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C_2-Symmetric bimorpholines as chiral ligands in the asymmetric hydrogenation of ketones

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Abstract—2,2′-Bimorpholine and 3,3′-bimorpholine were used as chiral ligands in Rh-mediated asymmetric hydride transfer reduction of prochiral aromatic ketones affording corresponding alcohols with good ee (up to 75%).

1. Introduction

Various non-racemic chiral nitrogen-containing compounds have been successfully used as chiral ligands[1] in different asymmetric reduction reactions (reduction of C=C, C=O and C=N groups[2–5]) and in the addition reaction of organo-zinc reagents to carbonyl compounds.[6] Nitrogen-containing compounds, if used as chiral ligands, have several positive properties (stability, separability, recyclability, etc.) that have made them competitive with the more traditionally used diphenylphosphine ligands[4] in catalytic reductions.

We have recently reported the synthesis of two novel nitrogen-containing heterocycles—(3*S*,3′*S*)-bimorpholine **1** and (2*S*,2′*S*)-bimorpholine **2** (Fig. 1).[7] Herein, we describe the use of these bimorpholines as chiral ligands in transition metal-mediated hydrogenations. An asymmetric hydride transfer reduction[3]of prochiral aromatic ketones was used as the model process because this reaction is easy to perform and requires neither high-pressure equipment nor use of hydrogen gas.

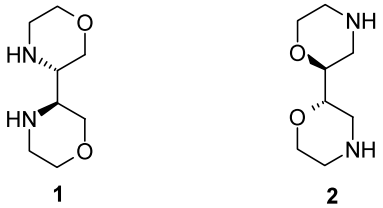

Figure 1.

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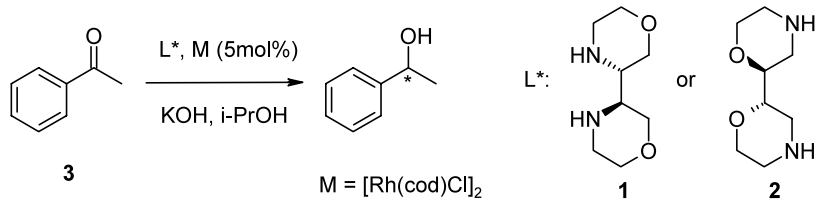
Also, we have selected *i*-PrOH for the hydride source because that solvent is widely used together with a basic co-catalyst and chiral rhodium, ruthenium or iridium nitrogen-containing complexes.[8–10] The reduction of acetophenone was selected as a model process: Lemaire et al. have reported asymmetric reduction of this compound using chiral C_2-symmetric Rh–diamine complex with ee 67%.[11,12]

2. Results and discussion

2.1. Reduction of acetophenone with Rh-catalyst using bimorpholines 1 and 2 as chiral ligands

We investigated the use of $[Rh(cod)Cl]_2$ as a catalyst precursor with the chiral bimorpholines **1** and **2**. There is contradictory data in the literature about the structure of the active complex derived from the Rh-compound and the chiral diamine that participates in the catalytic reduction. Gladiali[13] has claimed that an active complex contains two bidentate ligands (diamines) per rhodium atom. More recently, Lemaire has calculated and proved experimentally that in the active species, only one diamine molecule and one diene molecule are bound to the metal.[14] Bimorpholines **1** and **2** are ambidentate ligands, which may lead to the formation of dimeric complexes. Therefore, we studied the influence of the molar ratio of bimorpholines **1** or **2** and of the metal in the catalytic complex on the enantioselectivity of reduction of acetophenone. In a typical experiment, the catalytic complex (5 mol% towards substrate) was synthesized in situ from bimorpholine, $[Rh(cod)Cl]_2$ and KOH in *i*-PrOH by stirring the mixture at room temperature for 1 h prior to the addition of the substrate (Table 1).

Table 1. Asymmetric reduction of acetophenone under different conditions



Entry	Molar ratio of L*:M[c]:KOH	Ligand L*	Time (h), temperature	Yield[a] (%)	Ee[b] (%)
1	2:1:6	**1**	21, rt	98	27
2	4:1:6	**1**	21, rt	96	32
3	4:1:6	**1**	168, 0°C	81	34
4	4:1:6	**2**	21, rt	1.5	–
5	4:1:6	**2**	15, 82°C	70	0

[a] Determined as area% by GC analyses.
[b] Determined by chiral HPLC.
[c] $[Rh(cod)Cl]_2$ is a dimeric complex; in the Table the molar ratio of L*/M = 2:1 corresponds to 1 molecule of ligand per 1 atom of Rh.

The catalyst derived from bimorpholine **1** as a ligand did exhibit high activity in the reduction. Thus, 98% conversion of acetophenone was observed at room temperature after 21 h. The amount of ligand had little effect on the enantioselectivity. As seen in Table 1, using 4 mol instead of 2 mol of ligand per 1 mol of Rh-precatalyst caused only a slightly higher ee value (32% versus 27%, Table 1, nos 1 and 2). Also, decreasing the reaction temperature has very little effect on stereoselectivity: Conducting the reaction at 0°C instead of room temperature, afforded only a modest increase in the enantioselectivity of the reduction (Table 1, no. 3). In the latter case however, the reaction rate was considerably lower and 81% conversion of acetophenone was obtained only after 7 days (instead of 21 h).

The catalyst derived from bimorpholine **2** and $[Rh(cod)Cl]_2$ had a very low activity and stereoselectivity. Within the typical reaction time (21 h) only 1.5% of the conversion was observed (Table 1, no. 4). Thus, a higher temperature (82°C) was used to perform the reaction; however, the product obtained was racemic (Table 1, no. 5). Despite a structural similarity in both the bimorpholines (C_2-symmetric bridged compounds with four donor sites), a substantial difference occurs in the geometry of the metal-chelated complexes: bimorpholine **1** can form a five-membered ring in the metal complex (Fig. 2, **A**) like a typical rhodium complex with N,N-donor ligand.[14] The complexation with bimorpholine **2** gives a less stable seven-membered ring (Fig. 2, **B**) with a similar chelation. This is the reason why only bimorpholine **1** proved to be a suitable ligand for the hydride transfer reduction.

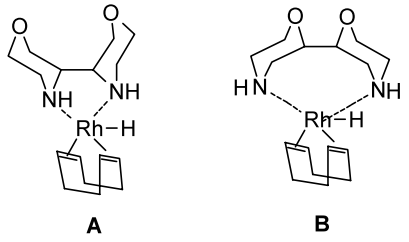


Figure 2. Possible five-membered **A** and seven-membered **B** complexes.

2.2. Reduction of acetophenone with Rh- and Ru-catalyst bearing bimorpholine 1 ligand

We investigated the influence of the catalyst precursor (source of the transition metal) on the enantioselectivity of the reduction of acetophenone. The results obtained are presented in Table 2.

No reaction was detected when the dimeric complex $(RuCl_2C_6H_6)_2$ was used as the transition metal source at room temperature. When the reaction temperature was increased to 82°C, the reaction proceeded to a certain extent, but as a result the enantioselectivity of it was lower than in the case of $[Rh(cod)Cl]_2$ (Table 2, nos 1 and 2).

Kim et al.[15] have reported that the $RuCl_2(PPh_3)_3$ devised complex with a chiral diamine effectively catalyses hydride transfer reduction of aryl ketones: We used this as the source of the metal together with ligand **1** and found that the catalytic activity of the complex is highly dependent on the conditions of its formation. When the catalyst was generated from its metal precursor, bimorpholine **1** (the molar ratio of $RuCl_2(PPh_3)_3$/bimorpholine **1** was 1:1.5 because of the monomeric nature of the metal source and base at room temperature) we obtained a completely inactive catalyst with no reduction of the acetophenone occurring. Increasing the temperature (reflux in *i*-PrOH) resulted in 1-phenylethanol in a 52% yield while the selectivity of the catalyst remained moderate (ee 27%; Table 2, no. 3). When the complex was prepared in boiling *i*-PrOH without the base (it was added together with the substrate), we obtained an almost racemic product (ee 5%; Table 2, no. 4). Changing the conditions of the catalyst

Table 2. Influence of the metal precursor on the enantioselectivity of the reduction of acetophenone[a]

Entry	Metal precursor	Molar ratio of L*:M	Temperature, time (h)	Yield[b] (%)	Ee[c] (%)
1	$[Rh(cod)Cl]_2$	4:1	rt, 21	96	32
2	$(RuCl_2C_6H_6)_2$	4:1	rt to 82°C, 5	41	20
3	$RuCl_2(PPh_3)_3$	1.5:1	rt to 82°C, 23	52	27
4	$RuCl_2(PPh_3)_3$	1.5:1	82°C, 1.5	97.5	5

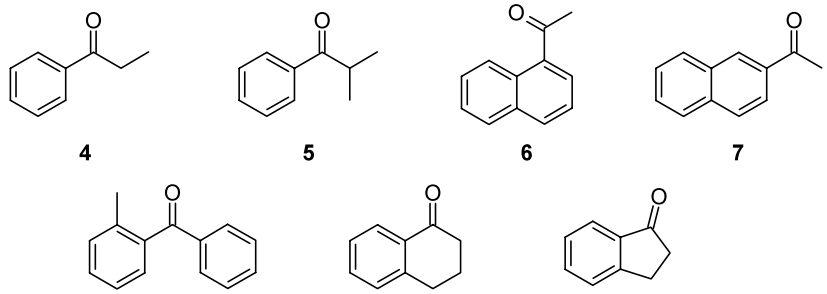
[a] 5 mol% of the catalyst derived from bimorpholine **1** and metal precursor was used.
[b] Determined as area% by GC analyses.
[c] Determined by chiral HPLC.

formation led to clearly different catalytic systems, but all these complexes have quite poor activity and selectivity. So, the best results (yield and ee of the product) were obtained with $[Rh(cod)Cl]_2$ as the catalyst precursor and bimorpholine **1** as the chiral ligand, and as a result this system was used in the following experiments.

2.3. Reduction of aromatic ketones with $[Rh(cod)Cl]_2$/bimorpholine 1 catalyst

Ketones **3**–**10** were reduced under the conditions found above (ligand/metal molar ratio 4:1, room temperature). The obtained results are presented in Table 3. As seen in Table 3, the highest yield was obtained in the case of acetophenone **3** (Table 3, no. 1). However, the enantiomeric purity of the obtained alcohol was quite low. Also this reaction was relatively fast (96% in 21 h) as most of the other substrates required much longer reaction times. As a result we prolonged the reaction time up to 46 h. Thus using the extended reaction time, propiophenone **4** was reduced to (*S*)-1-phenylpropanol giving a 77% yield and isobutyrophenone **5** to (*S*)-2-methyl-1-phenylpropanol giving a 55% yield. The stereoselectivity of the reduction was moderate (ee 40% and 44%, respectively, Table 3, nos 2 and 3). The hydride transfer reduction of 1- and 2-substituted acetonaphthones **6** and **7** gave the corresponding alcohols with a high yield but with a considerable difference in their enantiomeric purity: the 1-naphthone was reduced with higher selectivity than the 2-naphthone (ee 63% versus 21%; Table 3, nos 4 and 5). The highest selectivity (ee 75%) was observed in the case of a 'flat' substrate 2-methylbenzophenone **8**. However, in that case, the yield remained low (33%; Table 3, no. 6). The cyclic ketones, 1-tetralone **9** and 1-indanone **10**, were converted to the corresponding alcohols with a satisfactory yield but with a significantly lower enantioselectivity

Table 3. Asymmetric reduction of ketones **3**–**10** catalyzed by Rh–**1** complex



Entry	Ketone	Time (h)	Yield[a] (%)	Ee (%), (*R*/*S*)[b]
1	**3**	21	96	32 (*S*)
2	**4**	46	77	40 (*S*)
3	**5**	46	55	44 (*S*)
4	**6**	46	83	63 (*S*)
5	**7**	46	82	21 (*S*)
6	**8**	46	33	75 (*S*)
7	**9**	21	61	12 (*R*)
8	**10**	21	63	3

[a] Determined as area% by GC analysis.
[b] Enantiomeric excess was determined by chiral HPLC and absolute configuration of the main enantiomer by comparing the specific rotation with the reference value.

(Table 3, nos 7 and 8). The reason for the drop in enantioselectivity was due to conformational flexibility of the alicyclic system.

In all cases, the selectivity of the catalytic system appeared to be driven by steric differences in the groups around the C=O bond. Branching in the alkyl chain at the α-position of the carbonyl group led to a higher selectivity. Also, comparing 1- and 2-substituted naphthalene derivatives **6** and **7**, the sterically more hindered one, with a bridge at the α-position, afforded higher reduction selectivity.

3. Conclusion

We demonstrated that bimorpholine **1** is a promising ligand for Rh-catalyst. In the reduction of aromatic ketones, the corresponding alcohols were obtained with ee up to 75%. It is most probable that the difference in the stereoselectivity of Rh–**1** and Rh–**2** complexes is due to their geometric properties. Thus, bimorpholine **1**, which is able to form conformationally more rigid five-membered ring complex, has a better catalytic property than bimorpholine **2**, which may form a seven-membered ring complex. The enantioselectivity of the hydride transfer reduction of prochiral aromatic ketones is also clearly dependent on the structure of the substrate-sterically more hindered carbonyl compounds bring to a higher enantioselectivity.

4. Experimental

The conversions were measured by capillary gas chromatography on a Shimadzu GC-14B (column 122-5022 DB-5, length 25 m, I.D. 0.25 mm, film 0.25 μm). Enantiomeric excesses were determined by HPLC on a LKB 2150 system using a Chiralcel OD-H column. Mass spectra were recorded on a Hitachi M80B spectrometer, using electron ionization at 70 eV. Optical rotations were measured on a Krüss Optronic GmbH automatic digital polarimeter P 3002.

4.1. General procedure for the reduction of ketones

A solution of bimorpholine (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. A solution of ketone (0.52 mmol) in *i*-PrOH (5 mL) was added, and the reaction mixture stirred at room temperature for an appropriate time. The reaction was monitored by capillary gas chromatography. After completion of the reaction, Et_2O (80 mL) was added and the catalyst removed by filtration through a pad of Celite®. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash chromatography on silica gel.

4.1.1. (*S*)-(−)-1-Phenylethanol. Table 3, entry 1; 32% ee (*S*), HPLC (hexane:*i*-PrOH = 9:1, 0.7 mL/min, (*R*)-isomer 7.5 min, (*S*)-isomer 8.3 min); Table 1, entry 1; 27% ee (*S*), $[\alpha]_D = -14.0$ (*c* 1.56, CH_2Cl_2) (lit.[16] $[\alpha]_D = -48.8$ (*c* 1.0, CH_2Cl_2), 91% ee (*S*)); MS *m*/*z* (%): 122 (24) [M$^+$], 107 (92), 91 (3), 79 (100), 77 (84), 51 (76), 43 (87).

4.1.2. (*S*)-(−)-1-Phenylpropanol. Table 3, entry 2; 40% ee (*S*), HPLC (hexane:*i*-PrOH = 95:5, 0.7 mL/min, (*R*)-isomer 9.7 min, (*S*)-isomer 10.4 min); $[\alpha]_D = -12.5$ (*c* 1.10, EtOH) (lit.[16] $[\alpha]_D = -33.0$ (*c* 5.15, EtOH), 86% ee (*S*)); MS *m*/*z* (%): 136 (6) [M$^+$], 107 (74), 91 (4), 79 (100), 77 (50), 51 (34).

4.1.3. (*S*)-(−)-2-Methyl-1-phenylpropanol. Table 3, entry 3; 44% ee (*S*), HPLC (hexane:*i*-PrOH = 95:5, 0.7 mL/min, (*S*)-isomer 8.3 min, (*R*)-isomer 9.8 min); $[\alpha]_D = -22.7$ (*c* 0.84, Et_2O) (lit.[16] $[\alpha]_D = -21.0$ (*c* 1.05, Et_2O), 43% ee (*S*)); MS *m*/*z* (%): 150 (4) [M$^+$], 107 (100), 91 (3), 79 (84), 77 (52), 51 (32).

4.1.4. (*S*)-(−)-1-(1′-Naphthyl)ethanol. Table 3, entry 4; 63% ee (*S*), HPLC (hexane:*i*-PrOH = 9:1, 0.7 mL/min, (*S*)-isomer 11.6 min, (*R*)-isomer 18.8 min); $[\alpha]_D = -51.8$ (*c* 2.92, Et_2O) (lit.[16] $[\alpha]_D = -79.6$ (*c* 1.02, Et_2O), 94% ee (*S*)); MS *m*/*z* (%): 172 (16) [M$^+$], 157 (16), 129 (100), 43 (48).

4.1.5. (*S*)-(−)-1-(2′-Naphthyl)ethanol. Table 3, entry 5; 21% ee (*S*), HPLC (hexane:*i*-PrOH = 9:1, 0.7 mL/min, (*S*)-isomer 12.1 min, (*R*)-isomer 12.6 min); $[\alpha]_D = -10.8$ (*c* 0.91, EtOH) (lit.[16] $[\alpha]_D = -34.3$ (*c* 1.10, EtOH), 86% ee (*S*)); MS *m*/*z* (%): 172 (30) [M$^+$], 157 (33), 129 (100), 128 (69), 43 (93).

4.1.6. (*S*)-(+)-2-Methylbenzhydrol. Table 3, entry 6; (*S*), $[\alpha]_D = +4.0$ (*c* 2.7, EtOH) (lit.[17] ee > 95% (*R*)-isomer by $[\alpha]_D = -7.5$ (*c* 5.1, EtOH)); 75% ee, HPLC (hexane:*i*-PrOH = 98.5:1.5, 1.0 mL/min, (*R*)-isomer 31.8 min, (*S*)-isomer 33.6 min); MS *m*/*z* (%): 198 (58) [M$^+$], 180 (66), 165 (26), 119 (98), 105 (100), 91 (80), 77 (100).

4.1.7. (*R*)-(+)-1,2,3,4-Tetrahydro-1-naphthol. Table 3, entry 7; 12% ee (*R*), HPLC (hexane:*i*-PrOH = 97:2.5, 0.7 mL/min, (*S*)-isomer 14.6 min, (*R*)-isomer 15.8 min) (lit.[16] 98% ee (*S*) by HPLC (Chiralcel OD, hexane:*i*-PrOH = 98:2, 0.9 mL/min, (*S*)-isomer 17.4 min, (*R*)-isomer 19.8 min)); MS *m*/*z* (%): 148 (20) [M$^+$], 130 (73), 120 (100), 115 (6), 105 (22), 91 (50), 77 (21).

4.1.8. 1-Indalol. Table 3, entry 8; 3% ee, HPLC (hexane:*i*-PrOH = 95:5, 0.7 mL/min, isomers 10.4 and 11.5 min); MS *m*/*z* (%): 134 (76) [M$^+$], 133 (100) [M−1$^+$], 115 (24), 105 (32), 91 (29), 77 (33), 51 (26).

Acknowledgements

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References

1. Fache, F.; Schulz, E.; Tommasino, L. M.; Lemaire, M. *Chem.Rev*. **2000**, *100*, 2159–2231.
2. Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev*. **1992**, *92*, 1051–1069.
3. Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061.
4. Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.. Engl*. **2001**, *40*, 40–73.
5. Noyori, R. *Angew. Chem., Int. Ed. Engl*. **2002**, *41*, 2008–2022.
6. Pu, L.; Yu, H.-B. *Chem. Rev*. **2001**, *101*, 757–824.
7. Kanger, T.; Kriis, K.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2002**, *13*, 857–865.
8. Püntener, K.; Schwink, L.; Knochel, P. *Tetrahedron Lett*. **1996**, *37*, 8165–8168.
9. Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 285–288.
10. Touchard, F.; Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron Lett*. **1997**, *38*, 2275–2278.
11. Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett*. **1993**, *34*, 6897–6898.
12. Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1995**, *6*, 705–718.
13. Gladiali, S.; Pinna, L.; Delogu, G.; De Martin, S.; Zassinovich, G.; Mestroni, G. *Tetrahedron: Asymmetry* **1990**, *1*, 635–648.
14. Bernard, M.; Guiral, V.; Delbecq, F.; Fache, F.; Sautet, P.; Lemaire, M. *J. Am. Chem. Soc*. **1998**, *120*, 1441–1446.
15. Kim, G.-J.; Kim, S.-H.; Chong, P.-H.; Kwon, M.-A. *Tetrahedron Lett*. **2002**, *43*, 8059–8062.
16. Palmer, M. J.; Kenny, J. A.; Walsgrove, T.; Kawamoto, A. M.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 416–427.
17. Brown, E.; Leze, A.; Touet, J. *Tetrahedron: Asymmetry* **1992**, *3*, 841–844.