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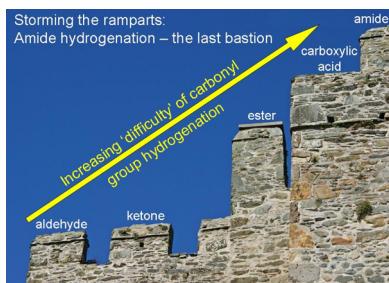
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Review of Methods for the Catalytic Hydrogenation of Carboxamides

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1. INTRODUCTION

Reduction reactions are among the simplest transformations in organic chemistry, and are extensively used in both laboratory and industrial processes.^{1,2} Although reduction of a carbonyl functionality to the corresponding alkyl group is by far the most commonly used and relatively straightforward, hydrogenation of carboxylic acids and their derivatives, for example, carboxylate esters and carboxamides (amides), proves considerably more difficult. Traditionally such reactions are carried out using stoichiometric (and in practice, excess) quantities of hydride reagents, either lithium aluminum hydride (LiAlH₄) at room temperature, or sodium borohydride (NaBH₄) at higher temperatures.^{3–7} Although effective, principal disadvantages of these reagents are the coproduction of stoichiometric amounts of waste metal salts, which require separation and disposal, and their universal reducing properties, which result in incomplete control over regioselectivity during reduction. The latter represents a major problem that is especially pertinent to multistage syntheses, in which other reactive functional groups are often present in the molecules of interest. An alternative approach involving catalytic reduction with H₂ is obviously more attractive, in principle providing not only considerably more atom efficient, but also more environmentally and economically acceptable solutions to the problem; moreover, heterogeneous catalysts can frequently be recycled without significant loss of activity. Although the catalytic hydrogenation of aldehydes and ketones is well documented in the literature, and used commercially, the reduction of carboxylic acids and their derivatives under mild reaction conditions presents much

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more severe challenges, with the relative order of difficulty, originally determined by McAlees and McCrindle,⁸ as amide > carboxylic acid > ester > anhydride > ketone \approx aldehyde > acid chloride, a trend that also parallels the increasing order of susceptibility toward nucleophilic attack at the carbonyl group. Thus, the least electrophilic amide functional groups represent the most extreme difficulty with respect to reduction.

Selective catalytic hydrogenation of a carboxamide to the corresponding amine clearly represents the simplest route to this important class of compound. With a production capacity in excess of 100 000 tonnes per year, amines are of significance not only as bulk chemicals, but also as high value intermediates in organic synthesis. They are used in the manufacture of plastics, surfactants, textiles, dyes, agrochemicals, and in the paper industry, and as intermediates in the fine chemicals industry in general. Although direct catalytic hydrogenation of amides was first reported over 100 years ago, early processes involved the use of both very high reaction temperatures and hydrogen gas pressures, and were typified by generally low carboxamide conversions and poor amine product selectivity. These disadvantages acted as a disincentive to further pursue this important area. Nevertheless, during the last 20 years, developments in catalytic science have led to significant reductions in the severity of reaction conditions required for hydrogenation. These developments, which have involved the discovery and use of new "second generation" catalysts, have provided both improved activity and reaction selectivity under much more readily accessible conditions of pressure and temperature. This has resulted in a very recent renaissance of interest in this area of catalysis.

There appears to be no comprehensive and critical assessment of catalytic methods for the hydrogenation of amide functional groups in the primary scientific literature. The most detailed account of heterogeneous catalyst systems refers primarily to the use of Cu–Ba–Cr oxide catalysts under the initial very severe reaction conditions.⁹ In addition, an excellent review entitled "Catalytic Transformations of Carboxylic and Carbonic Acid Derivatives Using Molecular Hydrogen", containing a short section on the hydrogenation of amides (carboxamides) using homogeneous-based systems, has appeared,¹⁰ together with a second very recent commentary, which appeared while this work was approaching completion, in which the emphasis is also on homogeneous (and hydrosilylation) methods of reduction.¹¹ Neither represent a critical and comprehensive assessment of the overall field of carboxamide hydrogenation. Furthermore, largely because of the previous paucity of research, very little is known about the possible reaction mechanisms involved, particularly in relation to factors that control (i) selective hydrogenation of a carboxamide to the corresponding amine, and (ii) reaction selectivity with respect to C–O versus C–N bond scission, the latter alternative leading to the formation of the generally less desired alcohol products. It is therefore timely to redress these deficiencies with the specific aim of stimulating further work in this still very challenging area. Although utilized extensively, there is also surprisingly little detailed information (and particularly understanding) concerning mechanisms of reduction using hydride reagents. Consequently, both as a prelude to catalytic methods, and for perspective, a resume of this approach has been included.

2. PROPERTIES OF THE CARBOXAMIDE GROUP

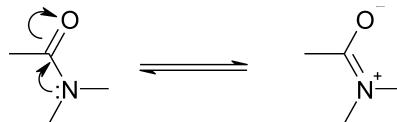
Amides are derivatives of carboxylic acids in which the hydroxyl group is replaced by an amino group and are usually formed simply via the reaction of carboxylic acids with amines (Scheme 1).¹² The common amides are solids at room temperature, with

Scheme 1. Amide Formation from Carboxylic Acids



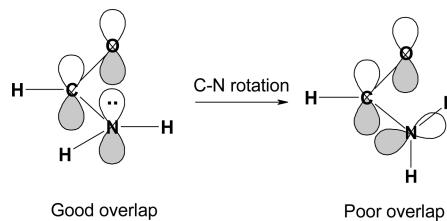
only the simplest amide HC(O)NH_2 , formamide, and DMF, its *N,N*-dimethyl derivative, liquids; all have low vapor pressures and very high boiling points. The general resistance of amides toward chemical reaction, and particularly reduction, is associated with an electronic stabilization, which is attributed to the difference in electronegativity between the nitrogen and oxygen atoms. This leads to a charge contribution from both O (δ^-) and N (δ^+) atoms, thereby allowing the amide group to be formally expressed in either a neutral or a zwitterionic configuration (Scheme 2).¹³ The presence of the donor

Scheme 2. Neutral and Zwitterionic Configurations of the Amide Group



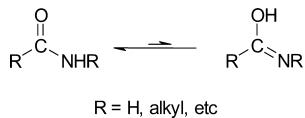
$\text{R}_2\text{N}-$ ($\text{R} = \text{H}$, alkyl, aryl, etc.) functionality adjacent to the acceptor carbonyl group of the amide contributes to a remarkably short C–N bond as compared to those in amines; conversely, the C–O bond length has been calculated to be longer than those found in carboxylic acids, esters, and ketones.¹⁴ The nature of R clearly influences the overall inductive effect of $\text{R}_2\text{N}-$, for example, in the order $\text{CH}_3 > \text{C}_6\text{H}_5 > \text{H}$, with $(\text{CH}_3)_2\text{N}-$ being the most strongly donating, resulting in minor variations in C–N bond length. The partial double-bond character of the C–N bond, which is closer to 127 pm, the length of a typical C=N bond, than the 149 pm of a single C–N bond⁴ has been used to account for the rigidity of the amide group, with further support from a crystallographic and ab initio investigation.¹⁵ Donation of the nitrogen lone pair into the C p-orbital is clearly of overriding importance, and the combination of sp^2 hybridized $\text{R}_2\text{N}-$ and carbonyl groups results in a strong preference for planarity. Only then are the three p-orbitals aligned to overlap (Scheme 3).¹⁶ This is a restraint that is also of far-reaching significance in the structure of proteins, which are polyamides. If a carboxamide group is

Scheme 3. Bonding of the Amide Group, Illustrating the Strong Preference for Planarity



artificially distorted by incorporating it into a bicyclic ring system, the normal conjugation cannot take place and the carbonyl group is ketone-like. Wiberg et al. have proposed that the oxygen atom is a spectator to rotation, although it induces a positive charge on the carbon atom of the amide carbonyl group.¹⁷ The significant energy barrier to rotation of the C–N bond has been determined by NMR spectroscopy to be 75–80 kJ mol⁻¹,^{18,19} that is, approximately a quarter of the bond strength of a single C–N bond (308 kJ mol⁻¹). The dipole moment of formamide has been found experimentally to be 3.71 D at an angle of 39.6° to the C–N bond,²⁰ giving rise to the generally strong hydrogen-bonding character associated with amides,²¹ a factor that may also be relevant to the resistance of amides toward chemical reaction, particularly reduction. Moreover, it is pertinent to note the existence, for primary and secondary amides, of the equilibrium between an amide and its iminol tautomer (Scheme 4). Although strongly

Scheme 4. Amides and Their Iminol Tautomers



disfavored (for secondary amides, an equilibrium constant of $K = 10^{-8}$ has been estimated for this amide–iminol conversion²²), “hydrogen bond-stabilized” iminols could still comprise kinetically significant intermediates during amide hydrogenation (see section 6.1).

3. NONCATALYTIC METHODS OF CARBOXAMIDE REDUCTION

A summary of the general characteristics of noncatalytic methods for the reduction of amides is provided in Table 1.

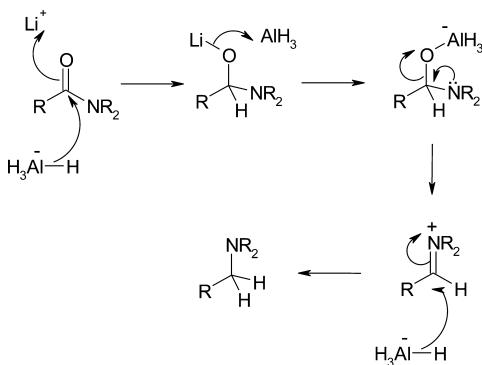
3.1. LiAlH₄ and NaBH₄

The main group metal hydrides LiAlH₄ and NaBH₄ are currently the most practical choice favored by synthetic chemists for the transformation of amides into amines,^{6,7} avoiding the vigorous conditions required by early catalytic systems. Use of the former, a strong Lewis acid, has been known for over 65 years,^{23,24} and although a universal reducing agent, particularly for carbonyl functionalities, some control over reaction selectivity is provided by the fact that alkenes are not usually susceptible to reduction. However, in the majority of cases, all other functional groups susceptible to reduction are also readily reduced; moreover, these reagents are hazardous, suffering from both air and moisture sensitivity. Although unsubstantiated, reduction with LiAlH₄ seems generally accepted to proceed as shown in Scheme 5.⁵ In practice, excess quantities of LiAlH₄ are used, but the exact stoichiometric requirements of the reaction depend on the degree of *N*-substitution of the amide, tertiary amide substrates consuming 0.5 mol of LiAlH₄ for each equivalent of amide, with an additional 0.25 mol of LiAlH₄ required for each active hydrogen in the case of secondary (i.e., monosubstituted) and primary (i.e., unsubstituted) amides.²⁵ Providing that they are not excessively hindered, tertiary (disubstituted) amides are therefore reduced most rapidly.²⁶ Hinman²⁷ has attributed the lower activity of primary and secondary amides to the formation of aluminum enolate-type species by replacement of active hydrogen atoms (Scheme 6), a stabilization that is clearly not applicable to tertiary amides.

Table 1. Summary of Noncatalytic Methods Used for the Reduction of Acyl Functional Groups

reducing agent	reaction conditions	functional groups reduced	advantages	disadvantages	refs
LiAlH ₄	ambient	carboxamides, acids, esters, acyl halides, aldehydes, ketones, nitriles, no reduction of alkenes	mild conditions, efficient	stoichiometric reaction, limited selectivity, hazardous, difficult to handle, workup/waste disposal	23–31
NaBH ₄	ambient	aldehydes, ketones, acyl halides	mild conditions, less hazardous than LiAlH ₄	stoichiometric reaction, dehydration to nitrile (for primary amides), workup/waste disposal	32, 36–41
NaBH ₄	>100 °C	all acyl groups, nitriles	efficient, selective, quantitative yields of amine	stoichiometric reaction, higher reaction temperatures, workup/waste disposal	33–35
B ₂ H ₆ /THF	ambient	preferred for carboxamides, carboxylic acids, and nitriles	mild conditions	stoichiometric reaction, hazardous/pyrophoric, workup/waste disposal	45–50
electrolytic reduction	ambient, H ₂ , e ⁻	all groups	less energy intensive than hydrogenation using H ₂ (until recent developments)	stoichiometric reaction, limitation to substrates generating aryl radicals, product selectivity, energy intensive	51–58
				indirect, multistage, stoichiometric, waste disposal costs	61, 62

Scheme 5. Standard Representation of the Reaction Pathway for the Reduction of Amides Using LiAlH_4 ^a



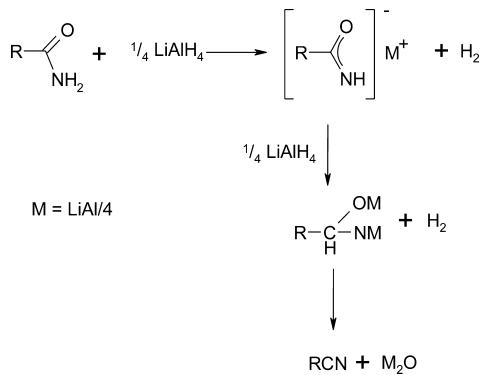
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Scheme 6. Replacement of Active Hydrogen in Primary and/or Secondary Amides by $[\text{AlH}_4]^{-27}$



When less than stoichiometric quantities of LiAlH_4 are used for the reduction of primary amides, the corresponding nitrile may be formed (Scheme 7).²⁸ Moreover, high selectivity

Scheme 7. Nitrile Formation during the Reduction of Primary Amides Using LiAlH_4 ²⁸

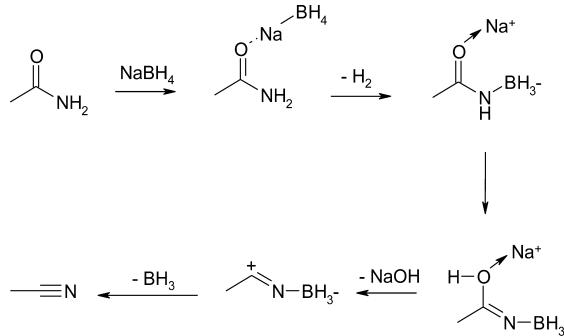


toward the nitrile is also observed with amides containing electron-rich quinoline systems.²⁹ If traces of water are present, partial reduction of amides to aldehydes over LiAlH_4 can also comprise an undesirable competing reaction.³⁰ Hydrolysis to the alcohol product has also been reported for secondary amide substrates.^{25,31}

Although effective, the use of the much milder reducing agent NaBH_4 requires elevated temperatures and long reaction times for complete amide conversion. Also, dehydration of primary amides to the corresponding nitrile is again viable at room temperature.³² Reaction selectivity, in pyridine under reflux, is dependent on the degree of amide *N*-substitution: primary amides yield nitriles, secondary amides are unreactive, while tertiary amines give a moderate yield of the corresponding amine (see also section 6.4.4).³³ It is noteworthy that secondary amides generally appear to offer greater resistance to reduction than either primary or tertiary derivatives. This trend has recently been investigated by

Pittman et al., using computational methods to calculate the transition state energies.³⁴ A postulated mechanism for borohydride-mediated dehydration of acetamide to acetonitrile is shown in Scheme 8. Because the nitrogen atom must

Scheme 8. Proposed Mechanism for Acetonitrile Formation from Acetamide Using NaBH_4 ³²



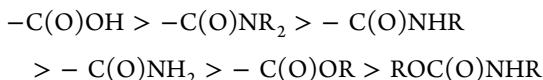
accommodate both a proton and a BH_3 group, this pathway is however inaccessible to secondary or tertiary amides. The first example of a successful NaBH_4 -mediated primary amide reduction (benzamide to benzylamine), using diglyme as solvent at 162 °C, has also been reported by Pittman et al.³⁵

The addition of Lewis acids to NaBH_4 was first reported by Brown et al.,³⁶ who noted the use of $\text{NaBH}_4/\text{AlCl}_3$ for the reduction of tertiary amides to their corresponding tertiary amines. However, the availability of active protons in secondary and primary amides was found to result in the formation of the corresponding amine salts. Since the early 1960s, there have been numerous reports of modified metal hydride systems for the facile conversion of amides to amines at room temperature. These include the addition of $[\text{Et}_3\text{O}]^+[\text{BF}_4]^-$,³⁷ CoCl_2 ,³⁸ Co_2B ,³⁹ POCl_3 ,⁴⁰ or R_2SeBr_2 ,⁴¹ to NaBH_4 , and the use of $\text{Zn}(\text{BH}_4)_2$,⁴² and $\text{LiBH}_4/\text{Me}_3\text{SiCl}$.⁴³

Because tertiary amides are known to be reduced more rapidly than secondary amides (see above), in molecules containing mixed functionalities, selective hydrogenation of the latter functional group in the presence of the former clearly proves difficult. Lee and Clothier⁴⁴ found that protection of the N–H bond by reaction with an oxycarbonyl CBZ (CBZ = carboxybenzyl) moiety led to the formation of an activated amide, the carbonyl group of which was more susceptible to reduction with LiBH_4 or NaBH_4 , producing a hemiaminal (carbinolamine), while the carbonyl of the tertiary amide group remained unchanged. Deprotection and hydrogenation then led to products in which the tertiary amide functional group remained intact.

3.2. Boranes

Boranes have been shown to provide a clean alternative method to the use of LiAlH_4 and NaBH_4 for amide reduction. As very mild reducing agents, they can be used in the presence of other sensitive functional groups such as ketones or esters.^{45,46} Moreover, because no C–N bond cleavage occurs, near quantitative yields of the amine may be obtained. They are particularly effective for the reduction of hindered tertiary amides,⁴⁷ reaction rates being lower with primary amide substrates.⁴⁸ A general order of ease of functional group reduction using boranes has been established as:



and used by Roeske et al.⁴⁹ to reduce peptides. Variants such as $\text{BH}_3\text{-THF}$, a borane–methyl sulphide complex, and $\text{NaBH}_4\text{-BF}_3$ have also been successfully applied to amide reduction in situations where LiAlH_4 is unsatisfactory.⁵⁰ In most cases, heating the reaction mixture in a solvent such as THF under reflux is required, giving yields in the order of 60–90%.

Nevertheless, notwithstanding progressive improvements in activity for the reduction of carboxamides, all of the reagent hydride systems summarized in sections 3.1 and 3.2 suffer the clear economic and environmental disadvantages outlined in section 1.

3.3. Electrochemical Routes

Electrochemical reduction of carboxamides, $\text{RC(O)NR}'\text{R}''$, has been known since the 1940s, yielding aldehydes (RCHO), amines ($\text{RCH}_2\text{NR}'\text{R}''$), or primary alcohols (RCH_2OH) depending on the nature of the amide substrates and reaction conditions.^{51–54} Aldehyde formation, followed by further reduction to alcohol, is assumed to occur via rapid fragmentation of hemiaminal (carbinolamine) intermediates (see section 6.1). Electrochemical reduction suffers from a significant limitation in that it is restricted to amides that form stable anion radicals, for example, aromatic amides; with nonaromatic amides the only products are alcohols⁵⁵ or aldehydes.⁵⁶ Cathodic reduction of the carbonyl group is thus only possible when it is directly linked with the aryl radical.⁵⁷ As an example, benzamide can be reduced to benzylamine in 85% selectivity at a lead cathode using a 1:1 $\text{H}_2\text{SO}_4\text{/EtOH}$ electrolyte; minor products comprise the corresponding alcohol⁵⁸ and aldehyde.²¹ The requirements outlined above severely limit any significant applications of amide reduction on the large scale. Moreover, a general conclusion reached in the early 1980s, that notwithstanding energy savings possible through improved reactor design, electrochemical routes will never be viable if acceptable product selectivity may be obtained via standard catalytic routes, is still relevant today.^{59,60} Given that electrochemistry and electrochemical reductions date back over two centuries, history seems to support this point.

3.4. Other Noncatalytic Routes

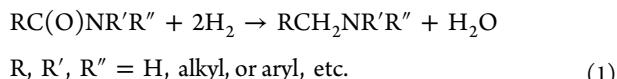
Alternative noncatalytic routes, such as reaction of the amide with halogens or hypohalites in the presence of alcohols, followed by either hydrolysis or the application of reductive methods, allow conversion of the intermediate reaction products into amines (see, for example, refs 61,62). Nevertheless, in addition to being noncatalytic, these routes also suffer from the disadvantages of multistage processing, expensive raw materials, and excessive waste disposal costs.

Recently, two significant metal-free reagent methods for the controlled and chemoselective reduction of tertiary and secondary amides under ambient conditions have been reported.^{63,64} For the former, Hantzsch ester hydride is used as a mild reducing agent for the reduction of tertiary amides previously activated by trifluoromethanesulfonic anhydride, giving the corresponding amine in good yields.⁶³ Addition of a silane such as HSiEt_3 (see also section 5.2) allows the highly chemoselective reduction of a range of secondary amide substrates to the corresponding secondary amines in 70–90% yields.⁶⁴ Moreover, both methods have been found to tolerate

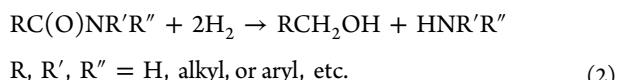
various functional groups that are usually reactive under reducing conditions. In addition, use of a combination of triflic anhydride amide activation with a weak base such as 2-fluoropyridine allows the product distribution from secondary amides to be tuned to give good selectivity toward imines and/or aldehydes.

4. HETEROGENEOUS CATALYTIC HYDROGENATION OF CARBOXYAMIDES

The simple stoichiometry for the reduction of a carboxamide to the corresponding amine (eq 1), involving C–O bond cleavage, requires 2 equiv of molecular hydrogen, one of which serves for hydrogenolysis of the carbonyl oxygen as water.



Thus, the commonly used term “hydrogenation” is not totally representative of the individual processes involved. An alternative reaction pathway (eq 2), and one that is less desirable in the context of selective hydrogenation of the amide directly to the corresponding amine, concerns C–N rather than C–O bond cleavage with the formation of an alcohol and the elimination of ammonia (for R', R'' = H) or primary/secondary amines.

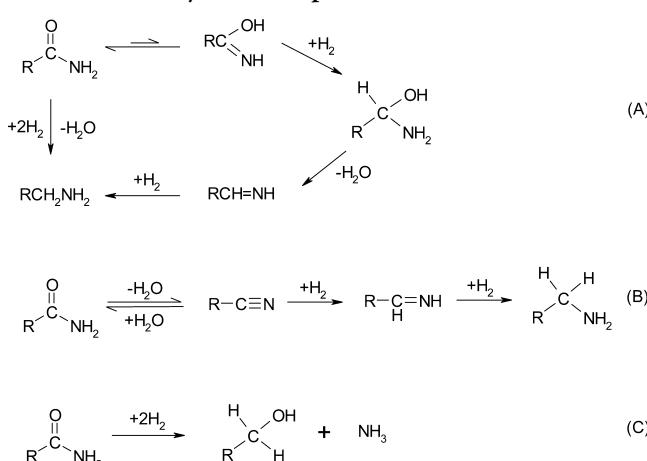


Nevertheless, this simplistic picture of amide hydrogenation is frequently not realized in practice because of the accessibility of competing side reactions of lower activation energies. In truly seminal work, decades before the term itself came into common parlance, both primary bond hydrogenolysis steps in the reduction of amides (eqs 1 and 2) were unequivocally identified and substantiated by Wojcik and Adkins.^{65,66} In addition, a number of side reactions leading to loss of product selectivity were also identified. Such side reactions, most commonly observed with secondary and tertiary carboxamides, were found to be dependent on various factors, including the degree of N-substitution, reaction pressure and temperature, solvent, and type of catalyst used. From an analysis of reaction products from the reduction of N-alkyl, N-aryl, mono-, and disubstituted amides, they were found to comprise both primary/secondary amines and hydrocarbons, arising from hydrogenolysis of R'–N, R''–N, and/or C–N bonds, respectively (cf., eqs 3–7).



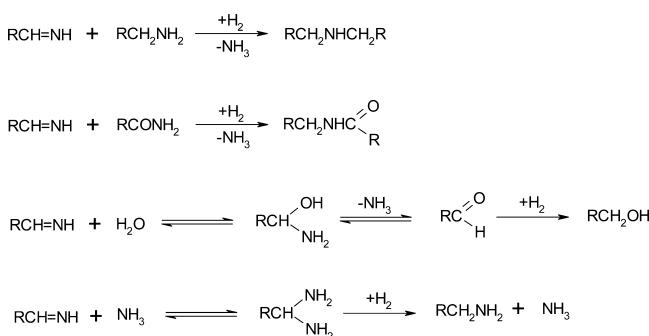
The identification and substantiation of these alternative competing reaction pathways clearly demonstrated the need for selectivity control as an aspect of high priority in any useful catalytic amide hydrogenation process (see also Schemes 9 and 10).

Scheme 9. Primary Amide Hydrogenation: Alternative Reaction Pathways to Principal Products^a



^aPathways (A) and (B) involve C–O bond cleavage, and pathway (C) involves C–N bond cleavage.

Scheme 10. Primary Amide Hydrogenation: Reaction Pathways to Observed Byproducts, Highlighting the Significance of the Postulated Imine Intermediate^a



^aA role for ammonia, liberated during imine hydrolysis and secondary amine formation, in enhancing primary amine formation is also evident.

4.1. Early Developments

Initial reports of catalytic hydrogenation of carboxamides concerned the use of traditional base metal (Co, Ni, Cu) and metal oxide (Cr) catalysts, all of which required very severe reaction conditions. Some typical results and product distributions associated with these are summarized in Table 2, entries 1–7, Table 3, entries 1, 2, and Table 4, entries 1–5.

The first reference to catalytic amide hydrogenation was that of Maihle⁶⁷ in 1908, in which the vapor phase hydrogenations of acetamide, $\text{CH}_3\text{C}(\text{O})\text{NH}_2$ (bp 221 °C), and propionamide, $\text{C}_2\text{H}_5\text{C}(\text{O})\text{NH}_2$ (bp 213 °C), over a Ni catalyst were reported to yield mixtures of the corresponding primary and secondary amines, RNH_2 and R_2NH ($\text{R} = \text{C}_2\text{H}_5-$ and $n\text{-C}_3\text{H}_7-$, respectively), although neither conversions nor product yields were quantified. In view of the low volatility of all amides (cf., section 2), the use of truly vapor phase conditions seems remarkable (see also section 4.6).

Subsequently, a German patent claimed the “selective” hydrogenation of amide functional groups using activated Co and Ni catalysts at 200 bar H_2 , 230, 270 °C, respectively, over a reaction time of 8 h.⁶⁸ Substrates included several long-chain primary amides such as stearamide [octadecanamide, $\text{C}_{17}\text{H}_{35}\text{C}(=\text{O})\text{NH}_2$] and lauramide [dodecanamide, $\text{C}_{11}\text{H}_{23}\text{C}(\text{O})\text{NH}_2$], both of which were hydrogenated primarily to the respective secondary amines, for example, *N*-lauryldodecylamine, although once again no detailed product quantifications were provided. Benzamide yielded a mixture of benzylamine and di(benzyl)-amine, in approximately equal amounts, C–O bond hydrolysis occurring in preference to reduction of the aromatic ring, possibly the consequence of high reaction temperatures favoring retention of aromatization (cf., Table 2, entries 1, 2). Similar results under comparable reaction conditions were also described in two DuPont patents, the former also describing the use of Ni catalysts with substrates including lauramide, phthalimide, acetanilide, and succinimide.⁶⁹ The latter provided the first example of the use of an intriguingly named “combined hydrogenation–dehydration catalyst” containing Zn, Cu, and Cr, for the coreaction/hydrogenation of carboxylic acid derivatives with ammonia, primary, and/or secondary amines,⁷⁰ an aspect that has been developed further over 65 years later (see sections 4.2.3.3 and 4.6).

Nevertheless, the key early developments were without doubt associated with the pioneering work of Adkins et al., using copper–chromium oxide catalysts and numerous primary, secondary, and tertiary amide substrates.^{65,66,71–73} Under typical reaction conditions of 200–300 bar H_2 and 250 °C, the hydrogenation of primary amides resulted in the secondary amine comprising the major product; for example, heptanamide was reduced to *n*-heptylamine (39%) and di(*n*-heptyl)amine (58%), with similar behavior noted using dodecanamide (Table 2, entries 3, 4).^{65,66} A high catalyst loading (typically in excess of 15 mol % catalyst per mol amide) was found necessary to counteract the strong adsorption of the amine product on the catalyst surface. Other side reactions, in addition to those depicted in eqs 2–7, were also found to accompany the severe reaction conditions required for high conversions over copper–chromium oxide catalysts. Thus, with mono- and disubstituted amides, cleavage of C–N bonds was shown to result in alcohol formation (cf., eq 2), while cleavage of C–O bonds, especially in the case of secondary amides, yielded hydrocarbons. These cleavage reactions yielded NH_3 and H_2O as coproducts, the presence of which led to the possibility of further secondary reactions such as hydrolysis, ammonolysis, or aminolysis of the starting amide. In attempts to counteract these side reactions, very short reaction times were used as standard.^{65,66}

The preparation of these catalysts, typically containing 33–67 wt % copper and 12–30 wt % chromium, was described in detail by Adkins et al.^{71,73} In light of experience from the use of these catalysts for the hydrogenation of esters,⁷³ the presence of additional Ba (also Ca or Mg)-containing compounds in the copper–chromium oxide catalysts proved beneficial in either inhibiting, or at least retarding, reduction of the catalyst during reaction.⁷¹ The nature and properties of these catalysts were further described by Adkins et al.⁷⁴ In a later paper, it was implied that standard copper–chromium oxide catalysts were actually more effective for the hydrogenation of amides,⁷⁵ in contrast to the section in Nishimura,⁹ which referred almost exclusively to the use of Cu–Ba–Cr catalysts. Also, in some cases it was demonstrated that hydrogenation of certain unsubstituted amides over Cu–Ba–Cr catalysts led to alcohol rather than amine as a major product.⁷⁶ Similar catalysts were also used for the selective reduction of more complex molecules, including substituted pyrrolidones, piperidones, quinolones, and open-chain amido esters.⁷⁷ Furthermore, to

Table 2. Selected Examples of Catalytic Hydrogenation of Primary Amides: Reaction Conditions, Major Products, Yield (y), Selectivity (s), and Conversion

entry	amide substrates	catalyst components	reaction conditions			products	% yield/ selectivity	% conversion ^b	ref
			bar H ₂	°C	h				
1	C ₁₁ H ₂₃ C(O)NH ₂	Co, Ni	200	230	8	(C ₁₂ H ₂₅) ₂ NH			68
2	PhC(O)NH ₂	Co, Ni	200	270	8	PhCH ₂ NH ₂ (PhCH ₂) ₂ NH			68
3	C ₁₁ H ₂₃ C(O)NH ₂	Cu/Cr	200–300	250	0.8	C ₁₂ H ₂₅ NH ₂ (C ₁₂ H ₂₅) ₂ NH	48y 49y		65, 66
4	C ₆ H ₁₃ C(O)NH ₂	Cu/Cr	200–300	250	7.5	C ₇ H ₁₅ NH ₂ (C ₇ H ₁₅) ₂ NH	39y 58y		65, 66
5	C ₇ H ₁₅ C(O)NH ₂	Cu/Cr	250–330	275–350		C ₈ H ₁₇ NH ₂ (C ₈ H ₁₇) ₂ NH	9y 83y	92	78
6	C ₇ H ₁₅ C(O)NH ₂	Cu/Cr/NH ₃ ^a	250–330	275–350		C ₈ H ₁₇ NH ₂ (C ₈ H ₁₇) ₂ NH	90y 10y	>99	78
7	C ₇ H ₁₅ C(O)NH ₂	Ni/NH ₃	370	280		C ₈ H ₁₇ NH ₂ (C ₈ H ₁₇) ₂ NH	55y 21y		78
8	CH ₃ C(O)NH ₂	ReO ₃	205	200	18	C ₂ H ₅ NH ₂	88y		83
9	PhC(O)NH ₂	ReO ₃	205	220	49	PhCH ₂ NH ₂ PhCH ₃	69y 10y		84
10	H ₂ NC(O) (CH ₂) ₄ C(O)NH ₂	Ru/alumina/NH ₃	100	240–290	12	H ₂ N(CH ₂) ₆ NH ₂	poor selectivity		85
11	C ₂ H ₅ C(O)NH ₂	Pd/Re/graphite/ zeolite 4A	130	200	6	mixture of 1°, 2°, and 3° amines	74% amine selectivity	96	88
12	CyC(O)NH ₂	Ru/Mo	20–100	140–160	16	CyCH ₂ NH ₂ (CyCH ₂) ₂ NH CyCH ₂ OH	85–95s 0–4s 10–13s	95	96
13	CyC(O)NH ₂	Ru/Re	50–100	160	16	CyCH ₂ NH ₂ (CyCH ₂) ₂ NH CyCH ₂ OH	90–95s 0–1s 5–8s	100	97
14	CyC(O)NH ₂	Rh/Mo	50–100	130–160	16	CyCH ₂ NH ₂ (CyCH ₂) ₂ NH CyCH ₂ OH	85–90s 8–9s 0–5s	100	95
15	CyC(O)NH ₂	Rh/Re	50–100	150–160	16	CyCH ₂ NH ₂ (CyCH ₂) ₂ NH CyCH ₂ OH	90s 3s 6s	98	97
16	PhC(O)NH ₂	Ru/Mo	100	160	16	CyCH ₂ NH ₂ CyCH ₂ OH	83s 16s	100	96
17	PhC(O)NH ₂	Rh/Mo	100	160	16	CyC(O)NH ₂ CyCH ₂ NH ₂ (CyCH ₂) ₂ NH CyCH ₂ OH	53s 32s 8s 4s	100 (47)	95
18	C ₃ H ₇ C(O)NH ₂	Ru/Mo	100	160	16	C ₄ H ₉ NH ₂ C ₄ H ₉ OH	77s 22s	100	96
19	C ₃ H ₇ C(O)NH ₂	Rh/Mo	100	160	16	C ₄ H ₉ NH ₂ (C ₄ H ₉) ₂ NH C ₄ H ₉ OH	>35s	100	95
20	(CH ₃) ₃ CC(O)NH ₂	Ru/Mo	100	160	16	(CH ₃) ₃ CCH ₂ NH ₂ (CH ₃) ₃ CCH ₂ OH	40s 60s	100	96

^aSecondary:primary amine selectivity reversed in the presence of ammonia under the same reaction conditions. ^bValues in parentheses correspond to conversions to nonamide products. In these instances, the overall conversion is greater due to reduction of the aromatic ring, but not the amide carbonyl group.

minimize hydrolysis of unreacted amide by the water formed during amide reduction, the use of a solvent such as 1,4-dioxane proved useful as a diluent (see below).

Later, the use of Raney Ni- and copper–chromium oxide-based catalysts for the hydrogenation of caprylamide [octanamide, C₇H₁₅C(O)NH₂] was reported by Guyer et al.⁷⁸ using similar reaction conditions, 250–330 bar H₂ and 275–350 °C for Cu/Cr (Table 2, entries 5, 6) and 370 bar H₂ for Ni (entry 7). In the case of copper–chromium oxide, it was

very clearly demonstrated that the addition of ammonia at the start of the reaction could effectively lead to suppression of secondary amine formation and a reversal of product selectivity in favor of the primary amine in up to a 90:10 product ratio at the highest level of ammonia added (cf., Table 2, entry 6). Addition of ammonia to Raney nickel catalysts under similar reaction conditions (entry 7) was rather less effective in directing the product selectivity in favor of the desired primary amines, thus confirming a general preference for the use of

Table 3. Selected Examples of Catalytic Hydrogenation of Secondary Amides: Reaction Conditions, Major Products, Yield (y), Selectivity (s), and Conversion

entry	amide substrates	catalyst components	reaction conditions			products	% yield/selectivity	% conversion ^a	ref	
			bar H ₂	°C	h					
1	C ₁₁ H ₂₃ C(O)N(H)Cy	Cu/Cr	200–300	250		C ₁₂ H ₂₅ N(H)Cy (C ₁₂ H ₂₅) ₂ NH CyNH ₂ (C ₁₂ H ₂₅)(Cy)NH	62y 24y 15y 16y		65	
2	C ₁₁ H ₂₃ C(O)N(H)Ph	Cu/Cr	200–300	250	3.2	C ₁₂ H ₂₅ N(H)Ph (C ₁₂ H ₂₅) ₂ NH C ₁₂ H ₂₅ NH ₂ PhNH ₂ Ph ₂ NH	37y 2y 14y 29y 5y		65	
3	CH ₃ C(O)N(H)Ph	Re ₂ O ₇	280	170	52	C ₂ H ₅ N(H)Ph PhNH ₂	66y 34y		83	
4	CH ₃ C(O)N(H)Ph	ReO ₃	205	185	31	C ₂ H ₅ N(H)Ph PhNH ₂	71y 29y		84	
5	CyC(O)N(H)CH ₃	Ru/Mo	100	160	16	CyCH ₂ N(H)CH ₃	trace		5	96
6	PhC(O)N(H)CH ₃	Ru/Mo	100	160	16	CyC(O)N(H)CH ₃ CyCH ₂ N(H)CH ₃	85s	100 (15)	96	
7	CyC(O)N(H)CH ₃	Rh/Mo	100	160	16	CyCH ₂ N(H)CH ₃	>80s		45	95
8	CH ₃ (CH ₂) ₂ N(H)C(O)CH ₃ and 47 other examples (see text)	Pd/Re/C	30	160	20	CH ₃ (CH ₂) ₂ N(H)C ₂ H ₅	100s	>99	99	
9	PhCH ₂ N(H)C(O)CH ₃	Pd/Re/C	30	160	20	CyCH ₂ N(H)C(O)CH ₃ CyCH ₂ N(H)C ₂ H ₅	77s 22s	>99 (23)	99	

^aValues in parentheses correspond to conversions to nonamide products. In these instances, the overall conversion is greater due to reduction of the aromatic ring, but not the amide carbonyl group.

classic copper–chromium oxide containing catalysts in amide hydrogenation. This work was also notable for providing the first information on the effects of variation of reaction solvents on carboxamide conversions and product distributions during hydrogenation (see section 4.5), in the absence of any added ammonia. Subsequent developments with copper–chromium oxide catalysts in amide hydrogenation included attempts to develop what were termed continuous “solvent-free” processes, particularly for the reduction of higher alkyl tertiary amides^{79–81} (see also sections 4.2.3.3 and 4.6).

A further advance, which led to a reduction in the standard operating hydrogen pressure requirement associated with copper–chromium oxide catalysts, concerned the observation of cooperative effects when used in tandem with a range of zeolites. A patent assigned to Proctor and Gamble⁸² described the use of a standard copper–chromium oxide catalyst together with a 4A zeolite for the reduction of a tertiary amide such as N,N-dimethyldodecanamide [(CH₃)₂NC(O)R, R = C₁₁H₂₃–, lauryl], at 140 bar H₂ (rather than the hitherto more typical values of 250–350 bar H₂ employed) giving (CH₃)₂NCH₂R in 92% conversion and 81% selectivity (Table 4, entry 2). Comparative figures in the absence of the zeolite were much lower (entry 3), and accompanied by the formation of numerous byproducts arising from reactions of the types shown in eqs 3–7.

Broadbent et al.⁸³ first reported the possibility of amide hydrogenation using Re as a catalyst (2 wt % “rhodium black”), prepared *in situ* from Re₂O₇, for the reduction of acetamide at 312 bar H₂, 217 °C, and 6 h, giving ethylamine in 39% yield, although significant loss of the volatile product due to an autoclave leak was experienced. Subsequently, a more reliable result using a catalyst derived from Re (VI) oxide was reported, giving ethylamine in 88% yield at 205 bar H₂, 200 °C, 18 h

(Table 2, entry 8). This catalyst was also used for the selective hydrogenation of benzamide to benzylamine in 69% yield (and 10% toluene byproduct) at 205 bar H₂, 220 °C, 49 h, with ethanol as solvent (Table 2, entry 9).⁸⁴ Surprisingly, the formation of neither cyclohexylamine nor N-ethyl-substituted secondary or tertiary amine derivatives was reported. The preference for reduction of the amide group rather than the aromatic ring seems surprising under such conditions, and may again be attributed to the high temperatures favoring retention of aromatization (cf., ref 68). These results with Re catalysts represent the first examples of primary amide hydrogenation in which, without recourse to the addition of ammonia, good selectivity to primary rather than secondary amine products was demonstrated. Acetanilide (*N*-phenylacetamide) yielded 66–71% *N*-ethylaniline and 34–29% aniline after 52–31 h reaction times over catalysts derived from Re(VII) and Re(VI) oxides, respectively (Table 3, entries 3 and 4),^{83,84} the longer reaction times relative to the 18 h required for CH₃C(O)NH₂ hydrogenation (Table 2, entry 8) suggesting that secondary amides offer greater resistance to reduction than their primary amide counterparts.

In what probably represents the first example of the use of a platinum group metal in amide hydrogenation was the publication of an ICI patent⁸⁵ in which Ru/Al₂O₃ catalysts were used, with the additional presence of ammonia, for the reduction of hexanedioic diamide (1,4-diamidobutane, adipamide) at 100 bar H₂ and 240–290 °C, to give rather modest selectivities to 1,6-hexamethylenediamine (Table 2, entry 10), for potential applications in nylon manufacture.

Notwithstanding these developments, copper–chromium oxide catalysts, with some modifications, discovered some 80 years ago, have until recently remained the standard system for the heterogeneous catalytic reduction of carboxamides at 250–

Table 4. Selected Examples of Catalytic Hydrogenation of Tertiary Amides: Reaction Conditions, Major Products, Yield (y), Selectivity (s), and Conversion

entry	amide substrates	catalyst components	reaction conditions			products	% yield/ selectivity	% conversion ^a	ref	
			bar H ₂	°C	h					
1	C ₁₁ H ₂₃ C(O)N(C ₂ H ₅) ₂	Cu/Cr	200–300	250	0.5	C ₁₂ H ₂₅ N(H)C ₂ H ₅ (C ₁₂ H ₂₅) ₂ NH	64y 32y		65	
2	C ₁₁ H ₂₃ C(O)N(CH ₃) ₂	Cu/Cr/4A zeolite	140	287	1	C ₁₂ H ₂₅ N(CH ₃) ₂	81s, 72y	92	82	
3	C ₁₁ H ₂₃ C(O)N(CH ₃) ₂	Cu/Cr	140	287	1	C ₁₂ H ₂₅ N(CH ₃) ₂	46s, 17y	47	82	
4	(C ₁₂ –C ₁₄ alkyl)C(O)N(CH ₃) ₂	Cu/Cr/MnO ₂ /DMA	30	235	5	(C ₁₃ –C ₁₅ alkyl)N(CH ₃) ₂ (C ₁₃ –C ₁₅ alkyl) ₂ NCH ₃	92s, 87y 7s	99+	86	
5	(C ₁₂ –C ₁₄ alkyl)C(O)N(CH ₃) ₂	(i) Cu/Cr/NaOCH ₃ (ii) Cu/Cr/NaOCH ₃ /DMA	30	250	3–4	(C ₁₃ –C ₁₅ alkyl)N(CH ₃) ₂	95–96s	95	116	
			10	250	11–12	(C ₁₃ –C ₁₅ alkyl)N(CH ₃) ₂	98–99s	99		
6	CH ₃ C(O)N(C ₂ H ₅) ₂	Re ₂ O ₇	352	245	22	(C ₂ H ₅) ₂ NPh	95y		83	
7	PhC(O)N(CH ₃) ₂	Ru/Mo	100	160	16	CyC(O)N(CH ₃) ₂ CyCH ₂ N(CH ₃) ₂ CyCH ₂ OH	65s 30s 5s	100 (35)	96	
8	CyC(O)N(CH ₃) ₂	Ru/Mo	100	160	16	CyCH ₂ N(CH ₃) ₂ CyCH ₂ OH	73s 27s	30	96	
9	CyC(O)N(CH ₃) ₂	Rh/Mo	100	160	16	CyCH ₂ N(CH ₃) ₂	80s	45	95	
10	C ₂ H ₅ C(O)N(CH ₃) ₂	Ru/Mo	100	160	16	C ₃ H ₇ N(CH ₃) ₂	major product	100	96	
11	N-acetyl piperidine	Rh/Mo	100	160	16	N-ethyl piperidine	95s		94	91, 92, 95
12	N-acetyl piperidine	Ru/Mo	100	160	16	piperidine N-ethyl piperidine	5s 90s		100	96
13	N-acetyl piperidine	Rh/Re	100	160	16	N-ethyl piperidine	10s			
14	N-acetyl pyrrolidine	100 bi- and trimetallic variants (see text)	10	100–160	16	N-ethyl piperidine N-ethyl pyrrolidine	>85s		>80	97
15	N-acetyl pyrrolidine	PtIV/TiO ₂	10	130	16	N-ethyl pyrrolidine	100s, 20y			100
16	N-methyl pyrrolidin-2-one	PtRe/TiO ₂	20	120	24	N-methyl pyrrolidine	99s		>90	101
17	N-acetyl pyrrolidine (and 57 other examples, see text)	Pd/Re/graphite	30	160	20	N-ethyl piperidine	100s		>99	99
18	(C ₂ H ₅) ₂ NC(O)CH ₃	Pd/Re/graphite	30	160	20	N(C ₂ H ₅) ₃	100s		>99	99

^aValues in parentheses correspond to conversions to nonamide products. In these instances, the overall conversion is greater due to reduction of the aromatic ring, but not the amide carbonyl group.

350 bar H₂ and 250–330 °C. As an example of the type of modifications used, a patent by Forquy et al.⁸⁶ claimed the addition of MnO₂ to a standard copper–chromium oxide catalyst to allow hydrogenation of *N,N*-dimethylalkylamides to *N,N*-dimethylalkylamines at reduced operating pressures (range 10–100 bar H₂), also with reduced alkanol formation, although high temperatures in the range 220–280 °C were still required. This work was notable for providing some of the first information on catalyst recycle using copper–chromium (and Mn) oxide systems, with mean amide conversions (98.5%) and amine product selectivities (85.1%) maintained over five reduction cycles. In the absence of MnO₂, product distributions comprised 81% of the desired tertiary amine, 7% secondary amine, and 11% alkanol, at 100% amide conversion. An additional development was the use of minor quantities of an auxiliary dialkylamine source, for example, (CH₃)₂NH (dimethylamine, DMA) as a reagent, added either at the start, or as a second reaction stage, using a recirculating H₂

stream (see also sections 4.2.3.3 and 4.6). This allowed in situ conversion of unwanted alkanol byproduct into the desired amine, thereby improving overall reaction selectivity. In this manner, at >99% amide conversion, up to 92% of the corresponding tertiary amines could be produced at 30 bar H₂ and 235 °C (Table 4, entry 4).

The overall severity of the reaction conditions, often poor product selectivity, and large number of potential byproducts, clearly acted as a deterrent to pursue extensive further work on the direct catalytic hydrogenation of carboxamides. Indeed, even as late as 1991, catalytic amide hydrogenation was referred to as “only for the desperate”!⁸⁷

4.2. Developments during the Past Two Decades

The “desperate” did however continue to make progress in this challenging area, the more recent advances in general being associated with the concept of “bifunctional”, “bimetallic”, or indeed “multimetallic” catalysis, and the recognition that the

presence of two (or more) judiciously chosen different elemental components could lead to synergistic behavior. This has ultimately led to real step changes (a significant decrease) in the severity of reaction conditions required for the hydrogenation of carboxamide functional groups. For example, a BP patent claimed the use of a Pd/Re/high surface area graphite (HSAG)/zeolite 4A combination, dispersed in a solvent such as 1,4-dioxane, for the hydrogenation of amides at 130 bar H₂ and 200 °C. When using propionamide as substrate, the 74% amine product distribution comprised a mixture of primary, secondary, and tertiary amines (see Table 2, entry 11).⁸⁸ In the absence of the zeolite, amide conversion was reduced from 96% to 9%, although with 100% selectivity to mixed amines, the products once again comprising predominantly secondary amines.

Furthermore, although Broadbent et al.⁸³ had previously described the use of Re₂O₇ as a catalyst precursor for the hydrogenation of carboxylic acids under the severe reaction conditions (312 bar H₂, 217 °C, 6 h) typically required by standard copper–chromium oxide catalysts, a significant advance was reported in 1990 by Yoshino et al.⁸⁹ Here, the addition of Os (using OsO₄ as catalyst precursor) to Re₂O₇ led to the generation of a bimetallic Re/Os catalyst,¹⁴ which was found to be active for the reduction of carboxylic acids under considerably milder reaction conditions (25–100 bar H₂, 100–120 °C, 6 h), with highest selectivity toward alcohols being favored at the higher pressures. This catalyst also proved active for the hydrogenation of amides.¹⁴ More recently, Pt/TiO₂ and PtRe/TiO₂ catalysts have also been shown to be active for the hydrogenation of carboxylic acids under similar reaction conditions.⁹⁰

The concept of “bimetallic”, or perhaps more correctly, “bifunctional” catalysis, although until recently unproven in the context of amide hydrogenation, has subsequently led to significant reductions in the severity of reaction conditions, relative to the copper–chromium oxide catalysts, required for the hydrogenation of amide functional groups. A landmark paper by Fuchikami et al.⁹¹ reported the use of catalyst systems prepared from combinations of groups 8–10 transition metals, such as Rh and Ru, with groups 6, 7 transition metals.^{92,93} Although described as “bimetallic” catalysts, they were formed *in situ* under the processing conditions and not characterized by physical techniques. The most active systems were derived from metal carbonyl-containing precursors, for example, Rh₆(CO)₁₆ and Mo(CO)₆, and exhibited improved reducing abilities, with the amine formed at 100 bar H₂, 160 °C, and 16 h reaction time (Table 4, entry 11). During the reduction of *N*-acetylN-ethylS)-*N*-(1-phenylethyl)acetamide, at 100 bar H₂, 120 °C, and 16 h, to give 94% (*S*)-*N*-(1-cyclohexylethyl)ethylamine in 85% ee.⁹³ Nothing was known about the composition of this type of catalytic system, and indeed it has been implied that they were homogeneous in nature.^{91,94} More recent work^{95,96} has revealed a more complete understanding of their detailed nature, advantages, and limitations, led to the ability to operate under milder reaction conditions than those originally indicated, and shown that these catalysts may be recycled without significant loss of either activity or selectivity. Moreover, the knowledge generated during the course of this

work has enabled some initial attempts at the development of a mechanistic picture for amide reduction, hitherto lacking in both stoichiometric hydride-mediated reactions and catalytic systems.⁹⁷

From the limited amount of comparative experimental information available, a qualitative evaluation of the relative ease of amide hydrogenation has revealed the order primary > tertiary > secondary,⁹⁶ a sequence similar to that commonly observed during metal hydride reduction, secondary amides providing the greatest challenge.⁴ This ordering has been exemplified by the behavior of optimum Ru/Mo catalysts toward a representative selection of aliphatic, cyclo-aliphatic, and aromatic primary, secondary, and tertiary amide substrates, including in particular, close derivatives of cyclohexanecarboxamide (CyC(O)NH₂, Cy = cyclohexyl-), as shown in the results summarized in Tables 2–4, which also substantiate the general applicability of Ru/Mo catalysts toward amide reduction.⁹⁶ Furthermore, this family of catalysts may also be applied to the marginally less demanding hydrogenation of carboxylic acids. For example, CyCO₂H was found to undergo 85% conversion to CyCH₂OH and methylcyclohexane (in 75% and 18% selectivity, respectively), with traces of additional coupled products, using a Ru/Mo catalyst (100 bar H₂, 160 °C, 16 h).⁹⁶ Further details of these new developments with bi-, and indeed tri-, metallic catalysts for the hydrogenation of primary, secondary, and tertiary amides are described in sections 4.2.1, 4.2.2, and 4.2.3.

4.2.1. Primary Amides. Selective hydrogenation of primary amides to the corresponding primary amine is not only of greatest commercial significance among all three classes of amide but has also historically presented the greatest difficulty because of the occurrence of side reactions leading to the formation of, among others, secondary and tertiary amine byproducts (see sections 4 and 4.1). Several examples of secondary amines comprising the major component of the product distribution from the hydrogenation of primary amides using, in particular, copper–chromium oxide catalysts have already been provided (see also Table 2, entries 3–6). Although substantive evidence is lacking, these side reactions have been attributed to the formation and high reactivity of imine intermediates during amide reduction, which react readily with the initially formed primary amine (see section 6.1 and Scheme 10).

In contrast to virtually all of the earlier work, the bimetallic catalysts referred to in section 4.2 have been demonstrated, for the first time, to allow the direct hydrogenation of primary amides to the corresponding amines in high selectivity (>85%), without the requirement for the addition of ammonia and/or amines to suppress secondary reactions, particularly when using CyC(O)NH₂ as substrate (Table 2, entries 12–15).^{95–97} These Ru/Mo, Rh/Mo, Ru/Re, and Rh/Re catalysts are effective over a wide range of reaction conditions, within some limiting M:M' stoichiometric ratios. Thus, using Ru/Mo catalysts, this adventitious control of selectivity to the desired product CyCH₂NH₂, with barely detectable evidence of (CyCH₂)₂NH, and only minor amounts of CyCH₂OH, represents a very significant, and presently unique, development in this area of catalysis. Moreover, this exclusive selectivity was retained, at slightly reduced amide conversion, at working pressures as low as 20 bar H₂ (Table 2, entry 12).⁹⁶ Furthermore, high primary amine selectivity was not limited to CyC(O)NH₂ as substrate, with similar selectivity noted using a range of other standard primary amides (Table 2, entries 16, 18, 20) using these Ru/

Mo catalysts. Thus, benzamide, the aromatic analogue of CyC(O)NH₂ that should be more highly activated toward reduction because of the electron-withdrawing nature of the aromatic ring, did indeed display extremely similar behavior in respect to both conversion and selectivity (Table 2, entries 12, 16). With Rh/Mo catalysts, however, some evidence of catalyst inhibition toward CyC(O)NH₂ reduction was apparent, with the phenyl ring in benzamide being hydrogenated predominantly to CyC(O)NH₂ (53%), and only 32% selectivity to CyCH₂NH₂ (Table 2, entry 17).⁹⁵ Equivalent behavior toward the aliphatic primary amide butanamide (*n*-butyramide) was observed using Ru/Mo and Rh/Mo catalysts. Although the former afforded *n*-butylamine in high selectivity with no detectable secondary amine formation, considerably reduced selectivity toward the primary amine was noted with the latter (cf., Table 2, entries 18, 19). In contrast, using Ru/Mo catalysts and the more sterically hindered substrate 2,2-dimethylpropanamide (trimethylacetamide), the product distribution comprised predominantly 2,2-dimethylpropan-1-ol with only 40% selectivity toward the expected product, 2,2-dimethylpropanamine (Table 2, entry 20).⁹⁶

In general, catalytic activity and selectivity were significantly affected by the catalyst precursors, bimetallic ratio M:M' (M = Ru, Rh; M' = Mo, Re), reaction temperature, and pressure. The most active catalysts were prepared from metal carbonyl precursors. In particular, the use of alternative sources of Mo (Mo powder, MoO₃, etc.) did not provide any noticeable enhancement over the poor performance of the monometallic (control) Ru (or Rh) systems. In contrast to the behavior of the Ru/Mo catalysts, incremental decrease in the reaction pressure from 100 to 50 to 20 bar H₂ with Rh/Mo catalysts led to decreased primary amine selectivity with correspondingly increased amounts of secondary amine formation. Nevertheless, these all clearly provide significant advances over the previous work of Broadbent et al. using, for example, monometallic Re catalysts.⁸⁴

In contrast to subsequent work with supported materials, the unsupported Ru/Mo and Rh/Mo catalysts were demonstrated to be readily recyclable with negligible reduction in conversion of CyC(O)NH₂ and, in the case of Ru/Mo, only minor loss of primary amine selectivity over at least six reaction cycles (see Figure 1 and section 4.4.1).⁹⁶ Moreover, prior to cycle 6, the

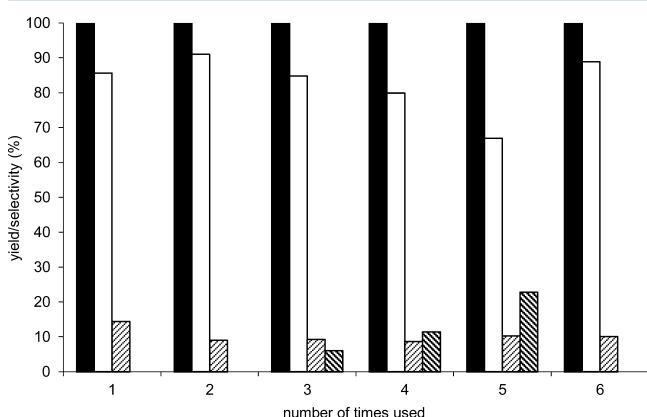


Figure 1. CyC(O)NH₂ hydrogenation using an unsupported bimetallic Ru/Mo (Mo:Ru = 0.57) catalyst: Product selectivity vs recycle. Cycle 6 was performed with addition of LiOH. Key: ■ Conversion, □ CyCH₂NH₂, ▨ CyCH₂OH, ▨ (CyCH₂)₂NH. (Reprinted with permission from ref 96. Copyright 2010 Wiley-VCH.)

addition of a minor quantity of LiOH readily led to restoration of the 92% primary amine selectivity noted after the second recycle.

Factors that appear common to this family of catalysts are (i) the synergistic behavior between each pair of elements in promoting amide reduction under reaction conditions that encompass the ranges 20–100 bar H₂ and 130–160 °C, (ii) intrinsically high selectivity of these catalysts toward hydrogenation of the primary amide CyC(O)NH₂ to the primary amine CyCH₂NH₂, and (iii) their recyclability (see also section 4.4.1).

Ru/Mo, Rh/Mo, Ru/Re, and Rh/Re catalysts were comparable in requiring only small amounts of the more oxophilic metals, Re and Mo, for high primary amine selectivities, although Rh/Re catalysts required higher Re content to allow full amide conversion. Contrasting features that emerge from the substitution of Re for Mo are (i) little significant catalyst deactivation at high Re levels, possibly because oxides of Re are much more readily reduced to the metallic state than Mo oxides, and (ii) the requirement for more severe reaction conditions, ca. 50–100 bar H₂ and 150–160 °C with Ru/Re and Rh/Re containing catalysts (cf., 20 bar H₂, 150 °C with Ru/Mo catalysts). Minimum acceptable reaction conditions required by Ru/Mo and Ru/Re catalysts are 20/50 bar H₂ and 160 °C, respectively, with almost identical (84% vs 81%) primary amine selectivities, and thus Ru/Mo catalysts appear preferable to their Ru/Re analogues, particularly in light of higher TONs for Ru/Mo⁹⁶ relative to Ru/Re⁹⁷ in comparable experiments.

Additional research⁹⁸ has revealed that alternative, more accessible, catalyst precursors, for example, Ru(acac)₃, Rh(CO)₂(acac) (acac = acetylacetato-, 2,4-pentanedionato-), and Re₂O₇, also lead to the generation of catalysts of comparable activity and selectivity. Nevertheless, formally zerovalent Mo precursors such as Mo(CO)₆, or its substituted derivatives, for example, Mo(CO)₅(CH₃CN), do appear to comprise essential precursors to active and selective catalysts that contain molybdenum.

Finally, the Pd/Re/graphite catalyst reported very recently,⁹⁹ which proved very active toward secondary and tertiary amide substrates (see sections 4.2.2 and 4.2.3), although active, proved ineffective for the selective hydrogenation of CyC(O)NH₂, giving (CyCH₂)₂NH as the main product. More surprisingly, based on previous work with both copper–chromium oxide and Pd/Re/graphite/zeolite 4A catalyst systems,⁸² inhibition of the reaction was found to occur in the presence of added ammonia. This lends even further significance to the presently unique behavior associated with the unsupported bimetallic catalyst systems described above. It would appear that much new chemistry awaits discovery in this area.

4.2.2. Secondary Amides. It is significant to note that, relative to their primary and tertiary counterparts, until very recently (see below) there has been a general paucity of examples in the literature associated with the hydrogenation of secondary amides. The early work of Adkins et al. using copper–chromium oxide catalysts provided good evidence of poor reaction selectivity during the reduction of C₁₁H₂₃C(O)-N(H)R, where R = Cy, Ph, with the formation of numerous byproducts (Table 3, entries 1, 2), although the hydrogenation of CH₃C(O)N(H)Ph over rhenium catalysts gave C₂H₅N(H)-Ph in good selectivity (Table 3, entries 3, 4).

A comparison between the data in Tables 2 (entries 12, 16), 3 (entries 5, 6), and 4 (entries 7, 8) also reveals that the secondary amides *N*-methylbenzamide and *N*-methylcyclohexanecarboxamide prove significantly more resistant to hydrogenation than either primary or tertiary amides over Ru/Mo catalysts.⁹⁶ Although the aromatic ring in *N*-methylbenzamide was readily reduced, only minor amounts of *N*-methylcyclohexylamine were detected under the standard reaction conditions (100 bar H₂, 160 °C, 16 h) used (Table 3, entry 6). In contrast, using a Rh/Mo catalyst, hydrogenation of CyC(O)N(H)CH₃ proceeded smoothly to give CyCH₂N(H)CH₃ in high (80%) selectivity, with no detectable CyCH₂OH formation (Table 3, entry 7), although at reduced conversion (45%), thus providing a sharp contrast with the complete conversions noted using CyC(O)NH₂ (Table 2, entry 14). These variances suggest subtle, presently unexplained, differences in catalytic behavior, which clearly merit further investigation to allow optimization.

As a counter to the foregoing comments on a dearth of examples of secondary amide hydrogenation in the literature, Stein and Breit⁹⁹ have very recently redressed the balance by reporting the results of testing a total of 108 amides, of which 49 were secondary substrates. Using an automated multiple catalyst screening system comprising four autoclave blocks each containing 10 reaction vessels, and a Pd(2%)/Re(10%)/high surface area graphite (HSAG) (4 mol % Re) catalyst, the 49 secondary amides were tested under reaction conditions comprising 30 bar H₂, 160 °C, 20 h. The majority of these substrates gave good to high amide conversions, dependent to some extent on the degree of steric hindrance imposed by the substituents attached to the amide nitrogen, and almost uniformly high selectivity to the corresponding secondary amine (see, for example, Table 3, entries 8 and 9). Notwithstanding this development, some similarities were however evident between the behavior of this catalyst and that of the Ru/Mo catalysts described previously.⁹⁶ Thus, comparison between the use of Ru/Mo catalysts for the reduction of *N*-methylbenzamide, (Table 3, entry 6) [which gave mainly aromatic ring hydrogenation to CyC(O)N(H)CH₃ (85%) and only minor amounts of CyCH₂N(H)CH₃ (8%)], and that of PhCH₂N(H)C(O)CH₃, using the Pd/Re/graphite catalyst (Table 3, entry 9), reveals a strong similarity. This emphasizes the point that the specific nature of an amide substrate comprises a significant factor in determining the activity of a given catalyst system. The work of Stein and Breit⁹⁹ also reinforces the view that amides containing the N-atom encapsulated within a five- or six-membered ring system are most susceptible to 100% conversion under a given set of reaction conditions (see also section 4.2.3.2). Some caution must therefore be exercised in attempting to generalize relative orders of reactivity toward primary, secondary, and tertiary amides (see section 6.4.4).

Finally, a significant exception to the general comments concerning the low reactivity of secondary amides toward reduction is provided by the report of a homogeneous Ru catalyst system for the highly selective hydrogenation of *N*-phenylnonamide to *N*-phenylnonamine (see section 5.1.1). In general, however, the reduced conversions relative to those observed with the corresponding primary amides do still provide exemplification of the point that secondary amides present greatest resistance of all three classes of amide to hydrogenation under catalytic conditions (also during stoichiometric reduction using hydride reagents such as LiAlH₄, see also section 6.4.4).

4.2.3. Tertiary Amides. A discussion of catalytic hydrogenation of tertiary amides may conveniently be divided into two distinct classes of amide substrate, first, those of high boiling point, typically *N,N*-dialkylamides containing long-chain alkyl and/or aromatic groups, and second, those in which the amide nitrogen atom is encapsulated within a hydrocarbon ring structure. The former are useful as intermediates and building blocks in the chemical industry, whereas the latter are generally more appropriate for use in model studies, for the reasons indicated below.

4.2.3.1. Typical Tertiary Amides. Early work, using copper-chromium oxide catalysts, featured the more typical tertiary amides that contained (long-chain) alkyl, and other, side chains.^{65,66} Many showed poor reaction selectivity, yielding secondary amines as the principal products (cf, Table 4, entry 1), thus providing ample evidence of competing reactions, such as C–N and C–O bond cleavage, leading to alcohol and hydrocarbon formation, respectively.⁶⁵ Later, with the additional beneficial presence of 4A zeolite in the catalyst formulation, high conversions of (CH₃)₂NC(O)R (R = C₁₁H₂₃–, lauryl) to (CH₃)₂NCH₂R in good selectivity could be achieved (cf, Table 4, entry 2).

A Re catalyst derived from Re₂O₇ was found to give very good tertiary amine product yield during the reduction of CH₃C(O)N(C₂H₅)Ph (*N*-ethylacetanilide, *N*-ethyl-*N*-phenylacetamide) to *N,N*-(C₂H₅)₂NPh (Table 4, entry 6).⁸³ In recent work with Ru/Mo catalysts (100 bar H₂, 160 °C, 16 h),⁹⁶ *N,N*-dimethylbenzamide (Table 4, entry 7) showed behavior equivalent to that of benzamide (Table 2, entry 16) in terms of preferred aromatic ring reduction, although the high residual CyC(O)N(CH₃)₂ content and only 35% overall carbonyl group reduction to CyCH₂N(CH₃)₂ and CyCH₂OH (in an ca. 6:1 product ratio similar to that observed with CyC(O)NH₂) suggested catalyst inhibition. Using *N,N*-dimethylcyclohexanecarboxamide (Table 4, entries 8, 9) as substrate with Ru/Mo and Rh/Mo catalysts, similar inhibition was noted, with significantly larger alcohol content evident in the product distribution. *N,N*-Dimethylpropionamide (entry 10), an example of a conventional aliphatic tertiary amide, gave *N,N*-dimethylpropylamine as the major product.

4.2.3.2. Amides Containing Nitrogen Atoms Encapsulated within Five- and Six-Membered Rings. Much of the recent work with tertiary amides has featured substrates in which the N-atoms comprise integral components of either five- or six-membered rings, for example, *N*-acetylpyrrolidine, *N*-acetylpyrrolidine, *N*-methylpyrrolidin-2-one, and 2-pyrrolidone. These have proved popular choices as convenient model compounds for amide hydrogenation largely because of their ready availability, physical properties, and limited number of potential reduction products. However, it should be emphasized that they are not representative of the more typical tertiary amides that are arguably of most commercial interest, that is, those described in section 4.2.3.1 (and 4.2.3.3), as a direct consequence of their ring structures. Encapsulation of the amide nitrogen atoms within a ring structure seems likely to cause some disruption of the planarity of the amide group, weakening the p-orbital overlap, cf., Scheme 3, and leading to greater susceptibility to reaction (see also section 2); the formation of charge-stabilized zwitterions (Scheme 2) is an additional factor.

Amine product selectivity problems are also considerably less with this class of tertiary amide, being limited between C–O bond cleavage to give the corresponding the amine, and alcohol

Table 5. Continuous/Slurry/Vapor Phase Catalytic Hydrogenation of *N,N*-Dimethyllauramide, $C_{11}H_{23}C(O)N(CH_3)_2$, Using Cu-Based Catalysts^a

entry	catalyst components	reaction conditions			product selectivity (%)			ref
		bar H ₂	°C	h	$C_{12}H_{25}N(CH_3)_2$	$(C_{12}H_{25})_2NCH_3$	$C_{12}H_{25}OH$	
1	Cu/Ca(4:1)/Zeolum F9	5–50	250		84	7	8	102
2	Cu/Ba(4:1)/Zeolum F9	5	230–250		85	5	8	102
3	Cu/Mn(4:1)/Zeoleum F9	5	250		82	7	9	102
4	Cu/Mn/Ru(4:1:0.1)/Zeoleum F9	5	250		79	12	6	102
5	Cu/Zn(4:1)/Zeoleum F9	5	250		77	21	6	102
6	Cu/Mg(4:1)/Zeoleum F9	5–15	250	6–9	84	9	7	103
7	(i) leached Cu/Zn/Mg/Al alloy	15	250	6	87	3	7	104
	(ii) leached Cu/Zn/Mg/Al alloy + DMA ^b	15	250	2	93	4	<1	
8	(i) Cu/Mg(4:1)/hydrotalcite	15	230	6	86	3	9	105
	(ii) Cu/Mg(4:1)/hydrotalcite + DMA ^b	15	230	2	95	4	<0.5	

^aAll entries at >99% amide conversion. ^b“Solvent free”, DMA = auxiliary amine, dimethylamine.

production via C–N bond hydrogenolysis; of these, the former pathway is almost exclusively preferred. Thus, much of the Japanese work featured the use of *N*-acetylpyrrolidine,^{91,92} and more recently this substrate was also found to be readily reduced to *N*-ethylpyrrolidine, in greater than 90% selectivity, using Ru/Mo, Rh/Mo, Ru/Re, and Rh/Re catalysts under similar reaction conditions (Table 4, entries 11–13).^{95–97} However, traces of ethanol, derived from C–N bond cleavage, which were not reported by Fuchikami et al.,⁹¹ were also detected as a byproduct from *N*-acetylpyrrolidine reduction.

What is undoubtedly a very exhaustive data set derived from molecules of the above type, *N*-acetylpyrrolidine and *N*-acetylpyrrolidine, was achieved via high throughput catalyst screening, using both continuous flow and batch processing, as revealed in a patent assigned to Avantium (Table 4, entries 14, 15).¹⁰⁰ Here, ca. 100 bimetallic combinations containing Co, Fe, Ir, Pt, Rh, and Ru with Cr, Mo, Re, and V, and trimetallic combinations also incorporating Cu, In, and Zn, each of which were supported (principally) on both carbon and silica, were examined under reaction pressures of 10 bar H₂ and temperatures of 70, 100, 130, and 160 °C, in acidic media, acetic acid in continuous mode (entry 14), and BF₃ in batch experiments (entry 15). In the latter, *N*-acetylpyrrolidine gave *N*-ethylpyrrolidine in ca. 20% yield as the sole product over a PtV/TiO₂ catalyst at 10 bar H₂, 130 °C, and 16 h. With *N*-acetylpyrrolidine, the more active metal/catalyst combinations, giving *N*-ethylpyrrolidine in similar modest yields, were found to be PtReCu, PtRe, PtMo, IrReZr, PtMoCu, and PtReIn, with poor reactivity uniformly evident below 100 °C.

A significant disadvantage of the catalyst systems studied by Avantium must be the requirement for the use of the corrosive acids such as acetic acid and BF₃ as solvents. Furthermore, no investigations of the behavior of these bi- and trimetallic catalysts toward the reduction of the more demanding (in terms of both activity and product selectivity) standard primary, secondary, and tertiary amides were reported.

The predominance of Pt and Re in the more highly active catalysts described above has clearly prompted the report of the reduction of *N*-methylpyrrolidin-2-one to *N*-methylpyrrolidinone (NMP) using PtRe/TiO₂ catalysts under similarly mild reaction conditions (typically ca. 20 bar H₂, 120 °C, 24 h), giving ca. 90% conversion but on a longer reaction time scale than used in the previous work (Table 4, entry 16).¹⁰¹ A requirement for the use of *n*-hexane as solvent would seem to be a significant drawback to more general use in amide reduction, simply because of the very limited solubility of amides in hydro-

carbons. Significantly, considerable deactivation, attributed to disruption of the initial Pt–Re interaction, which was established by DFT calculations in the as-prepared catalysts, occurred during attempts at catalyst recycle (see also sections 4.4.2 and 4.5).

A very recent report concerns the testing of a total of 59 tertiary amides, the majority of which contain the N-atom encapsulated within five- and six-membered rings, over the Pd/Re/graphite catalyst (see also section 4.2.2) at 30 bar H₂, 160 °C, 20 h, also using high throughput procedures.⁹⁹ Here, the corresponding amines were obtained in both very good conversions and selectivity (see, for example, Table 4, entries 17, 18). The use of amides containing increasingly lengthy alkyl side chains led to decreased conversions, although high reaction selectivity was maintained. Depending on the degree of steric hindrance contained within the substrate, the rate of reaction could be improved by increasing the temperature, thereby allowing very sterically hindered amides to be hydrogenated in high yields. This catalyst is claimed to display the highest carboxamide reduction activity reported to date, with 85% conversion of *N*-acetylpyrrolidine at 10 bar H₂, 120 °C, and 20 h. In general, however, at their present stage of development, these lactam-type substrates require minimum reaction conditions in the region of 20 bar H₂, 130 °C, and 16 h, giving only modest yields of the corresponding tertiary amines; temperatures of 150–160 °C still appear necessary for acceptable amide conversions.

4.2.3.3. Nonchromium Catalysts for Tertiary Amide Hydrogenation. The well-known toxicity and carcinogenicity associated with chromium has stimulated a general requirement to develop Cr-free heterogeneous catalysts. In the context of amide hydrogenation, several patents concerned with the production and application of copper-based catalysts for the selective hydrogenation of tertiary amides containing long-chain aliphatic groups have recently emerged from Kao Corp.^{102–105} In addition to copper, these catalysts include some of the more typical elements featured in both sections 4.2.3.1 and 4.2.3.2. Thus, according to the patent claims, in addition to Cu, these systems require “at least one element from groups 2, 3, 7 and optionally 8–10, and 12 elements of the Periodic Table” (cf., refs 99, 100). Thus, Cu/Ca, Cu/Ba, Cu/Mn (4:1), and Cu/Mn/Ru (4:1:0.1) catalysts, prepared in combination with a synthetic zeolite (e.g., Zeolum F9) support (also alumina and zirconia), have been used for the selective hydrogenation of tertiary amides such as *N,N*-dimethyllauramide; in addition, a process for production of the amine oxide

by subsequent reaction of the first formed amine with hydrogen peroxide has been described.¹⁰² The reductions were carried out in rotary reactors and appear to have been operated as slurry systems, requiring only very low initial operating hydrogen pressures (5–15 bar H₂) relative to those used in most previous work, although high reaction temperatures, for example, 230–250 °C, are still a necessary requirement. Preferred catalyst combinations (cf., Table 5, entries 1–3) gave, at >99% amide conversions, typical amine product selectivities comprising 84% *N,N*-dimethylauramine, 6% dilaurylmono-methylamine, and 8% lauryl alcohol. The incorporation of ruthenium into a Cu/Mn catalyst (Cu:Mn:Ru = 4:1:0.1) resulted in slightly lower selectivity to the primary amine (entry 4). Cu/Zn/Zeolium F9 catalysts were also slightly inferior in terms of selectivity (entry 5), although sequential increase in reaction pressure from 5 to 80 bar H₂ resulted in a marginal sequential increase in tertiary amine selectivity, from ca. 85% to 88%. Subsequent patents, claiming further improvements to amine reaction product selectivity, have included the use of supported Cu/Mg (typically 4:1) catalysts, which have been exemplified with a wider range of tertiary amides (Table 5, entry 6),¹⁰³ and sponge copper catalysts prepared by alkali leaching of alloy particles containing, for example, Cu/Al and Cu/Zn/Al, followed by drying.¹⁰⁴ Although destructive sintering occurred during amide hydrogenation using these bi- and tricomponent alloy catalysts, the inclusion of a fourth element, such as Mg, V, Mn, Mo, and Ru, into the alloys resulted in sustainable catalytic activity and highly selective tertiary amine formation (cf., Table 5, entry 7). A further development, using both these¹⁰⁴ and a similar range of copper catalysts, including, for example, Cu/Mg/hydrotalcite (entry 8),¹⁰⁵ concerned the introduction of a second reaction stage following completion of amide hydrogenation in the first step [cf., Table 5, entries 7(ii) and 8(ii)]. Addition of, and reaction with, an auxiliary amine such as dimethylamine at this stage had the effect of converting the residual alcohol byproduct of amide reduction, lauryl alcohol, into the desired tertiary amine product via secondary reactions, thereby enhancing the overall selectivity of the process (see also Table 4, entry 4, and ref 86).

These improved slurry phase catalysts (see also section 4.6) are suited to either batch or continuous operation at 230–250 °C, with continuous feed of hydrogen, and are able to provide uniformly high selectivities (>90%) to the desired corresponding amine after a total reaction time of ca. 6 h. Use of the leached alloy sponge catalysts¹⁰⁴ has been claimed to be operated under “solvent-free” conditions (cf., sections 4.1 and 4.3), at reaction temperatures of 230–250 °C, allowing facile removal of the water formed during amide reduction.

The use of copper-based catalysts offers a significant potential economic advantage over the precious metal systems described in the earlier parts of section 4.2. Moreover, their performance appears to match those of the copper–chromium catalysts shown in Table 4 (entries 4 and 5). However, although ideally suited to the hydrogenation of simple, thermally stable long-chain tertiary amides, these catalysts are clearly of very limited use for the reduction of more complex tertiary (and other) amides containing sensitive functional groups simply because of the very high reaction temperatures required.

4.3. Supported Catalysts for Carboxamide Hydrogenation

One of the most important aspects in any ultimate application of heterogeneous catalysts for amide hydrogenation concerns the design, development, and use of appropriate catalyst supports, and the behavior of the resultant supported catalysts during recycle, areas in which there is currently very little information. Some of the more significant results to date, particularly in the context of the highly selective hydrogenation of primary amides such as CyC(O)NH₂, have been obtained using unsupported bimetallic nanocluster catalysts.^{95–97} These catalysts could be readily separated and recycled without significant loss of activity or selectivity (cf., Figure 1 and ref 96). Nevertheless, they did exhibit some rather unexpected sensitivity, as summarized in the following comments. Thus, on consideration of the fact that the origins of the bimetallic catalysts for amide hydrogenation described by Fuchikami, Behr, and Beamson et al. are metal carbonyls,^{91–97} a rather unexpected feature of these catalysts proved to be their extreme sensitivity to subsequent exposure to traces of carbon monoxide. On attempted recycle of a highly selective Ru/Mo catalyst for CyC(O)NH₂ hydrogenation in DME,⁹⁶ introduction of these components to a reaction vessel that had previously been flushed with an atmosphere of CO, followed by subjecting to the standard reaction conditions (100 bar H₂, 160 °C), resulted in complete suppression of amide reduction. Rather remarkably, both full catalytic activity and original high primary amine selectivity could be restored by simply cooling the autoclave to room temperature, depressurizing, purging, and repressurizing with pure H₂, followed by reheating to 160 °C. The extreme sensitivity of these catalysts to traces of CO is presumably a consequence of strong competitive adsorption of CO on catalytically active sites. Nevertheless, it does appear surprising that traces of CO are so destructive, particularly because Ru is a well-known, and commercially utilized, catalyst for CO methanation (eq 8) at ppm levels in the gas phase.



Evidently, the combination of additional more oxophilic Mo and/or Re components and use of a liquid-phase system serve to completely inhibit methanation once the bifunctional catalyst has been formed.

Furthermore, inadequate displacement of the ambient atmosphere, that is, air, from the reaction vessel prior to reaction led to a significant reduction both of conversion (from 100% to 74%), and of primary amine selectivity (85% to 68%), and increased formation of the byproducts CyCH₂OH (14% to 25%) and (CyCH₂)₂NH (0% to 5%).⁹⁶ The sensitivity of the Ru/Mo catalysts to exposure to traces of air also appears unusual, and merits further investigation in both these and other catalytic systems. Careful attention to the detail of catalyst pretreatment in general is clearly important, even before consideration of the preparation and use of supported catalysts.

Although no detailed study was undertaken, two examples of combinations of supported catalysts (Rh/C + Re/C; Ru/Al₂O₃ + Re/Al₂O₃) used in batch experiments for *N*-acetylpyrrolidine hydrogenation were reported by Fuchikami et al.⁹¹ These showed a close similarity to the performance of catalysts derived from the corresponding metal carbonyl precursors. Subsequently, preliminary attempts have been made to prepare and evaluate in *N*-acetylpyrrolidine hydrogenation, silica-supported Rh/Mo catalysts derived from the respective metal carbonyls.⁹⁵ Here, the activity of a supported catalyst prepared

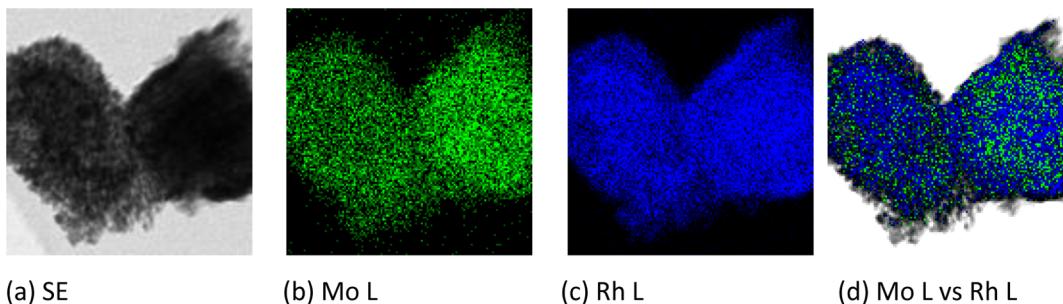


Figure 2. EDX-STEM analysis of Mo:Rh = 0.44 catalyst used in CyC(O)NH₂ hydrogenation: (a) bright field image of typical area, (b) Mo L (2.293 eV), (c) Rh L (2.697 eV), and (d) Mo L vs Rh L maps. (Reprinted with permission from ref 95. Copyright 2010 Elsevier).

by sequential deposition [first Mo(CO)₆, followed by Rh₆(CO)₁₆] onto silica proved higher than one prepared by single stage deposition, and both significantly exceeded the TON of the optimum unsupported Rh/Mo catalysts. Nevertheless, progressive deactivation during recycle, which appeared to be a consequence of the accumulation and increased retention of C_xH_yN-containing residues on the support, rendered them unsatisfactory for extended use. Also, a very significant reduction in amide conversion with decreasing temperature (over the range 160–130 °C) was noted, relative to that observed using unsupported catalysts over the same temperature range. This effect may be a consequence of temperature-dependent limitations to diffusion and substrate adsorption/product desorption on/from the catalyst surface,⁹⁵ and suggests that further careful consideration of the design and development of appropriate catalyst supports may be a key to significant future progress.

During the high throughput screening exercise using *N*-acetylpyrrolidine as substrate, the numerous multimetallic catalyst combinations tested, using both continuous flow and batch modes of operation, were supported on both carbon and silica (and, to a much lesser extent, titania and silica–alumina).¹⁰⁰ Unfortunately, no indications of either catalyst lifetime or potential catalyst recyclability were reported. However, in one comparative example cited, a PtRe/TiO₂ catalyst, which showed significantly improved performance over the Rh/C, Re/C system of Fuchikami, has been re-examined subsequently in much greater detail¹⁰¹ with, once again, considerable deactivation during recycling. Moreover, the initial activity could not be fully restored by drying and recalcination, treatment that would have removed any residual surface carbon and nitrogen. The loss of activity of the PtRe/TiO₂ catalyst¹⁰¹ was attributed to progressive catalyst degradation through destruction of the initial Pt–Re interaction that had been established using EXAFS¹⁰⁶ and DFT calculations on the fresh catalysts (see section 4.4). Similar behavior was observed with the Breit and Stein Pd/Re/graphite catalyst, the initial 100% conversion observed using *N*-acetylpyrrolidine as substrate decreasing irreversibly to 80% and 70% during the first and second catalyst recycle, respectively.⁹⁹ Application of other, unspecified, recycling techniques led to no further improvement in catalyst performance.

Further to the high throughput screening work in continuous flow mode mentioned above,¹⁰⁰ a very recent report describing the development of a continuous flow reactor has been exemplified, using the PtRe/TiO₂ catalyst also described above,¹⁰¹ for the hydrogenation of both *N*-methylpropanamide and *N*-methylpyrrololidin-2-one at 20 bar H₂ and 120 °C.¹⁰⁷

With the former substrate, both high conversion (75–99%) and selectivity toward the secondary amine (80–86%) were achieved and maintained for over 8 h on stream. Similarly, using *N*-methylpyrrololidin-2-one under similar reaction conditions, *N*-methylpyrrolidine was obtained as the only product. The lack of any catalyst deactivation, in comparison with the batch experiments,¹⁰¹ was attributed to maintenance of the catalyst and reactants under reducing conditions at all times; moreover, the extent of metal leaching was shown to be negligible.¹⁰⁷

To date, these appear to be the only examples where the recyclability of supported amide hydrogenation catalysts has been investigated, with some limited success, providing a marked contrast with the behavior of the unsupported Ru/Mo and Rh/Mo catalysts (see section 4.2.1). The question of suitable catalyst supports represents a challenging aspect of future work in this area, requiring the innovative design, choice, and selection of appropriate materials.

Finally, with the exception of the work of Forquy et al. (see section 4.1),⁸⁶ essentially no information relating to recycle of the bulk copper–chromium oxide catalysts is available, notwithstanding clear catalyst stability issues relating to over-reduction during reaction.⁷¹ However, it does seem likely that these catalysts would be readily regenerated *in situ* under the severe reaction conditions, particularly high temperatures, used relative to those required by the later generation of catalysts.

4.4. Characterization of Carboxamide Hydrogenation Catalysts

No specific attempts at catalyst characterization appear to have been reported for any of the early catalysts used for amide hydrogenation (other than establishing variations in elemental Cr, Cu, etc. catalyst compositions), presumably because of both the very severe reaction conditions typically used and a general lack of the suitable diagnostic analytical probes that are available today. With the second generation catalysts that have been shown to operate under much milder reaction conditions, some meaningful catalyst characterization data are however beginning to emerge.

4.4.1. Bimetallic Ru/Mo, Rh/Mo, Ru/Re, and Rh/Re Catalysts. These catalysts were prepared from homogeneous solutions containing the organometallic metal carbonyl precursors.^{91,95–97} Notwithstanding an initial conception that they might be homogeneous in nature,^{91,94} the results of catalyst genesis studies using *in situ* high pressure FTIR spectroscopy unambiguously revealed that they were indeed heterogeneous. Amide reduction only proceeded after an induction period during which the starting metal carbonyls, for example, Ru₃(CO)₁₂, Rh₆(CO)₁₆, Mo(CO)₆, and Re₂(CO)₁₀, underwent decomposition (as verified by a

reduction in intensity and eventual disappearance of $\nu(\text{CO})$ absorptions) with the formation of solids that could be separated after reaction, recycled, and reactivated under hydrogen pressure without further treatment. Whereas Ru/Mo, Rh/Mo, and Rh/Re combinations were comparable in exhibiting significant induction periods ranging between 2 and 6 h prior to initiation of catalysis, Ru/Re only required heating to reaction temperature, at which point modest amide conversions commenced, increasing significantly during the subsequent reaction period. This was attributed to the extremely rapid rate of decomposition of $\text{Ru}_3(\text{CO})_{12}$, relative to $\text{Re}_2(\text{CO})_{10}$, which, Re being a third row transition element, would be expected to exhibit a slower rate of decomposition. A consequence of this was the generation of a bimodal size distribution of Ru and Ru/Re nanoparticles (see comment below).

The results of catalyst characterization, using a combination of microanalysis, XRD, EDX-STEM (Figure 2), and XPS (Figures 3 and 4), both before and after use in amide

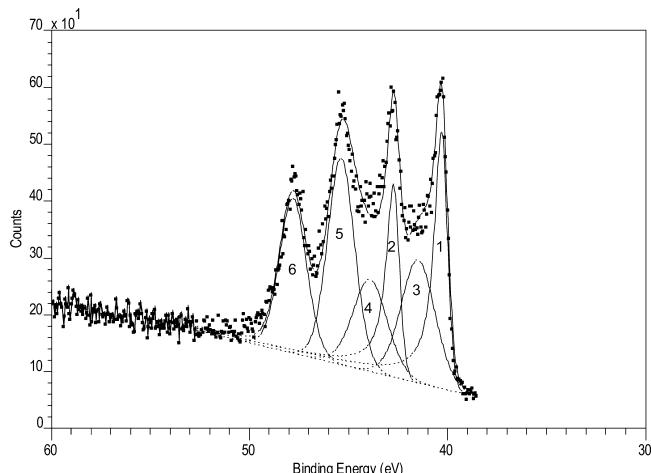


Figure 3. XPS data: curve fit to Re 4f region of Re:Rh catalyst = 1.0 after use in $\text{Cyc}(\text{C(O)NH}_2)$ hydrogenation, showing significant concentrations of oxidized Re surface states. Components 1, 2: $\text{Re(0)} 4f_{7/2, 5/2}$; components 3, 4: $\text{Re(III)} 4f_{7/2, 5/2}$; components 5, 6: $\text{Re(VI)} 4f_{7/2, 5/2}$. (Reprinted with permission from ref 97. Copyright 2011 Elsevier).

hydrogenation, were interpreted in terms of the formation of intimately mixed ca. 2–4 nm bimetallic nanoclusters, which, in the most active catalysts, contained significant amounts of oxidized surface states of the more oxophilic elements Mo and Re.^{95–97} For example, Figure 3 shows the partitioning of surface states derived from curve fitting of Re XPS data. Further analysis of the XPS data (Figure 4), exemplified by spectra of Ru/Re and Rh/Re catalysts, (a) and (b), respectively, revealed that the bimetallic systems contained metallic (Ru, Rh) and partially oxidized (Mo, Re) surface states after use in amide hydrogenation. Here, both (a) and (b) show significant evidence of oxidized Re surface states, in contrast to retention of the predominantly metallic state of Re during the nominally anhydrous hydrogenation reaction using a similar Ru/Re catalyst (Figure 4c).⁹⁷ This behavior seems likely to be a consequence of the formation and accumulation of the coproduct water during reaction, leading to hydrolytic oxidation of the more oxophilic Re surface (cf., Figure 3) and indicating the possibility of redox behavior on the surface

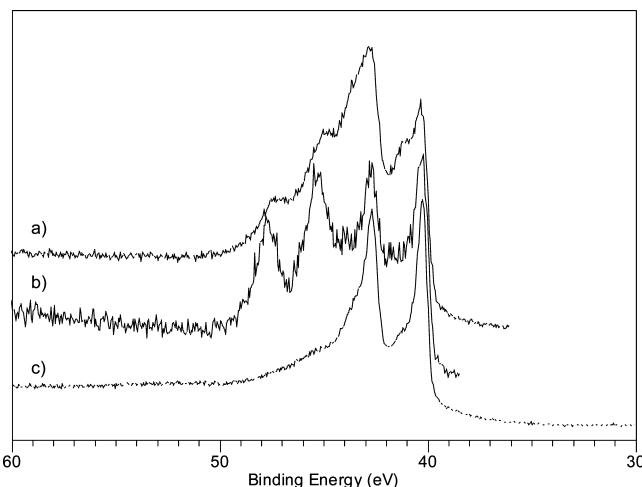


Figure 4. XPS data: overlay of Re 4f spectra for (a) $\text{Re:Ru} = 0.54$ and (b) $\text{Re:Rh} = 1.0$ catalysts after use in CyC(O)NH_2 hydrogenation, and for (c), $\text{Re:Ru} = 0.12$ catalyst after use in cyclohexene hydrogenation. (Reprinted with permission from ref 97. Copyright 2011 Elsevier).

during amide reduction.⁹⁷ Significant support for this interpretation, particularly for Rh/Re catalysts, has been provided by a report of the formation and characterization of stable two-dimensional ReO_x clusters on Rh metal surfaces in silica-supported Rh- ReO_x catalysts used for the hydrogenolysis of ethers (Figure 5). Some additional relevant work

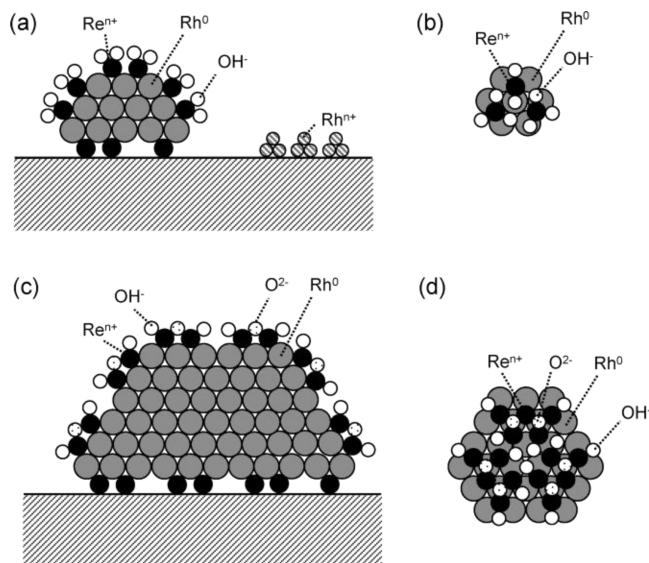


Figure 5. Model structures of $\text{Rh}-\text{ReO}_x/\text{SiO}_2$ during reduction at 365 K (a and b) and 595 K (c and d). (a and c): Side view, (b and d): Top view. (Reprinted with permission from ref 108. Copyright 2012 ACS).

describing the effect of Re on Ru dispersion in $\text{Ru-Re}/\gamma-\text{Al}_2\text{O}_3$ catalysts has also just appeared.¹⁰⁹ Using a range of techniques, and a comparison with the chemisorption properties of standard monometallic Ru and Re catalysts, it was concluded that Re modifies the interaction of hydrogen with Ru surface sites. Moreover, in establishing that Ru is easier to reduce than Re in bimetallic catalysts, the first nucleation centers of metallic Ru could be formed before reduction of Re commences, with excess Re formed separately as larger particles. During the genesis of the Ru/Re catalysts derived

from metal carbonyls (see above), the bimodal distribution of ca. 8 nm Ru crystallites and ca. 2–4 nm Ru/Re nanoclusters can be attributed to a converse effect, initial rapid decomposition of $\text{Ru}_3(\text{CO})_{12}$ and formation of the larger Ru particles, combined with slower codecomposition of $\text{Re}_2(\text{CO})_{10}$ subsequently leading to generation of the bimetallic Ru/Re nanoclusters. As a consequence, turnover numbers for Ru/Re nanoclusters in amide hydrogenation may in fact be significantly higher than those of Ru/Mo catalysts (cf., section 4.2.1 and Table 2, entries 12, 13) when the copresence of largely inactive 8 nm Ru particles⁹⁶ is taken into account.

The redox behavior apparently associated with Ru/Re and Rh/Re catalysts also proved to be a point of some significance in relation to mechanistic aspects of amide reduction when comparisons were made with the essentially “anhydrous” hydrogenation of nitriles to amines over the same catalysts (see section 6.4.1).

XPS data for Ru/Mo and Rh/Mo systems, which were prone to deactivation at higher Mo:Ru or Mo:Rh catalyst precursor levels,^{95,96} revealed the presence of highly oxidized surface states of Mo, together with metallic Rh or Ru. This provided a conclusive explanation for the observed catalyst deactivation, blockage of active sites by molybdenum oxides. In view of the origins of these Ru/Rh/Mo/Re catalysts, metal carbonyls, some consideration was given to the formation and possible role in catalysis of, for example, Mo carbides, but neither XPS nor XRD provided any supporting evidence for their formation; furthermore, an independently prepared and characterized Rh/Mo bronze proved inactive toward amide hydrogenation.⁹⁵

4.4.2. PtRe/TiO₂ and PdRe/Graphite Catalysts. In recent work reported by Hardacre et al.,¹⁰¹ PtRe/TiO₂ and related catalysts used for *N*-methylpyrrolidin-2-one hydrogenation were characterized using TPR, XRD, and EXAFS,¹⁰⁶ the results showing that, under both gas-phase and liquid-phase reduction conditions, the predominant state of both Pt and Re was zerovalent, irrespective of the catalyst support used. A lack of evidence for Re or Pt in the XRD patterns was attributed to very small particle sizes, although these were not quantified by EDX-STEM techniques. Measurement of reaction rate as a function of stirring speeds confirmed the absence of gas to liquid mass transfer limitations at higher rates of stirring, and a linear dependence of the initial rate of reaction with catalyst mass, indicating that liquid to solid mass transfer limitations were negligible at the catalyst masses typically used. Complementary kinetic tests showed that the reaction was zero order in amide, first order in hydrogen, and that reaction rates were kinetically controlled. Additionally, in one of the first applications to amide hydrogenation, density functional theory (DFT) calculations were used to investigate potential reaction mechanisms on four transition metal surfaces, Re, Ru, Rh, and Pt, the results of which provided clear pointers in relation to amide hydrogenation reaction mechanisms (see section 6.3). Overall, this PtRe/TiO₂ catalyst clearly represents the most well-characterized system for the hydrogenation of a tertiary amide. Subsequently, a DFT study on the cleavage mechanism of the carbonyl bond in *N,N*-dimethylacetamide, on flat and stepped surfaces of an idealized single metal (Ru) surface, has appeared.¹¹⁰ Direct C–O bond cleavage was concluded to be preferred over an alternative hydrogen-induced mechanism on both surfaces. How the significance of this finding may relate to the behavior of the current preferred bimetallic/bifunctional catalysts for amide hydrogenation does however remain open to question. Examination of the Pd/Re/graphite catalysts⁹⁹ by

TEM showed them to be comprised of 2–6 nm nanoparticles deposited on a graphite layer, giving a high surface/volume ratio, which was suggested to be responsible for the good activity of the catalyst.⁹⁹ However, in common with the PtRe/TiO₂ catalyst,¹⁰¹ recyclability in batch experiments (cf., section 4.2.3.2) proved problematic with amide conversions decreasing irreversibly with each attempted recycle (see section 4.3).

4.5. Solvent Effects on Carboxamide Hydrogenation

The roles played by solvents in liquid-phase heterogeneous catalytic reactions comprise possibly both the least investigated and the least well understood of all aspects of this form of catalysis, and amide hydrogenation is no exception. Solvents are frequently simply considered to be convenient “inert” dispersing agents for the catalysts. Nevertheless, a consideration of aspects such as reactant solubility in and/or miscibility with solvents, together with variation in their polarity and solvation properties, is clearly of importance, particularly where more polar reactants (and products) are involved. A further factor for consideration concerns the use of gaseous coreactants. The solubility of gases is known to vary widely with solvent, leading to potential rate-determining diffusion limitation situations for access of gaseous reactants (and products) to (and from) the catalyst surface, particularly at low gas pressures where equilibrium concentrations might be established rather slowly.

In the case of carboxamide substrates, solvent effects are perhaps most likely to be associated with (i) enhancement of adsorption of the amide substrate on the catalyst surface and (ii) rapid desorption of amine products (and/or water) from the catalyst surface immediately on formation, leading, in some (but not all) examples, to inhibition of reactions that leads to secondary products. In the early work using copper–chromium oxide catalysts, Adkins et al.⁶⁵ reported that solvents such as 1,4-dioxane were beneficial, an effect that was ascribed to facile water removal, and possibly thereby preventing extensive oxidation of the catalyst surface. Subsequently, Guyer et al.,⁷⁸ also using copper–chromium oxide catalysts, demonstrated variations in both amine product selectivity and overall amide conversions, as a function of different solvents, including 1,4-dioxane, high boiling point hydrocarbons (180–280 °C), *m*-xylene, and ethylbenzene. Minor, but significant, variations in primary:secondary amine product ratios, ranging between ca. 9:83 (dioxane) and 17:78 (aliphatic hydrocarbon), were noted (in the absence of any added ammonia). 1,2-Dimethoxyethane (DME) has been a common choice throughout the more recent work, which all utilizes less severe reaction conditions, and also appears to exhibit an appropriate balance of physical properties.^{61,95–97} Being devoid of active protons, DME and 1,4-dioxane would both be expected to be chemically inert, but the availability of O-donor groups could be of importance both (i) during catalyst genesis from the metal carbonyls in these particular systems, and (ii) through hydrogen bonding to the H–N functionalities of the amide substrates and amine products.¹¹¹ Their higher polarity in relation to paraffin hydrocarbons leads to improved solubility/miscibility with a wide range of substrates, although both exhibit similar H₂ solubility.

Ethanol and *n*-octane were examined as potential alternative solvents for amide reduction using Ru/Mo catalysts.⁹⁶ As a consequence of the presence of active hydrogen atoms, the former proved unsuitable, particularly for the hydrogenation of a primary amide such as CyC(O)NH₂, yielding additional unwanted *N*-ethyl-substituted secondary and tertiary amine

products above threshold reaction temperatures of 120 °C. The paraffin hydrocarbon *n*-octane proved an acceptable alternative to DME, yielding the primary amine in the same selectivity, the sole byproduct again comprising CyCH₂OH.⁹⁶ Nevertheless, the very sparing solubility of the amide in *n*-octane at room temperature, combined with a requirement for very effective stirring to disperse the molten amide layer in the hydrocarbon solvent at 160 °C, represented disadvantages over the use of DME.

A rather more detailed account of solvent effects on amide hydrogenation has recently been described in the report of the PtRe/TiO₂ catalyst system used for hydrogenation of *N*-methylpyrrolidin-2-one.¹⁰¹ Here, the rate of hydrogenation at 20 bar H₂ and 120 °C was measured using solvents of various estimated degrees of polarity. Reaction rates were found to be highest for the least polar solvent, *n*-hexane, and lowest for the most polar, methanol (see Table 6 and Figure 6).

Table 6. Comparison of the % Conversion of *N*-Methylpyrrolidin-2-one after 24 h Using 4 wt % Pt–4 wt % Re/TiO₂ at 20 bar H₂ and 120 °C as a Function of the Solvent Used, and the Hydrogen Solubility and Polarity Parameter E^T_N for Each Solvent^a

solvent	% conversion	10 ³ x _{H₂} at 20 bar and 25 °C	polarity parameter E ^T _N
hexane	94	13.4	0.009
tetrahydrofuran	35	5.4	0.207
diethyl ether	30		0.117
methanol	15	3.2	0.762
methyl <i>tert</i> -butyl ether	0		0.124

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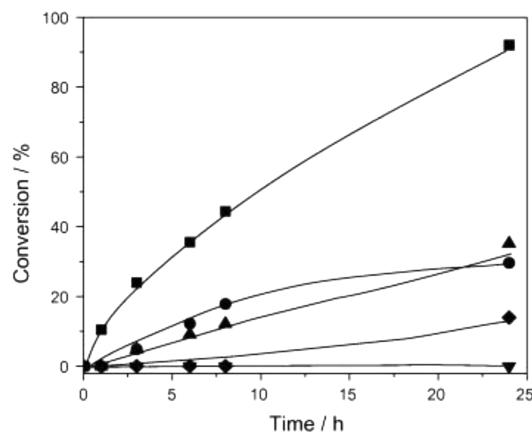


Figure 6. PtRe/TiO₂ catalyst for *N*-methylpyrrolidin-2-one hydrogenation: Variation of amide conversion as a function of solvent. Key: (■) hexane, (▲) tetrahydrofuran, (●) diethyl ether, (◆) methanol and (▼) methyl *tert*-butyl ether. (Reprinted with permission from ref 101. Copyright 2011, Elsevier).

This effect was attributed to the lower miscibility/solubility of the substrate in the nonpolar solvent leading to stronger adsorption of the amide on the catalyst surface, and ultimately resulting in a higher reaction rate. Variations in the solubility of hydrogen in the different solvents were also considered, this being the highest in hexane, and least with the most polar solvent used, methanol; reaction rate was found to increase with increasing H₂ solubility. Previously, estimates of hydrogen

solubility in DME, as functions of pressure and temperature, were made to ascertain whether a deficiency of hydrogen in solution might be responsible for the generally low rates of amide hydrogenation.⁹⁷ With estimated H₂:amide (CyC(O)-NH₂) molar ratios of 17:1 and 13:1 in DME under standard working conditions of 100 bar H₂, 160 and 130 °C, respectively, this could however be effectively discounted. Nevertheless, at 20 bar H₂, this ratio decreased to 4.6:1, implying that H₂ starvation might pose a more significant problem, particularly with the most polar solvents used in the N-methylpyrrolidin-2-one work.¹⁰¹

Finally, the solvent effects noted in Stein's and Breit's⁹⁹ work on PdRe/graphite catalysts provide a stark contrast with the earlier results obtained using PtRe/TiO₂ catalysts.¹⁰¹ With the former the optimum combination of *N*-acetyl piperidine conversion (81%) and selectivity to *N*-ethyl piperidine (100%) was achieved with DME (not used in the work of Hardacre et al.¹⁰¹), with 1,4-dioxane, diglyme, and cyclohexane all proving inferior. The use of other solvents such as water, ethanol, THF, and toluene led to inhibition of all catalytic activity. Notwithstanding the use of different catalysts, the extreme variations in the solvent effects observed, relative to those listed in Table 6, could possibly be a consequence of the different experimental methods used, well-stirred standard autoclaves versus small-scale high throughput testing methods. If rapid gas/liquid (H₂/solvent) equilibration was not achieved using the latter approach, this could account for the disparity. Whatever the explanation, solvent effects can clearly play a significant role in the overall chemistry associated with carboxamide hydrogenation, and careful attention should be directed toward selection of the most appropriate solvents in future work.

4.5.1. Effect of Water on Activity/Selectivity. As a further point in the context of solvent effects, the role of water, the coproduct of carboxamide hydrogenation (eq 1), also deserves consideration. Using standard liquid-phase procedures, water accumulates in solution as a function of conversion, up to stoichiometric amounts in relation to the starting amide. The question posed concerns whether the presence of water is beneficial, deleterious, or neither, to reaction rate and product selectivity. Reference to the proposed reaction pathways for amide reduction (Schemes 9 and 10) suggests that CyCH₂OH formation may occur via competitive hydrogenolysis of the intermediate hemiaminal with the loss of ammonia (hence the reasoning for the conventional addition of NH₃ to suppress secondary amine formation). Because water is released during dehydration of hemiaminal to the postulated imine, accumulation of additional water during amide hydrogenation would presumably serve to inhibit this step, leading to a higher standing hemiaminal concentration, and thereby favoring CyCH₂OH formation. Using Ru/Mo catalysts, the incorporation of 1 and 5 equiv of water (relative to amide) prior to the start of the reaction was in fact found to lead to incremental reductions in selectivity to primary amine, in favor of CyCH₂OH, once again with little or no secondary amine formation.⁹⁶ When added in significantly greater amounts (30 equiv), a drastic reduction in conversion (from 100% without water to 30%) was noted, with a complete switch in selectivity in favor of CyCH₂OH (CyCH₂NH₂:CyCH₂OH = 1:3). The addition of water in greater than equivalent amounts certainly appears to have a deleterious effect on conversion and product selectivity, and the development of methods for water removal immediately on formation during amide hydrogenation could

indeed be beneficial. Although a previous unsuccessful attempt was made to remove water by the addition, at the outset, of molecular sieves to a Rh/Mo amide hydrogenation catalyst system,⁹⁵ this approach has now been shown to have a beneficial effect on the reactivity of the PdRe/graphite catalyst, and attributed as potentially due to removal of water on formation during *N*-acetyl101 This approach might therefore benefit from further attention in subsequent research on catalytic amide hydrogenation.

A further potential consequence of the presence of additional water is enhancement of an alternative competing amide reaction pathway to hydrogenation, hydrolysis to the corresponding carboxylic acid, followed by reduction (eq 9).



This is well-known to be unfavorable in thermodynamic terms, requiring rather forcing reaction conditions, prolonged heat in the presence of either strong acid or base catalysts.³ As a consequence, the viability of this route seems rather less likely, particularly at the final stoichiometric water concentration levels normally present during standard amide hydrogenation reactions. Also, the question of water miscibility with the solvent may present an additional significant factor. Finally, a point that is relevant to the second step in eq 9 is the demonstration of the hydrogenation of CyCO₂H to CyCH₂OH using Ru/Mo catalysts (see section 4.2).⁹⁶

4.6. Carboxamide Reduction in the Vapor Phase

Following the very early unsubstantiated report of gas-phase catalytic amide hydrogenation,⁶⁷ almost all subsequent catalytic reaction systems have been conducted in the liquid phase. As indicated in section 2, amides are characterized by involatility, low vapor pressure, and very high boiling points. As a consequence, high reaction temperatures (in excess of 250 °C) are required for true vapor phase catalytic reactions, thereby minimizing the viability of vapor phase reduction methods. In view of the original claim for vapor phase catalytic hydrogenation, however, a brief investigation of the most volatile representative substrates, for example, *N*-methylformamide (mp -4 °C, bp 183 °C) and *N,N*-dimethylpropionamide (mp -45 °C, bp 174–175 °C), was undertaken using a fixed bed flow reactor⁹⁸ and catalysts comprising examples of Rh/Mo,⁹⁵ Ru/Mo,⁹⁶ and copper–chromium oxide (5 wt % CuO–Cr₂O₃). Over a range of H₂:substrate ratios and temperatures between 180 °C and as high as 400 °C, no products of amide hydrogenation were detected. Similarly, the use of butanamide (*n*-butyramide, mp 114 °C, bp 216 °C) over the same copper–chromium oxide catalyst [H₂:*n*-C₃H₇C(O)NH₂ = 7.5 and 400 °C] resulted in zero amide conversion. By contrast, vapor phase hydrogenation of propionitrile (the dehydration product of butanamide) gave 100% conversion to di(*n*-butyl)amine in ca. 90% selectivity over a bimetallic Rh/Mo catalyst at 160–200 °C,⁹⁸ a value that appears comparable with those obtained by Huang and Sachler using monometallic Rh/NaY catalysts.¹¹² In view of these observations, the viability of simple, effective catalytic hydrogenation of amides in the vapor phase may conclusively be discounted.

Nevertheless, previous reports had described attempts, using copper–chromium oxide catalysts, to develop what were described as continuous “solvent-free” processes for the reduction of tertiary amides, typically *N,N*-dimethyl-substituted C₁₂–C₁₄ amides^{79–81} (see section 4.1). The first⁷⁹ involved sequential removal of gaseous components and replacement by

hydrogen using typical reaction conditions of ca. 30–40 bar H₂, 260 °C, 5 h. Although described as “solvent-free”, the process required addition of dimethylamine for removal of the water formed as a product of amide reduction, this comprising the “gaseous component”. The second report⁸⁰ described continuously contacting similar tertiary amides “in the vapor phase” with hydrogen at 50–300 bar and 200–350 °C, also in the presence of the same auxiliary amine. However, it was not unequivocally established in either case if the reaction did actually occur truly “in the vapor phase”.

In a subsequent development, in which amide vapor pressure versus temperature relationships were considered in detail, the conclusion was reached that the amide hydrogenation reactions described in refs 79 and 80 could not have been carried out truly “in the vapor phase”.^{113–115} However, by feeding a carboxamide in combination with an auxiliary amine, in the vaporized form with H₂ (at 2–50 bar), over a copper–chromium oxide catalyst at ca. 250 °C, it has proved possible to obtain the expected product of amide reduction in high yield and high selectivity.^{113–115} (See also section 4.1, Table 4, entries 4, 5, section 4.2.3.3, Table 5.) The process, which may also be carried out in a continuous fixed bed reactor, has been exemplified for the following amide/amine/ammonia combinations: *N,N*-dimethyldecylamide/(CH₃)₂NH, *N,N*-dimethylacetamide/(CH₃)₂NH, and acetamide/NH₃. The product distribution obtained from acetamide, at 10 bar H₂ and 250 °C, comprised C₂H₅NH₂, (C₂H₅)₂NH, and (C₂H₅)₃N (95.5%, 3.5%, and 0.5%) respectively.

In a related development using copper–chromium oxide catalysts, an apparent adventitious discovery showed that the inclusion of a nucleophilic reagent such as a hydroxide, methoxide, or halide, etc., with the standard reaction components could not only lead to both improved tertiary amine product selectivity and conversions, but also facilitate reduction at considerably lower hydrogen pressures than had previously proved possible.¹¹⁶ Thus, high boiling mixtures of *N,N*-dimethylalkylamides, (CH₃)₂NC(O)R, in which R = C₁₂–C₁₄ aliphatic alkyl chains, were hydrogenated to the corresponding tertiary amines in 99% conversion and 99% selectivity at ca. 30 bar H₂, 3–4 h, and/or ca. 10 bar H₂, 11–12 h, respectively, at 250 °C (Table 4, entry 5(i) and (ii), cf., Cu/Zn example, Table 5, entry 5). Although high amide conversions were also maintained without the use of the nucleophile, unacceptably low selectivities to the tertiary amine, typically 79% with 21% mixed amine byproduct, were evident. These reactions were carried out in continuous mode, using a closed loop amidation reactor, which allowed convenient removal of the water formed during hydrogenation by condensation, thereby presumably limiting oxygenated by-product formation. The presence of an additional primary or secondary amine such as dimethylamine (cf., ref 84) used as an auxiliary was also found to improve the process. Although the effect of the nucleophile was claimed for primary, secondary, and tertiary amides, it was however only exemplified for the high boiling mixtures of *N,N*-dimethylalkylamides referred to above (see also section 4.2.3.3).

In summary, therefore, for the reasons outlined above simple, direct, vapor phase reduction of amides to the corresponding amine is not viable. However, by careful attention to the equilibrium concentrations of the amide of interest in the vapor phase as a function of temperature, in combination with the use of an auxiliary amine and/or nucleophile (the exact roles of which, although presumably related to suppression of

Table 7. Selected Examples of Homogeneous Catalysts for Amide Hydrogenation: Reaction Conditions, Major Products, Selectivity (s), and Conversion^a

entry	amide substrates	catalyst components	reaction conditions				% yield/ selectivity	% conversion	ref
			bar H ₂	°C	h	products			
1	C ₃ H ₇ C(O)NH ₂	Ru(acac) ₃ /triphos	40	200 ^b	14	(C ₄ H ₉) ₂ NH (C ₄ H ₉) ₃ N	47s 52s	100	118– 120
2	C ₈ H ₁₇ C(O)N(H)Ph	Ru(acac) ₃ /triphos	40	200 ^b	14	C ₉ H ₁₉ N(H)Ph C ₉ H ₁₉ OH	99s 1s	100	118, 121
3	RC(O)N(H)Ph (12 secondary amides)	Ru(acac) ₃ /triphos/MSA	10	200–220	16	RCH ₂ N(H)Ph	75–93	90–100	120
4	N-phenylpyrrolidin-2-one	Cp*[Cp* = C ₅ (CH ₃) ₅] RuCl(PtN)]/KO'Bu	50	100	24	PhN(CH ₂) ₄ OH	73y	84	125, 126
5	CH ₃ OCH ₂ C(O)N(H) CH ₂ Ar	[BPy-PPN-Ru(II)] pincer complex	10	110	48	CH ₃ OCH ₂ CH ₂ OH H ₂ NCH ₂ Ar	89y 90y		127
6	N-acetylpyrrolidin-2-one	Ru(H ₂)[Ph ₂ (CH ₂) ₂ NH ₂] ₂ / KN[Si(CH ₃) ₃] ₂	50	80	16	HO(CH ₂) ₄ N(H) C(O)CH ₃	minor		129
						pyrrolidine-2-one	major		
7	CH ₃ C(O)N(CH ₃) ₂	Ru(H ₂)[Ph ₂ (CH ₂) ₂ NH ₂] ₂ / KN[Si(CH ₃) ₃] ₂	50	100	24	C ₂ H ₅ OH HN(CH ₃) ₂	50y 50y		129
8	PhC(O)NH ₂	RuCl ₂ (PtN) ₂	80	160	216	PhCH ₂ OH	74–83y	84–87	132
9	PhC(O)N(H)CH ₂ Ph	RuCl ₂ (PtN) ₂	80	160	24	PhCH ₂ OH PhCH ₂ NH ₂	92y 92y	92	132

^aEntries 1–3, C–O bond cleavage predominates; entries 4–9, exclusively C–N bond cleavage. ^bA reaction temperature of 164 °C was quoted in the initial report.¹¹⁸ MSA = methanesulfonic acid.

secondary reactions, are not entirely clear, and both of which must of course require separation and recycling), the very desirable prospect of continuous catalytic amide reduction truly “in the vapor phase” is proving possible. The newer generation of bifunctional/bimetallic heterogeneous catalysts described in this Review should certainly merit investigation in this context. Once again, however, the high temperature requirements demanded by the vapor phase work, which is ideally suited to the hydrogenation of simple long-chain tertiary amides, clearly limit any application to the reduction of more complex amides that contain other sensitive functional groups.

5. HOMOGENEOUS CATALYSTS FOR CARBOXYAMIDE REDUCTION

5.1. Organometallic Catalyst Precursors

There have been several recent accounts of the use of Ru-containing organometallic complexes as homogeneous catalyst precursors for the reductive cleavage, not only of C–O, as preferred for the formation of the corresponding amine, but also of C–N bonds contained in a wide range of amides.^{10,11,117–132}

5.1.1. C–O Bond Cleavage over Ru Catalysts. Of greatest relevance to the foregoing text relating to heterogeneous catalysts are reports of the use of thermally robust Ru precursor complexes containing the ligand 1,1,1-tris(diphenylphosphinomethyl)ethane, the so-called “triphos”, formed *in situ*, for the hydrogenation of carboxylic acids¹¹⁷ and amides.^{118–121} Products obtained from a primary amide such as butanamide, C₃H₇C(O)NH₂, comprised an approximately 1:1 mixture of (C₄H₉)₂NH and (C₄H₉)₃N (the exact ratio being dependent on the amount of added water, see comment below), minor amounts of the secondary amide C₃H₇C(O)N(H)C₄H₉, but none of the primary amine (Table 7, entry 1). The absence of any primary amine in the product distribution is very reminiscent of the pioneering work of Adkins using heterogeneous copper–chromium oxide catalysts

(see section 4.1).⁶⁵ Furthermore, coaddition of ammonia was found to effectively reverse the selectivity order, giving the primary amine, *n*-butylamine (85%), and the coproduct *n*-butanol (15%). Coincidentally, this 6:1 ratio also bears a striking resemblance to the results described in section 4.2.1 on heterogeneous Ru/Mo catalysts for CyC(O)NH₂, PhC(O)NH₂, and C₃H₇C(O)NH₂ hydrogenation (cf., Table 2, entries 12, 16, and 18).⁹⁶ In the initial work, the presence of water at the start of the reaction was found to lead to a reduction in selectivity, with increased formation of *n*-butanol. Nevertheless, water, which, as a mandatory coproduct of amide hydrogenation via C–O bond hydrolysis, is subject to increasing concentration during the course of reduction, was found to be essential to maintain catalyst stability. There must therefore be some concern over the long-term integrity of such a “homogeneous” system, particularly in light of the fact that the simple addition of an amine such as aniline (instead of ammonia) to the system also led to reduced catalyst stability. No attempts at catalyst recycle were reported.

Subsequently, a significant portion of this work proved irreproducible,⁹⁹ largely as a consequence of an inaccuracy in the measurement of the initially reported reaction temperature of 164 °C.^{118,119} After correction to the true value of 200 °C, thereby representing a significant increase in the severity of the overall reaction conditions, reproducibility under these modified reaction conditions was independently confirmed in three separate research laboratories, Freiburg,⁹⁹ Aachen, and St. Andrews.¹²⁰

In contrast to the above findings using butanamide as substrate, using the same catalyst and revised reaction conditions (less the requirement for ammonia), the secondary amide N-phenylnonamide (Table 7, entry 2) was reduced to the corresponding secondary amine in up to 99% selectivity,^{118,121} thereby providing a rare example of a more facile reduction of a secondary amide (cf., section 4.2.2). Also of significance, in providing an additional contrast with the majority of heterogeneous catalysts that have been described

for amide hydrogenation, a desirable feature is that the aromaticity of the phenyl ring is retained during reduction of the amide carbonyl group. However, aromatic rings were only retained when using Hastelloy C rather than stainless steel pressure vessels. The use of glass liners, as the standard procedure to be adopted in all catalytic hydrogenation work, was found to circumvent phenyl ring hydrogenation when using stainless steel autoclaves.

The most recent development concerns the beneficial effect of addition of an acid such as methanesulfonic acid (MSA) to the Ru/triphos catalyst, which appears to lead to a more stable and reproducible system.¹²⁰ This allows hydrogenation of secondary (Table 7, entry 3) and tertiary amides to the respective amines in up to 93% selectivity at pressures as low as 10 bar H₂, the penalty being the need for particularly high temperatures (220 °C) in the case of the latter. With the addition of both aqueous ammonia and MSA to the reaction system, it proved possible to obtain *n*-butylamine in 61% selectivity and 100% butanamide conversion at reduced hydrogen pressure (10 bar H₂, 200 °C, and 16 h). However, the primary amine selectivity under these reaction conditions actually compares unfavorably with that reported in the initial work using the coaddition of ammonia to the system (see above).¹¹⁸ A range of Ru methylsulfonate complexes, formed from Ru(acac)₃, triphos, and MSA, were prepared in an attempt to probe the mechanistic role of MSA in these reactions, although the actual reaction mechanism of bond cleavage still remains obscure. Finally, the presence of the aforementioned phenyl ring in the secondary amide substrate appears to represent an essential feature associated with ensuring more facile and efficient catalysis, an explanation for which is not obvious at the present time.

5.1.2. C–N Bond Cleavage over Ru Catalysts. Of perhaps greater significance to homogeneous catalysis, certainly in mechanistic terms, has been the application, by Ikariya et al.,^{122–124} of bifunctional molecules of the type [Cp*Ru(P \cap N)], in which Cp* = η^5 -C₅(CH₃)₅ and P \cap N comprise a wide range of P- and N-functionalized bidentate ligands, for the highly selective hydrogenation of various carboxylic acid derivatives including imides and *N*-acylcarbamates. In subsequent work,^{125,126} the reductive cleavage of amide C–N bonds during the homogeneous catalytic hydrogenation of tertiary amides such as *N*-phenyllactams and benzamides has been reported, thereby providing a further example of the C–N bond-breaking mode initially exemplified by Adkins et al.⁶⁵ The catalysts used comprised [Cp*RuCl(P \cap N)] (Cp* = η^5 -C₅(CH₃)₅, and P \cap N, for example, Ph₂P(CH₂)₂NH₂) at 30–50 bar H₂, 80–100 °C, 2–72 h, in the co-presence of ca. 1–2.5 equiv of a base such as KO^tBu. A specific example included the hydrogenation of *N*-phenylpyrrolidin-2-one to 4-(phenylamino) butan-1-ol (Table 7, entry 4). Because *N*-benzylpyrrolidin-2-one proved unreactive, it was concluded that a key requirement for substrate activity was the direct attachment of an aryl group to nitrogen (cf., section 5.1.1).

Subsequently, Milstein et al.¹²⁷ demonstrated the use of dearomatized, bipyridyl-based PNN Ru(II) pincer complexes [PNN = 2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl) pyridine] (Figure 7), as homogeneous catalysts for the selective reduction of secondary and tertiary amides of the type ArCH₂N(H)C(O)R, in which R contains an ether group, to ArCH₂NH₂ and RCH₂OH (eq 10) (i.e., not the secondary amine ArCH₂N(H)CH₂R, the expected product of C–O bond cleavage).

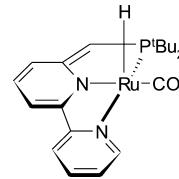
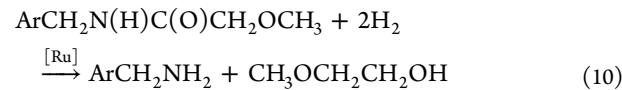
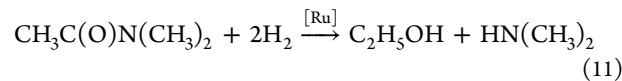


Figure 7. Ru(II)/bipyridyl-based pincer precatalyst for hydrogenation of amides to alcohols and amines.¹²⁷



This reaction took place under reasonably mild conditions, 10 bar H₂, 110 °C, 48 h (Table 7, entry 5), giving generally high reaction selectivity at moderate conversions. In very recent work, new PNN ruthenium pincer complexes based on both 2,2'-bipyridinemethane phosphine derivatives and 2,2'-oxobispyridine phosphine ligands have provided further examples of metal-linked cooperation in cyclometalation and catalysis.¹²⁸ The new complexes have been shown to act as suitable precursors for the catalytic hydrogenation of secondary amides (at 10 bar H₂, 110 °C, 48 h) with moderate activity, via C–N bond scission, giving alcohols and amines (cf., eq 2).

John and Bergens¹²⁹ described the use of what is presumably a closely related Ru catalyst system, derived from Ph₂P(CH₂)₂NH₂ and *cis*-[Ru(CH₃CN)₂(η³-C₃H₅)(COD)]BF₄ (COD = 1,5-cyclooctadiene) in the presence of a large excess of a base such as KN[Si(CH₃)₃]₂, for the reduction of *N*-acetylpyrrolidin-2-one. Using reaction conditions of 50 bar H₂, 80 °C, and 16 h (Table 7, entry 6), the ring-opened *N*-acetyl amino alcohol HO(CH₂)₄N(H)C(O)CH₃ and pyrrolidine-2-one were formed as minor and major products, respectively. Other amides, including *N,N*-dimethylacetamide, were also shown to undergo C–N in preference to C–O bond cleavage under similar reaction conditions (eq 11) (Table 7, entry 7).



In general, secondary amides were found to be less reactive than tertiary amides.

Subsequent work with Ru catalyst precursors of this type enabled the demonstration of a base-catalyzed bifunctional addition to amides and imides at low temperature, the results of which have led to a proposed new pathway for carbonyl group hydrogenation in homogeneous systems.¹³⁰

The relative energetics of C–N versus C–O bond cleavage has been thoroughly explored for the first time using DFT calculations relating to the Milstein catalyst system,¹³¹ leading to the conclusion that the former is energetically favorable to the tune of 10 kcal mol⁻¹, thereby accounting for the observed reaction selectivity. Whether this favored C–N bond cleavage applies to homogeneous catalyst systems other than those containing Ru as the active transition metal center is currently open to debate. The apparent preference for reductive cleavage of C–N rather than C–O bonds over these organometallic [Ru(P \cap N)] containing catalysts is clearly of considerable mechanistic significance. Nevertheless, at the current stage of development, any application of such systems for the direct hydrogenation of amides to the corresponding amines (cf., eq 1), as available to many heterogeneous catalysts, is precluded.

Table 8. Hydrosilylation Catalyst Systems for Amide Reduction

entry	amide substrate	catalyst precursor	hydrosilane/hydrosiloxane	temp, °C	time	yield (%)	ref
1	CH ₃ C(O)N(CH ₂ Ph) ₂	RhH(CO)(PPh ₃) ₃	Ph ₃ SiH ₂	20	1	86–95	133
2	N-acetylpyrrolidine, and derivatives	various group 7–10 transition metal complexes	Et ₃ SiH, and other mono-hydrosilanes	100	16	80–99	134
3	PhCH ₂ CH ₂ C(O)N(CH ₃) ₂	[(acenaphthylene)Ru ₃ (CO) ₇]	Me ₂ EtSiH	20	0.5	75	135
4	N,N-substituted acetamides	TiCp ₂ X ₂ (X = F, Me)	PhMeSiH ₂	80		>90	136
5	as 4 above, with bulky N-substituents	MoO ₂ Cl ₂	PhSiH ₃	100	20	81–87	137
6	PhCH ₂ CH ₂ C(O)N(CH ₃) ₂	H ₂ PtCl ₆	TMDS ^a	50–75	5	98	138
7	PhCH ₂ C(O)N(CH ₃) ₂ , and numerous –NPh ₂ derivatives	Fe ₃ (CO) ₁₂	PhSiH ₃ and/or PMHS ^b	80	8–24	97	139, 140
8	PhCH ₂ C(O)N(CH ₃) ₂ , and numerous derivatives	Zn(OAc) ₂	(EtO) ₃ SiH	25	22	97	141
9	PhC(O)N(CH ₃) ₂	Fe(OAc) ₂ /([PhHEMIM][OTf]) ₂ ^c	PHMS	65	16–18	75	142
10	PhCH ₂ C(O)N(CH ₃) ₂ , and derivatives	(POCOP)Ir(H) ₂ (acetone) ^{+d}	Et ₂ SiH ₂ /H ₂	60	1.5	>90	143
11	PhC(O)N(H)CH ₃	[RuCl ₂ (CO) ₃] ₂ /EtI/Et ₂ NH	Et ₃ SiH	100	16	97	144
12	PhCH ₂ CH ₂ C(O)N(H)Et, and numerous derivatives	[(acenaphthylene)Ru ₃ (CO) ₇]	TMDS ^a	40	8	86	144
13	PhCH ₂ CH ₂ C(O)N(H)Bu ^t	H ₂ PtCl ₆	TMDS ^a	75	8	79	138
14	secondary amides, particularly 2,2'-difluoramides	RhCl ₃	PhSiH ₃	20	0.5–24	98	145
15	PhC(O)N(H)CH ₃ , and numerous Ph ₂ N-derivatives	Fe ₃ (CO) ₁₂	PMHS ^b	100	24	99	139
16	PhC(O)N(H)CH ₂ Ph and derivatives	Cu(pybox) ^e	TMDS ^a	65–100	24	70–90	136
17	PhC(O)N(H)CH ₃ and 22 derivatives	[Ir(COE) ₂ Cl] ₂ ^f	Et ₂ SiH ₂	23	7	98	147
18	n-C ₇ H ₁₅ C(O)NH ₂	[Ir(COE) ₂ Cl] ₂ ^f	Et ₂ SiH ₂	23–80	1–30	95–99	147
19	PhC(O)NH ₂ , and substituted derivatives	Os ₃ (CO) ₁₂ /Et ₂ NH	Et ₃ SiH	100	16	56	134
20	CH ₃ (CH ₂) ₁₆ C(O)NH ₂	Ti(OPr ⁱ) ₄	PMHS ^b	100	24	>95	148
		Ti(OPr ⁱ) ₄	PMHS ^b	100	24	90	148

^aTMDS = 1,1,3,3-tetramethyldisiloxane, (HMe₂Si)₂O. ^bPMHS = polymethylhydroxysiloxane. ^c[PhHEMIM][OTf] = 1-(2-hydroxy-2-phenylethyl)-3-methylimidazolium triflate. ^dPOCOP = 2,6-bis(di-tert-butylphosphinito)phenyl. ^eFor "pybox", see Figure 8. ^fCOE = cyclooctene. Me = CH₃, Et = C₂H₅, Ph = C₆H₅, Prⁱ = iso-C₃H₇, Bu^t = tert-C₄H₉. All reactions were carried out at ambient pressure.

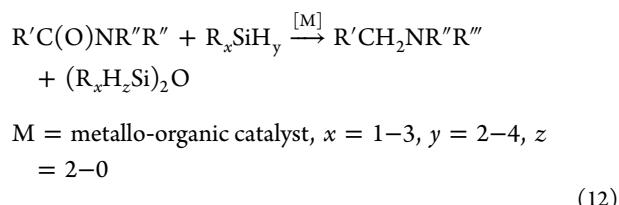
Additional examples of C–N bond scission have very recently been reported by Saito et al.¹³² Using the combination of a sterically congested and coordinatively unsaturated Ru complex, together with a bulky base such as sodium 2-methyl-2-adamantoxide, this catalyst system has been shown to be effective for the hydrogenation of a range of unactivated amides under the general reaction conditions 20–80 bar H₂, 120–160 °C, and 24–216 h, with entries 8 and 9 of Table 7 providing specific examples. Thus, the secondary amide PhC(O)N(H)CH₂Ph, and derivatives thereof, may be hydrogenated to a 1:1 mixture of PhCH₂OH and PhCH₂NH₂ (cf., eq 2), via C–N bond scission, consistent with earlier work using homogeneous Ru catalysts. With the use of much longer reaction times (216 h), the primary amide benzamide, PhC(O)NH₂, may also be reduced to PhCH₂OH (and presumably NH₃), via the C–N bond cleavage pathway. Both reactions are characterized by high conversions and product selectivity, and a two-step reaction pathway for reduction has been suggested.¹³²

In conclusion, it is important to recognize that reports of the use of truly homogeneous catalysts in carboxamide hydrogenation are very much in their infancy, examples currently being restricted to the use of catalyst precursor complexes containing a single element, ruthenium (cf., Table 7). As a consequence, much new science in other areas must await discovery.

5.2. Metallo–Organic Catalyst Precursors and Hydrosilylation Reagents

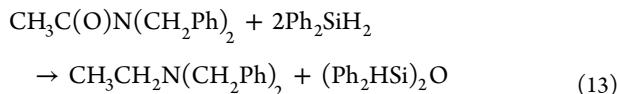
Given their air and water stability, easy manipulation, and generally low toxicity, organo-hydrosilanes and -hydrosiloxanes,

in combination with organometallic/metallo-organic catalyst precursors, have emerged during the past 15 years as effective alternatives to existing hydride reagent sources such as LiAlH₄, NaBH₄, and boranes (see sections 3.1, 3.2), certainly for small-scale amide reductions. These reactions proceed according to the general, and idealized, eq 12.



The rate of new, and significant, discoveries is rapidly increasing, and effective metallo–organic precursors now include examples containing the following transition metal centers: Ti, Mo, Mn, Re, Fe, Ru, Os, Rh, Ir, Pd, Pt, Cu, Au, and Zn, in very marked contrast to results described in the preceding section 5.1. Most of these hydrosilylation reductions are highly chemoselective and display tolerance toward other reducible functional groups, thereby offering a distinct advantage over reagents such as LiAlH₄, NaBH₄, B₂H₆, etc. A general trend that has emerged from this work is an order of reactivity toward reduction comprising tertiary > secondary > primary amide, the last proving the most problematic. Selected examples of applications are summarized in Table 8 (tertiary amides, entries 1–10, secondary amides, entries 11–17, and primary amides, entries 18–20), to highlight the rapidly expanding range of available options. Tertiary amide substrates,

including *N,N*-disubstituted acetamides (entries 1, 4, 5), *N,N*-dimethyl-3-phenylpropionamide (entries 3, 6), and *N,N*-dimethyl-2-phenylacetamide (entries 7, 8, 10), have featured most strongly, thereby allowing some comparative information concerning choice of metal, organohydrosilane and hydrosiloxane combinations. One of the first examples of this approach was the report of Ito et al.¹³³ (Table 8, entry 1), in which the reduction of *N,N*-dibenzylacetamide using a Rh-containing catalyst, for example, HRh(CO)(PPh₃)₃, activated by Ph₂SiH₂, was found to proceed under ambient conditions in THF as solvent, giving *N,N*-dibenzylethylamine in up to 95% yield (eq 13).



A wide range of tertiary amides was investigated, including those containing bromo, ester, or epoxy functional groups, all of which were converted in a chemoselective manner into the corresponding amines. However, primary and secondary amides proved unreactive toward Ph₂SiH₂, as proved to be a general feature of hydrosilylation catalysts, prior to the more recent developments.

Although a monohydrosilane such as Et₃SiH, which is more stable and less expensive than a polyhydrosilane, was ineffective as a reagent at room temperature, Igarishi and Fuchikami¹³⁴ reported that at higher temperatures (100 °C) *N*-acetylpyrrolidine could be effectively reduced to *N*-ethylpyrrolidine (in 80–99% yields) using Et₃SiH in combination with a range of transition metal complex precursors. The additional use of an amine (Et₂NH) and/or iodoalkane such as EtI as cocatalysts, the reasons for which were not explained, led to improvements in catalytic productivity (Table 8, entry 2). Et₃SiH and other monohydrosilanes (at amide:R₃SiH = 1:3–4 equiv) were also found to be applicable to the reduction of a range of tertiary (including cyclic and acyclic) amides. Furthermore, although secondary amides were reduced in good yields (cf., entry 11), primary amides proved considerably more resistant to these catalysts (cf., entry 18).

Subsequently, Nagashima et al. (entry 3) reported the successful reduction of tertiary amides at room temperature when using a triruthenium carbonyl cluster containing a bridged acenaphthylene ligand, $[(\mu_3,\eta^2,\eta^3,\eta^5\text{-acenaphthylene})\text{-Ru}_3(\text{CO})_7]$, as catalyst precursor, after activation with a trialkylsilane such as Me₂EtSiH.¹³⁵ Other catalyst systems that have been reported to promote hydrosilylation of *N,N*-substituted acetamides, at 80–100 °C, include Cp₂TiX₂ (X = F, CH₃)/MePhSiH₂ (entry 4),¹³⁶ and MoO₂Cl₂/PhSiH₃ (entry 5), the latter also proving suitable for the reduction of substrates containing bulky cyclic substituents.¹³⁷

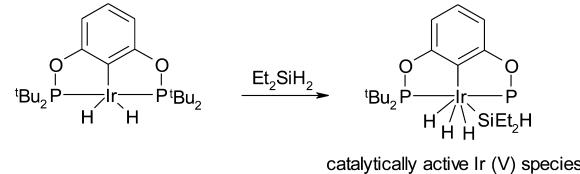
The recognition of synergistic behavior associated with hydrosiloxanes containing dual Si–H groups was exploited in the first use of Pt catalysts for the reduction of a range of tertiary [also secondary (see below)] amides¹³⁸ (entry 6). The reduction of amides containing other reducible functional groups such as NO₂, CO₂R, CN, C=C, Cl, and Br moieties proceeded with all of these groups remaining intact. Nevertheless, attempted Pt-catalyzed reductions of primary amides such as decanamide and *p*-toluamide were unsuccessful.

Beller et al.^{139,140} described the iron-catalyzed reduction of *N,N*-dimethylbenzylamide, and numerous derivatives thereof, activated either by PhSiH₃ or, more significantly, by the

inexpensive PMHS (PMHS = polymethylhydrosiloxane) (entry 7) at 80 °C, a discovery that was rapidly followed by the announcement of a Zn(OAc)₂/(EtO)₃SiH combination that was effective for an equally highly chemoselective reaction at room temperature (entry 8).¹⁴¹ Subsequently, an in situ-generated Fe/N-heterocyclic carbene complex, formed from an imidazolium salt, has also been utilized in tandem with PMHS for the direct hydrosilylation of tertiary amides such as *N,N*-dimethylbenzamide at 65 °C and 16–18 h (entry 9). Significant findings from this work concern a substantial reduction in reaction time (from 16–18 to 5–7 h) and an increased chemoselectivity, following the addition of catalytic quantities of LiCl to the system. This has been attributed to Lewis acid-mediated decomposition of the quaternary intermediate during the first step of the reduction reaction. The new development has been applied to an extended range of tertiary benzamides, giving amine yields in the range 92–77%,¹⁴² primary and secondary amides once again proving unreactive.

In a landmark development, Brookhart et al. have described the use of a cationic Ir(III) pincer complex, (POCOP)Ir(H)₂(acetone)⁺ [POCOP = 2,6-bis(di-*tert*-butylphosphinito)-phenyl], to catalyze the reduction of a range of tertiary amides using Et₂SiH₂ as reductant (entry 10).¹⁴³ Remarkably, the neutral silyl trihydride Ir(V) complex (POCOP)IrH₃(Et₂SiH) (Scheme 11) has been identified as the catalytically active species. However, these systems proved unreactive toward secondary amides.

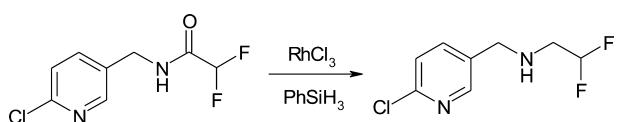
Scheme 11. A Highly Efficient Ir(V) Silyl Complex [(POCOP)Ir(H)₂(acetone)]⁺ for the Catalytic Hydrosilylation of Tertiary Amides¹⁴³



The first evidence of successful selective catalytic hydrosilylation of secondary amides was provided by Igarashi and Fuchikami¹³⁴ using a Ru/Et₃SiH/EtI/Et₂NH catalyst combination (entry 11). Subsequently, using the aforementioned Ru carbonyl cluster catalyst precursor,¹³⁵ Nagashima et al. also reported the reduction of secondary amides of the type PhCH₂CH₂C(O)N(H)R (R = Me, Et, Pr^t) (entry 12).¹⁴⁴ Here, although the product distribution from Me₂EtSiH comprised a mixture of secondary amines, tertiary amines, and silyl enamines, use of a bifunctional siloxane such as 1,1,3,3-tetramethyldisiloxane (TMDS) and higher catalyst concentrations led to considerable improvements in overall yields of the secondary amine. Acidic workup of the reaction mixtures afforded the corresponding ammonium salts, which, after treatment with base, facilitated the isolation of secondary amines in high purity. Reactivity of these catalyst systems toward primary amides was, once again, very low. Nagashima's Pt/TMDS-catalyzed system was also found to be effective for the hydrosilylation of secondary amides, for example, PhCH₂CH₂C(O)N(H)Bu^t (entry 13).¹⁴⁴

A patented application of this general approach concerns the production of a range of 2,2'-difluoroethylamine derivatives, by reduction of secondary amides of the type shown in Scheme 12 (entry 14)¹⁴⁵ for use as intermediates in the manufacture of

Scheme 12. Hydrosilylation of Fluorine Containing Functionalized Amides Using $\text{RhCl}_3/\text{PhSiH}_3$ ¹⁴⁵



insecticides. Amide reduction is carried out via hydrosilylation using RhCl_3 and PhSiH_3 (alternatively $\text{NaBH}_4/\text{BF}_3\text{-Et}_2\text{O}$), giving the corresponding amines in 98% yield.

The $\text{Fe}_3(\text{CO})_{12}$ /PMHS catalyst combination was also found to be effective for the reduction of a secondary amide, *N*-methylbenzamide, in excellent yield (entry 15).¹³⁹ In a further development, the use of *in situ*-generated cationic copper/‘pybox’/TMDS catalyst systems (pybox = sterically hindered tridentate nitrogen ligands, particularly substituted pyridinebisoxalidines, Figure 8) has been demonstrated for the selective

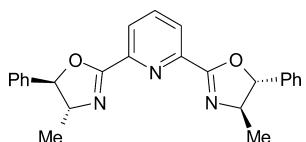
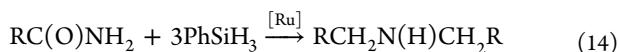


Figure 8. Example of a preferred ‘pybox’ ligand used in hydrosilylation of secondary amides using copper catalysts.

reduction of a range of secondary amides, particularly *N*-benzylbenzamides, substituted derivatives thereof, and $\text{RC(O)-N(H)CH}_2\text{Ph}$ ($\text{R} = \text{CH}_3, \text{Et}$), giving the corresponding amines in 70–90% yields (entry 16).¹⁴⁶ Finally, the use of a catalyst precursor system comprising $[\text{Ir}(\text{COE})_2\text{Cl}]_2/\text{Et}_2\text{SiH}_2$ (4 equiv) (COE = cyclooctene) has been demonstrated for the reduction of secondary amides such as *N*-methylbenzamide at ambient temperature (entry 17). The reaction proceeds via an imine intermediate that, remarkably (see also section 6.1), could be isolated and characterized when using 2 rather than 4 equiv of hydrosilane.¹⁴⁷ This also appears to be the first hydrosilylation catalyst system that allows the reduction of secondary amides at room temperature.

The most demanding challenge, successful application of this general approach to the reduction of primary amides, only partially achieved in Igarishi and Fuchikami's work (entry 18),¹³⁴ has also recently been met by Lemaire et al.,¹⁴⁸ using a Ti(OPr)₄/PMHS catalyst system. Here, several substituted benzamides (entry 19), and a long alkyl amide chain substrate (entry 20), afforded the products as amine hydrochloride salts after acidic workup of the reaction mixtures, from which, after treatment with base, the amines could be readily recovered in high purity. However, in such a system the Ti component also requires expensive recycle!

Finally, a very recent development is the report of selective hydrosilylation of a range of primary amides to secondary amines (eq 14).¹⁴⁹



The system uses a $[\text{RuCl}_2(\text{mesitylene})]_2$ catalyst precursor in combination with 3 equiv of PhSiH_3 and mild reaction conditions. While this may have synthetic application, it is clearly of no value for the catalytic hydrosilylation of a carboxamide to the corresponding primary amine.

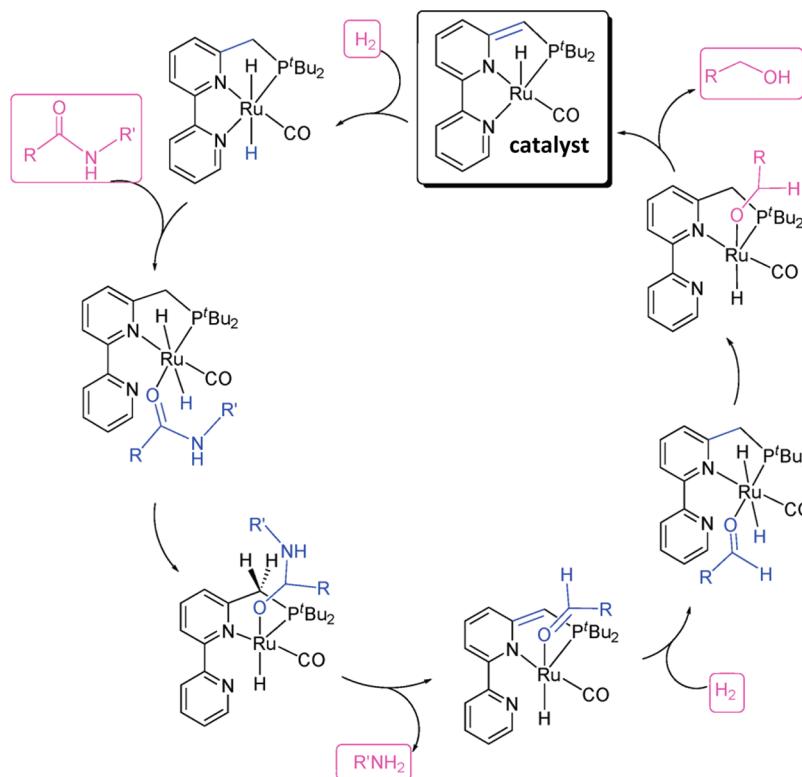
Numerous metallo-organic catalyst/hydrosilylation reagent combinations are thus now available for the reduction of each class of amide. General advantages of the hydrosilylation procedures described here include the mild reaction conditions, moderate reaction temperatures (20–100 °C) and ambient pressures, leading to extensive functional group tolerance. Notwithstanding the point that these transformations are in part catalytic, they require at least stoichiometric amounts of (usually expensive) hydrosilane or hydrosiloxane reagents as the hydrogen source, which ultimately require separation, recovery, and regeneration, that is, disadvantages that are very much in common with those associated with the use of LiAlH₄, NaBH₄, and boranes. Moreover, polymerization of the hydrosilane during the reaction is also recognized to be a problem. Even though this may very effectively serve to remove metal-containing residues from the reaction systems, product separation from resultant rather intractable reaction mixtures generally leads to a reduction in overall amine yield. Of equal, if not possibly greater, importance for any large-scale use are the potential hazards associated with the use of hydrosilanes, related in particular to the adventitious generation of the toxic, pyrophoric, and explosive gas, silane, SiH₄.^{150–152} In this context, the successful use of the inherently safer (in relation to both hydrosilanes and other hydride sources such as LiAlH₄), and inexpensive, polymethylhydrosiloxane (PMHS) clearly represents a significant advance. However, it must be self-evident that hydrosilylation is likely to prove a preferred option over continued use of traditional copper-chromium oxide-based catalysts under the very severe reaction conditions used at their inception.

In summary therefore, a wide range of hydrosilylation options is now becoming available for the reduction of tertiary, secondary, and primary amides under mild reaction conditions. Although these methods are certainly appropriate for amide reductions on the small scale, they are clearly unsuited to those represented by the more traditional larger scale processes. While clearly of considerable current academic interest, they seem unlikely to have significant potential industrial impact, as a consequence of the disadvantages described above, the only possible exception being highly specific applications arising during the synthesis of fine chemicals and pharmaceutical intermediates. Finally, although described as "homogeneous", there must also be uncertainties associated with retention of a truly homogeneous state in many of these catalyst systems, given some of the reaction conditions used (extended reaction times, and in some cases high temperatures), when viewed in light of the previous history of the so-called "homogeneous" Pt-containing hydrosilylation catalysts,^{153,154} although this possibility does appear to have been discounted in the case of Pt-catalyzed amide reductions.¹³⁸ Here, what is probably the first indication of potential catalyst reuse (Pt encapsulated in silicone resin) has also been reported, albeit at decreased conversion during second and third cycles.

6. REACTION MECHANISMS OF CATALYTIC CARBOXYAMIDE HYDROGENATION

No definitive account of the reaction mechanism of amide hydrogenation using either heterogeneous catalysts or stoichiometric hydride reagents such as LiAlH_4 is evident in the primary scientific literature. For the latter case, a chemically reasonable pathway is depicted in Scheme 5, which includes potential roles for both Li and Al, frequently lacking in other proposed mechanistic schemes.⁵ Here, attack of $[\text{AlH}_3]^-$ at the

Scheme 13. Postulated Reaction Mechanism for the Homogeneous Catalytic Hydrogenation of Amides to Amines and Alcohols via C–N Bond Cleavage^a



^aReprinted with permission from ref 127. Copyright 2010 American Chemical Society.

carbonyl group (which may also be stabilized as its Li salt) yields an iminium ion, which then abstracts a second hydride from the metal complex to form the amine during workup. While perfectly plausible, direct supporting evidence is however lacking. In contrast, the reaction mechanism presented in Scheme 13 (cf, section 5.1.2 and eq 10) has been postulated for the homogeneous Ru-catalyzed hydrogenation of secondary amides to amines and alcohols. Because the reaction was very effective under anhydrous conditions, the mechanism shown invokes metal–ligand cooperation by aromatization–dearomatization of the heteroaromatic pincer core rather than hydrolytic cleavage of the amide, and is supported by a combination of more recent results and the known chemistry of Ru pincer complexes.^{127,128}

The lack of mechanistic evidence for the significantly more difficult area involving heterogeneous catalysts has, however, almost certainly been a consequence of the severe reaction conditions originally used, which, until the most recent developments, did not generally lend themselves amenable to detailed kinetic studies.

In light of the absence of extensive significant mechanistic information, and also as an attempt directed toward the initiation of both discussion and further research associated with heterogeneous catalytic hydrogenation, the following commentary is based largely on recent experience with bimetallic catalysts using, in particular, the primary cycloaliphatic and aromatic amide substrates CyC(O)NH₂ and PhC(O)NH₂,^{95–97} and cyclic tertiary amide substrates such as *N*-methylpyrrolidin-2-one.^{101,106,110}

Possible reaction pathways, and key intermediates, in the hydrogenation of primary amides, which can also account for

the formation of the known secondary amine and alcohol products, are shown in Schemes 9 and 10, respectively. Potential transient, and possibly key, intermediates include the iminol tautomer of the amide, hemiaminal, and imine, each of which comprise elusive molecules that merit more detailed comment.

6.1. Iminols, Hemiaminals (Carbinolamines), and Imines

As indicated in section 2, although iminol tautomers are thermodynamically strongly disfavored, this does not necessarily exclude their role as kinetically significant intermediates during amide hydrogenation. There is one example of an amide containing a bulky aryl group, *N*-methyl bis (2,4,6-tri-*iso*-propyl phenyl, Ar) acetamide, which has a measurable content of the enol form, Ar₂C=C(OH)(NHCH₃), as determined by ¹H NMR spectroscopy;¹⁵⁵ moreover, an isomeric solid amide CH₃N(H)CSC(H)(CN)C(O)N(H)CH₃ and its enol form CH₃N(H)CSC(CN)=C(OH)N(H)CH₃ have both been isolated and crystallographically characterized.¹⁵⁶ Although hemiaminals are generally considered to be thermodynamically unstable with respect to either elimination of water and formation of the corresponding imine, or aldehyde formation with the elimination of NH₃ (cf, section 3.3), some evidence for their existence, and indeed isolation, has been provided from the reactions of aldehydes and ketones with primary amines.¹⁵⁷

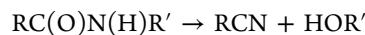
Imine intermediates were first postulated during the pioneering work of Adkins et al.,⁶⁵ particularly in attempts to account for the formation of secondary amines during primary amide hydrogenation. More recently, they have frequently been proposed as intermediates in the reduction of nitriles,^{158,159} and the apparent lack of direct evidence for their existence was

attributed to high reactivity. Evidence for the formation of simple imines (other than sterically hindered Schiff base derivatives) is scarce, although spectrophotometric evidence from the reaction of *p*-dimethylaminobenzaldehyde with ammonia has been interpreted in terms of the formation of a simple imine.¹⁶⁰ It is also pertinent to note that coordinated imines have been isolated and characterized during model studies in organometallic chemistry, which were directed toward the definition of intermediate stages in the reduction of nitriles.^{161,162} Moreover, using NMR spectroscopy, Fryzuk et al.¹⁶³ demonstrated the formation of bridged imines and their conversion to coordinated secondary amines during stoichiometric reactions of nitriles with Rh hydride-containing complexes. Here, temperatures as low as 77 K were required to monitor their reactions because of the extremely high lability of even these organometallic systems, in which the imine would be expected to be stabilized by coordination, thus providing unequivocal confirmation of their extremely high reactivity. In a very recent development concerned with hydrosilylation of the secondary amide *N*-methylbenzamide, using an Ir catalyst, Brookhart et al.¹⁴⁷ demonstrated that the reaction proceeded via an imine intermediate, PhC(H)=NMe, which could, remarkably in view of hitherto generally perceived wisdom, be isolated and characterized when insufficient equivalents of the hydrosilane necessary for complete reaction were used (cf., section 5.2). Also, *N*-benzylideneaniline, PhC(H)=N(H)Ph, has recently been detected as a very minor coproduct formed during the hydrogenation of benzanilide, PhC(O)N(H)Ph, using the homogeneous Ru(acac)₃/triphos/MSA catalyst system at 10–40 bar H₂, 220 °C, 16 h.¹²⁰

Notwithstanding little direct evidence for the involvement of imine intermediates, postulation of their transient existence certainly conveniently accounts for formation of the secondary and tertiary amine byproducts commonly formed during the hydrogenation of both amides (Scheme 10) and nitriles.^{158,159} Furthermore, the detection and unequivocal characterization of the secondary amide CyC(O)N(H)CH₂Cy as a minor byproduct during the reduction of CyC(O)NH₂ over Rh/Mo catalysts,⁹⁶ and C₃H₇C(O)N(H)C₄H₉ from C₃H₇C(O)NH₂^{118,121} using the homogeneous Ru catalyst system,¹²¹ provides further circumstantial evidence in support of the transient existence, and participation of the corresponding imines, in these respective reactions. Some precedent for the existence of iminol tautomers of amides, hemiaminals, and imines is therefore evident from a careful scrutiny of the literature.

6.2. Possible Mechanistic Pathways

With reference to Scheme 9, three molecular reaction pathways are potentially available for primary (and possibly secondary) amide reduction, and two for tertiary amides. Pathway (A) involves addition of H₂ across either (or both) the strongly deactivated C=O group of the amide and the C=N bond of the thermodynamically disfavored iminol tautomer, to give the hemiaminal. In a subsequent step, either the thermodynamically favored dehydration to the imine, followed by direct addition of hydrogen, or the addition of a second equivalent of hydrogen, with concerted elimination of water, would complete the reduction sequence. Pathway (B), Scheme 9, accessible to primary (and possibly secondary amides, via elimination of R'OH rather than H₂O from RC(O)N(H)R', eq 15), concerns initial dehydration of the amide to the corresponding nitrile, followed by sequential hydrogenation, via the imine, with 2 equiv of hydrogen.



R' = H, alkyl, aryl, etc.

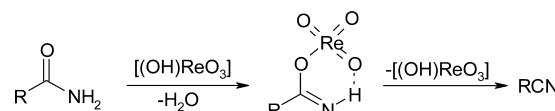
(15)

Pathway (C) (cf., also eq 2), involving C–N rather than C–O bond cleavage, although clearly preferred for homogeneous catalyst systems (see section 5 and Scheme 13), generally comprises only a minor pathway with heterogeneous catalysts, as shown by the data contained in Tables 2–5.

Estimates of free energy changes for potential intermediates in the two principal alternative hydrogenation pathways, (A) and (B), have shown that the former (formation of the hemiaminal CyCH(OH)NH₂ from CyC(O)NH₂) is far in excess of the amide dehydration barrier for R = Cy, cyclohexyl, thereby implying that amide dehydration could actually provide a more favorable reaction pathway for the reduction of primary amides.⁹⁷ Because hemiaminals are unstable with respect to imine formation and elimination of water, this option may be favored relative to the alternative addition of H₂ and concerted elimination of water referred to above.

Evidence in support of an amide dehydration route in “homogeneous” systems has been provided by the report of the selective conversion of a primary amide such as PhC(O)NH₂ to PhCN (in preference to reduction to PhCH₂NH₂) when using a hydrosilylation catalyst comprising [Et₃NH][Fe₃(CO)₁₁] and (EtO)₂MeSiH (see section 5.2).^{140,164} This is in marked contrast to the reactions of secondary amides, which, as might be expected, are readily reduced to the corresponding amines by the same catalyst system. It is also relevant to note that when hydride reagents are used with primary amide substrates, the corresponding nitrile may be formed if less than the required stoichiometric quantities of LiAlH₄ for full reduction are used (cf., Scheme 7).²⁸ Furthermore, a report of Re(VII) oxo complexes such as [(OH)ReO₃] as highly active homogeneous catalysts for the dehydration of amides (Scheme 14)¹⁶⁵ is more directly significant. Collectively therefore, these observations provide a precedent for dehydration reaction pathway (B) in homogeneous catalyst systems.

Scheme 14. Catalytic Amide Dehydration Using Re(VII) Oxo Complexes^a



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Nevertheless, it must of course be recognized that while providing useful background information, the free energy estimates for the different pathways proposed above only give an idealistic representation of the real events occurring during heterogeneous catalysis because they do not take any account of the effect of the requirement for adsorption of the reactants and intermediates (i.e., hemiaminals, imines, or their derivatives) on the catalyst surfaces.

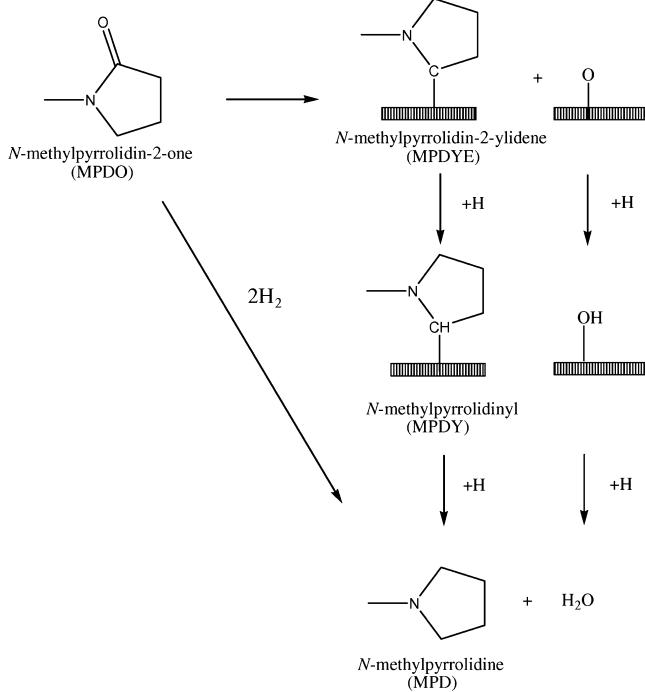
6.3. Tertiary Amides

The dehydration route (B) is clearly unavailable to the hydrogenation of tertiary amides, with principal mechanistic pathways limited to (A) and (C). Moreover, reference to the results in Tables 2–5 reveals that although pathway (C) generally comprises a minor pathway with heterogeneous catalysts, it is one that may nevertheless be very significant in

mechanistic terms (see section 6.4.3). Taken together with the extensive use of “model” substrates in which the N-atom is encapsulated within a ring structure (see section 4.2.3.2), limited mechanistic options are therefore available to tertiary amides with respect to byproduct formation, the reactions of which are thereby considerably simpler in relation to those available to their primary and secondary amide counterparts.

In what probably provides the simplest schematic representation of the reduction of a typical cyclic form of tertiary amide, *N*-methylpyrrolidin-2-one (MPDO) to *N*-methylpyrrolidine (MPD) and water, via initial C=O bond cleavage, followed by hydrogenation, is presented in idealized form in Scheme 15, showing *N*-methylpyrroldin-2-ylidene (MPDYE) and *N*-methylpyrrolidinyl (MPDY) as postulated intermediates.¹⁰¹

Scheme 15. Schematic Reaction Pathway for the Catalytic Hydrogenation of *N*-Methylpyrrolidin-2-one (MPDO) to *N*-Methylpyrrolidine (MPD) and Water via an Initial C=O Bond Cleavage Followed by Hydrogenation^a

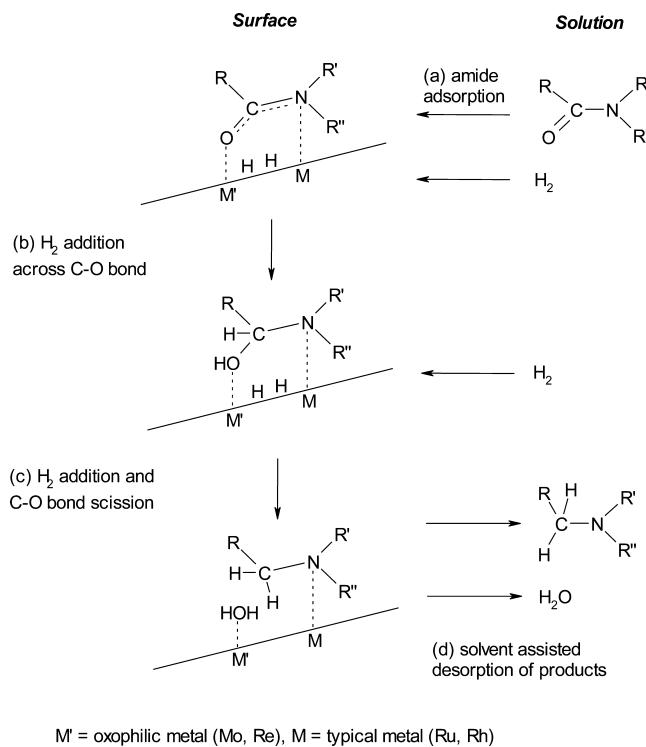


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6.4. Primary and Secondary Amides

Although assuming significantly higher complexity than in tertiary amide reduction, simply because of the larger number of potential pathways to byproducts (cf., Scheme 10), extension of the idealized mechanism in Scheme 15 provides a useful basis for the postulation of reaction steps involved in the hydrogenation of standard noncyclic carboxamides RC(O)-NR'R'' , where $\text{R}', \text{R}'' = \text{H}$, and R' or $\text{R}'' = \text{H}$, etc., particularly via pathway (A), as shown in Scheme 16. As a consequence of their strongly preferred planar configuration (cf., Scheme 3), amide adsorption onto the surface of highly dispersed nanocluster catalysts such as those described recently^{95–97} seems most likely to occur via a concerted interaction between (i) the carbonyl oxygen atom and the most oxophilic (δ^+) metal center (Mo, Re) and (ii) the nitrogen lone pair and the more

Scheme 16. General Idealized Schematic Representation of Carboxamide Hydrogenation via Reaction Pathway (A) over Highly Dispersed Bifunctional M/M' Catalyst Surfaces



typically metallic (Ru, Rh) centers, as depicted in step (a) of the hypothetical representation. Subsequently, sequential transfer of surface hydrogen across the carbon–oxygen bond, leading initially to an adsorbed form of hemiaminal, $[\text{RCH}(\text{OH})\text{NR}'\text{R}'']$, step (b), followed by further hydrogen transfer with cleavage of the carbon–oxygen bond, step (c), would lead to the formation of adsorbed amine $\text{RCH}_2\text{NR}'\text{R}''$ and H_2O , the latter on the oxophilic metal (Mo, Re) surface. Solvent-assisted desorption of amine and water, step (d), together with concerted reduction of the oxophilic metal surface, to allow catalyst regeneration, would complete the reaction sequence. The contrasting nature of Re surface species identified from XPS measurements with Ru/Re catalysts used in both amide hydrogenation, with coformation of amine and water, and “anhydrous” reduction reactions (see section 4.4.1, Figures 3 and 4), provides some supporting evidence for the sequence of events postulated here.⁹⁷

Furthermore, in the context of a potential role for oxidized states of Mo (and Re) during amide reduction, a relevant point has also emerged from a report of the MoO_2 -catalyzed isomerization of alkanes.¹⁶⁶ Here, the existence of MoO_3 and Mo_2O_5 phases on the surface of MoO_2 was demonstrated using XPS and postulated to comprise the origin of both metallic and acidic functions that were responsible for unusual catalytic isomerization activity associated with this “bifunctional” material. Analogous behavior could equally well be of relevance to amide reduction, with the Mo- (and Re-) components of the bimetallic catalysts providing the acidic function responsible for enhancement of strong initial adsorption of the amide carbonyl bond, leading to synergistic hydrogen reduction at the Ru/Mo or Rh/Mo core, and a consequent enhancement of overall conversion, consistent with experimental observations.

Of the two principal mechanistic pathways potentially available for the reduction of primary (and secondary) amides using heterogeneous catalysts, some evidence in support of the possibility of dehydration pathway (B) has been presented in section 6.2. Furthermore, although relatively rare, in relation to the reagent-based transformations common to organic chemistry, examples of heterogeneous catalysts for dehydration of carboxamides to nitriles, including solid acids such as sulfated zirconia¹⁶⁷ and vanadium oxide/hydrotalcite,¹⁶⁸ respectively, are beginning to assume greater significance, thus providing further support for the operation of reaction pathway (B) over heterogeneous catalysts. Mechanistically, such reactions may parallel the standard acid-catalyzed dehydration route commonly encountered in standard organic chemistry texts (see, for example, ref 3, pp 1549–1550).³

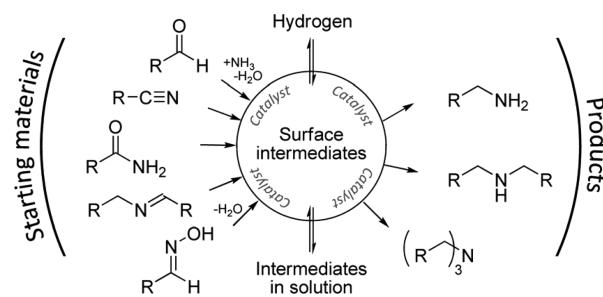
Nevertheless, at the present level of knowledge, it is clearly impossible to be prescriptive concerning factors that may lead to a dominance of reaction pathway (A) over (B) or vice versa; moreover, each could operate concurrently. Indeed, the generally higher activity of primary amides in relation to secondary amides might also provide an indication of a significant contribution of pathway (B) (see also sections 6.4.3 and 6.4.4) in the overall reduction reaction.

The results of DFT calculations on Re, Ru, Rh, and Pt surfaces¹¹⁰ provide support for other aspects of the mechanistic proposals described above by indicating, in particular, why it is difficult for pure metals to catalyze the hydrogenation of an amide because of the need to establish an appropriate balance between (i) sufficient oxophilicity to activate the C–O bond, while (ii) also facilitating oxygen hydrogenation. In contrast, bimetallic catalysts can provide the necessary bifunctional sites to enable both carbon–oxygen bond cleavage and oxygen reduction. The results of a combination of catalyst characterization and DFT calculations on a PtRe/TiO₂ catalyst were therefore interpreted in terms of a crucial requirement for the provision of good catalytic activity being a close interaction between Re and Pt. Here, it was concluded that the primary role of Re comprised activation of the amide C–O bond, with Pt acting as the hydrogenation catalyst to reduce (i) the surface amide intermediates and (ii) the Re–O bond, with consequent desorption of amine and water from the catalyst surface (see section 6.2). The rate enhancement observed on the TiO₂ support was ascribed to the presence of oxygen vacancies allowing adsorption and weakening of the C–O bond.

These conclusions, and the consequent advantages derived from the use of such heterogeneous catalysts, may also go some way toward explaining why the principal monometallic homogeneous catalyst systems described to date may follow the thermodynamically preferred C–N bond scission route, pathway (C) exemplified in Scheme 13, as predicted by the results of DFT calculations,¹³¹ leading to the formation of alcohols and amines (or NH₃ in situations where R' and R'' = H, see eqs 2, 10, and 11).

6.4.1. Potential Relationship between Amide and Nitrile Hydrogenation Catalysts. A recent report by Müller et al.¹⁶⁹ has highlighted the close general relationship between different routes to amine synthesis from different unsaturated precursors (see Scheme 17). A common reaction network, via hydrogenation of several unsaturated nitrogen precursors, was exemplified by the hydrogenation of aldoximes such as 2-ethylbutyraldoxime, using Ni/SiO₂, Pd/C, and Rh/C catalysts. The influence of water and ammonia was also considered in this work. As might be expected from the early work on amide

Scheme 17. Common Reaction Network in Amine Synthesis via Hydrogenation of Unsaturated Nitrogen Precursors^a



^aReprinted with permission from ref 169. Copyright 2012 ACS.

hydrogenation (see section 4.2), addition of ammonia led to suppression of secondary amine formation, thereby enhancing selectivity to primary amine; moreover, the addition of water also led to a slight improvement in the selectivity toward the primary amine (73.9% vs 71.1%).

The relationship proposed by Müller et al. prompts some comments in the context of the mechanism of carboxamide reduction. If reaction pathway (B) were to be favored, a close correlation between the respective product distributions obtained from the use of the same catalysts for the hydrogenation of both a primary amide and its dehydration product, the corresponding nitrile, might intuitively be expected. However, an investigation using several Ru, Ru/Re, Ru/Mo, Rh, and Rh/Mo catalysts preformed from the respective metal carbonyl precursors proved this not to be the case;⁹⁷ moreover, some unexpected differences between these and standard nitrile hydrogenation catalysts were also evident. First, all of the catalysts required minimum pressures and temperatures of 90 bar H₂ and 140 °C for complete nitrile conversion, thereby providing a sharp contrast with standard nitrile hydrogenation catalysts, which are generally effective under considerably milder reaction conditions (e.g., 10 bar H₂, <100 °C).^{158,159} In this instance, the reaction is most likely temperature rather than pressure limited, with zero nitrile hydrogenation evident at 120 °C, higher pressures having been used for the purposes of a closer comparison with those initially used for carboxamide reduction. Second, CyCN hydrogenation proved very selective throughout, with the production of only primary and secondary amine products, CyCH₂NH₂ and (CyCH₂)₂NH (ca. 85–95% and 5–15%, respectively) and minimum hydrocarbon formation. Third, this selectivity pattern was observed with both monometallic (Ru, Rh) and bimetallic (Ru/Mo, Ru/Re, and Rh/Mo) catalysts, thereby providing a complete contrast with the behavior of the same catalysts when used in amide hydrogenation, in which Ru and Rh alone performed very poorly indeed.^{95,96} The behaviors of the same catalysts toward hydrogenation of carboxamides and nitriles thus clearly bear little relationship to each other. Nevertheless, the differences between surface oxidation states of Re and Mo, evident when these elements were used in amide hydrogenation, and the “anhydrous” reaction conditions used for nitrile reduction appear to provide a ready rationalization in this case (cf., section 4.4.1). As a consequence, although providing a valuable conceptual approach, any attempts at mechanistic considerations associated within this common reaction network should be approached with caution.

Further evidence that is directly relevant to a discussion of the mechanism of amide hydrogenation over bimetallic

catalysts is detailed in sections 6.4.2–6.4.4, indicating aspects that will merit more detailed exploration as catalysts that operate under the very mildest reaction conditions continue to be developed.

6.4.2. Deuterium Isotope Studies. In principle, it should be possible to distinguish between different mechanistic pathways using deuterium labeling studies, and preliminary experiments were undertaken to check this possibility.⁹⁸ Cyclohexanecarboxamide, CyC(O)NH₂, was reduced using a Ru/Mo catalyst in *n*-octane under 20 bar D₂ at 160 °C for 20 h. Extensive scrambling of the D-label was observed, including some D-exchange with protons of the cyclohexyl ring. Nevertheless, careful analysis of mass spectra of the O-containing products from the reaction with D₂ provided some useful information, an H₂O to DHO ratio of ca. 1:1. This is close to that expected for the theoretical value from initial addition of D₂, presumably to the iminol tautomer, followed by loss of H₂O and DHO (i.e., Scheme 9, pathway (A)). In contrast, preference for an initial amide dehydration step would have led to elimination of H₂O alone, although of course secondary D₂ exchange with H₂O cannot be excluded (given that some D-exchange of the cyclohexyl group had also occurred). Nevertheless, if this were significant, complete H–D exchange might have been expected given the excess of D₂ present in solution at 20 bar pressure. This does therefore provide some circumstantial evidence in favor of initial addition of D₂, and against the amide dehydration route for CyC(O)-NH₂. Furthermore, CyC(O)ND₂ was prepared from CyCN and D₂O using the extremely effective Pt-containing homogeneous nitrile hydration catalyst developed by Parkins et al.,¹⁷⁰ and amide hydrogenation was carried out using the same Ru/Mo catalyst under the standard reaction conditions of 100 bar H₂, 160 °C, and 16 h, also with *n*-octane as solvent.⁹⁶ Here, extensive scrambling of the D-label also occurred, perhaps not unexpectedly given the reaction conditions. On the basis of these preliminary observations therefore, further investigations using catalysts that operate under the mildest of reaction conditions, for example, 10 bar H₂ and temperatures significantly less than 100 °C, would appear to be necessary to facilitate any definitive mechanistic solutions using deuterium isotope labeling.

6.4.3. Origins of High Selectivity of Bimetallic Catalysts toward Primary Amide Hydrogenation. In much of the previous work on primary amide hydrogenation,^{65,78} the addition of ammonia and/or amines appeared to be a prerequisite for suppression of the postulated imine–amine coupling reactions responsible for secondary amine byproduct formation (cf., Scheme 10). Although Broadbent's work⁸⁴ with monometallic Re catalysts provided some early clues, the seemingly intrinsic highly selective behavior of Ru/Mo⁹⁶ and Ru/Re⁹⁷ catalysts toward hydrogenation of a primary amide such as CyC(O)NH₂ with, using the most favorable catalyst compositions, no secondary or tertiary amine formation currently appears unique in the history of amide hydrogenation, and renders the deliberate addition of ammonia totally unnecessary. It seems appropriate therefore to consider possible factors that may favor these intriguing, currently unique, properties.

First, operation of the amide dehydration pathway (B) (Scheme 9) could conceivably play a role in controlling the unusually high selectivity toward CyCH₂NH₂ in the bimetallic systems,^{95–97} because removal of water in the first step should lead to inhibition of CyCH₂OH formation via C–N rather than

C–O bond cleavage. Furthermore, in these particular catalyst systems, if dehydration to the nitrile were to be rate-limiting, and in consideration of the higher reaction temperatures, that is, 130–160 °C, required in relation to those needed by standard nitrile hydrogenation catalysts^{158,159} (see section 6.4.1), the low standing concentration of nitrile, and presumably very rapid subsequent reduction to amine, could reasonably be expected to lead to a limitation of secondary amine byproduct formation, as is observed experimentally. It could also account for the switch in product distribution observed between the use of *n*-butyramide and 2,2-dimethylpropionamide as substrates over Ru/Mo catalysts (cf., Table 2, entries 18 vs 20).⁹⁶ Because amide dehydration to the nitrile is clearly not possible with the tertiary amide, the alternative C–N bond cleavage pathway would then become more dominant in yielding greater amounts of 2,2-dimethylpropanol, as also observed experimentally. A corollary of this particular observation is the quite reasonable point that both postulated mechanistic pathways (A) and (B) in Scheme 9 may operate concurrently.

A second potential explanation for the “unique” behavior of these catalysts may actually lie in the coformation of CyCH₂OH, the only significant byproduct detected (in ca. 13% and 10% selectivity, respectively) over a majority of the above Ru/Mo and Ru/Re catalysts under optimum reaction conditions. In the latter case, this leads to the overall idealized reaction stoichiometry depicted in eq 16.



Thus, for every 10 equiv of CyC(O)NH₂ consumed, 1 equiv of NH₃ is liberated via this minor reaction route (pathway C, Scheme 9), derived from C–N rather than C–O bond scission of the amide substrate (cf., eqs 1 and 2), leading to the possibility that this *in situ* generation of ammonia may be sufficient to effectively inhibit (CyCH₂)₂NH formation.

Third, an important role played by the solvent in the mechanistic processes of all of these liquid phase hydrogenation reactions may be to promote desorption of both reaction products immediately on formation (note the preference for solvents such as 1,4-dioxane and DME, with which amide substrates and amine products are highly miscible, cf., section 4.5), thereby limiting secondary reactions leading to byproduct formation. This point may be particularly relevant to the reduction of primary and secondary amides (see also section 6.4.4).

In relation to the earliest work on amide hydrogenation, additional factors that may also be significant include the considerably reduced reaction temperature and pressure requirements relative to those needed by copper–chromium oxide-based catalysts, coupled with both the small (2–4 nm) sizes of the well-dispersed nanoclusters, and the absence of a catalyst support, which may also facilitate rapid, solvent-assisted, desorption of primary amine into the liquid phase immediately after formation on the catalyst surface.

6.4.4. Amide Reduction Reactivity Ranking (Primary > Tertiary ≫ Secondary). The observed augmentation of primary amides relative to tertiary counterparts within the activity ranking order CyC(O)NH₂ > CyC(O)N(CH₃)₂ ≫ CyC(O)N(H)CH₃⁹⁶ may also be accounted for by a contribution from pathway (B), Scheme 9, which is available to primary amides but specifically excluded from tertiary

amides. What has become less clear with the advent of recent work is the position of secondary amides in the above series. Virtually all early work was consistent with the above ordering found using Ru/Mo catalysts. It is also reasonable to expect that operation of pathway (B), Scheme 9, would be considerably less favored with secondary relative to primary amides. One possible explanation may be associated with the degree of steric hindrance presented by *N*-alkyl (or other) substituents during amide adsorption onto the catalyst surface (see Scheme 16). In simplistic terms, tertiary amides would therefore be expected to present even greater resistance to reduction than their secondary amide counterparts, but an additional important factor for consideration must be the steric bulk of the substituents attached to the amide nitrogen and the respective orientation of each amide on the catalyst surface. Also, notwithstanding the strong hydrogen-bonding character generally associated with amide molecules,²¹ an additional factor contributing toward the apparent resistance of secondary amides to reduction concerns stabilization as a consequence of their propensity to form exceptionally strong hydrogen-bonded dimers in solution, as exemplified in peptide chemistry,²² which may be a significant inhibiting factor, particularly at low reaction temperatures. The recent report of the use of a Pt/Re/graphite catalyst with a range of secondary amides largely containing the N-atoms encapsulated within ring structures (in which strongly hydrogen-bonded dimers may be less prevalent) has shown that these are almost all susceptible to reduction under mild conditions.⁹⁹ Further development of the knowledge base is clearly required in this area.

Finally, it is appropriate to note that the above ordering of reactivity in general parallels the trend noted using standard stoichiometric hydride reduction methods with, for example, LiAlH₄.⁴ Reports of the use of the less aggressive reducing agent NaBH₄ toward reduction of amides at high temperatures^{33,34} are also instructive. Here, secondary amides proved unreactive, tertiary amides gave the corresponding amine in moderate yield, whereas primary amides underwent initial dehydration to the nitrile (see above) followed by slow reduction to the amine.

7. CONCLUSIONS AND FUTURE RESEARCH OPPORTUNITIES

This Review has described key developments in carboxamide hydrogenation, from its discovery over a century ago to the current recent renaissance of interest today. Advances in catalytic chemistry have led to the progression of catalytic amide hydrogenation from the position of a largely neglected and very unselective reaction that required extremely severe reaction conditions, to one where, with judicious choice of catalysts, direct and selective amide reduction is now viable at ca. 10–20 bar H₂ and, in the most favorable cases, minimum reaction temperatures of 100 °C. The availability of catalysts that operate under much milder reaction conditions than their first generation counterparts should clearly allow considerable functional group tolerance during the reduction of complex organic molecules containing other susceptible groups in addition to the amide linkages, and therefore be of direct interest to those involved in fine chemicals manufacture. Moreover, these advances are also clearly beneficial to those involved in the hydrogenation of the more simple amides, that is, those containing long-chain alkyl substituents, which are typical of much of the earliest work, but nonetheless equally relevant in the commercial world. In this context, although the

traditional use of Cr-based catalysts is in decline because of carcinogenicity concerns, potential alternatives, particularly in the form of Cu-based systems, are becoming available for the hydrogenation of such tertiary amides under much lower operating pressures than those used hitherto.

The current advances, associated with the development of “bifunctional”/“bimetallic” systems, have started to offer real potential for the development of direct catalytic hydrogenation routes that may effectively compete with, and ultimately supersede, the traditional stoichiometric (and atom inefficient) hydride reagent-based methods of reduction. Significant challenges remain, including an improved mechanistic understanding of carboxamide hydrogenation, a need for the design of suitable recyclable supported catalysts, and continued discovery and development of active catalysts that operate under ever milder reaction conditions. Reports of effective continuous flow fixed bed, and slurry, reactor systems for carboxamide hydrogenation have been featured in different sections of this Review (sections 4.1,⁸⁶ 4.2.3.2,¹⁰⁰ 4.2.3.3,^{102–105} 4.3,¹⁰⁷ and 4.6^{113–116}), and their further development can be expected to provide a key feature of future work in this area.

Exactly where the monometallic homogeneous Ru catalyst systems (section 5.1) fit into the overall amide reduction picture is currently unclear, particularly because this field is very much in its infancy. With the sole exception of the [Ru(triphos)] catalyst for the highly selective hydrogenation of a secondary amide to the corresponding amine,^{118–121} all of the currently available examples exclusively favor C–N bond scission (eq 2) over C–O bond cleavage (eq 1), a preference for the former bond-breaking mode having been confirmed by DFT calculations.¹³¹ Although of considerable mechanistic interest, the vast majority of the homogeneous systems are therefore, at their present stage of development, generally of little use for the direct catalytic hydrogenation of carboxamides to the corresponding amine, with loss of 1 equiv of water. Future research work might be profitably directed toward the design and synthesis of bi-, tri-, or multimetallic complexes containing appropriate combinations of the typical “metallic” and more highly oxophilic elements for use as catalyst precursors, such as those exemplified by the recent developments associated with heterogeneous catalysts.

Finally, some of the bimetallic/bifunctional catalyst systems described here may also be relevant to reduction reactions associated with other members of the family of carboxyl-containing functional groups, particularly carboxylic acids (see sections 4.2 and 4.5.1) and esters, which have been recently reviewed in detail elsewhere,^{171–174} and which pose less stringent requirements toward reduction in relation to those associated with carboxamides.⁸

In conclusion, we believe that this Review has provided a comprehensive and critical assessment of the current state of the art with respect to carboxamide hydrogenation. Although much remains to be learned, we hope that it will serve to stimulate interest and further significant advances from the practitioners of both heterogeneous and homogeneous catalysis in this challenging area of great longevity, and one that possibly comprises the “last bastion” of the more traditional catalytic methods for the production of important chemical intermediates.

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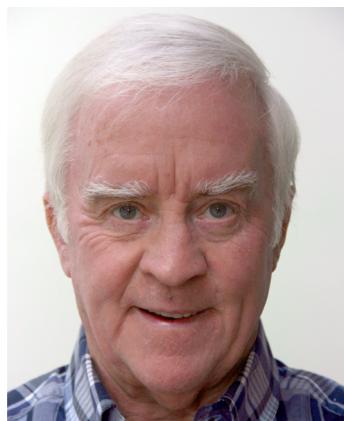
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Notes

The authors declare no competing financial interest.

Biographies

Andrew Michael Smith studied chemistry at Imperial College of Science, Technology and Medicine in London, graduating with a MSci Hons (2002), followed by a Ph.D. at the University of Liverpool entitled "Bimetallic Catalysts for the Hydrogenation of Amides and Nitriles" (2006) under the supervision of Dr. Robin Whyman. Since 2007, Andrew has been employed by Tata Steel Europe Ltd. (formerly Corus Group plc) in the north east of England, previously as a Technical Manager at the hot-rolling mills in Teesside and Skinningrove, and currently as a Researcher within the Steelmaking and Casting Department at Teesside Technology Centre, located in Middlesbrough, UK.



Robin Whyman studied chemistry at the Victoria University of Manchester, United Kingdom, graduating with a BSc Hons (1962) and Ph.D. (1965) from the group of Prof. (now Lord) J. Lewis. After two years as a research associate with (the late) Prof. William E. Hatfield at the University of North Carolina, Chapel Hill, NC, he returned to the UK and spent 25 years at the ICI Ltd. Corporate Research Laboratory in Runcorn, Cheshire, where he developed research interests that included a wide range of aspects of homogeneous and heterogeneous catalysis, together with the interface between the two, metal clusters and nanoparticles, and spectroscopic methods of catalyst characterization. In furtherance of these interests, he joined the University of

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ABBREVIATIONS

Acac	2,4-pentanedionato-, acetylacetonato-
Bu ^t	tert-butyl, C(CH ₃) ₃
CBZ	carboxybenzyl
COD	1,5-cyclooctadiene
COE	cyclooctene
Cy	cyclohexyl, C ₆ H ₁₁
DMA	dimethylamine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DFT	density functional theory
EDX-STEM	energy dispersive-scanning transmission electron microscopy
Et	ethyl, C ₂ H ₅
EXAFS	extended X-ray absorption fine structure
FTIR	Fourier transform infrared spectroscopy
HSAG	high surface area graphite
IR	infrared spectroscopy
Me	methyl, CH ₃
MPD	N-methylpyrrolidine
MPDO	N-methylpyrrolidin-2-one
MPDY	N-methylpyrrolidinyl
MPDYE	N-methylpyrrolidin-2-ylidene
MSA	methanesulfonic acid
NMP	N-methylpyrrolidine
Ph	phenyl, C ₆ H ₅
[PhHEMIM][OTf]	1-(2-hydroxy-2-phenylethyl)-3-methylimidazolium triflate
PMHS	polymethylhydrosiloxane
PNN	2-(di- <i>tert</i> -butylphosphinomethyl)-6-(diethylaminomethyl) pyridine
POCOP	2,6-bis(di- <i>tert</i> -butylphosphinito)phenyl
Pr ⁱ	iso-propyl, <i>i</i> -C ₃ H ₇
PYBOX	sterically hindered tridentate nitrogen ligands, particularly substituted pyridine-bisoxalidines
STEM	scanning transmission electron microscopy
TEM	transmission electron microscopy
TMDS	1,1,3,3-tetramethyldisiloxane
TON	turnover number
TRIPHOS	1,1,1-tris(diphenylphosphinomethyl)-ethane
TPR	temperature-programmed reduction
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction

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