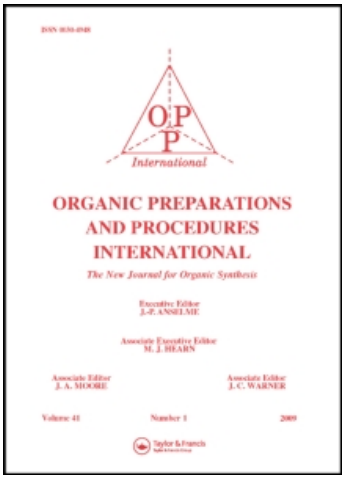

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HOMOGENEOUS RHODIUM(I)-CATALYZED REDUCTIVE AMINATIONS

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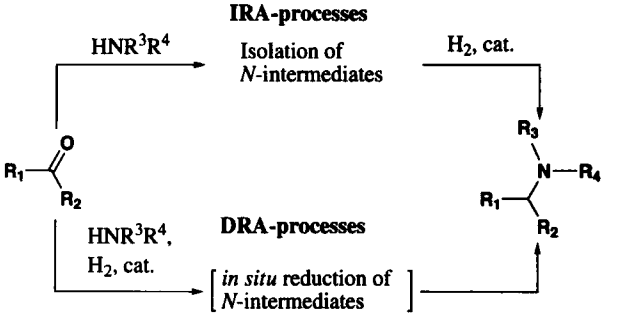
INTRODUCTION

The conversion of aldehydes and ketones into primary or secondary amines is an important reaction in organic chemistry with a huge synthetic potential for applications in academia and industry.[1] The most straightforward reaction for this chemical transformation is the reductive amination of suitable carbonyl compounds *(Scheme 1)*. Different reducing agents, such as $LiAlH_4$, $NaBH_4$, $NaBH_3CN$, $Zn(BH_4)_2$, DIBAL-H, etc., have been suggested for this conversion.[2] Taking into account the demand for atom economy, the most appealing hydrogen source is molecular hydrogen,[3,4] which has to be activated by a catalyst during the reaction.



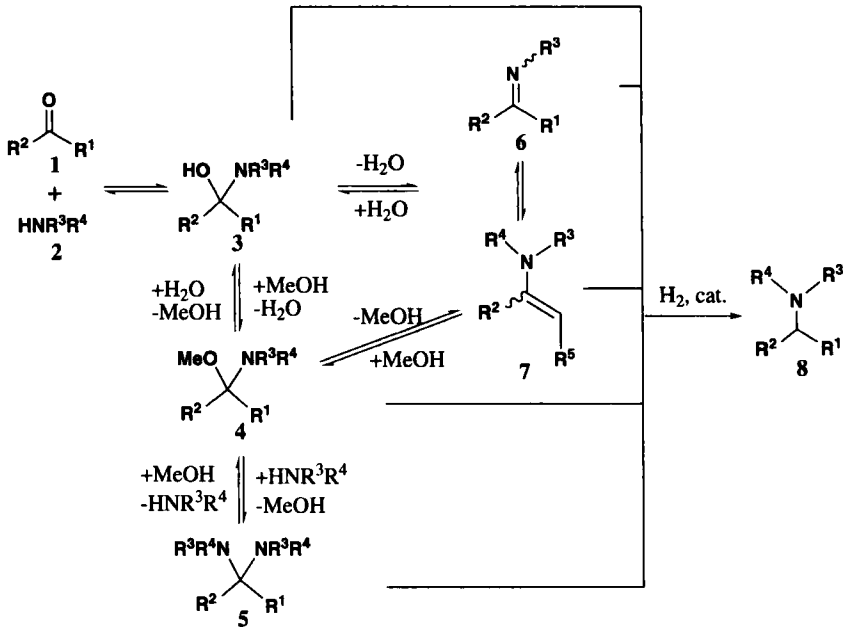
General Approaches for Reductive Aminations

Scheme 1

Usually the reductive amination is concerned with the hydrogenation of imines and enamines easily available by condensation of ketones and aldehydes, with the appropriate amines. This method requires two steps and includes the prior synthesis and isolation of corre-

sponding substrates. For this method, the terms indirect reductive amination (***IRA***) or *aminoalkylation* were introduced. In an alternative approach, a mixture of carbonyl compound and amine is directly treated in the presence of a reducing agent. This methodology is called direct reductive amination (***DRA***)[2] or *single stage* amination.[5]

In contrast to IRA-processes, where a defined starting material is employed for the hydrogenation step, in DRA *N*-intermediates of different nature may be subjected to hydrogenation. For example in MeOH as solvent such intermediates are hemi-aminals **3**, *N,O*-acetals **4**, aminals **5**, imines **6** and enamines **7** being essential for the outcome of the reaction (*Scheme 2*).[6]



Possible Intermediates in Direct Reductive Amination (DRA)

Scheme 2

In specific cases, such as with formaldehyde and ammonia for example, some additional intermediates are possible in the equilibrium. The occurrence of each intermediate is influenced by the nature of the carbonyl compound **1** and starting amine **2** as well as by the reaction conditions. Reductive aminations with H_2 can be mediated by heterogeneous platinum, palladium, nickel or ruthenium catalysts.[3] Several amines have been prepared by this methodology even on an industrial scale. However, heterogeneous catalysts may have serious disadvantages, such as low reproducibility of preparation. Since well defined homogeneous catalysts can be synthesized and manufactured in a reproducible manner, they are better suited for this task.[7] The possibility of using enantioselective catalysts for asymmetric synthesis broadens their potential. In particular rhodium(I)-complexes bearing trivalent phosphorus compounds as ancillary ligands have a large potential for the activation of hydrogen.

The present review will summarize some recent developments in the field of IRA- and DRA- processes catalyzed with homogeneous rhodium(I)-catalysts. When appropriate, non-

asymmetric and asymmetric reactions will be compared. Other hydrogenation reactions leading to amines such as the reduction of nitriles or oximes will not be considered.

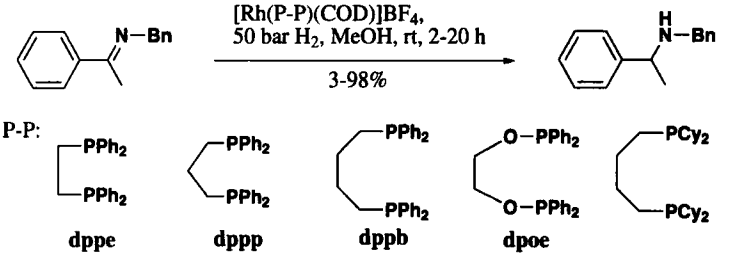
I. HYDROGENATION OF UNSATURATED AND SATURATED NITROGEN SUBSTRATES

Among possible precursors for amines in reductive aminations, unsaturated substrates such as imines and enamines are the most prominent. The reduction of saturated nitrogen species like hemi-aminals, *N,O*-acetals and aminals have been less investigated.

1. Hydrogenation of Imines

a) General Aspects

Up to now, non-stereoselective hydrogenations of imines have been mainly achieved by heterogeneous catalysts.[8] In a systematic study concerning the identification of the most reactive homogeneous catalysts, we found that Rh(I)-complexes bearing ancillary *P*-ligands can also be useful for this reaction.[9] *N*-(1-Phenylethylidene)benzylamine was employed as a test substrate (*Scheme 3*). In the presence of 0.2 mol% of the catalyst and under an initial H_2 pressure of 50 bar, the substrate was smoothly converted into the desired amine. Chelating diphosphines,



Homogeneous Catalyzed Hydrogenation of Imines

Scheme 3

capable of forming 7-membered metallacycles with the metal, displayed higher activities than catalysts based on smaller chelate rings. Dialkylphosphines as ligands performed inferior compared to diarylphosphines. Interestingly, the use of a Rh(I)-complex bearing an electron-deficient ligand, such as the diphosphinite [*dpoe* = 1,2-*O*-dihydroxyethane-bis(diphenylphosphinite)] resulted in a rather efficient hydrogenation of the imine. Obviously, the hydrogenation of imines is not subject to the same effects as the reduction of ketones, where the use of electron-rich phosphine ligands have been shown to be advantageous.[10] When phosphines as ligands were employed, the addition of TsOH increased the rate of the reaction, whereas in case of the phosphinite complex, the addition of this acid had no effect.

b) Enantioselective Hydrogenation of Imines

In contrast to the high enantioselectivities reported in the hydrogenation of olefins and ketones, only limited success has been achieved in the catalytic asymmetric hydrogenation of

prochiral imines although the reaction is of considerable industrial interest.[11] Up to now, a range of Rh-, Ir- and Ru-complexes have been investigated in detail.[12] Chiral biphenyl-bridged titanocene complexes also exhibited good to excellent enantioselectivities.[13]

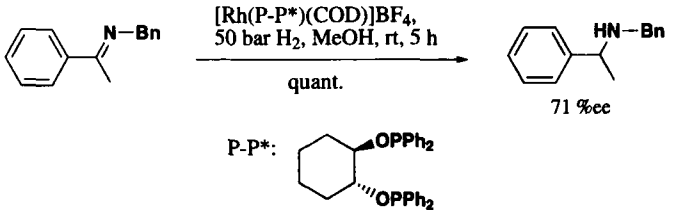
As ligands for rhodium(I), chiral diphosphines were preferred. Unfortunately, in comparison to other homogeneous catalysts, the activity of Rh-diphosphine complexes is low and therefore most of them are of limited practical use. Interestingly, several diphosphines which are reputed to induce high enantioselectivity in hydrogenation of other prochiral substrates fail or give poor results in this particular reaction. In several instances, Ir-catalysts were found to be superior.[14]

The presence of additives such as amines,[15] imides,[16] halides[17] or sulfonates[18] is frequently required to avoid deactivation of the Rh-catalyst and to achieve satisfactory yields or/and enhanced degree of enantioselection. The highest enantioselectivities (94-96% *ee*) reported up to now were obtained with chiral sulfonated diphosphines as ligands in an aqueous biphasic medium.[19] Interaction of the sulfonate anion with the metal may play an important role for the achievemenent of a high percentage *ee*.[18]

As alternative substrates, *N*-acylhydrazones[20] or *N*-diphenylphosphinyl ketimines were considered.[21] From the mechanistic point of view, in addition to the imine moiety the C=O/P=O-functionalities could act as second anchoring group and facilitate the chelation of the substrate to rhodium. This arrangement is considered as a precondition for the achievement of high enantioselectivity. However, this approach would require additional reaction steps and it seems therefore only of academic value.

It is interesting to note that, besides diphosphines, other chelating *P*-ligands were rarely employed.[22,23] We found that the asymmetric Rh-catalyzed hydrogenation of *N*-(1-phenylethylidene)benzylamine with diphosphinites and diphosphites as ligands is possible (*Scheme 4*).[9] In non-polar solvents such as toluene or methylene chloride, the conversion was less efficient. By addition of *p*-toluenesulfonic acid, the degree of the conversion could be improved in some instances. The presence of iodide or *t*-BuOK diminished the rate of the hydrogenation. Addition of alkoxides increased the *ee* slightly. Best results were obtained with a rhodium(I)-complex with (*R*,*R*)-1,2-cyclohexanol-bisdiphenylphosphinite [(*R*,*R*)-bdpch] as chiral ligand. This reaction proceeded to completion without any additive within 5 h in 71% *ee* enantioselectivity.

The problem of poor reproducibility of the *ee* observed in some cases is noteworthy.[9,17a] Redistillation of the solvent, repeated recrystallizations of the substrate and addition of water or acetophenone did not improve the *ee*. It was found that distillation of the substrate *in vacuo* was important to reproduce the enantioselectivity. The *ee* value of the product did not depend on the pressure (50 bar and 100 bar), the temperature (15 and 25°C) and the concentration of the catalyst (1.0 and 2.5 mmol/L) as well as the on concentration of the substrate (0.5 and 0.1 mol/L). It was also found that, at a molar substrate:[Rh(bdpch)COD]BF_4 ratio of 500:1, more than 98% of the substrate was converted into the product within 5 h at room temperature. A cationic Rh-NBD (NBD = norbornadiene) complex was as efficient as the COD (COD = 1,5-cyclooctadiene) pre-catalyst.



(*R*,*R*)-bdpch

Homogeneous Catalyzed Enantioselective Hydrogenation of Imines

Scheme 4

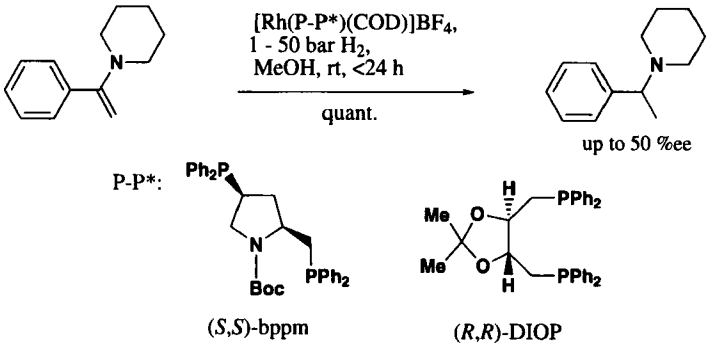
In addition, results described by Fernandez *et al.* showed that rhodium complexes bearing chiral phosphonite and phosphite ligands derived from BINOL are powerful catalysts for the hydrogenation of *N*-aryl and *N*-alkylimines.[24]

2. Enantioselective Hydrogenation of Enamines

Much effort has been focused on the hydrogenation of enamine derivatives with Rh(I)-complexes bearing chiral phosphorus ligands. For example the preparation of optically active amino acids by enantioselective hydrogenation of *N*-acyl-dehydroamino acids and their esters is an important method and has been extensively reviewed.[25] This reaction serves also as a benchmark test for new chiral ligands and catalysts. Currently, a broad range of catalysts, which provide the desired *N*-acylamino acids in extremely high enantioselectivities, is available.[26] Some of the Rh-complexes are also useful for the enantioselective reduction of less functionalized enamides forming *N*-acyl amines.[27]

It is widely accepted that the formation of a chelate ring of the enacylamide moiety with rhodium is crucial for the achievement of high enantioselectivity (see also Section 1b).[28] Therefore, it is not surprising that very little is known concerning the hydrogenation of non-functionalized enamines. However, this reaction offers several advantages from the synthetic point of view. Since the introduction of *N*-acyl groups is not required, the product amines are obtained directly from the hydrogenation procedure. With the remarkable exception of chiral titanocene catalysts,[29] which frequently require rather severe reduction conditions, other homogeneous transition metal complexes have been rarely described for the asymmetric hydrogenation of electron-rich enamines. It is worth mentioning however, that hydrogenation of enamines has been observed under hydroformylation conditions (CO/H_2) with $[Rh(COD)Cl]_2$ as a precatalyst.[30]

Recently, we investigated some examples of the asymmetric hydrogenation of enamines with cationic Rh(I)-catalysts bearing chiral *P*-ligands, such as diphosphines and diphosphinites.[31] As a test substrate α-*N*-piperidinylstyrene was chosen which was reduced to α-*N*-piperidinylethylbenzene (*Scheme 5*). The reactions were carried out at varying initial H_2 pressures between 1 and 50 bar. Unexpectedly, under these conditions the Rh(I)-catalyst (0.2 mol%) of (*S*,*S*)-*bppm* mediated the full conversion of the substrate within 18 h and afforded the (*R*)-configurated amine in 50% *ee*.

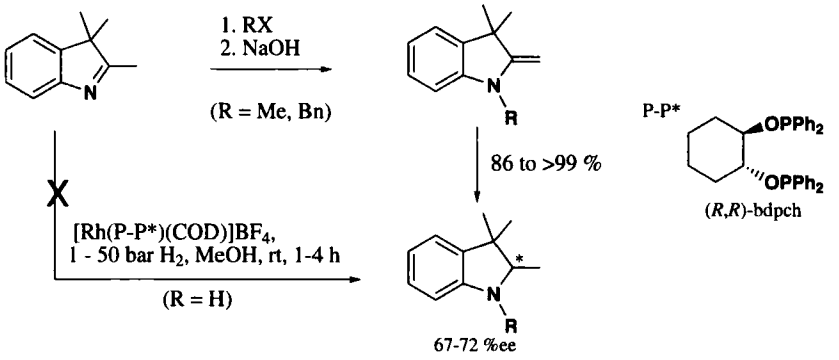


Homogeneous Catalyzed Enantioselective Hydrogenation of Enamines

Scheme 5

Similarly, high conversion was observed with the corresponding (*R,R*)-DIOP catalysts although the enantioselectivity was lower. Comparison of the degree of conversion achieved after 2 h clearly showed that the *bppm* catalyst was much less effective than the corresponding DIOP complex. Even under an initial pressure of 1 bar, the DIOP catalyst (2 mol%) gave full conversion after 2 h. It is noteworthy, that reduced pressure slightly increased the enantioface discriminating ability of the DIOP complex in this reaction. It is remarkable that under these conditions applied Rh(I)-complexes with diphosphinites also reduced the enamine to the desired amine in quantitative yields.

Hydrogenation of enamines may, in principle, be a useful alternative to the reduction of the corresponding imines. Thus, up to now 2,3,3-trimethylindolenine could only be reduced by employment of iridium complexes, whereas rhodium catalysts failed (*Scheme 6*).[32] However,



Imine *versus* Enamine in Enantioselective Hydrogenation

Scheme 6

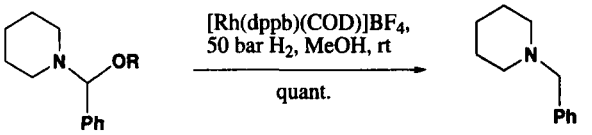
after prior alkylation of the imine to the corresponding *N*-methyl- or *N*-benzylenamines, these enamines were quantitatively reduced in MeOH to give the desired amines by application of the Rh(I)-(*R,R*)-*bdpch* catalyst (1 mol%) at 1 bar of hydrogen within 4 h.[31] The *N*-methylamine derivatives were obtained by up to 86% *ee*. Increasing the initial hydrogen pressure to 50 bar

shortened the reaction time to 0.5 h even by the use of only 0.2 mol% of the catalyst. It is noteworthy that the corresponding DIOP complex afforded only racemic product, although its hydrogenation activity was also quite good.

3. Homogeneous Catalyzed Cleavage of N,O-Acetals and Related Compounds

a) General Aspects

As indicated in *Scheme 2*, hemi-aminals, *N,O*-acetals and aminals can be intermediates in IRA-processes. Hemi-aminals have been postulated as intermediates in the heterogeneously catalyzed DRA for amine production.[3] Unfortunately, they are rather unstable and undergo cleavage into aldehyde and amine. Therefore up to present, there is no proof for its reducibility. In contrast, *N,O*-acetals are much more stable. In a hydrogenation study with $[Rh(dppb)(COD)]BF_4$ as a pre-catalyst, we found that *N,O*-acetals derived from the reaction of PhCHO with piperidine in MeOH can be cleanly reduced to the corresponding amines at 50 bar initial hydrogen pressure *(Scheme 7)*.[33]

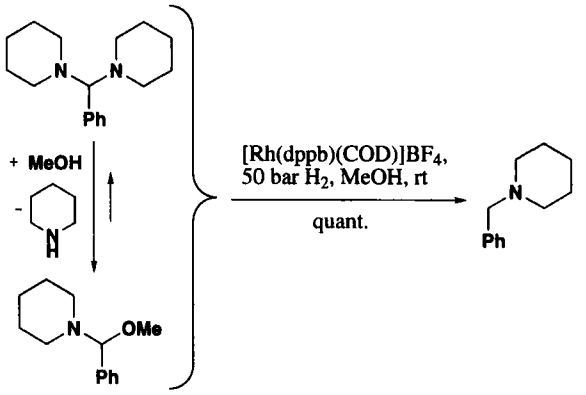


R = Me, *n*-Bu

Hydrogenation of *N,O*-Acetals

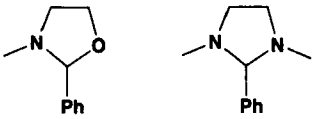
Scheme 7

A special problem concerns the hydrogenation of aminals. It was reported that they can be hydrogenated over a heterogeneous catalyst affording the corresponding amines.[34] Recently we provided proof that, under the homogeneous conditions detailed above, benzyl bispiperidine aminal can be cleanly and rapidly converted into *N*-benzylpiperidine.[33] Nevertheless, its reducibility is still questionable for the following reason. The aminal is remarkably stable in the solid state and in aprotic solvents, while in MeOH it rapidly forms an equilibrium mixture consisting of *N,O*-acetal and piperidine, with the equilibrium being shifted towards the *N,O*-acetal. *(Scheme 8)*. In THF where interconversion of *N,O*-acetal and aminal is not possible, the former was hydrogenated much faster than the latter. It is thus reasonable to propose that, in MeOH, rapid methanolysis of the aminal to the *N,O*-acetal takes place and only the latter is subjected to hydrogenation. The preferred hydrogenation of *N,O*-acetals is supported by the fact that a cyclic *N,O*-acetal derived from benzaldehyde was reduced under standard conditions to the corresponding 2-aminoethanol (see also next section), whereas the related cyclic aminal, which is remarkably stable in MeOH, was not affected. This observation might be taken as an indirect proof that aminals are not pivotal intermediates in ***DRA*** as will be discussed below.



Hydrogenation of Aminal versus *N,O*-Acetal

Scheme 8

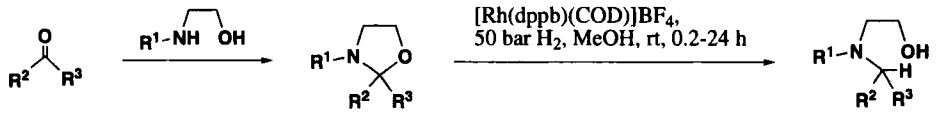


b) Hydrogenation of 1,3-Oxazolidines

i) General Aspects

The selective cleavage of a cyclic *N,O*-acetal under the formation of a substituted alkyl amino alcohol, as briefly mentioned in the preceeding section, has great synthetic potential. It offers an interesting alternative for the alkylation of secondary amines with functionalized alkyl halides. Hitherto, the only example described in the literature was concerned with the reduction of cyclic *N,O*-acetals under the conditions of heterogeneous catalysis.[35]

We investigated the cleavage of 1,3-oxazolidines in the presence of a Rh(I) catalyst which afforded *N*-trisubstituted 2-aminoethanol derivatives in excellent yields (*Scheme 9*).[36] The requisite 1,3-oxazolidines starting materials are easily prepared by acid-catalyzed condensation from a broad variety of commercially available 1,2-aminoalcohols with the corresponding aldehydes and ketones.



R^1 = H, Me; R^2 = H, Ph, 2-Me-C_6H_4, 4-HO-C_6H_4, 2-Furyl, *n*-C_7H_{15}, Ph(Me)CH; R^3 = H, Me

Synthesis and Hydrogenation of 1,3-Oxazolidines

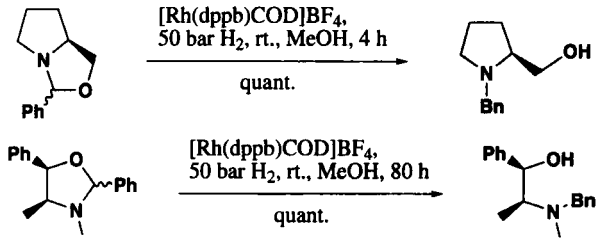
Scheme 9

Under rather mild conditions (50 bar H_2 initial pressure, ambient temperature) 1,3-oxazolidines were quantitatively converted. In all cases, rapid transformations were observed and amines were formed as the sole products. A nitrophenyl group in the substrate did not survive

under these conditions and was partially reduced to the amine derivative. A 1,3-oxazolidine derived from a substituted aniline was not affected. The hydrogenation could even be conducted under solvent-free conditions, although, under these conditions, the reactions required longer time to go to completion. After distillation, analytically pure amines were obtained in good yields.

General Procedure for the Hydrogenation of 1,3-Oxazolidines.- A solution of the pre-catalyst [Rh(dppb)COD]BF_4 (0.01 mmol, 7.2 mg) in methanol (10 mL) was transferred under argon into an autoclave. Then the substrate (5 mmol) was added. The autoclave was pressurized with H_2 (50 bar). The content of the autoclave was stirred by means of a magnetic stirrer. When the hydrogen consumption ceased, the autoclave was opened and the solution evaporated *in vacuo* to give desired 2-hydroxyethylamines. For purification, the products were subjected to distillation.

Diastereomeric oxazolidines can also be successfully subjected to hydrogenation. The two examples depicted in *Scheme 10* emphasize the importance of the new method for the selective *N*-benzylation of aminoalcohols, which can be useful for *N*-protection strategies in multi-step syntheses. In each case, the conversion proceeded quantitatively and both diastereomers were reduced affording a single stereoisomer.



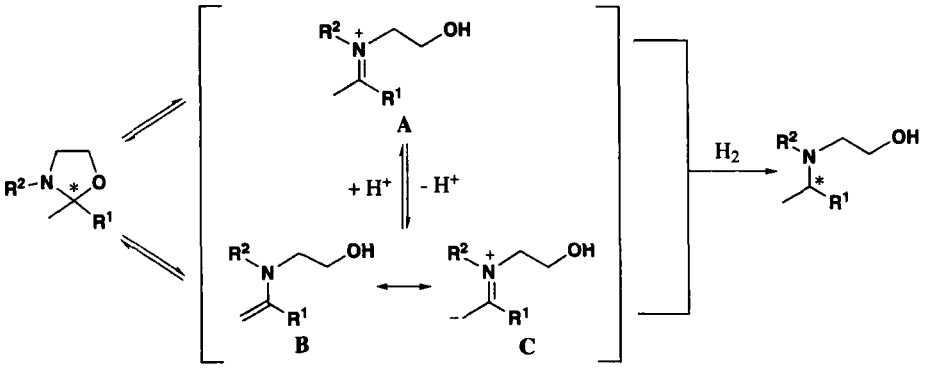
Cleavage of Diastereomeric 1,3-Oxazolidines

Scheme 10

It should be noted that the use of Rh(I)-diphosphine catalyst proved to be superior to the application of heterogeneous Pd-based catalysts since benzylic groups remains untouched.

ii) Kinetic Resolution of Racemic 1,3-Oxazolidines

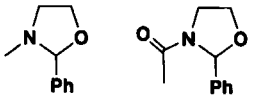
As detailed above, the reduction of 1,3-oxazolidines gives rise to hydroxyethylamines. From the stereochemical point of view the stereogenic carbon atom at C2 of the chiral 1,3-oxazolidine is transformed into another chiral center linked to the amine functionality in the product (*Scheme 11*). Mechanistic investigations using deuterium as reductant confirmed that the reaction proceeds *via* prochiral intermediates, preferentially an iminium cation **A** being in equilibrium with the 1,3-oxazolidine.[37] Depending on the substitution pattern of the 1,3-oxazolidine, the intermediate formation of an zwitterionic intermediate **C**, the charged resonance structure of enamine **B**, cannot be ruled out.



Reductive Cleavage of Racemic 1,3-Oxazolidines *via* Prochiral Intermediates

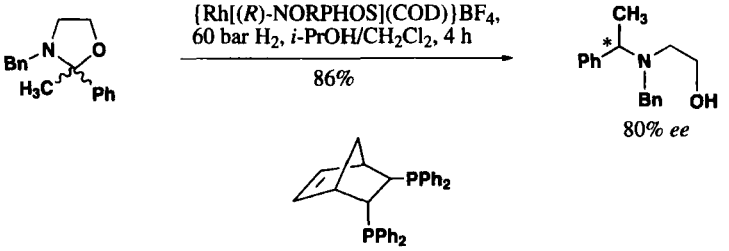
Scheme 11

Further evidence for the participation of the iminium cation **A** as a common intermediate in the reduction of 1,3-oxazolidines could be derived from comparison with 1,3-oxazolidines bearing *N*-substituents of different electronic properties.



Thus, the rapid hydrogenation of 3-methyl-2-phenyl-1,3-oxazolidine observed can only be rationalized by assumption of an iminium cation. In contrast, the structurally related *N*-acetyl-1,3-oxazolidine resisted the hydrogenation conditions described above. Evidently, the electron-withdrawing acetyl group prevents the intermediate formation of the iminium cation required for the hydrogenation. *The intermediate formation of iminium cations of type* **A** *is important for a wide range of reductive amination or reductive alkylation reactions in which hemi-aminals and iminium species were postulated as intermediates.*

Irrespective of whether the reaction proceeds *via* cation **A** or enamine **B,** both intermediates are prochiral. This fact opens up the opportunity to run the reaction stereoselectively by employment of a racemic 1,3-oxazolidine and a chiral catalyst as depicted in *Scheme 12* for



(*R*)-NORPHOS

Enantioselective Hydrogenation of Racemic 1,3-Oxazolidines

Scheme 12

example.[37] By means of high-throughput screening of 144 catalysts, a cationic Rh(NORPHOS)-complex was identified as the most efficient catalyst which, after optimization of solvent, temperature and H_2-pressure, afforded the corresponding chiral hydroxyethylamine in 86% yield and 80% *ee*. Alcohols such as MeOH, EtOH, *i*-PrOH were best suited as solvents for the hydrogenation. The reaction was sluggish in aprotic solvents (THF, DMF and CH_2Cl_2), giving either very low conversion or no product at all. An increase of the enantioselectivity was observed when methanol was replaced by isopropanol. Higher pressures led to an increase of the reaction rate. There was no obvious pressure effect on the degree of enantioselection. It is noteworthy that, even though the yields were quantitative, only 50% *ee* was obtained when the reaction was carried out in a large scale in pure isopropanol under those reaction conditions optimized on a small-scale. Careful studies of large-scale reactions showed that the presence of dichloromethane is essential for high enantioselectivity. Up to now, there is no rationalization for this solvent effect. In the presence of 6% dichloromethane, hydrogen uptake ceased after 4 hours affording 2-[benzyl(1-phenyl-ethyl)amino]ethanol in 80% *ee* in quantitative yield. The activity of the catalytic system dropped dramatically when alkylammonium halides (benzyl- and tetrabutylammonium chloride or iodide) were added even in small amounts.

Hydrogenation Procedure.- A solution of [Rh(NORPHOS)(COD)]BF_4 (114 mg, 0.15 mmol) in dichloromethane (3 mL) was placed in a 50 mL stainless steel autoclave under argon. Then a solution of 3-benzyl-2-methyl-2-phenyl-1,3-oxazolidine (3.81 g, 15 mmol) in isopropanol (30 mL) was added *via* a syringe and the autoclave pressurized with hydrogen to an initial pressure of 60 bar. After 4 h, the calculated amount of hydrogen was consumed and the hydrogen uptake ceased. A conversion of 99% was estimated by HPLC-analysis of the crude reaction mixture. The solvent was evaporated and the residue distilled *in vacuo* to give 3.28 g (86%) of 2-[benzyl(1-phenylethyl)amino]ethanol with 80% *ee*.

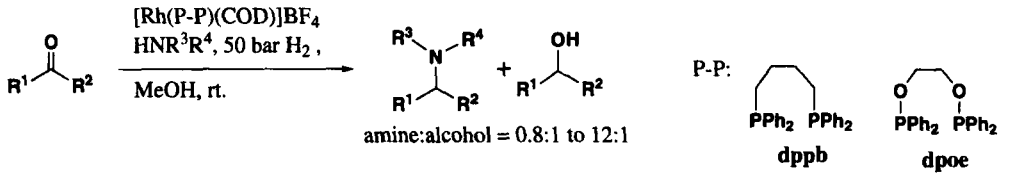
II. DIRECT REDUCTIVE AMINATION (DRA) OF CARBONYL COMPOUNDS

1) General Aspects

At present, numerous examples of the direct reductive amination (DRA) using H_2 and heterogeneous catalysts are known.[38,39] Some of these catalytic systems have even found application on an industrial scale.[40] Interestingly, only a few preliminary studies on the homogeneous version of this reaction can be found in the literature. For example, typical hydroformylation catalysts, such as rhodium carbonyls investigated by Markó and Bakos, required rather severe reaction conditions to achieve sufficient conversion (100-300 atm H_2, 100-200°C).[41] The selectivity and efficiency of some glyoxyme rhodium complexes in the reductive amination of cyclohexanone with ammonia have been studied by Klyuev and Khidekel.[42] Related cyano cobalt catalyst afforded only moderate yields of amines.[43] Recently, Salagre and Fernandez showed the

potential of rhodium(I)-PPh_3-complexes for the reductive amination of ketones with substituted anilines.[44] Tandem hydroformylation-amination reactions (*hydroaminomethylation*) also contain a reductive amination step; however, the range of products is limited due to the use of olefins as starting materials.[30]

In general, the activity of the catalyst and the selectivity for the formation of the desired amine is important for this reaction. The production of the alcohol as a result of the direct reduction of the ketone should be minimized. In a systematic study, we found that cationic rhodium(I) complexes [Rh(dppb)COD]BF_4 or [Rh(dpoe)COD]BF_4 (0.2 mol%) are useful for the direct reductive amination in MeOH at an initial H_2-pressure of 50 bar (*Scheme 13*).[45]



R^1= Alkyl, Aryl; R^2= H ; R^3, R^4 = Alkyl, Cycloalkyl

Direct Reductive Amination (DRA)

Scheme 13

It is noteworthy, that the desired amine and the corresponding alcohol were the sole products in all cases. Up to 12:1 ratios of amine:alcohol are achievable. Both catalysts were more effective and selective than the Wilkinson complex $Rh(PPh_3)_3Cl$. In addition, the hydroformylation pre-catalyst $Rh(PPh_3)_2(CO)Cl$ frequently applied in hydroaminomethylation was inferior. In comparison with the neutral complex $[Rh(dppb)Cl]_2$ prepared *in situ,* the cationic pre-catalyst [Rh(dppb)COD]BF_4 was more active.

The ratio of amine:alcohol was dependent on the aldehyde employed. In the series of substituted benzaldehydes, the beneficial effect of electron-withdrawing groups upon the selectivity is evident (*Table 1*). The *o*-tolyl group exhibited no steric effect on the selectivity. Unfortunately, NO_2- and CN-groups did not survive under the reaction conditions. An alkyl substituent in the α-position to the carbonyl group strongly affected the selectivity of the amination. The highest selectivity was observed with *n*-octanal.

The results of the reductive amination of PhCHO with various amines are summarized in *Table 2*. In general, a good correlation between the selectivity of the reaction and the basicity of the amine was observed. Steric effects can excert a strong influence. Thus, with 2-methylpiperidine, which has approximately the same basicity as piperidine as the substrate but is sterically more hindered, only traces of the desired amine were formed.

Table 1. Comparison of the Selectivity and Rate of Amination of Various Aldehydes with Piperidine Using [Rh(dppb)(COD)]BF_4 as a Pre-catalyst

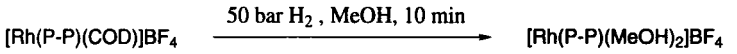
Aldehyde	Ratio amine/alcohol
4-HOC_6H_4CHO	0.8
4-$MeOC_6H_4CHO$	0.9
2-MeC_6H_4CHO	1.0
PhCHO	1.5
4-ClC_6H_4CHO	1.9
PhCHMeCHO	1.9
EtCHMeCHO	2.4
n-$C_7H_{15}CHO$	12.0

Table 2. Comparison of Reductive Amination of PhCHO with Various Amines Employing [Rh(dppb)(COD)]BF_4 as a Precatalyst

Amine	*pK*a of amine	Ratio produced amine/alcohol
pyrrolidine	11.27	2.30
piperidine	11.02	1.50
Me_2NH	10.73	0.43
Et_2NH	10.49	0.07
2-methylpiperidine	10.99	< 0.05

In contrast to the reductive amination of PhCHO with piperidine, the reaction with $PhCH_2NH_2$ was slow under the same conditions. However, the high (11:1) amine:alcohol ratio observed was remarkable.

An interesting but rather complicated relationship between the generation of the catalytically active species **B** by pre-treatment of the Rh-COD-pre-catalyst **A** with H_2 (*Scheme 14*) and



Generation of the Catalyst from the Precatalyst

Scheme 14

the results of the ***DRA*** was found in MeOH as solvent. In general, the generation of the catalyst takes place *in parallel* to the catalytic hydrogenation of the substrate. Therefore over a considerable period, the catalyst:substrate ratio increases continually. Since the generation of individual substrates in the reaction mixture may be time dependent as shown in *Scheme 2*, different selectivities may result at certain stages of the hydrogenation. Application of the catalyst instead of the pre-catalyst in several examples improved the amine:alcohol ratios.

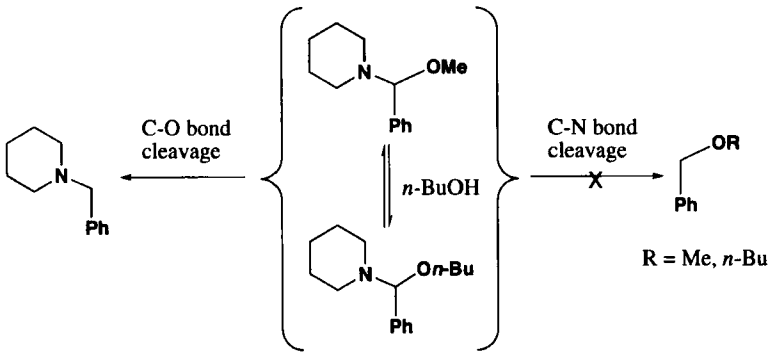
In general, it may be stated that, due to the large variety of equilibria involved including an accelerating effect of amines on the undesired hydrogenation of the carbonyl compound, ***DRA***

processes are difficult to assess. The development of more selective and active catalysts in the future will be therefore mainly based on trial and error.

2) Concerning the Formation of the Undesired Alcohol

An important characteristic of ***DRA*** is the selectivity of the process which can be expressed as a ratio of product amine to alcohol formed (P_{am}/P_{al}). Mechanistic investigations showed that the structure of the starting compounds influences the nature of the *N*-intermediates as illustrated in *Scheme 2* and could play a role in the ***DRA***.[33] However, due to the rapid and dominant formation of relevant *N,O*-acetals, there is some evidence that they are key intermediates in ***DRA*** processes.

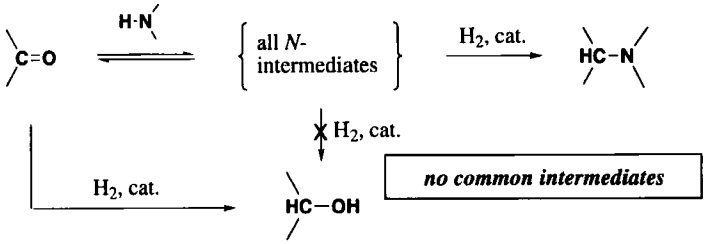
As shown in *Scheme 15,* two different products might be expected from *N,O*-acetals through reductive C-O and C-N bond cleavage, respectively. The absence of even trace amounts of ethers was confirmed by NMR spectroscopy and GLC analysis. These investigations gave



Hydrogenation of *N,O*-Acetals

Scheme 15

evidence that *N,O*-acetals (for hemi-aminals, no direct proof was possible up to now) cannot be direct precursor for alcohol in the homogeneously catalyzed ***DRA***. Nevertheless, the possibility of the decomposition of an hemi-aminal mediated by cationic rhodium complexes to the starting products followed by the subsequent reduction of the carbonyl compound to the alcohol has to be taken into consideration. On the basis of these results and taking into account that the hydrogenation of imines and enamines affords exclusively amines, the overall DRA process can be written as depicted in *Scheme 16*. The main conclusion is that the alcohol in ***DRA*** is produced only by



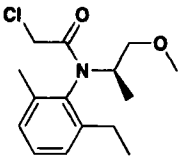
Pathways of Amine and Alcohol Production in DRA

Scheme 16

the reduction of the starting carbonyl compound. The challenge is to identify an appropriate catalyst which can selectively hydrogenate the *N*-intermediates the aldehydes or ketones. Under these conditions, high yields of tertiary amines could be achieved.

3) Enantioselective Reductive Amination

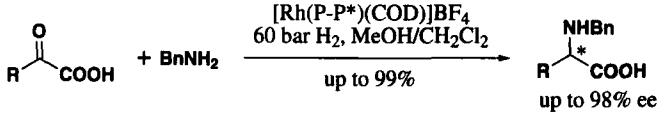
The occurrence of different substrates in ***DRA***-processes depending on the carbonyl compound and amine component, is certainly one of the reason that enantioselective ***DRA*** has only been rarely achieved. An important example involved in the synthesis of the herbicide, (*S*)-metolachlor, represents the reaction of a sterically hindered aniline with methoxyacetone in the presence of a chiral Ir-diphosphine catalyst reported by Blaser *et al.*[46]



(*S*)-Metolachlor

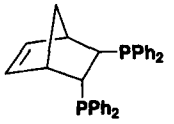
Recently, Zhang *et al.* provided evidence that aryl ketones can be reductively aminated with high enantioselectivities using a Ir-diphosphine catalyst in the presence of $Ti(O\text{-}iPr)_4$ and I_2 as additives.[47] Kadyrov and Riermeier investigated the asymmetric Leuckart-Wallach reaction of aryl ketones.[48] Among a series of catalysts bearing different late-transition metals tested, Ru-(tol-BINAP)-complexes gave the best results, whereas the use of Rh-catalysts resulted in poor enantioselectivities.[49]

In preliminary investigations, we found that, in the non-selective reductive amination of $PhCH_2COCOOH$ with benzylamine (*Scheme 17*) in the presence of $[Rh(dppb)COD)]BF_4$, *N*-benzyl phenylalanine could be obtained in a 71% yield.[45,50] Benzylamine was chosen because the benzyl group can be easily cleaved from the products. Moreover, *N*-protection is frequently required for further synthetic transformations of amino acids.

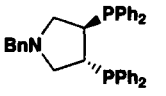


R = $PhCH_2$, Me, Ph, $HOOCCH_2CH_2$, $HOOCCH_2$, , $PhCH_2CH_2$, Me_2CHCH_2, Me_3CCH_2

P-P:



(*R*,*R*)-**Norphos**



(*R*,*R*)-**Deguphos**

Enantioselective Reductive Amination of α-Keto Carboxylic Acids

Scheme 17

In order to identify the most enantioselective catalyst and reaction conditions, application of a stepwise test methodology, including high-throughput screening, revealed to be the method of choice.[51] In the first stage, a library consisting of 96 chiral phosphorus ligands were tested in the asymmetric reductive amination of phenylpyruvic acid as a test substrate. The screening showed that ligands forming 5-membered chelates and bearing diphenylphosphino groups, in particular (*R,R*)-*norphos* and (*R,R*)-*deguphos*, gave the best results. Maximum yield and highest *ee*-values were obtained in alcohols as solvents. While the presence of an acid accelerated the reaction, strong bases and aprotic solvents had a negative effect. Based on these preliminary results, finally the asymmetric reductive amination of different α-keto carboxylic acids with benzylamine was possible in a 10 mmol substrate scale (*Table 3*).

Table 3. Yields and Enantioselectivities of the Reductive Amination of α-Keto Acids with Benzylamine with Precatalyst of the Type $[Rh(P\text{-}P^*)(COD)]BF_4$

R (Substrate)	Ligand (P-P*)	Product[a]	Yield [%]	*ee* [%]
$PhCH_2$	(*R,R*)-Deguphos	*N*-Bn-Phe	99	98 (*S*)
Me	(*R,R*)-Deguphos	*N*-Bn-Ala	43	78 (*S*)
Me	(*R,R*)-Norphos	*N*-Bn-Ala	32	43 (*S*)
Ph	(*R,R*)-Deguphos	*N*-Bn-Phg	27	19 (*R*)
Ph	(*R,R*)-Norphos	*N*-Bn-Phg	24	9 (*S*)
$HOOCCH_2CH_2$	(*R,R*)-Deguphos	*N*-Bn-Glu	19	60 (*S*)
$HOOCCH_2CH_2$	(*R,R*)-Norphos	*N*-Bn-Glu	31	13 (*S*)
$HOOCCH_2$	(*R,R*)-Deguphos	*N*-Bn-Ala	38	73 (*S*)[b]
$HOOCCH_2$	(*R,R*)-Norphos	*N*-Bn-Ala	86	39 (*S*)[b]
$PhCH_2CH_2$	(*R,R*)-Deguphos	*N*-Bn-Bn-Ala	79	81 (+)
$PhCH_2CH_2$	(*R,R*)-Norphos	*N*-Bn-Bn-Ala	79	35 (+)
Me_2CHCH_2	(*R,R*)-Deguphos	*N*-Bn-Leu	99	90 (*S*)
Me_2CHCH_2	(*R,R*)-Norphos	*N*-Bn-Leu	46	61 (*S*)
Me_3CCH_2	(*R,R*)-Deguphos	*N*-Bn-*t*-Bu-Ala	94	86 (+)
Me_3CCH_2	(*R,R*)-Norphos	*N*-Bn-*t*-Bu-Ala	32	60 (+)

[a]*N*-Bn-Phe = *N*-benzylphenylalanine, *N*-Bn-Ala = *N*-benzylalanine, *N*-Bn-Phg = *N*-benzylphenylglycine, *N*-Bn-Glu = *N*-benzylglutamic acid, *N*-Bn-Bn-Ala = *N*-benzylbenzylalanine, *N*-Bn-*t*-Bu-Ala = *N*-benzyl-*t*-butylalanine; [b]decarboxylation took place.

General Procedure for the Enantioselective Reductive Amination.- A solution of keto acid (10 mmol) and $\{Rh[(R,R)\text{-Deguphos}](COD)\}BF_4$ (0.05 mmol, 37 mg) in methanol (50 mL) was transferred under argon into the autoclave. Then under ice cooling, benzylamine (15 mmol, 1.6 mL) was added. The autoclave was flushed with hydrogen. The reaction was performed at an initial pressure of 60 bar at room temperature. When the hydrogenation consumption ceased, the autoclave was openend and the reaction mixture diluted with ether. The precipitated product was collected, washed with ether and dried.

III. HYDROGENATION OF INTERMEDIATES (IRA) VERSUS DIRECT REDUCTIVE AMINATION (DRA) - A COMPARISON

In all examples investigated up to now, homogeneous Rh(I) catalysts displayed significantly lower activity, in comparison with the hydrogenation of isolated intermediates in corresponding ***DRA*** reactions.[52] In general, the most effective catalyst was 100 times less efficient than in ***IRA***. For successful production of an amine by ***DRA***, elevated temperatures are required. In ***DRA***, the side-reaction giving rise to the undesired alcohol is significant, thus complicating the purification of the product amine in comparison to ***IRA***. Interestingly, in Rh-catalysis there is no correlation in the value and sign of asymmetric induction in the hydrogenation of intermediates and corresponding ***DRA***. This is in contrast to a report of a Novartis group using a chiral Ir-catalyst.[46] In the enantioselective ***DRA*** applied for the synthesis of metolachlor, they achieved the same configuration in the product and nearly the same value of enantioselectivity. Hence, evaluation of efficient selective and enantioselective catalysts for DRA is a separate task. Apparently, when it is possible to isolate intermediates, separate homogeneous hydrogenation of the latter is preferable to ***DRA***. However, this approach requires an additional step and is therefore economically less efficient. Moreover the ***DRA*** approach presents the only possibility to produce amines when intermediates are not stable as, for example in reductive amination of α-keto acids. In this case, for the rapid identification of suitable catalysts and reaction conditions, the application of high-throughput screening is recommended.

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