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Journal of Organometallic Chemistry 567 (1998) 133–136

Journal of Organometallic Chemistry

Optically active nitrogen ligands in asymmetric catalysis. Effect of nitrogen substitution on the enantioselective hydride transfer reduction of acetophenone

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Received 10 June 1997; received in revised form 13 January 1998

Abstract

Both theoretical calculations and experimental data have shown that only one diamine ligand was necessary for the Rh catalytic enantioselective hydride transfer reduction of acetophenone. A mechanism is proposed. Different aza ligands were also tested in the same reaction, using rhodium, ruthenium and iridium precursors. The structure-activity-selectivity relationship of the aza ligands is discussed. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Asymmetric catalytic hydride transfer reduction of ketones; Mechanism; Theoretical calculations; Aza ligands

1. Introduction

Optically active nitrogen compounds were proved to be efficient ligands in enantioselective hydride transfer reduction of ketones. Thus, different families of aza derivatives have been developed in the last few years such as phenanthrolines [1], aminoalcohols [2], sulfonylamines [3] and more particularly in our laboratory C_2-symmetric *N*,*N*′-alkyldiamines [4] and the corresponding ureas [5] and thioureas [6]. If excellent e.e. have been reached (up to 97% at 98% conversion in the case of acetophenone [3]), very few is known about the mechanism. Thus, Gladiali [1] using rhodium catalyst and phenanthroline ligands reported that the most active and stereoselective catalytic species might be a rhodium hydride complex containing two ligands, i.e. four nitrogen atoms. Noyori [3] described a Ru II complex with a square-planar geometry where the metal center was coordinated to two anionic nitrogen atoms from the *N*-*p*-toluenesulfonylethylenediamine ligand and to *p*-cymene from the catalyst precursor $[Ru(p\text{-cymene})Cl_2]_2$.

In this paper, we first describe our understanding of the mechanism of the enantioselective reduction of acetophenone by hydride transfer with rhodium and diamine ligands (Fig. 1). Then we report the effect of nitrogen substitution on both activity and selectivity.

2. Mechanistic study

In order to elucidate the mechanism of the reaction with an alkyldiamine ligand, the *N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine (R = Ph, R′ = H, R″ = CH3), we used both a theoretical and an experimental approach.

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PII S0022-328X(98)00675-5

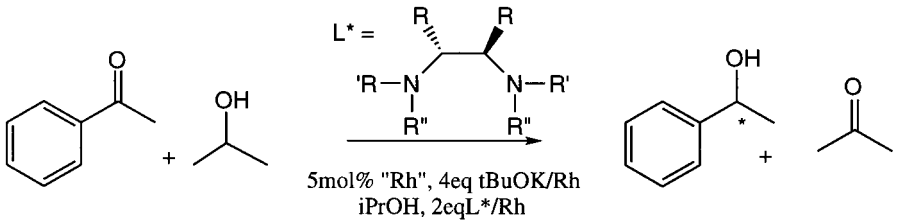
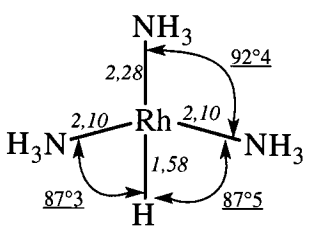


Fig. 1. Asymmetric hydride transfer reduction of acetophenone using diamine ligands.

Using the DFT theory and GAUSSIAN 94 [7] program, we first studied the d^8 $[RhH(NH_3)_4]$ complex as a model for the supposed $[RhH(diamine)_2]$ initial complex proposed by Gladiali. Full geometry optimization showed that a NH_3 is moved out of the coordination sphere to give a square planar ML_4 complex $[RhH(NH_3)_3]$. This indicates that a four NH_3 complex is not stable (Fig. 2).

Considering the metal precursor $[Rh(cod)Cl]_2$ we envisaged that one cyclooctadiene (cod) could still be bound to the active catalytic species. Modelling cod by two ethylenes, we performed a full geometric optimization on $[RhH(NH_3)_2(C_2H_4)_2]$ and found a stable structure (more details are given in Ref. [8]). The difference of stability with $[RhH(NH_3)_3]$ can be explained taking into account the orbital interactions. It is in fact important to have a bonding interaction between the metal dxy orbital and a π^* orbital from a ligand (backbonding interaction). In the case of our diamine ligands, σ-donors, the concomitant presence of a π-acceptor ligand is thus necessary. Therefore, we think that the active complex includes a diene and a diamine (Fig. 3).



bond lengths in Å

Fig. 2. Optimized structure for the ML_4 complex : $[RhH(NH_3)_3]$.

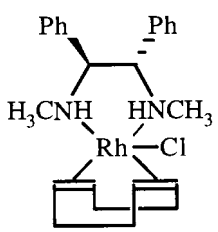


Fig. 3. Proposed structure of the active catalytic species.

In the case of phenanthrolines, $\sigma\pi^2$ ligands, the orbital interactions are probably different and our conclusion is still compatible with Gladiali's one.

Using the catalyst precursor $[Rh(cod)Cl]_2$, we tried to synthesize a rhodium complex containing two diamine ligands. Every attempt to do it was unsuccessful and we always isolated the structure described above (Fig. 3) with only one diamine ligand. Different tests carried out with one to four equivalents of ligands/Rh showed that only one equivalent of ligand per rhodium is necessary. Practically, an excess of ligand is required in order to stabilize the metal complex and to avoid the formation of metal particles. Therefore, in the rest of our study we will devote a great deal of attention to the optimization of the amount of ligands (Table 1). Several tests with increasing ligand/Rh ratio were performed with each ligand in order to obtain maximum e.e. and stable catalytic system.

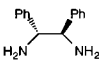
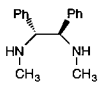
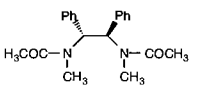
We thus proposed the following catalytic cycle where each supposed intermediate has only one diamine ligand and one cod bound to the rhodium (Fig. 4). The isopropylate intermediate **1** eliminated one equivalent of acetone to give the hydride species **2**. The acetophenone then approached complex **2** and a four electron concerted hydride transfer (**3**) led to the other alkoxy species **4**. The excess of 2-propanol allowed the elimination of the desired 2-phenylethanol and the regeneration of complex **1**. Further studies are in progress particularly to know whether the hydride intermediate **2** is formed or whether the hydride transfer proceeds via a concerted mechanism between the alkoxy complex **1** and acetophenone.

Table 1
Influence of the number of diamine ligand/Rh on the reactivity and selectivity of the reaction

Diamine equivalents/Rh	Conversion (%)	e.e. (%)
1	93	39
2	73	47
3	98	46
4	64	43

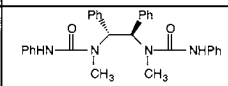
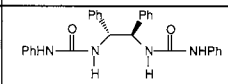
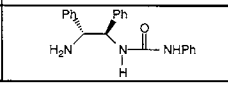
Conditions: [Rh]/[acetophenone] = 5%; [t-BuOK]/[Rh] = 4; [acetophenone] = 6×10^{-2} mol l^{-1} in iPrOH; 50 h; room temperature.

Table 2
Results obtained with diamine and diamide ligands

Entry	Ligand	Metal	eqL* /metal	Conversion% (time, day)	e.e.% (conf.)
1		Rh	2	94 (8)	17(S)
2		Rh	2	100 (7)	67(S)
3		Rh	2	90 (8)	4(R)

Conditions: [Rh]/[acetophenone] = 5%; [*t*-BuOK]/[Rh] = 4; [acetophenone] = 6×10^{-2} mol l^{-1} in *i*PrOH; 82°C; the synthesis of the ligands has been described in Ref. [4].

Table 3
Results obtained with urea ligands

Entry	Ligand	Metal	eqL* /metal	Conversion% (time, day)	e.e.% (conf.)
1		Rh	10	97 (7)	43(S)
2		Rh	6	89(3)	14(S)
3		Ir	2	91 (8)[a]	46(S)

Conditions: [M]/[acetophenone] = 5%; [*t*-BuOK]/[M] = 4; [acetophenone] = 6×10^{-2} mol l^{-1} in *i*PrOH; 82°C; the synthesis of the ligands has been described in Ref. [5].
[a] Room temperature.

3. Influence of nitrogen substitution

With the same basic skeleton, the 1,2-diphenyl-1,2-ethanediamine, we substituted the nitrogen atoms with different functional groups and tested the corresponding ligands. $[Ru(C_6H_6)Cl_2]_2$, $[Rh(cod)Cl]_2$, $[Ir(cod)Cl]_2$, were used as catalyst precursors with each new ligand structure and the number of ligand equivalents per metal atom was optimized. Typically, we have increased the number of ligand equivalents per metal atom until the enantioselectivity reached its highest level and remained constant. In all cases we observed that the activity decreased in the same time. Only the best results in terms of enantioselectivity are reported here.

In the diamine series (Table 2, entries 1 and 2), substitution of the nitrogen by a methyl group allowed to considerably increase the enantioselectivity as well as the activity. The nitrogen atom thus substituted by two different groups became a stereogenic center when bound to the rhodium, which could explain this improvement. Replacing the hydrogen by an acetyl group (Table 2, entries 2 and 3) drastically decreased the e.e. maybe because the hydrogen bond between acetophenone and the active catalytic species was suppressed. An increase of the bulkiness of the substituent from methyl (Table 2 entry 2) to propyl led to the same results in terms of activity and selectivity. Nevertheless, the isopropyl group caused a decrease of selectivities [4].

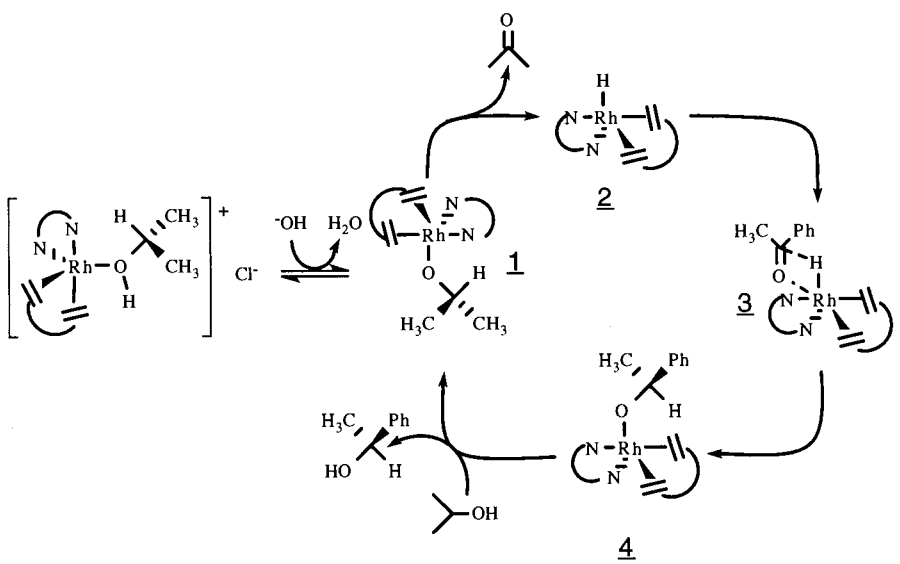
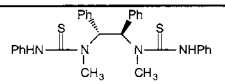
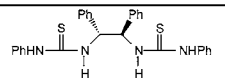
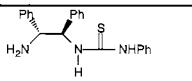


Fig. 4. Proposed catalytic cycle.

Table 4
Results obtained with the thioureas

Entry	Ligand	Metal	eqL*/metal	Conversion% (time, day)	e.e.% (conf.)
1		Ru	2	94 (1)	89(S)
2		Ru	2	15(3)	24(S)
3		Ru	2	99 (1)	57(S)

Conditions: [Ru]/[acetophenone] = 5%; [*t*-BuOK]/[Ru] = 4; [acetophenone] = 6×10^{-2} mol l^{-1} in *i*PrOH; 82°C; the synthesis of the ligands has been described in Ref. [9].

Rhodium gave the best results and two equivalents of ligand were used for the reasons stated before, even if one equivalent only was bound to the metal. Results obtained with the urea series are reported in Table 3.

Rhodium was the metal of choice for the diureas (Table 3, entries 1 and 2). Iridium allowed work at room temperature with monourea (Table 3, entry 3) whereas with the other ligands, it was necessary to work at 82°C, whatever the substituents on the nitrogens.

As for thioureas (Table 4), ruthenium gave the best results and only two equivalents of ligand per metal atom were necessary.

In the case of thioureas again, the compound bearing a methyl group on the nitrogen gave the best result.

If we compare the three families of ligands, the dithioureas with ruthenium gave the best e.e. and led to a far more active catalytic system than the others with only two equivalents of ligand/metal. With this last family of compounds, ruthenium was preferred whereas for the alkyldiamines and diureas rhodium was better.

4. Conclusion

We have shown that diamines but also diamides, ureas and thioureas (mono- or di-) could be efficient and selective ligands fot asymmetric catalysis and that substitution of the nitrogen atoms has a large effect on both activity and selectivity of the catalytic system, probably due to a different chelation pattern. Thus, the chemistry of nitrogen containing ligands being far easier than the phosphorus counterpart, there is no doubt that useful asymmetric catalytic systems could be obtained with such derivatives. Considering the mechanism of the hydride transfer reduction of acetophenone using rhodium and diamine ligand, our dual approach by theoretical calculation and practical experiments gave us serious evidence to propose a modified catalytic cycle with one diamine ligand and one cod bound to the rhodium. Further studies are in progress to find whether the same model is still valid for the dithiourea/ruthenium system.

5. Experimental

5.1. Typical procedure for the reduction of acetophenone

The appropriate amount of ligand was added to the catalyst precursor (6×10^{-3} mmol) in 2 ml of a solution of potassium terbutoxide in 2-propanol (0.012 mol l^{-1}) and stirred for 90 min under an inert atmosphere (*t*-BuOK/Rh = 4). After addition of acetophenone (0.12 mmol) the mixture was kept overnight at room temperature. The solution was then heated (82°C) unless overwise stated in order for the reaction to proceed. The reaction was monitored and the e.e. was measured by GC using a capillary column CYDEX-B from SGE.

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