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Synthesis of chiral amines catalyzed homogeneously by metal complexes

Brian R. James*

Department of Chemistry, University of British Columbia, Vancouver, BC, Canada V6T 1Z1

Abstract

This review describes developments in catalytic asymmetric hydrogenation of prochiral imines. The homogeneous systems were initially dominated by ones based on Rh complexes containing chiral, chelating diphosphine ligands, although related Ru- and Ir-based systems are becoming more prominent; a very recent, extremely effective hydrogen transfer system (from formic acid), based on Ru catalysts containing chiral 1,2-diamine ligands, is especially significant. A fundamentally different type involving an early transition-metal catalyst (a chiral titanocene) has been reported. Enantiomeric excess (e.e.) values in the range of 90–100% have now been achieved with certain substrates. Emphasis is given to some Rh and Ru catalysts developed in the Department of Chemistry, The University of British Columbia (UBC). Factors discussed include: dependence of conversions, rates and e.e. values on substrate and catalyst type; kinetic dependences; and mechanistic insights, especially possible roles of intermediate metal-hydride and -imine species.

1. Introduction

Development in, and understanding of, catalytic hydrogenation of C=X moieties decrease as X varies from C (olefinic substrates) to O (ketones/aldehydes) to N (ketimines/aldimines), and this is reflected in the corresponding decreasing availability of literature on these systems; this in itself relates directly to increasing difficulty, in terms of reaction conditions, in effecting these hydrogenations. The fundamentals of H_2-activation by transition-metal complexes are well understood, but relatively little is known about activation of imines (i.e., azomethine moieties) and the required H-atom transfer steps.

Several factors contribute to the more difficult hydrogenation of imines. For the net hydrogenation processes outlined in Eq. (1), a smaller thermodynamic (exothermicity) gain is realized from reduction of C=N or C=O bonds (approx. -60 kJ mol^{-1}), relative to olefinic bonds (approx. -130 kJ mol^{-1}) [1].

$$R^1(R^2)C{=}X \xrightarrow[\text{cat.}]{H_2} R^1(R^2)C^*H - XH; \quad X = CR_2, O, NR; \; C^* = \text{chiral carbon center} \tag{1}$$

The typical end-on, η^1-binding mode of the azomethine (and carbonyl) groups contrasts with the side-on, η^2-binding of olefins; this results in less effective orbital overlap with, and lower affinity for, the metal center [2], while η^2-binding is usually considered a requirement within a catalytic hydrogenation cycle (see below). Competitive

*Tel.: (1-604) 822-6645; Fax: (1-604) 822-2847.

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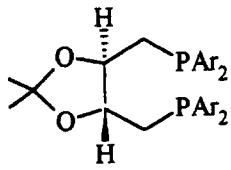
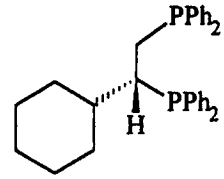
coordination of the hydrogenation products (amines>alcohols>saturated hydrocarbons) may also play a role in 'catalyst poisoning'. Finally, increased steric hindrance at the unsaturated moiety is expected to retard hydrogenation rates: this is well established with olefinic substrates [3,4], less so within ketones (and aldehyde vs. ketone) [4], and is now evident in imine systems, particularly where hydrogenation of prochiral ketimines ($R^1R^2C{=}NR$) requires more forcing conditions than hydrogenation of the achiral aldimines ($R^1C(H){=}NR$) (see below). Increasing substitution hampers coordination of the imine but, by the same token, catalyst poisoning by the amine product may be likewise hindered.

Table 1
Abbreviation of some ligand structures[a]

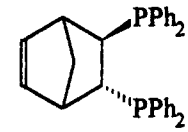
General: Ar=aryl subsituent, nbd=norbornadiene, cod=1,5-cyclooctadiene, dmf= *N,N*-dimethylformamide. Phosphines: generally presented in the order of their first mention in the text.



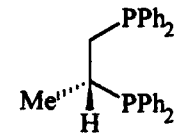
diop[b]
mod-diop[c]



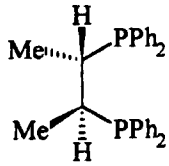
cycphos



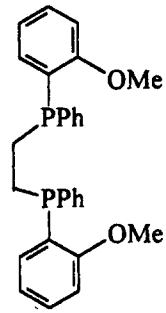
norphos



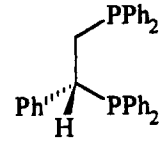
prophos



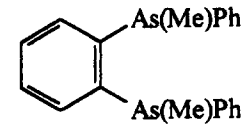
chiraphos



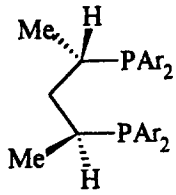
dipamp



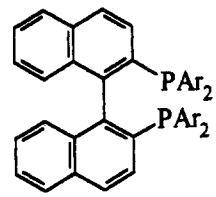
phenphos



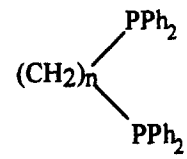
MP(diars)



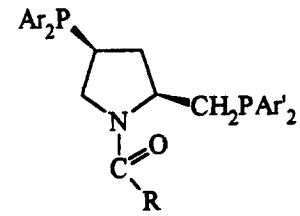
bdpp(skewphos),
Ar = Ph
mod-bdpp[c]



binap[b]
tol-binap[d]

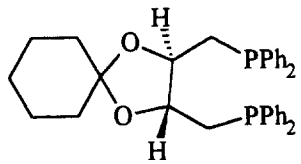


diphos, n = 2
dppb, n = 4

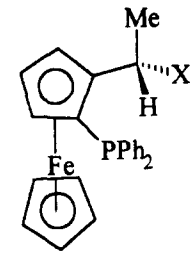


bppm[e]
mod-bppm[f]
bcpm[g]
mccpm[h]

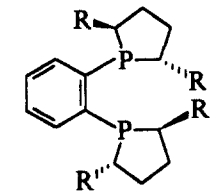
Table 1
(Continued)



diop'



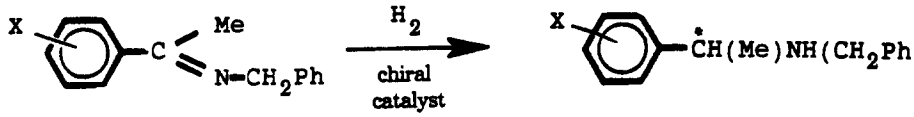
ferrocenylphosphines
X = PR_2^i, NMe_2



Et-duphos, R = Et
^{n}Pr-duphos, R = ^{n}Pr

[a] The ligand *R*- and *S*- configurations are generally omitted in the text and are not indicated in the structures.
[b] Ar=Ph.
[c] Ar=*p*-MeO-*m*,*m*'-$Me_2C_6H_2$.
[d] Ar=*p*-tolyl.
[e] Ar=Ar'=Ph, R =^{t} BuO.
[f] Ar=Ar'=*p*-MeO-*m*,*m*'-$Me_2C_6H_2$, R =^{t} BuO.
[g] Ar=cyclohexyl, Ar'=Ph, R =^{t} BuO.
[h] Ar=cyclohexyl, Ar'=Ph, R=MeNH.
[i] R=*m*,*m*'-$Me_2C_6H_3$.

Until the late 1980s, relatively little attention had been paid to catalytic asymmetric hydrogenation of prochiral imines compared to analogous prochiral ketone and olefin substrates [5,6]. From the earliest reported work in 1975 [7], where for reaction (2) (X=H) e.e. values of ~20% were obtained using a Rh-diop catalyst (see Table 1 for ligand structures), e.e. values had 'advanced' by ~1987 to only the 60–70% range for the same, typical Schiff-base ketimine substrates, and again Rh-chiral phosphine catalysts were optimum; roughly 20 publications to this time, which were largely empirical in reporting recipes for obtaining optimum e.e. values, can be traced through [5,6,8–13]. In the last 8–9 years or so, about 35 further publications have appeared, and these report not only on e.e. values up to ~90% for reactions such as Eq. (2) (and close to 100% e.e. for other specific ketimine substrates), but



(2)

1 [X = H(**a**), *p*-OMe(**b**), *o*-OMe(**c**), *m*-OMe(**d**)]

sometimes also on mechanistic insights; Rh- and Ir-chiral phosphine catalysts, and increasingly Ru catalysts containing phosphines or chiral amines, dominate this newer literature, but one very different, chiral titanocene catalyst has been reported.

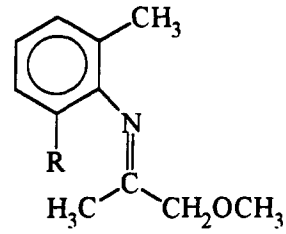
Table 1 lists the abbreviations and structures of some of the ligands mentioned. Table 2 lists the structures of the various imine substrates **2–18**. In each case the product results from addition of H_2 across the (C=N) imine moiety (cf., Eq. (2)). As for the ligand enantiomer used (Table 1), the *R*- and *S*-configurations obtained for the dominant amine product are not presented; such details are to be found in the literature quoted.

The less direct method to chiral amines from imines using a catalytic asymmetric hydrosilylation–hydrolysis procedure [5,9,10], and stoichiometric reductions of imines using chiral borohydride derivatives [14–16], which

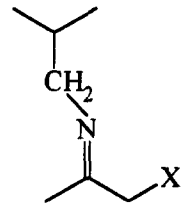
can give e.e. values >90%, are not discussed. Net addition of R–H to an aldimine, using reagents such as RLi and R_2Zn in the presence of a stoichiometric or catalytic amount of an asymmetric controller (typically a chiral ether or alcohol ligand) to give a chiral amine (Eq. (3)), has very recently been reviewed [17] and will also not be covered.

$$R'C(H)=NAr + \text{'RH'} \longrightarrow R'C^*H(R) - NHAr \quad (3)$$

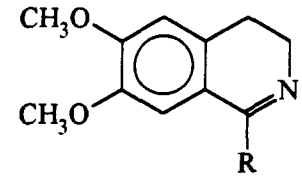
Table 2
Structures of imine substrates **2–18**[a]



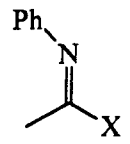
2a, R = Et
2b, R = Me



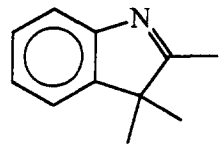
3a, X = H
3b , X = OMe



4
4a, R = Me



5 (X = ^{n}Pr, Ph)



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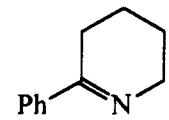

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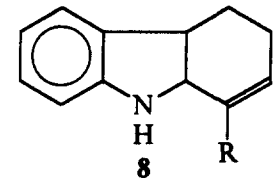

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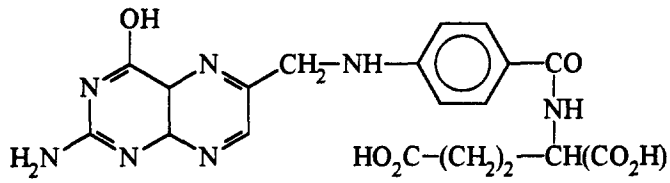

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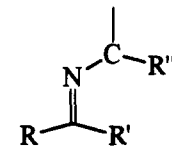

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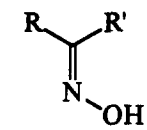

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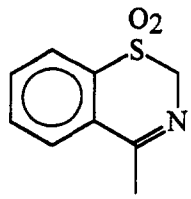

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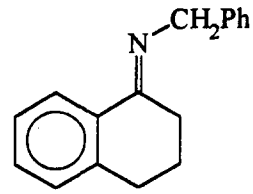

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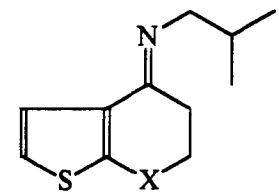

14 (X = S, SO_2)

Table 2
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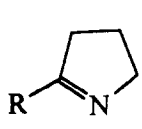

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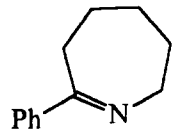

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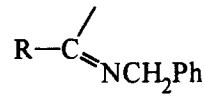
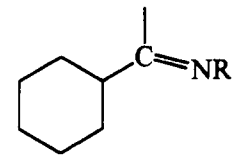


17 (R = alkenyl, alkyl, cyclohexyl, cyclopropyl, 2-furanyl, naphthyl)



18 (R = Me, ^{n}Pr)

[a]If not specified, R, R′ and R″ refer generally to alkyl or aryl groups; the imines are presented in the order of their first mention in the text.

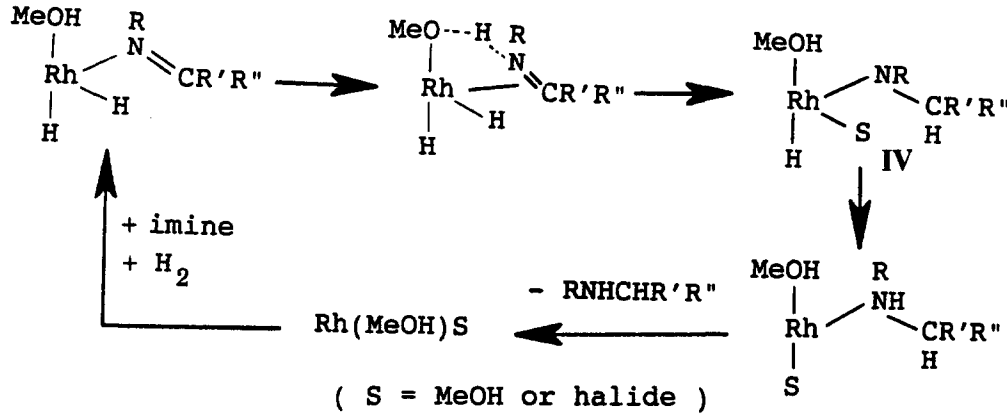
2. Rhodium and iridium systems

The UBC work was initiated through a search for a catalyst to effect enantioselective hydrogenation of **2a** to the secondary amine, which is a precursor to a herbicide, currently marketed as Metolachlor® in the racemic form by Ciba–Geigy [18,19]. Many Rh(I)/phosphine or arsine complexes (chiral and achiral ligands) were tested empirically in order to optimize conversions and e.e. values of **2a** and **2b** [11,13,20]. Parameters tested included: ligand structure, solvent composition, H_2-pressure, temperature, and cocatalysts such as halides and amine bases, the latter being known to promote formation of monohydride species from metal dihydrides, Eq. (4)[3–6].

$$M^{III}X(H)_2 + \text{base} \rightarrow M^{I}(H) + \text{base} \cdot HX \quad (4)$$

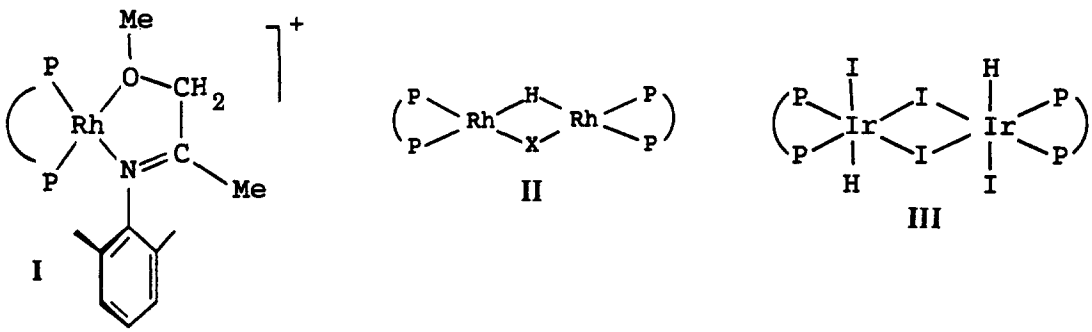
In situ Rh(I) species containing one (P–P) chelating diphosphine/Rh, formed from neutral precursors such as $[RhCl(nbd)]_2$, were more effective than synthesized $Rh(nbd)(P{-}P)^+PF_6^-$ complexes, implying a role for halide (see below), while conversions at 20°C and 70 atm H_2 were optimized in 1:1 $MeOH/C_6H_6$; optimum rates were obtained using diphosphines with a 2-carbon backbone (PR_2–C–C–PR_2), with R=Ar being better than R=alkyl and, of these that were chiral, the cycphos ligand system gave the highest e.e. (53%) with **2b** (norphos gave 45%, prophos 40%, chiraphos 38%, dipamp 25%, phenphos 21%, MP(diars) 3%; the 3- and 4-carbon backbone ligand systems with bdpp and binap, respectively, gave negligible conversions). By 1990 [13], an optimum e.e. value of 69% had been obtained for 100% conversion of **2b** at −25°C in MeOH/toluene, although a 70 h reaction time was needed at 5 mM [Rh] and 0.5 M [**2b**]. Of note, **2b** is available as an approximately 5:1 ratio of *anti*- and *syn*-isomers (determined by geometric arrangements of groups around the planar (C=N) moiety; Table 2 illustrates *anti*-**2**) and, during the hydrogenation, this ratio and the e.e. value were essentially unchanged. This implies that the stereoisomers are either (a) reduced at the same rate (leading in this system to a maximum possible 67% e.e.), or (b) in rapid equilibrium and are reduced at different rates. This point about possible geometrical isomerism of imines was often ignored in earlier imine hydrogenation papers, but clearly may be critical and is now being addressed: such imines isomerize thermally with $\Delta G^{\neq} \sim 80$ kJ mol^{-1} [21], but this barrier for a coordinated imine might be lower.

NMR data at ambient conditions give evidence for species such as **I** with imine **2b** coordinated through the N-lone pair and OMe, and the diphos analog was isolated as $[Rh(diphos)(\mathbf{2b})]BF_4$ [13,20]. The hydrogenation rates increased with H_2 pressure (500–1400 psi) and were independent of [**2b**], findings that favor an 'unsaturate route' in which a rapidly formed $Rh(P{-}P)(imine)^+$ species reacts in a rate-determining step with H_2 to form a $Rh(H)_2(P{-}P)(imine)^+$ intermediate. The essential use of MeOH as a cosolvent for effective conversion was rationalized in



Scheme 1. Suggested role of MeOH in catalytic hydrogenation cycle.

terms of it facilitating a change from η^1- to η^2-binding of the imine [20,22] (see Scheme 1); no such π-bonded imine (cf., olefins and acetylenes) has been reported within mononuclear platinum metal systems, but is probably essential for subsequent H-transfer and there is evidence for this within stoichiometric imine hydrogenations on Rh_2 and Fe_3 complexes [23,24]. Scheme 1 shows a plausible route from $Rh(H)_2$(imine) to the amine with regeneration of the precursor Rh(I) catalyst (the (P–P) ligand and the +1 overall charge for each of the species are omitted). The process invokes an alkylamido species (**IV**) rather than an aminoalkyl (Rh–CR′R″NHR) which would be formed if Rh–H adds across (C=N) in the reverse direction. Reversible β-hydride elimination from an amine ligand to give a *cis*-η^2-iminium hydride species, which is related to the pathway shown, has been demonstrated (at an Os center) [25]. Scheme 1 is shown merely to illustrate the types of intermediates likely involved in imine hydrogenations; corresponding pathways for a monohydride catalyst (cf., Eq. (4)) are readily envisaged, and the Rh–N bond could be cleaved via protonation rather than H-transfer from the metal. Binuclear



steps involving two Rh species (e.g., a hydride and an alkylamido or aminoalkyl) cannot be excluded, and indeed the system could operate via catalytically active dinuclear species (see below).

High-pressure NMR work [26] has revealed the existence of **II** at 1500 psi H_2 (P–P=diphos, X=halide or OMe) during catalyzed hydrogenation of **2b** using $[Rh(diphos)Cl]_2$ as precursor; **II**, however, is unreactive toward imines and no insertion products are detected. **II** could be involved in a rate-determining formation of an insertion product (cf., Scheme 1) that is hydrogenated relatively rapidly at the high H_2 pressure, or it may play no role in the catalysis. In the absence of H_2, in benzene/MeOH solution, RhCl(diphos)(**1b**) and$Rh(diphos)(\mathbf{1b})_2^+$ are formed, each containing η^1-bound imines; related complexes, including some containing chiral (P–P) ligands, have been made with a range of imines, as well as $Rh(P–P)(\eta^1\text{-imine})(MeOH)^+$ species, which in principle offer a direct precursor

to the starting dihydrido species of Scheme 1, although no such dihydride has been detected [13,20,26]. The imines may chelate as in **I** if an appropriate functionality is present (e.g., imine **1c**), but chelation is not essential for high optical yields; thus 90% e.e. values have been realized with **1a** and **1b** using the Rh/cyphos system at −25°C. The aliphatic imine **3a** is hydrogenated but the product is racemic, while **3b** is hardly reduced, and thus an aromatic or benzyl moiety on the imine-N (cf., **2** or **1**, respectively) seems essential for obtaining any chirality in the product, although there is no evidence for interaction of these moieties with the Rh. Cyclic imines exist as a single geometrical isomer and might be expected generally to yield products with higher e.e. values than amines formed from acyclic imines (see below). With the Rh/cycphos system, the cyclic imine **4a** is reduced but surprisingly with 0% e.e.; Rh(diphos)(**4a**)$_2^+$ has been characterized crystallographically [20]. The cyclic imines such as **4** (and **8**, see below) bearing 6-membered rings are of particular interest as the products are naturally occurring cyclic amines; **4a**, for example, generates salsolidine.

The use of halide as cocatalyst often gives improved e.e. values for imine substrates [9,11,20], but reduction of **2** is strongly inhibited by addition of I^-, possibly by preventing formation of the chelated species **I** [13]. Of note, the hydrogenations of the imines (at least with **1** and **2**) are not inhibited by build-up of the amine products which, perhaps because of their steric bulk, do not compete with imines for coordination sites. More work is needed on the appropriate Rh/amine systems; complications have been realized in some related Ru systems (see below).

Non-chiral systems using $[Rh(R_2PCH_2CH_2PR_2)]_2$ (μ-H)$_2$ species (R $=^i$ Pr, O^{i}Pr), cf., **II**, show marginal catalytic activity for hydrogenation of PhN=CHPh at ambient conditions and, although isolated bridged amido-hydride species (**II**, X=NPhCH$_2$Ph) appear plausible catalytic intermediates (cf., Scheme 1), these were inactive toward H_2 [23].

Of interest, the zwitterionic complex $Rh^+(cod)(\eta^6\text{-}PhBPh_3)^-$, containing a coordinated phenyl of BPh_4^-, in the presence of one equivalent of dppb, is effective for hydrogenation of aldimines and ketimines in THF/MeOH under ~500 psi H_2 at 40°C; the catalyst is more effective than the Rh(cod)(dppb)$^+BPh_4^-$ species, implying a role for the coordinated tetraphenylboron group [27]. Also, these non-chiral systems proceed almost as efficiently in neat THF [27].

Bakos et al. [12] have invoked a further role for the often required MeOH; they showed that within Rh(*S,S*-bdpp)(diene)X species, where X is ionic ClO_4^- or coordinated Cl^-, the conformation of the 6-membered (P–P) ring varies in the solid state with the diene (chair for nbd, and δ-skew for cod). NMR data in MeOH suggest that the δ-skew conformation is favored within square-planar Rh(P–P)(diene)$^+$, independent of diene, while in benzene a trigonal bipyramidal RhCl(diene)(P–P) species with a chair conformation is favored. Decreasing e.e. for substrate **1a** with decreasing MeOH content in MeOH/benzene mixtures (a maximum of 83% *R*, using 70 atm H_2 at 0°C), and a gradual change to predominantly *S* product at higher temperatures, were qualitatively correlated with the observed conformational changes.

In 1990, Osborn's group [28,29] and a Ciba–Geigy group [30] reported on the use of Ir-chiral (P–P) systems to hydrogenate **2**; further P–P ligands used include bppm and diop′. In situ systems [30], analogous to the Rh ones discussed above, gave similar yields and e.e. values under comparable conditions in MeOH/benzene, but now the bdpp system was optimum, especially in the presence of added I^-; other ketimines such as **5** and **6** gave e.e. values up to 66%.

Isolated Li[Ir(P–P)I$_4$] and [Ir(H)I(P–P)]$_2$(μ-I)$_2$ complexes were also used [28], and the latter, which exist as a mixture of two geometrical isomers with the hydrides transoid(**III**) or cisoid, gave an optimum 63% e.e. for substrate **2b** (P–P=diop) and 80% for **6** (P–P=bdpp) in 3:1 THF/CH_2Cl_2, MeOH again not being an essential ingredient. Remarkably, the optimum Ir systems utilize bdpp and diop, phosphines that are very ineffective with Rh, and the I^- cocatalyst is a poison in the Rh system for substrate **2**! Such findings lead to severe problems in designing effective catalysts by other than empirical testing; however, some consistency is present in that kinetic data on systems involving [Ir(H)I(diop)]$_2$(μ-I)$_2$ favored an unsaturate route akin to that given in Scheme 1, although no evidence was presented for the presence of Ir(imine) species [28].

Tani et al. [31] have found that primary and secondary amines are useful cocatalysts for in situ, neutral and cationic Ir(I)/binap (or tol-binap) catalytic systems in MeOH for hydrogenation (60 atm H_2 at 20°C) of **1a** and **7**;

thus addition of, for example, benzylamine (amine: Ir=5) increased e.e. values from ca. 20% to 70%, and from 40% to 90%, for complete conversion of **1a** and **7**, respectively. A neutral Ir/tol-binap catalyst was effective for **7** in benzene (up to 89% e.e.) and now addition of benzylamine essentially stopped activity, while addition of MeOH or EtOH enhanced conversion rates.

Of note, the Ciba–Geigy group has very recently reported on a commercially viable system for asymmetric hydrogenation of **2a** [19] by use of in situ $[IrCl(cod)]_2$/chiral ferrocenyl-diphosphine ligands, particularly the one shown in Table 1 with $X=PR_2$ [32]. Effective iodide-promoted systems were realized using neat imine/acetic acid (2.5:1) as medium under 25–80 atm H_2 at 30–50°C; e.e. values of 79% (with 'purified' imine) were recorded and, significantly, complete conversion with imine:catalyst=5×10^5 occurred within 12 h at 50°C and 80 atm H_2. A total turnover of 10^6 was achieved in 30 h. Rh(I) complexes with a ferrocenyl (P–N) ligand (Table 1, $X=NMe_2$) were not effective for hydrogenation of **2a** [13].

Achiwa's group [33] has used an in situ Ir(I) complex containing mod-diop or mod-bdpp ligands to effect complete hydrogenation of **1a** and **6** with e.e. values up to 46 and 81%, respectively (at 20°C, 100 atm H_2, benzene/MeOH (1:1) using $^nBu_4I$ or BiI_3 as iodide-promoter); diop- and bdpp-based catalysts were less effective, while the Rh(I) analogs with any of the 4 chiral (P–P) ligands generated only racemic amines. Related iodide-promoted Ir systems using bcpm or mccpm were also effective for **6** (up to 91% e.e. at −30°C) but less so for **1a** (up to 21% e.e.) [34]. An optimum e.e. of only 30% was obtained for **4a** and **8** using the various iodide-promoted Ir catalysts [33,34]. However, an extensive search unearthed 5-membered-ring imides (e.g., succinimide, phthalimide) as extremely effective promoters for enantioselective hydrogenation of **4a**, and with imide: Ir=4 in toluene at ~5°C, 93% e.e. was achieved [35]. The role of the imide remains to be clarified, although the imidato ligand formed by loss of a proton has strong σ-acceptor and moderate π-donor properties resembling those of a halogen ligand [36].

The possibility that imines might be hydrogenated via the enamine tautomer (e.g., $RC(Me)=NR' \rightleftharpoons RC(=CH_2)NHR'$) has been ruled out using D-labeling studies in some of the Rh– and Ir–(P–P) systems [26,29].

Bakos et al. [37] and a DSM group [38] have shown that imines **1** are completely hydrogenated to amines with up to 96% e.e. in a few hours using in situ $[Rh(cod)Cl]_2$/sulfonated-bdpp catalysts in a 2-phase H_2O/EtOAc system at 20°C and 70 atm H_2. The optimum catalyst is one containing a single $m-SO_3^-Na^+$ group in just one of the four phenyl groups of bdpp [38]; this monosulfonated bdpp ligand now consists of two epimers because of chirality induced at one P atom, but the catalysis is effected using the mixture of the two in situ Rh complexes.

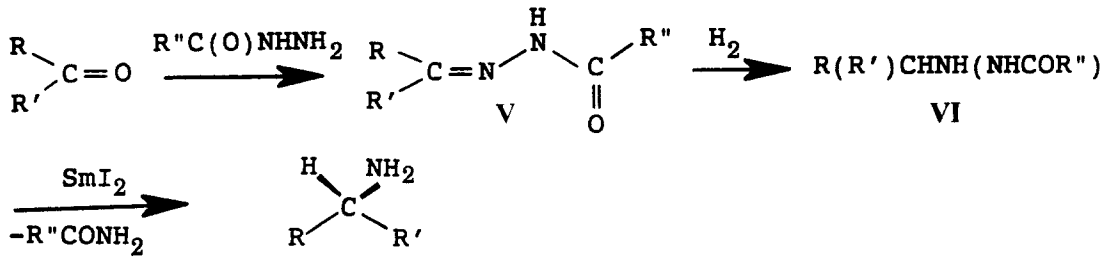
Immobilized Rh(I)(P–P) species supported on silica gel reduces the C=N bonds in the pyrazine rings of folic acid (**9**) under 40 atm H_2 in aqueous solution at 80°C; an optimum diastereomeric excess of 24% (there is an L-glutamic acid side-chain) was obtained using bdpp [39].

Attempts at reducing prochiral imines using hydrogen transfer, Rh-based catalysts, e.g., with 2-propanol as an H_2-source, have been largely unsuccessful thus far [40–42]; under such conditions, an isomerization of ketimine **1a** to the achiral aldimine PhCH(Me)N=CHPh has even been noted [42].

The DSM workers [43] have hydrogenated chiral imines such as **10**, using in situ Rh(I)–(P–P) catalysts under 70 atm H_2 (P–P=diop, prophos, chiraphos, and bdpp), with very high diasteroselectivity in the case of bdpp to give a single diastereomer of secondary α-methylbenzyl amines (e.g., when R=R″=Ph, R′=Me). The difference in hydrogenation rates of the imine enantiomers also led to successful kinetic resolution of racemic imine substrates (not necessarily prochiral at the imine bond) with remaining imine having 19–98% e.e.; the highest value was realized with **10** (R=2-MeO–Ph, R′=Me, R″=Ph).

Burk et al. [44,45] have devised an impressive route to optically active primary amines (as opposed to the secondary amines discussed so far) via hydrogenation of functionalized imines, followed by a reductive amination procedure, Eq. (5). Arylalkyl ketones and α-keto esters(e.g., $R'=CO_2Me$) are first converted to their *N*-aroylhydrazone derivatives (**V**), which are then hydrogenated catalytically with 1 atm H_2 from −10 to 20°C in 2-propanol using $Rh(cod)(Et\text{-}duphos)^+$ as precursor; subsequent cleavage of the N–N bond within **VI** using SmI_2 liberates the amines with 85–97% e.e. The α-keto ester substrates provide a simple route to chiral α-amino acids. The bdpp, chiraphos and binap systems were less effective (slower and a maximum 23% e.e.). The carbonyl function of the

hydrazones was essential, presumably for chelation of imine **V**, as simple imines such as **5** were not reduced. Hydrolysis of **VI** yielded the corresponding chiral hydrazine compounds R(R′)CHN(H)NH_2 [44,45].



(5)

3. Ruthenium systems

In 1981, the complex $Ru_4H_4(CO)_8(diop)_2$ was reported to catalyze hydrogenation of **1a** and oximes (**11**) (the latter yielding R′RCHNH_2) at 130°C, 100 atm H_2, but with <15% e.e. [8], while an observed phosphine-free, $Ru_3(CO)_{12}$-based transfer hydrogenation (from 2-propanol) of the achiral PhCH=NPh was later suggested to occur via an isolated $Ru_3(CO)_9(\mu_3$-PhNCPh) species in which hydrogen has been abstracted from the benzylideneaniline unit [46]; $Ru_3(CO)_{12}$ in DMF or pyridine has also been used under CO/H_2 (up to 100 bar) at ~100°C for reduction of **5** and related aldimines [47]. However, carbonyl-containing Ru species are generally rather poor hydrogenation catalysts [48].

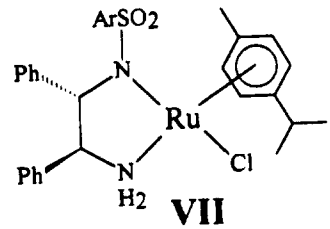
My group reported in 1985 [49] that RuCl(dppb)$(MeCN)_3^+$ catalyzed slowly the H_2-hydrogenation of aldimines (RCH=NR′) under mild conditions (1 atm H_2, 50°C), and then later reported that related trimeric hydride species $[Ru(H)Cl(P–P)]_3$ (P–P=dppb, chiraphos [50]) behaved similarly [5,51]. A range of neutral and cationic mononuclear Ru complexes and neutral dinuclear Ru_2 complexes containing chiral (P–P) ligands was then tested for hydrogenation of **1a**, and hydrogenation of PhC(R^1)=NR^2 substrates was tested with dppb systems (R^1=H or Me, R^2=Me, $CHMe_2$, CH_2Ph, cyclohexyl, Ph) [52]. The hydrogenations were best effected in MeOH under 70 atm H_2 at 20°C; alcohol solvents were essential and a reactivity trend (MeOH>EtOH>2-propanol) is consistent with an alcohol-binding step in the catalysis (cf., Scheme 1). The readily synthesized Ru_2(III,II) mixed-valence, air-stable $[RuCl(P–P)]_2(\mu$-$Cl)_3$ complexes may be used to generate in situ under H_2 the air-sensitive $[RuCl(P–P)]_2(\mu$-$Cl)_2$ species, which appear to be the optimum catalysts. High conversions were obtained with these species; a maximum of only 27% e.e. was realized with substrate **1a** using P–P=chiraphos (diop and binap are less effective), but conditions remain to be optimized [52]. The hydrogenations were not poisoned by build-up of the bulky secondary amine products, but were sensitive to the presence of primary amines derived from metal-promoted imine hydrolysis [52,53]. Kinetic and spectroscopic data again favored an unsaturate route, possibly involving a catalyst precursor of the type $RuCl_2(P–P)(MeOH)_2$ [52]; mononuclear Ru(II)-imine [53,54] and dinuclear Ru_2Cl_4 $(dppb)_2$(imine) species [53] invariably contain η^1-binding of the imine via the N-lone pair. The reduction rates were largely consistent with expected steric effects of the R^1 and R^2 substituents.

The complexes $[Ru(H)Cl(P–P)]_3$ (P–P=diop, chiraphos) effect complete conversion of imine **2b** (70 atm H_2, 20°C, MeOH/benzene), but with <10% e.e. [55,56]. An in situ catalyst formed from $[Ru(arene)Cl_2]_2$ and binap in MeOH/C_6H_6 with small amounts of water has been used at ~100 atm H_2 to hydrogenate oximes (**11**) to a mixture of RR′CH(NH_2) and RR′CH(OH) [57]; a maximum 29% e.e. was obtained for 1-phenyl-2-aminopropane (R=$PhCH_2$, R′=Me) with this catalyst system that was assumed to generate the known complex [RuCl(benzene)(binap)]Cl [58].

A notable hydrogenation of the cyclic imine **12** to the enantiomerically pure sultam product has been achieved using a residue formed from $[RuCl_2(cod)]_2$/binap/NEt_3 as a catalyst in EtOH/CH_2Cl_2 at 4 atm H_2 and 22°C [59]; the

catalyst was assumed to be $Ru_2Cl_4(binap)_2(NEt_3)$, or more precisely $RuCl(binap)(\mu\text{-}Cl)_3Ru(NEt_3)(binap)$ [58]. Many such triply chloride-bridged species containing (P–P) ligands are known [60]; whether under hydrogenation conditions the NEt_3 complex forms $[Ru(H)Cl(binap)]_3$, analogous species being known for chiraphos, diop and dppb [5,50,51,55,56], remains to be established. The $Ru_2Cl_4(binap)_2(NEt_3)$ readily undergoes dealkylation of the amine to generate $(NH_2Et_2^+)[Ru_2Cl_5(binap)_2^-]$ [53,61]; the anions within such complexes have been characterized structurally [62,63].

The above Ru systems all utilize H_2 gas as the hydrogen source. Preliminary studies using the less hazardous 2-propanol as the hydrogen source with Ru/chiral phosphine systems are not encouraging. Thus, although the $RuCl_2(PPh_3)_3$ complex catalyzes hydrogen transfer from basic 2-propanol solution to aldimine and ketimines [64,65], related dinuclear Ru_2 species containing binap or chiraphos, and $[Ru(H)Cl(chiraphos)]_3$, are not very effective [55,56]. However, a major breakthrough in effecting asymmetric hydrogenation of imines with Ru catalysts has very recently been reported by Noyori's group [66]. The catalyst precursors, containing chiral, *N*-tosylated 1,2-diamine ligands [67,68], are made from $[RuCl_2(arene)]_2$, arene=benzene or *p*-cymene, and a 5:2 formic acid/NEt_3 azeotropic mixture in MeCN provided an optimum medium with formic acid being the source of hydrogen (again, 2-propanol was not effective); **VII** with Ar=*p*-MeC_6H_4 gave complete reduction of **4a** at [substrate]:[Ru]=200–1000 in a few hours at 28°C with 95% e.e. – a truly remarkable achievement. Use of substrate **4** with R=alkyl, benzyl or aryl gave products with e.e. up to 95%, and provides a new general route to isoquinoline alkaloids. The same catalyst system in dmf allowed for synthesis of optically active indoles from **8** with up to 97% e.e. The acyclic imines **1a**, **13**, and **14** were reduced with up to 89% e.e.; the chiral amines formed from **14** serve as intermediates for the synthesis of a carbonic anhydrase inhibitor. Further, the systems show high chemoselectivity for C=N versus C=O moieties; e.g., **4a** can be reduced even in acetone with <5% production of 2-propanol [66].

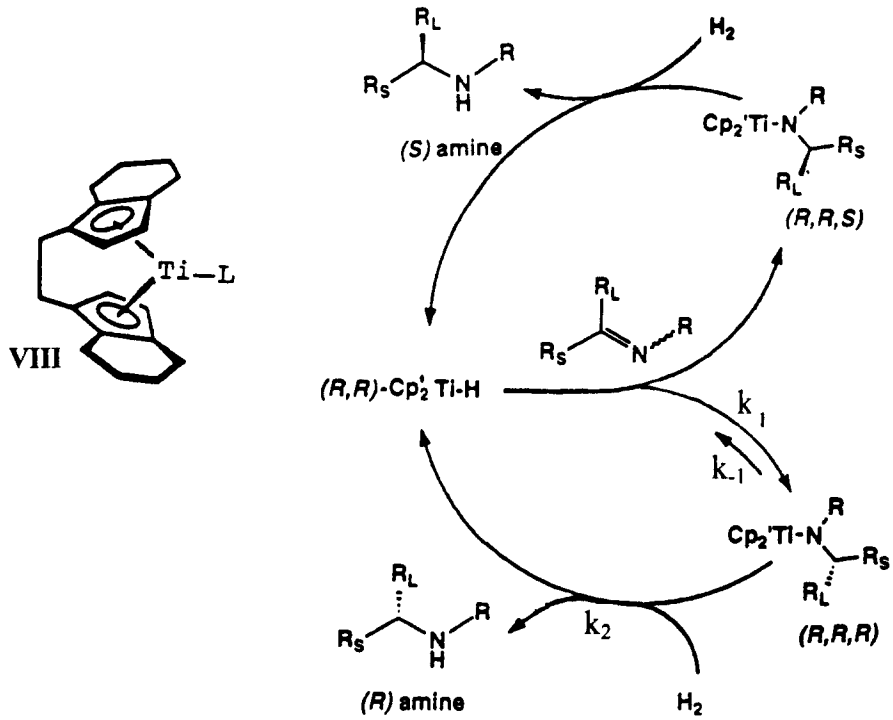


VII

4. Titanium systems

A very different type of catalyst has been reported by Willoughby and Buchwald [69–71], who have used the chiral *ansa*-titanocene **VIII** (L=chelated 1,1′-binaphthyl-2,2′-diolate) as catalyst precursor for hydrogenation (typically at 65°C, 6–145 atm H_2) of the cyclic imines **4a, 15** (and other 2-substituted pyrrolines), **7** and **16** to give products with 95–99% e.e.; acyclic imines such as **1a, 1b, 17** and **18** yielded products in the 53–92% e.e. range. The catalyst is preformed by treating **VIII** successively with ^{n}BuLi and phenylsilane, which is considered to generate a stabilized hydride (**VIII**, L=H). Such early transition-metal chiral catalysts have been developed previously for asymmetric reduction, and stereochemically controlled polymerizations, of olefins [72].

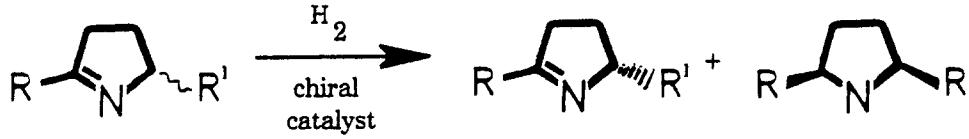
Kinetic and mechanistic studies (including deuterium labeling) on the catalyzed hydrogenation of **15** (R=Ph) and **17** (R=cyclohexyl) have been interpreted in terms of the basic pathways shown in Scheme 2, where the k_2 step (reaction of an alkylamido species with H_2) is rate-determining; the insertion (k_1 step) is considered to be fast relative to hydrogenolysis (k_2 step) and β-H elimination (k_{-1} step), while the β-H elimination (which generates some of the aldimine RCH(Me)N=CHPh from **17**) is slow relative to hydrogenolysis [71]. The rate-law (k_2[Ti][H_2]) parallels that found for a Rh system discussed earlier, and still corresponds to an 'unsaturate route' (cf., Scheme 1),



Scheme 2. Cp_2' =ethylene(bis-tetrahydroindenyl); R_S and $R_L$refer to the smaller and larger substituents, respectively.

but now modified because the precursor Ti catalyst is believed to be a monohydride, although there is no direct evidence for this [69–71]. The cyclic imines (of *anti* geometry) were reduced at lower pressures, while higher pressures were needed to reduce the acyclic imines that exist as interconverting *syn*- and *anti*-isomers during the catalysis with the *syn*-isomer being hydrogenated more rapidly. A stereochemical model based on steric and electronic considerations was proposed to account for the experimentally observed configurations of the amine products. Of note, η^2-bonded imines within mononuclear Ti species are known [73].

Buchwald's group has used the same Ti catalyst system for kinetic resolution of racemic disubstituted 1-pyrrolines [74]; e.g., after 50% conversion, the reactant pyrroline and the *cis*-pyrroline product of the reaction shown in Eq. (6) were obtained with e.e. values >95%. The Ti system is not sufficiently active for commercial application [19].



(6)

5. Conclusions

The 1988–1996 period has seen major developments in the field of catalytic asymmetric homogeneous hydrogenation of imines, even though most of the studies have involved empirical testing for a matching of

metal, ligand and substrate. Effective catalytic systems have been reported; cyclic or aryl-containing imines generally yield higher e.e. value products; metal-imine and -hydride species, present under catalytic conditions, have been characterized; and kinetic data tend to favor unsaturate routes. The Ciba–Geigy Ir/ferrocenyldiphosphine systems that operate under moderate H_2 pressures, and Noyori's Ru/chiral diamine/formic acid hydrogen transfer systems, prove that commercial, homogeneous catalytic processes will be developed for production of chiral amines.

Complications and further points that need addressing more generally in imine hydrogenations include: (a) the geometrical isomerization of imines, (b) the isomerization of ketimines to aldimines, (c) poisoning of the catalyst by amines formed as hydrogenation or hydrolysis products, (d) the general chemistry of the metal-imine and -amine species, particularly under catalytic conditions, (e) the reason(s) for the generally slow hydrogenations that often require H_2 pressure to obtain measurable rates and (f), possibly related to (e), are the non-detected η^2 (π-bonded) imine species required as intermediates, and is the sometimes required alcohol, H-bonding solvent playing a role in assisting their formation?

Acknowledgements

I thank sincerely: all my co-workers (students, postdoctoral fellows and faculty) who have worked on imine hydrogenations over the last 15 years or so – their names appear in Refs. [5,11,13,20,26,27,40,49–53,55,56,60,62]; NSERC of Canada for funding via Operating, Negotiated Development, and Collaborative Grants; Ciba–Geigy for financial support and samples of **2a** and **2b**; Research Fellowships from the Killam Foundation administered by the Canada Council and UBC; Johnson Matthey Ltd. and Colonial Metals Inc. for loans of Rh and Ru chlorides.

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