The Reductive Amination of Aldehydes and Ketones and the Hydrogenation of Nitriles: Mechanistic Aspects and Selectivity Control

Silvia Gomez, Joop A. Peters, Thomas Maschmeyer*

Laboratory of Applied Organic Chemistry and Catalysis, DelftChemTech, Delft University of Technology, Julianalaan 136, 2628 BL, Delft, The Netherlands
Fax: (+31)-15-2781415, e-mail: Th.Maschmeyer@tnw.tudelft.nl

Dedicated to Professor Roger A. Sheldon on the occasion of his 60th birthday.

Abstract: This review deals with two of the most commonly used methods for the preparation of amines: the reductive amination of aldehydes and ketones and the hydrogenation of nitriles. There is a great similarity between these two methods, since both have the imine as intermediate. However, due to the high reactivity of this intermediate, primary, secondary and/or tertiary amines are obtained (often simultaneously). The relation of the selectivity to different substrate structures and reaction conditions is briefly summarised, the main focus being on the catalyst as it is the most significant factor that governs the selectivity. Different mechanisms are discussed with the view to correlate the structure of the catalyst and, more particularly, the nature of the metal and the support with selectivity. The crucial point is the presumed location of the condensation and hydrogenation steps.

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1 Introduction

Amines are very important industrial organic compounds that have found widespread applications as solvents, intermediates for pharmaceuticals, raw materials for resins, textile additives, disinfectants, rubber stabilisers, corrosion inhibitors and in the manufacture of detergents and plastics. Two of the most common methods to prepare amines are the reductive amination of carbonyl compounds and the hydrogenation of nitriles.

The reductive amination of aldehydes or ketones proceeds in several consecutive steps. Condensation of the carbonyl compound and the amine forms a carbinolamine, which eliminates H_2O to give an imine or Schiff base. Subsequently, the imine intermediate is reduced to the amine. A carbonyl compound/amine mixture can often be reduced using formic acid (Leuckart–Wallach reaction)[1] or certain metal hydrides.[2] In the latter instance, sodium cyanoborohydride appears to be the most convenient reagent.[3] However, these routes are expensive and pose environmental problems. A more practical method calls for molecular hydrogen, in the presence of a supported or unsupported catalyst, as the reducing agent in this process.

For the synthesis of amines from nitriles, the catalytic reduction with hydrogen is also the most interesting process. Both processes, the reductive amination of carbonyl compounds and the hydrogenation of nitriles, are usually carried out in the liquid phase and at elevated hydrogen pressures. Furthermore, these reactions are rather similar from a mechanistic point of view, since both have the imine as intermediate.

Silvia Gomez was born in 1971 in Terrassa, Spain. She studied organic chemistry at the Universitat Autònoma de Bellaterra, graduating in 1994. Next, she did her PhD at the Institut de Ciència de Materials de Barcelona (CSIC), under the supervision of Professor Francesc Teixidor. After a postdoctoral fellowship at the Laboratoire de Chimie de Coordination (CNRS), Toulouse, France, with Professor Bruno Chaudret, she moved to her current position as a postdoctoral fellow at the Laboratory of Applied Organic Chemistry and Catalysis, at the Delft University of Technology, The Netherlands. Her research there involves high-throughput techniques as a tool in catalyst design for the reductive amination of benzaldehyde with NH$_3$.

Joop A. Peters was born in 1944 in The Hague, The Netherlands. He studied organic chemistry at the Delft University of Technology, where he remained as a staff member. He received his PhD in 1978 with Professor Herman van Bekkum. He is author/co-author of 210 research articles. His current research interests are focused on the use of catalysis for the conversion of renewables into useful products and on the development of paramagnetic contrast agents for magnetic resonance imaging.

Thomas Maschmeyer was born in 1966 in Hamburg, Germany. After emigration to Australia in 1986, he received his Bachelor of Science (Hons I), 1990, and PhD, 1994, from the University of Sydney, both under the supervision of Professor Tony Masters. In 1994, he went as Australian Bicentennial Fellow to the Royal Institution (RI), London, with Professor John Meurig Thomas. Subsequent positions include the Assistant Directorship of the Davy Faraday Laboratories, RI, 1995–1998, an Assoc. Lecturership at the University of Cambridge, in the group of Professor Brian F. G. Johnson, 1996–1998, and an affiliate Fellowship, Peterhouse, Cambridge, 1996–1998. In 1998, he took up the chair of Industrial Organic Chemistry at the Delft University of Technology. His current interests lie in the areas of process intensification, sustainability and targeted drug delivery, which are addressed within the framework of five subthemes: porous solids, chiral catalysis, computational chemistry, renewable resources and combinatorial catalysis.

Due to the high reactivity of these reaction intermediates, conventional reductive amination of aldehydes and ketones and hydrogenation of nitriles occur as a set of consecutive and parallel reactions, resulting in a mixture of primary, secondary and tertiary amines. Separation of the reaction products is usually difficult, due to small differences in boiling points.

The specifications for amines are often very strict from the point of view of purity. For this reason, one of the most important issues in the reductive amination of aldehydes and ketones and the hydrogenation of nitriles is the control of the selectivity. A non-exhaustive survey of the literature shows that a proper choice of catalyst is essential to achieve this. Although the nature of the catalyst is the most important parameter to control the selectivity, it is also the least understood. The structure of the substrate and the reaction conditions employed can also affect the selectivity to some degree.

An overwhelming amount of literature exists on these two reactions. The majority has appeared in patents.[4] A number of reviews and book chapters have been published on each of the methods separately.[5] The present review focuses on the similarities of the heterogeneous reductive amination of aldehydes and ketones and reduction of nitriles, particularly, with regard to the parameters that affect the selectivity and the relation between the structural properties of the catalysts and their performance. In this context, the literature, as found between 1940 and 2001, is covered.

2 Reaction Mechanisms and By-Products

For a rational discussion about how the structure of the substrate, the reaction conditions and the nature of the catalyst affect the selectivity, a study of the mechanisms of the reductive amination of aldehydes and ketones and the hydrogenation of nitriles is required. The reaction steps in both routes are widely documented in the literature. However, there are still some points of controversy concerning some of the elementary steps.
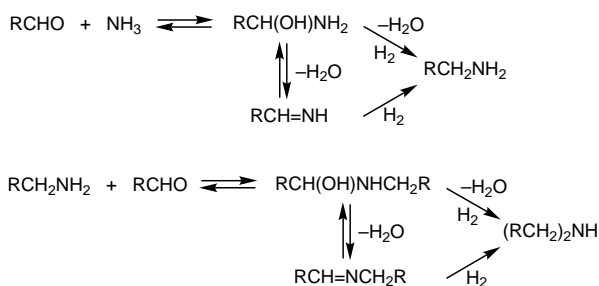
2.1 Reductive Amination of Aldehydes and Ketones

The preparation of amines through hydrogenation of the reaction products of carbonyl compounds with NH$_3$ was first utilised by Mignonac, who submitted solutions of aldehydes or ketones in the presence of NH$_3$ to the action of H$_2$ over Ni.[6] He proposed a sequence of steps in which primary and secondary amines are produced by hydrogenation of imines or direct hydrogenolysis of carbinolamines (Scheme 1). The initially formed primary amines can, in their turn, behave as aminating agents for carbonyl compounds to afford secondary amines.
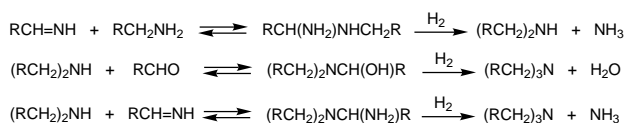
It was proposed as well that primary amines react with imines, forming an addition product, which can directly be reduced to the secondary amine. The secondary amine would react similarly with either the carbonyl compound or the imine to give the tertiary amine through hydrogenation of the corresponding carbinolamine or *gem*-diamine intermediate (Scheme 2).[7]

However, a kinetic study on the reductive amination of acetone with NH$_3$ revealed that both isopropylamine and diisopropylamine are obtained through hydrogenation of the imine intermediates formed from acetone and NH$_3$ or acetone and isopropylamine, respectively. A separate study of the reaction of acetone and isopropylamine showed that the diisopropylimine equilibration reaction is acid catalysed (Scheme 3).[8]
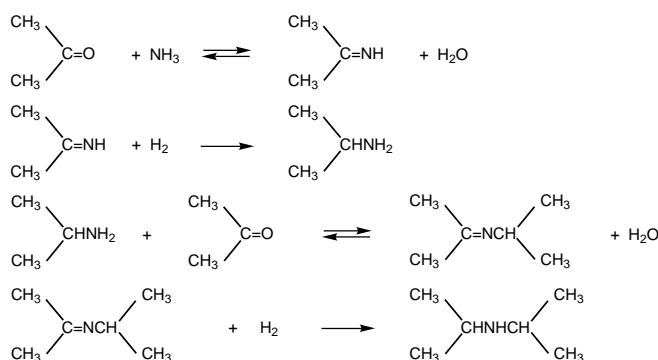
Subsequent work, on the preparation of tertiary amines from secondary amines and ketones, confirmed the idea that the secondary amine results from hydrogenation of the corresponding imine rather than from hydrogenolysis of the carbinolamine.[9] However, imine intermediates are not possible in the reductive amination with secondary amines. Formation of an enamine
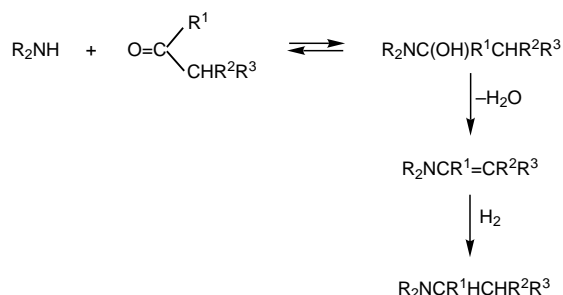
Scheme 3. Mechanism for the reductive amination of acetone with NH$_3$ *via* imines.

followed by its reduction to the corresponding tertiary amine was proposed as an alternative for the mechanism (Scheme 4). The use of D$_2$ would be a useful tool to prove this mechanism but, to the best of our knowledge, this has not been performed.
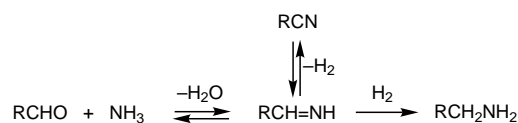
In cases where the enamine can also not be formed, the mechanism would exceptionally proceed through hydrogenolysis of the carbinolamine. In fact, because of steric hindrance, only when cyclisation is involved, the formation of tertiary amines occurs easily.[10]

The detection of nitriles, in the reaction mixture of the reductive amination of aldehydes with NH$_3$ over Ni/Al$_2$O$_3$, suggested another potential pathway, in which a dehydrogenation of the intermediate imine takes place on the catalyst (Scheme 5).[11]

When the carbonyl compound is introduced into the reaction mixture gradually, it was proposed that the reactions proceed not *via* an imine intermediate, but *via* N-adsorption of the carbinolamine to the catalysts

Scheme 1. Mechanism proposed by Mignonac. Similar reactions may occur when the carbonyl compound employed is a ketone.

Scheme 4. Formation of tertiary amines by hydrogenation of the enamine.

Scheme 2. Mechanism for the formation of secondary and tertiary amines *via* carbinolamines or *gem*-diamines.

Scheme 5. Mechanism for the reductive amination of aldehydes with NH$_3$ *via* nitriles.

followed by subsequent hydrogenolysis of the C-OH bond to the amine product. Carbinolamine intermediates are assumed to adsorb more strongly on the catalyst surface than the parent carbonyl compounds. The metal surface catalyses the dehydroxylation of the carbinolamine, which is probably faster than the homogeneous dehydration to the imine. The dehydroxylated species could form an imine by cleavage of a C-H bond but hydrogenolysis of the C-M bond leads directly to the reaction product.[12]

However, the formation of dibenzylimine was observed during the reductive amination of benzaldehyde with NH_3, suggesting once again the pathway that includes formation of imines.[13] The composition of the reaction mixture over time showed that both, benzylamine and dibenzylamine, are formed from dibenzylimine, in which the imine function is stabilised by mesomerism with the two aryl groups (Scheme 6).

It may be concluded that various mechanisms are possible in these reactions. The amine forms either by direct hydrogenolysis of the carbinolamine or *gem*-diamine adduct, or after dehydration to the imine or enamine followed by hydrogenation. The preferred pathway depends on the structure of the reactants and the reaction conditions.

The principal side-reactions in the reductive amination processes involve the formation of an alcohol from the competing hydrogenation of the unreacted carbonyl group. The formation of the alcohol constitutes a loss of material and may considerably disturb the course of the reaction. A requirement for a successful reaction is then that the hydrogenation of the carbonyl compound is relatively slow. The combination of reaction conditions with catalyst choice should be optimised so as to achieve this requirement. Therefore, many workers allow the amine and the carbonyl compound to stand together for some time to pre-equilibrate prior to hydrogena-

tion.[13,14] Other authors propose gradual addition of the carbonyl compound to the amine in order to maintain low concentrations of the carbonyl compound in the reaction mixture.[15] The isolation of the imine intermediate before hydrogenation has also been suggested.[16] However, this is only possible occasionally, since imines are generally not sufficiently stable. Usually, their formation and subsequent hydrogenation are achieved in a single operation. For instance, the reaction between benzaldehyde and NH_3 produces benzylimine, $PhCH=NH$, but this product is highly reactive and readily forms hydrobenzamide, the formation of which was already reported by Laurent in 1837.[17] Two mechanisms have been proposed for its formation: (i) trimerisation of benzylimine with loss of NH_3 [18] and (ii) condensation of benzaldehyde with either two benzylimine or α-aminobenzyl alcohol molecules, followed by dehydration (Scheme 7).[19]

At 90 °C, however, the equilibria shift back to benzylimine or benzylimine and benzaldehyde (depending on the mechanism of formation of hydrobenzamide). Therefore, reductive amination of benzaldehyde is performed at elevated temperatures.

The competing side-reaction of the carbonyl group to the alcohol can also be minimised by selection of a catalyst that reduces the carbonyl group with a relatively low rate. The formation of isopropanol in the reductive amination of acetone with NH_3 was suppressed by selectively poisoning with Sn the sites responsible for the hydrogenation of acetone in a Ni catalyst.[20] During a study of the reaction between acetophenone and aniline to yield *N*-phenyl-α-methylbenzylamine, it was observed that the alcohol formation can be reduced substantially by using sulphided noble metal catalysts (e.g., PtS_x/C).[21]

Birtill et al. noticed that, even though Pt/C was much more active, Pd/C produced less alcohol by-product than Pt/C in the reductive amination of methyl isopropyl ketone with ethylamine and benzaldehyde with dimethylamine. According to their proposed mechanism through carbinolamine intermediates, the alcohol would be formed by hydrogenolysis of the C-N bond of the carbinolamine, which seems to occur more readily over Pt than over Pd. The greater selectivity of Pd compared to Pt towards the amine would thus be a consequence of the relative stabilities of the various adsorbed fragments on the respective metal surfaces.[12]
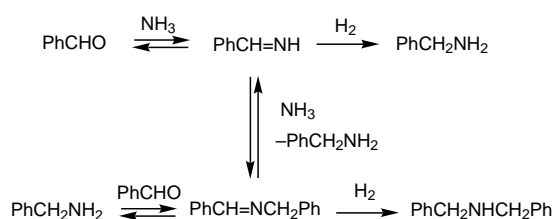
Scheme 6. Mechanism for the reductive amination of benzaldehyde with NH_3 *via* imines.
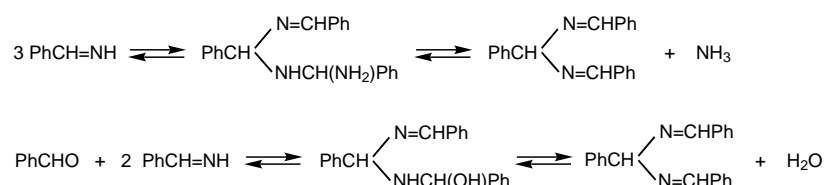
Scheme 7. Formation of hydrobenzamide from benzylimine.

Another important side-reaction is the aldol condensation of reactive carbonyl compounds. In the reaction of aliphatic aldehydes with NH_3, aldol condensation can be decreased by slow addition of the aldehyde to the reaction mixture at elevated temperature in order to quickly form and hydrogenate the intermediate imine.[22] Ketones are less susceptible to undergo aldol condensations.

Finally, alkanes can also be produced by hydrogenolysis of amines or of the alcohols obtained by direct reduction of the carbonyl compounds.[12]

2.2 Hydrogenation of Nitriles

Von Braun et al. presented a scheme for the mechanism in the hydrogenation of nitriles to explain the formation of secondary amines.[23] Nitriles were hydrogenated first to the imine and then to the primary amine. The primary amine could react with the intermediate imine and form the secondary amine *via* a *gem*-diamine that could undergo either direct hydrogenolysis or elimination of NH_3 followed by hydrogenation.

Kindler and Hesse proposed that tertiary amines are formed by addition of the secondary amine to the imine and subsequent hydrogenolysis of the *gem*-diamine intermediate.[24]

However, it was also postulated that NH_3 is first eliminated from the *gem*-diamine to form an enamine intermediate that is subsequently hydrogenated to the tertiary amine.[25]

A study of the hydrogenation of lauronitrile over a Co catalyst furnished evidence that the secondary amine is not formed in the Co-catalysed hydrogenolysis of the *gem*-diamine, since the secondary imine accumulates in the reaction mixture (as shown by chromatography and spectroscopy) and the secondary amine is formed only at the end of the reaction by hydrogenation of the imine.[26]

Contrary to imines, the presence of enamines was not confirmed, but experimental results led some authors to presume their participation in the formation of tertiary amines. The fact that the reduction of benzonitrile, over Pd and Pt catalysts, did not yield tribenzylamine served as an argument in favour of the enamine mechanism. Tribenzylamine should be formed as a result of the reaction between benzylimine and dibenzylamine. As the enamine is not possible because of the absence of hydrogen atoms in the α-position of the cyano group, the tertiary amine can not be formed (Scheme 8).[27]

PhCH=NH + PhCH₂NHCH₂Ph ⇌ PhCHN(CH₂Ph)(CH₂Ph) with NH₂
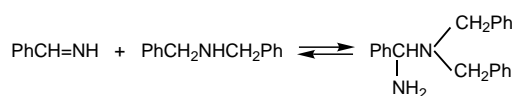
Scheme 8. Reaction between benzylimine and dibenzylamine.

In our research group, we have studied the reductive amination of benzaldehyde with NH_3 over Pd/C catalysts. In the presence of a molar ratio NH_3/benzaldehyde = 0.75, 8% tribenzylamine is observed in the reaction mixture after total conversion. Hence, the formation of tribenzylamine is possible and can be explained by a mechanism other than one that proceeds *via* enamines, i.e., hydrogenolysis of the carbinolamine intermediate.[28] This would be in agreement with the mechanism proposed by Kindler and Hesse for the hydrogenation of nitriles.[24] According to them, tribenzylamine could be obtained in the reduction of benzonitrile *via* hydrogenolysis of the *gem*-diamine intermediate formed from the addition of dibenzylamine to benzylimine (Scheme 8).

The general mechanism of the hydrogenation of nitriles and the reductive amination of aldehydes with NH_3, taking into account all the previous considerations, is depicted in Scheme 9.

Although much insight in these mechanisms has been obtained, some questions remain. It is still not always clear whether reductions take place through hydrogenolysis of carbinolamines or *gem*-diamines or by hydrogenation of imines or enamines (in the case of tertiary amines).

3 Effect of the Substrate Structure

3.1 Steric Effects

The rate of the reaction between an amine and a carbonyl group to form the intermediate imine and the rate of the hydrogenation of the imine both decrease with increasing the size of the groups in the neighbourhood of the mentioned functions. Therefore, yields and selectivities are strongly dependent upon the steric hindrance of the starting compounds. In general, more sterically hindered starting compounds afford higher selectivities to primary amines although it is necessary to take into consideration that a carbonyl compound with little tendency to undergo addition of NH_3 or an amine may also be reduced to the alcohol.

The reductive amination of methyl ethyl ketone with NH_3 afforded more secondary amine than that with diethyl ketone as the substrate. Similarly, the yield of secondary amine in the reaction between acetone, methyl ethyl ketone or diethyl ketone and cyclohexylamine decreased with increasing steric hindrance around the carbonyl function.[29]

Steric hindrance plays also a role around the amine function. For example, reductive amination of acetone with 2,4,6-trimethylaniline afforded the secondary amine, *N*-isopropyl-2,4,6-trimethylaniline, in only 36% yield while, with aniline, the yield of the corresponding secondary amine was 98% (Scheme 10).[30]
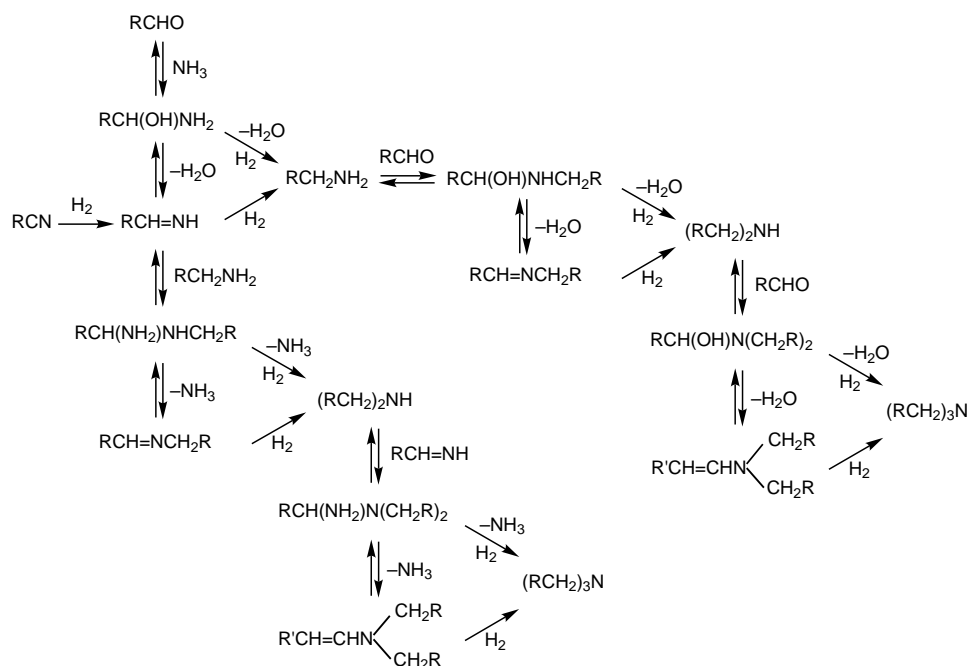
Scheme 9. Mechanism of the hydrogenation of nitriles and the reductive amination of aldehydes with NH_3.
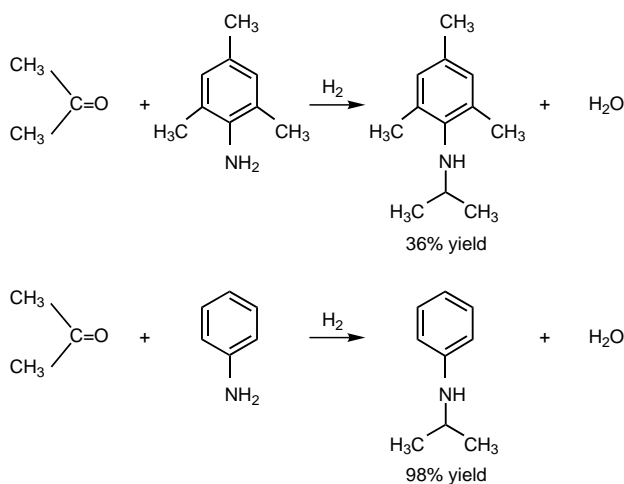
Scheme 10. Effect of the steric hindrance of the amine on the reductive amination of acetone with aniline and 2,4,6-trimethylaniline.

Likewise, cyclic ketones produce more secondary amine than the corresponding linear ketones.[31]

Rylander, while studying the reaction between 2-methyl- and 4-methylcyclohexanone with NH_3, observed that a methyl group at the 2-position offers more steric hindrance to the formation of the secondary amine (Table 1).[32]

Another interesting example of the influence of the steric hindrance of the starting compounds is found in the reductive amination of straight-chain aliphatic aldehydes, such as acetaldehyde, propionaldehyde and n-butyraldehyde, with glycine, which merely

yields the corresponding secondary amines. With branched-chain aliphatic aldehydes, such as isobutyraldehyde and isovaleraldehyde, as starting compounds, a mixture of primary and secondary amines is obtained (Table 2).[33]

Birtill et al. found that a methyl group at the 2-position of a ketone decreases the reaction rate over 5 wt % Pd/C but not over 5 wt % Pt/C.[12] As stated above, they suggested that the reductive amination reaction proceeds via hydrogenolysis of the carbinolamine intermediate. They postulated that the adsorption of the carbinolamine via formation of an M-N bond is followed

Table 1. Effect of the steric hindrance of the ketone on the selectivity in the reductive amination of methylcyclohexanones with NH_3.

R	selectivity [% weight][a]		
	primary amine	secondary amine	alcohol
2-methyl	80	0	20
4-methyl	44	40	16

[a] Each experiment was run at 70 bar and $T = 100\,°C$; no solvent was used, NH_3 was present as aqueous NH_3; the molar ratio NH_3/ketone was of 6.

Table 2. Effect of the steric hindrance of the aldehyde on the selectivity in the reductive amination of various aliphatic aldehydes with glycine.

aldehyde	molar ratio aldehyde/glycine	T [°C]	t [h]	yield [%]	
				primary amine	secondary amine
acetaldehyde	2	40–45	4	0	85
propionaldehyde	2	40–45	4	0	80
n-butyraldehyde	2	45–50	6	0	83
isobutyraldehyde	2	50–55	9	40	36
isovaleraldehyde	2	50–55	6	19	59

by cleavage of the C-OH bond and formation of a C-M bond, resulting in a close interaction between the metal surface and the 2-methyl groups. To explain the higher activity of Pt/C, it was assumed that this catalyst contains a greater number of corner and/or edge accessible sites to allow the adsorption of the carbinolamine.[12] The contribution of these authors is especially interesting, because they highlight the importance of the catalyst. In our opinion, however, similar steric arguments would hold if the intermediate were an imine rather than a carbinolamine.

Since steric hindrance can result in a low rate of formation of the imine, it may be necessary to operate under more severe conditions in these cases. Some authors allow the carbonyl compound and the amine to stand together for several hours or heat the mixture before hydrogenation.[34] Another possibility is to increase the amount of catalyst.[35] If the imine is formed too slowly, amines will be contaminated with alcohols.

The hydrogenation of the intermediate imine is also affected by the steric hindrance. 2-(1-Iminoethyl)-1,1,3-trimethylcyclohexane appeared to be abnormally stable and hydrogenation over PtO$_2$ could not be effected as, due to steric hindrance, there was little or no contact between the C=N bond and the catalyst (Figure 1).[36]

Regarding the same matter, Freifelder reported that ArCH=NR undergoes smooth hydrogenation to amines, except when R is a highly substituted alkyl group or a ring system with a bulky group at the 2-position or when the aromatic ring (Ar) also contains a large 2-substituent.[35]
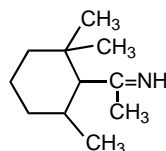
Figure 1. 2-(1-Iminoethyl)-1,1,3-trimethyl-cyclohexane.

3.2 Electronic Effects

In addition to steric effects, electronic effects may play a role in the reactions under study. Electron-withdrawing groups in the carbonyl compound or electron-releasing groups in the amine facilitate the addition reaction.

Surprisingly, the reductive amination of 1-naphthaldehyde with NH$_3$ over Raney Ni did not yield any trace of aminated product, the primary alcohol was obtained exclusively, while 2-methoxy-1-naphthaldehyde gave 61% primary amine and only 8% alcohol.[37] Even though the *o*-substitution is increasing the steric hindrance around the reaction centre, a higher yield of the addition product was obtained. Obviously, these results might be rationalised by electronic effects (Table 3).

Similarly, in the context of the hydrogenation of nitriles, the rate of secondary amine formation, by reaction between the imine and the primary amine, is influenced by the electron density on the nitrogen atom in the primary amine. A weak inductive effect (e.g., due to a benzyl group) decreases the nucleophilicity of the primary amine, thus, slowing down the nucleophilic attack on the intermediate imine and resulting in the lowering of secondary amine production. In the hydrogenation of valeronitrile, catalysed by Pd, 84% tripentylamine and no pentylamine were observed. Under the same conditions, benzonitrile yielded 63% benzylamine and 34% dibenzylamine. Valeronitrile initially yields pentylamine upon hydrogenation, which is very reactive with respect to pentylimine because of the high electron

Table 3. Effect of the *o*-substitution of the aldehyde on the reductive amination of 1-naphthaldehyde and 2-methoxy-1-naphthaldehyde with NH$_3$.

aldehyde	T [°C]	P [bar]	t [h]	yield [%]	
				primary amine	alcohol
1-naphthaldehyde	60–70	80	3	–	67
2-methoxy-1-naphthaldehyde	60	130	2	61	8

density on the nitrogen atom, and, for this reason, di- and tripentylamine are formed. Benzylamine has a lower electron density on the nitrogen atom and, consequently, is less reactive with respect to benzylimine. Therefore, a considerable amount of primary amine is obtained in this case.[27]

As already mentioned, when considering the effect of the substrate structure, it should be borne in mind that the catalyst is the most important parameter determining selectivities. For this reason, caution is required when evaluating reaction results obtained with different catalysts.

4 Effect of the Reaction Conditions

Good yields of primary amines are frequently difficult to achieve. By changing the reaction conditions, one can influence the relationship between the rates of condensation and hydrogenation and thus tune the composition of the reaction product.

4.1 Effect of Binding Primary Amines with Acids, Ammonium Salts and Acetic Anhydride

4.1.1 Effect of the Addition of Acids

Strongly acidic solutions prevent further reactions of the initially formed primary amine by formation of the ammonium salt. Hartung found in 1928 that it is possible to obtain the primary amine, without contamination from the secondary amine, by working in an alcoholic HCl solution and isolating the primary amine as the ammonium salt. Under these conditions, benzonitrile was gently reduced to benzylamine over Pd/C.[38] The same method was used for the inhibition of secondary amines in the Pd/C-catalysed hydrogenation of o-cyanobenzenesulphonamide to o-aminomethylbenzenesulphonamide (Scheme 11).[39]

Another example is the hydrogenation of cyanopropylsulphonamide to 4-amino-1-butanesulphonamide but PtO$_2$ was used as the catalyst because the reaction with Pd/C was too slow.[40]

CH$_3$COOH has also successfully been used for this purpose. Hydrogenation of benzonitrile in CH$_3$COOH over Pd on BaSO$_4$ gave over 80% yield of benzylamine. Hydrogenation of phenylacetonitrile gave best results when CH$_3$COOH contained H$_2$SO$_4$ or dry HCl.[41]
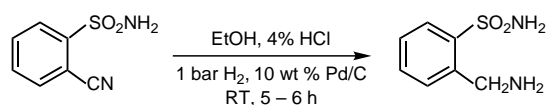
Smooth hydrogenation of nitriles in CH$_3$COOH in the presence of PtO$_2$ as the catalyst has also been reported by other authors.[42]

### 4.1.2 Effect of the Addition of Ammonium Salts

The presence of an ammonium salt can also lead to improved yield of primary amines. Alexander and Misegades found that, when NH$_4$Cl is introduced into the reaction mixture, the reductive amination of carbonyl compounds stops at the stage of primary amines. Ammonium ions protonate the primary amine to yield less nucleophilic alkylammonium ions.[43]

Similarly, introduction of CH$_3$COONH$_4$ and CH$_3$COOH into the reaction mixture of the reductive amination of 1-(2,5-dimethoxyphenyl)propan-2-one with NH$_3$ over Raney Ni permitted the synthesis of 2-amino-1-(2,5-dimethoxyphenyl)propane in 95% yield (Scheme 12).[44]

4.1.3 Effect of the Addition of Acetic Anhydride

Another effective way of minimising reaction towards secondary amines is to acetylate the primary amine, as it is formed, by carrying out the reduction in an anhydride solvent. The reduction of benzonitrile proceeded smoothly over PtO$_2$ in an acetic anhydride solution with the highly selective formation of the acetyl derivative of the corresponding primary amine. The secondary amine or its acetyl derivative were not observed. Hydrolysis of the reaction product by means of concentrated HCl gave benzylamine in good yield.[45]

This method was slightly modified by carrying out the hydrogenation of nitriles in acetic anhydride over Raney Ni and CH$_3$COONa or NaOH as co-catalyst. Addition of bases led to better yields and purer products and, particularly, NaOH made considerable re-use of the catalyst possible. For instance, reduction of tridecanenitrile over Raney Ni, in the presence of acetic anhydride and CH$_3$COONa, afforded 100% yield of N-acetyltridecylamine and reduction of adiponitrile under the same conditions, but using NaOH as the co-catalyst, yielded 80% N,N'-diacetylhexamethylenediamine (Scheme 13).[46]

Scheme 11. Hydrogenation of o-cyanobenzenesulphonamide in an alcoholic HCl solution.
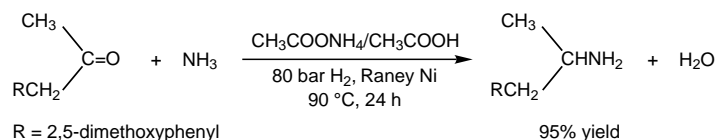
Scheme 12. Reductive amination of 1-(2,5-dimethoxyphenyl)propan-2-one with NH$_3$ in the presence of CH$_3$COONH$_4$/ CH$_3$COOH.

$$CH_3(CH_2)_{11}CN \xrightarrow[\substack{3 \text{ bar } H_2, \text{ Raney Ni} \\ 50\,°C, 1\,h}]{CH_3COONa/CH_3COOCOCH_3} CH_3(CH_2)_{12}NHCOCH_3$$
100% yield

$$NC(CH_2)_4CN \xrightarrow[\substack{3 \text{ bar } H_2, \text{ Raney Ni} \\ 50\,°C, 15\,min}]{NaOH/CH_3COOCOCH_3} H_3CCOHN(CH_2)_6NHCOCH_3$$
80% yield
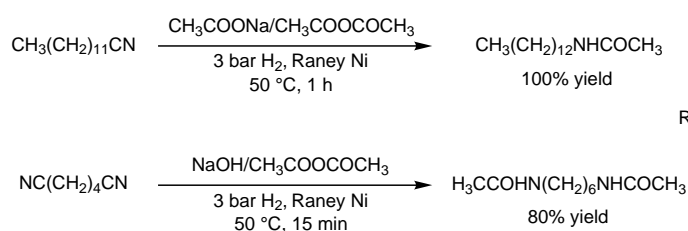
Scheme 13. Hydrogenation of tridecanenitrile and adiponitrile, in acetic anhydride, with CH_3COONa and NaOH, respectively, as co-catalyst.
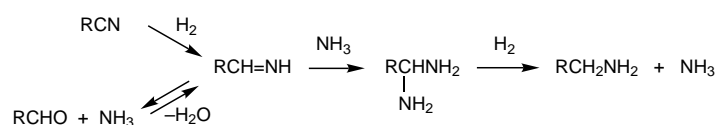
4.2 Effect of the Addition of NH$_3$

Application of an excess of NH_3 is another common technique to increase the selectivity to primary amine. This technique is probably one of the most reported and has allowed the development of several industrial processes. Winans, in 1939, observed that, in the reductive amination of an aldehyde with NH_3 over Raney Ni, one mole of aldehyde and one or more moles of NH_3 produce mainly primary amine, while a ratio of 3 moles of aldehyde to 2 moles of NH_3 gives a mixture of primary and secondary amine and 2 moles of aldehyde and 1 mole of NH_3 produce predominantly the secondary amine (Table 4).[4a,47]

Dibenzylamine was prepared by using Pd/C as the catalyst and a molar ratio of NH_3 to benzaldehyde between 0.55 and 0.7.[48] Our research group, while studying the same reaction over a Pd catalyst supported on an oxidised carbon support, found that 65% dibenzylamine and 35% benzylamine are obtained with a molar ratio NH_3/benzaldehyde = 16. Much higher selectivity to dibenzylamine was displayed with a molar ratio NH_3/benzaldehyde = 2. The product composition consisted in this case of 85% dibenzylamine, 7.5% benzylamine and 7.5% benzyl alcohol.[49]

Likewise, primary diamines were produced over Ni catalysts by using a molar ratio NH_3/dialdehyde = 10 – 30.[50]

Also, in the case of the hydrogenation of nitriles over Raney Ni, the formation of secondary amines can be almost entirely prevented by carrying out the reaction in the presence of sufficient NH_3.[7,51] The importance of the use of the proper amount of NH_3 has been

$$RCN \xrightarrow{H_2} RCH=NH \xrightarrow{NH_3} RCHNH_2 \xrightarrow{H_2} RCH_2NH_2 + NH_3$$
$$RCHO + NH_3 \underset{-H_2O}{\overset{}{\rightleftharpoons}} \qquad\qquad\qquad\qquad \underset{NH_2}{|}$$

Scheme 14. Mechanism proposed by Schwoegler and Adkins to explain the effect of NH_3 on the selectivity in the reductive amination of aldehydes with NH_3 and the hydrogenation of nitriles.

demonstrated in other nitrile reductions with Co,[52] Fe,[53] and Rh catalysts.[54]

According to Schwoegler and Adkins, the favouring role of NH_3 in the selective formation of primary amines can be rationalised with the mechanism depicted in Scheme 14.

In this mechanism, NH_3 adds to the primary imine, $RCH=NH$, and hydrogenolysis of the resulting *gem*-diamine intermediate gives the primary amine.[7]

Volf and Pasek argued that the selectivity to the primary amine could be ascribed to a protection of the primary imine against further hydrogenation by formation of the *gem*-diamine compound. These authors assumed that the primary amine is exclusively formed by hydrogenation of the imine. Therefore, they explained the slowing down in the formation of the secondary amine, under the action of NH_3, by proposing that the competitive reaction between the primary imine and NH_3 was lowering the concentration of primary imine available to undergo hydrogenation and to react with the primary amine. This was in accord with the results obtained for the hydrogenation of lauronitrile over a Co catalyst. The rate of didodecylimine formation was decreased by a factor of 5 in comparison with an experiment without NH_3, whereas the rate of hydrogenation was also lowered by a factor of about 2.[26] It should be noted, however, that these results can be explained with the mechanism proposed by Schwoegler and Adkins equally well.

Further studies on the reductive amination of benzaldehyde with NH_3, over Pd/C catalysts, demonstrated that dibenzylimine undergoes transimination with NH_3 to give benzylimine and benzylamine (Scheme 15).[13]

In agreement with this mechanism, the action of NH_3 in suppressing secondary and tertiary amine formation

Table 4. Effect of the ratio of NH_3 to aldehyde on the reductive amination of different aldehydes with NH_3.

aldehyde	yield [%][a]					
	1/2 equiv. NH$_3$		2/3 equiv. NH$_3$		1 equiv. NH$_3$	
	prim. amine	sec. amine	prim. amine	sec. amine	prim. amine	sec. amine
benzaldehyde	11.8	80.8	30.5	62.6	89.4	7.1
furfuraldehyde	12.2	65.5	30.3	66.5	79	6

[a] Each experiment was run at 90 bar and T = 40 °C in EtOH as the solvent.

PhCH=NCH₂Ph + NH₃ ⇌ PhCH=NH + PhCH₂NH₂

| H₂

PhCH₂NH₂

Scheme 15. Mechanism to explain the effect of NH_3 on the selectivity in the reductive amination of benzaldehyde with NH_3.

may be ascribed to a shift of this transimination equilibrium to the side of the primary imine and amine.

Other possible explanations – albeit mostly speculative – for the role of NH_3 are: (i) the selective poisoning of the sites responsible for the coupling reactions in the catalyst[55] and (ii) a modification of the electronic properties of the catalytic metal.[56]

4.3 Effect of the Addition of H₂O

It has been observed that addition of H_2O leads to a markedly lower tendency for the formation of undesired by-products and to an increased selectivity to primary amines. Volf and Pasek postulated that the positive influence of H_2O on the activity of the catalysts could be ascribed: (i) to an unspecified influence on the catalytic properties of the metal or (ii) to the solvation of the amines and subsequent suppression of the poisoning that they cause on the surface of the catalyst.[26] The higher selectivity towards primary amines could be explained as well by solvation with H_2O, which would lower the condensation rate between the primary imine and the primary amine. The decrease of the concentration of the primary imine due to the competitive reaction with H_2O could also justify the decrease in the formation rate of the secondary imine, analogously to what the same authors suggested for the effect of NH_3 on this reaction.

Greenfield reported a superior commercial process for the synthesis of dibenzylamine from benzonitrile over Pt/C without solvent and in the presence of H_2O. Surprisingly, H_2O was used in this case for the preparation of a secondary amine. The author ascribed the selective formation of dibenzylamine to the ability of H_2O to avoid catalyst poisoning.[4d,57]

H_2O was added in the hydrogenation of C_4 to C_{12} nitriles to primary amines over Cr-promoted Raney Co to maintain the catalyst activity for prolonged periods of time avoiding poisoning and formation of side-products (Table 5).[58]

The yield of *N,N*-dimethylcyclohexylamine from the reductive amination of cyclohexanone with dimethylamine, over Pd/C, was also increased by the presence of H_2O.[59]

In a recent work on the hydrogenation of butyronitrile over Pt- and Ru-based catalysts, it was found that the

Table 5. Effect of the addition of H_2O on the hydrogenation of 2-methylglutaronitrile.

H₂NCH₂CH(CH₂)₃NH₂
|
CH₃

2-methyl-1,5-pentanediamine

NCCHCH₂CH₂CN   →(H₂O, 40 bar H₂, Cr-Raney Co)→   +
|
CH₃

CH₃ ... NH₂ ... NH₂

3-methyl-1,2-cyclopentanediamine

H₂O [% weight]	yield [%]	
	2-methyl-1,5-pentanediamine	3-methyl-1,2-cyclopentanediamine
0	68.5	1.82
1	70.8	1.54
2	69.5	1.35

addition of H_2O is beneficial for the activity of the catalyst but has no effect on the selectivity.[60]

A combined action of H_2O and NH_3 is also sometimes described to promote high yields of primary amines. For instance, hydrogenation of crude palm oil fatty acid nitriles, in the presence of H_2O, yielded 64.9% primary amine while, with additional use of NH_3, the yield increased to 71%.[61] The same procedure was used for the hydrogenation of coconut oil fatty acid nitriles to provide primary amines with more than 95% selectivity.[62] This appears to be due to the alkaline conditions created when NH_3 and H_2O are used together. The alkaline conditions inhibit the acidic sites of the catalyst responsible of the coupling reactions.

4.4 Effect of the Addition of Hydroxides and Carbonates

Instead of imparting alkalinity by NH_3, the inhibition of the acidic sites of the catalyst responsible of the formation of secondary amines can also be reached by the addition of NaOH, KOH, LiOH, or Na_2CO_3. Greenfield stated that it was preferable to use NH_3 for the preparation of primary amines because these latter bases, particularly NaOH, seriously decreased the reaction rate while much larger amounts of NH_3 had no adverse effect.[25] However, their use has been preferred in a number of processes. The use of NH_3 has several disadvantages owing to the fact that it is a gas and, therefore, requires pressurised storage and increases time for loading and venting. Furthermore, the quantity used is so large that this brings about

environmental and economical problems (expensive recovery equipment is required).

Addition of NaOH was used to limit the formation of tertiary amine in the manufacture of *N*-methylbutylamine from butanal and methylamine.[63]
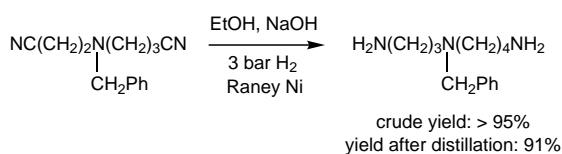
Hydrogenation of nitriles, in the absence of NH_3, yields predominantly primary amines when Ni is employed as the catalyst and NaOH as an additive.[61,64-68] Hydrogenation of phenylacetonitrile gave 51.2% primary amine and 37.5% secondary amine. In the presence of NaOH, the yield of primary amine was 92.5%.[65] Quantitative reduction of dinitriles to primary diamines could be effected in the presence of NaOH, which also allowed re-use of the catalyst. Surprisingly, substitution of NaOH by NH_4OH gave only 17% yield of the diamine despite the widespread use of NH_3 to prevent formation of secondary amines. Without any added base as co-catalyst, only 33% yield was found (Scheme 16).[66]

NaOH has also been added to favour selectivity in the hydrogenation of adiponitrile towards hexamethylenediamine.[67] Similarly, Thomas-Pryor et al. found that, in the hydrogenation of butyronitrile, the addition of NaOH strongly increases the selectivity towards butylamine. They proposed that the hydroxyl ions compete with butylamine for the adsorption sites responsible for the condensation reactions on the catalyst.[68]

The addition of NaOH to the reaction mixture has also been carried out in the hydrogenation of nitriles to primary amines over Rh/C. Under these conditions, 1,4-bis(β-cyanoethoxy)butane yielded 1,4-bis(γ-aminopropoxy)butane with 100% conversion after 3 h of reaction and a selectivity of 86.4%. In the absence of NaOH, only 23% conversion was observed after 3 h and 43% after 6 h, with only 28% primary amine and 72% secondary amine by-product. A second comparative hydrogenation was carried out identically to the above runs except that NaOH was substituted by the same amount of H_2O. Conversion was 100% after 4 h. However, the selectivity was poor (only 40% of the desired primary amine).[69]

The hydrogenation of nitriles to primary amines over Raney Co with a catalytic amount of LiOH and H_2O was also explored. LiOH enhanced the selectivity towards the primary amine while H_2O assisted in maintaining the catalytic activity.[70]

Finally, addition of Na_2CO_3 during hydrogenation of palmitic nitrile in the presence of Ni or Co catalysts lowered the formation of secondary amine. This was ascribed to a decrease in the adsorption of the products on the catalysts, which increases the rate of hydrogenation and, at the same time, decreases the activity of the catalysts for subsequent condensations.[71]

It can be concluded that the mechanisms that justify the effect of the addition of acids, bases, or H_2O on the activity and selectivity of the catalysts are not clear yet. Furthermore, the net results under particular reaction conditions will invariably depend on the type of catalyst used. Individual catalysts differ in their responses to a change in reaction conditions and, very often, contradictory results are encountered.

The effect of the acids is especially unclear. Some authors, in earlier contributions, propose the use of acids in the liquid phase to inhibit coupling reactions by protonation of the primary amine while, in other more recent contributions, the authors report that coupling reactions are acid-catalysed, and, therefore, are promoted by the increase in acidity of the reaction medium (this would be in agreement with the fact that the addition of bases inhibits the secondary amine formation). At this stage, it is unclear if the amount or the strength of the added acid has the principal influence on the selectivity. Equilibria may be shifted differently because of these parameters. To the best of our knowledge, there is no clear answer from literature. For instance, Galán et al. found that the preparation of secondary amines from nitriles, with a rhodium catalyst (supported on Al_2O_3 or C), in CH_3COOH as the solvent, is possible in very high yields, presumably, because the acidic solvent promotes condensation.[72] However, as stated above, CH_3COOH has also successfully been used to prevent condensation by formation of the ammonium salt of the primary amine.[41,42]

5 Effect of the Catalyst

The rate and the product composition in the reductive amination of carbonyl compounds and in the hydrogenation of nitriles are affected primarily by the type of catalyst used. Raney Ni, Raney Co, Pd/C, Pt/C, Ru/C, and Rh/C are suitable catalysts and rank among the most commonly used for both processes. The same metals but supported on SiO_2 or Al_2O_3 are often employed as well.[73]

PtO_2 has found very little application in reductive amination processes because of the difficulties to reduce it prior to contacting the substrates.[74] Sulphided platinum metal catalysts have given excellent results because of their particular resistance to poisoning and their ability to minimise reduction of the carbonyl to an alcohol, even if sometimes this is to the detriment of displaying a lower activity.[21,75]

Fe and Cu have also been used in the hydrogenation of nitriles, but much less often than the above-mentioned metals because they are considered to be less active.[53,76]

$$NC(CH_2)_2N(CH_2)_3CN \xrightarrow[\substack{3 \text{ bar } H_2 \\ \text{Raney Ni}}]{\text{EtOH, NaOH}} H_2N(CH_2)_3N(CH_2)_4NH_2$$
$$| \qquad\qquad\qquad\qquad\qquad\qquad |$$
$$CH_2Ph \qquad\qquad\qquad\qquad\qquad CH_2Ph$$

crude yield: > 95%
yield after distillation: 91%

Scheme 16. Hydrogenation of *N*-(2-cyanoethyl)-*N*-(3-cyanopropyl)-benzylamine in the presence of NaOH.

However, Fe has been claimed to have suitable properties for the hydrogenation of adiponitrile to 6-amino-capronitrile and hexamethylenediamine.[53b]

Raney Ni was, by far, the most frequently used catalyst in the early literature.[5a,34] Fairly good yields of benzylamine were obtained by high-pressure reductive amination of benzaldehyde and substituted benzaldehydes over this catalyst.[77] However, it has a number of less desirable properties. Environmental objections are associated with its preparation: it is fragile, it is comparatively difficult to handle, which renders its use less attractive, it shows low activity and selectivity, and it requires elevated temperatures and pressures. Co was used similarly and, sometimes, under even more severe conditions than Ni catalysts.[78] Later, more resistant supported noble metals were suggested as they allow milder conditions and, at the same time, give high yields and purities.[13,15b,48,79] These catalysts present, however, the disadvantage of being relatively expensive.

Some of the authors report that certain supports can increase the selectivity towards one or another amine [56,80] but others deny this.[26,81]

Despite all their inconveniences, and because they are economically more interesting than noble metal-based catalysts, slightly modified Ni- and Co-based catalysts still represent the best choice according to most of the recent patents. The greater part of these patents is focused on the selective industrial preparation of primary amines. Modifications include combination with other metals and/or addition of promoters with the aim of increasing selectivity, activity, or lifetime.[82–91]

Thus, Ni promoted by Zr,[82] Ni and Ru in combination with Pd, Re or Ir,[83] mixtures of Ni, Co, Cu and Mo,[84] mixtures of Co and/or Ni, Ru and Cu,[85] Raney Ni or Raney Co in the presence of borax,[86] Co containing $CaCO_3$ and/or La_2O_3,[87] and Raney Co promoted by Mn or Cr[88] have been patented for the reductive amination of carbonyl compounds.

Ni and Mg in a co-precipitated form,[89] Raney Ni promoted by Ti, Cr or Zr,[90] Ni and/or Co with potassium oxalate as co-catalyst,[52a] Co promoted by P and Mn,[52b] Raney Co promoted by Cr,[58] and mixtures of Co, Cu and Ni[91] have also been patented in the field of the hydrogenation of nitriles.

The results of the various works are difficult to compare as the experimental conditions are often not defined unambiguously and the data presented are mostly not comparable (different starting compounds, different equipment, disparate reaction conditions, etc.).

5.1 Location of the Reaction Steps

All reaction steps that were discussed in the section about mechanisms account for the formation of the major product types found in the nitrile hydrogenation and reductive amination reactions. However, they fail to account for the extraordinary differences in selectivity exhibited by the various catalysts.

A crucial point in the discussion about how the catalysts influence activity and selectivity is the assumed location of the reaction steps. The duality between reactions taking place at the surface of the catalyst and those in the liquid phase is still a matter of challenging research.

Earlier Mignonac's and von Braun's mechanistic proposals, for the liquid phase reductive amination of carbonyl compounds and hydrogenation of nitriles, were heavily founded on the competition between homogeneous condensation reactions and heterogeneous hydrogenation steps (at the surface of the catalyst).[6,23]

Le Bris et al. also reported that, in the reductive amination of acetone with NH_3, isopropylamine and diisopropylamine are formed from the heterogeneous hydrogenation of the imines that are produced, respectively, from the homogeneous reaction of acetone with NH_3 and acetone with isopropylamine. It was observed that, with a Ni catalyst, isopropylamine is the main product while diisopropylamine is formed nearly exclusively when using a Pt catalyst. As they considered the transformation in the liquid phase to be independent of the catalyst, the difference in the evolution of the system in these two situations was justified by the different behaviour of the intermediate imines and, more particularly, of the secondary imine towards the two catalysts used. It was concluded that Ni is not capable to hydrogenate the secondary imine in the presence of acetone and, therefore, yields selectively isopropylamine. In the case of the Pt catalyst, on the contrary, the secondary imine is very reactive towards hydrogenation.[8d]

To support these conclusions, the homogeneous reaction between acetone and isopropylamine and the heterogeneous hydrogenation of the resulting secondary imine were studied separately. It was observed that the reaction between the acetone and isopropylamine is an equilibrium catalysed by acids.[8a] When studying the hydrogenation process, it was noted that Ni is much less effective than Pt to yield diisopropylamine, in complete agreement with the results obtained from the reductive amination of acetone with NH_3.[8b]

Later, Volf and Pasek, in the hydrogenation of lauronitrile, observed that, in experiments with pure Co, the selectivity is independent of the catalyst concentration in the reaction mixture. In addition, the selectivity was not depending on the catalyst activity when Ni catalysts of different specific surface areas were used. If the catalyst were not involved in the condensation reactions, the selectivity would be affected by the concentration of catalyst and/or its activity. From the observation that the selectivity does not depend on these parameters, these authors concluded that the

condensation reactions leading to secondary amines are taking place, entirely or predominantly, on the catalytic surface rather than in the liquid phase. More precisely, they claimed that the active centres in the catalysis of condensation reactions are located on the metallic components whereas the support is merely helping to increase the dispersion of the metal and is not having any significant effect on the selectivity.[26]

Dallons et al. reported some results, on the hydrogenation of nitriles, which also ruled out that the condensation reactions proceed homogeneously.[80b]

The addition of NH₃ in the reaction mixture should favour the reaction between the secondary imine and NH₃ to give the primary amine and the primary imine. If the reaction with NH₃ would take place in the liquid phase, it should be possible to detect the resulting primary imine in solution but, contrarily, no primary imine is found. To justify this result, Dallons et al. proposed a mechanism. The first step is the semihydrogenation of the adsorbed nitrile compound. The very reactive primary imine that is formed swiftly reacts on the catalytic surface to lead to the primary amine through hydrogenation, hence, explaining why it is not possible to detect it in the liquid bulk. The reaction of the primary imine with a vicinal adsorbed primary amine yields a *gem*-diamine compound, which disproportionates, also on the catalytic surface, into NH₃ and the secondary imine (Scheme 17).[80b]

The mechanism of Dallons et al. is also consistent with the results that they obtained with different supports. They found that the influence of the support on selectivity is very extensive. Secondary amine formation was inhibited by acidic supports presumably because the primary amine is more strongly adsorbed on them, remaining, as a consequence, farther from the hydrogenation sites. Therefore, they claimed that the hydrogenation of nitriles is entirely involving heterogeneous processes through surface reactions. The reaction between amine and imine could take place on the metal surface, purely, or on both metal and support surfaces in the case of supported metal catalysts.[80b]

However, in our research group, the reaction between benzaldehyde and NH₃ to benzylimine has also been studied in the absence of a catalyst. In this study, ¹H NMR was used to follow the reaction. Benzylimine was not detected at any moment in the product composition because it is highly reactive and readily forms hydrobenzamide. Therefore, in our opinion, the
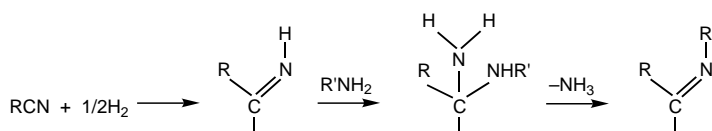
fact that the primary imine is not identified in the liquid solution does not prove that condensation reactions proceed heterogeneously.[13]

Verhaak et al. established that the selectivity of the gas phase hydrogenation of nitriles is greatly influenced by the nature of the support,[80c] in agreement with Dallons et al.[80b] but in complete disagreement with Volf and Pasek.[26] As mentioned above, the acid-base properties of the medium in which the reaction is performed have a marked effect on the selectivity of the reaction (addition of HCl, NH₃, NaOH, etc.). Therefore, Verhaak et al. studied the acid-base properties of the catalyst itself by using different supports.[80c]

Based on the results obtained in the gas phase hydrogenation of acetonitrile with Ni supported on either acidic or basic supports, they suggested a dual mechanism in which the hydrogenation function of the catalyst is located on the metal while the acidic function, responsible for the condensation reactions, is located on the support. Hydrogenation to the primary imine and the primary amine occurs on the metallic component of the catalyst. These compounds migrate then, probably through the gas phase, to acidic sites, where the primary imine is protonated and reacts with the primary amine. The resulting cationic *gem*-diamine derivative is then deprotonated and loses NH₃ to yield the secondary imine, which desorbs from the support migrating back to the metal, where it is hydrogenated to the secondary amine (Scheme 18).

Verhaak et al. also proposed that, since the carbonyl bond is isoelectronic with the imine bond, the reductive amination of carbonyl compounds could easily be explained by using the same mechanism. The condensation between the carbonyl and the amine functions is also acid-catalysed and would occur on the support of the catalyst. The acidic function of the catalyst may make the carbonyl group more electrophilic. After the nucleophilic attack, proton transfer and 1,2-elimination

Scheme 17. Mechanism proposed by Dallons et al. for the hydrogenation of nitriles.
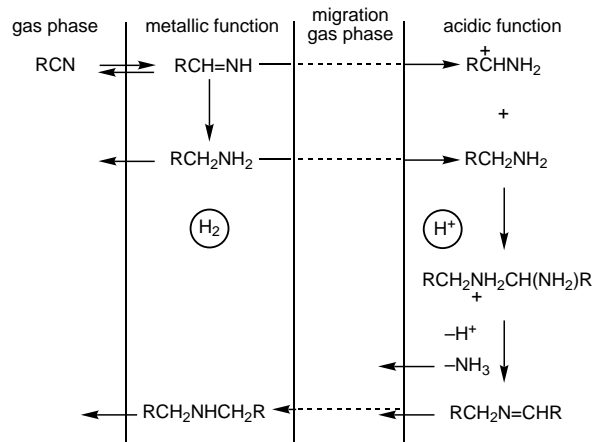
Scheme 18. Bifunctional mechanism proposed by Verhaak et al. for the hydrogenation of nitriles.

of H$_2$O produce the primary imine that migrates to the metallic function to be hydrogenated. Migration of the primary amine to the support allows the formation of the secondary imine, following an analogous mechanism, and the subsequent migration back to the metal affords the secondary amine by-product.[80c]

In agreement with this hypothesis, it was demonstrated that more acidic supports exhibit higher selectivity towards the secondary amine formation and more basic supports exhibit highly selective production of primary amines, even in the absence of NH$_3$.[80c] It should be noted that Dallons et al. obtained exactly contrary results while studying the influence of the support. As stated above, they found that more acidic supports inhibit the formation of the secondary amine.[80b]

In the case of unsupported catalysts, other authors suggested that the condensation reactions during gas phase hydrogenation of nitriles proceed on the metal surface.[92]

In 1998, a kinetic model for the reductive amination of aldehydes with aromatic amines was proposed. This model included a combination of homogeneous condensation reactions and heterogeneous hydrogenation steps.[93]

In our research group, we monitored the formation of dibenzylimine from benzaldehyde and benzylamine with in situ FT-IR spectroscopy. No difference in the formation rate of dibenzylimine was observed between the reaction carried out without catalyst and the reaction carried out in the presence of an acidic catalyst. This would suggest that condensation reactions proceed homogeneously.[28]

The above models assume that only hydrogen addition steps are taking place at the metal surface, while the liquid phase or the metal support is the locus of the subsequent reactions leading to secondary and tertiary amines. These models have recently been challenged by Huang and Sachtler.[81c] They argued that the bifunctional mechanism proposed by Verhaak et al. is unlikely because: (i) unsupported metals and metals supported on neutral supports form secondary and tertiary amines, (ii) acid sites in the catalyst are quickly neutralised by an atmosphere of strong bases such as amines and nitriles and, (iii) if it were true that only hydrogenation occurs at the metal surface, the selectivity to higher amines should not depend on the nature of the metal and no formation of secondary and tertiary amines would occur when the reactions are carried out in the gas phase. They compared the

hydrogenation of butyronitrile in the gas and in the liquid phase over different M/NaY catalysts (M = Ru, Rh, Ni, Pd, Pt). Secondary and tertiary amines were formed in comparable amounts in the liquid and in the gas phase hydrogenations, indicating that all the condensation reactions take place in the adsorbed layer and that the liquid phase is superfluous for these steps. The only role of the solvent would be to facilitate desorption and thus retard deactivation of the catalyst.

Despite using the same support, completely different selectivities were observed when tuning the nature of the active metal. Therefore, it was claimed that not only the hydrogenation steps but also the condensation reactions proceed on the metal surface and that the selectivity to the primary amine is only depending on the metal, regardless of the nature of the support, its acidity, and the presence of solvent.[81c]

The same authors carried out further studies to determine how the specific catalytic selectivity of the individual metals could be correlated with their properties. They suggested that the selectivity of the metals is related to their propensity to form multiple bonds. Ru is the metal with the highest propensity to do so and, consequently, it exhibits the highest selectivity to primary amines.[94]

Significant information on the chemistry of nitriles and amines at the surface of the metals was obtained from deuteration of acetonitrile. When a mixture of acetonitrile and D$_2$ was passed over the catalyst, most of the formed primary and secondary amine molecules had less D atoms than predicted by stoichiometry because D atoms were added to the C atom of the C≡N group while H atoms were preferentially added to the N atom. To explain these findings, the authors proposed that the precursor of the amine is bonded to the metal surface via the N atom and these M-N bonds are predominantly broken in a concerted mechanism when CH$_3$CN molecules transfer some of their H atoms to the N atom of the chemisorbed complex (Scheme 19). Thus, the formation of amines is not a simple addition of chemisorbed D atoms to the nitrile function.

As the Ru=N bond is very strong, CH$_3$CD$_2$N=Ru is an immobile adsorbed species. Formation of secondary and tertiary amines requires mobility of the adsorbed groups to allow them to react with each other, which explains why Ru catalysts are very selective towards primary amines.[94,95]

In the following two sections, some examples are given about the separate effects of the support and of the
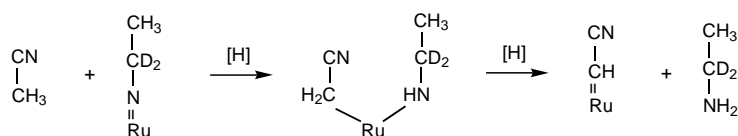
Scheme 19. Mechanism proposed by Huang and Sachtler for the deuteration of acetonitrile.

metal on the performance of the catalyst. These two effects are so closely related that, generally, it is difficult to isolate them.

5.2 Effect of the Support

The catalyst support can affect activity and selectivity. Critical properties are surface area, pore volume, and acidity. Metal dispersion increases with the support surface area. Support porosity affects not only metal dispersion but also metal sintering resistance and intraparticle diffusion of reactants, products, and poisons. On the other hand, addition of bases to the reaction medium has been found to decrease the formation of secondary and tertiary amines by a poisoning of the surface acidic sites, which are responsible for the coupling reactions. It is, therefore, to be expected that, on decreasing the acidity of the support, a change in the selectivity is found in favour of primary amines.

The effect of oxidative treatments on a C support for the reductive amination of benzaldehyde with NH_3 over Pd/C has recently been investigated. Oxidative treatments led to higher amounts of oxygen surface groups and, consequently, higher acidity of the support. The increase in the number of acidic sites on the support resulted in higher reaction rates. This was attributed to the acid-catalysis of the imine homogeneous equilibria formation and/or to a decrease in the concentration of the *gem*-diamine inhibiting intermediates.[13] In order to get more insight into the role of the support in the performance of the catalyst, our research group continued investigating the same reaction through a high-throughput approach that allowed the simultaneous screening of 24 catalysts with different metal components and different C supports.[96] In this study, it was observed that oxidative treatments in the support increase the activity of the catalyst, in agreement with the previous findings. However, this was ascribed to a higher metal surface area and metal dispersion in the catalyst due to the fact that the new surface functional groups can exchange protons with cationic metal complexes in the impregnation and reduction processes during the preparation of the catalyst.

Pd and Pt catalysts, with the same oxidised C support, displayed completely different activities. Hence, not only the nature of the support but also the nature of the metal plays a role on the activity.[96]

Regarding the selectivity, Ru and Pd catalysts with the same support displayed completely different product compositions under the same reaction conditions.[96] Furthermore, a commercial Ru catalyst with a non-treated support and another Ru catalyst, prepared in our laboratory, with an oxidised support, showed different activity but exactly the same selectivity.[49] From these results, one could deduce that the nature of the support is not decisive for the selectivity of the reaction.

Table 6. Selectivities towards the secondary amine of several industrial Ni catalysts in the hydrogenation of lauronitrile.

catalyst	metal content [wt %]	t [s][a]	sec. amine [mol %][b]
Ni/kieselguhr	50.6	420	20.1
Ni/Al$_2$O$_3$	48.8	820	21.5
Ni/Cr$_2$O$_3$	40.1	2500	22.4
Raney Ni	67.3	4800	15.8

[a] At total conversion.
[b] Each experiment was run at 45 bar and T = 160 °C.

The results that Pasek et al. obtained during the hydrogenation of lauronitrile on several industrial Ni catalysts indicated as well that the carrier is not affecting the selectivity (Table 6).[81a]

Contrary to expectations, acidic carriers such as kieselguhr, Al_2O_3, and Cr_2O_3 did not bring about a rise in the percentage of secondary amine (on pure Ni, even more secondary amine was obtained, 25.4%). The higher selectivity of Raney Ni towards the primary amine could be explained by the presence of residual NaOH in the catalyst.[81a]

In the gas phase hydrogenation of benzonitrile and acetonitrile with Ni on various supports, it was observed that the activity of the catalysts was greatly influenced by the type of support and decreased in the order Al_2O_3 > TiO_2 > SiO_2-Al_2O_3 > SiO_2. Exclusively primary amine was formed in all four cases, irrespective of the support used.[81b]

This is in disaccord with what a number of authors have been claiming in the recent literature. As already mentioned in the previous section, Verhaak et al. considered the support as the locus of the acid-catalysed condensation steps being, as a result, able to tune the selectivity of the global reaction.[80c]

Ni/SiO$_2$ catalysts with different degrees of reduction were tested in the gas phase hydrogenation of acetonitrile. A more reduced catalyst contains less nickel hydrosilicate and is, therefore, less acidic. With increasing reduction temperatures, the selectivity towards the condensation products decreased (Table 7).

Several Ni catalysts supported on Al_2O_3-based carriers were tested in the same reaction. The intrinsic acidity of the Al_2O_3 supports was decreased by covering their acidic sites with increasing amounts of K^+. Higher K^+ loadings induced higher catalytic selectivity towards ethylamine.[80c]

The same reaction was studied by Medina Cabello et al. but, in this case, over Ni/Mg(Al)O catalysts prepared by calcination of Ni/Mg/Al layered double hydroxides (LDH) of the hydrotalcite type.[56] The selectivity towards ethylamine depended on the Mg/(Mg + Ni) ratio. An optimal Mg content [Mg/(Mg + Ni) ≈ 0.23] was found for which ethylamine was obtained with 92.6% selectivity. The occurrence of this optimal value

Table 7. Effect of the different degrees of reduction of Ni/SiO$_2$ on the selectivity in the gas phase hydrogenation of acetonitrile.

reduction temperature of the catalyst [°C][a]	selectivity [%][b]			
	prim. amine	sec. amine	Schiff base	tert. amine
350	39	40	10	11
375	48	41	3	8
400	56	37	0	7
450	70	25	0	5

[a] Temperature applied during the preparation of the Ni/SiO$_2$ catalyst.

[b] Each experiment was run at 1 bar and T = 125 °C.

was due to the counteracting effects of the reducibility of Ni and the acidic character of the material, both decreasing with the increase in the Mg loading.

Both effects of Mg should lead to an increase in the selectivity towards primary amines. The reducibility of Ni remained roughly the same for the first additions of Mg, but underwent a steep decrease for Mg/(Mg + Ni) > 0.4, because of the charge transfer from Mg to the Ni sites. This decreases, in turn, the strength of the interaction of imines and amines (electron donor compounds) with the Ni surface and their faster desorption slows down the subsequent condensation reactions. With these explanations, the authors suggested that coupling reactions occur in both metal and acidic sites.[56]

The same research group, while studying the hydrogenation of acetonitrile and valeronitrile in gas and liquid phases, respectively, over the same type of catalysts, with different Mg/Ni molar ratios, obtained selectivities higher than 90% towards primary amines for Mg/Ni molar ratios = 0.3 – 1. As in the previous work, the influence of Mg was not limited to the inhibition of the acidic sites of the support, but also acted on the metallic Ni particles by increasing their electron density. A complementary explanation for the latter effect was given by suggesting that the electron enrichment of the Ni sites decreases the electron donation from the imine, attenuating, as a consequence, the nucleophilic attack from the amine. Therefore, the basicity of the support would decrease the coupling reactions in both Ni and support surfaces.[80d] More recently, while retesting the gas phase hydrogenation of acetonitrile under the same conditions, they ruled out that the increased selectivity towards ethylamine is correlated to the electronic modification at Ni sites and they concluded that this is merely due to the decrease of acidity of the catalyst.[80e]

Finally, in the context of the liquid phase hydrogenation of long chain nitriles, the selectivities of Co/SiO$_2$-Al$_2$O$_3$, Co/Al$_2$O$_3$, and Co/C towards the produc-

tion of the secondary amine were practically the same. However, with Co/ZnO, this selectivity was much lower. ZnO is the least acidic support and, therefore, it has the lowest catalytic activity in the reaction between the primary imine and the primary amine.[80a]
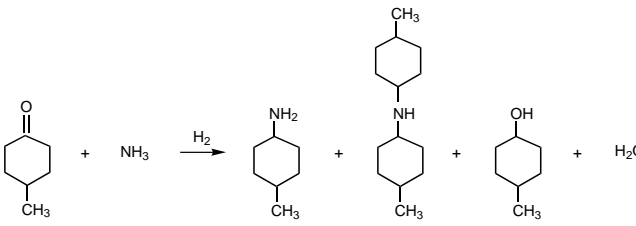
5.3 Effect of the Metal

The nature of the metal component is probably the parameter that is having a major influence on the activity and selectivity of the catalyst. The correlation "metal type/catalyst performance" is, however, not straightforward. There is an additional "metal structure/catalyst performance" relationship. Actually, the performance of the catalyst depends on the preparation method and, as a result, on the metal dispersion, metal distribution (eggshell or uniform), degree of metal reduction, etc. For instance, an increase in the metal surface area (a decrease in the metal crystallites size) is expected to increase the activity in the heterogeneous reaction. Uniformly impregnated catalysts show lower or higher activities than eggshell catalysts depending on diffusion limitations. Moreover, when the oxidation state of the metal component of the catalyst before use is 0, the dispersion of the metal in the catalyst is presumably not the same as when the catalyst is reduced *in situ* during the hydrogenation reaction. Anecdotal evidence, in the case of Pd, suggests that, when preparing highly dispersed clusters of just some Ångstroms in size, selectivity behaviour can be inverted compared to nano-sized metallic clusters.[28] Comparisons between various metal catalysts are only meaningful when using experiments in which all these parameters are identical. This is usually difficult to realise. For this reason, these considerations are often ignored.

The product composition is substantially influenced by the reaction conditions. However, in the reductive amination of carbonyl compounds, Ni and Co are generally used for the synthesis of primary amines while catalysts based on noble metals have proven to be very effective not only in the synthesis of primary, but also secondary and tertiary amines.

Reductive amination of 4-methylcyclohexanone with NH$_3$ afforded completely different product compositions with 5 wt % Rh/C, Ru/C, or Pd/C as the catalysts (Table 8).[32]

There was almost no detectable reduction of the ketone to the alcohol with 5 wt % Pd/C, more reduction with 5 wt % Rh/C and complete reduction with 5 wt % Ru/C. The Pd/C catalyst displayed higher selectivity towards the secondary amine while 5 wt % Rh/C afforded a mixture of primary and secondary amine.[32]

In the reductive amination of acetone with aniline, 5 wt % Ru/C appeared again not to be the most convenient catalyst because only hydrogenation of the

Table 8. Selectivities of Rh-, Ru-, and Pd-based catalysts in the reductive amination of 4-methylcyclohexanone with NH_3.

catalyst	selectivity [% weight][a]		
	prim. amine	sec. amine	alcohol
5 wt % Rh/C	44	40	16
5 wt % Ru/C	0	0	100
5 wt % Pd/C	27	72	1

[a] Each experiment was run at 70 bar and T = 100 °C; no solvent was used, NH_3 was present as aqueous NH_3; the molar ratio NH_3/ketone was 6.

aromatic ring and reduction of the ketone to the alcohol took place. A similar result was obtained with 5 wt % Rh/C. It appeared that 5 wt % Pd/C and 5 wt % Pt/C were more effective for the synthesis of the required *N*-isopropylaniline, although the low conversion with 5 wt % Pt/C indicated severe catalyst poisoning, presumably by the alicyclic and aliphatic amine by-products.[97] The susceptibility of Pt to be inhibited by amines is well-documented in literature.[98]

As already stated in the previous section, 5 wt % Ru- and Pd-based catalysts, supported on the same oxidised C, exhibit completely different selectivities in the reductive amination of benzaldehyde with NH_3. At total conversion, and with a molar ratio NH_3/benzaldehyde = 16, the reaction mixture consisted of 65% dibenzylamine and 35% benzylamine, when the Pd catalyst was used, while 98% benzylamine and only 2% dibenzylamine were found with the Ru catalyst. Under identical conditions, 5 wt % Pt/C catalysts showed very little activity, presumably due to the inhibition by amines. In this case, 5 wt % Ru/C is a highly active and selective catalyst (no side-products are detected). Even under more unfavourable conditions for the synthesis of the primary amine (molar ratio NH_3/benzaldehyde = 2), 77% benzylamine and only 19% dibenzylamine and 4% benzyl alcohol were obtained with the Ru catalyst. With the Pd catalyst, 85% dibenzylamine, 7.5% benzylamine and 7.5% benzyl alcohol were formed under these conditions.[49]

In the case of the hydrogenation of nitriles, there is a consensus that the selectivity towards secondary and tertiary amines increases in the order Co < Ni < Ru < Rh < Pd < Pt. However, the products obtained depend markedly not only on the catalyst but also on whether the nitrile is aliphatic or aromatic.

Greenfield compared several catalysts for the hydrogenation of butyronitrile. Ni and Co catalysts appeared to be the best for the preparation of butylamine, Rh was the best for the formation of dibutylamine, and Pt and Pd were the most convenient for tertiary amine formation.[25]

Co, Ni, and Cu catalysts were used for the hydrogenation of lauronitrile. Co appeared to be more selective towards the primary amine while Ni was more selective towards the secondary amine. In comparison with Co and Ni, Cu showed a considerably lower catalytic activity (Table 9).[80a]

The hydrogenation of butyronitrile in aqueous NH_3 showed also dissimilar selectivities when using Pd-, Pt-, Rh-, or Ru-based catalysts (Table 10).[25]

Different selectivities were also observed in the hydrogenation of benzonitrile with Pd/C, Pt/C, or Rh/C as the catalysts (Table 11).[55]

In this case, Pt and Rh behaved much alike and showed selectivity to the secondary amine whereas Pd gave mixtures of primary and secondary amine with the former predominating.[55]

Huang and Sachtler studied the liquid and gas phase hydrogenation of butyronitrile over various NaY-supported Ru, Rh, Ni, Pd, and Pt catalysts.[81c] In the liquid phase, Ru/NaY showed the highest selectivity to butylamine. Rh/NaY and Ni/NaY were more selective to the secondary amine but their selectivity towards the

Table 9. Selectivities of Co-, Ni-, and Cu-based catalysts in the hydrogenation of lauronitrile.

metal	t [min]	conversion [%][a]	selectivity [%]	
			prim. amine	sec. amine
Co	180	100	77	23
Ni	120	100	24	76
Cu	1200	20	–	100

[a] Each experiment was run at 1 bar and T = 120 °C.

Table 10. Selectivities of Pd-, Pt-, Rh-, and Ru-based catalysts in the hydrogenation of butyronitrile.

catalyst	T [°C]	t [h][a]	yield [mol %][b]		
			prim. amine	sec. amine	tert. amine
5 wt % Pd/C	125	0.8	–	3	97
5 wt % Pt/C	125	0.8	–	3	97
5 wt % Rh/C	75–110	1	–	100	–
5 wt % Ru/C	125	0.8	88.5	8.5	–

[a] Experiments continued until gas adsorption stopped or became very slow.
[b] Each experiment was run with 0.3 moles butyronitrile and 2.6 moles NH_3 in 175 mL H_2O at 30–40 bar.

Table 11. Selectivities of Pd-, Pt-, and Rh-based catalysts in the hydrogenation of benzonitrile.

catalyst	selectivity [%][a, b]	
	prim. amine	sec. amine
5 wt % Pd/C	59	41
5 wt % Pt/C	–	93
5 wt % Rh/C	–	100

[a] As determined by gas chromatography.
[b] Each experiment was run at 3 bar and T = 25 °C in EtOH as the solvent.

primary amine was still quite high. Pd/NaY and Pt/NaY produced almost exclusively dibutylamine (Table 12).

In the gas phase, Ru/NaY was highly selective to butylamine. Pd/NaY was highly selective to dibutyl-amine and Pt/NaY to tributylamine. Ni/NaY and Rh/NaY displayed selectivities intermediate between these extreme situations (Table 13).

The selectivity to each reaction product was similar in the gas and in the liquid phase indicating, according to these authors, that no liquid phase was required for the condensation steps.[81c] It followed from these data that the type of metal was decisive for the selectivity whereas the effect of the support was not significant.

Table 12. Selectivities of several NaY-supported catalysts in the liquid phase hydrogenation of butyronitrile.

catalyst	t [h]	nitrile conversion [%][a]	selectivity [mol %]			
			prim. amine	sec. imine	sec. amine	tert. amine
Ru/NaY	8	89.2	67.9	22.8	9.2	0.1
Rh/NaY	2	93.8	44.2	4.5	51.0	0.2
Ni/NaY	3	99.8	23.5	0.3	61.2	15.0
Pd/NaY	7	89.9	3.6	0.1	94.8	1.4
Pt/NaY	7	75.9	2.9	0.1	88.8	7.3

[a] Each experiment was run at 25 bar and T = 110 °C in heptane as the solvent.

Table 13. Selectivities of several NaY-supported catalysts in the gas phase hydrogenation of butyronitrile.

catalyst	t [h]	nitrile conversion [%][a]	selectivity [mol %]			
			prim. amine	sec. imine	sec. amine	tert. amine
Ru/NaY	5	1.75	69.7	26.4	3.14	0.84
Rh/NaY	5	11.7	45.2	12.0	40.4	2.47
Ni/NaY	5	23.4	19.9	9.89	37.9	32.3
Pd/NaY	5	1.0	2.58	0	88.1	9.34
Pt/NaY	5	8.6	0.76	0.65	23.1	75.5

[a] P (butyronitrile) = 0.03 bar; 30 mL/min H_2; T = 80 °C.

6 Conclusions

Despite the complexity of the reductive amination of carbonyl compounds and the hydrogenation of nitriles, both reactions can usually be controlled to some extent by the reaction conditions and, for the greater part, by the catalyst choice. To justify the contradictory results obtained with the various catalysts, different mechanisms have been proposed, in which the metallic component of the catalyst is always the locus of the hydrogenation reaction. More discrepancies exist concerning the location of the condensation reactions. Earlier proposals were heavily founded on homogeneous condensation steps while, more recently, it has been claimed that both condensation and hydrogenation reactions proceed heterogeneously. The locus of the condensation reactions would be, thus, the metal and/or the support of the catalyst. Some authors report that certain supports affect the selectivity and can, consequently, be considered as the locus of the condensation steps, while others deny this and propose the metallic component as the locus, not only of the hydrogenation steps, but also of the coupling reactions.

Unfortunately, none of these mechanistic proposals seems to hold the "absolute truth". A large variety of pre-equilibria is involved in these processes. This, together with the great number of parameters that define the structure of the catalysts, makes mechanistic studies very difficult and leads to inconsistencies when comparing experiments with disparate starting compounds, reaction conditions, and catalysts.

In our opinion, most evidence suggests that the selectivity is tuned by the nature of the metal, while the support merely helps to increase the metal dispersion and, therefore, the activity of the catalysts. However, it is still not completely clear whether the coupling reactions proceed in the liquid phase or at the surface of the metal. Our work on the reductive amination of benzaldehyde with NH_3 suggests that these steps most likely occur in the liquid phase, whereas the ability of the metal component of the catalyst to hydrogenate the secondary imine determines the selectivity. Further studies have to be carried out to get more insight into this issue.

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