Enantioselective Catalysis, XVII [1]. 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 diastereomerical catalysts. *70% ee* were obtained in hydrogenating butyrophenone, and 83.7% *ee* for pinacoline. The results depend strongly an 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 (Nakamuro [4]).

Aromatic and aliphatic ketones are reduced in the saure manner in very high *ee.* Pinacoline alcohol (3,3-dimethyl-2-butanol) is obtained in 97% *ee,* I-phenylethanol in 99% *ee.* Corey reports 98.3% *ee [5-7]* an 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 Ipc_2BC1 [14 - 16] and Brown's AlpineBorane [17, 18]. In this case, pinacoline alcohol is obtained with 100% *ee.* An example for the reduction of pinacoline with BH_3 as achiral hydride and with a chiral catalyst giving pinacoline alcohol with an *ee* > 90% was reported by UmaniRonchi [19]. Noyori and Mukaiyama describe the reduction of acetophenone [20, 21] with $LiA1H_4$ 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 Mark6 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 an 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 C_I 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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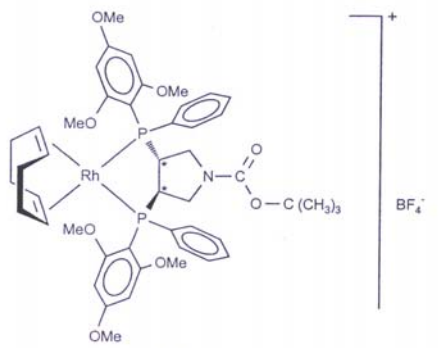

1, 2, 3

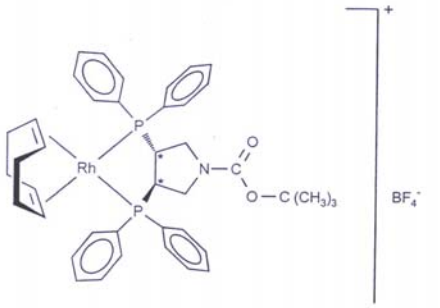

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Fig. 1. Structure of the catalysts **1, 2** and **3**. **4**: (3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3,4-bis(diphenylphosphanyl)-pyrrolidine (deguphos). The stereoisomers of **1, 2** or **3** are specified in Fig. 2.

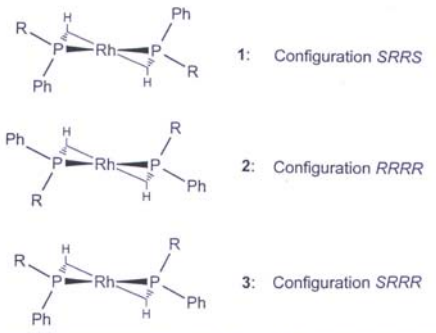

Fig. 2. Complexes **1**, **2** and **3**; R: 2,4,6-trimethoxyphenyl.

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 C, symmetrical isomer 3 for the substrates listed above. 3 yields relatively high *ee* values. With butyrophenone as substrate 69.8% *ee,* with pinacoline 83.6% *ee* are attained. This value is similar to the value obtained for pinacoline by the hydrogenation over modified Raney/Ni [26]. There is a strong solvent effect especially for the hydrogenation of pinacoline. The temperature is of little influence. At 25°C the *ee* values are always some what higher than at 50 °C. With the catalyst 3 at 50 °C *44% ee* are obtained in diethylether, 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 pinacoline isopropanol yields a somewhat higher *ee,* tert-butanol requires a shorter reaction time.

For comparison we have also hydrogenated pinacoline 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 pinacoline is hydrogenated with 4 the racemate is obtained. Based an our own unpublished results the *ee* depends an the number of methoxy groups. A strong salt effect is observed in hydrogenation of pinacoline 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 an *ee* or TO. An explanation for the uncomplete 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 an the substrate, the hydrogen pressure or the solvent used in many cases, 1 or 2 are more

Table 1. Enantioselective hydrogenation of ketones with **1, 2** or 3 and 4.

Nr.	Educt	Cat.	Temp. [°C]	Solvent	Time [h]	TO-Frequ: 10 min. [b]	TO-Frequ. 50 % [c]	Yield alcohol [%]	*ee [%]*
1	Acetophenone	1	50	MeOH	14	0.6	0.5	100	27.O S
2	Acetophenone	2	50	MeOH	30	0.16	0.004	30	46.9 R
3	Acetophenone	3	50	MeOH	14	0.38	0.1	100	49.8S
4	Acetophenone	3	25	MeOH	14	0.14	0.045	90	*55.OS*
5	Acetophenone	3	25	iPrOH	2	0.17	0.07	50	47.6S
6	Propiophenone	3	25	McO11	40	0.08	0.003	50	66.8S
7	Butyrophenone	3	25	McO1-1	20	0.23	0.021	70	69.8S
8	Ethylmethyl ketone	3	50	McOH	48	0.1	0.013	60	9.6S
9	Isopropylmethyl ketone	3	50	MeOH	4.7	0.44	0.25	60	22.4S
10	Pinacoline	1	50	MeOH	25	0.22	0.055	60	23.6S
11	Pinacoline	2	50	MeOH	3.5	0.42	0.23	70	*54.6S*
12	Pinacoline	3	50	MeOH	20	0.11	0.017	80	*65.OS*
13	Pinacoline	3	25	McO11	3	0.11	0.1	20	76.5S
14	Pinacoline	3	50	Et20	70	0.12	0.002	30	*46.OS*
15	Pinacoline	3	50	iPrOH	3	0.23	0.2	50	79.4S
16	Pinacoline	3	25	iPrOH	10	0.08	0.003	30	83.7S
17	Pinacoline	3	25	tert-butanol	2	0.06	0.035	30	82.O S
18	Pinacoline	4	50	MeOH	1.6	0.24	0.21	50	0
19	Pinacoline + PP113 (1 eq.)	4	50	McO1-1	2	0.27	0.17	70	25.8S
20	Pinacoline + [d]	4	50	MeOH	0.8	0.3	0.23	50	*30.OS*
21	Ketopantolactone	1	50	McO14	13	0.25	0.024	80	67.0 *R*
22	Ketopantolactone	2	50	MeOH	20	0.13	0.023	90	47.O S
23	Ketopantolactone	3	50	McOH	2.7	0.13	0.11	30	60.0 *R*
24	Ketopantolactone	4	50	McOH	10	0.3	0.26	40	0

[a] Yields were determined by H_2 consumption and the enantiomeric excess *(ee)* by gas chromatography an 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 solvent is removed at 30 °*C in vacuo.* The residue is taken up in 10 ml of CH_2Cl_2 and 10 ml of H_20. The aqueous phase is removed and the CH_2Cl_2 phase is evaporated to dryness after washing twice with 10 ml of H_20. 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-heptafluorobutanoyl-10methylidencamphorate]-polysiloxane (25 m) was used for 2-butanol and 3-metyl-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(-) E (50 m, 0.25 mm ID, Macherey-Nagel). The results are listed in

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