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Schiff Bases as Added Chiral Ligands for the $[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$ Catalysed Hydrogen-Transfer Reduction of Ketones with 2-Propanol

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ABSTRACT: *Ruthenium complexes generated in situ from $[Ru(C_6H_6)Cl_2]_2$ and chiral Schiff bases [derived from(1R,2R)-diaminocyclohexane] catalyse asymmetric hydrogen-transfer reduction of alkyl aryl ketones by 2-propanol to give the (S)-alcohol in up to 40% ee.*

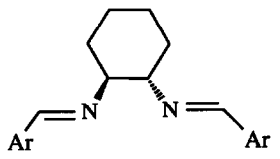
Asymmetric hydrogen-transfer reduction of ketones is an efficient method for the synthesis of chiral alcohols in optically active form.[1] In recent years major advances have been achieved in this field. The use of rhodium and iridium complexes with chiral nitrogen-containing ligands for the hydrogen-transfer reduction of alkyl aryl ketones was shown to give rise to optically active alcohols with moderate to high enantiomeric excesses.[1]

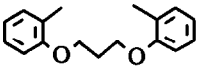
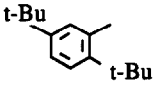
Little has been achieved thus far using ruthenium complexes for the asymmetric hydrogen-transfer reduction of ketones, an exception being that of Botteghi et al[2] who applied the $[H_4Ru_4(CO)_8$((-)-DIOP$_2]$ cluster for the enantiofacial transfer hydrogenation of ketones. Enantioselectivities in the range of 5-10% were achieved for most of the substrates used. Another report on enantioselective hydrogen-transfer reduction of ketones with Ru_2Cl_4((-)-DIOP$)_3$[3] claims 10% ee for the reduction of acetophenone with 2-propanol.

We now wish to report the asymmetric hydrogen-transfer reduction of ketones with isopropanol catalyzed by ruthenium complexes with chiral Schiff base ligands of (1R,2R)-diaminocyclohexane and aromatic aldehydes (Scheme 1). These and related Schiff base ligands have been used for several other asymmetric processes.[4,5]

SCHEME 1

L=



Ar	L
Ph	**1**
2MeO-C_6H_4	**2**
	**3**
	**4**
1-naphthyl	**5**
9-anthranyl	**6**
ferrocenyl	**7**

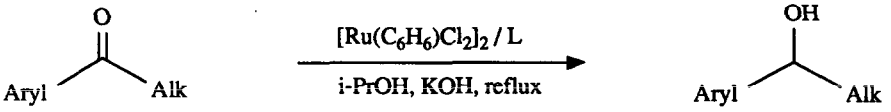
The required ligands can be synthesized in one step by condensation of commercially available (1R,2R)-diaminocyclohexane and an appropriate aldehyde. The relative bulkiness of the ligand can be easily modified by varying the aryl unit of the aldehyde.

Arene ruthenium complexes with chiral phosphine ligands (e.g., BINAP) have been successfully used for the hydrogenation of carbonyl compounds.[6] The hydrogen transfer reduction of ketones involving chiral diphosphine ruthenium complexes has appeared while this work was in progress.[7]

The catalysts used in the present study were prepared *in situ* from $[Ru(C_6H_6)Cl_2]_2$ and the corresponding chiral ligand and then activated in refluxing isopropanol with potassium hydroxide. It is known[8] that reaction of $[Ru(Arene)Cl_2]_2$ with chelating imines gives rise to the displacement of a chlorine atom in the coordination sphere of ruthenium by imine nitrogen with cleavage of the dimeric complex and formation of a cationic complex with two imine nitrogens, chlorine and arene coordinated to ruthenium. Therefore, it is likely that ruthenium-Schiff base complexes $[Ru(C_6H_6)(diimine))Cl]Cl$ are first formed in the reaction mixture and are subsequently converted into catalytically active species by use of potassium hydroxide in refluxing isopropanol. No reaction was observed in the absence of base even after extended reaction times.

Aryl alkyl ketones are reduced in refluxing 2-propanol in the presence of 1 mol % of catalyst (1-10 h depending on the chiral ligand and substrate) affording the corresponding S-alcohols in 80-90% yields (Equation 1).

Equation 1.



Acetophenone was chosen as a model substrate to examine the influence of steric bulk and coordination properties of the ligand on the outcome of the reaction. The hydrogen transfer reduction of acetophenone with $[Ru(C_6H_6)Cl_2]_2$ / **1** (Scheme 1, Ar=Ph) afforded 1-phenylethanol in low optical purity (8% ee, Table 1). Introduction of a methoxy substituent which is able to give an additional coordination to ruthenium in the 2-position of the aromatic ring of the aldehyde (L=**2**) resulted in an increase of the optical yield of the reaction to 20% ee. Further increase in the conformational rigidity of the ruthenium-imine complex, by connecting two aromatic rings with a propylenedioxy bridge (L=**3**), did not enhance stereoselectivity of the reaction (16 % ee). A diimine ligand derived from an aromatic aldehyde with a more bulky substituent (L=**5** , aryl= naphthyl) gave a catalyst with increased stereoselectivity (ee=28%). If the bulkiness of the diimine ligand (L=**4**) was increased by introducing a tert-butyl group in the ortho position of aromatic ring, the process became less stereoselective (ee=22%). The best results in asymmetric hydrogen-transfer hydrogenation achieved for the catalyst precursor with L=**5** (and similar with L=**6**) can be explained by the ability of the second aromatic ring of the naphthyl or anthranyl substituent to coordinate to ruthenium providing additional rigidity to the catalyst.

TABLE 1. Table 1. Asymmetric hydrogen-transfer reduction of acetophenone catalyzed by $[Ru(C_6H_6)Cl_2]_2$ / L complexes.

Ligand	Chemical yield[a]	% ee (Configuration)[b]
1	82	8 (S)
2	91	20 (S)
3	85	16 (S)
4	84	22 (S)
5	81	28 (S)
6	87	25 (S)
7	69	23 (S)

[a] isolated yield..

[b] determined by 300MHz ^{1}HNMR for α-(methoxy)-α-(trifluoromethyl)phenylacetic acid derivatives.

The catalyst precursor generated from $[Ru(C_6H_6)Cl_2]_2$ and **5** was found to be the most effective for asymmetric hydrogen-transfer reduction of alkyl aryl ketones. The results of the use of the Ru-**5** complex for the hydrogen-transfer reduction of different alkyl aryl ketones are listed in Table 2, with the highest percent enantiomeric excess achieved (40% ee of the S enantiomer) for the reduction of 2-methylpropiophenone.

The application of Ru-**5**, Ru-**6** and Ru-**7** complexes for the hydrogen-transfer hydrogenation of acetophenone gave 1-phenylethanol with similar enantiomeric purity (28, 25 and 23% respectively). To distinguish the stereodifferential ability of **5, 6** and **7**, they were used as chiral ligands for the hydrogen-transfer hydrogenation of 2-methyl-propiophenone (Table 3). The best enantioselectivity was realized using **5** as the chiral ligand.

TABLE 2.

Hydrogen-transfer reduction of alkyl aryl ketones catalyzed by $[Ru(C_6H_6)Cl_2]_2$ -5

Ketone	Chemical yield[a]	% ee (Configuration)[b]
acetophenone	89	28 (S)
1-propiophenone	85	29 (S)
2-methylpropiophenone	85	40 (S)
2,2-dimethylpropiophenone	82	26 (S)
2-acetonaphthone	74	16 (S)
α-tetralone	75	20 (S)

[a] isolated yield..

[b] determined by 300 MHz ^1H NMR for α -methoxy- α-(trifluoromethyl)phenylacetic acid derivatives.

TABLE 3. Hydrogen-transfer reduction of 2-methylpropiophenone catalysed by $[Ru(C_6H_6)Cl_2]_2$ -5.,6,7.

L	Chemical yield[a]	% ee (Configuration)[b]
5	85	40 (S)
6	84	35 (S)
7	86	28 (S)

[a] isolated yield.

[b] determined by 300MHz ^1H NMR for α-methoxy-α-(trifluoromethyl)phenylacetic acid derivatives.

In conclusion, the catalyst system $[Ru(C_6H_6)Cl_2]_2$ effects the hydrogen-transfer reduction of alkyl and ketones in moderate enantiomeric excess. Studies are in progress to improve the enantioselectivity and determine the mode of induction in this important reaction.

EXPERIMENTAL

General: Gas chromatographic analysis were carried out on a Varian 3400 GC equipped with FID detector and OV-17 column. ^1H NMR spectra were recorded on a Varian XL 300 or Gemini 200 MHz spectrometers using $CDCl_3$ as a solvent. $[Ru(C_6H_6)Cl_2]_2$, (1R,2R)-(-)1,2-diaminocyclohexane, alkyl aryl ketones and aromatic aldehydes were purchased from Aldrich Chemical Co. and used as received. 2,5-Bis-*tert*-butylbenzaldehyde was prepared by formylation of 1,4-bis-*tert*-butylbenzene.[9] The hydrogen-transfer reduction experiments were carried out under nitrogen. The optical purities of alcohols prepared were determined by 300MHz ^{1}HNMR for α-methoxy-α-(trifluoromethyl)phenylacetic acid derivatives.[10] Melting point determinations were made using a Fisher-Johns apparatus and uncorrected values are reported. Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ.

Synthesis of Schiff base ligands: A mixture of (1R,2R)-(-)1,2-diaminocyclohexane (100 mg, 0.88 mmol) and aromatic aldehyde (1.96 mmol)in CH_2Cl_2(2 ml) was stirred in the presence of 3Å molecular sieves for 12h. The molecular sieves were removed by filtration and the filtrate was concentrated by rotary evaporation. The residue was crystallised from hexane (for **2** or **4**), hexane:benzene (for **1** or **5**), or hexane: CH_2Cl_2 (for **6** or **7**). The following compounds were prepared by this procedure:

(1R,2R)-Bis-diphenylaminocyclohexane(**1**), 91% yield, white solid, m.p. 99-100°; ^1H NMR 1.4-1.6(m, 2H), 1.7-2.0(m, 6H), 3.3-3.5(m, 2H), 7.2-7.4(m, 6H), 7.5-7.65(m,4H), 8.2(s,2H); $[\alpha]_D^{25}$-263°(c 0.19, methanol), Found: C 83.04, H 7.72, $C_{20}H_{22}N_2$ requires C 82.72, H 7.64.

(1R,2R)-Bis-2-methoxyphenyliminocyclohexane(2), 89% yield, white solid, m.p.105-106°;^{1}H NMR 1.4-1.6(m,2H), 1.7-2.0(m,6H), 3.3-3.5(m,2H), 3.7(s,6H), 6.7-6.9(m,4H), 7.15-7.35(m,2H), 7.7-7.8(m,2H), 8.1(s,2H); $[\alpha]_D^{25}$-69.2°(c 0.5, methanol), Found: C 75.79, H 7.75, $C_{22}H_{26}O_2N_2$ requires C 75.40, H 7.46.

(1R,2R)-Bis-2,5-di-tert-butylphenyliminocyclohexane(4), 92% yield, white solid, m.p. 189-190°, ^{1}H NMR 0.95(s,18H), 1.3(s,18H), 1.45-1.6(m,2H), 1.6-1.75(m,2H), 1.75-2.0(m,4H), 3.4-3.6(m,2H), 7.15(s,4H), 7.35(s, 2H), 9.05(s,1H), $[\alpha]_D^{25}$-254° (c 0.3, methanol): Found: C 84.31, H 10.25, $C_{36}H_{54}N_2$ requires C 83.99, H 10.25.

(1R,2R)-Bis-1-naphthyliminocyclohexane(5), 87% yield, white solid, m.p. 131-132°, ^{1}H NMR: 1.45-1.76(m,4H), 1.8-2.5(m,4H), 3.5-3.75(m,2H), 7.1-7.25(m,2H), 7.3-7.4(m,4H), 7.6-7.8(m,6H), 8.55(d,2H), 8.90(s,2H), $[\alpha]_D^{25}$-202° (c 0.25, CH_2Cl_2); Found: C 86.27, H 6.71, $C_{28}H_{26}N_2$ requires C 82.12, H 6.71.

(1R,2R)-Bis-9-anthranyliminocyclohexane(6), 85% yield, yellow crystylline solid, m.p. 239-241°, ^{1}H NMR: 1.6-1.8(m,2H), 2.0-2.15(m,2H), 2.15-2.3(m,4H), 3.9-4.0(m,2H), 6.7-6.9(m,4H), 7.1-7.3(m,4H), 7.85(d,5Hz,4H), 8.15(d,4H), 8.4(s,2H), 9.35(s,2H), $[\alpha]_D^{25}$+283°(c 0.3, CH_2Cl_2); Found C 88.13, H 5.80, $C_{36}H_{30}N_2$ requires C 88.13, H 6.16.

(1R,2R)-Bis-ferrocenyliminocyclohexane(7), 89% yield, red crystalline solid, m.p. 193-195°, 1.3-1.5(m,2H), 1.5-1.75(m,4H), 1.8-1.9(m,2H), 3.95(s,10H), 4.2(s,4H), 4.5(s,2H), 4.6(s,2H), 8.1(s,2H), $[\alpha]_D^{25}$-114°, (c 0.32, CH_2Cl_2), Found C 65.90, H 6.21, $C_{28}H_{30}N_2Fe$ requires C 66.43, H 5.97.

Ligand 3 was prepared in situ as a ruthenium complex starting from (1R,2R)-diaminocyclohexane and bis-(2-formylphenyloxy)propane. A mixture of $[Ru(C_6H_6)Cl_2]_2$ (10 mg , 0.020 mmol) , (1R,2R)-1,2-diaminocyclohexane (4,6 mg, 0.04 mmol) and bis-(2-formylphenyloxy)propane (11.5 mg, 0.04 mmol) in EtOH (2 ml) was stirred under nitrogen at 60° for 0.5 h. The solvent was then evaporated under reduced pressure and the newly synthesized ruthenium complex was used for the hydrogen-transfer reduction.

Hydrogen-transfer reduction: A suspension of $[Ru(C_6H_6)Cl_2]_2$ (5mg, 0.01 mmol) and the Schiff base ligand (0.02 mmol) in i-PrOH (2 ml) was degassed and then heated under reflux for 0.5 h. To the reaction mixture (through a rubber septum), was added 0.04 mmol of KOH (as 0.02M solution in i-PrOH, 2ml) and reaction mixture was refluxed for an additional 0.5h. The ketone (2 mmol) was then added, and when reaction was complete (2-8h, monitored by GC), the solvent was evaporated and residue was then subjected to bulb to bulb distillation.

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