a typical experiment but showed residual activity when used in a subsequent experiment, implying that the reaction rate with a reused catalyst was significantly lower than that with a fresh catalyst. The deactivation was not only observed for the substrates hydrogenated in the scope of diastereoselective reactions, but also for simple substrates like o-xylene. In most hydrogenation reactions an alcoholic solvent, typically ethanol, was employed. To eliminate the possibility of ethanol contributing to the deactivation of the catalyst, some experiments with the (S)-proline-modified anthranilic acid substrate were conducted in water and some experiments with o-xylene were conducted without any solvent. The catalysts deactivated even in these circumstances. Moreover, the deactivation (i.e., the decrease in the reaction rate) could not be correlated with the turnover number of the catalyst, although a general trend of lowering in rate with increasing turnover numbers was observed. The deactivation was not limited to rhodium, but it also observed in the case of ruthenium catalyst in the hydrogenation of the (S)-proline-modified anthranilic acid substrate.

The reactivation of the rhodium catalysts was achieved simply by exposing it to the atmosphere for a prolonged period (about 36 h) or in an oven at 120 °C for 12 h. The catalyst regained up to 90% of its activity by using these simple pre-treatments before the subsequent run. A used catalyst which was left exposed to nitrogen for 36 h at room temperature in a glove box (oxygen concentration < 2 ppm) was considerably less active.
than the one after the corresponding pre-treatment in air. A patent reports a similar reactivation procedure for rhodium catalysts used in the hydrogenation of aromatic compounds involving heating the catalyst over 100°C in either vacuum or air [1]. Although oxidation methods for reactivating noble metal catalysts for hydrogenation reactions are frequently employed [2], the reasons for deactivation are often poorly understood. A notable exception is the deactivation of noble metal catalysts due to strong adsorption of sulfur-containing impurities. In almost all other cases it is presumed that polymeric carbonaceous deposits are combusted during the oxidation procedure, thus, restoring the activity.

It is interesting to note that a similar activation of supported and unsupported platinum oxide catalyst under mild conditions has been practiced since many decades. Adams and co-workers found that reactivation by air or oxygen was necessary to obtain good activity and/or reuse of their heterogeneous unsupported platinum catalyst in the hydrogenation of aldehydes [3, 4]. Willstätter and Jacquet used a similar reactivation procedure for a platinum catalyst used in the hydrogenation of phthalic anhydride involving shaking it with air at room temperature [5]. Vorhees and Adams speculated that the platinum catalyst deactivates only during hydrogenation of readily oxidizable compounds, due to removal of oxygen from the "active catalyst", which was presumed to be a lower oxide of platinum [6]. Rylander and Kaplan reported reactivation of supported platinum catalysts by periodic shaking with oxygen in the hydrogenation of heptaldehyde [7]. They found, however, that the beneficial effect of oxygen is not general and that in some substrates oxygen can have a deactivating effect on the hydrogenation reaction. In summary, most of the earlier reports on deactivation of platinum catalysts dealt with its application to the hydrogenation of carbonyl compounds, especially aldehydes. The explanation that only an oxide form of platinum is required for catalyzing hydrogenation reaction is not true because surface science techniques have provided ample proof of the hydrogen dissociation and hydrogenation capabilities of platinum metal. The observed deactivation was most likely due to decarbonylation of aldehydes and the formation of carbon monoxide on the surface of the catalyst, which is known to inhibit noble metal catalysts in hydrogenation reactions. Since platinum is a powerful oxidation catalyst, it probably oxidizes carbon monoxide
Deactivation of rhodium catalysts

to carbon dioxide and thus reactivates itself. Such a reactivation has been found to
restore completely the activity of a silica-supported platinum catalyst in the
hydrogenation of crotonaldehyde [8].

In our experiments, the deactivation was unrelated to the contamination of the reaction
mixture by impurities because of the fact that deactivation was observed with a wide
variety of substrates, with or without solvent, irrespective of the source or the nature of
the rhodium catalyst, and irrespective of the autoclave or the hydrogen gas bottle. Thus,
the catalyst deactivated exclusively under reaction conditions, either due to a change in
its oxidation state, its morphology, its dispersion or the formation of strongly adsorbing
by-products from the reactants. The alumina-supported rhodium catalyst used in the
hydrogenation of (S)-proline-2-methylanilide was studied by X-ray spectroscopy.
EXAFS analyses of a used and a fresh catalyst revealed that the change in dispersion
during reaction was negligible. Moreover, since almost complete activity was regained
by exposure to air at room temperature, it is unlikely that a small change in the
dispersion, if it occurred during the reaction, was responsible for catalyst deactivation.
XANES analyses indicated that the catalyst was incompletely reduced during the
reaction. The extent of reduction was about 50% when the reaction was conducted at 70
°C under 50 bar hydrogen pressure [9]. However, since the X-ray spectroscopy
techniques give average information about the bulk of the metal, it could well be that
the surface layer of rhodium is in a completely reduced state during reaction conditions.

We eliminated the possibility that rhodium catalysts were deactivated by carbon
monoxide similar to the platinum catalysts by conducting the reactions in water (i.e., in
absence of an alcoholic solvent). The fact that the catalyst deactivates in the reduction
of o-xylene without a solvent (where no conceivable source of carbon monoxide is
present) corroborates that other factors cause the deactivation of the rhodium catalyst. In
addition, IR spectroscopy of a used catalyst did not show the presence of carbon
monoxide adsorbed on the catalyst. It is highly unlikely that any polymeric
carbonaceous debris, if formed, is combusted by simple exposure of rhodium catalyst to
air. Moreover, TGA analysis did not reveal formation of a significant amount of
carbonaceous deposits on used catalysts. Like in the case of platinum catalysts, it is well
known that metallic rhodium can promote hydrogen dissociation as well as hydrogenation reactions and thus rhodium in a higher oxidation state is not essential for a good activity. These results indicate that the deactivation might be due to the formation of easily oxidized organometallic compounds of the surface rhodium atoms of the catalyst. Although we did not conduct any further investigations to ascertain the chemical nature or the structure of these compounds, we speculate that they are alkylidene type of complexes. This speculation is supported by the facts that deactivation is observed even during the hydrogenation of simple unsaturated hydrocarbon substrates and that reactivation of the catalysts is achieved on exposure to atmosphere.

References

Appendix 2

Protection and Coupling of Amino Acids

In the diastereoselective hydrogenation reactions conducted in the scope of this thesis, the amino acid (S)-proline was used as the chiral auxiliary. Proline was employed in preference to other amino acids because of its rigid five membered cyclic framework, and because of its low cost and ready availability ((S)-proline being one of the proteinogenic amino acid). The preparation of the aromatic compound-auxiliary moiety and the reference compounds involved the application of amino acid coupling techniques. These techniques have been developed and fine-tuned by chemists working in the field of peptide/protein synthesis. Procedures have been developed primarily with an aim to maintain a high chemoselectivity and integrity of the carbon center at the α-carbon atom of the amino acids. A strategy of selective and cyclical protection/de-protection of the amino (and the acid) group of the amino acid is used to achieve a high chemoselectivity during a stepwise peptide synthesis, starting from individual amino acids. This is illustrated in Scheme A2.1. Uncontrolled coupling of amino acids AA1 and AA2 can lead to products with all the possible amide linkages (P1-P4) between AA1 and AA2, excluding the possibility of formation of cyclic peptides.

If P1 is to be made selectively, the amino group of AA1 and the carboxylic group of AA2 have to be protected before the coupling step. The resulting doubly-protected peptide is then de-protected in a final step to get the required peptide, P1. Thus, primarily protection of the amino group and the carboxyl group is required before coupling. The protection techniques for these groups are described in the following two paragraphs.
The primary aim of protecting the amino group is to suppress its nucleophilicity by draining its electron density away into an appropriate substituent. Alkanoyl groups (e.g., acetyl group) although successful in draining the nucleophilicity, are not employed because they are unable to prevent racemization and their de-protection requires relatively severe reaction conditions. The alkoxy carbonyl group is the primary workhorse employed in amino group protection because of the mild conditions under which it can be de-protected and because it prevents racemization of the amino acid. The benzyloxy carbonyl (BzOCO or Z), tert-butoxycarbonyl (t-BuOCO or BOC) and 9-fluorenylmethoxy carbonyl (FluCH2OCO or FMOC) groups are used very frequently for protection of amino groups in amino acids. The reagents used for introducing this protection group and the de-protection reaction conditions are listed in Table A2.1. Very often the protection and de-protection are conducted in an organic medium and at
Protection and coupling of amino acids

ambient or sub-ambient temperatures. Since these protecting groups are orthogonal to each other, selective de-protection of some amino groups can be achieved by using reaction conditions under which only one type of alkoxy carbonyl group is removed.

Table A2.1 Protection and de-protection of the amino group

<table>
<thead>
<tr>
<th>Group</th>
<th>Protection reagent</th>
<th>Deprotection reagent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>BzOCOCl</td>
<td>HBr/AcOH or catalytic hydrogenolysis</td>
</tr>
<tr>
<td>BOC</td>
<td>BuOCOOCOOBu</td>
<td>Neat trifluoroacetic acid</td>
</tr>
<tr>
<td>FMOC</td>
<td>FluCH₂OCOCl</td>
<td>Piperidine or a comparable organic base</td>
</tr>
</tbody>
</table>

Although carboxyl group protection can be obviated by selecting a suitable coupling procedure, it is employed, nevertheless, for its solubilization and product isolation advantages. The carboxyl group is protected typically by ester formation. Methyl and ethyl esters can be used but these are relatively hard to de-protect. Protection in this case is achieved by treating the amino acid with methanolic (or ethanolic) hydrogen chloride or with thionyl chloride and the corresponding alcohol. Benzyl, t-butyl and phenyl esters are also used. Benzyl esters are prepared from benzyl alcohol as with the methyl or the ethyl esters. They are particularly useful because de-protection can be achieved by milder methods using HBr/AcOH or catalytic hydrogenolysis using a Pd/C catalyst. t-Butyl esters are prepared by an acid catalyzed technique using isobutylene or a base catalyzed technique using t-BuOH. They can be de-protected with trifluoroacetic acid as in the case of de-protection of the BOC group attached to an amino group. Phenyl esters are prepared by using a amino acid coupling reagent like dicyclohexylcarbodiimide (DCC) and phenol. Phenyl esters are unique in that they are easily de-protected under very mild ambient and close to neutral conditions by using hydrogen peroxide.

There are so many methods for coupling amino acids without allowing their racemization that it is impossible even to mention them here. Therefore, only a selection of methods of particular relevance to the present work, is briefly discussed here. For information on a variety of other techniques refer to the book by Jones [1]. For recipes of coupling procedures using various techniques refer to the treatise by Bodanszky and Bodanszky [2].
Almost all methods rely on activation of the carboxyl group of an amino acid (or peptide) to make it electrophilic enough for a nucleophilic attack of the amino group of another amino acid (or peptide).

A2.1 Acid Halide Method

\[
\begin{align*}
&\text{SOCl}_2, \text{CH}_2\text{Cl}_2, \text{reflux} \\
&\text{R}^1\text{C}O\text{H} \\
&\text{H} \text{NHFMOC} \\
&\text{R}^2\text{C}O\text{Cl} \\
&\text{Cyanuric Fluoride, Py} \\
&\text{CH}_3\text{CN, r.t.} \\
&\text{H} \text{NHFMOC} \\
&\text{R}^1\text{C}O\text{F} \\
&\text{Na}_2\text{CO}_3, \text{H}_2\text{O}, \text{CHCl}_3 \\
&\text{R}^2\text{OOC} \\
&\text{H}_2\text{N} \text{H} \\
&\text{H} \text{NHFMOC} \\
&\text{N} \text{H} \\
&\text{R}^2\text{COO}^\text{R}^3 \\
&\text{triethylamine, CH}_2\text{Cl}_2 \\
&\text{H} \text{NHFMOC} \\
&\text{R}^1\text{C}O\text{N} \text{H} \\
&\text{R}^2\text{H} \\
&\text{COO}^\text{R}^3
\end{align*}
\]

Scheme A2.2 Amino acid coupling using the acid halide method

The conversion of carboxylic acid to the acid chloride of an amino-protected amino acid is one of the simplest ways of facilitating nucleophilic attack at the carbonyl carbon. However, the reagents used traditionally for converting acids to acid chlorides are too harsh for the sensitive amino acids (or peptides) and their conventional amino-protecting groups (Z or BOC). The discovery of relatively stable FMOC-protected amino acid chlorides and fluorides [3] has rejuvenated interest in the use of acid halides for amino acid coupling. The acid fluorides are accessible via a simple treatment of the
Protection and coupling of amino acids

FMOC-protected amino acid by cyanuric fluoride at ambient conditions. The acid chlorides are accessible by a routine treatment of the FMOC protected amino acid with thionyl chloride. The acid chloride is coupled to another amino acid by a two phase technique involving a saturated Na₂CO₃ solution and a CHCl₃ solution. The acid fluoride can be coupled identically to an acid chloride or under simpler single-phase conditions in the presence of a tertiary organic base (see Scheme A2.2).

A2.2 Asymmetric Anhydride Method

![Diagram of asymmetric anhydride method]

Scheme A2.3 Amino acid coupling using the asymmetric anhydride method

In the asymmetric anhydride method, an asymmetrical anhydride of an amino-protected amino acid and a carbonic acid is generated by treating the amino acid with alkyl chloroformate in the presence of a tertiary base in an organic solvent at sub-ambient temperatures. Typically, ethyl or isobutyl chloroformate is employed. The nucleophilic attack of the amino group of another amino acid occurs exclusively at the carbonyl carbon of the amino-protected amino acid because it is more electrophilic than the carbonyl carbon of the carbonic acid (which is connected to two oxygen atoms). The
advantage of this coupling reagent over others is a simple work-up because the only byproducts of the reaction are a tertiary amine hydrogen chloride salt, an alcohol and carbon dioxide which are all relatively easily removed (see Scheme A2.3). Like the acid halide method, two separate steps comprising of activation of the amino acid and subsequent coupling are involved.

A2.3 Carbodiimide Method

The carbodiimide method is one of the very important methods of peptide coupling and essentially is a one step procedure involving mixing the amino-protected amino acid, the carboxy-protected amino acid and the carbodiimide reagent in an organic solvent at ambient or sub-ambient temperatures. Typical carbodiimide reagents are DCC and EDC (see Scheme A2.4). The first step in the coupling involves attack of the carboxyl oxygen of the amino-protected amino acid on the diimide carbon giving the O-acylisourea. The aminolysis of the isourea or the symmetrical anhydride (which can be subsequently formed) gives the required peptide. Urea is obtained as the by-product. The urea obtained from DCC is sparingly soluble in most solvents and precipitates out and thus is easily separated by filtration. The urea obtained from EDC has a tertiary amino group and hence is removed by washing with a dilute acid. The O-acylurea is very reactive and can undergo several undesirable side reactions. To prevent these reactions a nucleophilic reagent such as HOBt is added. This reagent cleaves the isourea rapidly before side reactions can intervene and forms an acylating agent which is still susceptible to aminolysis.
**Scheme A2.4** Amino acid coupling using the carbodiimide method

### A2.4 N-Carboxyanhydride Method

This method is of minor importance in peptide synthesis as compared to the other methods described previously, but is included since it was used in Chapter 3 to prepare
reference compounds. The cyclic N-carboxyanhydride or Leuchs' anhydride is generated easily by treatment of an α-amino acid by phosgene (Scheme 5). In the case of reference compounds in Chapter 3 N-carboxyanhydride of the β-amino acid (2-aminocyclohexane carboxylic acid) was generated by treatment of hexahydro-phthalic anhydride with trimethylsilyl-azide and subsequent hydrolysis of the resulting product by water. The N-carboxyanhydride on treatment with an amino acid opens up as a result of nucleophilic attack and gives the corresponding amide.

![Scheme A2.5 Amino acid coupling using the N-carboxyanhydride method (Notice the similarity between the asymmetric anhydride in Scheme A2.3 and the N-carboxyanhydride)](image)

References

Appendix 3

Analytical Data for Identification of Configuration

Figure A3.1 Two dimensional $^1$H NOE spectrum (CDCl$_3$, 500 MHz, r.t.) of the reference mixture of the cis diastereomers 5aR, 9aS and 5aS, 9aR. Numbers which are suffixed with a prime correspond to protons on the carbon atoms of the 5aS, 9aR diastereomer.
Figure A3.2 Wedge formula and ball and stick model of the crystal structure of the N-benzoyl derivative of cis-trans perhydro-1-aminoindane
Analytical data for identification of configuration

Table A3.1 Crystal data and structure refinement of the crystal structure of \( N \)-benzoyl-cis-trans perhydro-1-aminoindane

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>( \text{C}<em>{16}\text{H}</em>{21}\text{NO} )</td>
</tr>
<tr>
<td>Formula weight</td>
<td>243.34</td>
</tr>
<tr>
<td>Temperature</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>( \text{P2}_1/\text{n} )</td>
</tr>
<tr>
<td>Temperature</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>( \text{P2}_1/\text{n} )</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>( a = 7.944(4) ) Å; ( \alpha = 90^\circ )</td>
</tr>
<tr>
<td></td>
<td>( b = 21.48(2) ) Å; ( \beta = 112.80(6)^\circ )</td>
</tr>
<tr>
<td></td>
<td>( c = 8.969(7) ) Å; ( \gamma = 90^\circ )</td>
</tr>
<tr>
<td>Volume</td>
<td>1411(2) Å(^3)</td>
</tr>
<tr>
<td>( Z )</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.146 g/cm(^3)</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.547 mm(^{-1})</td>
</tr>
<tr>
<td>( F(000) )</td>
<td>528</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.3 x 0.2 x 0.1 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>4.12° to 50.01°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>(-7 \leq h \leq 7, 0 \leq k \leq 21, 0 \leq l \leq 8)</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>1440</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>1440 [( R(\text{int}) = 0.0000 )]</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Integration</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>.937 and .868</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on ( F^2 )</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1440 / 0 / 164</td>
</tr>
<tr>
<td>Goodness-of-fit on ( F^2 )</td>
<td>1.101</td>
</tr>
<tr>
<td>Final R indices [( \text{I} &gt; 2\sigma(\text{I}) )]</td>
<td>( R1 = 0.0590, \text{wR}2 = 0.1536 )</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>( R1 = 0.0697, \text{wR}2 = 0.1641 )</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.0005(8)</td>
</tr>
<tr>
<td>Largest diff. Peak and hole</td>
<td>0.186 and -0.203 e/Å(^3)</td>
</tr>
</tbody>
</table>
Figure A3.3 Two-dimensional NOE $^1$H NMR spectrum (DMSO, 500 MHz, r.t.) of a mixture of the two isomers of 3-propyl-3H-hexahydroisobenzofuran-1-one. Numbers which are suffixed with a prime correspond to protons on the carbon atoms of the minor diastereomer.
Glossary of Terms

BET area  Brunauer Emmett Teller area
BINAP    2,2'-Bis-diphenylphosphanyl-(1,1)binaphthalenyl
BIPHEMP  2,2'-Bis-diphenylphosphanyl-6,6'-dimethyl-biphenyl
BPPM     N-(t-Butoxycarbonyl)-4-diphenylphosphino-2-
           ((diphenylphosphino)methyl)pyrrolidine
DEPT     Distortionless Enhancement by Polarization Transfer
DIOP     4,5-Bis-((diphenylphosphanyl)-methyl)-2,2-dimethyl-1,3-dioxolane
DIPAMP   1,2-Bis((o-methoxyphenyl)phenylphosphine)ethane
DUPHOS   1,2-Bis-(2,5-dimethylphospholano)benzene

Diastereomeric Excess
\[
d.e. = \frac{[1S,2R \text{ diastereomer}] - [1R,2S \text{ diastereomer}]}{[1S,2R \text{ diastereomer}] + [1R,2S \text{ diastereomer}]} \quad \text{Chapter 1}
\]
\[
d.e. = \frac{[1R,2S \text{ diastereomer}] - [1S,2R \text{ diastereomer}]}{[1R,2S \text{ diastereomer}] + [1S,2R \text{ diastereomer}]} \quad \text{Chapter 2}
\]
\[
d.e. = \frac{[5aR,9aS \text{ diastereomer}] - [5aS,9aR \text{ diastereomer}]}{[5aR,9aS \text{ diastereomer}] + [5aS,9aR \text{ diastereomer}]} \quad \text{Chapter 3}
\]

Diastereomeric Ratio
\[
d.r. = \frac{[\text{trans diastereomer}]}{[\text{cis diastereomer}]} \quad \text{Chapter 1}
\]
\[
d.r. = \frac{[\text{cis} - \text{cis diastereomer}]}{[\text{cis} - \text{trans diastereomer}]} \quad \text{Chapters 4 and 5}
\]

EXAFS  Extended X-ray Absorption Fine Structure
Enantiomeric Excess

\[ ee = \frac{[\text{enantiomer 1}] - [\text{enantiomer 2}]}{[\text{enantiomer 1}] + [\text{enantiomer 2}]} \]

INADEQUATE Incredible Natural Abundance Double Quantum Transfer Experiment

NOE Nuclear Overhauser Effect

r.t. room temperature

Selectivity to the cis-cis diastereomer = \[ \frac{[cis-cis]}{[cis]} \]

& Incremental selectivity to the cis-cis diastereomer = \[ \frac{[cis-cis]_2 - [cis-cis]_1}{[cis]_2 - [cis]_1} \]

where, \[ [cis] = [cis-cis] + [cis-trans] \], and point 2 follows point 1 in kinetic analysis

TGA Thermal Gravimetric Analysis

XANES X-ray Absorption Near Edge Structure
Curriculum Vitae

Vidyadhar Sudhir Ranade

Date of Birth: 16th Sep 1973
Nationality: Indian

Dec 1996 - Mar 2000 Doctoral studies at Eidgenössische Technische Hochschule, Zurich, Switzerland

Nov 1994 - Nov 1996 Process Development Course at University of Twente, Enschede, The Netherlands

Jun 1990 - May 1994 Bachelor of Chemical Engineering at University Department of Chemical Technology (U.D.C.T.), University of Bombay, Bombay, India

Jun 1988 - May 1990 Higher Secondary Education at V.G. Vaze College, Bombay, India

Jun 1978 - May 1988 Primary and Secondary Education at New English School, Thane, India