

Amines as ligands in transfer hydrogenation catalysts

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Abstract

Rhpy_3Cl_3 (py = pyridine) has been found to be a versatile catalyst in selective transfer hydrogenation of α,β -unsaturated ketones to saturated ketones, dienes to monoenes, acetylenes to olefins, and Schiff bases to amines. With catalytic systems formed "in situ" from $\text{RhCl}_3 \cdot x\text{H}_2\text{O}$ and chiral monodentate amines such as *R,S*-(–)-ephedrine, enantioselective reduction of ketones takes place but the optical yields are rather low.

Introduction

The rhodium(III) complex, $\text{Rhpy}_2\text{Cl}_2(\text{dmf})(\text{BH}_4)$ (dmf = dimethylformamide) formed in situ from Rhpy_3Cl_3 (py = pyridine) and sodium borohydride has been extensively used in direct catalytic hydrogenation of a wide range of organic substrates, even in asymmetric reduction using chiral amide solvents [1–3], but the homogeneity of the system is questionable [4]. However, the Rhpy_3Cl_3 precursor or the amide catalyst has never been used in hydrogen transfer processes.

The synthesis of chiral alcohols can be accomplished by asymmetric transfer hydrogenation of ketones but only a few catalysts have been described so far [3,5]; these are iridium, rhodium or ruthenium complexes containing chiral phosphine [6,7], Schiff base [8,9], carboxylate [10,11], phosphinite [12], or bidentate amine [13] ligands. However, while chelating nitrogen donor ligands have found widespread application in hydrogen transfer processes [14–18] little attention has been paid to monodentate ones [18,19] and there is no example of the use of chiral nitrogen donor ligands.

We report here the results obtained in hydrogen transfer from alcohols, mainly propan-2-ol, to various substrates involving a base-activated Rhpy_3Cl_3 catalyst and on enantio-selective reduction of ketones with a $\text{RhCl}_3 \cdot \text{H}_2\text{O}$ + chiral monodentate amine catalytic system prepared "in situ".

Results and discussion

We found earlier [20] that the $\text{Rhpy}_3\text{Cl}_3 + \text{NaBH}_4 + \text{dmf}$ system [1] did not catalyze hydrogen transfer, either in neat dmf or in the presence of alcohol donors. Attempts to activate it by bases such as KOH were unsuccessful. However, it was found that the Rhpy_3Cl_3 complex itself could be successfully activated by addition of alkoxy base or KOH (or even by $\text{Ca}(\text{OH})_2$) in alcohol or in a small amount of water, which transformed the system into a dark-brown or yellow solution of acceptable activity both for the reduction of benzylideneacetophenone (BAP) to the saturated ketone and the hydrogenation of 1,5-cyclooctadiene to the corresponding monoene selectively. Data for typical runs are shown in Fig. 1.

In the activation procedure the base must usually be added after the substrate to avoid precipitation of metallic rhodium. When activating Rhpy_3Cl_3 is treated with NaOMe a white substance, identified as NaCl (2 mole/mol Rhpy_3Cl_3), separates within a few seconds.

In accordance with earlier reports [16–18] the activity of the catalytic system is influenced not only by the strength of the base but also by the base Rh ratio (Fig. 2). However, the reaction rates are not dependent on added pyridine and chloride ion (as NaCl) in the range investigated (Table 1).

In the light of this information we suggest that activation occurs by removal of two chloride ligands to give an alkali salt and formation of an active $\text{RhClpy}_3(\text{OMe})_x$ monomer or some kind of polynuclear species [21].

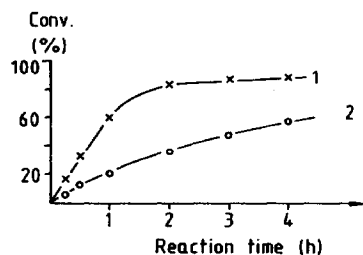


Fig. 1. Transfer hydrogenation of benzylideneacetophenone (1) and 1,5-cyclooctadiene (2). $2 \times 10^{-3} M$ catalyst; 1 mmol substrate in 12 ml 2-propanol; $\text{NaOMe}:\text{Rh} = 10$; 83°C .

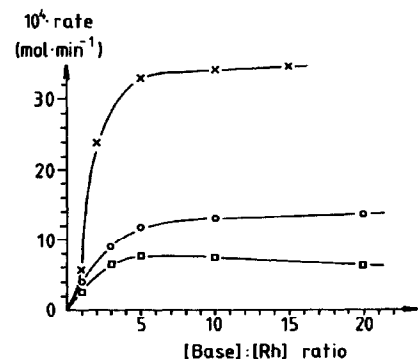


Fig. 2. Dependence of the reduction rate on the base-Rh ratio. Substrate: benzylideneacetophenone; $2 \times 10^{-3} M$ catalyst; 0.08 M substrate in 12 ml 2-propanol; 83°C . $\times$: KOH; $\circ$: KOBu^t ; $\square$: NaOMe.

Table 1

Reduction of benzylideneacetophenone; effect of added pyridine and chloride ion ^a

Added pyridine/Rh	10 ⁴ rate (mol/min)	Added Cl ⁻ /Rh	10 ⁴ rate (mol/min)
0	7.2	0	7.2
1	6.8	5	7.7
5	7.4	10	7.5
10	7.5	20	7.0
20	7.1		

^a Reaction conditions: 2×10^{-3} M catalyst, 0.08 M substrate, NaOMe/Rh = 10, 84 °C.

In the hydrogenation reactions not only various secondary but also primary alcohols, even methanol, were successfully used (Table 2).

Reduction of various substrates

Results in the reduction of various substrates with our catalytic system are listed in Table 3. In reactions involving olefins such as heptene-1 or cyclooctene, no saturated products were observed, and instead metallic rhodium separated. Acetylenes such as phenyl- or diphenyl-acetylene were reduced selectively to styrene and *trans*-stilbene, but again no saturated products were formed at all, a fairly rare observation in this type of reaction [22].

The course of hydrogen transfer to dienes is strongly dependent on the structure of the diene used. With 1,5-hexadiene along with partial saturation of the substrate there was also isomerisation, to form 1,3-hexadiene and several hexene isomers, but no hexane was detected. 1,5-Cyclooctadiene is also reduced selectively to cyclooctene. Hydrogenation of this diene can take place through its initial isomerisation to 1,3- and/or 1,4-cyclooctadiene [23,24], but the fact that selective hydrogenation of these isomers is slower than that of 1,5-COD, and that none of them could be detected as intermediates, indicates a direct reduction pathway for 1,5-COD.

While our catalytic system is highly selective towards the C,C-double bond in reduction of α,β -unsaturated ketones, some alkyl-aryl ketones such as acetophenone, propiophenone can also be reduced at the carbonyl function. This behaviour could

Table 2

Reduction of benzylidenacetophenone with various alcohols ^a

Alcohol	ITO ^b (cycles/min)	Conversion (%) after reaction (3 h)
Methanol	0.02	4
Ethanol	0.12	28
1-Propanol	0.53	60
1-Butanol	0.46	54
Isobutanol	0.48	59
Benzylalcohol	0.43	51
s-Butanol	0.21	45
α -Phenylethanol	0.24	35

^a Reaction conditions: 2×10^{-3} M catalyst in 12 ml alcohol, [S]/[Rh] = 50, KOH/Rh = 10, 83 °C,^b ITO = mol product/mol Rh · min.

Table 3

Reduction of various substrates with propan-2-ol catalyzed by Rhpy_3Cl_3 precursor ^a

Substrate	Product	ITO (cycles/min)	Conversion (%) after 3 hrs
1-Heptene ^b	—	—	—
Cyclooctene ^b	—	—	—
Phenylacetylene	styrene	0.32	72
1,3-Cyclooctadiene	cyclooctene	0.11	26
1,4-Cyclooctadiene	cyclooctene	0.04	11
1,5-Cyclooctadiene ^c	cyclooctene	0.27	59
Benzylidenacetophenone	$\text{PhCH}_2\text{CH}_2\text{COPh}$	0.37	88
Benzylidenacetone	$\text{PhCH}_2\text{CH}_2\text{COOH}_3$	0.22	64
Methyl ethyl ketone ^b	—	—	—
Acetophenone	α -phenylethanol	0.09	11
Propiophenone	α -phenylpropanol	0.07	10
Benzylideneaniline	benzylaniline	0.17	52

^a Reaction conditions: 2×10^{-3} M catalyst in 12 ml 2-propanol, $[\text{S}]/[\text{Rh}] = 40$, $\text{NaOMe}/\text{Rh} = 10$, 83°C .^b Metallic rhodium precipitated. ^c With KOH as base: ITO = 0.71.

be attributed to C,C-double bond hydrogenation of the enolic form ($K = 3.5 \times 10^{-4}$ for acetophenone), although an inhibitory effect of enolic forms has been observed previously [25]. With substrates having no enolizable hydrogen atom(s) (benzophenone, benzil) no reduction takes place, and rhodium metal precipitates. In the case of readily enolizable substrates (such as acetylacetone and benzoylacetone) the reduction is inhibited and no rhodium precipitates, an inactive stable complex being formed. More detailed studies are needed to provide better understanding of this problem.

In one experiment a $\text{RhCl}_3 \cdot x\text{H}_2\text{O}$ + pyridine system prepared in situ was used for transfer hydrogenation of benzylidenacetophenone, and the rate was comparable to that with the Rhpy_3Cl_3 catalyst. This observation, together with the fact, that the system also catalyses reduction of acetophenone, prompted us to investigate some catalysts prepared in situ from $\text{RhCl}_3 \cdot x\text{H}_2\text{O}$ and chiral monodentate amines.

Reduction of ketones with these systems (Table 4) showed that chiral amine catalysts were mainly formed. Their activities and enantioselectivities are in the

Table 4

Reduction of acetophenone with propan-2-ol catalyzed by $\text{RhCl}_3 \cdot x\text{H}_2\text{O}$ + chiral amine ^a

Amine	Amine/Rh	Time	Conv. (%)	ee ^b (%)
<i>S</i> -(−) $\text{C}_6\text{H}_5\text{CH}(\text{NH}_2)\text{CH}_3$	3	8	60	3.2 ^c (<i>R</i>)
	6	6	68	2.8 (<i>R</i>)
	3 ^d	7	32	2.1 (<i>R</i>)
<i>R,S</i> -(−) $\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{CH}(\text{NHCH}_3)\text{CH}_3$	3	9	42	6.0 ^c (<i>R</i>)
	6	7	45	3.4 (<i>R</i>)
	3 ^e	10	52	5.4 ^c (<i>R</i>)
<i>R</i> -(+) $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{NMe}_2$	6	8	50	3.3 (<i>S</i>)

^a 4×10^{-3} catalyst in 12 ml propan-2-ol and 8 mmol ketone; $\text{KOH}/\text{Rh} = 10/1$, 90°C . ^b Optical rotation measured of the neat distillate. ^c Confirmed by the method NMR involving the chiral shift reagent Eu-Opt° (Alfa). ^d NaOMe as base. ^e Propiophenone as substrate.

range observed previously in transfer hydrogenation with catalysts containing bidentate amine ligands [13].

Further studies on our new catalytic systems, aimed at better understanding of their selectivities and the special role of the substrate in the catalytic process, are in progress.

Experimental

Chemicals. Propan-2-ol was distilled from magnesium before use and stored under argon. α,β -Unsaturated ketones and benzylidenaniline were prepared by standard methods. Other starting materials were purchased from Fluka and Aldrich and were distilled immediately before use (acetophenone, dienes, etc.) or used as received. Rhodium trichloride trihydrate and Rhpy_3Cl_3 were purchased from Strem Chemicals.

Procedures. Hydrogen transfer reactions were carried out in refluxing alcohol under argon with magnetic stirring. The equipment consisted of a 20 ml thermo-statted double-necked reaction flask fitted with a condenser.

(a) *Experiments with Rhpy_3Cl_3 .* RhCl_3py_3 and the substrate were dissolved in propan-2-ol and the base was injected through a serum cap; the colour changed from pale yellow to yellow or dark brown depending on the substrate and base. (Conditions are given in Tables 1–3). The reaction was monitored by GLC by use of a HP5830 chromatograph equipped with an appropriate column and detector.

(b) *Asymmetric hydrogen transfer experiments.* Rhodium trichloride trihydrate and the required amount of chiral amine (see Table 4) were dissolved in propan-2-ol under argon and the mixture was stirred at the reflux temperature for 1 h. The substrate was then added, and the reaction started by addition of a solution of the base in propan-2-ol. (Conditions are given in Table 4). At the end of the reaction the solvent was evaporated, the residue distilled at reduced pressure, and its composition determined by GLC. Optical yields were determined by optical rotation measurements on a Schmidt polarimeter by use of $[\alpha]_D$ values taken from the literature ((*S*)(–)-1-phenylethanol $[\alpha]_D^{21} - 43.5^\circ$ (neat), (*S*)(–)-1-phenylpropanol $[\alpha]_D^{22} - 28.1^\circ$ (neat) [6]) and corrected to the composition of the distillate. Enantiomeric excess values were checked in some cases by the NMR spectroscopic method involving CS_2 as solvent and the Eu-Opt® (Alfa) Chiral shift reagent.

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