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# ENANTIOSELECTIVE TRANSFER HYDROGENATION CATALYZED BY IRIDIUM(I) COMPLEXES WITH NITROGEN DONOR LIGANDS

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## Summary

The reduction of prochiral ketones by hydrogen transfer from isopropanol is catalyzed by cationic iridium(I) complexes containing optically active Schiff bases. Optical yields of up to 33% have been obtained.

## Introduction

Hydrogen transfer from a donor to an acceptor molecule provides a method of reduction of multiple bonds and can be catalyzed by heterogeneous [1] or homogeneous systems. Among the latter, good activity is showed by rhodium, ruthenium and iridium complexes containing phosphines and DMSO as ligands, especially for the reduction of olefins [2], ketones [3—6], $\alpha,\beta$-unsaturated ketones [7], $\alpha,\beta$-unsaturated carboxylic acids [8—9], Schiff bases [10] and nitro-derivatives [11]. However, reduction of ketones [12], $\alpha,\beta$-unsaturated ketones [13] and Schiff bases [14] can be better accomplished by the use of complexes of iridium(I) containing nitrogen donor ligands, such as 2,2′-bipyridine, 1,10-phenanthroline and their derivatives. Furthermore, iridium(I) complexes with Schiff bases as ligands are effective species for transfer hydrogenation from alcohols to ketones, as we previously reported in a preliminary communication [15]. In particular, use of the optically active Schiff base 2-pyridinalphenylethylimine (PPEI) makes possible the asymmetric reduction of prochiral ketones to optically active alcohols [15].

In this paper we describe a more detailed study of such enantioselective reductions.

## Results and discussion

The chiral compounds, we used as catalyst precursors were cationic species of the type $[Ir^{I}(COD)chel]^{+}ClO_4^{-}$ (I) [COD = 1,5 cyclooctadiene; chel = (+)-

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and (—)2-pyridinalphenylethylimine (PPEI); (+) and (—)2-pyridinal-3-(iminomethyl)pinane (PIMP)]. The ligands can be readily obtained by condensation of pyridine 2-aldehyde with (+) or (—)α-phenylethylamine (chel = PPEI) and (+)or (—)3-(aminomethyl)pinane (chel = PIMP) respectively. The syntheses of (+) and (—)[Ir(COD)PPEI]$^+ClO_4^-$ complexes were reported previously [16]. The corresponding PIMP derivatives we made in a similar way by treatment of ethanol solution of $[Ir(COD)Cl]_2$ with the chelating ligand followed by precipitation as perchlorate.

The formation of catalytically active species from the complexes I requires the displacement of the COD from the coordination sphere of the metal, and this can be carried out as in the case of the analogous compounds with 2,2′-bipyridine and 1,10-phenanthroline [11] as ligands.

The prochiral ketones used together with the hydrogenation results are reported in Table 1, in which the experimental conditions are also indicated.

Both complexes proved to be good catalysts (conversions 80% in 120—210 min); the iridium PPEI is more selective than the iridium PIMP complex, although the reduction rates are practically the same.

As for the influence of the substrate, it can be seen that alkyl phenyl ketones are reduced with a higher selectivity than the alkyl methyl ketones, as noted for other homogeneous catalytic systems [6,17]. Another difference between the aromatic and aliphatic ketones relates to the configuration of the reduction products, as the alcohols obtained in the former case always have the *R* configuration, whereas those in the latter case have the *S* configuration. Optical yields do not seem to be seriously affected by steric hindrance in the substrate.

Both the catalytic activity and the optical yield are also related to the KOH concentration and the percentage of conversion. The influence of KOH concen-

TABLE 1

REDUCTION OF PROCHIRAL KETONES BY HYDROGEN TRANSFER FROM ISOPROPANOL WITH [Ir(COD)chel]$^+ClO_4^-$ AS CATALYST PRECURSOR

| Substrate | Time (min) | Conversion (%) | $[\alpha]_D^T$ (deg) | e.e. [a] (%) | Configuration |
|---|---|---|---|---|---|
| *Precursor (—)[Ir(COD)PIMP]$^+ClO_4^-$* | | | | | |
| $C_6H_5COCH_3$ | 120 | 84 | 0.59 | 1.5 | *R*(+) |
| $C_6H_5COCH_2CH_3$ | 150 | 96 | 1.75 | 6.5 | *R*(+) |
| $C_6H_5CO(CH_2)_2CH_3$ | 180 | 88 | 2.34 [b] | 7.2 | *R*(+) |
| $C_6H_5COCH(CH_3)_2$ | 150 | 96 | 0.30 [c] | 9.5 | *R*(+) |
| $CH_3CO(CH_2)_5CH_3$ | 180 | 87 | 0.21 | 2.5 | *S*(+) |
| *Precursor (+)[Ir(COD)PPEI]$^+ClO_4^-$* | | | | | |
| $C_6H_5COCH_3$ | 120 | 91 | 5.65 | 13.6 | *R*(+) |
| $C_6H_5COCH_2CH_3$ | 180 | 96 | 4.96 | 18.4 | *R*(+) |
| $C_6H_5CO(CH_2)_2CH_3$ | 150 | 89 | 6.84 [b] | 21.2 | *R*(+) |
| $C_6H_5COCH(CH_3)_2$ | 150 | 96 | 0.72 [d] | 19.8 | *R*(+) |
| $CH_3CO(CH_2)_5CH_3$ | 180 | 84 | 0.44 | 4.8 | *S*(+) |
| $CH_3CO(CH_2)_8CH_3$ | 210 | 80 | 0.03 [e] | 7.5 | *S*(+) |

Reactions conditions: $4 \times 10^{-5}$ mol of [Ir(COD)chel]$^+ClO_4^-$ in 100 ml i-PrOH; [KOH]/[cat.] = 3.6, [subs.]/[cat.] = 1000. [a] e.e. % = optical yield (see experimental section); [b] λ = 546 nm. [c] Measured in solution (*c* = 6.67, diethyl ether). [d] Measured in solution (*c* = 7.62 in diethyl ether). [e] Measured in solution (*c* = 3.99 in benzene).

TABLE 2

REDUCTION OF PROPIOPHENONE BY HYDROGEN TRANSFER WITH (+)[Ir(COD)PPEI]$^+ClO_4^-$ AS CATALYST PRECURSOR

| [KOH]/[cat.] | Time (min) | Conversion (%) | $[\alpha]_D^T$ | e.e. (%) [b] |
|---|---|---|---|---|
| 1.2 [a] | 20 h | 96 | 6.81 | 26.5 |
| 1.4 | 480 | 95 | 6.62 | 25.2 |
| 1.8 | 210 | 95 | 4.90 | 18.0 |
| 3.6 | 180 | 96 | 4.96 | 18.4 |
| 7.2 | 120 | 94 | 5.21 | 19.8 |

Reaction conditions: $4 \times 10^{-5}$ mol of (+)[Ir(COD)PPEI]$^+ClO_4^-$ in 100 ml i-PrOH; [subst.]/[cat.] = 1000. [a] [subst.]/[cat.] = 500. [b] e.e. (%) = optical yield (see Experimental section).

tration is shown in Table 2, which summarizes the results obtained at various [KOH]/[cat] ratios for the reduction of the propiophenone with (+)[Ir(COD)-PPEI]$^+ClO_4^-$ as catalyst precursor. It will be seen that the reduction rate increases on increasing the [KOH]/[cat] ratio, this being more pronounced in the range [KOH]/[cat] 1.2—2. Correspondingly, the enantiomeric excess falls towards a value, which then stays almost constant for higher ratios.

Table 3 shows that the optical yield decreases as the degree of conversion increases. Such a decrease can be ascribed to racemisation of the alcohol catalyzed by the metal complex. No racemisation occurs in the absence of the catalyst under our conditions.

Finally, an increase in the enantiomeric excess is observed on increasing the [i-PrOH]/[subst.] ratio (Table 3), owing to the fact that under such conditions the reverse reaction is less thermodynamically favoured.

The enantioselectivity observed for our catalysts can be explained taking account of the equilibria between the diastereoisomeric forms of the catalytically active species (Scheme 1). Each of them has two chiral centres, the pentacoordinated iridium(I) and the asymmetric carbon atom in the ligand. The

TABLE 3

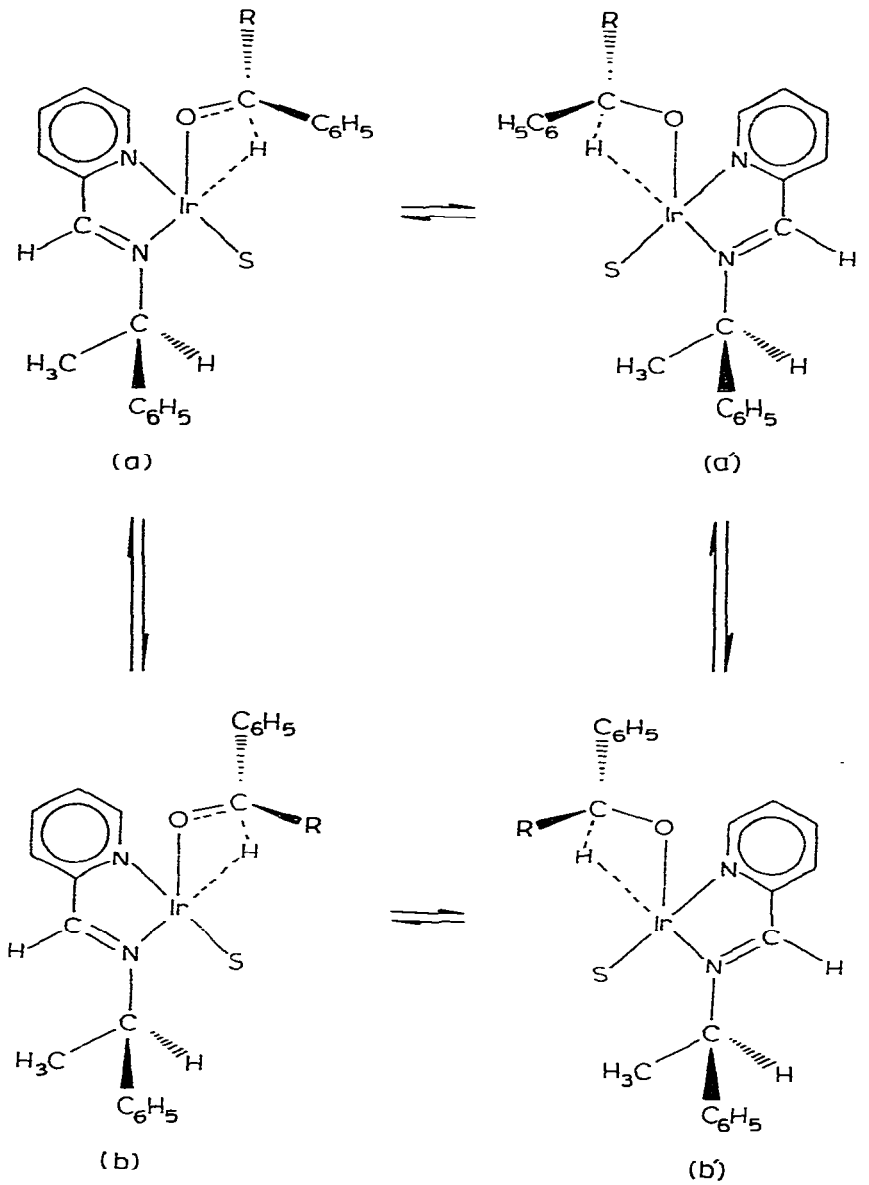
REDUCTION OF PROPIOPHENONE BY HYDROGEN TRANSFER WITH (+)[Ir(COD)PPEI]$^+ClO_4^-$ AS CATALYST PRECURSOR

| [KOH]/[cat.] | Conversion (%) | e.e. (%) |
|---|---|---|
| 1.4 | 60 | 32.5 |
| 1.4 | 80 | 28.7 |
| 1.4 | 95 | 25.2 |
| 1.4 [a] | 75 | 33.0 |
| 1.4 [a] | 99.9 | 30.0 |
| 1.8 | 75 | 22.1 |
| 1.8 | 95 | 18.0 |
| 3.6 | 70 | 22.2 |
| 3.6 | 96 | 18.4 |

Reaction conditions: $4 \times 10^{-5}$ mol of (+)[Ir(COD)PPEI]$^+ClO_4^-$ in 100 ml i-PrOH; [subst.]/[cat.] = 1000; [i-PrOH]/[subst.] = 32.5. [a] 250 ml i-PrOH [i-PrOH]/[subst.] = 81.5.

SCHEME 1

PROPOSED MECHANISM OF ENANTIOSELECTIVE REDUCTION OF KETONES WITH ISOPROPANOL (S) IN THE PRESENCE OF $Ir^{I}$ COMPLEXES WITH SCHIFF BASES




optical yield will depend on both the equilibrium ratios for the diastereoisomers and the orientation of the ketone itself in the transition state, in which a new chiral centre is created by the hydride transfer. If this orientation is specific, the enantiomeric excess must depend on the equilibrium between (a) and (a') or between (b) and (b').

Since no striking variation in the optical yield is observed on increasing the bulk of the substituents at the prochiral centre (Me < Et < n-Pr < i-Pr), the

ketone orientation is probably highly selective. In contrast, a significant variation in the enantiomeric excess is observed on varying the nature of the chiral ligand, and this is related to the equilibrium ratio between (a) and (a′) or (b) and (b′). Thus larger values of optical yield would be obtained by shifting the diastereoisomeric ratio far over to one side by changing the substituents at the chiral carbon atom of the ligand. As reported by Brunner [18], it is possible to vary the equilibrium induction at the chiral metal atom over a wide range by changing the substituents in a given asymmetric ligand. A similar investigation is now in progress in our laboratory.

## Conclusions

The reported reactions represent the first example of enantioselective hydrogen transfer reduction of ketones in the presence of iridium complexes containing a chiral nitrogen donor ligand. These catalyst systems are more active than the rhodium and ruthenium-phosphine derivatives previously used in asymmetric C=O hydrogenation and the optical yields are moderately good and can probably be improved.

## Experimental

### *Syntheses of the ligands*

2-Pyridinalphenylethylimine (PPEI) was prepared as described in ref. [12]. 2-Pyridinal-3-(iminomethyl)pinane (PIMP). 1 g (5 mmol) or (+) or (—)3-(aminomethyl)pinane hydrochloride (97%) in EtOH (95%) was treated with 0.2 g (5 mmol) of NaOH (s), and after the complete dissolution of NaOH the NaCl was filtered off and 0.5 ml (5 mmol) of freshly distilled pyridine-2-aldehyde was added to the filtrate. The solution was set aside for 1 h at 40°C then used directly for the subsequent reactions, without isolation of the ligand.

### *Preparation of complexes*

The complexes were prepared under nitrogen using deaerated solvents and were dried in vacuo at room temperature. The complexes $[Ir(COD)Cl]_2$ and (+) and (—)$[IrCOD(PPEI)]^+ClO_4^-$ were synthesized by published methods [19,16].

*(+)[Ir(PIMP)COD]$^+ClO_4^-$*. 0.25 g (0.37 mmol) of $[Ir(COD)Cl]_2$ was suspended in $CH_3OH$ (6 ml) and treated dropwise with an ethanolic solution of the PIMP (obtained from (+)3-(aminomethyl)pinane) to give a deep violet solution. After stirring for 10 min, addition of solid $NaClO_4$ caused an immediate precipitation of the microcrystalline complex, which was filtered off and washed with water and diethyl ether. The levo isomer was similarly prepared starting from the (—)3-(aminomethyl)pinane.

(+)$[Ir(COD)PIMP]^+ClO_4^-$. Found: C, 44.7; H, 5.32; N, 4.06. $C_{25}H_{36}IrN_2ClO_4$ calcd.: C, 45.7; H, 5.52; N, 4.26%. $[\alpha]_D^{20}$ + 111 ($c = 1.53 \times 10^{-2}$ in $CH_2Cl_2$).

(—)$[Ir(COD)PIMP]^+ClO_4^-$. Found: C, 44.9; H, 5.30; N, 4.16%. $[\alpha]_D^{20} = -111$ ($c = 1.53 \times 10^{-2}$ in $CH_2Cl_2$).

### *Materials*

Isopropanol (C. Erba) was distilled before use. Acetophenone (Riedel),

TABLE 4

MAXIMUM ROTATORY POWER REPORTED IN THE LITERATURE FOR THE ALCOHOLS OBTAINED

| Alcohol | $[\alpha]_D^T$ (deg.) | $T$ (°C) | Medium | Ref. |
|---|---|---|---|---|
| $C_6H_5CH(OH)CH_3$ | 44.2 | 25 | neat | 20 |
| $C_6H_5CH(OH)CH_2CH_3$ | 28.1 | 22 | neat | 21 |
| $C_6H_5CH(OH)(CH_2)_2CH_3$ | 36.6 [a] | 40 | neat | 22 |
| $C_6H_5CH(OH)(CH)(CH_3)_2$ | 47.7 | 20 | $c$ = 6.8, diethyl ether | 23 |
| $CH_3CH(OH)(CH_2)_5CH_3$ | 9.9 | 17 | neat | 24 |
| $CH_3CH(OH)(CH_2)_8CH_3$ | 10.9 | 20 | benzene | 24 |

[a] $\lambda$ = 546 nm.

propiophenone (Ega), n-butyrophenone (Aldrich), iso-butyrophenone (Aldrich), 2-octanone (Fluka) and 2-undecanone (Ega) were purified by distillation under reduced pressure and stored under an inert atmosphere.

*Procedure*

Appropriate amounts of the complexes (usually $4 \times 10^{-5}$ mol) were suspended in 100 ml of isopropanol and oxidized with air at room temperature. The orange solutions were transferred to a three-necked flask and heated under reflux in a nitrogen stream. Appropriate amounts of deareated isopropanol solution of KOH were added to the boiling solution. After 30 min the distilled and deareated substrate was added, and the mixture was refluxed, the progress of the reaction being monitored by GLC of samples removed under nitrogen at appropriate times. (The withdrawn samples were immediately oxidized by air and the reaction thus stopped.) The isopropanol was evaporated off and the product was isolated by distillation at reduced pressure.

The composition of the distillate was determined by GLC. The optical rotations of the resulting alcohols (neat or solution) were measured at the temperature for which the maximum value of specific rotation is known. The optical purities, calculated from values for the pure enantiomers listed in Table 4, were corrected for the presence of unreacted material. In the reduction of propiophenone, the e.e. values were corrected by using a plot of the optical activity of alcohol-ketone mixture against the alcohol concentration.

GLC analyses were performed on Dani 3400 and 6800 instruments Rotatory powers were measured with a Perkin-Elmer 141 polarimeter.

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