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THE RUTHENIUM CATALYZED ASYMMETRIC HYDROGENATION OF OXIMES USING BINAP AS THE CHIRAL LIGAND

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Summary: The ruthenium BINAP complex, [RuX(arene)[(R)-BINAP]]X, can catalyze the hydrogenation of oximes to amines in moderate enantiomeric excess.

INTRODUCTION

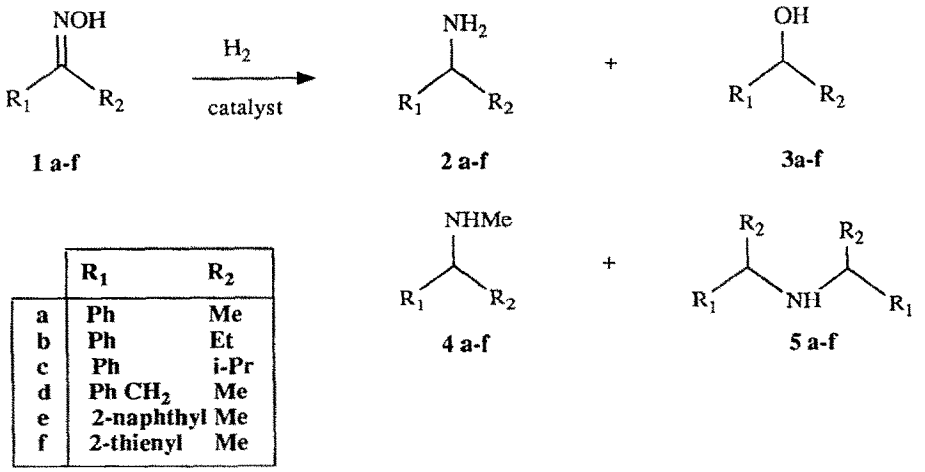
Homogeneous enantioselective hydrogenation is an important method for the synthesis of optically active compounds, the emphasis having been on functionalized olefins or ketones[1]. Several publications have appeared concerning the asymmetric hydrogenation of the carbon-nitrogen double bond of imines to form chiral secondary amines[2]. To our knowledge, there is only one paper in the literature concerning the asymmetric hydrogenation of oximes [3]. Botteghi et al. have reported the use of the chiral ruthenium catalyst, $H_4Ru_4(CO)_8$[(-)-DIOP]$_2$, for the asymmetric hydrogenation of the oximes of 3-buten-2-one, 1-phenyl-1-ethanone and 1-phenyl-2,2-dimethylpropanone. The best result (14% ee) was achieved for 1-phenyl-2,2-dimethylpropanone oxime.

RESULTS AND DISCUSSION

We now wish to report the asymmetric hydrogenation of alkyl aryl ketoximes, catalyzed by {RuX(arene)[(R)-BINAP]}X (BINAP=2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)[4] for the preparation of optically active primary amines (Scheme 1).

The catalysts were prepared *in situ* from [RuX_2(arene)]$_2$ (X= Cl, I) and (R)-BINAP in a 5:1 mixture of methanol and benzene. The prochiral ketoximes **1a-f**, synthesized from the corresponding ketones, can exist as a mixture of *E* and *Z* isomers, and this mixture was used in the asymmetric hydrogenation reaction.

The hydrogenation reaction proceeds according to Scheme 1, affording primary amines in good chemical and moderate optical yields. Several by-products: i.e. alcohols **3** and secondary amines **4**, **5**, were formed in the reactions. The alcohols **3** likely arise from hydrogenation of the



	R_1	R_2
a	Ph	Me
b	Ph	Et
c	Ph	i-Pr
d	Ph CH_2	Me
e	2-naphthyl	Me
f	2-thienyl	Me

Scheme 1.

corresponding ketones which in turn can be produced by the hydrolysis of **1**. The beneficial effect of water on the catalytic process is discussed below. The secondary amine **4** may result from the dehydrogenation of methanol[5] generating formaldehyde which can then react with amines to give imines. Subsequent hydrogenation of imines can produce secondary amines **4**. The secondary amines **5** could be generated by the ruthenium catalyzed alkyl group exchange reactions[6] of primary amines **2**.

It is noteworthy that the activity of the catalysts and the reaction path depend significantly on the amount of water in the reaction mixture. When prepared under anhydrous conditions the catalyst, {(benzene)RuCl[(R)-BINAP]}Cl(**6**) showed modest activity (Table 1, run 1) and only secondary amines **4d**, **5d** were detected. When **6** was generated in the presence of water a mixture of primary amine **2d** and alcohol **3d** was obtained. The composition of the mixture depended on the amount of water added. (Table 1, runs 2, 3)

Table 1. The effect of water on the hydrogenation of the oxime of 1-phenyl-2-propanone (**1d**) with (**6**)[a].

Run No	Reaction media MeOH:C_6H_6:H_2O	Conversion (%)	Products(%) 2	3	4	5
1	8.7 : 0.3 -	40	-	-	16	8
2[b]	8.7 : 0.3 -	100	42	49	-	-
3	8.7 : 0.3 : 0.3	100	5	94	-	-

[a] Reaction conditions : 90°C, 24h, 1300 psi of hydrogen. Substrate concentration 0.22M, 1 mol% of catalyst.
[b] The catalyst was prepared from a MeOH-C_6H_6-H_2O (5:1:0.5) mixture and then dried under vacuum.

All subsequent reactions were carried out in the reaction media containing water. The only by-products formed were the alcohols **3**. Secondary amines **4** and **5** were detected in trace amounts in all cases. In order to avoid an undesirable excess of water, 3A° molecular sieves were added to the reaction mixture. As 1-phenyl-2-aminopropane **2d** is of commercial importance the hydrogenation of its precursor, **1d**, was chosen as the model reaction. The influence of different factors on the conversion of **1d** to **2d** and the optical yield is discussed below.

(a) Catalyst.

The results of the hydrogenation of 1-phenyl-2-propanone oxime (**1e**) are listed in Table 2. The catalysts were prepared *in situ* from $[Ru(arene)X_2]_2$, (arene= benzene, p-cymene; X=Cl, I), with

Table 2. Asymmetric hydrogenation of 1-phenyl-2-propanone oxime (**1d**) catalyzed by {RuCl(benzene)-(R)-BINAP}Cl (**6**) and {RuI(p-cymene)[(R)-BINAP]}I (**7**).[a]

Catalyst	Yield of 1-phenyl-2-propylamine [b] %	% ee [c]
6	76	29
6[d]	75	25
6[e]	57	22
7[f]	60	18

[a] Reaction conditions: 90°C, 24h., 1300 psi of hydrogen in MeOH-C_6H_6-H_2O (8.7: 0.2: 0.006), in the presence of 3A° molecular sieves . Substrate concentration 0.22 M.
[b] Isolated yield.
[c] % ee determined by ^1H NMR for mixture of MTPA derivatives of **2d** and **3d**.
[d] 2 mol % of catalyst.
[e] Catalyst was prepared using a 1:3 ratio of $[RuCl_2(benzene)]_2$ and BINAP.
[f] Solvent MeOH-dichloroethane-H_2O (8.7:0.3:0.06).
MTPA= α-methoxy-α-(trifluoromethyl)phenylacetic acid

{RuCl(benzene)[(R)-BINAP]}Cl (**6**) being the most effective catalyst for the asymmetric reduction of oximes. An increase of the molar ratio of catalyst/substrate did not improve the chemical yields or % enantiomeric excess, while the presence of an excess of added BINAP reduced both the yield and % ee.

(b) Solvent composition.

The best solvent mixture for the hydrogenation of 1-phenyl-2-propanone oxime (**1d**) was found to be a mixture of methanol-benzene (8.7-0.3) containing 0.006 vol% of water. A decrease in the polarity of the media resulted in a somewhat lower yield of the desired product without a significant effect on the ee values. (Table 3).

Table 3. Effect of solvent on the hydrogenation of 1-phenyl-2-propanone oxime (**1e**) with **6**.[a].

Solvent composition	Yield of **2e** (%)[b]	%ee [c].
MeOH-C_6H_6-H_2O (8.7:0.3:0.006)	76	29
EtOH-C_6H_6-H_2O (8.7:0.3:0.006)	68	18
MeOH-C_6H_6-H_2O (1 : 8 : 0.006)	54	27

[a] Reaction conditions: 90°C, 24h., 1300 psi of hydrogen in the precence of 3A°molecular sieves. Conversions: 100%. Substrate concentration 0.22M, 1 mol% of catalyst.
[b] Isolated yield.
[c] % ee determined by ^{1}H NMR for MTPA derivatives of a mixture of **2e** and **3e**.

(c) Temperature.

Lower yields of **2d** resulted with decreasing temperature. Surprisingly, the percent enantiomeric excess was also lower at reduced temperature (Table 4).

Having optimized conditions for the asymmetric hydrogenation, we successfully hydrogenated a number of aryl alkyl oximes. Good chemical yields and moderate optical yields were obtained in all cases (Table 5).

Table 4. Influence of the temperature on the hydrogenation of the 1-phenyl-2-propanone oxime (**1d**) with **6**.[a]

Temperature	Reaction time (h)	Yield of **2d** (%)[b]	% ee[c]
90	24	76	29
75	48	64	20
45 [d]	48	5	-

[a]Reaction conditions: 1300 psi of hydrogen , substrate concentration 0.22M, 1 mol% of catalyst ,in the presence of 3A° molecular sieves . 100% conversion, unless otherwise specified.
[b] Isolated yield.
[c] % ee determined by ^{1}H NMR for MTPA derivatives of a mixture of **2d** and **3d**.
[d] Conversion: 34%.

Table 5. Asymmetric hydrogenation of alkyl aryl oximes with **6**.[a]

Substrate	Reaction time(h)	Yield of amine (%) [b]	% ee[c] (Configuration)
1a	48	85	20(S)
1b	48	89	26(S)
1c	76	78	12(R)
1d	24	76	29(S)
1e	80	64	8(R)
1f[d]	48	48	12(S)

[a] Reactions conditions : 90°C and 1300 psi of hydrogen in the presence of 3A° molecular sieves , substrate (0.22M), 1 mol. % of catalyst. Conversion was 100% in all cases.
[b] Isolated yields.
[c] % ee determined by ^{1}H NMR for MTPA derivatives .
[d] Reaction temperature 110°.

The catalytic hydrogenation of oximes is very sensitive to changes in the structure of the substrate, affecting both the chemical yield and the extent of asymmetric induction. It is noteworthy that the % enantiomeric excess does not correlate directly with the steric bulk of alkyl substituents, and this may be due to the fact that *E/Z* ratios for oximes also depend on the same parameter[7].

In conclusion, although the % ee's are modest the chemical yields are good for the hydrogenation of oximes, and **6** is the best catalyst found thus far for the asymmetric process.

EXPERIMENTAL

General. The oximes were synthesized from the corresponding ketones and hydroxylamine liberated from hydroxylammonium chloride[7]. $[Ru(benzene)Cl_2]_2$ (Aldrich) and (R)-BINAP (Strem Chemicals, Inc.) were used as received. Gas chromatographic analyses were carried out on a Varian 3400 GC equipped with FID detector and an OV-17 column. 300 ^1H NMR spectra were recorded on a Varian XL 300 spectrometer.

Typical hydrogenation procedure. A suspension of $[Ru(benzene)Cl_2]_2$ (5 mg, 0.01 mmol) and BINAP (12 mg, 0.0204 mmol) in 2 ml MeOH-C_6H_6-H_2O (5:1:0.018) was degassed by three freeze-pump-thaw cycles and then stirred for 40 min at 60-65^{0}C under nitrogen. A solution of oxime (2 mmol) in 7 ml of degassed methanol[8] was added and the reaction mixture was transferred by syringe to a stainless steel autoclave, containing 1g of 3A° molecular sieves . The hydrogenation was performed under conditions specified in Tables 1-5. The hydrogenation products (mixtures of **2** and **3**) were isolated from the catalyst by distillation. Conversions were determined by GLC. The optical yields were measured by 300 MHz ^1H NMR for α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) derivatives[9]of mixtures of **2** and **3**. For all the obtained mixtures of the corresponding diastereomeric esters and amides distinct separation of the methoxy group signals was observed. Methoxy group signals of amides located within 3.34-3.44 ppm region and those of esters in 3.45-3.59 ppm area. As an example the spectrum of a mixture of (R)-MTPA-**2e** and (R)-MTPA-**3e** gave the following signals: 3.36 -(R)-MTPA -(S)-**2e**, 3.42-(R)-MTPA-(R)-**2e**, 3.455-(R)-MTPA--(R)-**3e**,3.575-(R)-MTPA -(R)-**3e**.

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