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Enantioselective Catalytic Reduction of Ketones using C2-Symmetric Diamines as Chiral Ligands.

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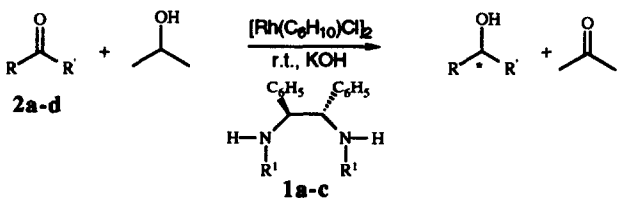
Abstract: The catalytic enantioselective reduction of various prochiral ketones is reported using C_2-symmetric diamines as ligands. Up to 99% e.e. at 100% conversion are obtained.

The enantioselective reduction of unsymmetrical ketones into their corresponding alcohols has been performed using a great number of catalytic methods affording good selectivity (> 90% enantiomeric excess)[1]. Recently, rhodium complexes containing unsymmetrical tertiary diamine ligands, 3-alkylphenanthrolines, have been developed for ketone reduction[2]. We now report the enantioselective reduction of various ketones by hydride transfer using C_2-symmetric 1,2-diamines as chiral ligands[3]. These diamines synthesized according to a method already described[4] are of easy access in their enantiomeric pure forms.

In a preliminary study, we have checked the influence of the nature of the diamine ligand **1** on the enantioselectivity of the rhodium-catalyzed reduction of acetophenone into 1-phenylethanol by hydrogen transfer from 2-propanol[5] (Scheme 1, Table 1).



Scheme 1 : asymmetric reduction of various substrates using chiral diamines.

Table 1. Influence of the Diamine Structure on the Enantiomeric Excess in the Reduction of Acetophenone **3a**.

Entry	Ligand[a]	R^1	Time (days)	Conversion (%)	Configuration	e.e.[b] (%)
1	**1a**	H	8	94	R	17
2	**1b**	CH_3	7	100	R	67
3	**1c**	iPr	8	8	R	28
4	(-) **DIOP**	-	7	11	-	<1
5	(-) **DIOP**	-	7	88[c]	-	<1
6	(-) **CHIRAPHOS**	-	7	3	-	<1
7	(-) **CHIRAPHOS**	-	7	31[c]	-	<1

a) all the diamines **1** are of (S,S) configuration; b) determined by gas chromatography; c) at 82°C.

The best results were obtained with diamine **1b**. This diamine has already been used in asymmetric synthesis via the corresponding aminal[6]. In such compounds, it has been shown by X-ray and NMR studies that the nitrogen substituent adopts a trans conformation with respect to the α substituent on the carbon. We can assume that the metal-ligand complex takes the same conformation. The nitrogen atom becomes a stereogenic center, which is not the case with diamine **1a**. In the case of the hindered diisopropyldiamine **1c**, the substrate cannot approach the metal, leading to weak conversion (8% in 8 days) and poor e.e. (28%). By hydride transfer, diphosphine ligands give low conversions at room temperature (entries 4 and 6) and no e.e. (entries 4 to 7, Table 1). Nevertheless, up to 80% e.e. have been reported with DIOP and Rhodium for the hydrogenation of acetophenone[7] in optimized conditions (70atm H_2, 50°C, Et_3N), which is better than with our catalytic system. This one should be optimized (ligand structure, reaction conditions, ...) even though, in some cases, it turns out to be excellent (>99% e.e., Table 2, entry 4).

Table 2. Asymmetric Reduction of Various Substrates using Diamine **1b**

Entry	**2a-d**	R	R'	Time*	Configuration	e.e.(%)[a]	$[\alpha]_D^{20}$(EtOH)
1	**2a**	C_6H_5	CH_3	7d	R	67(64)	+27[b]
2	**2b**	CN-C_6H_4	CH_3	8d	R	73(74)	+20[c]
3	**2c**	C_6H_{13}	CH_3	9d	R	40(40)	+3[d]
4	**2d**	C_6H_5	$COOCH_3$	1h	R	99(97)	-140[e]

* at 100% conversion; a) measured by: gas chromatography on the crude product (by polarimetry on the isolated pure product); b) $[\alpha]_D^{20}$ + 41.9 (C=5, EtOH)[8]; c) $[\alpha]_D^{20}$ +27.3 (C=5, EtOH)[9]; d) $[\alpha]_D^{20}$ +8.5 (C=5, EtOH)[8]; e) $[\alpha]_D^{20}$ -144.0 (C=1, MeOH)[10].

Aromatic compounds (Table 2, entries 1 and 2) give better results than the corresponding alicyclic compounds (entry 3, Table 2). Nevertheless, the 40% e.e. obtained with our system on cyclohexylmethylketone are encouraging in the perspective of reduction of even less differentiated ketones. The best result is obtained with the methyl benzoylformate which has been easily reduced (100% conversion in 1h, entry 4) with more than 99% e.e. (only one enantiomer is detected by gas chromatography).

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5. Typical procedure for the reduction of ketones: diamine (0.125mmol), the catalyst precursor $[Rh(C_6H_{10})Cl]_2$ (13.8mg, 0.062mmol) and potassium hydroxyde (20.9mg, 0.372mmol) were dissolved in 2-propanol (39ml) under an inert atmosphere and stirred for 1h. Then, ketone (1.25mmol) was added and the mixture was stirred at room temperature under nitrogen. The reaction was monitored by capillary gas chromatography and the enantiomeric excesses were measured by this method using a chiral column Macherey-Nagel-Düren, Lipodex E (25m x 0.25mm Ø). Optical rotations were measured with a Perkin-Elmer 241 polarimeter after purification.
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