A Scrutiny on the Reductive Amination of Carbonyl Compounds Catalyzed by Homogeneous Rh(I) Diphosphane Complexes

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Abstract: The reductive amination of a series of aldehydes with secondary amines and H_2 in the presence of a homogeneous Rh-diphosphane catalyst was studied in order to establish a general mechanism of this reaction and to identify conditions for the improvement of the amine/alcohol ratio in the product. Several possible intermediates as constituents of changing equilibria like half-aminals, *N*,*O*-acetals and aminals were observed in the reaction mixture by means of ^{1}H NMR spectroscopy. In individual trials, these compounds could be successfully hydrogenated under the conditions applied for reductive amination (50 bar H_2 pressure, MeOH). Some evidence is accumulated that half-aminals and *N*,*O*-acetals might be key intermediates of the reductive amination. Moreover, it was found that the formation of the undesired product alcohol is likely based on the reduction of the starting carbonyl compound. However, due to numerous equilibria consisting of several intermediates, general conclusions are hard to be drawn. Proof will be given that, in several cases, the efficiency of the reductive amination of aliphatic aldehydes can be significantly improved by prehydrogenation of the cationic $[Rh(dppb)(COD)]^+$ complex.

Keywords: amination; homogeneous catalysis; phosphane; reduction; rhodium.

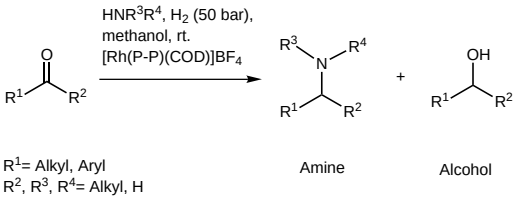
Introduction

The conversion of aldehydes and ketones into primary or secondary amines is an important reaction in modern organic chemistry with a great synthetic potential for application in academia and industry. The most straightforward reaction for this chemical transformation comprises the reductive amination of appropriate carbonyl compounds. Usually, it involves the reduction of imines and enamines that are easily available by prior condensation of ketones and aldehydes, respectively, with the appropriate amines. This method requires two steps. The direct conversion (aminoalkylation), when a mixture of carbonyl compound and amine is treated in the presence of a reducing agent, seems to be superior. However, in this approach the situation might be more complicated due to the large number of possible equilibria and intermediates involved. In general, for the semantic differentiation between both methodologies recently the term indirect reductive amination (IRA) was introduced for the former and direct reductive amination (DRA)[1] or single stage amination[2] for the later reaction type.

Hitherto, a range of chemical reducing agents has been shown to be valuable for DRA giving rise to the alkylated amines in good yields.[3] In particular, the catalytic DRA with molecular hydrogen is promising from the economic and ecological point of views. Up to now, a plethora of examples is known using H_2 and heterogeneous catalysts.[2] Some of these catalytic systems have seen even application on an industrial scale. In contrast, much less is known about the homogeneous version of this reaction. Thus, in 1974, Markó and Bakos tested successfully cobalt and rhodium carbonyls.[4] However, these typical hydroformylation catalysts require rather severe conditions. Just recently, Blaser et al.[5] and Fernandez et al.[6] showed the interesting potential of iridium(I) diphosphane complexes for the reductive amination of ketones with substituted anilines.

In a preliminary communication, we reported for the first time that cationic complexes of the type [Rh(P-P)(COD)]BF_4 (P-P: diphosphane, diphosphinite) are efficient precatalysts for the homogeneous DRA of aldehydes and α-keto acids under relatively mild conditions (*ca.* 50 bar H_2 pressure, room temperature, molar ratio substrate/precatalyst 500:1, methanol) affording the desired amines in good yield (Scheme 1).[7]

We could also provide proof that even an asymmetric version of the homogeneously catalyzed DRA is possible. A first trial to reduce phenylpyruvic acid together with benzylamine in the presence of a chiral Rh(I)-diphosphane complex and hydrogen afforded *N*-benzyl (*S*)-phenyl alanine in 38% ee.



Scheme 1.

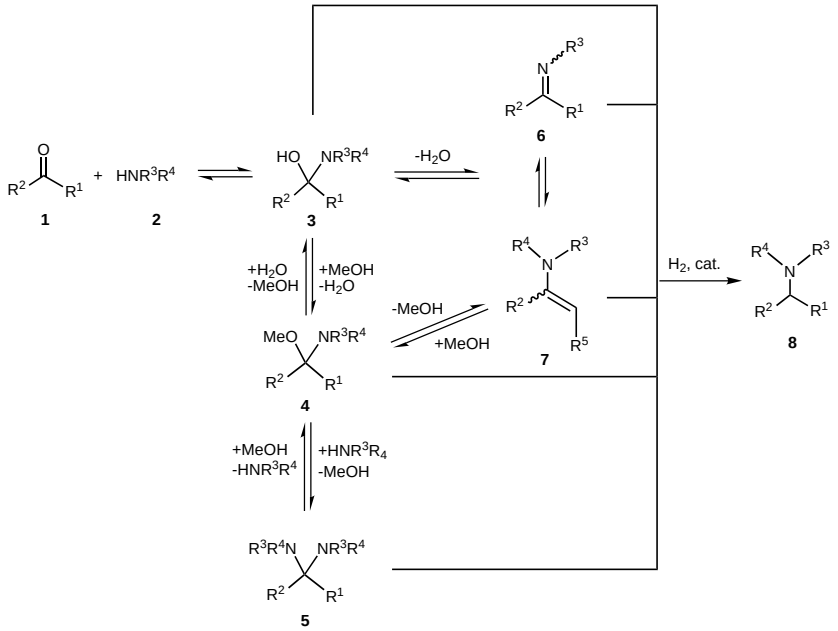
An important characteristic of DRA is the selectivity of the process which can be expressed as a ratio of product amine to alcohol formed (P_{am}/P_{al}). In our investigations we found selectivities ranging from 0.05/1 to 12/1.[7] Best selectivities were obtained with sterically non-hindered aldehydes and amines as reagents. Moreover, a good correlation between the selectivity of the reaction and the basicity of the amine was observed.

The work detailed here was undertaken to improve the formation of the product amine in the DRA using cationic Rh(dppb)-catalysts [dppb = 1,2-bis(diphenylphosphanyl)butane]. For this purpose DRA processes were studied along with the hydrogenation of potential intermediates.

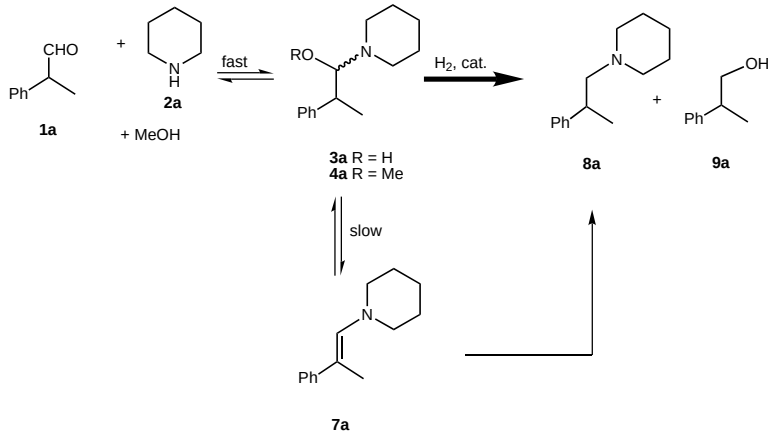
Results and Discussion

It is reasonable to assume that the production of amines **8** based on DRA in methanol is associated with the formation of adducts and condensation products of carbonyl compound **1** and amine **2** (Scheme 2). Such intermediates are preferentially half-aminals **3**, *N*,*O*-acetals **4**, aminals **5**, imines **6** and enamines **7** (in specific cases, for example, formaldehyde and ammonia, some additional intermediates can be found in the equilibrium which are not considered in this work). The occurrence of each individual intermediate is influenced by the nature of carbonyl compound and amine as well as by the reaction conditions. Recently, we presented evidence that imines[8] as well as enamines[9] possessing double bonds of different natures can be cleanly reduced with the same homogeneous Rh-catalyst. It is worth mentioning that the hydrogenation of enamines proceeded at lower H_2 pressure than the reduction of imines. In contrast to these reports, much less is known about the homogeneous hydrogenation of half-aminals **3**, *N*,*O*-acetals **4** and aminals **5** which lack double bonds. Markó and Bakos postulated half-aminals **3** in order to rationalize amine formation in homogeneously catalyzed DRA of PhCHO with secondary amines.[4] Also in heterogeneous catalysis only a very few examples are concerned with the hydrogenation of *N*,*O*-acetals[10a, b] and aminals.[10b]

It has been generally accepted that in the first stage of the reaction between the carbonyl compound and the amine the relevant half-aminal **3** is formed. The other intermediates **4** – **7** are produced later on the reaction time scale. This time-dependent formation of intermediates is important in DRA since all equilibria shown in Scheme 2 are not immediately established in the initial mixture of amine **2** and carbonyl compound **1**. Moreover, the formation of these intermediates could be seriously perturbed by the irreversible formation of product amine **8** emerging in the reaction mixture due to the reduction process.



Scheme 2.



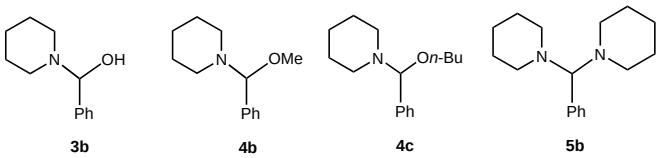
Scheme 3.

In a preliminary experiment on DRA of hydratropaldehyde (**1a**) with piperidine (**2a**) (1:1 ratio) using [Rh(dppb)(COD)]BF_4 as a precatalyst in methanol under standard conditions (*ca.* 50 bar H_2 initial pressure, room temperature, 5 mmol of aldehyde, 0.01 mmol of the precatalyst in 10 mL of MeOH) we observed complete conversion of the aldehyde within 2 h (Scheme 3). The product amine **8a** and the corresponding alcohol **9a** were formed in a ratio of 0.5/1. ^{1}H NMR investigations using the same concentrations of **1a** and **2a** in CD_3OD revealed that already after 9 min the whole amount of the aldehyde was consumed. A complex mixture consisting preferentially of diastereomeric half-aminals **3a** and *N*,*O*-acetals **4a** were found. Surprisingly, the formation of enamine **7a** was found to be rather slow. Only *ca.* 10% of the enamine was detected in the reaction mixture after 24 hours and *ca.* 30% after 12 days. Interestingly, the individual hydrogenation of enamine **7a** catalyzed by [Rh(dppb)-(COD)]BF_4 was extremely slow as compared with the corresponding DRA process (after 20 h only 80% of amine **8a** was produced).

These findings are in agreement with the participation of half-aminals or *N*,*O*-acetals rather than enamines in DRA. It is interesting to note that half-aminals in the heterogeneous DRA were already proposed in the past,[2] but hitherto no direct evidence was given.

Reduction of Half-Aminals, N,O-*Acetals and Aminals*

To show the generality of half-aminals and *N*,*O*-acetals, respectively, in DRA we initiated a more detailed study concerning the hydrogenation of these particular substrates. Due to their facile preparation, half-aminal **3b**,[11] *N*,*O*-acetals **4b**, **4c**[12] and aminal **5b**[13] were chosen to represent possible intermediates in the DRA of PhCHO with piperidine.



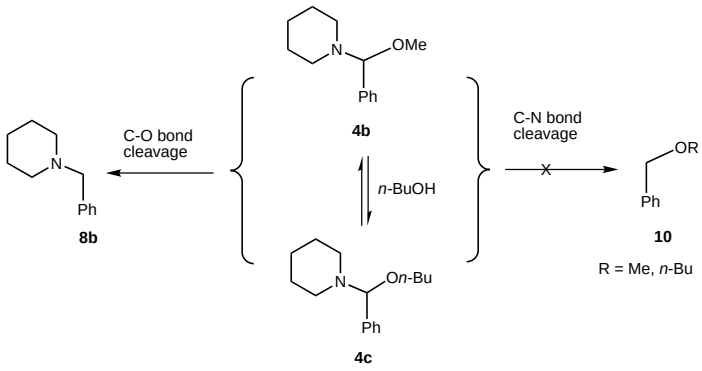
In a first experiment half-acetal **3b** was reduced with H_2 producing a 1.5/1 mixture of *N*-benzylpiperidine (**8b**) and benzyl alcohol (**9b**) (Scheme 4).

Recently, the half-aminal **3b** was postulated in the heterogeneously catalyzed DRA as a common intermediate for amine and alcohol production.[2] Unfortunately compound **3b** is rather unstable. Slow disproportionation into PhCHO and **5b** occurs even in the solid state.[10] Due to this feature it was impossible to show unambiguously whether **3b** was responsible for the formation of alcohol **9b** or not.

To clarify this problem, the presumably more stable model compound **4c** was employed. Hydrogenation of **4c** in MeOH in the presence of [Rh(dppb)(COD)]BF_4 gave *N*-benzylpiperidine (**8b**) as the sole product ($t_{1/2}$ *ca.* 3 min). The ^{1}H NMR experiment with an excess of CD_3OD as solvent showed exchange of butoxide in the *N*,*O*-acetal **4c** and the formation of the corresponding methoxy derivative **4b** (Scheme 5). Nevertheless, hydrogenation of independently synthesized **4b** yielded again exclusively **8b** ($t_{1/2}$ *ca.* 30 sec).

As shown in Scheme 5 two different products might be expected from *N*,*O*-acetals **4** through reductive C-O and C-N bond cleavage, respectively, amine **8b** or/and ether **10**. The absence of even traces of $PhCH_2O(n\text{-Bu})$ and

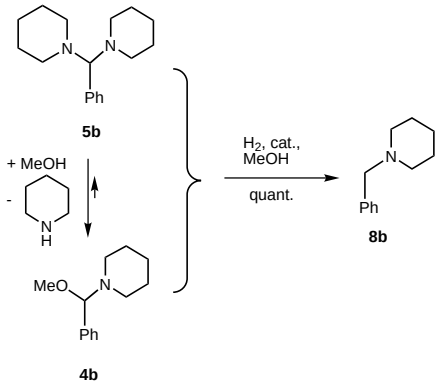
Scheme 4.



Scheme 5.

$PhCH_2OMe$ was confirmed by GLC analysis in additional to NMR spectroscopy. Since no C-N bond cleavage was observed in the hydrogenation of **4b** or **4c**, half-aminal **3b** is also unlikely to be a direct precursor for alcohol in the homogeneously catalyzed DRA. Nevertheless, the possibility of the decomposition of half-aminal **3** mediated by cationic rhodium complexes giving rise to the starting compounds **1** and **2** and the subsequent reduction of the aldehyde **1** under the formation of the alcohol cannot be ruled out.

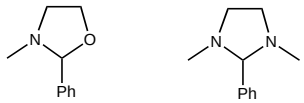
It is quite surprising that, although aminals **5** have been shown to be hydrogenated over heterogeneous catalyst affording the corresponding amines **8**,[10b] their intermediacy in DRA has never been discussed. Now we report for the first time that under the conditions given above aminal **5b** is cleanly and rapidly hydrogenated in the presence of $[Rh(dppb)(COD)]BF_4$ ($t_{1/2}$ *ca.* 5 min) giving *N*-benzylpiperidine **8b** (Scheme 6). Nevertheless, its intermediacy in DRA is still questionable for the following reasons. Aminal **5b** is remarkable stable in the solid state and in aprotic solvents, while in MeOH it forms an equilibrium mixture consisting of *N,O*-acetal **4b** and piperidine with the equilibrium being shifted towards the *N,O*-acetal (in accordance with NMR investigations in CD_3OD).



Scheme 6.

In THF when formation of *N,O*-acetal **4b** from aminal **5b** is not possible the former is hydrogenated much faster than the latter (after 7 h quantitative hydrogenation of **4b**: after 30 h only 33% conversion of **5b**). Due to this fact it is reasonable to propose that in MeOH fast methanolysis of **5b** affording **4b** takes place and only the latter is subjected to hydrogenation.

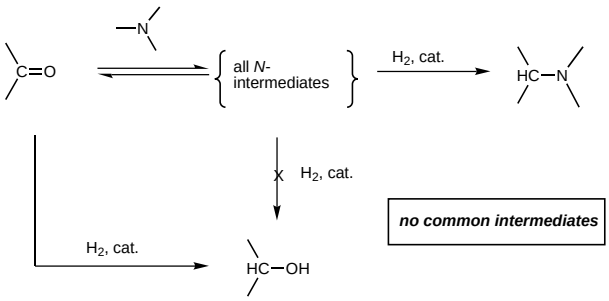
The preferred hydrogenation of *N,O*-acetals finds support by the fact that the cyclic *N,O*-acetal **4d** is reduced under standard conditions, whereas the cyclic aminal **5c** is not affected. This observation may serve as an indirect proof that aminal **5b** is not a pivotal intermediate in the DRA.



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 in general as displayed in Scheme 7. Principally, it can be concluded that alcohol in DRA is produced only by the reduction of the starting carbonyl compound and that the rate of this undesired hydrogenation can be influenced by amines (*vide infra*). Nevertheless, with an appropriate catalyst that is selective for the *N*-intermediate hydrogenation rather than for the hydrogenation of aldehydes or ketones, high yields of tertiary amines should be achieved. Moreover, as will be shown below, water has no influence on the outcome of the DRA in this case.

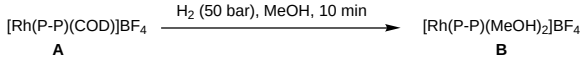
Direct Reductive Amination of Aldehydes with Secondary Amines

After studying the reduction of relevant intermediates we turned our attention to the DRA of aldehydes with secondary amines.



Scheme 7.

Scheme 8.



Scheme 9.

First, DRA of benzaldehyde (**1b**) with piperidine (**2a**) was studied. Immediate hydrogenation of a 1:1 mixture in the presence of [Rh(dppb)COD]BF_4 after mixing gave a fast reaction ($t_{1/2}$ *ca.* 17 min) with the formation of amine **8b** and alcohol **9b** in a ratio of 0.9/1 (Scheme 8).

In contrast, hydrogenation of the same mixture kept for 30 min before treatment with H_2 gave a 2.6/1 mixture of amine **8b** and alcohol **9b.** No significant change in the rates was observed. To rationalize the change in selectivity, NMR investigations of the mixture were undertaken. These measurements revealed the time-dependent formation of half-aminal **3b**, *N,O*-acetal **4b** and aminal **5b** (Table 1).

As shown in Table 1, the sum of the concentrations of *N*-intermediates **3b**, **4b** and **5b** increases whereas the concentration of PhCHO decreases with the time. In particular, the dramatic increase in the concentration of **4b** is worthy of note. This feature is obviously the main reason (see Scheme 7) for the improvement in the amine selectivity of the DRA with the time. The enhancement of the amine/alcohol ratio (to 1.4/1) with increase of the initial piperidine concentration (PhCHO:piperidine = 1:2) can be also rationalized from this point of view.

As outlined above, the establishment of pre-equilibria is strongly time-dependent and of relevance to the DRA and the hydrogenation of the carbonyl compound. Consequently, different amine/alcohol ratios were observed due to varying times of pre-equilibration. Similar features should also hold for the catalyst. It should be mentioned that in our experiments usually a Rh(I)-diphosphane precatalyst instead of the catalyst was used. The former is stabilized by an ancillary COD ligand. It is well-known from other hydrogenation reactions that in MeOH complete formation of the catalytically active species **B** by reductive replacement of the di-olefin by two alcohol molecules in the precatalysts **A** can require a considerable period (Scheme 9).[15] Thus, the time for the establishment of pre-equilibria in the DRA and the time for prehydrogenation of the precatalyst proceeding in parallel should influence the outcome of the DRA.

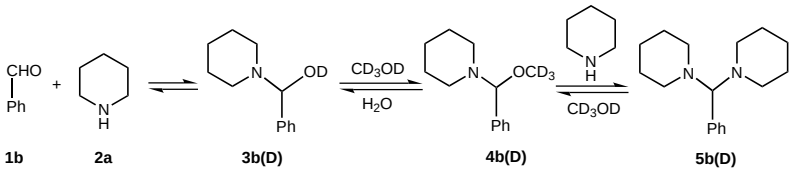
In order to verify this hypothesis we converted the precatalyst into the catalytically active species by hydrogenation with H_2 (10 min, 50 bar) in MeOH before the DRA was initiated.

As listed in Table 2 in several instances (runs 3, 6 – 8), a significant influence on the selectivity of DRA of aldehydes with piperidine was observed when the precatalyst was treated with H_2 prior to the DRA.

In the series of aromatic aldehydes the effect of substituents in the 4-position was impossible to rationalize in both cases (Table 2, runs 1 – 5). When the precatalyst **A** is employed the reaction is only slightly sensitive to electronic changes. The nitro group does not survive under the conditions of the DRA. Aromatic amines derived from this side reaction subsequently react with the aldehyde affording a complex mixture of condensation products. The friendly behaviour in DRA of the phenolic OH group is worthy of mention.

In the series of aliphatic aldehydes (Table 2, runs 6 – 8) a considerable dependency of the selectivity on the degree of α-alkyl branching was observed. The effect

Table 1. Time-dependent composition of an equimolar mixture of PhCHO (**1b**)/piperidine (**2a**) in CD_3OD.



Time	**1a** [%]	**3b** [%]	**4b** [%]	**5b** [%]
ca. 10 min	69	6	22	3
30 min	36	3	58	3
6 h	18	2	78	2
δ [ppm][a]	9.9 (br, s)	5.56 (br, s)	4.69 (s)	3.57 (s)

[a] Chemical shifts indicated are those of PhC**H.** Similar chemical shifts measured in DMSO-d_6 for compounds of type **3** and **5** were reported in Ref.[14]. Values are closely related to shifts of **3b** and **5b** in THF-d_8 detailed in this work. Chemical shifts in $CDCl_3$ of **4b**: 4.72 ppm and of **5b**: 3.48 ppm.

Table 2. The influence of the aldehyde structure on the selectivity of DRA with piperidine (aldehyde/piperidine ratio 1:2) using precatalyst **A** and prehydrogenated precatalyst **B**.[a]

Run	Aldehyde	P_{am}/P_{al} without prehydrogenation	P_{am}/P_{al} with prehydrogenation
1	4-HOC_6H_4CHO	27.0	> 99
2	4-$MeOC_6H_4CHO$	0.8	2.1
3	PhCHO	1.4	4.7
4	4-ClC_6H_4CHO[b]	1.6	1.2
5	4-$NO_2C_6H_4CHO$[b]	complex mixture	complex mixture
6	PhCHMeCHO	0.9	7.7
7	EtCHMeCHO	2.4	18.0
8	*n*-C_7H_5CHO	12.0	> 99.5

[a] Conditions: H_2 pressure 50 bar, 5 mmol aldehyde, 0.01 mmol precatalyst, 10 mL MeOH.
[b] Formation of dimethyl acetals observed was not due to Rh(I) catalysis as was confirmed by separate experiments. Acetal formation was only found when relevant aromatic aldehydes were kept for 10 – 15 min in MeOH. However, in the presence of piperidine no acetals were detected.

Table 3. Comparison of DRA of PhCHO with amines catalyzed with precatalyst **A** and prehydrogenated precatalyst **B**.[a]

Amine	pK_a of amine	P_{am}/P_{al} without prehydrogenation	P_{am}/P_{al} with prehydrogenation
pyrrolidine	11.27	2.9	> 99.5
piperidine	11.02	1.4	4.7
Me_2NH	10.73	0.4	0.7
Et_2NH	10.49	0.1	0.1
2-methylpiperidine	10.99	< 0.01	< 0.01

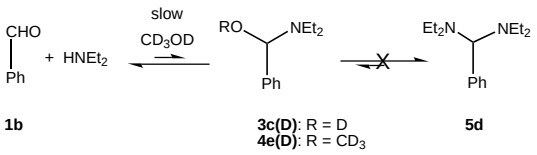
[a] Conditions: 5 mmol of aldehyde, 10 mmol of amine, 0.1 mmol of Rh complex, 10 mL of MeOH, 50 bar initial H_2 pressure.

became more pronounced when the solvent complex **B** was used instead of the precatalyst **A**.

The pK_a of amines has a striking influence upon the selectivity of the DRA of PhCHO as shown with a series of simple secondary amines. This effect was already noted in our preliminary publication by application of the precatalyst **A**.[7] The same, but more pronounced, trend is present using the solvent complex **B**. A comparison of the results is given in Table 3.

^{1}H NMR investigations of a mixture containing PhCHO and Et_2NH (1:1) in CD_3OD revealed that the rate of the formation of deuterated half-aminal **3c** and *N,O*-acetal **4e** was slower than with piperidine as amine (Scheme 10). Only 6% and 5%, respectively, of these intermediates were observed after 10 min. The corresponding aminal **5d** was not found in the mixture.

Obviously, this effect is related to the increased steric demand of the amine in the formation of the half-aminal. Indeed, in the case of 2-methylpiperidine having pK_a 10.99 (10.02 for piperidine) no *N*-intermediates



Scheme 10.

were found by ^{1}H NMR spectroscopy. Consequently, no amine was formed in the DRA. However, it is important to note that the amine may affect the hydrogenation of the aldehyde. Thus, in the presence of Et_3N the half-time of the reduction of PhCHO was dramatically reduced from 85 to 15 min.

Interestingly, the superior selectivity of the solvent complex **B** was observed only when hydrogenation was started immediately after the addition of PhCHO and amine. When a mixture of PhCHO and amine was kept for 30 min prior to the addition of the catalyst **B** the subsequent hydrogenation gave a lower P_{am}/P_{al} ratio. This effect was observed when piperidine and pyrrolidine were used as amines (compare P_{am}/P_{al} ratios 3.5 and 2.2 with the corresponding data for complex **B** given in Table 4).

To find explanations for the decreased selectivity with progressing DRA the influence of water and aminal was considered. Thus, the DRA of PhCHO with pyrrolidine using complex **B** was conducted in the presence of 0.55 mmol of water. This amount corresponds to 11% of all water that is expected after completion of the DRA process. Under the conditions given in Table 2 we observed no influence of water on the selectivity. It is interesting that the addition of an excess of water, e.g., 11.1 mmol, decreased the P_{am}/P_{al} ratio to 11. But this selectivity is still rather high and thus the conclusion outlined in Scheme 7 is confirmed. The next candidate

for the decrease of selectivity may be aminal **5** which is not produced in the first stage of the reaction between PhCHO and amine. Unfortunately, due to the instability of this compound in MeOH (*vide supra*) we were unable to propose any experimental evidence for this hypothesis.

The last question to be discussed concerns the mechanism of the reduction of half-aminal **3**, *N,O*-acetal **4** and aminal **5**. Since diacetal $PhCH(OMe)_2$ can be excluded as precursor of the product amine it is necessary to assume that hydrogenation of *N,O*-adducts should not proceed *via* a substitution mechanism. The only intermediate for hydrogenation is therefore an iminium cation $C=N^+$ which can also be produced from half-aminal **3** and aminal **5.** This has been confirmed in the present work by observation of the interconversion of these species in MeOH. The time-dependence of the outcome of DRA processes found suggest that half-aminal **3**, *N,O*-acetal **4** and aminal **5** may be coordinated to the Rh centre with different rates (or equilibria). Moreover, also different rates producing the iminium species are possible.

Conclusions

The reductive amination (DRA) of a range of aldehydes and aliphatic secondary amines with cationic rhodium(I) complexes was studied. Ratios of product amine:alcohol by up to 99:1 were achieved. The role of possible intermediates like half-aminals, *N,O*-acetals, aminals in the DRA was investigated by individual hydrogenations. It is shown that in dependence upon the structure of the starting compounds in principal all *N*-intermediates could play a role in the DRA. However, due to the fast and dominant formation of relevant *N,O*-acetals there is some evidence that they are key intermediates in DRA processes. An interesting relation between the generation of the catalytically active species by pretreatment of the COD complex with H_2 and the DRA proceeding in parallel was found. Thus, by application of the catalyst in several examples improved amine:alcohol ratios were achieved. However, in general it has to be stated that due to the large variety of pre-equilibria involved, including the accelerating effect of amines on the undesired hydrogenation of the carbonyl compound, DRA processes are very difficult for mechanistic studies. The development of more selective and active catalysts in the future will, therefore, be mainly based on trial and error. The data presented above show, however, that careful screening and consideration of all relevant influences allow one to find efficient and selective homogeneous catalysts for DRA.

Experimental Section

General Remarks

All solvents and liquids used in hydrogenations were distilled and kept under Ar. NMR spectra were recorded with Bruker ARX 400. Chemical shifts (δ, in ppm) are given for ^1H relative to TMS as internal standard and for ^{13}C relative to residual $CDCl_3$ peak (77.36 ppm). Spin-spin coupling constants (*J*) are given in Hz. α-Piperidinobenzyl alcohol (**3b**),[11] 1-(butoxyphenylmethyl)piperidine (**4c**),[12] 1,1′-benzylidenedipiperidine (**5a**)[13] were prepared according published procedures. All operations were conducted under Ar.

1-(Methoxyphenylmethyl)piperidine (4b)

1,1′-Benzylidenebispiperidine (**5a**; 17.1 g, 66 mmol) was dissolved in 100 mL of *n*-hexane containing MeOH (5 mL, 123 mmol) and cooled to 0 °C. A 4 M solution of HCl in dioxane (16.5 mL, 66 mmol) was slowly added and the mixture was stirred at ambient temperature for 2 h. The precipitated piperidine hydrochloride was filtered off and washed with an additional portion of hexane. The clear solution was evaporated and the residual liquid was distilled in vacuum. Yield: 74%; bp 78 °C/0.06 mbar; ^1H NMR ($CDCl_3$): δ = 1.35 – 1.44 (m, 2H, γ-CH_2), 1.44 – 1.59 (m, 4H, β-CH_2), 2.54 (t, 4H, *J* = 5.4 Hz, α-CH_2), 3.37 (s, 3H, OCH_3), 4.72 (s, 1H, N-CH-O), 4.74 – 7.38 (m, $5H_{arom}$); ^{13}C NMR ($CDCl_3$): δ = 25.1 (γ-CH_2), 26.5 (β-CH_2), 48.9 (α-CH_2), 56.7 (OCH_3), 98.7 (N-CH-O), 127.6 (CH), 127.8 (CH), 128.1 (CH), 138.7 (C).

General Procedure for DRA

Method A using precatalyst ***A****:* A glass beaker with 0.01 mmol of the precatalyst and a stirring bar was placed in a standard stainless autoclave (25 mL inner volume) equipped with a valve and connected to a vacuum pump, Ar and H_2 lines. The vessel was evacuated and then filled with Ar. The cycle was repeated 2 – 3 times. Under a flow of Ar through the open valve 10 mL of MeOH and liquid reaction components (or solution of components in 10 ml of MeOH) were added by means of syringes. (In the case of solid aldehydes they were placed together with the precatalyst.) The valve was closed and the autoclave was pressurized with H_2. The contents of autoclave was stirred with a magnetic stirrer.

Method B using prehydrogenated precatalyst ***B****:* The autoclave containing a glass beaker with the precatalyst and the stirring bar was deoxygenated as described above. 10 mL of MeOH were added through the open valve in an Ar flow and the precatalyst was hydrogenated for 10 – 15 min under 50 – 52 bar of H_2 pressure. Then the valve was slowly opened. When the pressure had dropped to normal a flow of Ar was immediately allowed to pass. Liquid reaction components were introduced and then the valve was closed and the autoclave pressurized with H_2. With solid aldehydes the precatalyst was hydrogenated in 3 mL of MeOH and then the aldehydes were introduced in the autoclave as a solution in 7 mL of MeOH. (Additionally when using PhCHO/piperidine and PhCHO/pyrrolidine mixtures it was confirmed that the last procedure did not result, within the experimental error, in a

Table 4. NMR characterization of alcohols of the general formula R^1CH_2OH (chemical shifts of aromatic H and C are omitted) recorded in $CDCl_3$.

R^1	$\underline{CH_2}OH$		R^1	
	^1H	^{13}C	^1H	^{13}C
4-HOC_6H_4	4.43 (s)	64.3		
4-$MeOC_6H_4$	4.47 (s)	64.7	3.69 (s, 3H, OCH_3)	55.6 (OCH_3)
Ph	4.51 (s)	65.5		
4-ClC_6H_4	4.55	64.6		
Ph(Me)CH	3.55 (dd, 1H, $J=7.0$ and 10.7); 3.59 (dd, 1H, $J=7.0$ and 10.7)	68.9	1.22 (d, 3H, $J=7.0$, CH_3), 2.85 (ddd, 1H, $J=7.0$, CH)	18.1 (CH_3), 42.8 (CH)
Et(Me)CH[a]	3.33 (m)	68.9		
n-C_7H_{15}[a]	3.51 (t, $J=6.7$)	62.5		

[a] Only characteristic resonances are listed.

Table 5. NMR characterization of tertiary amines of general formula $R^1CH_2NR^2_2$ (chemical shifts of aromatic H and C are omitted) recorded in $CDCl_3$.

R^1	R^2	$CH_2NR^2_2$		R^1		R^2	
		^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
4-HOC_6H_4	C_5H_{10}	3.31 (s)	63.1			1.27 – 1.39 (m, 2H, γ-CH_2), 1.42 – 1.56 (m, 4H, β-CH_2), 2.31 (m, 4H, α-CH_2)	24.3 (γ-CH_2), 25.4 (β-CH_2), 54.1 (α-CH_2)
4-$MeOC_6H_4$	C_5H_{10}	3.29 (s)	63.7	3.66 (s, 3H, CH_3O)	55.5 (CH_3O)	1.25 – 1.37 (m, 2H, γ-CH_2), 1.39 – 1.52 (m, 4H, β-CH_2), 2.24 (m, 4H, α-CH_2)	24.9 (γ-CH_2), 26.4 (β-CH_2), 54.8 (α-CH_2)
Ph	C_5H_{10}	3.37 (s)	64.4			1.27 – 1.40 (m, 2H, γ-CH_2), 1.42 – 1.57 (m, 4H, β-CH_2), 2.27 (m, 4H, α-CH_2)	24.9 (γ-CH_2), 26.5 (β-CH_2), 55.0 (α-CH_2)
4-ClC_6H_4	C_5H_{10}	3.34 (s)	63.5			1.27 – 1.40 (m, 2H, γ-CH_2), 1.43 – 1.57 (m, 4H, β-CH_2), 2.27 (m, 4H, α-CH_2)	24.8 (γ-CH_2), 26.4 (γ-CH_2), 55.0 (α-CH_2),
Ph(Me)CH	C_5H_{10}	2.32 (d, $J=7.0$)	67.4	1.18 (d, 1H, $J=7.0$), 2.85 (6 lines, 1H, $J=7.0$, CH)	20.3 (CH_3), 37.8 (CH)	1.25 – 1.36 (m, 2H, γ-CH_2), 1.37 – 1.52 (m, 4H, β-CH_2), 2.12 – 2.39 (m, 4H, α-CH_2)	24.8 (γ-CH_2), 26.3 (β-CH_2), 55.2 (CH_2N)
Et(Me)CH	C_5H_{10}	2.66 – 2.79 (m)	66.9	0.80 (t, 6H, $J=7.2$, CH_3), 0.92 – 1.18 (m, 1H, CH), 1.93 (dd, 1H, $J=7.7$ and 12.1, MeC$\underline{H}$H), 2.03 (dd, 1H, $J=6.7$ and 12.1, MeCH$\underline{H}$)	11.9 (CH_3), 18.4 (CH_3), 28.4 (CH_2), 32.5 (CH)	1.27 – 1.40 (m, 2H, γ-CH_2), 1.41 – 1.57 (m, 4H, β-CH_2), 2.21 (m, 4H, α-CH_2)	25.1 (γ-CH_2), 26.5 (β-CH_2), 55.6 (α-CH_2)
n-C_7H_{15}	C_5H_{10}	2.19 (t, $J=7.8$)	59.9	0.80 (t, 3H, $J=6.8$, CH_3), 1.13 – 1.27 (m, 10H, 5CH_2), 1.30 – 1.46 (m, 2H, CH_2),	14.3 (CH_3), 22.9 (CH_2), 27.2 (CH_2), 28.0 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 32.1 (CH_2)	1.30 – 1.46 (m, 2H, γ-CH_2), 1.46 – 1.51 (m, 4H, β-CH_2), 2.27 (m, 4H, α-CH_2)	24.7 (γ-CH_2), 26.2 (β-CH_2), 54.9 (α-CH_2)
Ph	C_4H_8	3.52 (s)	61.3			1.62 – 1.78 (m, 4H, β-CH_2), 2.34 – 2.51 (m, 4H, α-CH_2)	23.9 (β-CH_2), 54.7 (α-CH_2)
Ph	Me	3.31 (s)	64.7			2.09 (s, 6H, CH_3)	45.6 (CH_3)
Ph	Et	3.46 (s)	57.5			0.94 (t, 6H, $J=7.1$, CH_3); 2.40 (q, 4H, $J=7.1$, CH_2);	11.53 (CH_3), 46.7 (CH_2)

change of the P_{am}/P_{al} ratio. When 4-ClC_6H_4CHO and 4-$NO_2C_6H_4CHO$ were applied as substrate during their dissolution in MeOH the formation of corresponding dimethoxy acetals was observed. Storage of these solutions for 10 min increased the yields of acetals.) The same approach (prehydrogenation in 3 mL of MeOH) was used when the mixture of an aldehyde and an amine in 7 mL of MeOH was pre-equilibrated for 30 min.

The consumption of H_2 was monitored as a decrease of pressure by means of a pressure detector. When the consumption of hydrogen ceased the autoclave was opened, the solution evaporated in vacuum and the residue analyzed by integration of ^1H NMR signals. Additionally, the structure of the products was confirmed by ^{13}C NMR spectroscopy. NMR spectral data for produced alcohols and amines are given in Tables 4 and 5.

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