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Enantioselective Catalytic Hydrogenation of Unfunctionalized Ketones
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Three diastereomeric rhodium bisphosphane complexes have been applied to asymmetric hydrogenation of unfunctionalized, non-chelating aliphatic and aromatic ketones. The ee values of the catalysis products differ considerably for the diastereomeric catalysts. 70% ee were obtained in hydrogenating butyrophenone, and 83.7% ee for pinacoline. The results depend strongly on the solvent used.

Introduction
Chiral alcohols derived from ketones are important starting molecules for the synthesis of various biological target molecules. There are several well known pathways for the transformation of ketones into alcohols and only a few examples can be given here. The reaction can be effected by asymmetric enzymatic reduction with gluconobacter oxydans (Adlercreutz [2,3]) or geotrichum candidum (Nakamura [4]).

Aromatic and aliphatic ketones are reduced in the same manner in very high ee. Pinacoline alcohol (3,3-dimethyl-2-butanone) is obtained in 97% ee, 1-phenylethanol in 99% ee. Corey reports 98.3% ee [5-7] on reducing 3,3-dimethylbutanone with borane in presence of oxazaborolidines. Other reductions yielding pinacoline alcohol or 1-phenylethanol with an ee > 90% are listed in [8-13]. The reaction can also be carried out with Brown’s 1Pc2BCl [14-16] and Brown’s Alpine-Borane [17,18]. In this case, pinacoline alcohol is obtained with 100% ee. An example for the reduction of pinacoline with BH₃ as achiral hydride and with a chiral catalyst giving pinacoline alcohol with an ee > 90% was reported by Umani-Ronchi [19]. Noyori and Mukaiyama describe the reduction of acetophenone [20, 21] with LiAlH₄ and a chiral catalyst (ee > 90%). Noyori [22] obtains 1-phenylethanol in 98% ee by asymmetric transfer hydrogenation of acetophenone catalyzed by chiral ruthenium complexes. Frejd [23] obtains it in 97% ee by the Ti(IV) induced reduction with catecholborane. There are only a few examples for the hydrogenation of simple aliphatic and aromatic ketones with molecular hydrogen giving ee > 70%. Osawa [24-26] reports the hydrogenation of isopropyl methyl ketone and pinacoline with a modified Raney/Ni catalyst giving 85% ee. The top ee values with homogeneous catalysts were obtained by Markó hydrogenating acetophenone to 1-phenylethanol (82% ee with (S,S)-BDPP [27] and 80% ee with (S,S)-Diop [28] as ligands). Other examples are the hydrogenation of pinacoline (43% ee with BPPFOH as ligand, by Hayashi [29]), of propiophenone (34% ee, by Selke [30]) and of butyrophenone (11% ee, by Spogliarich [31]).

Results
In this work we report on the asymmetric hydrogenation of unfunctionalized aliphatic and aromatic ketones catalyzed by the rhodium complexes 1, 2 or 3. The synthesis of the ligands, their separation and the synthesis of the catalysts is described in lit. [32, 33].

The catalysts 1 and 2 are C₂ symmetrical, 3 is C₁ symmetrical. As substrates aceto-, propio- and butyrophenone, ethylmethyl, and isopropylmethyl ketone (3-methyl-2-butanone), ketopantolactone, and pinakoline (3,3-dimethyl-2-butanone) were hydro-

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Fig. 1. Structure of the catalysts 1, 2 and 3: 4: (3R,4R)-1-(tert-butoxycarbonyl)-3,4-bis(diphenylphosphanyl)-pyrrolidine (deguphos). The stereoisomers of 1, 2 or 3 are specified in Fig. 2.

Fig. 2. Complexes 1, 2 and 3; R: 2,4,6-trimethoxyphenyl.

Fig. 1. Structure of the catalysts 1, 2 and 3: 4: (3R,4R)-1-(tert-butoxycarbonyl)-3,4-bis(diphenylphosphanyl)-pyrrolidine (deguphos). The stereoisomers of 1, 2 or 3 are specified in Fig. 2.

What higher than at 50 °C. With the catalyst 3 at 50 °C 44% ee are obtained in diethyl ether, 65% in methanol, and 79.4% in isopropanol. At 25 °C in tert-butanol ee values are lower than in isopropanol (82.0% compared to 83.7%). For a hydrogenation of pinacolone in isopropanol yields a somewhat higher ee, tert-butanol requires a shorter reaction time.

For comparison we have also hydrogenated pinacolone with deguphos 4 as catalyst. 4 does not contain the six methoxy groups present in 1 or 3, but otherwise 4 possesses the same structure. When pinacolone is hydrogenated with 4 the racemate is obtained. Based on our own unpublished results the ee depends on the number of methoxy groups. A strong salt effect is observed in hydrogenation of pinacolone with deguphos. 30% ee and 50% conversion are achieved with added sodium tetraphenylborate. Adding sodium tetraphenylborate to hydrogenations catalyzed by 1 or 3 has only a small effect of ee or TO. An explanation for the incomplete conversions during our hydrogenations can be given by the fact that we have worked with a substrate/catalyst ratio of 1000:1 instead the most commonly used ratio of 100:1. The hydrogen uptake slows down with increasing turnover and we did not wait for completion. Catalyst 3 seems to be specific for monofunctional substrates because in preliminary trials with bifunctional substrates like ethyl acetoacetate or 2,5-hexanedione we got only low ee values.

The fact, that an asymmetric catalyst has a superior enantioselectivity is not surprising [34, 35]. Depending on the substrate, the hydrogen pressure or the solvent used in many cases, 1 or 2 are more
genated. The ee values of the catalysis products differ considerably for the diastereomeric catalysts 1, 2, or 3. The two C2 symmetrical catalysts 1 or 2 in most cases yield significantly lower ee values than the C1 symmetrical isomer 3 for the substrates listed above. 3 yields relatively high ee values. With butyrophenone as substrate 69.8% ee, with pinacolone 83.6% ee are attained. This value is similar to the value obtained for pinacolone by the hydrogenation over modified Raney/Ni [26]. There is a strong solvent effect especially for the hydrogenation of pinacolone. The temperature is of little influence. At 25°C the ee values are always some-
Table I. Enantioselective hydrogenation of ketones with 1, 2 or 3 and 4.

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Educt</th>
<th>Cat.</th>
<th>Temp. [°C]</th>
<th>Solvent</th>
<th>Time [h]</th>
<th>TO-Frequ. 10 min. [b]</th>
<th>TO-Frequ. 50 % [c]</th>
<th>Yield alcohol [%]</th>
<th>ee [%]</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetophenone</td>
<td>1</td>
<td>50</td>
<td>MeOH</td>
<td>14</td>
<td>0.6</td>
<td>0.5</td>
<td>100</td>
<td>27.0 S</td>
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<td>2</td>
<td>Acetophenone</td>
<td>2</td>
<td>50</td>
<td>MeOH</td>
<td>30</td>
<td>0.16</td>
<td>0.004</td>
<td>30</td>
<td>46.9 R</td>
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<td>3</td>
<td>Acetophenone</td>
<td>3</td>
<td>50</td>
<td>MeOH</td>
<td>14</td>
<td>0.38</td>
<td>0.1</td>
<td>100</td>
<td>49.8 S</td>
</tr>
<tr>
<td>4</td>
<td>Acetophenone</td>
<td>3</td>
<td>25</td>
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<td>0.045</td>
<td>90</td>
<td>55.0 S</td>
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<td>5</td>
<td>Acetophenone</td>
<td>3</td>
<td>25</td>
<td>iPrOH</td>
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<td>0.17</td>
<td>0.07</td>
<td>50</td>
<td>47.6 S</td>
</tr>
<tr>
<td>6</td>
<td>Propiophenone</td>
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<td>25</td>
<td>MeOH</td>
<td>40</td>
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<td>0.003</td>
<td>50</td>
<td>66.8 S</td>
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<tr>
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<td>Butyrophenone</td>
<td>3</td>
<td>25</td>
<td>MeOH</td>
<td>20</td>
<td>0.23</td>
<td>0.021</td>
<td>70</td>
<td>69.8 S</td>
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<td>Ethylmethyl ketone</td>
<td>3</td>
<td>50</td>
<td>MeOH</td>
<td>48</td>
<td>0.1</td>
<td>0.013</td>
<td>60</td>
<td>9.6 S</td>
</tr>
<tr>
<td>9</td>
<td>Isopropylmethyl ketone</td>
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<td>50</td>
<td>MeOH</td>
<td>4.7</td>
<td>0.44</td>
<td>0.25</td>
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<td>Pinacoline</td>
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<td>MeOH</td>
<td>25</td>
<td>0.22</td>
<td>0.055</td>
<td>60</td>
<td>23.6 S</td>
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<td>11</td>
<td>Pinacoline</td>
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<td>MeOH</td>
<td>3.5</td>
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<td>0.23</td>
<td>70</td>
<td>54.6 S</td>
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<tr>
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<td>Pinacoline</td>
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<td>MeOH</td>
<td>20</td>
<td>0.11</td>
<td>0.017</td>
<td>80</td>
<td>65.0 S</td>
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<tr>
<td>13</td>
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<td>25</td>
<td>MeOH</td>
<td>3</td>
<td>0.11</td>
<td>0.1</td>
<td>20</td>
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<td>30</td>
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<td>50</td>
<td>iPrOH</td>
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<td>0.23</td>
<td>0.2</td>
<td>50</td>
<td>79.4 S</td>
</tr>
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<td>25</td>
<td>iPrOH</td>
<td>10</td>
<td>0.08</td>
<td>0.003</td>
<td>30</td>
<td>83.7 S</td>
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<tr>
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<td>25</td>
<td>tert-butanol</td>
<td>2</td>
<td>0.06</td>
<td>0.035</td>
<td>30</td>
<td>82.0 S</td>
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<td>50</td>
<td>MeOH</td>
<td>1.6</td>
<td>0.24</td>
<td>0.21</td>
<td>50</td>
<td>0</td>
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<tr>
<td>19</td>
<td>Pinacoline + PPh3 [1 eq.]</td>
<td>4</td>
<td>50</td>
<td>MeOH</td>
<td>2</td>
<td>0.27</td>
<td>0.17</td>
<td>70</td>
<td>25.8 S</td>
</tr>
<tr>
<td>20</td>
<td>Pinacoline + [d]</td>
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<td>50</td>
<td>MeOH</td>
<td>0.8</td>
<td>0.3</td>
<td>0.23</td>
<td>50</td>
<td>30.0 S</td>
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<td>MeOH</td>
<td>13</td>
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<td>MeOH</td>
<td>20</td>
<td>0.13</td>
<td>0.023</td>
<td>90</td>
<td>47.0 S</td>
</tr>
<tr>
<td>23</td>
<td>Ketopantolactone</td>
<td>3</td>
<td>50</td>
<td>MeOH</td>
<td>2.7</td>
<td>0.13</td>
<td>0.11</td>
<td>30</td>
<td>60.0 R</td>
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<td>MeOH</td>
<td>10</td>
<td>0.3</td>
<td>0.26</td>
<td>40</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Yields were determined by H2 consumption and the enantiomeric excess (ee) by gas chromatography on a chiral phase. The hydrogenations were conducted in an autoclave with a stirrer with 1.5 mmol of substrate, 1.5 μmol of catalyst and 25 ml of solvent. The hydrogenation was carried out under a pressure of 75 bar H2, substrate/catalyst ratio 1000:1. The proceeding was described earlier [34]. [b] Turnover-Frequency: Number of substrate molecules hydrogenated per second. This value was measured after 10 min of hydrogenation. [c] TO-Frequency after a conversion of 50 % of the amount consumed. [d] 1.5 μmol of sodium tetraphenylborate added.

selective than 3. As an example the hydrogenation of ketopantolactone is included in Table 1. 1 gives 67% ee, 3 60% ee, and 2 47% ee, but the opposite product configuration. At the moment we are not able to predict nor to explain the selectivity or to suggest the best solvent for a given catalysis.

**Experimental**

3: The preparation was described previously in lit. [32, 33]. 1, 2: The preparation is analogous to that of 3 up to the separation of the palladium from the ligand. 0.2 mmol of the Pd complexes and 2 mmol of NaCN are suspended in 10 ml of absolute ethanol and stirred for 10 h at room temperature. The solution is removed at 30 °C in vacuo. The residue is taken up in 10 ml of CH2Cl2 and 10 ml of H2O. The aqueous phase is removed and the CH2Cl2 phase is evaporated to dryness after washing twice with 10 ml of H2O. The optically pure phosphanes are obtained as white crystalline products. The hydrogenations are conducted as described in lit. [34].

Workup: The solution was concentrated by evaporation to 3 ml and passed through a 2 cm silica gel column with the eluent tert-butyl methyl ether. The eluate obtained after dilution was used directly for GC analysis. The chiral phase nickel(II)-bis([1S](-)-3-heptafluorobutanyl-10-methylidendcamphorate)-polysiloxane (25 m) was used for 2-butanol and 3-methyl-2-butanol. Pinacoline alcohol was analyzed by GC with the chiral phase Chirasil-Dex (20 m) [36], pantolactone and the aromatic alcohols were analyzed with the chiral phase Lipodex(r) E (50 m, 0.25 mm ID, Macherey-Nagel). The results are listed in Table I.

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[36] These columns were prepared in the research group of Prof. Dr. V. Schurig. The measurements of the aliphatic ketones have been partly carried out by this group. We thank especially H. Czesla for some measurements and helpful discussions.