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Asymmetric transfer hydrogenation of aromatic ketones by Rh(I)/bimorpholine complexes

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Abstract—The asymmetric hydride transfer reduction of aromatic ketones, using a $[Rh(cod)Cl]_2$ complex as a catalyst and (3*S*,3′*S*)-bimorpholine as a chiral ligand, was studied. By varying the amount of ligand, basic co-catalyst and temperature, high yields (>90%) and good enantiomeric excesses of the alcohols (ee up to 83%) were achieved.

1. Introduction

The significance of transition metal assisted asymmetric catalysis is constantly growing.[1] The chiral catalyst is required in small amounts and usually consists of a metal and a chiral organic ligand (or ligands). High asymmetric induction is achieved only with a suitable combination of the molecular structure of the chiral metal complex and the substrate under appropriate reaction conditions.

Nitrogen-containing ligands are widely used in asymmetric catalysis.[2] These ligands have good chelating abilities with various metals. Nitrogen-containing ligands can be separated from the nonbasic reaction products and thus are easily recyclable. Many successful examples of catalytic asymmetric transfer hydrogenation have demonstrated that this type of ligands can afford similar or even higher selectivity than can be achieved with the chiral phosphines.[3–5] Excellent enantioface-discrimination abilities have been obtained with ruthenium catalysts (using different sources of hydrogen, e.g., isopropanol,[6–9] formic acid[10,11]).

It is assumed that the mechanism of the hydride transfer reduction involves a step of formation of nonracemic metal hydride.[3] The structure of this chiral intermediate complex is responsible for the stereodifferentiation of the faces of the prochiral ketone. This nonracemic complex can only be formed by ligand exchange between the initial achiral metal complex and the chiral N-containing ligand. Therefore, the structure of the catalytic complex has been thoroughly studied with help of spectroscopic methods and theoretical calculations.[12,13] However, it is complicated to draw a general conclusion from these data because the stereoselectivity of the reduction usually depends on many factors: the source of the metal, the structure of the ligand, the structure of the substrate, the reaction conditions, etc. For these reasons, each particular case (substrate) has to be investigated and optimised individually in order to find an appropriate combination of the catalyst, the ligand and the reaction conditions.

Special attention in a wide variety of chiral ligands used in hydride transfer reductions has been paid to the compounds with a C_2-symmetry because there is no possibility of enantioface discrimination over the course of ligand exchange during the chiral catalyst formation.[7,9,14–17] Our contribution to this field is the novel chiral C_2-symmetric bimorpholines.[18] We previously reported the first application of (3*S*,3′*S*)-bimorpholine **1** as a ligand in the metal mediated hydride transfer reduction of aromatic ketones by help of $[Rh(cod)Cl]_2$ as metallic precursor (ee up to 75%, Scheme 1).[19] However, the data obtained were not sufficient enough to predict the behaviour of the catalyst with different substrates.

Herein we report a detailed study of the main factors (ratio of the chiral ligand and base to the metallic precursor, ratio of the catalyst to the substrate, temperature, concentration) that influence the stereoselectivity of the reduction. The results obtained reveal a complex influence of separate factors on the whole process.

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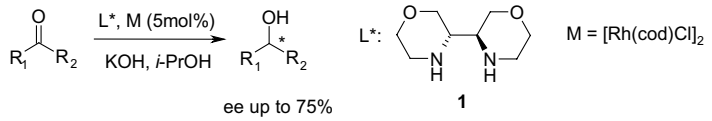


Scheme 1. Asymmetric hydride transfer reduction of aromatic ketones using bimorpholine **1**.

2. Results and discussion

2.1. Influence of the molar ratio of bimorpholine 1 and $[Rh(cod)Cl]_2$ on the transfer hydrogenation of aromatic ketones

Although the excellent stereodifferentiation ability of many catalytic systems has been observed, only a few structures of complexes have been defined. Lemaire and co-workers has investigated the catalytic complex derived from $[Rh(cod)Cl]_2$ and chiral 1,2-diamine.[13] According to his studies, the active complex species consists of a rhodium atom complexed with one diamine and one diene ligand. Despite that, an excess of diamine is used to stabilise the complex and to prevent the formation of black particles of rhodium, leading to the racemic product.

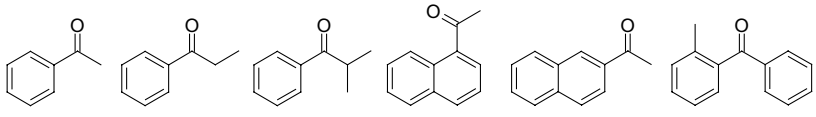
Our previous results were obtained using the same model: $M/L^* = 1:4$ (4 moles of bimorpholine **1** (L^*) per 1 mole of the metallic precursor (M); as $[Rh(cod)Cl]_2$ is a dimeric metal complex, the molar ratio of $M/L^* = 1:4$ corresponds to two molecules of bimorpholine **1** per one Rh atom).[19] In a typical experiment, the catalytic complex (5 mol%) was synthesised in situ from bimorpholine **1**, $[Rh(cod)Cl]_2$ and KOH in *i*-PrOH by stirring the mixture at room temperature (20 °C) for 1 h prior to the addition of the substrate (Table 1).

We carried out our experiments using the molar ratio of $M/L^* = 1:2$ with different substrates. Comparing these results, a higher activity of the latter catalytic system is clearly seen (Table 1): the corresponding alcohols were formed in excellent yield (>90%) and at least two times faster (reaction time 21 h instead of 46 h) than with the catalyst derived from 4 moles of the ligand and metal precursor. Extending the reaction time further did not increase the yield in the case of M/L^* molar ratio 1:4. It is possible that the excess of the ligand (M/L^* molar ratio 1:4) inhibits the catalyst by saturating the metal.[20]

The stereoselectivity of these two different catalytic systems clearly depends on the substrate. Generally, the complex derived using M/L^* molar ratio 1:2 gives higher ee values of alcohols (Table 1, entries 2–4 and 6). The most remarkable increase of the enantioselectivity was determined in the reduction of isobutyrophenone **4** (ee increased from 44% to 57%). A considerable difference in the value of the enantiomeric excess of the products formed in the reduction of 1- and 2-acetonaphthones **5** and **6** remained (Table 1, entries 4 and 5). For 1-acetonaphthone **5**, the preferable M/L^* molar ratio was 1:2, but for 2-acetonaphthone **6**, the ratio 1:4 gave a slightly higher ee value. The highest enantioselectivity was observed with 2-methylbenzophenone **7**, using the M/L^* molar ratio 1:2. In addition, an excellent yield of the product was obtained (Table 1, entry 6, ee 83% vs 75%, yield increased from 33% to 95%). Only in the case of acetophenone **2** and 2-acetonaphthone **6**, the M/L^* molar ratio 1:4 was preferable (Table 1, entries 1 and 5).

These results indicate that by using a different metal/ligand molar ratio, different catalytic complexes are formed. These complexes have different catalytic properties, causing changes in the stereoselectivity of the reduction.

Table 1. Asymmetric reduction of ketones **2**–**7** catalysed by Rh-bimorpholine **1** complex[a]



2 **3** **4** **5** **6** **7**

Entry	Ketone	Molar ratio of M:L*:KOH					
		1:4:6[19]			1:2:6		
		Time (h)	Yield (%)[b]	Ee (%)[c]	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**2**	21	96	32	21	98[19]	27[19]
2	**3**	46	77	40	21	95	46
3	**4**	46	55	44	21	95	57
4	**5**	46	83	63	21	91	68
5	**6**	46	82	21	21	94	16
6	**7**	46	33	75	21	95	83

[a] Molar ratio of $M/L^* = 1:2$ corresponds to one molecule of ligand per one atom of Rh. Concentration of catalyst was 0.004 M in its synthesis step. Initial concentration of substrate was 0.05 M.
[b] Determined as area % by GC analysis.
[c] Enantiomeric excess of obtained alcohol was determined by chiral HPLC (column: Chiralcel OD–H).

2.2. Influence of the amount of the basic co-catalyst

It is known that the base activates the catalyst markedly.[21] The base has to deprotonate *i*-PrOH, allowing the complexation of the metal and isopropoxide ion, followed by the formation of the nonracemic metal hydride and elimination of acetone. Lemaire et al. have shown that their $[Rh(cod)Cl]_2$/chiral 1,2-diamine catalytic system is inactive without the base.[14] We have studied the effect of the concentration of the basic co-catalyst in the reduction of 1-acetonaphthone **5**.

These results indicate that an increase as well as a decrease in the base concentration had a lowering effect on the stereoselectivity of the reaction. The best molar ratio of $[Rh(cod)Cl]_2$ to KOH in our catalytic system was 1:6. Smaller amounts of the base (3 equiv instead of 6) led to a drop in the enantioselectivity from 68% to 62% (Table 2, entries 2 and 1). The use of 3 equiv of the base obviously could not generate a sufficient amount of active chiral species resulting in a decrease of catalyst concentration.

Table 2. Influence of the amount of the basic co-catalyst on the enantioselectivity of the reduction of 1-acetonaphthone **5**[a]

Entry	Molar ratio of M:L*:KOH	Yield (%)[b]	Ee (%)[c]
1	1:2:3	48	62
2	1:2:6	96	68
3	1:2:8	89	65

[a] 5 mol% of the catalytic complex was synthesised in situ from bimorpholine **1**, $[Rh(cod)Cl]_2$ and KOH in *i*-PrOH by stirring the mixture at 20 °C for 1 h prior to the addition of the substrate. Yield and ee were determined after 46 h.
[b] Determined as area % by GC analysis.
[c] Enantiomeric excess was determined by chiral HPLC.

The same effect was observed when a larger amount of the base was used (Table 2, entries 2 and 3, from ee 68% to 65%). Also, the activity of the catalytic system is affected by this change. The yield of 1-(1′-naphthyl)ethanol decreased twice with lowering the amount of the base (Table 2, entry 1 vs 2, from 96% yield to 48%). An increase in the amount of KOH did not noticeably change the activity of the catalyst.

It is difficult to find a reasonable explanation for the results with a higher concentration of KOH. It is assumed that isopropoxide competes with chiral diamine in the complexation with the metallic precursor.[14] The activation of the catalyst without a chiral ligand leads to the formation of a racemic product. In our case that model can be excluded because the catalyst derived from $[Rh(cod)Cl]_2$ in the presence of KOH (without bimorpholine **1**) was very inactive. After 48 h of reduction under typical conditions, only 1.5% of alcohol was obtained.

2.3. Influence of other parameters (concentration of the catalytic complex, initial concentration of the substrate and temperature)

To find an appropriate concentration range, the reaction was performed at different catalyst and substrate concentrations. Usually, the amount of the chiral catalyst was connected with its activity in the reaction and thus it varied in a wide range (from 0.05 to 5 mol%).[14,22] We studied the effect of the concentration of the catalyst and substrate on the stereoselectivity and reactivity of the hydride transfer reduction. 1-Acetonaphthone **5** was selected as a model substrate (Table 3).

Table 3. Influence of the concentration of the catalyst and substrate on the enantioselectivity of the reduction of 1-acetonaphthone **5**[a]

Entry	Mol% of catalyst	Initial concentration of substrate (M)	Temperature (°C)	Yield[b] (%)	Ee[c] (%)
1	5	0.05	20	96	68
2	1	0.05	20	33	60
3	5	0.025	20	80	68
4	5	0.05	25	86	75
5	5	0.1	25	96[d]	64

[a] The catalytic complex was synthesised in situ from bimorpholine **1**, $[Rh(cod)Cl]_2$ and KOH (M:L*:KOH = 1:2:6) in *i* PrOH by stirring the mixture at room temperature for 1 h prior to the addition of the substrate. Yield and ee were determined after 46 h.
[b] Determined as area % by GC analyses.
[c] Determined by chiral HPLC.
[d] The reaction time was 21 h.

The best selectivity and reactivity were obtained with the 5 mol% catalyst (Table 3, entries 1, 3 and 4). Decreasing the amount of catalyst to 1 mol% at a constant substrate concentration led to a drop in yield and selectivity (from 96% to 33% and from 68% to 60%, respectively; Table 3, entries 1 and 2). We also noticed a decrease in enantioselectivity when the initial concentration of substrate was increased (Table 3, entries 4 and 5, with 0.05 M substrate concentration ee 75% was obtained against 64% at 0.1 M).

In most cases, an increase in temperature leads to an improvement in the catalytic activity. The influence of this factor on the stereoselectivity of the reaction is more complex. Many catalytic systems provide a high conversion and enantioselectivity at room temperature, while some catalysts show a high activity only at increased temperatures (80 °C).[9,16,23] However, some catalysts operate successfully even at −30 °C.[8] We studied the influence of the reaction temperature on the reduction of ketones **2**, **5** and **7** (Table 4).

In all cases, the temperature had a considerable influence on the stereoselectivity of the reduction. A drop in the temperature of the reduction of acetophenone **2** from room temperature to 5 °C resulted in a notable increase in enantioselectivity (ee 38% instead of 27%, Table 4, entry 1 vs 2). At the same time, the reaction rate decreased. However, in the case of 1-acetonaphthone **5** and 2-methylbenzophenone **7**, the lower temperature (5 °C) decreased the enantiomeric purity of the corresponding alcohols (Table 4, entries 3 vs 4 and 8 vs 9, ee 53% instead of 68% at 20 °C for 1-acetonaphthone **5**, ee 70% vs 83% for 2-methylbenzophenone **7**). During long reaction times, catalyst deactivation may take place. The optimal stereoselectivity value was very substrate dependent. Thus, the highest enantioselectivity

Table 4. Influence of the temperature on the enantioselectivity of the reductions of ketones **2**, **5** and **7**[a]

Entry	Ketone	Temperature (°C)	Time (h)	Yield[b] (%)	Ee[c] (%)
1	**2**	5	7 days	77	**38**
2	**2**	20	21	98	27
3	**5**	5	46	96	53
4	**5**	20	21	91	68
5	**5**	25	21	83	**75**
6	**5**	30	21	89	72
7	**5**	65	1	100	39
8	**7**	5	5 days	28	70
9	**7**	20	21	95	**83**
10	**7**	25	21	84	77

[a] The catalytic complex was synthesised in situ from bimorpholine **1**, $[Rh(cod)Cl]_2$ and KOH (M:L*:KOH = 1:2:6) in *i*-PrOH by stirring the mixture at room temperature for 1 h prior to the addition of the substrate.
[b] Determined as area % by GC analyses.
[c] Determined by chiral HPLC.

obtained for 1-acetonaphthone **5** was at 25 °C (Table 4, entry 5, ee 75%), while for 2-methylbenzophenone **7** it was 20 °C (Table 4, entry 9, ee 83%) and for acetophenone **2** 5 °C (Table 4, entry 1, ee 38%).

Generally, working at lower temperature leads to an increase in the enantioselectivity of the catalytic system. However, the experimental results are quite contradictory in this respect. It is possible that the co-existence of different active species in the reaction medium causes different effects and thus, the nonlinear dependence of the stereoselectivity on the temperature of reaction. On the other hand, a reverse reaction, the re-oxidation of the obtained alcohol, is also possible.[6,14] In this reaction, the chiral product competes with isopropanol for being a hydride source. The formation of the catalytically active hydride proceeds via diastereoisomeric complexes while the kinetics of this process influences the enantioselectivity of the reduction. As a result, the simultaneous co-existence of several factors does not lead to an unambiguous prediction of the stereoselectivity of the reduction.

3. Conclusion

Herein, we have shown that the change of the $[Rh(cod)Cl]_2$/bimorpholine **1** molar ratio from 1:4 to 1:2 leads to different catalytic systems. The catalyst derived from 2 moles of bimorpholine **1** and 1 mole $[Rh(cod)Cl]_2$ gave a clearly higher activity and generally higher enantioselectivity in the reduction of different ketones (ee up to 83%). However, the stereoselectivity of both catalytic systems depends on the structure of the substrate. The reduction of the sterically more hindered ketones afforded a higher enantioselectivity. The required catalyst loading is 5 mol% and yields of corresponding alcohols are excellent. The optimal $[Rh(cod)Cl]_2$/KOH molar ratio for our catalytic system is 1:6.

The results obtained indicate that the catalyst derived from $[Rh(cod)Cl]_2$ and bimorpholine **1** in the presence of KOH obviously contains a different catalytic species. Nevertheless, reduction under the optimised conditions gives enantiomeric alcohols with excellent yields and high enantiomeric excesses.

4. Experimental

The conversions were measured by capillary gas chromatography on a Dani GC-1000 (column 122-5022 DB-5, length 25 m, I.D. 0.25 mm, film 0.25 μm). Enantiomeric excesses of the alcohols obtained were determined by HPLC on a LKB 2150 system, using a Chiralcel OD–H column.[19]

4.1. General procedure for the reduction of ketones

A solution of bimorpholine (9 mg, 10 mol%, 0.053 mmol or 18 mg, 20 mol%, 0.105 mmol), $[Rh(cod)Cl]_2$ (13 mg, 5 mol%, 0.026 mmol) and KOH (1.56 mL, 30 mol%, 0.156 mmol, 0.1 M in *i*-PrOH) in dry degassed *i*-PrOH (5 mL) was stirred for 1 h under an Ar atmosphere at room temperature. A solution of ketone (0.52 mmol) in *i*-PrOH (5 mL) was added and the reaction mixture stirred for an appropriate time. Aliquots were taken at different times, Et_2O added, the precipitate centrifuged and the clear solution analysed by GC and HPLC. Detailed analytical data were provided in our previous publication.[19]

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