# Asymmetric Hydrogen Transfer Reactions Promoted by Homogeneous Transition Metal Catalysts

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## 1. Introduction

The reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst is known as hydrogen-transfer reaction or transfer hydrogenation (H-transfer).[1]

The process entails hydrogen abstraction from the reagent (hydrogen donor) by means of the catalyst, followed by (or in concert with) hydrogen addition to the unsaturated functional group of the substrate (hydrogen acceptor). This can be generalized as in eq 1.

$$DH_2 + A \overset{cat}{\rightleftharpoons} D + AH_2 \qquad (1)$$

$DH_2$ = hydrogen donor; A = hydrogen acceptor

Several different substrates have been successfully reduced by transfer hydrogenation in the presence of both heterogeneous and homogeneous catalysts.[1-5] The list of hydrogen acceptors (H-acceptors) includes ketones, $\alpha,\beta$-unsaturated carbonyl compounds, $\alpha,\beta$-unsaturated acids and esters, and imines and nitro compounds.

In hydrogen-transfer reactions the hydrogen source must be different from dihydrogen. Most of the reagents employed are organic molecules: unsaturated hydrocarbons such as cyclohexene or cyclohexadiene, primary or secondary alcohols like methanol, benzyl alcohol, or propan-2-ol, and formic acid and its salts have been successfully used to this purpose. The use of inorganic reagents like hydrazine is less frequent.[2]

The use of hydrogen donors had some advantages over the use of molecular hydrogen since it avoids the risks and the constraints associated with this reagent as well as the necessity of pressure vessels. Additionally, rate and selectivity of the reaction can be favorably affected by selecting the most appropriate hydrogen donor.

Chiral nonracemic hydrogen donors can be profitably employed as chirality sources for inducing enantioselectivity in the product, thus providing new routes to accomplish an asymmetric process. This expands the potential of asymmetric H-transfer and makes it more versatile than asymmetric catalytic $H_2$-hydrogenation.

In spite of these valuable features, hydrogen-transfer reduction with homogeneous catalysts has attracted much less attention than homogeneous hydrogenation during past years.[1,2] This can be in part a consequence of the low catalytic activity displayed by the first generation catalysts (e.g. $[RuCl_2(PPh_3)_3]$) which required high reaction temperature,[6] whereas homogeneous hydrogenation catalysts like $[RhCl(PPh_3)_3]$ were active under much milder conditions.[7,8]

In recent years, major advances have been achieved in this field. The discovery of more active catalysts[9-11] and more efficient hydrogen donors[12,13] has given the possibility of obtaining high reaction rates under mild conditions. The scope of transfer-hydrogenation reactions has been extended to include new substrates:

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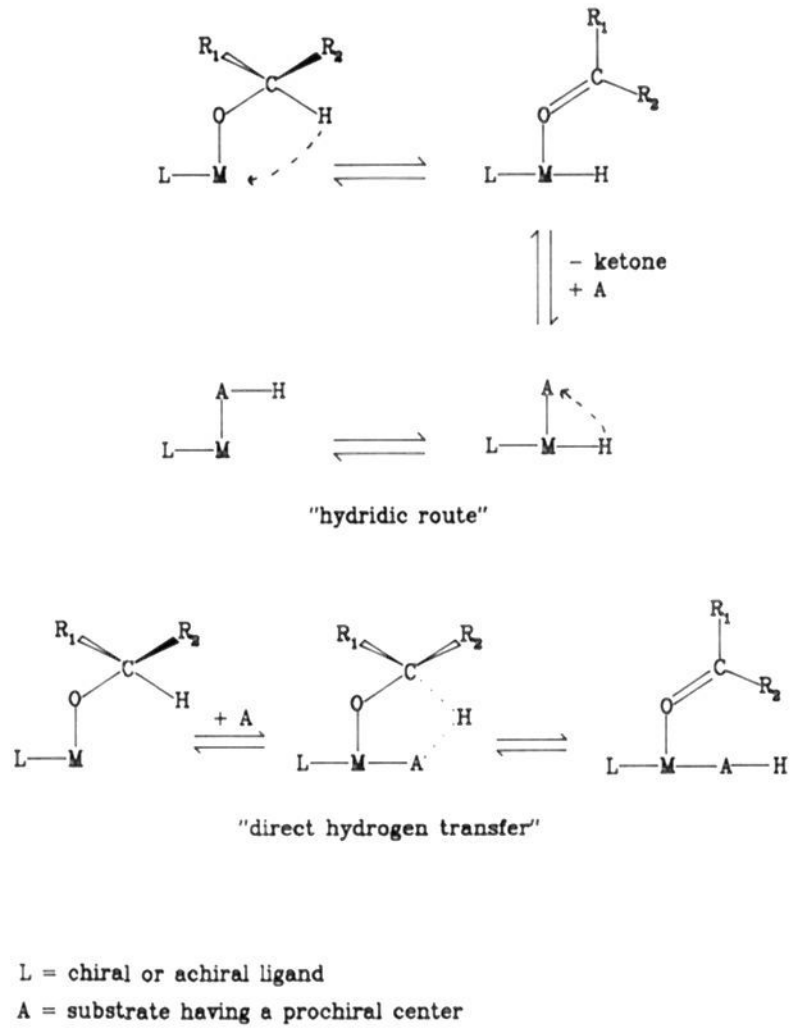



**Figure 1.** Possible paths for the hydrogen-transfer reactions.

epoxides have been selectively reduced to alcohols even in the presence of additional unsaturations like carbon–carbon or carbon–oxygen double bonds.[13,14] The introduction of a phase-transfer technique in transfer hydrogenation resulted in an easy recovery and recycling of the catalyst.[15,16]

The history of asymmetric transfer hydrogenation is quite similar. While until 1981 the optical yields were not higher than 20% ee[2] and consistently lower than the ones obtained in catalytic hydrogenation, quite recently ee's higher than 90% have been obtained in some cases.[12a,17-19] Presently, asymmetric hydrogen transfer can be quoted at the same level as asymmetric hydrogenation for several substrates.

In this review, asymmetric hydrogen transfer reactions are classified according to the nature of catalyst, hydrogen acceptor, and hydrogen donor. Within each type of reaction, the influence of chiral auxiliaries, metal ions, and substrates are examined, starting with chiral phosphine based catalysts. When possible, suggested reaction mechanisms and catalytic cycles are presented and discussed in more detail.

The review covers pertinent papers published before June 1991. Some unpublished results are also enclosed.

## *2. Discussion*

### 2.1. Classification of Asymmetric Hydrogen Transfer Reactions

There are two basic ways by which enantioselective hydrogen transfer can be achieved: enantioface selection by means of a chiral catalyst on achiral (often referred to as prochiral) substrates or enantiomer selection (often referred to as kinetic resolution) of a chiral racemic compound.

The chiral catalyst can be substituted as well by the combination of an optically active hydrogen donor with an achiral catalyst or, in more sophisticated modifications of these basic processes, enantioface selection can be coupled with kinetic resolution. Both H-acceptors and H-donors can undergo kinetic resolution in the presence of chiral catalysts resulting in scalemic products.[20]

Consequently, there are several modes to effect an enantioselective H-transfer, and according to a classification introduced some years ago,[3] the following basic types can be distinguished:

$$DH_2 + A(p) \overset{cat^*}{\rightleftharpoons} D + AH_2^* \quad (2)$$

$$DH_2^* + A(p) \overset{cat}{\rightleftharpoons} D(p) + AH_2^* \quad (3)$$

$$DH_2^* + A(p) \overset{cat^*}{\rightleftharpoons} D(p) + AH_2^* \quad (4)$$

$$2DH_2(r) + A \overset{cat^*}{\rightleftharpoons} DH_2^* + D(p) + AH_2 \quad (5)$$

$$DH_2 + 2A(r) \overset{cat^*}{\rightleftharpoons} D + AH_2^* + A^* \quad (6)$$

$$2DH_2(r) + A(p) \overset{cat^*}{\rightleftharpoons} D + DH_2^* + AH_2^* \quad (7)$$

where cat* = chiral nonracemic catalyst; $DH_2^*$ = chiral nonracemic hydrogen donor; A(p) = hydrogen acceptor having a "prochiral" center; D(p) = dehydrogenated hydrogen donor having a "prochiral" center; $DH_2(r)$ = racemic mixture of the hydrogen donor; A(r) = racemic hydrogen acceptor. An additional way to obtain an enantioselective H-transfer relies upon the ability of the chiral catalyst to discriminate between two enantiotopic reactive groups in the substrate. This process has not been explored so far but deserves particular attention since in principle it may succeed to asymmetrize achiral substrates with meso structures.

Diastereoselective processes are not included in this review and are not treated in detail.

The most common way to accomplish an asymmetric H-transfer is through enantioface discrimination. This process gives the chance to exploit both simple and double enantioselection, according to the fact that the chiral information resides only in the catalyst (eq 2) or in the H-donor (eq 3) or in both (eq 4). Most of the reactions we are going to deal with fall within this field.

Enantiomeric enrichment of racemic H-donors can take place in the presence of chiral catalysts (eq 5) and this has been observed in several instances.[21] Note that in most cases when the forward reaction corresponds to a kinetic resolution, the reverse is an enantioface discriminating process. The enzyme–coenzyme lactic acid dehydrogenase-nicotinamide adenine nucleotide operates the interconversion between pyruvic and lactic acid according to this scheme with complete enantioselectivity.[22]

Enantiomer discriminating H-transfers are particularly interesting since, when the appropriate experimental conditions are met, kinetic resolution and enantioselective reduction may occur simultaneously, producing two different optically active compounds in a single reaction. There are two ways to achieve this goal in the presence of chiral catalyst: either by reducing a racemic H-acceptor with a deficit of H-donor[3] (eq 6) or by reacting an excess of a racemic H-donor with a prochiral H-acceptor[23] (eq 7).

Only one isolated example of asymmetric intramolecular H-transfer has been reported so far. This involves isomerization of a chiral allyl alcohol to an achiral ketone[3] according to eq 5. Kinetic resolution of the substrate occurred to a small extent.

Among the various possibilities listed above, the most efficient and economic way to perform an asymmetric H-transfer is by means of an enantiomerically pure catalyst, where a single metal atom promotes the transformation of a great amount of substrate and reagent molecules, and at the same time, a single chiral information is reproduced several times (chiral multiplication).

This procedure seems even more appealing since it has been recently pointed out that the efficiency of the chiral transmission may surpass the enantiomeric purity of the chiral auxiliary when positive asymmetric amplification effects are operative. Thus, in the most fortunate cases, products of very high ee's might be obtained from catalysts of low optical purity[24] (chiral amplification).

## 2.2. Mechanism

From a mechanistic point of view, two general reaction paths can be envisaged for hydrogen transfer:[6] a stepwise process, called "hydridic route", and a concerted process, called "direct hydrogen transfer" (Figure 1).

The "hydridic route" involves the intermediate formation of a metal hydride derivative by interaction of the catalyst with the hydrogen donor, followed by hydride transfer from the metal to the substrate. The "direct hydrogen transfer" implies that hydrogen is transferred to the substrate in a concerted process where both the H-donor and the H-acceptor are held together in close proximity by the catalyst. A cyclic transition state such as the one proposed for Meerwein–Pondorf–Verley reduction is possibly involved.

If the "hydridic route" is operative, enantioface differentiating reactions of the type in the eq 4 should be only marginally affected by chiral H-donors, while type in eq 3 reactions in principle should give racemic products. Small differences of enantioselectivity between H-transfer and catalytic hydrogenation are expected in this case, other things being equal.

In contrast, enantiomer discriminating H-transfers of the types in eqs 5–7 should always lead to optically active products irrespective of the kind of mechanism.

It must be noted, however, that an optically active reagent can be a "noninnocent" spectator ligand in the stereodetermining step of the "hydridic route" and that it can equally influence, albeit moderately, the stereochemistry of the reaction.

## 2.3. Substrates

Most of the enantioselective hydrogen transfer reactions reported in the literature are concerned with the reduction of ketones, mainly aryl alkyl ketones,

and of activated carbon–carbon double bonds, mainly in $\alpha,\beta$-unsaturated acid derivatives. Particular attention has been paid to the chemoselectivity in the case of $\alpha,\beta$-unsaturated carbonyl derivatives, which can give rise to scalemic products upon reductions both at the carbon–oxygen and at the carbon–carbon double bond.[25]

It is well recognized that the reduction of carbon–carbon double bonds by alcohols and formic acid is thermodynamically favored and proceeds to completion under a great variety of conditions. In contrast, the reduction of carbonyl groups by alcohols suffers from unfavorable thermodynamics[26] and it can be anticipated that the equilibrium of H-transfer reduction of ketones by means of alcohols lies to the left side, particularly when primary alcohols are employed. Well-suited H-donors and appropriate reaction conditions are necessary in order to attain high conversions in this case.

### 2.4. Hydrogen Donors

The most popular H-donors are alcohols, including chiral ones, and formic acid.[3,27] More recently, alkylammonium formates, in particular triethylammonium formate (TEAF), have proven to be useful sources of hydrogen, due to their solubility in organic solvents.[12a] Since dehydrogenation of formic acid derivatives is an irreversible and exothermic process,[2] this usually overwhelms the energetic requirement of the reduction process. The use of such H-donors is recommended in reactions where unfavorable energetic balances are expected.

According to their relative oxidation potentials,[26] secondary alcohols are better H-donors than primary ones and can be successfully employed even in the reduction of ketones, provided they are present in great excess.[26] Among secondary alcohols, propan-2-ol is the reagent of choice because it is inexpensive and readily available, has an appropriate boiling point and solubility properties, and upon dehydrogenation gives acetone, which can be easily removed from the reaction mixture, if shifting an unfavorable equilibrium is necessary.

### 2.5. Catalysts

As to the catalyst, both mono- and polynuclear Ru(II),[12a,17,21,22,28-30] Rh(I),[27,31-41] and Ir(I)[18,19,25,42-52] complexes with chiral phosphorus and nitrogen ligands have been successfully employed to promote enantioselective H-transfer reactions. The use of chiral sulfur and oxygen ligands, respectively with Rh(I) and Ir(I) catalysts, has also been reported in two isolated cases.[53,54] Sometimes a metal complex still containing the chiral ligand (preformed catalyst) is used, while sometimes the catalyst is prepared in the reaction vessel by adding the appropriate amount of ligand to a suitable precursor (in situ catalyst). The precursors are often commercially available metal complexes containing easily displaceable ancillary ligands. Both of the procedures have advantages and limitations.

### 2.6. Promoters

Strong bases like KOH or NaOH or sodium alkoxides are frequently added as promoters in H-transfer reactions since often they exert a beneficial effect on reaction rates.[27] In the reduction of ketones with propan-2-ol, the base is essential, since no reaction occurs if its concentration is too low.[18,19,40] A notable exception to this rule is the reduction of ketones with iridium–phenanthroline catalysts in refluxing cyclopentanol.[11g]

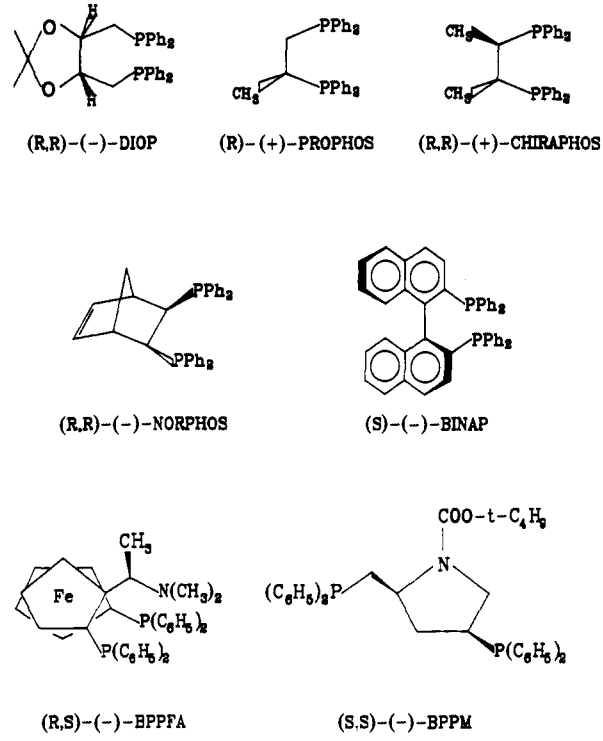



**Figure 2.** Chiral phosphine ligands.

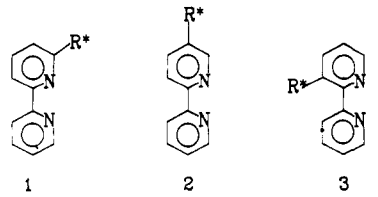
Finally, it seems worth mentioning that, in order to obtain highly active and reproducible catalytic systems, it is often required that the catalyst, either preformed or in situ, be subjected to preactivation in the absence of substrate. Usually this preliminary treatment is absolutely necessary when basic promoters are present and the result of the reaction may be critically dependent on the preactivation protocol.[31,47]

## 3. Chiral Auxiliaries for Asymmetric H-Transfer

The chiral ligands employed in asymmetric H-transfer reactions are basically the same that have been shown to be capable of spectacular enantioselectivities in asymmetric $H_2$-hydrogenation and related catalysis.[55-57] Chiral phosphines are surely the most popular ligands in asymmetric catalysis, and they have been employed in H-transfer since the very beginning with ruthenium, rhodium, and iridium catalysts. Besides a few tertiary monophosphines,[43] chelating bidentate diphosphines like DIOP, CHIRAPHOS, NORPHOS, and BINAP have been mainly used (Figure 2). The common feature of several of these ligands is the presence of a $C_2$ symmetry axis.[55]

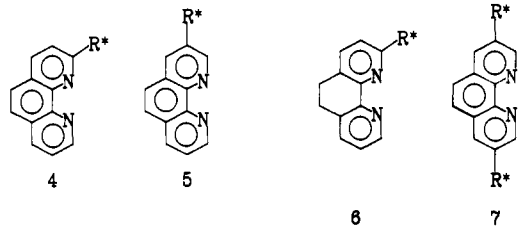
It should be noted, however, that unlike asymmetric hydrogenation, in the field of enantioselective H-transfer reactions the most used chiral auxiliaries contain nitrogen, not phosphorus, as the donor atom. This is likely the consequence of the high catalytic activity displayed in the H-transfer reactions by Rh(I) and Ir(I) complexes containing chelating bidentate nitrogen ligands such 2,2′-bipyridine (bipy), 1,10-phenanthroline (phen), and their substituted derivatives.[9-11]

Chiral bidentate nitrogen ligands used so far in enantioselective H-transfer reactions belong to four different



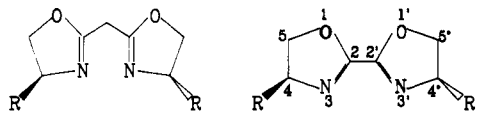
1 2 3

**Figure 3.** Chiral bipyridines.



4 5 6 7

**Figure 4.** Chiral phenanthrolines.



8 9

**Figure 5.** Chiral tetrahydro-bisoxazoles and tetrahydrobioxazoles.

categories: chiral alkyl-substituted bipyridines and phenanthrolines;[36-40] alkyl-substituted tetrahydrobioxazoles;[18] chiral 2-[[*N*-alkyl- and *N*-(arylalkyl)imino]methyl]pyridines;[19,44-48] and chiral alkyl- and (arylalkyl)(2-pyridylmethyl)amines[19,49-52].

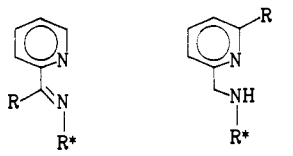
Optically active bipy **1–3** (Figure 3), phen, and 5,6-dihydro derivatives **4–7** (Figure 4), bearing one or two chiral alkyl substituents at different ring positions, have been recently synthetized.[36-40] Most of them have been employed in the enantioselective transfer hydrogenation of acetophenone in the presence of Rh(I) catalysts.

All these ligands have been prepared through multistep processes and different synthetic schemes have been used, depending on the position and the structure of the chiral alkyl substituent. All the schemes rely upon the same strategy involving the synthesis of the substituted pyridine ring through a racemization-free reaction path, starting from an optically active substrate, possibly available from the "chiral pool".

Alkyl-substituted tetrahydro-bis(oxazole) and tetrahydrobioxazoles **8** and **9** (Figure 5) have been introduced in enantioselective H-transfer[18] by Pfaltz quite recently, despite the fact that they have been known for several years.[58] Good to excellent enantioselectivities have been obtained in the reduction of alkyl aryl ketones in the presence of Ir(I) catalysts.

These ligands are readily prepared from easily available chiral $\beta$-amino alcohols and are characterized by $C_2$-symmetric arrangement of the stereogenic centers in close proximity to the coordination site.[18] When the ligand coordinates to the metal, the substituents at the stereogenic centers provide an efficient shielding to the metal ion from two opposite directions and should therefore have a distinct effect on the stereochemical course of the reaction occurring within the coordination sphere.[18]

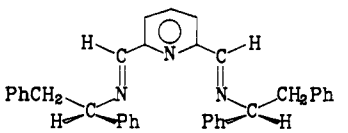
Chiral 2-[[*N*-alkyl and *N*-(arylalkyl)imino]methyl]pyridines **10** of the type reported in Figure 6 can be readily obtained in both enantiomeric form by condensation of 2-pyridinecarboxyaldehyde with the appropriate optically active primary amine.[44-52] They are similar to tetrahydrobioxazoles and -bis(oxazoles) in that the stereogenic center is quite close to the putative reactive site of the catalysts, but, unlike tetrahydrobioxazoles and -bis(oxazoles), they are devoid of the $C_2$-symmetry axis. They have been successfully employed both with Rh(I) and Ir(I) catalysts.[44-52] Since their synthesis is trivial, tuning the ligand by introducing different substituents either at the stereocenter(s) or at other position is an easy task.[47]



N-N-R* N-NH-R*

10 11

**Figure 6.** Chiral 2-[(*N*-alkylimino)methyl]pyridines and alkyl(2-pyridylmethyl)amines.



(R,R)-(+)-PDPBI

12

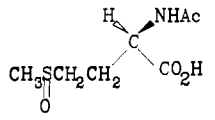
**Figure 7.** Chiral 2,6-bis[(*N*-alkylimino)methyl]pyridine ligand.

Chiral alkyl and (arylalkyl)(2-pyridylmethyl)amines **11** (Figure 6), such as the ones previously used by Brunner et al.[59] in enantioselective hydrosilylation, have been successfully introduced in asymmetric H-transfer by CIBA-GEIGY researchers.[49-52] These ligands can be easily prepared by hydrogenation in the presence of Pt/C catalyst of corresponding 2-[(*N*-alkylimio)methyl]pyridines **10**.[49-52] Ir(I) complexes with these ligands display high catalytic activities and fair to excellent enantioselectivities in H-transfer reduction of alkyl aryl ketones in propan-2-ol.[49-52]

The potentially terdentate Schiff base 2,6-bis[[*N*-(1,2-diphenylethyl)imino]methyl]pyridine (**12**, PDPBI; Figure 7), having two equivalent chiral substituents and a $C_2$-symmetry axis, has been recently prepared by condensation of pyridine 2,6-dialdehyde with (*R*)- or (*S*)-1,2-diphenylethylamine. The corresponding Ir(I) complex displayed high chemo- and enantioselectivities in the transfer reduction of 4-phenyl-3-buten-2-one in propan-2-ol.[25]

The nitrogen ligands listed above exhibit some common features: with the notable exception of alkylphenanthrolines, the most efficient terms of each class have a stereocenter(s) in close proximity to the nitrogen and several of them have a $C_2$-symmetry axis. The proximity effect of the lateral asymmetric center, as pointed out by Brunner few years ago,[60] should be responsible for the high efficiency displayed by these chiral auxiliaries in enantioselective H-transfer.

Among chiral sulfoxides[61] only the potentially bidentate *N*-acetyl-(*S*)-methionine (*R*,*S*)-*S*-oxide (**13**, AMSO; Figure 8), has been employed with good success



(R)-(-)-AMSO

13

**Figure 8.** Chiral sulfoxide ligand [*N*-acetyl-(*S*)-methionine (*R*,*S*)-sulfoxide].

**Table 1. Enantioface Discriminating Transfer Hydrogenation of Ketones by Propan-2-ol Using $[H_4Ru_4(CO)_8((-)\text{-DIOP})_2]$ at 120 °C[63]**

| substrate | *t* (h) | yield (%) | ee (%) |
|---|---|---|---|
| $PhCOCH_3$ | 111 | 34.9 | 4.3 (*S*) |
| $PhCOCH_3$[a] | 190 | 19.1 | 1.3 (*S*) |
| $PhCOCH_2CH_3$ | 139 | 44.1 | 4.8 (*S*) |
| $PhCO(CH_2)_2CH_3$ | 143 | 25.9 | 3.1 (*S*) |
| $PhCOCH(CH_3)_2$ | 255 | 39.0 | 3.9 (*S*) |
| $PhCO(CH_2)_3CH_3$ | 160 | 34.4 | 2.5 (*S*) |
| $PhCOCH_2CH(CH_3)_2$ | 86 | 37.1 | 9.8 (*S*) |
| $PhCOC(CH_3)_3$ | 283 | 36.3 | 6.7 (*S*) |
| $CH_3COCH_2CH_3$ | 326 | 26.9 | 0.3 (*R*) |
| $CH_3CO(CH_2)_2CH_3$ | 408 | 26.9 | 0.3 (*R*) |
| $CH_3COCH(CH_3)_2$ | 261 | 31.0 | 1.2 (*R*) |
| $CH_3COC(CH_3)_3$ | 476 | 21.8 | 1.9 (*S*) |

[a] Benzyl alcohol as hydrogen donor.

in the asymmetric H-transfer reduction of alkyl aryl ketones with Rh(I) catalysts.[53] This chiral sulfurated ligand is readily accessible from natural methionine through oxidation and acetylation.[62]

Both (*S*)- and (*R*)-mandelic acid and derivatives have been used with modest results as chiral auxiliaries for Ir(I) catalysts in the H-transfer reduction of acetophenone from propan-2-ol.[54]

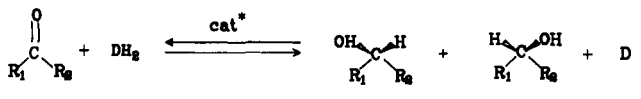
## 4. Complexes with Chiral Phosphines

### 4.1. Ruthenium Catalysts

#### 4.1.1. Ketones/$DH_2$/cat*

The asymmetric ruthenium-catalyzed H-transfer reductions reported so far have always employed phosphines as chiral auxiliaries. Since ruthenium catalysts have been introduced in asymmetric transfer hydrogenation since the very beginning, there are examples of each of the enantioselective processes listed in eqs 2–7 which make use of ruthenium derivatives. Most of these reports date back to the early times of asymmetric H-transfer reactions and have been exhaustively covered by a previous review.[3] Thus, we will restrict a detailed discussion to the most recent results in this field, although some of the most significant early results will be recalled when necessary.

Enantioface discriminating reduction of prochiral ketones by achiral alcohols (eq 8) attracted attention since the very beginning. Table 1 collects the enantioselectivities recorded in the first paper on this subject.[63]

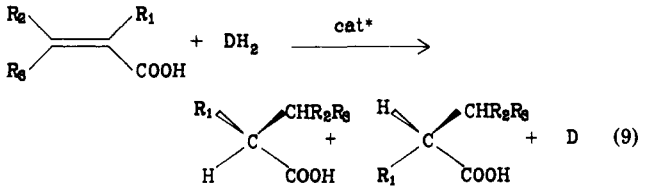


$DH_2$ = alcohols (8)

Very low optical yields (0.3–9.8%) were obtained with $[H_4Ru_4(CO)_8((-)\text{-DIOP})_2]$ as preformed catalyst and propan-2-ol or benzyl alcohol as H-donors at 120 °C.[63] Alkyl aryl ketones gave consistently better optical yields than dialkyl substrates, the best result being observed with phenyl isobutyl ketone (9.8%). In the aromatic series the prevailing enantiomer always had the (*S*) configuration.[63]

#### 4.1.2. α,β-Unsaturated Acids/$DH_2$/cat*

Asymmetric transfer hydrogenation of α,β-unsaturated carboxylic acids (eq 9) has been accomplished for the first time using benzyl alcohol as H-donor and chiral ruthenium phosphine catalysts.[64] The most significative results are summarized in Table 2. The highest ee (16.4%) was obtained with tiglic acid ($R_1$ = $R_2$ = $CH_3$; $R_3$ = H).



$DH_2$ = alcohols; $HCOOH/NEt_3$ (9)

Much better results have been obtained more recently by Brunner et al.[21a] in the same process using the azeotropic mixture formic acid–triethylamine (5:2) as the hydrogen source. Preformed catalysts of general formula $[Ru(acac\text{-}F_6)(\eta^3\text{-}C_3H_5)(P\text{-}P)]$ (P-P = (-)-DIOP, (-)-BPPM, (-)-BINAP, BPPFA) **14** (Figure 9) have been employed, the best result always being obtained with the BINAP containing complex.

A very high enantioselectivity has been recorded with this ligand (93.5% ee) in the reduction of itaconic acid ($R_2$ = $R_3$ = H; $R_1$ = $CH_2COOH$) (Figure 10). Substitution of BINAP with other phosphine ligands resulted in a net decrease of both the conversion and the enantioselectivity of the reaction, while with other substrates the ee's fluctuate between 61% (tiglic acid) and 13.4% (atropic acid; $R_2$ = $R_3$ = H; $R_1$ = Ph) (Table 3). The use of preformed catalysts of different structure, such as $[Ru_2Cl_4(DIOP)_3]$ or $[Ru(BINAP)(ac)_2]$, led to much lower asymmetric inductions.[12a]

Even higher enantioselectivities have been reported very recently by Ogasawara et al.[17] Itaconic acid was converted quantitatively into (*R*)-methylsuccinic acid in 92–97% ee by transfer hydrogenation from propan-2-ol in the presence of $[RuH((-)\text{-BINAP})_2]PF_6$ or $[RhH_2((-)\text{-BINAP})_2]$ as preformed catalysts (Figure 10). Ethanol as well as benzyl alcohol can be used in place of propan-2-ol with no detrimental effect, while with methanol both the rate and the enantioselectivity were strongly lowered.

This is the best stereoselectivity so far obtained for the enantioselective transfer hydrogenation and, at the same time, for the enantioselective reduction of itaconic acid, since it is somewhat higher than the value recorded in the high-pressure hydrogenation of the same substrate with related Ru/BINAP catalysts.[65]

Noticeably, the direction of the asymmetric induction in the reduction of itaconic acid does not depend on the nature of the hydrogen source, but only on the configuration of the phosphine ligand. In fact, (-)-BINAP-

Table 2. Enantioface Discriminating Transfer Hydrogenation of α,β-Unsaturated Acids by Benzyl Alcohol with [$Ru_2Cl_4$((−)-DIOP)$_3$] at 180 °C[64]

| substrate | $R_1$ | $R_2$ | $R_3$ | t (h) | yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| tiglic acid | $CH_3$ | $CH_3$ | H | 6 | 10 | 16.4 (*R*) |
| α-methylcinnammic acid | $CH_3$ | H | $C_6H_5$ | 6 | 36 | 15.9 (*R*) |
| itaconic acid | $CH_2CO_2H$ | H | H | 6 | 31 | 5.1 (*S*) |
| mesaconic acid | $CH_3$ | $CO_2H$ | H | 9 | 9 | 3.4 (*S*) |

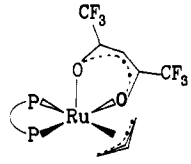


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**Figure 9.** [Ru(acac-$F_6$)][$\eta^3$-$C_3H_5$(P-P)]: P-P = (−)-DIOP, (−)-BPPM, (−)-BINAP.

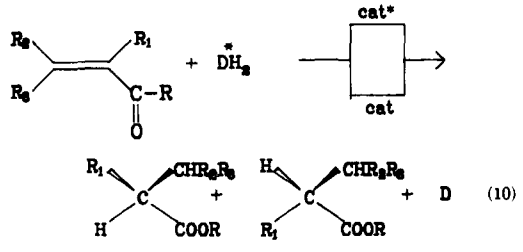
based catalysts invariantly give rise to (*R*)-methylsuccinic acid both with molecular hydrogen and with H-donors such as alcohols and formates.[12a,17,65]

Other unsaturated carboxylic acids, such as α-acetamido- or α-arylacrylic acids, have been reduced by these catalysts,[12a] the efficiency being comparable or slightly lower depending on the substrates. In the case of γ,δ-unsaturated acids isomerization of the double bond to the conjugated derivative precedes the H-transfer reduction, both processes being promoted by the ruthenium catalyst in a one-pot procedure.[17]

In the presence of a strong base, the same catalysts are otherwise much less efficient in the H-transfer reduction of acetophenone (max ee 40%).[17]

### 4.1.3. C-C Double Bond/$DH_2$*/cat or cat*

Enantioface discriminating H-transfer reduction of conjugated carbon–carbon double bond has been accomplished by means of optically active H-donors and in the presence of both achiral and chiral ruthenium catalysts[66,28] (eq 10).



(10)

1) $DH_2$* = optically active glucides

cat = $RuCl_2(PPh_3)_3$

cat* = $Ru_2Cl_4$(DIOP)$_3$

2) R = OH; $OCH_3$; $CH_3$; Ph

Optically active glucides were employed with fair success in the reduction of α,β-unsaturated ketones to saturated ones in the presence of [$RuCl_2(PPh_3)_3$].[66] The highest ee (34%) was obtained with 3,5,5,-trimethyl-2-cyclohexene-1-one. This is a surprisingly high value in view of the fact that the process is carried out with achiral catalysts and temperatures as high as 160 °C (Table 4).

Stereoselectivities up to 8.9% were reported by Ohkubo et al.[28] in the reduction of tiglic acid with the same catalyst and similar optically active H-donors (Table 5). Higher optical yields were obtained by the same author when the reaction was carried out in the presence of [$Ru_2Cl_4$((−)-DIOP)$_3$] (Table 5).[28,29] This was the first demonstration of a cooperative effect between a chiral catalyst and a chiral H-donor in a double stereoselection H-transfer reduction. An antagonistic effect was shown by (+)-DIOP derivative (Table 5).

### 4.1.4. cat*/$DH_2$(r)/A

Phosphine ruthenium catalysts are also capable of promoting kinetic resolutions in enantiomer discriminating processes according to eq 7. Thus, 11% optically pure 1-phenylpropan-1-ol was obtained when the racemic alcohol was heated at 165 °C with Ru(II)/chiral phosphine complexes in the presence of 1,3-diphenyl-2-propen-1-one[21,30] (Table 6).

Simultaneous formation of two different scalemic products, according to the scheme of eq 7, was obtained when racemic 1-phenylethanol was reacted with tiglic acid in the presence of [$Ru_2Cl_4$((−)-DIOP)$_3$].[23] Enantioface discrimination was more efficient (26.4% ee) than kinetic resolution (<4% ee) (Table 7).

### 4.1.5. Mechanism

Mechanistic considerations on the asymmetric H-transfer processes catalyzed by ruthenium chiral phosphine complexes are hampered by the absence of direct evidence and are basically speculative. Sasson and Blum,[6] in their pioneering investigation on [$RuCl_2(PPh_3)_3$]catalyzed H-transfer reactions from alcohols, provided kinetic evidence for a "direct hydrogen transfer" in the reduction of activated carbon–carbon double bonds, whereas a "hydridic route" mechanism was inferred for the transfer hydrogenation of saturated ketones.

This early hypothesis has been adopted by Okhubo et al. to rationalize his results on the asymmetric reduction of tiglic acid.[23]

More recent investigations on the dehydrogenation of propan-2-ol[67a] and H-transfer reduction of ketones with the same H-donor[67b] have added some refinement to this hypothesis. Formation of the intermediate ruthenium hydride has been suggested to occur through attack of alkoxide anion on the metal followed by β-hydrogen elimination. Protonation of the resulting anionic complex to give a ruthenium dihydride should be followed by reduction of the ketonic substrate by means of this last species. As in propan-2-ol/NaOH the presence of alkoxide anion in concentrations as high as to allow for a satisfactory reaction rate is questionable, an alternate route involving deprotonation of a coordinated alcohol molecule seems in our opinion more reliable to account for the formation of the isopropoxide ruthenium intermediate.

It seems easy to predict that application of NMR techniques to the kinetic study of highly enantiose-

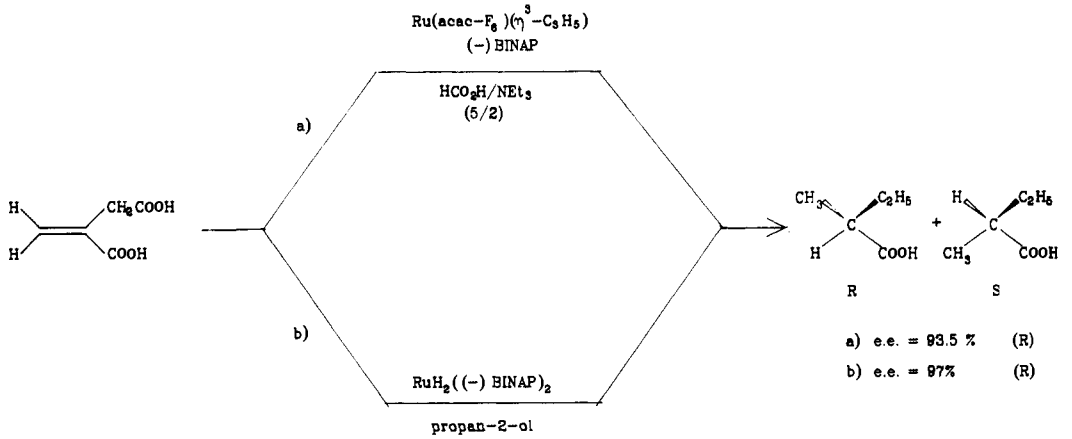
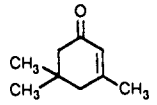
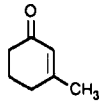



**Figure 10.** Reduction of itaconic acid with Ru/BINAP complexes.

**Table 3. Enantioface Discriminating Transfer Hydrogenation of α,β-Unsaturated Carboxylic Acids Catalyzed by Ruthenium Phosphine Complexes with HCOOH/NEt$_3$ at 70 °C[12a]**

| substrate | cat* | t (h) | yield (%) | ee (%) |
|---|---|---|---|---|
| itaconic acid | Ru(-)-DIOP | 23 | 51 | 42.5 (*S*) |
| | Ru(-)-BPPM | 23 | 62 | 5.8 (*S*) |
| | Ru(-)-BINAP | 10 | 100 | 93.5 (*R*) |
| phenylitaconic acid | Ru(-)-BINAP | 17 | 10 | |
| tiglic acid | Ru(-)-BINAP | 46 | 100 | 61.0 (*S*) |
| 2-acetamidoacrylic acid | Ru(-)-BINAP | 36 | 100 | 40.0 (*S*) |
| 2-acetamidocinnamic acid | Ru(-)-BINAP | 34 | 70 | 56.8 (*S*) |
| atropic acid | Ru(-)-BINAP | 24 | 89 | 13.4 (*R*) |

**Table 4. Enantioface Discriminating Transfer Hydrogenation of α,β-Unsaturated Ketones by Chiral Glucide (-)-1,2-*O*-Isopropylidene-α-D-glucofuranose Catalyzed by [RuCl$_2$(PPh$_3$)$_3$] at 160 °C[66]**

| substrate | t (h) | yield (%) | ee (%) |
|---|---|---|---|
|  | 4 | 100 | 5.0 (*S*) |
|  | 4 | 40 | 34.0 (*S*) |
|  | 4 | 10 | 29.0 (*S*) |

lective H-transfer processes, such as the ones promoted by Ru/BINAP catalysts recently introduced, will surely provide a decisive contribution to the comprehension of the mechanistic aspects of these reactions.

## 4.2. Rhodium Catalysts

Unlike ruthenium, rhodium chiral phosphine catalysts have been employed only in enantioface discriminating H-transfer reactions. The basic processes that have been investigated, according to eq 2, are the reduction of ketones with alcohols[31,32] and of α,β-unsaturated acids, esters, ketones, and olefins with formic acid or triethylammonium formate (TEAF).[27,33-35]

### 4.2.1. Ketones Reduction

Selected results obtained in the enantioselective transfer hydrogenation of several ketones in boiling propan-2-ol, in the presence of [Rh(L-L)(P-P)][PF$_6$] complexes [L-L = nbd, cod, or hd; P-P = (+)-PROPHOS, (-)-CHIRAPHOS, or (+)-DIOP (Figure 2)] are reported in Table 8.

**Table 5. Enantioface Discriminating Transfer Hydrogenation of Tiglic Acid by Chiral Glucides with Ruthenium Catalysts at 160 °C[28,29]**

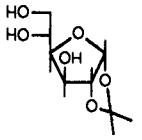
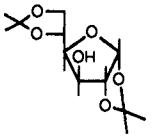
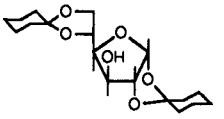
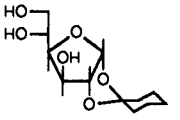
| hydrogen donor | cat | ee (%) |
|---|---|---|
|  | [RuCl$_2$(PPh$_3$)$_3$] | 8.9 (*R*) |
| | [Ru$_2$Cl$_4$((-)-DIOP)$_3$] | 22.5 (*R*) |
| | [Ru$_2$Cl$_4$((+)-DIOP)$_3$] | 3.9 (*S*) |
|  | [RuCl$_2$(PPh$_3$)$_3$] | 6.7 (*R*) |
| | [Ru$_2$Cl$_4$((-)-DIOP)$_3$] | 12.9 (*R*) |
| | [Ru$_2$Cl$_4$((+)-DIOP)$_3$] | 6.4 (*R*) |
|  | [RuCl$_2$(PPh$_3$)$_3$] | 3.1 (*R*) |
| | [Ru$_2$Cl$_4$((-)-DIOP)$_3$] | 7.4 (*R*) |
| | [Ru$_2$Cl$_4$((+)-DIOP)$_3$] | 1.2 (*R*) |
|  | [RuCl$_2$(PPh$_3$)$_3$] | 0.3 (*R*) |
| | [Ru$_2$Cl$_4$((-)-DIOP)$_3$] | 1.9 (*R*) |

**Table 6. Enantiomer Discriminating Hydrogen Transfer from (*R,S*)-1-Phenylpropan-1-ol to 1,3-Diphenyl-2-propen-1-one Using Ru(II) Complexes with Chiral Phosphines at 165 °C[21,30]**

| cat* | t (h) | yield (%) | ee (%) |
|---|---|---|---|
| [RuCl$_2$((+)-BMPP)$_3$] | 70 | 26.3 | 1.3 (*S*) |
| [RuCl$_2$((-)-PMPP)$_3$] | 3 | 40.5 | 0.3 (*S*) |
| [Ru$_2$Cl$_4$((-)-DIOP)$_3$] | 24 | 56.8 | 11.0 (*S*) |

**Table 7. Simultaneous Enantiomer Discriminating Dehydrogenation of 1-Phenylethanol and Enantioface Discriminating Hydrogenation of Tiglic Acid and Its Esters Catalyzed by [Ru$_2$Cl$_4$((-)-DIOP)$_3$][23]**

| substrate | T (°C) | t (h) | ee (%)[a] | yield (%) | ee (%) |
|---|---|---|---|---|---|
| tiglic acid | 170 | 10 | <4 | 13.0 | 26.4 (*R*) |
| methyl tiglate | 190 | 3 | 3.3 | 85.1 | 10.0 (*R*) |
| ethyl tiglate | 190 | 2.2 | <4 | 58.6 | 9.8 (*R*) |
| butyl tiglate | 190 | 4 | <4 | 94.3 | 7.4 (*R*) |
| benzyl tiglate | 190 | 5 | <4 | 75.4 | 8.4 (*R*) |

[a] ee of residual hydrogen donor.

**Table 8. Asymmetric Transfer Hydrogenation of Ketones with Propan-2-ol Using [Rh(nbd)(P-P)][$PF_6$] as Catalyst Precursors[31,32]**

| substrate | P-P | $t$ (h) | yield (%) | ee (%) |
|---|---|---|---|---|
| $PhCOCH_3$ | (-)-CHIRAPHOS | 4 | 46 | 6.6 (*R*) |
| | (+)-PROPHOS | 3 | 60 | 9.0 (*R*) |
| | (+)-DIOP | 5 | 61 | 1.5 (*S*) |
| $PhCOCH_2CH_3$ | (-)-CHIRAPHOS | 4 | 59 | 34.3 (*R*) |
| | (-)-PROPHOS | 4 | 54 | 11.6 (*R*) |
| $PhCO(CH_2)_2CH_3$ | (-)-CHIRAPHOS | 5.5 | 53 | 6.7 (*R*) |
| $CH_3COCH_2CH_3$ | (-)-CHIRAPHOS | 4 | 70 | 3.1 (*S*) |
| | (+)-PROPHOS | 1 | 80 | 1.2 (*R*) |
| $CH_3CO(CH_2)_5CH_3$ | (-)-CHIRAPHOS | 3 | 41 | 8.5 (*S*) |
| | (+)-PROPHOS | 3 | 87 | 4.7 (*R*) |
| $CH_3COCH(CH_3)_2$ | (-)-CHIRAPHOS | 3 | 60 | 4.6 (*S*) |
| $CH_3COC(CH_3)_3$ | (-)-CHIRAPHOS | 8 | 41 | 9.4 (*R*) |

**Table 9. Asymmetric Transfer Hydrogenation of (*Z*)-α-(Acetylamino)cinnamic Acid with Formic Acid at 120 °C[27]**

| cat* | [Rh]/[substrate] | $t$ (h) | ee (%) |
|---|---|---|---|
| [Rh(cod)(+)-NORPHOS]-[$BF_4$][a] | 1/37-41 | 15-17.5 | 19.1 (*R*) |
| [Rh(cod)(+)-NORPHOS]-[$BF_4$] | 1/22-39 | 16-24 | 30.4 (*R*) |
| [Rh(cod)Cl]$_2$/(-)-NORPHOS | 1/33-41 | 6-16 | 67.0 (*S*) |
| [Rh(cod)Cl]$_2$/(+)-PROPHOS | 1/30-68 | 16-21.5 | 52.2 (*S*) |
| [Rh(cod)Cl]$_2$/(-)-BPPFA | 1/16-91 | 6-24 | 30.0 (*R*) |
| [Rh(cod)Cl]$_2$/(-)-DIOP | 1/29-48 | 16.5-17.5 | 2.5 (*S*) |

[a] In the absence of sodium formate.

The presence of a strong base and an appropriate activation procedure[31,32] are required to achieve a high catalytic activity and this allows the reaction to operate at a substrate to metal ratio as high as 1000. Generally the enantioselectivity increases on going from DIOP to PROPHOS to CHIRAPHOS, but it remains rather low, since the best ee does not exceed 34.3%. Interestingly, aliphatic ketones also are smoothly reduced, with chemical and optical yields often comparable to aryl alkyl derivatives.

With the latter substrates, the enantioselectivity and the topicity of the reaction depend on the activation time. This fact has been attributed to the formation of trinuclear active species such as [$Rh_3(P-P)_3(OR)_2$]-[$PF_6$] from the putative mononuclear catalyst [Rh(P-P)$(ROH)_2$][$PF_6$].[31,32]

### 4.2.2. Activated C-C Double Bonds

Aqueous formic acid (80% solution) has been used as H-donor in the enantioselective H-transfer hydrogenation of (*Z*)-α-acetamidocinnamic acid.[27] *N*-Acetylphenylalanine was obtained in 19% optical yield using [Rh(cod)(+)-NORPHOS][$BF_4$] as catalyst precursor.[27] The optical yield increased to 30.4% upon addition of sodium formate and jumped up to 67% when the "in situ" [Rh(cod)Cl]$_2$/NORPHOS catalyst was employed in place of the preformed one.[27]

The enantioselectivity was strongly dependent on the structure of the phosphine ligand and decreased in the following order NORPHOS > PROPHOS > BPPFA > DIOP (Table 9).

Under these conditions, methyl (*Z*)-α-benzamido-2-butenoate is reduced by the PROPHOS-containing catalyst with concomitant hydrolysis of the ester group to give 2-(benzoylamino)butanoic acid in 53.7% ee.

**Table 10. Asymmetric Transfer Hydrogenation of (*Z*)-α-(Acetylamino)cinnamic Acid (A) and Itaconic Acid (B) with TEAF[33,a]**

| cat* | substrate | $T$ (°C) | yield (%) | ee (%) |
|---|---|---|---|---|
| [Rh(cod)Cl]$_2$/(-)-DIOP | A | 27 | 100 | 50.0 (*R*) |
| [Rh(cod)Cl]$_2$/(-)-BPPM | A | 45 | 100 | 71.7 (*R*) |
| [Rh(cod)Cl]$_2$/(-)-DIOP | B | 27 | 100 | 49.1 (*S*) |
| [Rh(cod)Cl]$_2$/(-)-BPPM | B | 45 | 100 | 83.8 (*S*) |

[a] [Ligand]/[Rh] = 1.3.

**Table 11. Asymmetric Reduction of Itaconic Acid with HCOOH/Amine Catalyzed by Rh(*S,S*)BPPM System[34]**

| amine | ee (%)[a] | ee (%)[b] |
|---|---|---|
| $NEt_3$ | 85 (*S*) | 92 (*S*) |
| $PhCH_2NH_2$ | 83 (*S*) | 89 (*S*) |
| (*R*)-$Ph(CH_3)CHNH_2$ | 75 (*S*) | 87 (*S*) |
| (*S*)-$Ph(CH_3)CHNH_2$ | 91 (*S*) | >97 (*S*) |

[a] [Rh(cod)Cl]$_2$ as procatalyst. [b] $Rh_2(ac)_4 \cdot XH_2O$ as procatalyst.

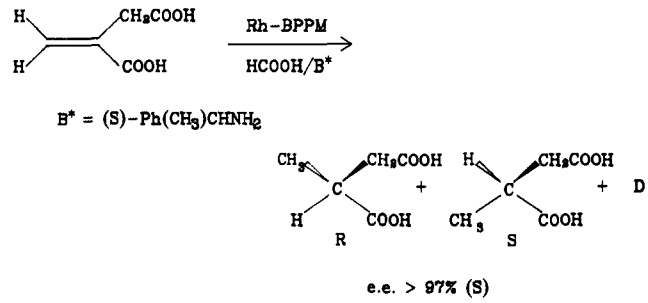



**Figure 11.** Reduction of itaconic acid with formic acid and (*S*)-1-phenylethylamine.

Use of TEAF instead of formic acid causes a substantial improvement of the reaction rate that can be thus performed at temperatures as low as 25-40 °C in polar aprotic solvents.[33] Probably as a consequence of the much milder conditions, increased enantioselectivities can be recorded in the reduction of (*Z*)-α-acetamidocinnamic acid (71.7%) and itaconic acid (83.8%) with BPPM as chiral ligand (Figure 2) and DMSO as solvent (Table 10).

Curiously, the dependence of the enantioselectivity on the structure of the ligand is in almost the opposite order than previously stated (BPPM > DIOP > PROPHOS ≈ NORPHOS).

Rate and enantioselectivity of the H-transfer reduction of itaconic acid with (*S,S*)-BPPM as chiral phosphine ligand are also dependent on the structure both of the amine and of the catalytic precursor. A net improvement of the enantioselectivity was noticed when $[Rh_2(ac)_4] \cdot XH_2O$ was employed instead of [Rh(cod)Cl]$_2$ as catalytic precursor.[34] A double enantioselection H-transfer was accomplished by substituting triethylamine with (*R*)- or (*S*)-1-phenylethylamine. While (*R*) enantiomer displayed a negative effect (Table 11), in the presence of (*S*) enantiomer, (*S*)-methylsuccinic acid that was more than 97% optically pure was obtained. (Figure 11). This value exceeds the best ee achieved for the same enantiomer in the asymmetric hydrogenation of itaconic acid with related Rh(I)/(S,S)-BPPM catalysts (94% ee).[68]

Taken together with ruthenium/BINAP catalyst, this is the second case where transfer hydrogenation affords

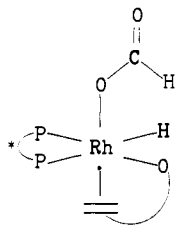


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**Figure 12.** The key intermediate proposed for transfer hydrogenation of unsaturated acids using Rh/BPPM as catalyst precursor.

excellent enantioselectivities, even higher that the ones obtained with gaseous hydrogen.

Some remarkable features of the H-transfer reduction of itaconic acid with TEAF have been pointed out by isotopic labeling studies and kinetic monitoring by NMR spectroscopy.[69] The mechanisms of the H-transfer and asymmetric hydrogenation of itaconic acid by means of Rh(I)/chiral diphosphine catalyst are probably similar and both should rely on the intermediacy of a Rh(III) dihydride.[69] This common intermediate is formed by oxidative addition of dihydrogen in the rate-determining step of the hydrogenation. In H-transfer its formation may occur through oxidative addition of formic acid to give the complex **15** (Figure 12) followed by rate-limiting decarboxylation of the formato ligand. The starting complex is then regenerated following the same path as in hydrogenation.[8]

Up to now the role of the chiral amine has not been determined.

According to the general trend observed in Rh(I)-catalyzed asymmetric hydrogenation, much lower enantioselectivites are obtained with substrates that, unlike itaconic and $\alpha$-acetamidoacrylic acids, are not capable of bidentate coordination to the metal. When a set of $\alpha,\beta$-unsaturated mono- and dicarboxylic acids were reduced by TEAF with Rh(I)/chiral diphosphine catalysts, the ee's fluctuated between 10–35% with the exception of mesaconic acid.[35] Esterification of the carboxylic group resulted in a sharp decrease of the asymmetric induction. Even lower enantioselectivities were recorded with simple alkenes such as 1-phenylbutene.[35] H-transfer reduction of 3-methyl-2-cyclopentenone occurred with complete selectivity on the carbon–carbon double bond, affording the corresponding saturated ketone in 30% ee.[35]

### 4.3. Iridium Catalysts

Iridium phosphine catalysts have been successfully used only in the H-transfer reduction of ketones with propan-2-ol as H-donor.[32,42,43]

Selected results obtained in the reduction of a set of dialkyl and phenyl alkyl ketones with Ir(I) catalysts prepared in situ from $[Ir(cod)Cl]_2$[32,42] or [Ir(cod)-(acac)][43] with the chiral monodentate phosphines NMDPP, MDPP, and DMPP are collected in Table 12.

With acetophenone the optical yield increases from 18.2%[42] to 47.8%[43] upon changing NMDPP to MDPP and lowering the reaction temperature from 82 to 25 °C. DMPP affords comparable stereoselectivity, but opposite enantioselection. The enantioselectivity was higher for phenyl alkyl ketones than for dialkyl ketones, and within the aromatic substrates, it decreased upon increasing the bulkyness of the aliphatic group, when using NMDPP.[42]

**Table 12. Enantioselective Transfer Hydrogenation of $PhCOCH_3$ with Boiling Propan-2-ol Promoted by Iridium Phosphine Derivatives[32,42,43]**

| ligand | $t$ (h) | yield (%) | ee (%) |
|---|---|---|---|
| NMDPP | 6 | 96 | 18.2 (*R*) |
| MDPP | 8 | 87.4 | 42.4 (*R*) |
| MDPP[a] | 188 | 29.9 | 47.8 (*R*) |
| DMPP | 16 | 81.6 | 39.5 (*S*) |

[a] 25 °C.

**Table 13. Enantioselective Transfer Hydrogenation of Ketones with Propan-2-ol Using $[Ir(cod)(P-P)][PF_6]$ as Procatalysts[42]**

| substrate | P–P | ee (%) |
|---|---|---|
| $PhCOCH_3$ | (+)-DIOP | 14 (*S*) |
| | (–)-CHIRAPHOS | 24 (*S*) |
| | (+)-PROPHOS | 58 (*S*) |
| $PhCOCH_2CH_3$ | (+)-PROPHOS | 66 (*S*) |
| $PhCO(CH_2)_2CH_3$ | (+)-PROPHOS | 56 (*S*) |
| $PhCOCH(CH_3)_2$ | (+)-PROPHOS | 51 (*S*) |
| $CH_3CO(CH_2)_5CH_3$ | (+)-PROPHOS | 17 (*S*) |

Complexes of the type $[Ir(cod)(P-P)][PF_6]$ (P–P = (–)-CHIRAPHOS, (+)-PROPHOS, and (+)-DIOP)[42] displayed a good activity in H-transfer reduction of ketones in the presence of aqueous KOH as procatalyst. The enantioselectivity was strongly dependent on the nature of the phosphine ligand, the highest value (66% ee) being recorded with propiophenone in the presence of PROPHOS (Table 13). Lower selectivities were obtained with CHIRAPHOS.[42]

In the presence of a suitably strong base, a catalytic system of good activity, but low enantioselectivity can be generated by addition of bidentate phosphorated ligands, such as BDPOP [(2*R*,4*R*)-(–)-bis[(diphenylphosphino)oxy]pentane], BPDODP [(1*R*,3*R*)-(–)-bis[(diphenylphosphino)oxy]-1,3-diphenylpropane] and BDPP [(2*R*,4*R*)-bis[(diphenylphosphino)pentane], to Ir(I) complexes $[Ir(L)_2Cl]_2$, (L = coe; $^1/_2$cod).[70] The stereoselectivity increases in the order coe > cod and is strongly dependent on the nature of the base employed as cocatalyst (18% ee with NaOMe vs 2% ee with KOH). Notably, $\omega$-(diethylamino)acetophenone is reduced at the same rate both in the presence and the absence of base. In the first case, a 26% optical yield is recorded, whereas a racemic product is formed in the second case.[70]

## *5. Complexes with Chiral Ligands Containing Nitrogen Donors*

### 5.1. Rhodium Catalysts

Work in this field has mainly been concerned with optically active ligands containing pyridine-derived ring systems.

Optically active alkyl-2,2′-bipyridines and alkyl-1,10-phenanthrolines have been shown to be efficient chiral auxiliaries in the Rh(I)-catalyzed enantioselective H-transfer reduction of acetophenone.[36–40] The experimental procedure implies generation of "in situ" catalysts by addition of the chiral ligand to $[Rh(L-L)Cl]_2$

**Table 14. Asymmetric Transfer Hydrogenation of Acetophenone with Propan-2-ol Catalyzed by Rhodium Complexes with Chiral Bipyridines and Phenanthrolines[36,37]**

| ligand | [ligand]/[Rh] | turnover no. (cycles/h) | ee (%) |
|---|---|---|---|
| **16** | 5 | 154 | 1.1 (*R*) |
| **17** | 5 | 29 | 1.6 (*R*) |
| **18** | 5 | 67 | 7.2 (*R*) |
| **19** | 5 | 39 | 4.3 (*R*) |
| **20** | 5 | 85 | 14.8 (*R*) |
| **21** | 2 | 42 | 9.4 (*S*) |
| **22** | 2 | 45 | 15.4 (*S*) |
| | 5 | 180 | 12.0 (*S*) |
| **23** | 2 | 510 | 20.5 (*S*) |
| | 5 | 255 | 17.0 (*S*) |
| **24** | 2 | 360 | 25.5 (*S*) |
| | 4 | 144 | 20.5 (*S*) |

(L–L = cod or hd) in propan-2-ol. KOH is then added, and the solution is refluxed before adding the substrate in order to obtain high and reproducible reaction rates.

Usually an excess of ligand, which may vary depending on its structure, is required in order to avoid decomposition of the catalyst to inactive metallic rhodium. It must be noted that, in the absence of ligands, the procatalysts employed are almost devoid of any catalytic activity since, upon heating with KOH in propan-2-ol, they are readily and quantitatively reduced to metallic rhodium.[36]

A first set of selected results obtained in the H-transfer hydrogenation of acetophenone are reported in Table 14.

The behavior of chiral bipyridines roughly conforms to most obvious expectations: within the set of ligands bearing the same substituent, the stereoselectivity increases from 1.1% to 7.2% as the substituent is moved closer to the coordination site, while, within the set of 6-substituted alkyl derivatives, the bulkiest substituent is the most efficient. All bipy ligands favored the formation of (*R*) enantiomer, but the highest optical yield did not exceed 15%[36] (Figure 13).

Introduction of a more demanding alkyl substituent on the bipy framework, as in the case of the conformationally rigid ligand **21** derived from (+)-camphor, unfavorably affected both the rate and the enantioselectivity.[38]

On the contrary, stiffening the heterocyclic matrix from bipyridine to phenanthroline brought about a sharp enhancement both of the rate and of the asymmetric induction. As a general trend, the reaction rates recorded with phen-based catalysts are always higher than with bipy derivatives by at least 1 order of magnitude. The same is true for the stereoselectivities: phen-based catalysts always give the opposite prevailing enantiomer and much higher stereoselectivities than the bipy derivative, with the exception of 2-substituted derivatives for which the top optical yields were almost identical for both.[36,37]

These differences are macroscopic: under the same reaction conditions, 3-*sec*-butyl-1,10-phenanthroline affords 25.5% ee to be compared with 1.6% obtained with the structurally related 5-*sec*-butylbipy.[36,37] The reversed topicity and the enhanced stereoselectivity must be associated with the greater rigidity of the phenanthroline than the bipyridine ligand.

The result obtained with 3-*sec*-butylphen[40] (up to 31.5% ee under optimum conditions) is particularly intriguing for three reasons. First, because a 3-*sec*-butyl substituent is usually poorly efficient in chirality transfer processes.[47] Second, because the stereogenic center of the alkyl group is not less that four bonds away from the reactive site. Third, because in the phen series the proximity effect does not seem to hold, since 3-substituted derivatives are more efficient than the corresponding 2-substituted.

The enantioselectivity is almost doubled (up to 63%) without any detrimental effect on the reaction rate when the (*S*)-3-*sec*-butyl group is substituted with the bulkier (*S*)-3-(1,2,2-trimethylpropyl).[40] On the contrary, the $C_2$ symmetry 3,8-di-*sec*-butylphenanthroline **26** generated a catalytic system of poor activity and devoid of enantiodifferentiating ability. With phen ligands, the use of $[Rh(hd)Cl]_2$ instead of the corresponding cod derivative speeds up the rate of almost 2 order of magnitude (Table 15).

With both chiral phenanthrolines a decrease in the concentration of the metal had a beneficial effect both on the specific activity and on the stereoselectivity (Table 16).

Addition of increasing amounts of ligands at constant catalyst concentration has a pronounced influence on the reaction. Operating at [substrate]/[Rh] = 2000 with $[Rh(hd)Cl]_2$ and (−)-(*S*)-3-(1,2,2-trimethylpropyl) phenanthroline as the ligand,[40] both the activity and the stereoselectivity jump up abruptly as the [ligand]/[Rh] ratio increases from 1 to 1.5, and then they steadily improve upon further increases up to a ratio of 4 (Table 17). The same trend is observed with the 3-*sec*-butylderivative.[40]

These results indicate that the most active catalytic species is at the same time the most stereoselective and provide strong evidence that it should contain two molecules of phenanthroline coordinated to the metal.[40]

This assumption has been recently substantiated by the observation of the occurrence of nonlinear effects[24] in this reaction. When a 67% enantiomerically enriched sample of **25** was used as ligand, both rate and enantioselectivity were almost unchanged with respect to the enantiomerically pure ligand.[71]

A remarkable improvement of the catalytic activity has been obtained by using the commercially available $Rh_2(ac)_4 \cdot 4H_2O$ as catalytic precursor and (+)-(*S*)-3-*sec*-butylphenanthroline as ligand.[71] Turnover numbers up to 12 000 cycles per hour (cycles/h) have been attained. With such a system, operating at [substrate]/[phen]/[Rh] = 2000:8:1, a quantitative conversion of acetophenone is obtained within 5 min.[71]

A decrease in the reaction temperature brings about a decrease in the stereoselectivity and inversion of the configuration of the prevailing enantiomer from (*S*) to (*R*) occurs at about 60 °C. The ee recorded for the (*R*) enantiomer at 50 °C is however low (Table 18).[71] A similar dependence of the enantioselectivity on the reaction temperature, which may result in inversion of the topicity of the process, has been observed in the asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate and related substrates by rhodium/chiral diphosphine complexes.[8]

The overall results obtained in the H-transfer reduction of acetophenone with Rh(I)–chiral phenanthro-

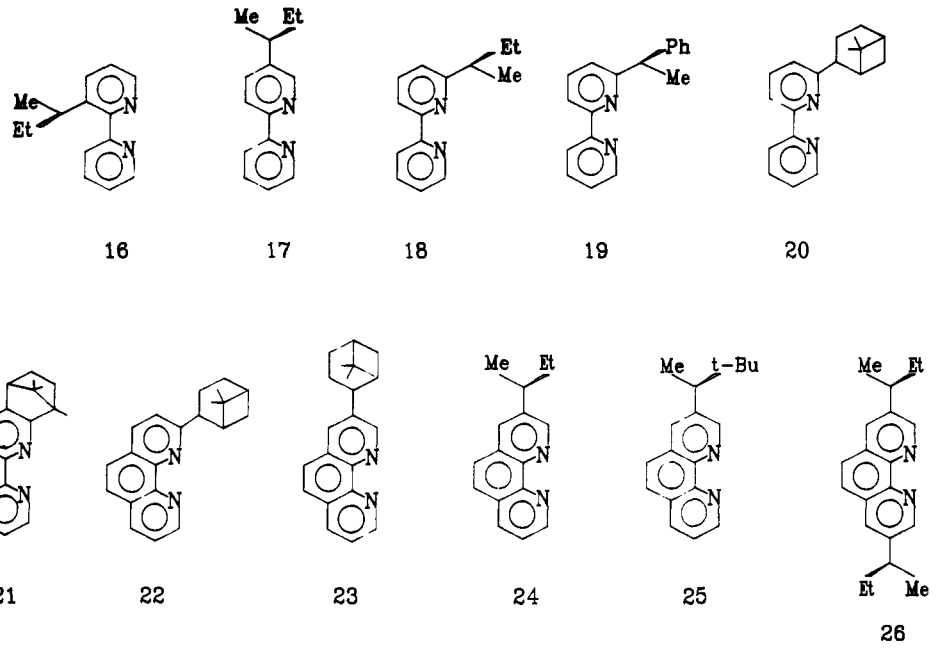



**Figure 13.** Chiral bipyridines and phenanthrolines.

**Table 15. Asymmetric Transfer Hydrogenation of Acetophenone with Propan-2-ol Catalyzed by [Rh(L-L)Cl]$_2$ and Chiral Phenanthrolines[40]**

| ligand | L-L | yield (%) | $t$ (min) | ee (%) |
|---|---|---|---|---|
| **24** | cod | 66 | 420 | 31.5 (*S*) |
| | hd | 95 | 10 | 18.5 (*S*) |
| **25** | cod | 89 | 240 | 63.0 (*S*) |
| | hd | 97 | 10 | 57.5 (*S*) |
| **26** | hd | 16 | 360 | 0 |

**Table 16. Asymmetric Transfer Hydrogenation of Acetophenone with Propan-2-ol Catalyzed by [Rh(hd)Cl]$_2$ and Chiral Phenanthrolines[40]**

| ligand | [Rh][a] | turnover no. (cycles/h) | ee (%) |
|---|---|---|---|
| **24** | $3.2 \times 10^{-4}$ | 2850 | 18.5 |
| | $1.6 \times 10^{-4}$ | 5040 | 25.0 |
| | $8.0 \times 10^{-5}$ | 7320 | 28.0 |
| | $8.0 \times 10^{-5}$ | 8640 | 30.0 |
| **25** | $3.2 \times 10^{-4}$ | 2900 | 57.5 |
| | $1.6 \times 10^{-4}$ | 5750 | 61.5 |
| | $8.0 \times 10^{-5}$ | 8150 | 60.5 |

[a] [Substrate] = $1.6 \times 10^{-1}$ M.

**Table 17. Asymmetric Hydrogen Transfer of Acetophenone with Propan-2-ol Catalyzed by [Rh(hd)Cl]$_2$ and (−)-(*S*)-3-(1,2,2-Trimethylpropyl)-1,10-phenanthroline[40]**

| [ligand]/[Rh] | turnover no. (cycles/h) | ee (%) |
|---|---|---|
| 1.0 | 575 | 10.5 |
| 1.5 | 7450 | 56.5 |
| 2.0 | 8150 | 60.5 |
| 4.0 | 9900 | 62.0 |

line catalyst clearly indicate that more than one catalytic species is formed when [Rh(cod)Cl]$_2$ is combined with a chiral phenanthroline in propan-2-ol and that the most active and stereoselective species contains 2 mol of ligand per rhodium atom.[40]

Thus, a catalytic cycle has been suggested, where a pentacoordinated rhodium(I) hydride complex containing two phenanthrolines coordinated to the metal is assumed as the key intermediate.

**Table 18. Asymmetric Hydrogen Transfer of Acetophenone with Propan-2-ol Catalyzed by [Rh$_2$(ac)$_4$·4H$_2$O] and (+)-(*S*)-3-*sec*-Butyl-1,10-phenanthroline[71,a]**

| T (°C) | yield (%) | $t$ (min) | turnover no. (cycles/h) | ee (%) |
|---|---|---|---|---|
| 83 | 97 | 20 | 10 735 | 24.9 (*S*) |
| 75 | 95 | 20 | 10 310 | 14.3 (*S*) |
| 70 | 94 | 20 | 8 867 | 8.2 (*S*) |
| 65 | 92 | 20 | 7 888 | 2.2 (*S*) |
| 60 | 97 | 30 | 4 852 | 1.6 (*R*) |
| 55 | 95 | 42 | 2 546 | 4.2 (*R*) |
| 50 | 95 | 70 | 352 | 5.9 (*R*) |

[a] [Ligand]/[Rh] = 4.

In the suggested catalytic cycle (Figure 14), deprotonation of propan-2-ol by KOH should occur on the solvated complex. Hydride abstraction from the 2-propoxy ligand generates the hydrido derivative that, in the stereodetermining step, should preferentially add to the *re* face of acetophenone to give the (*S*)-alkoxy derivative. Displacement of 1-phenylethanol by propan-2-ol would then restore the starting complex.

Although the high dilution precluded obtaining direct evidence of the formation of the hydridic derivative during the catalytic runs, its participation seems quite reasonable in view of several literature reports on the analogue [Rh(bipy)$_2$H].[72a,b] Recently, evidence for the formation of this species also during the catalytic ethanol dehydrogenation promoted by [Rh(bipy)$_2$]Cl in the presence of NaOH has been produced.[72c]

Electronic and steric considerations suggest a distorted trigonal bipyramidal structure as the most probable for such a hydride. Since the two nitrogens of a monosubstituted phenanthroline are not equivalent, three isomers can be anticipated for a bipyramidal structure, in each of which the phen ligands are assembled around the metal like the two blades of a propeller around its axis. This makes the rhodium atom chiral too, and Figure 15 reports the couple of diastereoisomers corresponding to the most probable geometrical isomer.

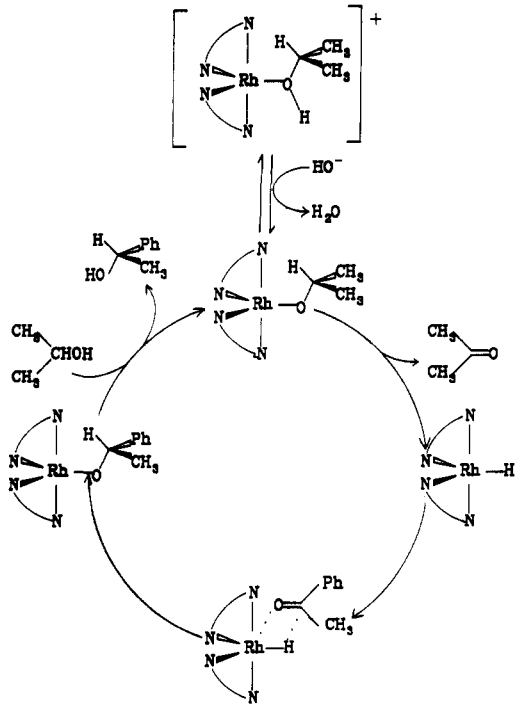
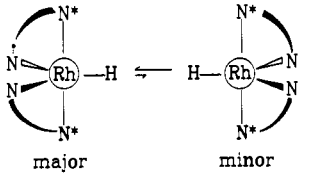


**Figure 14.** Proposed catalytic cycle for transfer hydrogenation of ketones using rhodium complexes with chiral nitrogen ligands as catalyst precursors.




N*= substituted ring

**Figure 15.** Diastereoisomeric equilibrium of hydrido species.

The transmission of the chiral information from the stereogenic carbon atom in the remote position is then enhanced through the chiral assembly of the two phen ligands, which makes the metal atom chiral and, additionally, provides a $C_2$ symmetry to the catalytic species.

While the catalytic system Rh(I)/chiral alkylphen have been investigated in some detail, only preliminary results have been reported on the related system derived from chiral bidentate 2-[(*N*-alkylimino)methyl]pyridines.[41] The "in situ" catalyst generated from [Rh(hd)Cl]$_2$ and (-)-(*R*)-2-[[*N*-(1-phenylethyl)imino]methyl]pyridine **10**, PPEI (Figure 6), catalyzes the H-transfer from refluxing propan-2-ol to aryl alkyl ketones to give the (*R*) alcohols in up to 23% ee. Activity and stereoselectivity decrease upon increasing the steric bulk of the alkyl group.

Even lower enantioselectivities (up to 6% ee) were recorded in the H-transfer hydrogenation of acetophenone in propan-2-ol with the "in situ" catalytic system formed from $RhCl_3 \cdot xH_2O$ and chiral amines such as (*S*)-(-)-PhCH(CH$_3$)NH$_2$, (*R*,*S*)-(-)-PhCH(OH)-CH(CH$_3$)NHCH$_3$, and (*R*)-(+)-PhCH(CH$_3$)N(CH$_3$)$_2$.[73]

## 5.2. Iridium Catalysts

2-[(*N*-Alkylimino)methyl]pyridines and alkyl(2-pyridylmethyl)amines are the kind of nitrogen ligands that have been more extensively employed as chiral modifiers in the Ir(I) catalyzed H-transfer hydrogenation of ketones.[44-52] Other types of nitrogen derivatives have been occasionally used in the same process and will be reported first.[71]

**Table 19. Asymmetric Transfer Hydrogenation of Acetophenone with Propan-2-ol Catalyzed by [Ir(coe)$_2$Cl]$_2$ and (+)-(*S*)-3-*sec*-Butyl-1,10-phenanthroline[71]**

| [substrate]/[Ir][a] | yield (%) | *t* (min) | ee (%) |
|---|---|---|---|
| 2 000 | 91 | 60 | 8.2 (*R*) |
| 4 000 | 90 | 90 | 8.8 (*R*) |
| 8 000 | 87 | 270 | 7.0 (*R*) |
| 12 000 | 87 | 540 | 4.7 (*R*) |

[a] [Ligand]/[Ir] = 2.

**Table 20. Asymmetric Transfer Hydrogenation of Alkyl Aryl Ketones with Propan-2-ol Catalyzed by [Ir(cod)Cl]$_2$ and Tetrahydrobioxazole Derivatives 9[18,a]**

| substrate | R | yield (%) | ee (%) |
|---|---|---|---|
| PhCOCH$_3$ | Bz | 89 | 47 (*R*) |
| PhCOCH$_3$ | *i*-Pr | 89 | 58 (*R*) |
| PhCOCH$_3$ | *t*-Bu | <5 | - |
| PhCOCH(CH$_3$)$_2$ | *i*-Pr | 70 | 91 (*R*) |
| *p*-MeOC$_6$H$_4$COCH$_3$ | *i*-Pr | 71 | 57 (*R*) |
| 2-naphthylCOCH$_3$ | *i*-Pr | 94 | 63 (*R*) |

[a] [Ligand]/[Ir] = 1.3; [substrate]/[Ir] = 100; time = 3 h.

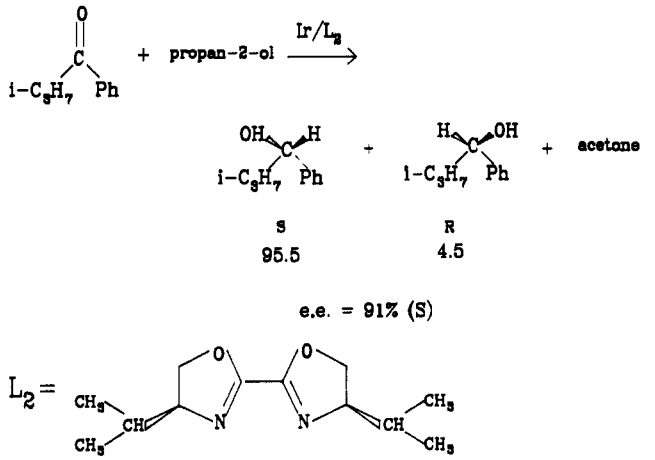
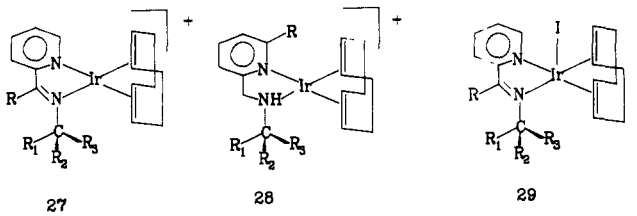



**Figure 16.** Reduction of isopropyl phenyl ketone with propan-2-ol.

The "in situ" catalyst generates from [Ir(coe)$_2$Cl]$_2$ and (+)-(*S*)-3-*sec*-butylphen promotes the enantioselective reduction of acetophenone in refluxing propan-2-ol.[71] High reaction rates and excellent conversions at elevated substrate to metal ratios are observed, but the ee's are not higher than 10% (Table 19). The sense of the asymmetric induction is opposite to the rhodium case. Chiral bipy ligands have not been tested so far.

A recent paper by Pfaltz and co-workers[18] points out that Ir(I) catalysts prepared "in situ" from [Ir(cod)Cl]$_2$ and enantiomerically pure, $C_2$-symmetric 4,4',5,5'-tetrahydro-2,2'-bioxazoles (**9**) (Figure 5) displays a good activity in the H-transfer reduction of ketones in refluxing propan-2-ol in the presence of KOH. Alkyl aryl ketones were readily reduced, affording the corresponding carbinol in 47-91% ee, whereas dialkyl ketones were less reactive and gave low yields of racemic products (Table 20).



27 28 29

**Figure 17.** Ir(I) complexes with 2-(*N*-alkylimino)pyridine and alkyl(2-pyridylmethyl)amine ligands.

**Table 21. Asymmetric Transfer Hydrogenation of Acetophenone with Propan-2-ol Catalyzed by [Ir(cod)(N-N-R*)][ClO$_4$] 27; R = H[47,a]**

| $R_1$ | $R_2$ | $R_3$ | N-N-R* | $t$ (min) | yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| H | Me | Et | (*R*)-PMEI | 250 | 94.5 | 1.5 (*R*) |
| H | Me | Ph | (*R*)-PPEI | 210 | 93.5 | 15.0 (*R*) |
| H | Et | Ph | (*R*)-PPPI | 290 | 94 | 15.5 (*R*) |
| H | Bz | Ph | (*R*)-PPBI | 60 | 93 | 41.5 (*S*) |
| H | Me | 1-Np | (*R*)-PNEI | 240 | 96 | 5.5 (*S*) |

[a] [Substrate]/[Ir] = 1000.

The best result has been obtained wih the isopropyl-substituted ligand (Figure 16) and isopropyl phenyl ketone as the substrate (91% ee at 70% conversion). It turned out that the size of the chelate ring of the tetrahydrobioxazole ligands is very critical in this process since six-membered Ir(I) complexes derived from neutral or anionic 2-methyl tetrahydrobioxazoles did not show any significant activity.[18]

A set of preformed tetra- and pentacoordinated Ir(I) complexes (Figure 17) with bidentate 2-[(*N*-alkylimino)methyl]pyridines and alkyl(2-pyridylmethyl)amines has been prepared and tested in the H-transfer hydrogenation of ketones with propan-2-ol as H-donor.[19,44-52] Most of the derivatives tested were good catalysts, affording, in the presence of KOH, conversions higher than 90% in a few hours at a substrate to iridium ratio of 1000. Activity and enantioselectivity were strongly dependent on the structure of the chiral ligand and optical yields ranging from 1.5% to 95% were recorded.

The results collected in Table 21 indicate that in the reduction of acetophenone with square planar complexes **27** (Figure 17) introduction of a phenyl group in place of an alkyl at the stereogenic carbon improves both the activity and the stereoselectivity of the catalyst. The configuration of the prevailing enantiomer was reversed when PPBI complex ($R_1$ = H; $R_2$ = Bz; $R_3$ = Ph; R = H) was used in place of PPEI one ($R_1$ = H; $R_2$ = Me; $R_3$ = Ph; R = H) and 41.5% ee was recorded with the first ligand.[47] Lower values were obtained when the catalyst was prepared "in situ" from [Ir(coe)$_2$Cl]$_2$ and PPBI.[25]

With PPEI as ligand, an increase in the bulkiness of the alkyl group of the substrate resulted in a sharp increase of the activity of the catalyst, *tert*-butyl phenyl ketone being reduced very fast. With the other two catalysts, isopropyl phenyl ketone was reduced faster than the *n*-propyl derivative (Table 22). With [Ir(cod)(PPEI)][ClO$_4$] and [Ir(cod)(PPPI)][ClO$_4$] [PPPI = 2-[[*N*-(1-phenylpropyl)imino]methyl]pyridine] as preformed catalysts, introduction of bulkier alkyl substituents and reduction of the electrophilic character of the carbonyl group have a positive effect on the stereoselectivity. The opposite trend is observed with the PPBI derivative.[47] Noteworthy, even dialkyl ketones are reduced by this catalyst, although in low ee.[46]

**Table 22. Asymmetric Transfer Hydrogenation of PhCOR with Propan-2-ol Catalyzed by [Ir(cod)(N-N-R*)][ClO$_4$] 27[47,a]**

| N-N-R* | R | $E°$ (mV) | turnover no. (cycles/h) | yield (%) | ee (%) |
|---|---|---|---|---|---|
| PPEI | $CH_3$ | 118 | 270 | 94 | 15 (*R*) |
| | $CH(CH_3)_2$ | 125 | 306 | 97.5 | 22 (*R*) |
| | $C(CH_3)_3$ | 169 | 918 | 100 | 50 (*R*) |
| PPPI | $CH_3$ | 118 | 194 | 94 | 15.5 (*R*) |
| | $CH_2CH_3$ | 118 | 186 | 93 | 24 (*R*) |
| | $(CH_2)_2CH_3$ | 113 | 59 | 41 | 40.5 (*R*) |
| | $CH(CH_3)_2$ | 125 | 169 | 93 | 30 (*R*) |
| PPBI | $CH_3$ | 118 | 930 | 93 | 41.5 (*S*) |
| | $CH_2CH_3$ | 118 | 470 | 94 | 36 (*S*) |
| | $(CH_2)_2CH_3$ | 113 | 104 | 87 | 19 (*S*) |
| | $CH(CH_3)_2$ | 125 | 375 | 94 | 24 (*S*) |

[a] [Substrate]/[Ir] = 1000.

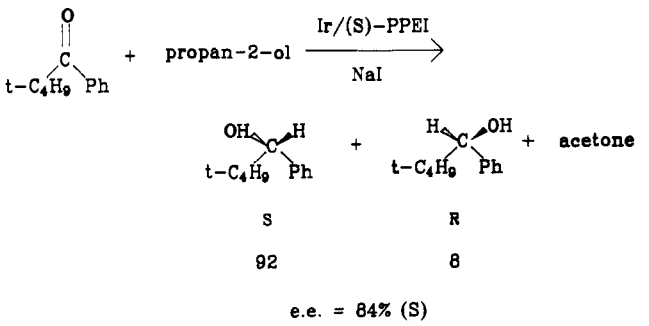



**Figure 18.** Reduction of *tert*-butyl phenyl ketone with propan-2-ol.

This behavior should result from the compromise of two contrasting parameters that determine the basic reactivity of the substrates, namely the steric hindrance and the electrophilicity of the carbonyl group. The latter has been in turn related to the redox potential ($E°$) of the ketone/alcohol couple and increases with increasing $E°$.[26]

As a general trend, in the case of phenyl alkyl ketones, an increase of the bulkiness of the alkyl group is associated to an increase of the $E°$ of the carbonyl group. The reactivity of the carbonyl group in H-transfer reductions is then dictated by the steric hindrance of the alkyl group, when sterically demanding catalysts are involved, while, with less hindered catalysts,[47] it is mainly dependent on the electrophilicity.

A significative improvement of the stereoselectivity of the H-transfer reduction has been obtained upon introduction of pentacoordinated neutral iridium complexes such as the diastereomeric [Ir(cod)(PPEI)I] as preformed catalysts. The crystal structure of this complex as well as of the related (*S*)-APPEI derivative **27** (Figure 17: R = Me; $R_1$ = H; $R_2$ = Me; $R_3$ = Ph) have been determined.[48] Both complexes showed a distorted square pyramidal geometry, with the iodine atom in the apical position and with absolute (*S*) configuration at the iridium center.[48]

The PPEI complex promotes the H-transfer hydrogenation of *tert*-butyl phenyl ketone in 79.5% optical yield. An even better value (84%) can be obtained when the reduction is carried out in the presence of additional NaI (Figure 18).[48] Lower enantioselectivities are recorded with the APPEI derived catalyst.

**Table 23. Asymmetric Transfer Hydrogenation of $PhCO(CH_2)_2CH_3$ with Propan-2-ol Catalyzed by [Ir(cod)(N–NH–R*)][$BF_4$] 28 at 60 °C[19]**

| $R_1$ | $R_2$ | $R_3$ | R | t (h) | yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| H | Me | Et | H | 17 | 32 | 12.5 (*R*) |
| H | Ph | Me | H | 20 | 72 | 19 (*R*) |
| Ph | H | Me | Me | 3 | 92 | 54.2 (*S*) |
| H | Ph | Bz | Me | 12 | 91 | 60.4 (*R*) |
| H | 1-Np | Me | Me | 17 | 33 | 64.8 (*R*) |

**Table 24. Asymmetric Transfer Hydrogenation of PhCOR with Propan-2-ol Catalyzed by [Ir(cod)(DHPPEI)][$BF_4$] at 60 °C[19]**

| substrate | relative rate | ee (%) |
|---|---|---|
| $PhCO(CH_2)_2CH_3$ | 1 | 54.2 (*S*) |
| $PhCO(CH_2)_3CH_3$ | 2 | 54.0 (*S*) |
| $PhCO(CH_2)_3C_6H_5$ | 0.12 | >90[a] |
| $PhCOCH(CH_3)_2$ | 2.5 | 57.3 (*S*) |
| $PhCOC(CH_3)_3$ | 1.2 | 51.2 (*S*) |

[a] The chiral alcohol is not described in the literature.

This result is the best obtained so far in the enantioselective H-transfer hydrogenation of this sterically hindered ketone which usually is reduced with difficulty by the other catalysts previously considered.[41] Sterically hindered ketones are not reduced by enzymes.[22]

A set of Ir(I) complexes containing bidentate 2-pyridylmethylamine ligands as chiral modifiers have been synthesized and tested as H-transfer catalysts in the reduction of *n*-propyl phenyl ketone in propan-2-ol in the presence of NaOH as cocatalyst.[19,49-52] It must be noted that this reaction is particularly unfavored on thermodynamics grounds.[26]

When the reaction is carried out at 60 °C at a [substrate]/[Ir] ratio = 1000, optical yields in the range 12.5–64.8% are obtained. A significant improvement of the optical yield, from 19% to 54.2% and a 10-fold increase of the reaction rate are obtained when a methyl group is introduced onto the 6-position of the pyridine ring. A further increment, up to 64.8%, is observed upon changing the substituents at the stereogenic carbon: for instance, a methyl with a benzyl group or a phenyl with a α-naphthyl group (Table 23).

The results observed on different aryl alkyl ketones with the preformed catalyst derived from DHPPEI **28** (Figure 17: $R_1$ = H; $R_2$ = Me; $R_3$ = Ph; R = H) are collected in Table 24.[19] Among simple alkyl phenyl ketones, an increase of the steric bulk of the alkyl substituent affected only slightly the enantioselectivity and the relative rates, which ranged between 51.2 and 57.3% and between 1 and 2.5, respectively. As the highest values were both ascribed to isopropyl phenyl ketone, this trend is similar to PPEI, even if less pronounced.

A sharp improvement of the stereoselectivity is obtained when one more phenyl group is introduced in the alkyl chain: phenyl 3-phenylpropyl ketone is reduced in more than 90% optical yield. As phenyl *n*-butyl ketone, the methyl analogue of this substrate, is reduced about 20 times faster in 54% ee, it appears that a slower rate allows for a better stereoselectivity in this system.

Two styryl complexes have been also synthesized and used either as homogeneous catalysts **30** and **31** or, after immobilization, as heterogenized catalysts **32** and **33** (Figure 19).[19] Immobilization was accomplished through copolymerization with 2-ethylhexyl methacrylate in the presence of di-2-butylbenzene as cross-linking agent and resulted in a more active catalytic system (Table 25). Sharp differences of stereoselectivity are observed on changing from the homogeneous to the heterogenized system: the ee's increase from 46.6 to 85.3% and from 51.9 to 84.3% with the methyl and with the benzyl-substituted ligands, respectively (Table 25). In both cases the optical purity of the product does not change as the reaction proceeds.

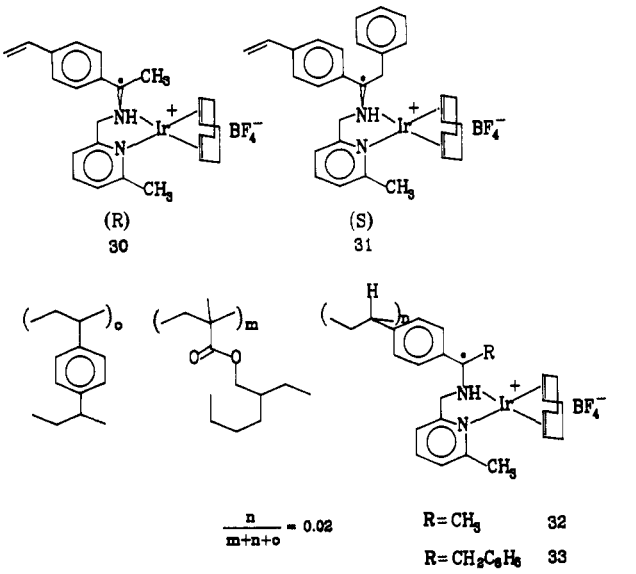



**Figure 19.** Heterogenized and homogeneous Ir(I) complexes with bidentate chiral nitrogen ligands.

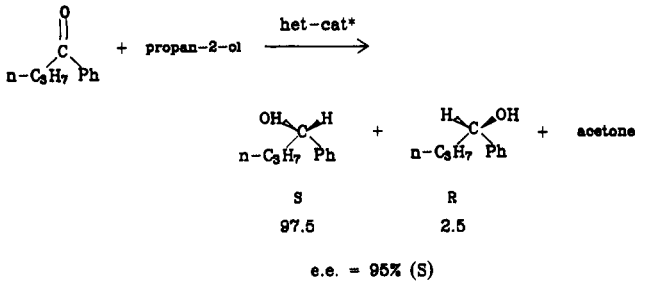


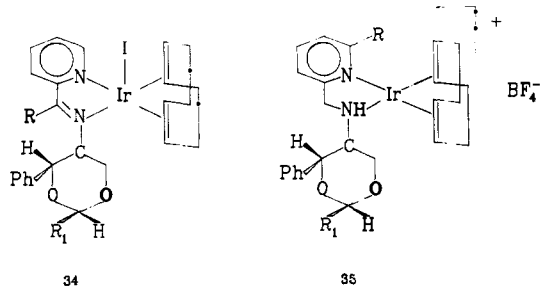

**Figure 20.** Reduction of *n*-propyl phenyl ketone with propan-2-ol.

**Table 25. Asymmetric Transfer Hydrogenation of $PhCO(CH_2)_2CH_3$ with Propan-2-ol Catalyzed by Homogeneous and Heterogenized Iridium Complexes at 60 °C[19,a]**

| cat* | t (h) | yield (%) | ee (%) |
|---|---|---|---|
| 30 | 15 | 97 | 46.6 (*R*) |
| 32 | 6 | 93 | 83.5 (*R*) |
| 31 | 10 | 98 | 51.9 (*S*) |
| 33 | 5 | 92 | 84.3 (*S*) |

[a] [Substrate]/[Ir] = 1000.

Polymer parameters are also important and moderate, but definite improvements of the enantioselectivity have been achieved by changing the ester moiety of the methacrylate monomer. The heterogenized catalyst (het-cat*) derived from *tert*-butyl methacrylate promotes the H-transfer reduction of butyrophenone in up to 95% optical yield at 20% conversion (Figure 20). Unlike the previous cases, the optical purity of the product is affected by the reaction time and decreases with increasing conversions (90% ee at 65% conversion).



34 35

**Figure 21.** Iridium complexes with 2-(*N*-alkylimino)pyridine and alkyl(2-pyridylmethyl)amine ligands.

**Table 26. Asymmetric Transfer Hydrogenation of $PhCO(CH_2)_2CH_3$ with Propan-2-ol Catalyzed by Homogeneous and Heterogenized Iridium Complexes at 60 °C[19,a]**

| complex | R | $R_1$ | X | *t* (h) | yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| **34** | H | Ph | I | 25 | 68 | 64.2 (*S*) |
| **34** | Me | Ph | I | 25 | 26 | 2.8 (*S*) |
| **35** | H | Ph | $BF_4$ | 24 | 33 | 65.5 (*S*) |
| **35** | Me | Ph | $BF_4$ | 24 | 13 | 23.9 (*S*) |
| **35** | H | 4-styryl | $BF_4$ | 20 | 19 | 68.2 (*S*) |
| **35** | H | 4-styryl | $BF_4$ | 20[b] | 86 | 76.8 (*S*) |

[a] [Substrate]/[Ir] = 1000. [b] Heterogenized complex.

Preformed Ir(I) complexes with 2-[(*N*-alkylimino)methyl]pyridines **34** and with the alkyl(2-pyridylmethyl)amines derived thereof by reduction of the carbon–nitrogen double bond **35** (Figure 21) have been compared in the H-transfer reduction of butyrophenone in propan-2-ol at 60 °C with NaOH as a cocatalyst[19] (Table 26). Unlike the previous case, both activity and stereoselectivity are sharply reduced when a methyl group is introduced onto the 6-position of the pyridine ring. This effect is macroscopic for the iodo derivative (64.2 vs 2.8% ee).

Where a comparison can be made, tetracoordinated cationic complexes and pentacoordinated neutral species display similar efficiencies (65.5 vs 64.2% ee). The heterogenized catalyst, obtained as before from the styryl monomeric ligand by copolymerization with 2-ethylhexyl methacrylate in the presence of di-2-butylbenzene, was more active and enantioselective than the monomeric catalyst (76.8 vs 68.2% ee). In all these experiments the product showed (*S*) prevailing configuration.[19]

Unlike the rhodium-based catalysts, in the case of H-transfer hydrogenation with Ir(I) catalysts containing nitrogen ligands, in particular when preformed complexes of type **27** and **29** are used, a pentacoordinate Ir(I) species containing one chelate chiral ligand has been assumed as the key intermediate in the catalytic cycle.[11d,f,47,48] The sharp variations observed in the catalytic activity and selectivity upon changing the nature of the coordinating anion[11d,g] are indicative of the presence of this ligand within the coordination sphere of the metal. Thus, three coordination positions are occupied by the supporting ligands, the remainder being taken by the H-donor and -acceptor, respectively.

A direct H-transfer from a coordinated 2-propoxy group to the O-coordinated ketone has been suggested as the rate-determining and stereodetermining step of the process (Figure 22). In agreement with such a hypothesis the reaction rate depends on both the nature of the H-donor and -acceptor,[11f] and moreover such

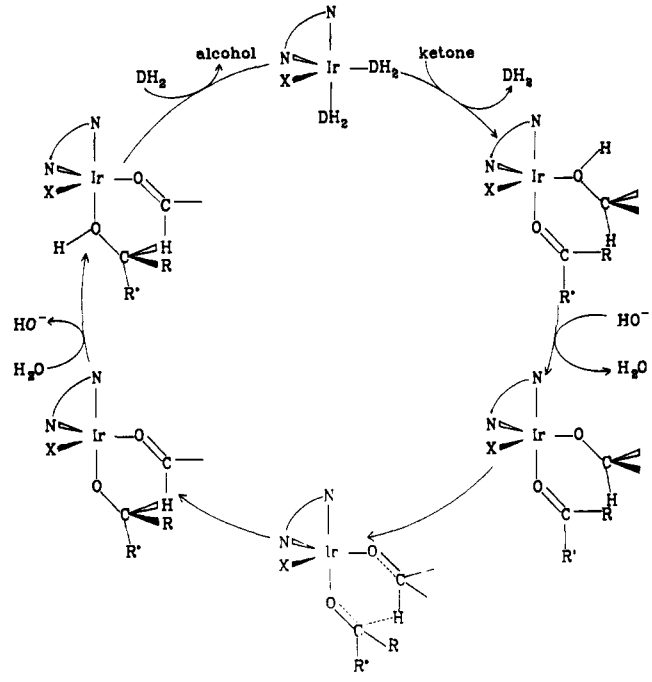



**Figure 22.** Proposed catalytic cycle for transfer hydrogenation of ketones using iridium complexes with bidentate chiral nitrogen ligands.

**Table 27. Enantioselective Transfer Hydrogenation of 4-Phenyl-3-buten-2-one (A) and 6-Methyl-5-hepten-2-one (B) with Propan-2-ol by $[Ir(coe)_2Cl]_2$ and chel[25]**

| substrate | chel | *t* (min) | yield (%) | sel (%)[a] | ee (%) |
|---|---|---|---|---|---|
| A | (*R*,*R*)-PDPBI | 120 | 90 | 93 | 67.0 (*S*) |
| | | 45 | 43 | 94 | 82.0 (*S*) |
| | (*R*)-PPBI | 390 | 88 | 76 | 17.0 (*S*) |
| B | (*S*,*S*)-PDPBI | 135 | 91 | 100 | 13.0 (*S*) |

[a] Unsaturated alcohol/% yield.

complexes are practically inactive as hydrogenation catalysts of ketones.[74]

The catalyst generated "in situ" from $[Ir(coe)_2Cl]_2$ and the potentially terdentate ligand, PDPBI **12** (Figure 7), displayed a high activity, but a poor stereoselectivity in the H-transfer reduction of acetophenone in propan-2-ol.[25] More satisfactory results have been obtained with α,β-unsaturated ketones like 4-phenyl-3-buten-2-one,[25] where a good catalytic activity is associated with a high chemo- and enantioselectivity that allows the corresponding allyl alcohol (*S* configuration) to be obtained in 95% and 67% chemical and optical yields, respectively. Even higher optical purities (82%) and unchanged chemoselectivity can be obtained if the reaction is stopped at lower conversion (Table 27; Figure 23).

Reduction of 6-methyl-5-hepten-2-one occurs with complete selectivity at the carbonyl group. The corresponding alcohol, sulcatol, is obtained in an optical purity only moderate, but comparable to the natural product (Figure 23).[75] It is worth mention that, in the H-transfer reduction of α,β-unsaturated ketones, PDPBI is much more efficient than the corresponding bidentate derivative.

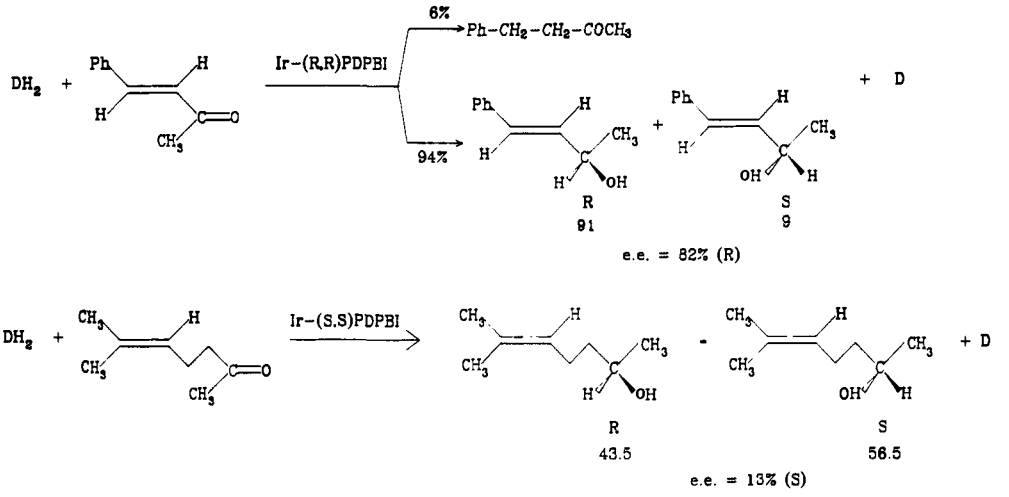



**Figure 23.** Reduction of unsaturated ketones with propan-2-ol.

**Table 28. Asymmetric Transfer Hydrogenation of Ketones with Propan-2-ol Using Rhodium/AMSO Catalyst[53]**

| substrate | [AMSO]/[Rh] | yield (%) | ee (%) |
|---|---|---|---|
| $PhCOCH_3$ | 2 | 45 | 63 (*R*) |
| | 2[a] | 8 | 1.2 (*R*) |
| | 2[b] | 48 | 22 (*R*) |
| $PhCOCH_2CH_3$ | 2 | 21 | 71 (*R*) |
| *p*-$MeC_6H_4COCH_3$ | 2 | 31 | 75 (*R*) |

[a] KOH added as aqueous solution. [b] NaOMe added as base.

The results reported above point out that, although Ir(I) catalysts with chiral nitrogen ligands so far cannot compete with the most efficient reagents that have been developed for the enantioselective reduction of ketones,[76] the rather high enantioselectivities induced by some of these ligands look promising for further advances in the future.

### 6. Complexes with Chiral Ligands Containing Sulfur Donors

The "in situ" complex prepared from $[Rh(hd)Cl]_2$ and *N*-acetyl (*S*)-methionine (*R*,*S*)-sulfoxide (AMSO, **13**; Figure 8), catalyzes the enantioselective H-transfer hydrogenation of alkyl aryl ketones in refluxing propan-2-ol in the presence of strong bases[53] (Table 28). Although the catalytic activity was rather low and less than 50% conversions were attained after 8–10 h, fair to good enantioselectivities were recorded with acetophenone (63% ee), propiophenone (71% ee), and *p*-methylacetophenone (75% ee). This last value is the best so far recorded in the H-transfer hydrogenation of this substrate.

Less than 10% ee were obtained when $[RhCl(cod)]_2$ and $[RhCl(coe)_2]_2$ complexes were employed as procatalysts, while use of iridium(I) precursors such as $[Ir(cod)Cl]_2$ or $[Ir(coe)_2Cl]_2$ gave similar conversions, but negligible ee's. The catalytic system was not suitable for the reduction of dialkyl ketones and was dramatically sensitive to the presence of water that even in small amount almost inhibited the reaction.

Remarkably, with AMSO high asymmetric inductions are obtained in spite of the fact that the configuration of the sulfur atom is undefined.[77]

### 7. Complexes with Chiral Ligands Containing Oxygen Donors

The asymmetric H-transfer hydrogenation of acetophenone has been accomplished by means of Ir(I) complexes prepared "in situ" from $[Ir(coe)_2Cl]_2$ and trialkyl phosphites, using (*R*)- or (*S*)-mandelic acid or suitable derivatives as the chiral modifiers and propan-2-ol as H-donor.[54] Although chemical and optical yields were as low as 20% and 12%, respectively, this establishes a new procedure for enantioselective H-transfer reductions which is available also for double enantioselection experiments and makes use of inexpensive and readily available chiral sources.

### 8. Concluding Remarks

In the most recent years remarkable advances have been achieved in enantioselective H-transfer reactions catalyzed by homogeneous transition metal complexes and in a few instances more than 90% ee's have been recorded in the reduction both of activated carbon–carbon double bond and of carbonyl group. Although these performances are relatively isolated, now H-transfer reduction can be quoted at the same level of other enantioselective processes promoted by chiral transition metal complexes and, at least in some cases, can compete favorably with asymmetric hydrogenation.

This is particularly true for the reduction of $\alpha,\beta$-unsaturated acids catalyzed by Rh(I) or Ru(II) phosphine complexes, where equal or even better values of asymmetric induction are achieved at atmospheric instead of at high pressure. The same occurs in the case of H-transfer hydrogenation of ketones where, at atmospheric pressure, Ir(I) or Rh(I) complexs with nitrogen ligands consistently display a much higher catalytic activity and afford better ee's than homogeneous hydrogenation catalysts under high pressure.

In spite of these excellent achievements, however, much work remains to be done in asymmetric H-transfer reactions.

The overall results obtained in the reduction of unactivated carbon–carbon double bond and, in general, of olefinic substrates which are incapable of chelate coordination to the metal are far from being satisfactory and a more efficient and selective catalyst would be welcome.

The catalysts developed for the H-transfer reduction of ketones are characterized by high efficiency and enantiodifferentiating ability, but these features are restricted to aryl alkyl ketones. Reduction of dialkyl ketones in high rate and stereoselectivity is still an open question, as well hydrogenation of ketones which contain additional functionalities. The few results available on the chemo- and enantioselective H-transfer hydrogenation of $\alpha,\beta$-unsaturated ketones are encouraging, but sparse. This is a topic of remarkable synthetic interest and should be investigated in more detail.

Extension of enantioselective H-transfer hydrogenation to include further substrates such as epoxides, Schiff bases, and so on should be also undertaken to expand the scope of these processes.

Application of phase-transfer techniques to asymmetric H-transfer hydrogenation seems surely feasible in view of the available literature reports, but has not been reported on so far. This should be recommended in view of the promising results recently obtained in asymmetric hydrogenation in biphasic systems.[78]

Our knowledge of the mechanisms that regulate H-transfer processes is limited and the catalytic cycles that have been suggested so far are mainly based on speculative rather than on kinetic arguments. These hypotheses should be substantiated by direct experimental evidences in order to address the research of more active and selective catalysts on a more rational basis. The highly enantioselective H-transfer reductions quite recently achieved under mild conditions seem to be particularly well-suited subjects for these kind of studies.

More attention should be paid also to the role of the H-donor and to the potential of double stereoselection processes where chiral H-donors are involved. As it is well documented that enantiomer discriminating processes may be very efficient (cf. the Sharpless epoxidation of racemic allylic alcohols[79]); coupling of kinetic resolution with enantioface selection might proceed with high optical yields for both the products.

Finally, a notable feature of H-transfer hydrogenation, which has not been exploited so far, is that, with the appropriate combination of substrate, catalyst, and H-donor, in principle up to three optically active compounds may be produced in a single step. If nonlinear effects of chiral amplification were involved in this scenario, unpredictable, but surely exciting, results should be expected.

## Abbreviations

| | |
|---|---|
| ac | acetate |
| AMSO | *N*-acetyl (*S*)-methionine (*R,S*)-sulfoxide |
| APPEI | 2-[[*N*-(1-phenylethyl)imino]ethyl]pyridine |
| BINAP | 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl |
| bipy | 2,2′-dipyridyl |
| BDPOP | 2,4-bis[(diphenylphosphino)oxy]pentane |
| BDPP | bis(diphenylphosphino)pentane |
| BPDODP | [(diphenylphosphino)oxy]-1,3-diphenylpropane |
| BPPFA | *N,N*-dimethyl[1-[2-(diphenylphosphino)ferrocenyl]ethyl]amine |
| BMPP | benzylmethylphenylphosphine |
| BPPM | *N*-(butoxycarbonyl)-4-[(diphenylphosphino)methyl]pyrrolidine |
| CHIRAPHOS | bis(diphenylphosphino)butane |
| cod | 1,5-cyclooctadiene |
| coe | cyclooctene |
| DHPPEI | (1-phenylethyl)-2-pyridylmethylamine |
| DIOP | (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-butylene)bis(diphenylphosphine) |
| DMPP | dimenthylphenylphosphine |
| DMSO | dimethyl sulfoxide |
| hd | 1,5-hexadiene |
| MDPP | menthyldiphenylphosphine |
| nbd | norbornadiene |
| NMDPP | neomenthyldiphenylphosphine |
| NORPHOS | 2(*exo*),3(*endo*)-bis(diphenylphosphino)-bicyclo[2.2.1]heptene |
| phen | 1,10-phenanthroline |
| PDPBI | 2,6-bis[[*N*-(1,2-diphenylethyl)imino]methyl]pyridine |
| PMEI | 2-[[*N*-(1-methylethyl)imino]methyl]pyridine |
| PNEI | 2-[[*N*-(1-naphthylethyl)imino]methyl]pyridine |
| PPBI | 2-[[*N*-(1,2-diphenylethyl)imino]methyl]pyridine |
| PPEI | 2-[[*N*-(1-phenylethyl)imino]methyl]pyridine |
| PPPI | 2-[[*N*-(1-phenylpropyl)imino]methyl]pyridine |
| PROPHOS | 1,2-bis(diphenylphosphino)propane |
| TEAF | triethylammonium formate |

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**Registry No.** Ruthenium, 7440-18-8; rhodium, 7440-16-6; iridium, 7439-88-5.