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Letter

Asymmetric hydrogenation of α-keto ester with diamine-complexed metal

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Abstract

Asymmetric catalytic hydrogenation of methyl phenylglyoxylate with diamine-chelated metal was studied. Enantiomeric excesses of up to 50% were obtained using a rhodium complex prepared in situ by mixing bis(1,5-cyclooctadiene)dirhodium(I) dichloride with two equivalents of (*N*,*N*′)dimethyl (1*R*,2*R*)diphenylethylene diamine **1a** in methanol. The e.e. decreases by using aqueous solvent. However, when cyclodextrin was added in MeOH/H_2O (70/30); similar e.e. to that observed in pure methanol was obtained. Application in biphasic medium could be envisaged.

Keywords: Asymmetric hydrogenation; Diamine ligands; Cyclodextrin

1. Introduction

Most of the chiral ligands used in asymmetric catalysis are diphosphines. However, the synthesis of these ligands are in general neither easy nor inexpensive. On the contrary, many optically active amines are widely available in the chiral pool although their use as ligand for asymmetric catalysis is more recent and less documented [1].

Major results were obtained by using sp^2-nitrogens as ligands: Pfaltz developed the use of semicorrins in hydride transfer (Meerwein–Ponndorf–Verley type reaction) of aromatic ketone with iridium complex giving the corresponding alcohol with a high e.e. (of up to 91%) [2]. Recently, Gladiali has developed the use of chiral 3-alkyl phenanthroline chelated to rhodium in asymmetric hydride transfer [3]. Reduction of acetophenone in the presence of potassium hydroxide as cocatalyst gave 89% of (*S*)-phenylethanol with 63% enantiomeric excess. We have demonstrated that optically active sp^3 1,2-diamino-1,2-diphenylethane **1a** (Fig. 1) acts as chelating ligand of rhodium to give a catalyst for the same reaction [4]. Acetophenone and methyl phenylglyoxylate were reduced with 67 and 99% e.e., respectively, after complete conversion. With the same slightly modified diamine **1b** chelated to ruthenium, Noyori and coworkers obtained, by using a similar procedure, enantiomerically pure (*S*)-phenylethanol [5]. Enantioselective reduction of aryl methyl ketones with an aminodiol-chelated samarium

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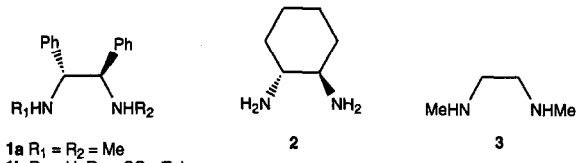


1a $R_1 = R_2 = Me$
1b $R_1 = H$, $R_2 = SO_2pTol$

2 **3**

Fig. 1. Structures of **1a**, **1b**, **2** and **3**.

complex was also performed with high e.e. (up to 97%) [6].

Corma prepared rhodium complexes with N-containing ligands, derived from L-proline. These complexes were bound to a modified zeolite via a carbon bridge. Reduction of α-acylaminocinnamate derivatives was performed with these homogeneous supported complexes and corresponding substituted phenylalanine derivatives were obtained with quantitative conversion and e.e. of up to 99% [7].

To our knowledge, no reduction via molecular hydrogen has been performed using C_2 symmetric chiral sp^3-diamines as ligands. One of the main potential advantages of amine ligands in homogeneous catalysis is their relatively high solubility in aqueous medium, which allows their use in biphasic systems. In addition, they are generally much more stable than phosphine towards oxidation and easier to separate. We now wish to present uses of C_2 symmetric chiral diamines complexed to transition metals in the asymmetric hydrogenation of the prochiral keto group.

2. Experimental

General procedure of hydrogenation with rhodium catalyst: In a typical experiment, 19.7 mg of bis(1,5-cyclooctadiene) rhodium(I)dichloride (0.08 mmol) and 77 mg of (*N*,*N*′)-dimethyl (1*R*,2*R*)-diphenyl ethylene diamine **1a** (0.32 mmol, 2 equiv./Rh) were introduced in 4 ml degassed methanol in a Schlenk vessel, under argon. After stirring for 2 h at room temperature, the yellow solution was transferred into a 30 ml Teflon-coated stainless steel autoclave and 525 mg of phenylglyoxylate methyl ester (3.2 mmol) were added. The autoclave was purged with 3 argon cycles followed by 3 hydrogen cycles and then 50 atm of hydrogen were introduced. The solution was stirred for 15–20 h. Yields and enantiomeric excesses were determined by gas chromatography.

3. Results and discussion

Different metal complexes were prepared in order to compare their stability under hydrogenation conditions as well as their activity and their enantioselectivity for the reaction.

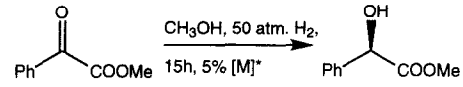
Treatment of commercial bis(1,5-cyclooctadiene)dirhodium(I) dichloride $[Rh(COD)Cl]_2$ with chiral diamine in methanol for 2 h gave an in situ complex which was used directly for hydrogenation. The same procedure was developed for preparing Ir and Pd complexes from $[Ir(COD)Cl]_2$ and $[Pd(\eta^3\text{-allyl})]_2$ or $Pd(OAc)_2$, respectively. A ruthenium complex was prepared by heating $(COD)Ru(metallyl)_2$ in hexane in the presence of chiral diamine **1a**, as described for diphosphine complexes [8]. However, this complex was not isolated.

The ruthenium complex was stable under hydrogenation conditions and showed low enantioselectivity (Table 1, entry 1).

With 1 equivalent of diamine per rhodium, the complex was not stable, black metal precipitated and partial reduction of the aryl group occurred during the reaction (Table 1, entry 2) [9]. Stabilization of the complex was achieved using 2 equivalents of diamine. Under such conditions, only 10% enantiomeric excess was observed when using (1*R*,2*R*)-cyclohexyldiamine **2** as the ligand (Table 1, entry 3). In contrast, a significant enantioselectivity of 50% was reached when (*N*,*N*′)-dimethyl (1*R*,2*R*)-diphenylethylenediamine [1] was used. Hydro-

[1] **1a** is prepared according to [10]; **2** and **3** are commercially available.

Table 1
Hydrogenation of phenylglyoxylate methyl ester in the presence of diamine-complexed transition metals



Yield = 95-100%

Entry	Metal	Diamine	*n*(diamine)/*n*(metal)	e.e. (%) (conf.)[a]	Comments
1	Ru	**1a**	1	19 (*R*)[b]	
2	Rh	**2**	1	3 (*R*)	Rh metal
3	Rh	**2**	2	10 (*R*)	
4	Rh	**1a**	2	50 (*R*)	
5	Pd	**1a**	2	4 (*R*)	Pd metal
6	Pd	**1a**	2	2 (*R*)[c]	Pd metal
7	Ir	**1a**	1	21 (*R*)[d]	
8	Ir	**1a**	2	40 (*R*)	
9	Ir	**2**	2	32(*R*)	

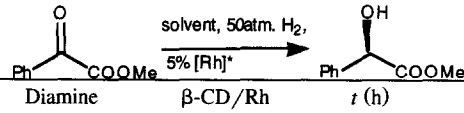
None of these transition metal complexes were isolated.
[a] Yields and enantiomeric excesses were determined by gas chromatography (Lipodex E Macherey–Nagel, Duren).
[b] Yield = 78%.
[c] Reaction run under 4 atm H_2.
[d] Complete conversion in 42 h.

genation of methyl α-acetamidoacrylate was also performed with this system (pH_2 = 3 atm, RT, 20 h); unfortunately the corresponding alanine derivative was obtained as a racemate (appearance of black metal was observed).

As with ruthenium, the iridium complex was stable with one equivalent of diamine, best selectivity was obtained with 2 equivalents while the reaction rate was lower than for rhodium (Table 1, entry 8). Interestingly, the use of the (1*R*,2*R*)-cyclohexyldiamine **2** as ligand gave a reasonable e.e. (Table 1, entry 9) contrary to the case of the rhodium.

There are few examples in the literature dealing with the use of organometallic Pd-catalyst for asymmetric hydrogenation and none concerning the reduction of the C=O bond [11]. The main problem is due to the low stability of the palladium(0) complex under hydrogen pressure. Nevertheless, we tested the in situ formed

Table 2
Influence of solvent and cyclodextrin on rate and selectivity



Entry	Solvent	Diamine	β-CD/Rh	*t* (h)	Yield (%)	e.e.(%) (conf.)
1	MeOH	(*R*,*R*)**1a**	0	15	100	50 (*R*)
2	iPrOH	(*R*,*R*)**1a**	0	15	37	48 (*R*)
3	CH_2Cl_2	(*R*,*R*)**1a**	0	87	7	20 (*R*)
4	MeOH/H_2O 70/30	(*R*,*R*)**1a**	0	40	25.5	36 (*R*)
5	MeOH/H_2O 70/30	(*R*,*R*)**1a**	0.2	19	25	45 (*R*)
6	MeOH/H_2O 70/30	(*R*,*R*)**1a**	1	24	99	50 (*R*)
7	MeOH/H_2O 70/30	**3**	0	24	14	0
8	MeOH/H_2O 70/30	**3**	1	24	87	0

Pd-catalyst. Unfortunately, it was not stable under hydrogenation conditions whatever the source of palladium, even under low hydrogen pressure, and an almost racemic product mixture was observed (Table 1, entries 5, 6).

The role of the solvent was also examined in the case of the reduction with a rhodium complex (entry 4, Table 1).

Alcoholic solvents give the better enantioselectivities (up to 50%) with a slower reaction in iPrOH than in MeOH (entries 1, 2, Table 2). In iPrOH without hydrogen no reaction occurs, showing that there is no hydride transfer. In an aprotic solvent, such as dichloromethane, reaction occurs with lower enantiomeric excess and very low reaction rate. In $MeOH/H_2O$ (70/30), both reaction rate and enantioselectivity decreased as it was already observed in previous work with aqueous soluble diphosphine ligands [12]. Turning our attention to this last result we studied the influence of the addition of β-cyclodextrin (β-CD), since it forms inclusion complexes with organic compounds (especially aromatics) and increases their apparent solubility in aqueous medium [13].

Addition of β-cyclodextrin (Table 2, entries 5, 6) increases both the reaction rate and the enantiomeric excess. With 1 equivalent of cyclodextrin, results are similar to those obtained in methanolic solvent. The increasing enantioselectivity is probably not due to the intrinsic chirality of the cyclodextrin since with achiral amine **3** no enantioselectivity was observed (Table 2, entry 8), but may almost certainly be attributed to a medium effect. Probably, an inclusion complex between the β-cyclodextrin and the substrate (or the ligand) is formed, which modified the environment where the reaction proceeds. The reduction occurred mainly when the ketone was complexed (higher reaction rate; compare entries 7 and 8). It has to be supposed that at this stage the medium around the substrate is then similar to methanol because of the reduced hydrophilic character of the cyclodextrin cavity. As the dissociation constants are higher for the alcohol than for the ketone [14], the former is easily decomplexed giving free cyclodextrin.

4. Conclusion

This work shows the possibility of using diamines instead of bidentate phosphines for the asymmetric metal-catalyzed reduction of ketones. Ruthenium(II), rhodium(I) and iridium(I) complexes are efficient. Although an excess of diamine is required to avoid the formation of metallic rhodium; mechanisms should be close to this proposed for bidentate phosphine. Considering the ready availability of this type of diamine (see footnote 1), a new field in asymmetric reduction might be open. Moreover, such complexes can be used in aqueous medium without degradation and a synergetic effect of cyclodextrin is observed. These preliminary results are encouraging for the possible future use of this system in biphasic medium. The efficiency of diamine complexes under such conditions has to be studied, and further investigations are in progress.

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