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Catalytic Amination of Alcohols, Aldehydes, and Ketones

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Data on the catalytic amination of alcohols and carbonyl compounds are examined, the catalysts for these processes are described, and the problems of their effectiveness, selectivity, and stability are discussed. The possible mechanisms of the reactions indicated are presented.
The bibliography includes 266 references.

CONTENTS

I. Introduction 14
II. Catalytic amination of alcohols 14
III. Catalytic reductive amination of carbonyl compounds 19

I. INTRODUCTION

Amines are the most important products of basic and fine organic syntheses. They are used extremely widely and for different purposes in the national economy. Amines and their derivatives are employed, in particular, as antioxidants in fuel oils and as rubber stabilisers, in the manufacture of water-impermeable fabrics and effective medicinal drugs, in road building, in the manufacture of detergents, as extractants of rare metals (U, Th, Pu, Au, Zr, V. Pa, and others), and in the manufacture of herbicides. They have found applications in the synthesis of dyes and accelerators of the polymerisation of rubber. A wide variety of plastics are obtained from alicyclic and aromatic amines.

Amines are obtained by the amination of saturated and unsaturated hydrocarbons, alcohols, halogeno-compounds, and carbonyl compounds, by the reduction of a wide variety of nitro-compounds, and by the Hofmann, Curtius, and other reactions. The synthesis of amines from alcohols was first achieved by Sabatier and Mailhe[1] in 1909 and the reductive amination of aldehydes and ketones was first carried out by Mignonac[2] in 1919. Since then, numerous studies on particular aspects of the above reactions as well as a number of reviews have been published[3-7], the results of pre-war investigations (particularly those of Emerson[3]) being surveyed most completely.

This review is devoted to the literature on the synthesis of amines by the catalytic amination of alcohols and carbonyl compounds. An attempt is made to reflect the achievements and trends in the study of these reactions.

II. CATALYTIC AMINATION OF ALCOHOLS

The modern industrial method for the preparation of primary, secondary, and tertiary aliphatic amines consists in passing the vapour of the corresponding alcohol and ammonia over oxide catalysts such as Al_2O_3, ThO_2 etc. heated to 350–450 °C. Apart from amines, unsaturated and saturated hydrocarbons, water, nitriles, aldehydes or ketones, hydrogen, and ethers are detected in the reaction products. The presence of these substances in the reaction medium has been explained in different ways by various investigators. There is as yet no unanimous view concerning the mechanism of the amination of alcohols.

The original discoverers of the reaction assumed that[8] the alcohol initially reacts with the catalyst (thorium oxide) and forms an unstable ester—alkyl thorate [reaction (1)], which then reacts rapidly with ammonia [reaction (2)]. The authors assumed that the olefins obtained are the products of secondary reactions. Secondary and tertiary amines are formed by the interaction of alkyl thorate with primary [reaction (3)] and secondary [reaction (4)] amines:

$$ROH + ThO_2 \rightarrow ThO(OR)_2 + H_2O\,, \quad (1)$$

$$ThO(OR)_2 + NH_3 \rightarrow RNH_2 + ThO_2 + H_2O\,, \quad (2)$$

$$ThO(OR)_2 + RNH_2 \rightarrow R_2NH + ThO_2 + H_2O\,, \quad (3)$$

$$ThO(OR)_2 + R_2NH \rightarrow R_3N + ThO_2 + H_2O\,. \quad (4)$$

Baum[9] assumed that the ethers formed from the alcohols via reaction (5) are intermediates in the synthesis of amines in the presence of alumina [reaction (6)–(8)]:

$$RCH_2OH \rightarrow (RCH_2)_2O + H_2O\,, \quad (5)$$

$$(RCH_2)_2O + NH_3 \rightarrow RCH_2OH + RCH_2NH_2\,, \quad (6)$$

$$(RCH_2)_2O + RCH_2NH_2 \rightarrow (RCH_2)_3NH + RCH_2OH\,, \quad (7)$$

$$(RCH_2)_2O + (RCH_2)_2NH \rightarrow (RCH_2)_3N + RCH_2OH\,. \quad (8)$$

Schwegler and Adkins[10] suggested that the alcohols are initially dehydrogenated via reaction (9) to aldehydes or ketones, which react with ammonia to form imines [reaction (10)]. The latter are then reduced with hydrogen to primary amines via reaction (11). While reacting with fresh molecules of the carbonyl compounds via reactions (12)–(14), the primary amines give rise in their turn to secondary and tertiary amines via the intermediate Schiff bases:

$$RCH_2OH \rightarrow R{-}C\!\!<\!\!\begin{matrix}O\\H\end{matrix} + H_2\,, \quad (9)$$

$$R{-}C\!\!<\!\!\begin{matrix}O\\H\end{matrix} + NH_3 \rightarrow RCH{=}NH + H_2O\,, \quad (10)$$

$$RCH{=}NH + H_2 \rightarrow RCH_2NH_2\,, \quad (11)$$

$$RCH_2NH_2 + RC\!\!<\!\!\begin{matrix}O\\H\end{matrix} \rightarrow RCH_2N{=}CHR + H_2O\,, \quad (12)$$

$$RCH_2N{=}CHR + H_2 \rightarrow (RCH_2)_2NH\,, \quad (13)$$

$$RCH_2N{=}CHR + RC\!\!<\!\!\begin{matrix}O\\H\end{matrix} \xrightarrow{+H_2} (RCH_2)_3N + H_2O\,. \quad (14)$$

Popov[11] assumed that the first stage in the amination process is reaction (15) involving the dehydration of alcohols with formation of olefins, which then react with ammonia, primary, and secondary amines to form primary [reaction (16)]. secondary [reaction (17)], and tertiary [reaction (18)] amines respectively:

$$RCH_2CH_2OH \rightarrow RCH{=}CH_2 + H_2O\,, \quad (15$$

$$NH_3 + RCH{=}CH_2 \rightarrow RCH_2CH_2NH_2\,, \quad (16$$

$$RCH{=}CH_2 + RCH_2CH_2NH_2 \rightarrow (RCH_2CH_2)_2NH\,, \quad (17)$$

$$RCH{=}CH_2 + (RCH_2CH_2)_2NH \rightarrow (RCH_2CH_2)_3N \ . \qquad (18)$$

It has been shown[12-14] that amines are formed in the amination of alcohols by direct substitution of the alcoholic hydroxy-group by the amino-group [reaction (19)]. Secondary [reaction (20)] and tertiary [reaction (21)] amines are obtained similarly:

$$RCH_2OH + NH_3 \rightarrow RCH_2NH_2 + H_2O \ , \qquad (19)$$

$$RCH_2OH + RCH_2NH_2 \rightarrow (RCH_2)_2NH + H_2O \ , \qquad (20)$$

$$RCH_2OH + (RCH_2)_2NH \rightarrow (RCH_2)_3N + H_2O \ . \qquad (21)$$

The alcohols, unsaturated hydrocarbons, carbonyl compounds, and ethers formed in the amination process were regarded[13] as the products of the dehydration and dehydrogenation [side reactions (5), (9), and (15)] occurring on the surface of the catalysts at elevated temperatures.

In contrast to this view, Bashkirov and coworkers showed in relation to the amination of deuteroalcohols[15-20] that the reaction proceeds via the mechanism proposed by Schwegler and Adkins[10]. In their study of the interaction of labelled ethanol with ammonia, they noted[15-20] that the ethanol is initially dehydrogenated, the abstraction of hydrogen atoms from the α-position in the alcohol molecule being the rate-limiting stage of the process. The β-hydrogen atoms in the alcohol are not involved in the rate-limiting stage. It was found that this stage proceeds with participation of two active centres of the catalyst. Secondary amines are formed in consequence of the addition of primary amines to the double bonds of aldimines. On raising the temperature and at a low hydrogen partial pressure, aldimines can be dehydrogenated to nitriles. It was established that ammonia and primary and secondary amines as well as the saturated hydrocarbons produced do not influence the rate of reaction. The addition of water greatly lowers the rate of amination. The authors[15-20] proposed the following reaction mechanism (Z is a catalyst active centre):

$$RCH_2OH + Z \rightleftarrows RCH_2OHZ \ , \qquad (22)$$

$$H_2 + Z \rightleftarrows H_2Z \ , \qquad (23)$$

$$NH_3 + Z \rightleftarrows NH_3Z \ , \qquad (24)$$

$$RCH_2OHZ + Z \rightarrow RCHOZ + H_2Z \ , \qquad (25)$$

$$RCHOZ + NH_3Z \rightarrow RCH{=}NHZ + H_2OZ \ , \qquad (26)$$

$$RCH{=}NHZ + H_2Z \rightleftarrows RCH_2NH_2Z + Z \ , \qquad (27)$$

$$RCHOZ + RCH_2NH_2Z \rightarrow RCH{=}N{-}CH_2RZ + Z \ , \qquad (28)$$

$$RCH{=}N{-}CH_2RZ + ZH_2 \rightarrow (RCH_2)_2NHZ + Z \ , \qquad (29)$$

$$RCH_2NH_2Z \rightleftarrows RCH_2NH_2 + Z \ , \qquad (30)$$

$$(RCH_2)_2NHZ \rightleftarrows (RCH_2)_2NH + Z \ , \qquad (31)$$

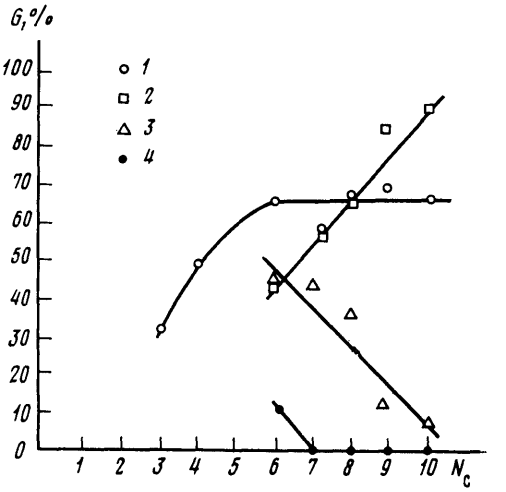
$$H_2OZ \rightleftarrows H_2O + Z \ . \qquad (32)$$

Stage (25) is slow, while all the remaining stages are fast or correspond to equilibrium. We believe that this mechanism is the most probable.

1. The Synthesis of Aliphatic Amines

(a) The Synthesis of Aliphatic Amines in the Presence of Dehydrating Catalysts

The principal disadvantage of the synthesis of amines from alcohols is the occurrence of a number of side reactions, particularly the dehydration of the initial alcohols. One of the ways of suppressing the dehydration involves the use of a high ammonia pressure in the reaction zone. With the aid of this method, Kozlov and coworkers established[21,22] that with increase of ammonia pressure the yield of amines rises. With increase of the molecular weight of the alcohol, the yield of amines falls (Table 1, Nos.1–7). For alcohols having the same molecular weight[22], the yield of amines depends on the degree of branching of the carbon chain, other conditions being equal. Indeed the yield of amines obtained from 1-butanol was 89.9% while that from triethylmethanol was only 25.5% with respect to the alcohol which has reacted (Table 1, Nos.1 and 8). It is noteworthy that secondary and tertiary amines are obtained with lower yields than primary amines. This probably occurs because a transamination reaction takes place when amines are passed over heated oxide catalysts, i.e. ammonia and two new amines are obtained from the initial amine[23,24]. It has been established[25] that the predominance of the primary amine in the products is associated with the fact that an increase of ammonia pressure greatly displaced the reaction equilibrium between the alcohol and ammonia towards the formation of the primary amine. This was confirmed in a study of the thermodynamics of the reaction[26].



Dependence of the yield of amines G on the number of carbon atoms in the alcohol N_C (according to the data of Kozlov and Kirichenko[27]); 350–400 °C; $p_{NH_3} = 7$–11.5 atm; Al_2O_3–SiO_2 catalyst: 1) overall yield of amines; 2) primary amines; 3) secondary amines; 4) tertiary amines.

Another approach to the problem of improving the selectivity in the amination of alcohols involved the promotion of alumina by other metal oxides. It has been shown[27] that a mixed aluminosilicate catalyst dehydrogenates alcohols to a lesser extent, so that C_3–C_{10} straight-chain aliphatic alcohols can be converted into amines in yields up to 70%. The Figure shows that, with increase of the length of the carbon chain of the alcohol, there is not only an increase of the yield of amines in the presence of this catalyst under conditions analogous to the use of activated alumina but there is also an increase of selectivity in relation to primary amines

Table 1. Catalytic amination of aliphatic alcohols in the presence of dehydrogenating catalysts.

No.	Alcohol	Catalyst	t, °C	p, atm	Overall yield of amines, %	Yields of amines, %			Remarks	Refs.
						primary	secondary	tertiary		
1	1-Butanol	act. Al_2O_3	370—380	9	89.9	62.0	29.8	8.2	yield w.r.t. alcohol which has reactd.	21,22
2	Isobutyl alcohol	act. Al_2O_3	370—380	9	68.8	51.4	40.7	7.7	ditto	21,22
3	Isopentyl alcohol	act. Al_2O_3	370—380	9	76.4	51.2	30.6	18.2	" "	21
4	Methylpropylmethanol	act. Al_2O_3	370—380	9	44.2	—	—	—	" "	21
5	Ethyldimethylmethanol	act. Al_2O_3	370—380	9	25.8	—	—	—	" "	21
6	1-Octanol	act. Al_2O_3	370—380	9	18.1	53.5	34.4	12.1	" "	21
7	1-Nonanol	act. Al_2O_3	370—380	9	11.9	61.0	25.5	13.5	" "	21
8	Trimethylmethanol	act. Al_2O_3	370—380	9	25.3	—	—	—	" "	21
9	1-Butanol	$Al_2O_3 + Cr_2O_3$	330	9	42.8	25.5	17.3	—	$C_4H_9OH:NH_3 = 1:4$	31
10	1-Butanol	$Al_2O_3 + V_2O_5$	347	9	54.1	24.9	29.2	—	$C_4H_9OH:NH_3 = 1:4$	32
11	1-Butanol	$Al_2O_3 + 5\%$ TiO_2	370	8,5	36.1	80.1	19.9	—	yield w.r.t. alcohol used	13
12	Isobutyl alcohol	$Al_2O_3 + 5\%$ TiO_2	370	8,5	35.3	76.8	23.2	—	ditto	13
13	Ethanol	$Al_2O_3 + 10\%$ Fe_2O_3	370—380	7—10	45	—	—	—	$C_2H_5OH:NH_3 = 1:3$	37
14	1-Butanol	bauxite + 3% Fe_2O_3	320	—	58.5	20.6	28.8	9.1	$C_4H_9OH:NH_3 = 1:1.6$	39
15	1-Butanol	mordenite	200	—	70	—	—	—	—	40
16	1-Dodecanol	12% $Th(SO_4)_2$ on kieselguhr	360	—	95	—	—	95	$(CH_3)_2NH$: alcohol = 2 : 1	53

The decrease of the yield of secondary amines and the disappearance of tertiary amines from the reaction mixture are probably associated either with a decrease in the surface area of the catalyst or with steric hindrance. However, the aluminosilicate catalyst was less active and the yield of amines in its presence was lower than in the presence of alumina. From earlier studies[21-22,27-29], Kozlov et al.[30] suggested that the catalysts described be used to synthesise amines from the waste in the manufacture of synthetic methanol and ethanol.

Catalysts based on Al_2O_3 and SiO_2, promoted with chromium, nickel, vanadium, molybdenum, magnesium, iron, titanium, and other oxides, have been investigated[13,31-38]. Typical examples of the conditions in the amination processes in their presence as well as the yields of products are listed in Table 1 (Nos. 9–13).

Natural aluminosilicates (bauxites, gumbrin, mordenite, etc.) have been studied as amination catalysts[39-44]; even under fairly severe conditions, the yield of amines is as a rule low (Table 1, Nos. 14 and 15). We may note that in the presence of H-substituted mordenite ($Na_2Al_2Si_{10}O_{24}.7H_2O$), only the formation of primary and secondary amines is observed[40]. The author[40] believes that the reaction selectivity depends on the pore size in the catalyst and the associated steric hindrance to the formation of tertiary amines.

It has been suggested that methylamines be synthesised in the presence of various mixtures of H_3BO_3 and H_3PO_4 on kieselguhr or pumice[45,46] or in the presence of pure Al_2O_3.[47-49] It is of interest that, when acid-treated alumina was employed, the preferential formation of secondary amines was observed[50], other conditions being equal. Alumina[51] or thorium sulphate[52] have been used in the amination of alcohols by primary or secondary amine. A particularly high yield of *N*-alkylated amines (95%) was obtained in the presence of a catalyst containing 12% $Th(SO_4)_2$ on kieselguhr[53] (Table 1, Nos. 16).

(b) The Synthesis of Aliphatic Amines in the Presence of Hydrogen

Dehydration and hydrogenation[54] or dehydrogenation and hydrogenation[55] catalysts have been used in succession to synthesise amines in a number of studies. Thus a mixture of alcohol vapour with ammonia was passed initially[54] over an iron catalyst at 300–470 °C and the resulting condensate was then hydrogenated on a nickel catalyst at 80–160 °C and a hydrogen pressure of 100–150 atm, the product consisting mainly of primary amines. Up to 100% of amines was obtained[55] when nickel on kieselguhr at 200 °C (a dehydrogenation catalyst) and copper at 180 °C or nickel at 100 °C (hydrogenation catalysts) were used in succession.

Very many studies have been devoted to the amination of alcohols on hydrogenation catalysts. Raney nickel has been widely used; with its aid, amines have been alkylated by alcohols[56,57], aminoalcohols have been synthesised[58], and amines have been obtained from butyl[59] and isooctyl[60] alcohols. Raney nickel proved to be a non-selective catalyst and in addition it must be consumed in large amounts for high yields of amines to be attained. Other nickel-containing catalysts[61-67] suffer from the same disadvantages (Table 2, Nos. 1 and 2). When nickel and Cr_2O_3 on kieselguhr were used (Table 2, No. 1), water was continuously removed from the reaction mixture, which made it possible to displace the equilibrium towards the formation of the tertiary amine[61].

Catalysts containing cobalt[68-70] or noble metals[71-73] proved to be much more active than nickel catalysts; up to 97% of amines has been obtained in their presence (Table 2, Nos. 3–5). Their high selectivity, the relatively mild conditions required for their application, and their low cost make cobalt catalysts extremely promising for the amination of alcohols.

Bashkirov and coworkers[74] suggested that fused Fe_3O_4, promoted by acid and amphoteric oxides, be used for the amination of alcohols. This catalyst has been employed in a number of subsequent studies[15-20,75-89]. The authors found the optimum conditions for the synthesis of butylamines[76] (Table 2, No. 6) and investigated in detail the amination of octyl alcohols with a wide variety of structures[77]. It was shown that the branching of the carbon skeleton entails a sharp increase in the yield of side products. At the same time the branching of the carbon chain of the initial alcohol lowers its capacity for the formation of secondary and tertiary amines, probably owing to the increasing steric hindrance.

In the amination of various aliphatic alcohols (C_5–C_{18}) the authors[79] found that, with increase in the length of the carbon chain of the alcohol, its capacity for the formation of

secondary amines also increases. Subsequently Bashkirov and coworkers showed that it is possible to obtain preferentially either primary[80], or secondary[81], or tertiary[82] amines by altering the reaction conditions. By using an optimisation method, the authors[83–86] determined the best conditions for the synthesis of normal primary, secondary, and tertiary amines as well as branched amines (Table 3). If the alcohol is in the liquid state then, other conditions being equal, the amount of secondary amines obtained increases by a factor of 1.5.

The kinetics of the amination of 1-octanol have been studied in detail[88]. In particular, it was shown that the addition of water lowers the rate of reaction, while the addition of hydrogen and the concentrations of other reactants do not influence the rate of amination.

Using primary amines (CH_3NH_2, $C_4H_7NH_2$, $C_7H_{10}NH_2$) as the aminating agents, Bashkirov and coworkers[89] obtained between 60 and 85% of secondary amines (with respect to the alcohol which has reacted). They used Fe_3O_4 with added 0.8–1.0% of beryllium or vanadium oxide as the catalyst at 230–240 °C and a hydrogen pressure of 20 atm.

The catalytic properties of the fused iron catalyst[74], iron ε-nitride (ε-Fe_2N), and iron carbonitride ($Fe_2C_{0.29}N_{0.71}$) were compared[90] in the amination of butanol. It was found that mainly primary amines are obtained in the presence of ε-Fe_2N, secondary amines are the main products in the presence of $Fe_2O_3 + V_2O_5$, while the carbonitride can serve as a catalyst for the synthesis of butyronitrile.

2. The Synthesis of Alicyclic Amines

There are very few data on the amination of alicyclic alcohols, although this reaction has much in common with the amination of aliphatic analogues and proceeds in the presence of similar catalysts.

Thus Al_2O_3 has been used[91] (Table 4, No.1). The authors found that the application of an increased ammonia pressure suppresses (as for aliphatic alcohols[21]) the dehydration of cyclohexanol and drives the process towards the formation of cyclohexylamines.

Subsequently the amination of cyclohexanol and cyclopentanol was investigated[92] over Al_2O_3, Al_2O_3–SiO_2, Al_2O_3 activated with 2% KOH or 2% LiOH, Cu/Al_2O_3, and Ni/Al_2O_3. It was found that, for a copper content above 0.5%, cyclohexylamine was obtained with a maximum yield (76.5%); with increase of the copper content to 20%, the main amination product became dicyclohexylamine.

When Ni/Al_2O_3 was used, aniline and *N*-cyclohexylaniline as well as pyridine and 2-methylpyridine were detected in the reaction products. It is noteworthy that the formation of pyridines was observed also in the presence of copper catalysts. It had been suggested earlier[93] that 2-methylpyridine may be obtained from cyclohexylamine. This was subsequently confirmed by Kozlov et al.[92] Under the conditions of the amination of alicyclic alcohols, these workers obtained 52–70% of 2-methylpyridine and 5–10% of pyridine respectively from cyclohexyl- and cyclopentyl-amines. It

Table 2. Catalytic amination of aliphatic alcohols in the presence of hydrogen.

No.	Alcohol	Catalyst	*t*, °C	*p*, atm	Overall yield of amines, %	Yield of amines, %			Remarks	Refs.
						primary	secondary	tertiary		
1	Isononyl alcohol	Ni, Cr_2O_3 on kieselguhr	190	—	—	—	—	83.0	$NH_3:H_2=1:1$	61
2	1-Propanol	Ni on Al_2O_3 treated with $Ba(OH)_2$	195	20	—	24.3	42.6	12.0	—	63
3	Isopropyl alcohol	Co, Mn, Cr	300	—	97	90.5	6.5	—	—	69
4	1-Dodecanol	Co, ZnO, Al_2O_3	180	—	—	95.3	—	—	$NH_3:H_2=3:1$	70
5	Isobutyl alcohol	Pt on SiO_2	400	—	86.34	15.33	11.90	59.11	—	72
6	1-Butanol	Fe_3O_4	230	20	76	95.7	4.3	—	—	76

Table 3. Optimum conditions for the synthesis of amines in the presence of a fused iron catalyst.

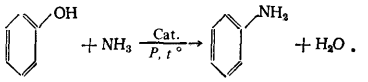
No.	Alcohol	*t*, °C	*p*, atm	Rate of supply of alcohol, mol litre^{-1} h^{-1}	Flow rate of gas mixture, cm s^{-1}	NH_3 content, vol.%	Overall yield of amines, %	Yield of amines, %			References
								primary	secondary	tertiary	
1	Normal C_6–C_{13}	258	50	14.4	1.8	43	90–93	88–92	—	—	83
2	Normal C_6–C_{12}	280	50	11.0	0.16	35	50–59	11–25.5	45–49	29.5–35	84
3	Normal C_6–C_{12}	295	50	12.3	0.03	23	60–70	12.5–20.5	18.5–25.5	59–69	85
4	2-Ethyl-1-hexanol	293	50	8.5	18	45	—	99	—	—	86

has been suggested that alicyclic alcohols be aminated in the presence of aluminosilicates[94-97]. The yield of the corresponding amines was 51–90% (Table 4, Nos.2–4).

Catalysts working under hydrogenation conditions have been investigated[93-104]. Whereas in the presence of nickel or iron catalysts the amination products are the corresponding amines (Table 4, No.5), in the presence of noble metals anilines are obtained (Table 4, Nos.6–8). Richardson and coworkers believe[101] that the reaction proceeds in the presence of these catalysts via the intermediate cyclohexylamine, which is strongly retained and is then dehydrogenated with the desorption of aniline.

3. The Synthesis of Aromatic Amines

In industry aromatic amines are obtained mainly by the reduction of the corresponding nitro-compounds. Together with the wide-scale development of this method, reports have appeared of the synthesis of aniline and its homologues by the catalytic amination of phenol and its analogues:



It has been found[21,105] that industrial activated alumina catalyses the conversion of phenol, *o*- and *p*-cresols, and *m*-xylenol into the corresponding primary amines. The highest yield (88% of aniline) was obtained in the amination of phenol (Table 5, No.1). The effectiveness of Al_2O_3 increases after its preliminary treatment with alkali and a carboxylic acid[106] or H_3BO_4 [107] (Table 5, Nos.2 and 3). The same catalysts have been proposed also for the synthesis of *m*- and *p*-toluidines, diphenylamine, β-naphthylamine, etc. The above amines are also obtained when (2–10% $AlCl_3$)/Al_2O_3 or Al_2O_3–SiO_2 are used under analogous conditions (365 °C, p_{NH_3} = 16 atm).[108] In addition, other oxide catalysts have been proposed[109-115]. The yield of aniline is 80–99% (Table 5, Nos.4–6).

The properties of mixed oxide catalysts in the amination of phenol have been studied in detail[116-119] and it has been established that SiO_2–TiO_2, TiO_2–WO_3, TiO_2–Nb_2O_5, TiO_2–ZrO_2, ZrO_2–Nb_2O_5, and other mixtures of oxides showed a higher catalytic activity and selectivity in this reaction than SiO_2–Al_2O_3. It has been found with the aid of thermogravimetric analysis[119] that the amination proceeds via the adsorption of phenol on the acid centres of the catalyst and that the more acid centres of the mixtures of oxide proved to be more effective than the less acid centres of SiO_2–Al_2O_3. It is noteworthy that phenol and aniline poison catalysts containing highly acid and therefore highly active centres.

Yamamoto et al.[120] investigated the amination of phenol in the presence of type Y zeolites at 350–380 °C. In terms of their catalytic activity, the zeolites can be arranged in the following sequence: HY > CaY > CuY. The yield of aniline is 11–14 mol.%. In addition, the influence of the amount of Cu^{2+} in the zeolite on the yield of products has been studied. The maximum yield of aniline was obtained in the presence of 80% of the metal. It is noteworthy that, when aniline or pyridine is added to CuY, the yield of aniline falls, while in the presence of added HCl it increases. This suggests that amination proceeds in this case via the adsorption of phenol on the acid centres of the zeolites.

Hydrogenation catalysts have been used to aminate benzyl and β-phenylethyl alcohols as well as phenol[69,121-123] (Table 5, Nos.7–9). When catalysts based on noble metals

Table 4. Catalytic amination of alicyclic alcohols.

No.	Alcohol	Catalyst	*t*, °C	*p*, atm	Product	Yield, %	Remarks	Refs.
1	Cyclohexanol	Al_2O_3	260-300	8-10	cyclohexylamine	90-95	yield w.r.t. reacted alcohol	91
2	Cyclohexanol	$Ca/Al_2O_3.SiO_2$	245-330	14	" "	67-82	NH_3:alcohol = 8:1-15:1	94
3	Cyclohexanol	gumbrin + 8% Fe_2O_3	300	1	" "	90.6	ditto	95
4	1-Methyl-1-cyclopentanol	gumbrin + 8% Fe_2O_3	280	1	1-methyl-1-cyclopentylamine	51.08	" "	97
5	Cyclohexanol	Fe_3O_4	240-260	50	cyclohexylamine	85	" "	99
6	Cyclohexanol	Pt/C	315	1.8	aniline	89	NH_3:H_2:alcohol = 16:1:1	102
					cyclohexylamine	5		
7	Cyclohexanol	Pd/SiO_2	330	–	N-methylaniline	70	$MeNH_2$:H_2:alcohol = 5:5:1	102
8	Cyclohexanol	Pt/SiO_2	315	4	aniline	89	NH_3:H_2:alcohol = 8:4:1	103

Table 5. Catalytic amination of aromatic alcohols [and phenol].

No.	Alcohol	Catalyst	*t*, °C	*p*, atm	Product	Yield, %	Remarks	Refs.
1	Phenol	Al_2O_5	475	9	aniline	88.3	–	21
2	Phenol	γ-Al_2O_3, treated with H_3BO_3	365	16	aniline	87.0	phenol:NH_3 = 1:20	106
3	Phenol	γ-Al_2O_3, treated with acid and alkali	365	16	aniline	98.0	phenol:NH_3 = 1:20	107
4	Phenol	Al_2O_3 + 1% Na_2O	363	16.9	aniline	98.9	phenol:NH_3 = 1:20	112
5	Phenol	SiO_2-Al_2O_3 + V_2O_5	300-600	7	aniline	80.0	–	114
6	Phenol	9.9% Al_2O_3 on SiO_2	383	16.8	aniline	93	–	115
7	Benzyl alcohol	Fe_3O_4	200	50	benzyl- and dibenzylamines	53.5	H_2:NH_3:alcohol = 9.7:22.2:1	121
8	β-Phenylethyl alcohol	Co, Cr, Mn	220	300	phenylethylamine	90.0	–	69
					Di(phenylethyl)amine	10.0	–	
9	Phenol	NH_4Cl	400	1000	aniline	90	–	122
10	Phenol	5% Ru on charcoal + sodium phenoxide	110	13-14	cyclohexylamine	85.2	–	126
11	Phenol	5% Pd on charcoal	110	10	dicyclohexylamine	82.5	–	127

were used, the hydrogenation of the aromatic ring was observed and cyclohexylamines and cyclohexanol were obtained from phenol[124,125]. It was found[126] that the addition of 0.015–10 wt.% of sodium phenoxide lowers the fraction of cyclohexanol in the product and that cyclohexylamine is obtained in 85.2% yield (Table 5, No.10). In the presence of (5% Pd)/C phenol is converted preferentially into dicyclohexylamine[127] (Table 5, No.11).

We shall consider separately data for the alkylation of aniline by alcohols and for the amination of phenol–aliphatic alcohol mixtures. Evans and Bours[128] postulated that the best catalyst for the gas-phase alkylation of aniline by methanol is activated alumina; it has been established[39] that natural aluminosilicates can also be used to alkylate aniline by alcohols. Thus, in the presence of bauxite containing 6% Fe_2O_3 at 275 °C, at atmospheric pressure, and for the ratio ethanol : aniline = 1.45, 83.9% of ethylaniline and 3.3% of diethylaniline were obtained. It has been shown[129] that, when aniline and ethanol are passed over Nb_2O_5 heated to 350–408 °C, 10% of *N,N*-dimethylaniline and 20–25% of *N*-ethylaniline are obtained during one pass.

Alumina, various aluminosilicates, as well as Al_2O_3 promoted by other metal oxides and hydroxides have been investigated[130–133] in the amination of the phenol–aliphatic alcohol system. The best catalyst proved to be the Al_2O_3 + 1% LiOH mixture[132]. The yield of arylamines in the presence of this catalyst at 450 °C and $p_{NH_3} = 12$ atm was in excess of 60%. With increase of the LiOH content, the yield of amines fell to 28%, probably owing to the blocking action of the lithium cations, which covered a proportion of the aprotic centres of Al_2O_3 responsible for the amination reaction. It has also been found that, with increase of the molecular weight of the alcohol, the yield of arylamines falls from 69% (for CH_3OH) to 18% (for C_4H_9OH) and that for branched alcohols the yield is smaller by a factor of two than for normal alcohols.

It has been suggested[134–136] that aniline be alkylated by alcohols in the presence of acids. Thus using H_2SO_4, 99% of *N,N*-dimethylaniline was obtained on heating a methanol–aniline mixture to 190–210 °C under a pressure of 5 atm.[135]

A number of studies[57,137–140] have been devoted to the synthesis of mixed amines by the reaction of aromatic amines with aliphatic alcohols in the presence of Raney nickel. The yield of amines is fairly high (41–90%) and the alkylation conditions in the presence of Raney nickel are comparatively mild. The main disadvantage of the method is the high consumption of the catalyst.

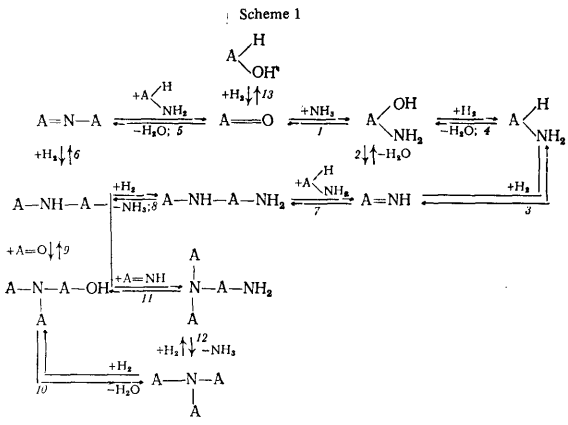
It has been found[141] that phenylacetylmethanols can be alkylated by primary amines also by a non-catalytic procedure, in the presence of sodium tetrahydroborate. The main disadvantage of this method is the high cost of $NaBH_4$.

III. CATALYTIC REDUCTIVE AMINATION OF CARBONYL COMPOUNDS

The catalytic reductive amination of carbonyl compounds is usually carried out in the presence of catalysts based on transition metals. Studies on the use of complex catalysts have been carried out recently. In addition, there have been reports of the electrocatalytic synthesis of amines from ketones and by non-catalytic amination with the aid of tetrahydroborates.

We shall consider certain general postulates underlying the reductive amination of carbonyl compounds. The synthesis of amines by this procedure (Scheme 1) consists in the addition of ammonia to a carbonyl compound with subsequent reduction of the adduct (pathway *1*, *4*)

Scheme 1



where A=O represents R–C(=O)–R′ and R, R′ = alkyl, aryl, or H.

It may be that the adduct is initially dehydrated and the dehydration product is subsequently reduced (pathway *1–2–3*). The primary amine formed ultimately can also behave as an aminating agent for carbonyl compounds, forming Schiff bases, which are reduced to secondary amines (pathway *5–6*). The addition of a primary amine to imines with subsequent reduction of the adduct also leads to secondary amines (pathway *7–8*). Secondary amines react similarly in their turn with carbonyl compounds (pathway *9–10*) or with an imine (pathway *11–12*), forming tertiary amines. The principal side reactions involve the formation of an alcohol (pathway *13*) and aldol condensation. In order to prevent the formation of an alcohol, it has been recommended in a number of studies that ammonium[6,147–148] or sodium[149] acetates or chlorides be added to the reaction mixture. The aldol condensation is retarded or is not observed at all when the reaction mixture is cooled before hydrogenation[6] or when the contact time between the carbonyl compound and ammonia is reduced[150]. The kinetics of the reductive amination of aldehydes and ketones have been studied in detail[142–146] and we shall not consider them in the present review.

Numerous catalysts for the reductive amination of carbonyl compounds have now been investigated. From these, Freifelder[6] selected nickel catalysts, believing them to be the most effective and most readily available. Together with nickel catalysts, Augustine[151] recommends also platinum catalysts for this reaction. The use of catalysts containing platinum group metals has been most fully described by Rylander[7]. This review covers studies which are not included in the books by Freifelder[6] and Rylander[7] and in Augustine's review[151].

(a) Reductive Amination of Aliphatic Aldehydes and Ketones

Nickel catalysts have been used in many studies on the synthesis of amines from aliphatic carbonyl compounds. Raney nickel has been investigated[152–160]. Table 6 (Nos.1–11) shows that the yield of amines depends on the structure of the carbonyl compound. The rate of reaction also depends on the structure of the substrate employed. Thus it has been established[155] that the rate of amination decreases in

the sequence ethyl methyl ketone > isobutyl methyl ketone > diethyl ketone. The advantages of Raney nickel as a catalyst include ready availability, the possibility of carrying out experiments under mild conditions, and fairly high selectivity, while its main disadvantages are high consumption and lack of safety. These disadvantages can be eliminated by employing catalysts containing nickel on various carriers.

Nickel deposited on alumina proved to be an effective catalyst for the amination of carbonyl compounds[161-174]. Analysis of the literature data showed that the conditions under which Ni/Al_2O_3 is used are as a rule similar to those employed for Raney nickel (Table 6, Nos.12–14), but, in contrast to the latter, it is more active and stable in the reaction under discussion. Thus it has been shown[164] that Ni/Al_2O_3 is three times more active than freshly prepared Raney nickel and it has been reported[161] that Ni/Al_2O_3 is stable for 2000 h.

In some cases, when the amination reaction was carried out in the presence of Ni/Al_2O_3, nitriles were detected in the reaction mixture. Popov and Shuikin[168] suggested that the amination proceeds via the formation of nitriles and put forward the following reaction mechanism:

$$R{-}CHO + NH_3 \rightarrow R{-}C(H)(NH_2){-}OH \xrightarrow[-H_2O]{} R{-}C(H){=}NH \xrightarrow[-H_2]{} RC{\equiv}N \xrightarrow{+2H_2} RCH_2NH_2 .$$

Next the primary amine is converted into a secondary amine and the secondary amine is converted into a tertiary amine.

Among other carriers, kieselguhr has been widely used. Thus, considerable amounts of ethylamines have been obtained[175] by the amination of acetaldehyde in the presence of a catalyst containing 52.2% Ni, 14% Cu, 2% Mo, and 31.5% of kieselguhr (Table 6, No.15); the synthesis of tertiary amines by the reaction of ketones with secondary amines in the presence of a catalyst consisting of 50% Ni and 2% Zr on kieselguhr has been reported in a number of patents[176,177].

Analysis of studies in which cobalt catalysts for reductive amination have been used[178-180] shows (Table 6, Nos.16–18) that these catalysts give rise to a high yield of amines, but require more severe conditions than nickel catalysts. Copper catalysts have been studied in a number of investigations[181-183]. Among these, the greatest interest attaches to the hydroamination of ketones by benzonitrile in the presence of $(20\%\ Cu)/Al_2O_3$. Various *N*-alkylated benzylamines have been obtained by this method. It has been reported in a patent[184] that alkylidenealkenylamines are obtained in yields up to 98% when a mixture of the corresponding aldehyde and ammonia is passed through a column heated to 150–400 °C and filled with pumice containing 7.5% Zn and 1.5% Cr. Catalysts based on platinum[148,185,186] work under milder conditions (20–100 °C, $p_{H_2} = 1$–4 atm), but the yield of amines is as a rule low (10–65%). With increase of hydrogen pressure to 50–125 atm, the use of PtO_2,[187] Pd/C,[188,189] and Rh/Al_2O_3 [190] gives rise to 81–95% of secondary amines (Table 6, Nos.19–21).

There is very little information about the electrocatalytic amination of carbonyl compounds. It has been reported[191,192] that, using electrodes activated by Raney nickel, it was possible to convert acetone into isopropylamine in 78% yield. On these electrodes, ketones with identical hydrocarbon groups are aminated more readily than those with different hydrocarbon groups[149]. When a porous palladium electrode was used[193], the opposite behaviour was noted: the yield of the primary amine from ethyl methyl ketone was higher than that from diethyl ketone.

(b) Reductive Amination of Alicyclic Carbonyl Compounds

Nickel catalysts have been widely investigated, most studies being devoted to the synthesis of cyclohexylamine. Analysis of the literature data on the use of reduced nickel and Raney

Table 6. Reductive amination of aliphatic carbonyl compounds.

No.	Carbonyl compound	Catalyst	*t*, °C	*p*, atm	Product	Yield, %	Remarks	Refs.
1	Diethylaminoacetone	Raney Ni	20	1	3-diethylamino-2-propylamine	65	—	153
2	4-Diethylamino-2-butanone	Raney Ni	20	1	4-diethylamino-2-butylamine	75	—	153
3	5-Diethylamino-2-pentanone	Raney Ni	20	1	5-diethylamino-2-pentylamine	85	—	153
4	Acetone	Raney Ni	60—100	15	isopropylamine	98.7	acetone : NH_3 = 1 : 3	154
5	Ethyl methyl ketone	Raney Ni	150	45	2-aminobutane	93	—	155
6	Isobutyl methyl ketone	Raney Ni	150	45	3-amino-2,2-dimethylbutane	97	—	155
7	Diethyl ketone	Raney Ni	150	45	3-aminopentane	12—22	—	155
					bis(-α-ethylpropylamine)	40—66	—	
					3-pentanol	4	—	
8	Acetaldehyde	Raney Ni	150—160	35	ethylamine	83	—	156
9	Glyoxal	Raney Ni	200—210	77	imidazole	85	—	158
10	1-Butanal	Raney Ni	90	5—10	n-butylamine	74—80		160
11	1-Butanal	Raney Ni	80	15	dibutylamine	50	1-butanal : n-butylamine = 1 : 2	160
12	Acetone	Ni/Al_2O_3	150	46	isopropylamine	92		161
13	Acetone	Ni/Al_2O_3	100—150	1—4	isopropylamine	70—96	acetone : H_2 : NH_3 = 1 : 4 : 4—1 : 5 : 5	162
					dipropylamine	0.1—21.0		
					2-propanol	3—11		
14	1-Butanal	Ni/Al_2O_3	240	—	mixture of butylamines	50	1-butanal : NH_3 = 1 : 3	168
15	Acetaldehyde	Ni, Cu, and Mo on kieselguhr	180	—	ethylamine	53.4	acetaldehyde : H_2 : NH_3 = 1 : 5 : 5	175
					diethylamine	38.8		
					triethylamine	7.9		
16	Ethyl methyl ketone	17% Co; 0.9% Cr; 0.5% H_3PO_4 on Al_2O_3	110	300	s-butylamine	95.5	—	176
17	Acetone	77.5% Co; 4.5% Mg; 18% Mn	>140	100÷125	isopropylamine	95.5	—	179
18	C_{13}-C_{15} aldehydes	Co, 5% Zr	110—120	140—160	mixture of primary amines	97.1	—	180
19	Isobutyl methyl ketone	PtO_2	20	50	*N,N'*-dialkylhexamethylenediamines	85	aminating agent—hexamethylenediamine	187
20	Ethyl methyl ketone	Pd/C	85—105	65—100	s-butylmethylamine	88.3	aminating agent—methylamine	188,189
21	1-Butanal	(5% Rh)/Al_2O_3	0—125	180	dibutylamine	95	1-butanal : n-butylamine = 1 : 1.1	190

nickel[194-199] shows that these catalysts proved to be extremely selective and effective in the synthesis of cyclohexylamine (Table 7, Nos.1–3). In the reductive amination of more complex alicyclic compounds it is impossible to achieve a high yield of amines even under severe conditions (Table 7, No.4). It has been established[196] that the yield of amines depends on the solvent employed and falls in the sequence ethanol > water > methanol > isopropyl alcohol. The authors suggest that in alcoholic solution the reaction proceeds via the intermediate cyclohexanone–cyclohexylimide. Cyclohexylamine is obtained also in the electrocatalytic reduction of cyclohexanone[200] in the presence of Raney nickel electrodes.

Other nickel-containing catalysts are also known. It is suggested in a patent[201] that nickel be modified by the addition of H_3PO_4 or H_3BO_3 for the synthesis of cyclohexylamine. A number of studies have been made[202-204] on nickel–chromium catalysts. They do not require high pressures and are more stable than Raney nickel, although they are inferior to it as regards selectivity (Table 7, No.5).

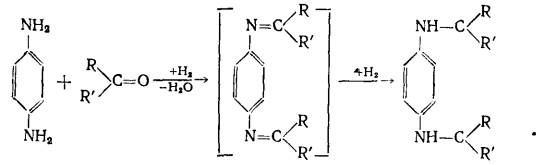
Nickel on alumina proved to be a less effective catalyst[205], but in its presence certain aliphatic ketones have been aminated[206] by pyridine bases, while dicyclohexylamine has been obtained from cyclohexanone and aniline at $p_{H_2} = 20$ atm at 250 °C.[207] We may note that, in the presence of Cu/Al_2O_3, *N*-cyclohexylaniline was obtained under the same conditions. Aliphatic cyclic amines have been synthesised using a catalyst containing Ni, MgO, and kieselguhr[208], and 1-*N*-cycloalkylaminocyclododecene which has been obtained[209] from cyclododecanone and morpholine, piperidine, and pyrrolidine in the presence of $TiCl_4$.

Table 7 (Nos.6–11) shows that catalysts based on noble metals[148,185,186,188,190,210,213] proved to be effective, with the exception of the study of Popov and Shuikin[185], only for the synthesis of secondary and tertiary amines. We may note that, when platinised quartz or certain other catalysts are used, mainly aniline is obtained from cyclohexanone[214].

(c) Reductive Amination of Aromatic Carbonyl Compounds

Raney nickel proved to be extremely suitable for the amination of aromatic carbonyl compounds[153,215-219]. Examples of its use (Table 8, Nos.1–5) shows that the yield of amines is fairly high and depends on the structure of the initial carbonyl compounds and on the reaction conditions.

As in the reductive amination of aliphatic and alicyclic carbonyl compounds, catalysts based on noble metals[148,190,220-228] proved to be effective only for the synthesis of secondary and tertiary aromatic amines (Table 8, Nos.6–8). The use for this purpose of platinum group metal sulphides[229-233] or catalysts based on these metals with added sulphur-containing compounds[234,235] (Table 8, Nos.9–11) proved to be particularly successful. It has been suggested[232] that the alkylation of *p*-phenylenediamine proceeds via the intermediate formation of Schiff bases:



In another study by the same workers[236] it was shown that, in the presence of the same catalysts and under similar conditions, the reduction of Schiff bases does indeed occur.

Among non-noble metal sulphides, rhenium sulphide proved to be the most active catalyst[232,237] (Table 8, No.12). The sulphides of basic metals proved to be relatively insensitive to poisons and in their presence virtually no hydrogenation of the benzene ring was observed and in many instances the initial carbonyl compound was not reduced to the corresponding alcohol.

Copper catalysts modified with barium sulphate[182] or chromium oxide[238,239] have been used[182,238,239] to synthesise secondary aromatic alkylamines. The yield of amines under conditions close to those employed for sulphide catalysts is appreciably lower (38–74%).

(d) Reductive Amination of Carbonyl Compounds in the Presence of Tetrahydroborates

Lane[240] believes that the reductive amination of an aldehyde or ketone is possible when the carbonyl compound interacts with an amine or ammonia at pH 6–8 in the presence of $NaCNBH_3$. The explanation is that the imino-group is reduced much faster than the carbonyl group. It has been suggested[241-245] that $LiCNBH_3$ in methanol at pH 5–6 and 25 °C be used together with $NaCNBH_3$ for reductive amination. However, lithium cyanotrihydroborate proved to be

Table 7. Reductive amination of alicyclic carbonyl compounds.

No.	Carbonyl compound	Catalyst	*t*, °C	*p*, atm	Product	Yield, %	Remarks	References
1	Cyclohexanone	Ni	140	28	cyclohexylamine	98.5	—	194
2	Cyclohexanone	Ni	130	30	cyclohexylamine	97.5	—	195
3	Cyclohexanone	Raney Ni and Co	80	5–15	cyclohexylamine	90–95	—	196
					dicyclohexylamine	0.2		
					cyclohexanol	0.2–3.1		
4	Cycloheptanone	Raney Ni	70	100	cycloheptylamine	61	—	199
5	Cyclohexanone	45% Ni; 1.8% Cr on kieselguhr	140	—	cyclohexylamine	84–86	—	204
					dicyclohexylamine	12–14	—	
6	Cyclohexanone	Pd/C	89–94	60–130	dicyclohexylamine	86.2	—	188
7	Cyclohexanone	PtO_2	20	1–3	cyclohexylamine	44–50	—	148
8	Cyclohexanone	Pt/SiO_2	200	—	cyclohexylamine	89.6	—	185
9	Cyclopentanone	Pt/SiO_2	170–240	—	cyclopentylamine	11.3	—	186
10	Formaldehyde	(5% Rh)Al_2O_3	20	180	cyclohexylmethylamine	68.8	aminating agent–cyclohexylamine	190
11	Cycloalkanones	AgO, PdO, and MnO on SiO_2	150–180	200	secondary and tertiary amines	98	aminating agent–secondary amines	212

a milder reductant than $NaBH_4$ and reductive amination did not go to completion in its presence. This may be associated with the choice of solvent. It is known[246] that $NaBH_4$ reduces the $>C=N$ bond more readily in dimethyl sulphoxide than in alcohols.

Using sodium cyanotrihydroborate, Borch and coworkers aminated cyclohexanone with methyl- and propyl-amines[243], methyl phenyl ketone with ammonia[242], and formaldehyde with aniline[245]. This yielded 78.5% of cyclohexylpropylamine, 53% of cyclohexyldimethylamine, 76% of 1-phenyl-1-aminoethane, and 92% of dimethylaniline. Together with the examples described, a considerable number of analogous syntheses of primary, secondary, and tertiary amines have been carried out[241-245] at room temperature and atmospheric pressure. This undoubtedly demonstrates the importance of the synthetic application of tetrahydroborates in the reductive amination of aldehydes and ketones. At the same time, in view of the high cost of tetrahydroborates, the large scale industrial production of amines by this procedure is not very promising.

(e) Reductive Amination of Carbonyl Compounds in the Presence of Complex and Catalysts

The reductive amination of carbonyl compounds in the presence of complex catalysts has been so far inadequately investigated. In a number of studies[247-252] the reductant was the complex tetracarbonylhydroferrate $[HFe(CO)_4]^-$ in an equimolar amount relative to the carbonyl compound. The reaction was carried out in an atmosphere of CO at room temperature in alcohol; $[HFe(CO)_4]^-$ was obtained *in situ* by the reaction of $Fe(CO)_5$ with alkali. Under these conditions, Watanabe et al. synthesised *N*-alkyl- and *N*-aryl-glycines from glyoxylic acid[249] and *N*-substituted piperidines from glutaraldehyde[250] and also carried out the amination[247] of acetone by isopropylamine (Table 9, No.1), of butanol by aniline (Table 9, No.2), and of cyclohexanone by cyclohexylamine (Table 9, No.3). *N,N*-Dimethyl-, *N,N*-diethyl, *N,N*-dipropyl-, *N,N*-dibutyl-, *N,N*-ethylmethyl-, and other *N,N*-substituted anilines have been obtained from aniline and the corresponding aldehydes in quantitative yields[248]. The reaction has been shown to proceed via *N*-substituted anilines[251].

Certain aromatic amines have been alkylated by formaldehyde under analogous conditions[252]. The yield of the corresponding secondary and tertiary amines was ~80%. The authors suggested that the reaction proceeds via the formation of intermediate Schiff bases, which are reduced irreversibly by $[HFe(CO)_4]^-$ to the corresponding amines. The $[HFe(CO)_4]^-$ ion cannot be regarded as a catalyst, since it is active only in stoichiometric amounts.

The reductive amination of aldehydes and ketones by ammonia and primary and secondary amines has been investigated[253] in the presence of catalytic amounts of cobalt and rhodium carbonyls at 100–160 °C and $p_{H_2} = 100$–300 atm. Amines were obtained in very high yields in this homogeneous process. Thus (2-ethylhexyl)isopropylamine (Table 9, No.4), cyclohexylisopropylamine (Table 9, No.5), and benzylmethylamine (Table 9, No.6) have been obtained from α-ethylhexanal and isopropylamine, from cyclohexanone and isopropylamine, and from benzyl methyl ketone and ammonia respectively.

A cobalt cyanide complex has been used[254,255] as a catalyst of the homogeneous reductive amination of benzylacetone (Table 9, No.7) and benzylacetophenone (Table 9, No.8). Previously aminoacids had been obtained[256-258] from α-hydroxyacids with the aid of this catalyst.

In enzymatic catalysis reductive amination constitutes the main pathway for the conversion of ammonia into compounds with α-amino-groups[259]. It is to be expected that compounds which are models of enzymes will prove active in the reductive amination reaction. Indeed it has been reported[260] that *N*-methylaniline can be obtained from aniline and formaldehyde under mild conditions in the presence of vitamin B_{12r} or its model—diaquocobaloxime(II).

It has been found[261] that hydridobis(dimethylglyoximato)-aquorhodium(III) is a catalyst of the reductive amination of formaldehyde by aniline and of cyclohexanone by ammonia (Table 9, No.9). At the same time, in contrast to claims by Schrauzer and Windgassen[260], it has been shown[261] that in the presence of diaquocobaloxime(II) the process is not catalytic and stops at the stage involving the formation of the complex

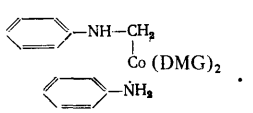


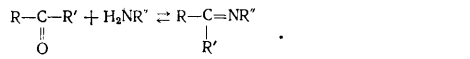
Table 8. Reductive amination of aromatic carbonyl compounds.

No.	Carbonyl compound	Catalyst	*t*, °C	*p*, atm	Product	Yield, %	Remarks	Refs.
1	Phenylacetone	Raney Ni	20	1	2-amino-3-phenylpropane	85	—	153
2	Benzylacetone	Raney Ni	20	1	2-amino-4-phenylbutane	67	—	153
3	Acetophenone	Raney Ni	110—130	25	α-phenylethylamine	90.7	—	215
4	Acetophenone	Raney Ni	110—150	50—150	α-phenylethylamine	94	—	216
5	2,5-Dimethoxyphenylacetone	Raney Ni	90	70	2-amino-3-(2,5-dimethoxyphenyl)propane	95	aminating agent—CH_3COONH_4	218
6	1-Butanal	(5% Rh)/Al_2O_3	75	50	N-butylaniline	93	aminating agent—aniline	190
7	Acetophenone	PtO_2	20	1—3	α-phenylethylamine	69	—	148
8	Octadecanone	Pt	26	—	2-benzylaminooctadecane	89.9	aminating agent—benzylamine	222
9	Acetone	(5% RhS)/C	140	80	*N,N*-diisopropyl-1,5-naphthylenediamine	96	aminating agent—1,5-naphthylenediamine	233
10	Ketones	PdS	150—200	110—150	*N,N*-dialkyl-*p*-phenylenediamines	60—90	aminating agent—*p*-phenylenediamine	232
11	Ketones	Pt/Al_2O_3+0,005÷2% S	120—175	14—105	*N,N*-dialkyl-*p*-phenylenediamines	50—90	aminating agent—*p*-phenylenediamine	235
12	Acetone	Re_2S_7	140	80	*N*-isopropylaniline	90	aminating agent—aniline	237

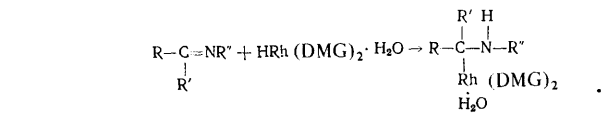
Table 9. Reductive amination of aldehydes and ketones in the presence of complex compounds.

No.	Carbonyl compound	Complex compound	*t*, °C	*p*, atm	Product	Yield, %	Remarks	Refs.
1	Acetone	$Fe(CO)_5$	20	1	diisopropylamine	93	amination with isopropylamine in an atmosphere of CO	247
2	1-Butanal	$Fe(CO)_5$	20	1	*N*-n-butylaniline	100	aminating agent—aniline; in an atmosphere of CO	247
3	Cyclohexanone	$Fe(CO)_5$	20	1	dicyclohexylamine	100	aminating agent—cyclohexylamine; in an atmosphere of CO	247
4	α-Ethylhexanal	$Rh_6(CO)_{16}$	110—160	100—300	(2-ethylhexyl)isopropylamine	98	aminating agent—isopropylamine; in an atmosphere of CO and H_2	253
5	Cyclohexanone	$Rh_6(CO)_{16}$	110—160	100—300	cyclohexylisopropylamine	100	ditto	253
6	Benzyl methyl ketone	$Co_2(CO)_8 + P(C_4H_9)_3$	150—180	100—300	benzylmethylamine	69	reaction in an atmosphere of H_2 and CO	253
7	Benzylacetone	cobalt cyanate complex	70	50	2-amino-4-phenylbutane	73.2	ditto	255
8	Benzylacetophenone	cobalt cyanate complex	70	50	2-amino-1,4-diphenylbutane	53.3	" "	255
9	Cyclohexanone	$HRh(DMG)_2.H_2O$	45	1	cyclohexylamine, dicyclohexylamine	74 9	yield w.r.t. cyclohexanone employed	261

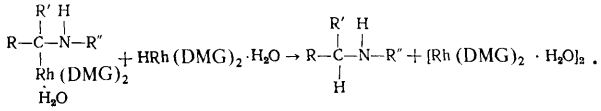
It has been postulated[261] that the reaction proceeds via the following mechanism: there is initial condensation of the carbonyl compound with ammonia or the amine:



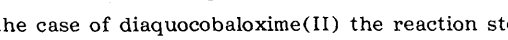
The resulting imine or Schiff base reacts with the catalyst to form an intermediate complex:



The complex reacts with a new catalyst species and forms amines:



The resulting dimer is reduced in its turn by hydrogen with formation of two molecules of the initial catalyst:



In the case of diaquocobaloxime(II) the reaction stops in the second stage. In this connection one may note that, in a number of other reduction reactions, rhodium complexes proved to be more active than the corresponding cobalt analogues[262].

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It is seen from the data presented that considerable advances have been made in recent years in the catalytic amination of carbonyl compounds and alcohols. Thus, on the basis of developments in recent years, a large-scale industrial production of aniline from phenol has been established in the USA;[263] many valuable medicinal drugs have been obtained[6] by the reductive amination of various carbonyl compounds.

Despite the fact that the vast majority of amines are obtained nowadays by traditional methods (from alcohols or halogeno-compounds or by the reduction of nitro-compounds), in the immediate future the reductive amination of carbonyl compounds may become one of the main procedures for the synthesis of amines. This appears possible primarily because of the considerable advances in the field of oxo synthesis (see, for example, Alekseeva et al.[264]), which made it possible to reduce the cost of carbonyl compounds. Many aldehydes and ketones are now cheaper than the corresponding alcohols[265].

The most important task at the present time is the selection of highly effective and selective catalysts for the reductive amination of carbonyl compounds, because only on the basis of such catalysts is it possible to set up a modern waste-free industry. Great expectations are associated with the employment of the principles of molecular catalysis[266]. The first studies on the use of complex catalysts for reductive amination give rise to the hope that in their presence it will be possible to carry out the process under mild conditions and extremely selectively.

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