Direct Reductive Amination *versus* Hydrogenation of Intermediates – A Comparison

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Dedicated to Professor Reinhard Schmutzler on the occasion of his 70th birthday.

Abstract: The direct reductive amination of acetophenone with benzylamine or piperidine was studied in comparison with the hydrogenation of possible intermediates like a corresponding imine or enamine. No common features in terms of productivity and stereocontrol (in the case of chiral catalysts) have been found for both processes. Hence evaluation of efficient, selective and enantioselective catalysts for direct reductive amination appears to be a separate task.

Keywords: amination, enantioselective reduction, homogeneous catalysis, hydrogen, hydrogenation, rhodium, P ligands

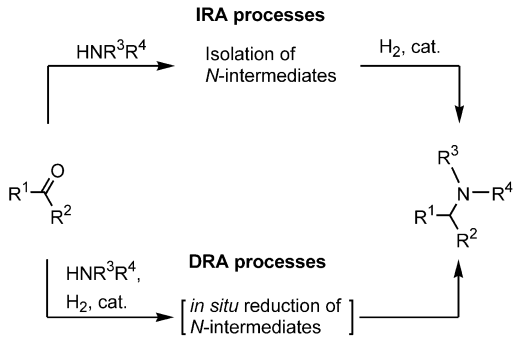
Introduction

The direct reductive amination (DRA) of aldehydes and ketones is an important reaction in organic chemistry with a great potential for application in industry.[1] Particularly interesting are those DRA processes which employ catalytically activated dihydrogen. The decisive advantage of such hydrogenation reactions – to date mainly carried out with heterogeneous catalysts[2] – over the use of other reducing agents, e.g., boranes,[1a] consists in the avoidance of any waste production. Undoubtedly such environmentally friendly processes belong to "green chemistry". Recently, evidence was given that DRA can also be successfully catalyzed under smooth conditions by homogeneous metal complexes.[3] Moreover, we and others have provided proof that even an asymmetric version of DRA using homogeneous chiral Ir(I),[4] Rh(I)[5] or Ru(II)[6] catalysts bearing chiral *P*-ligands is possible, hence the potential of this methodology has been multiplied.

From the practical point of view DRA reactions could be superior to the hydrogenation of appropriate intermediates, e.g., imines or enamines (indirect reductive amination, IRA) since the first step of the synthesis and the isolation of the unsaturated *N*-substrate is spared (Scheme 1). But this superiority may be questionable because of the changing performance of the same catalyst in DRA and in the corresponding IRA reactions.

Recently, the Novartis group reported the first example of an enantioselective DRA as part of the total synthesis of the grass herbicide Metolachlor.[4a] In comparison with the hydrogenation of a corresponding imine, representing a potential intermediate of the reductive amination, they observed the same configuration and nearly the same degree of enantioselectivity in the product. However, in all trials the best productivity of the catalyst remained 100 times lower than in the reduction of the imine.

To the best of our knowledge no other literature reports concerning such comparisons are available. We believe that such a comparison must be important since it can help to select the optimal strategy for the achievement of high chemical yields and, in the case of an asymmetric synthesis, to produce highest ees.



Scheme 1. General approaches for reductive aminations.

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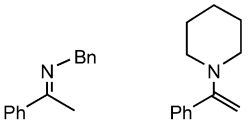
A few years ago we investigated the Rh(I)-catalyzed enantioselective hydrogenation of imine **1**[7] and enamine **2**[8] derived from acetophenone and benzylamine and piperidine, respectively. Both substrates can be considered as probable intermediates of a DRA reaction.

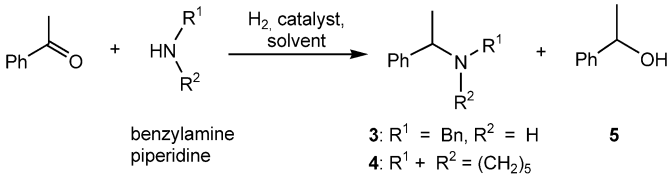


1 **2**

In order to clarify the relation of DRA to these hydrogenations, we have now investigated the Rh(I)-catalyzed reductive amination of acetophenone with benzylamine and piperidine, respectively. Herein these results will be detailed and compared with the data mentioned above.

Results and Discussion

The reductive amination of acetophenone can be schematically represented as shown in Scheme 2.



Scheme 2. Reductive amination of acetophenone.

Usually the main side reaction in DRA is the formation of an alcohol. This side reaction imposes additional demands on the catalyst performance. Therefore, in DRA processes not only the productivity (and the enantioselectivity in the case of the asymmetric version) but also the selectivity in favour of the formation of the amine is important.[3a] The selectivity can be expressed as the simple [amine]/[alcohol] ratio or as a quota of an amine, [amine]/[amine] + [alcohol]. Unfortunately this characteristic of the catalysts is still not yet accepted generally, thus making it impossible to compare different catalysts.

Direct Reductive Amination of Acetophenone with Benzylamine

First, in order to find appropriate conditions for DRA, the achiral precatalyst [Rh(dppb)COD]BF_4 [dppb = 1,4-bis(diphenylphosphanyl)butane (formula see Fig. 2); COD = 1,5-cyclooctadiene] was tested. At ambient temperature, hydrogenation of a 1 : 1 mixture of acetophenone (5 mmol) and $BnNH_2$ in MeOH (10 mL) at 50 bar H_2 pressure in the presence of 0.2 mol % of [Rh(dppb)COD]BF_4 gave poor conversion (*ca.* 10%) and low selectivity in favour of the production of the amine **3** (*ca.* 9%). Obviously, the formation of an intermediate, presumably **1**, is the rate-determining step in this DRA. We were not able to detect by ^{1}H NMR spectroscopy even traces of imine **1** (as well as other *N*-containing intermediates) in the model system in MeOH-d_4 at room temperature. In contrast, hydrogenation of imine **1** under the same conditions and catalyst loading was rather fast. Complete conversion of imine **1** and exclusive formation of amine **3** was observed within 1 h.

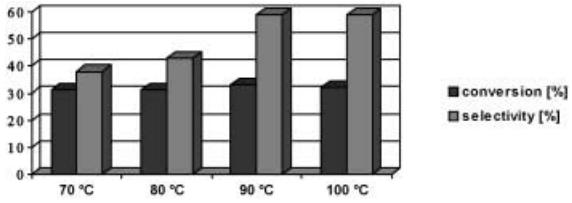


Figure 1. Influence of the temperature on conversion and amine selectivity of the DRA of PhCOMe with $BnNH_2$ {conditions: 5 mmol PhCOMe, 5 mmol $BnNH_2$, 0.01 mmol [Rh(dppb)COD]BF_4, 10 mL MeOH, 50 bar initial H_2 pressure (measured at RT), exposition time 9 h}.

In order to improve the efficiency and the selectivity of the DRA process we studied the effect of the temperature. The data are presented in Figure 1. As can be seen in the range of 70–100 °C there is almost no dependence of the conversion on the temperature. But the increase in the temperature has a strong effect on the selectivity. Between 90–100 °C the formation of the amine is favoured over the production of the undesired alcohol.

At 100 °C two other achiral catalysts, [Rh(dppp)COD]BF_4 [dppp = 1,3-bis(diphenylphosphanyl)propane] and [Rh(dpoe)COD]BF_4 (dpoe = 1,2-diphenylphosphanyloxyethane), were tested. The comparison of conversion and selectivity of these three catalysts is illustrated in Figure 2.

The data depicted in Figure 2 clearly show that the activity of [Rh(dppp)COD]BF_4 bearing a 6-membered chelate ring is approximately the same as that of [Rh(dppb)COD]BF_4 representing a 7-membered chelate. When the diphosphine dppb was substituted by the diphosphinite ligand dpoe also forming a seven-membered chelate ring the activity of the catalyst was significantly increased. The selectivity is dependent on the structure of the ligand in the order [Rh(dppp)COD]BF_4 < [Rh(dppb)COD]BF_4 < [Rh(dpoe)COD]BF_4. This order corresponds to the decrease of the steric hindrance of the ligands.[9] Moreover, also the Lewis basicity of ligands forming 7-membered chelates might play an important role.

For asymmetric DRA, we tested as a precatalyst {Rh[(*R*,*R*)-bdpch]COD}BF_4 {for the structure of the ligand (*R*,*R*)-bdpch,[10] see Table 3}. This diphosphinite

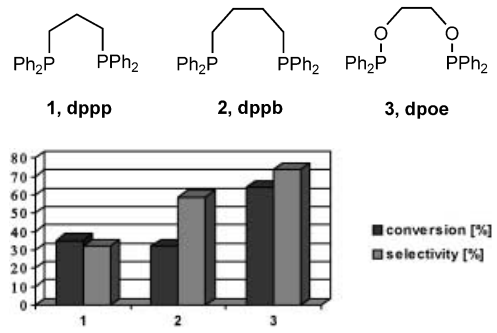


Figure 2. Comparison of the performance of different catalysts in the DRA of PhCOMe with $BuNH_2$. **1**: [Rh(dppp)COD]BF_4; **2**: [Rh(dppb)COD]BF_4; **3**: [Rh(dpoe)-COD]BF_4 at 100 °C (for other conditions see Fig. 1).

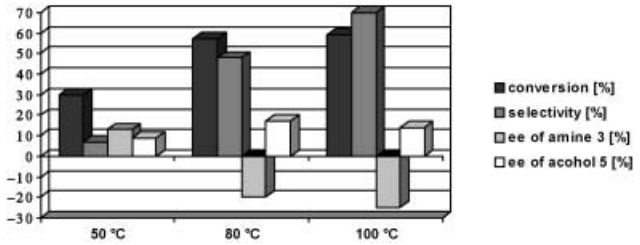


Figure 3. Influence of the temperature on the catalytic performance of {Rh[(*R*,*R*)-bdpch]COD}BF_4 in the asymmetric DRA of PhCOMe with $BnNH_2$ (for conditions see Fig. 1). Positive ee values correspond to the (*R*)-configuration and negative to the (*S*)-configuration.

complex exhibited the highest enantioselectivity among others Rh precatalysts in the hydrogenation of the imine **1**.[7] The performance of this precatalyst is represented in Figure 3.

All parameters are dependent on the temperature. Although conversions measured at 80 °C and 100 °C are fast and quite the same, the selectivity of DRA is higher at 100 °C. The same trend can be deduced from Figure 1. The enantioselectivity induced in the alcohol **5** is slightly dependent on the temperature. Interestingly, the enantioselectivity of amine **3** varies dramatically with the temperature. Thus, the configuration changes from (*R*) at 50 °C to (*S*) at 80–100 °C. At 100 °C the selectivity and enantioselectivity do not depend on the catalyst loading which is in the range of 0.2–0.8 mol %. Only an increase of the conversion to 60% and 84% was observed with 0.4 mol % and 0.8 mol %, respectively.

In comparison to the DRA of PhCOMe with $BnNH_2$, the asymmetric hydrogenation of imine **1** which can be regarded as a possible intermediate of this transformation occurred at room temperature and 50 bar initial H_2 pressure with {Rh[(*R*,*R*)-bdpch]COD}BF_4 as a precatalyst (0.01 mmol) in MeOH and gave amine (*R*)-**3** in 71% ee.[7] Five mmol of imine **1** were quantitatively reduced under these conditions in 10 mL of MeOH within 5 h. At 100 °C and 10 h reaction time the conversion of imine **1** dropped to 88%. Simultaneously, the ee decreased to 12% but nevertheless the (*R*)-configuration in the product amine **3** remained.

The inversion of the configuration of amine **3** with the temperature produced in DRA is difficult to rationalize. Taking into account that the configuration and the ee of alcohol **5** is not dependent on the temperature, it is reasonable to assume that the catalytically active Rh(I) species is quite the same in the temperature range of 50–100 °C. Hence we can assume that imine **1** is not an intermediate in the DRA considered herein and that other species produced from PhCOMe and $BnNH_2$ are hydrogenated at elevated temperatures. Another possibility which could not be experimentally confirmed up to now is the temperature dependent (*Z*)/(*E*) isomerization of imine **1**.

Three other catalysts have been tested in the reductive amination of PhCOMe with $BnNH_2$. Relevant data are collected in Table 1.

As clearly seen again, a diphosphinite complex derived from $K_{\beta+}$-OH as ligand shows enhanced activity and selectivity in comparison with two diphosphine complexes.

Table 1. Comparison of the catalytic performance in asymmetric DRA of PhCOMe with $BnNH_2$ and hydrogenation of imine **1** with precatalysts of the type [Rh(Ligand)COD]BF_4.[a]

Run	Ligand	Conversion of PhCOMe [%]	Selectivity [%]	ee of amine **3** [%]	ee of amine **3** [%] from imine **1** (RT)
1	(*R*,*R*)-DIOP[b]	32.2	32	2 (*R*)[e]	19 (*R*)[h]
2	**6**[c]	59.3	43	6 (*R*)[f]	35 (*R*)
3	$K_{\beta+}$-OH[d]	69.4	66	20 (*R*)[g]	28 (*S*)[h]

[a] Structure of the ligands, see Table 3; conditions: 5 mmol PhCOMe, 5 mmol $BnNH_2$, 0.01 mmol [Rh(Ligand)COD]BF_4, 10 mL MeOH, 50 bar initial H_2 pressure (measured at RT), 100 °C, exposition time 8 h.
[b] Ref.[11]
[c] Ref.[12]
[d] Ref.[13]
[e-g] ee (configuration) of alcohol **5**: [e] 4% (*R*); [f] 15% (*R*); [g] 5% (*R*).
[h] Ref.[7]

With the latter the enantioselectivity of amine **3** production in the direct process is significantly reduced in comparison with the hydrogenation of imine **1**. In the case of the $K_{\beta+}$-OH catalyst the configuration of the amine **3** is opposite in the IRA.

Direct Reductive Amination of Acetophenone with Piperidine

In the DRA of PhCOMe with piperidine (Scheme 2), enamine **2** can be assumed as an intermediate for the formation of amine **4**. The reduction of this substrate in MeOH at 50 bar H_2 initial pressure with $[Rh(dppb)COD]BF_4$ as a precatalyst occurred at room temperature within less than 1 h with quantitative formation of amine **4** [enamine **2** can be hydrogenated also at 1 atm H_2 pressure with a variety of other Rh(I) precatalysts].[8]

Under the same conditions the hydrogenation of a 1:1 mixture of MeCOPh (5 mmol) and piperidine (5 mmol) gave only 25% of conversion of ketone and alcohol **5** as the main product after 20 h (Table 2, run 1). Raising the temperature increased the yield of amine **4** in DRA (runs 2–4) but, nevertheless, the formation of alcohol **5** is significant. It is interesting to note that an increase in the temperature from 80 to 100 °C does not have a pronounced influence on conversion and selectivity (runs 3 and 4). In contrast to the DRA with benzylamine in case of piperidine the use of the diphosphinite precatalyst does not improve the selectivity although the conversion increases (run 5). In general, the efficiency of DRA is not comparable with the hydrogenation of enamine **2**.

Only poor results were obtained in the asymmetric version of this DRA reaction. The comparison with enamine **2** hydrogenation is given in Table 3.

As clearly shown, diphosphine complexes as catalysts in DRA display lower activity in comparison with diphosphinite complexes (Table 3, compare runs 1 and 2 and 3–5). This behaviour in DRA with piperidine is similar to the DRA with $BnNH_2$. But the selectivity in the former process does not correlate with the electronic properties of the ligands (Table 3, compare runs 1 and 2 and 3–5). Although the catalysts tested display moderate enantioselectivity in the hydrogenation of enamine **2** they failed completely in the corresponding DRA reaction. Meanwhile, precatalysts $K_{\beta+}$ and $K_{\beta+}$-OH display moderate enantioselectivity in the undesired reduction of PhCOMe affording the alcohol.

Table 2. Direct reductive amination of PhCOMe with piperidine in 1:1 ratio applying precatalysts of the type [Rh(Ligand)COD]BF_4.[a]

Run	Ligand	Time [h]	Temp. [°C]	Conversion of PhCOMe [%]	Selectivity [%]
1	dppb	20	25	25	9
2	dppb	23	50	46	17
3	dppb	10	80	41	36
4	dppb	10	100	39	39
5	dpoe	10	100	86	34

[a] For conditions see Table 1.

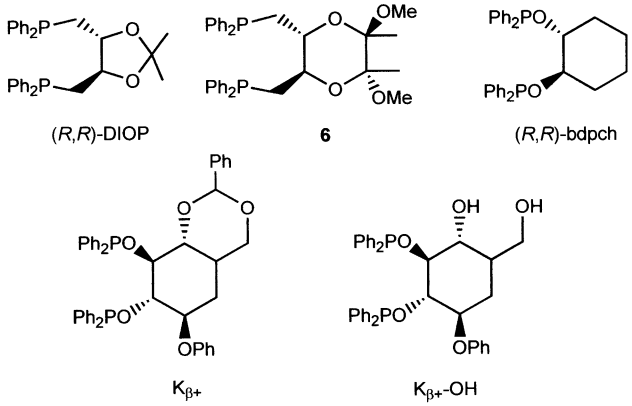
Conclusions

In comparison with the hydrogenation of selected isolated *N*-intermediates in the corresponding DRA reactions, homogeneous Rh(I) precatalysts display significantly lower activity. For a successful production of an amine by DRA, elevated temperatures are required. In addition, in DRA the side reaction giving rise to the undesired alcohol is significant thus complicating the purification of the amine. It should be noted that investigations on the DRA of benzaldehyde with pyrrolidine at room temperature revealed that water might not play a significant role in the course of the reaction.[1b] In contrast to the results of the Novartis group observed in the Metolachlor synthesis mediated by an Ir(I) catalyst,[4a] we found no parallel in the degree and the sign of the asymmetric induction in the hydrogenation of single intermediates and the corresponding DRA. Hence evaluation of efficient selective and enantioselective catalysts for DRA seems to be a separate task. Obviously in some cases first isolation of intermediates, e.g., imines, enamines or even sometimes *N,O*-acetals[15] and subsequent hydrogenation is preferred over DRA. On the other hand, the DRA approach presents the only possibility to produce amines in those cases when intermediates are not stable as has been proven in the reductive amination of α-keto acids.[5] In these investigations striking differences in the enantioselectivities in dependence on the nature of the prochiral substrate were noted.

Experimental Section

MeCOPh, $BnNH_2$ and piperidine were distilled and kept under an Ar atmosphere. All hydrogenations were carried out according to the protocol detailed in Ref.[1b] After the hydrogenation the reactions mixtures were analyzed by NMR, HPLC and GC on chiral columns. The conversions and selectivities were estimated on the basis of ^1H NMR spectra. The signals with following chemical shifts (in ppm, measured in $CDCl_3$ relative to TMS) were evaluated: 1.24 (d, $J = 6.5$ Hz; CH_3 group of amine **3**), 1.33 (d, $J = 6.3$ Hz; CH_3 group of alcohol **5**), 1.35 (d, $J = 6.7$ Hz; CH_3 group of amine **4**), 2.18 (s, CH_3 group of imine **1**), 2.48 (s, CH_3 group of MeCOPh). The ee of amine **3** was determined by HPLC on Chiralcel OD-H column (eluent: hexane). The ees of amine **4** and alcohol **5** were determined by GC on CP Chirasildex-CB.

Table 3. Comparison of DRA of PhCOMe with piperidine and hydrogenation of enamine **2** applying precatalysts of the type [Rh(Ligand)COD]BF_4.[a]



Run No	Ligand	Conversion of PhCOMe [%]	Selectivity [%]	ee of amine **4** [%]	ee of amine **4** [%] from enamine **2**[a]
1	(*R*,*R*)-DIOP	55	42	0[c]	39 (*R*)[h]
2	**6**	62	53	0[d]	45 (*R*)[h]
3	(*R*,*R*)-bdpch	74	63	6 (*R*)[e]	32 (*R*)[h]
4	$K_{\beta+}$[b]	88	32	0[f]	25 (*S*)[i]
5	$K_{\beta+}$-OH	89	34	4(*R*)[g]	36 (*S*)[h]

[a] Prepared at RT.
[b] Ref.[14]
[c-g] ee (configuration) of alcohol **5**: [c] 0%, [d] 3% (*R*); [e] 0%; [f] 31% (*S*); [g] 24% (*S*).
[h] Reduced at 1 bar H_2, see also Ref.[8]
[i] Reduced at 50 bar H_2.

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