1

CATALYTIC REDUCTION OF AMIDES AVOIDING $LiAlH_4$ OR B_2H_6

DEBORAH L. DODDS[1,2] AND DAVID J. COLE-HAMILTON[1]

[1]*School of Chemistry, University of St. Andrews, North Haugh, Fife, Scotland, UK*
[2]*Johnson Matthey plc, Billingham, UK*

1.1 INTRODUCTION

Amines are key components in a variety of pharmaceutical compounds, chemical intermediates, and commodity chemicals. A detailed review by Jung and coworkers describes the synthesis of secondary alkyl and aryl amines [1]. The synthesis of amines by metal-catalyzed reactions generally falls into one of two categories: (i) reduction of an unsaturated nitrogen-containing species or (ii) tandem reactions involving amination and reduction steps. Synthetic routes to primary amines include the reduction of nitro arenes, nitriles, or amides; amination of alcohols; and hydroaminomethylation of alkenes (Scheme 1-1).

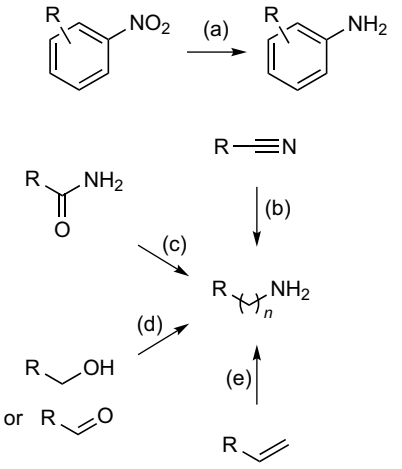
Routes to secondary and tertiary amines are more limited, but they can generally be made via amide reduction, amination of alcohols, and alkene hydroaminomethylation (Scheme 1-2).

This chapter focuses primarily on the synthesis of amines via amide hydrogenation. Particular aspects considered are the atom economy (AE) of the reactions, the operating conditions, and the safety of the reagents/processes. These catalyzed processes are then compared with stoichiometric metal hydride reagents.

1.2 AMIDES

Amides are particularly challenging substrates for hydrogenation reactions, which is a consequence of their stable resonance structure. The conjugation of the nitrogen's electron

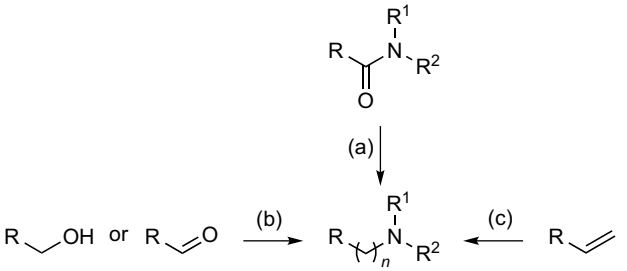
Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries, First Edition. Edited by Peter J. Dunn, K. K. (Mimi) Hii, Michael J. Krische, and Michael T. Williams.



SCHEME 1-1. Homogeneously catalyzed routes to primary amines: (a) hydrogenation of nitro arenes (H_2); (b) hydrogenation of nitriles (H_2, $n = 1$); (c) hydrogenation of amides (H_2, $n = 1$); (d) amination of alcohols (H_2, NH_3, $n = 1$); (e) hydroaminomethylation of alkenes (CO/H_2, NH_3, $n = 3$).

lone pair with the π-bond of the carbonyl is so effective that the double-bond character is shared across both the C−O and C−N bonds, leading to planarity within the molecule. The delocalization extends to the first carbon of a substituent attached to the carbonyl or nitrogen, such that there is no longer free rotation about the C−N bond, an effect that is readily observed by ^{1}H NMR spectroscopy. This resonance adds stability to the amide functionality, making them significantly harder to reduce than other carbonyl groups, such as ketones.

In addition, the reaction is less favorable at higher temperatures as a result of a negative ΔS of hydrogenation, which in turn leads to a more positive ΔG. Despite a lower, more favorable ΔG value observed at lower temperatures, the reaction has a high kinetic barrier that requires high temperatures for the reaction to proceed. This is why heterogeneous amide hydrogenations traditionally require extremely forcing reaction conditions.



SCHEME 1-2. Homogeneously catalyzed routes to secondary ($R^1 = H$) and tertiary amines: (a) hydrogenation of amides (H_2, $n = 1$); (b) amination of alcohols (H_2, HNR^1R^2, $n = 1$); (c) hydroaminomethylation of alkenes (CO/H_2, HNR^1R^2, $n = 3$).

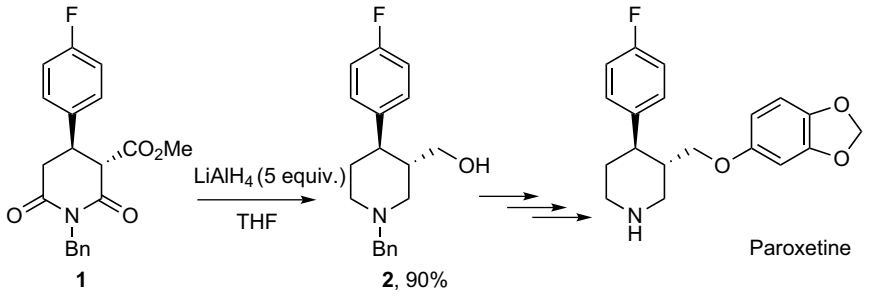
1.3 IMPORTANCE OF AMIDE REDUCTIONS IN PHARMACEUTICAL SYNTHESIS

Amide formation followed by reduction to the amine is a common route to C−N bonds as they are very reliable, yet versatile. The reduction step is, more often than not, carried out with a stoichiometric amount of a metal hydride reducing agent such as lithium aluminum hydride ($LiAlH_4$) or borane (B_2H_6); however, these types of reagents have a number of inherent problems associated with their use, particularly on a large scale. First, they are difficult and potentially hazardous to handle and have complex workup procedures. Second, there is a large amount of waste generated as a by-product, such as mixed metal hydroxides or boric acid, which must be disposed of in a responsible manner—this is both an environmental and an economic drawback. As a result, amide reduction avoiding the use of $LiAlH_4$ and B_2H_6 has been identified as a key area of development by the ACS Green Chemistry Institute and members of the pharmaceutical round table [2].

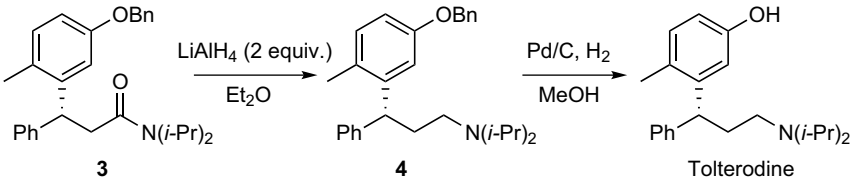
In 2006, a study of the synthesis of 128 drug candidates carried out in the process chemistry departments of GlaxoSmithKline, AstraZeneca, and Pfizer highlighted the popularity of metal hydride reducing agents [3]. Of the 94 reduction reactions in the study, 44% were heterogeneous hydrogenations, 41% were metal hydride/borane reductions, and only 4% represented homogeneous hydrogenations. In fact, no carboxylic acid derivatives were reduced using homogeneous methods. Although this is not the whole picture, it does give a reflection of the trends that are present in industrial process chemistry.

Stoichiometric amide reductions are commonplace in the pharmaceutical industry. In this section, examples are chosen to highlight the various challenges faced by the synthetic chemists in the reduction of a molecule with multiple functional groups. The synthesis of paroxetine, a selective serotonin reuptake inhibitor used to treat depression, involves the reduction of an imide intermediate **1** that incorporates an ester side chain (Scheme 1-3). The global reduction of all three C=O units is carried out in one step (90%) using 5 equiv. of $LiAlH_4$ as the reducing agent to give the cyclic amine **2** [4]. Clearly, the AE and safety of this reaction could be significantly improved with a homogeneous catalytic hydrogenation using molecular hydrogen, as water would be the only by-product.

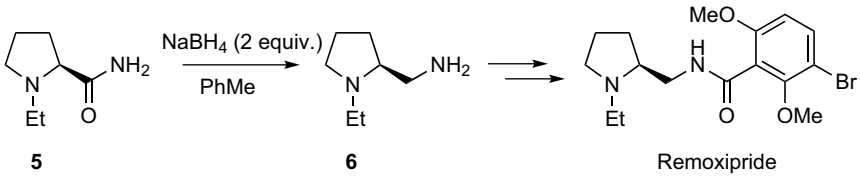
Another example of $LiAlH_4$ amide reduction can be found in the synthesis of tolterodine (Scheme 1-4), an anticholinergic used to treat urinary incontinence. One step in its preparation involves the reduction of an amide **3** prior to the final debenzylation



SCHEME 1-3. Imide/ester reduction step in the synthesis of paroxetine.



SCHEME 1-4. Amide reduction step in the synthesis of tolterodine.



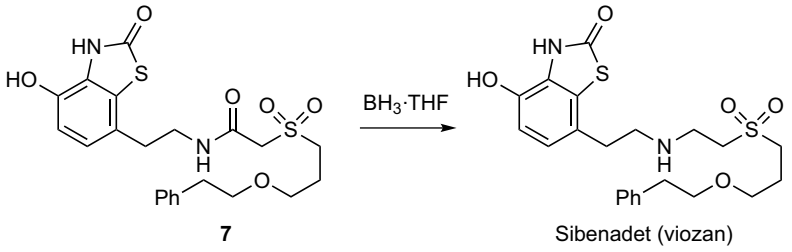
SCHEME 1-5. Amide reduction step in the synthesis of remoxipride.

step [5]. This proceeds with an overall yield of tolterodine of 74%. A combined amide reduction/debenzylation would improve AE and remove the need to workup and isolate the intermediate, which has significant cost and time implications.

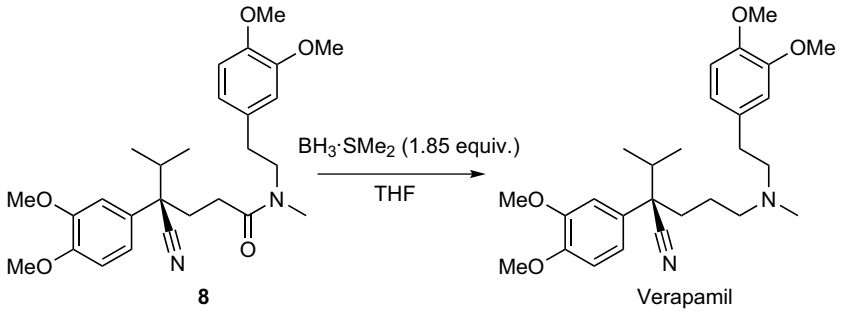
Remoxipride is an atypical antipsychotic drug that has been used to treat schizophrenia. The amine intermediate **6** was prepared via a sodium borohydride reduction of the primary amide **5** to the primary amine (Scheme 1-5), which proceeded in 54% yield (crude) [6]. As is the case for paroxetine (Scheme 1-3), the reduction occurs adjacent to a stereogenic center, which must not racemize during the reaction.

One of the late-stage transformations in the synthesis of sibenadet, which is used to treat chronic obstructive pulmonary disease [7], is a borane reduction of the secondary amide **7** to a secondary amine, which is then isolated as the hydrochloride salt (Scheme 1-6). The overall yield over these two steps was only 20%, a result of competitive reduction of the benzothiazolone. The impurities were not only difficult to separate and remove; they also appeared to hamper the crystallization of the product.

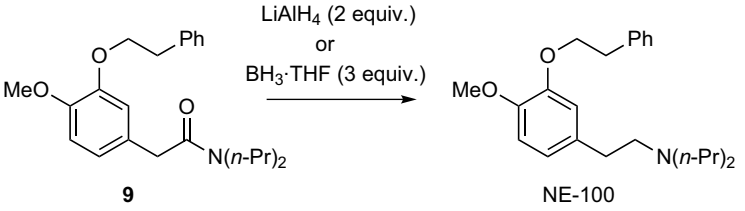
Selective reactions are particularly important in pharmaceutical processes, as the final molecule often has more than one functional group. Verapamil, a calcium channel blocker used in the treatment of cardiovascular ailments, provides a good example of this [8], where the last step of the synthesis is the borane reduction of tertiary amide **8** in the presence of a nitrile group (Scheme 1-7), which proceeds in 60–73% yield.



SCHEME 1-6. Amide reduction step in the synthesis of sibenadet.



SCHEME 1-7. Amide reduction step in the synthesis of verapamil.



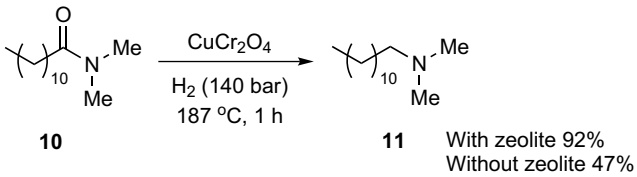
SCHEME 1-8. Amide reduction step in the synthesis of NE-100.

Finally, an example of a tertiary amide (**9**) reduction by either $LiAlH_4$ or BH_3 is provided in the case of NE-100, a σ receptor antagonist with potent antipsychotic effects (Scheme 1-8) [9].

From these examples, it is clear that metal hydride and borane reductions of amides represent important and widely used reactions in the pharmaceutical industry, and improvements need to be made to obtain a safer, greener, and more efficient transformation. Catalytic methods may fulfill these requirements, although steps need to be taken to ensure that procedures can be carried out with high selectivity under relatively mild conditions, preferably without the need for specialist equipment.

1.4 HETEROGENEOUS AMIDE HYDROGENATION

Catalytic hydrogenation of amides was first reported by Adkins and Wojcik in 1934 [10], which was achieved by using heterogeneous copper chromite catalysts under extremely forcing reaction conditions (300 bar, 250 °C), under which the reactions were prone to side reactions, such as further alkylation of the product (primary amides) and C−N bond cleavage (mainly secondary and tertiary amides) [10]. Improvements to the copper chromite method were reported in 1984 by King, of the Procter & Gamble Company, where the introduction of zeolite resulted in milder reaction conditions of 140 bar and 287 °C [11]. This allowed the reduction of *N*,*N*-dimethyldodecanamide (**10**) in 1 h, with a conversion of 92% and 81% selectivity to **11** (Scheme 1-9). The reaction without zeolite under the same conditions only gave 47% conversion and 47% selectivity.



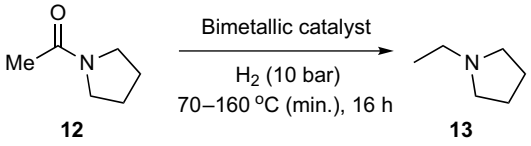
SCHEME 1-9. Hydrogenation of *N*,*N*-dimethyldodecanamide **10** to *N*,*N*-dimethyldodecylamine **11**.

Obviously, these extreme conditions are incompatible with pharmaceutical and fine chemical synthesis, where compounds may contain many thermally sensitive functional groups. However, recent advances in heterogeneous bimetallic catalyst systems have allowed drastically improved conditions to be developed. For example, Fuchikami and coworkers [12] reported the use of bimetallic catalysts comprising rhodium and rhenium carbonyl species, capable of reducing primary, secondary, or tertiary amides under milder conditions (typically 160–180 °C and 100 bar). However, the reaction is hampered by overreduction, including of phenyl groups to cyclohexyl groups.

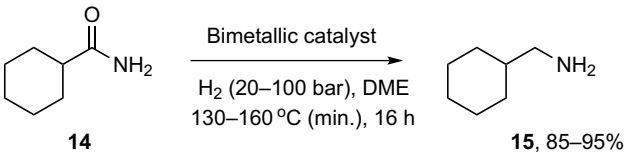
An extensive patent published in 2005 by Smith et al. [13] at Avantium International B. V. describes the screening of bi- and trimetallic catalysts for amide reduction, using the reduction of *N*-acetylpyrrolidine (**12**) as a test substrate. Typical tests were carried out at 10 bar and temperatures of 70–160 °C, screening hundreds of catalysts (Scheme 1-10). Combinations of Pt, Rh, or Ir with Re, Mo, or V provided the most active catalysts, achieving yields in excess of 80% at 130 °C.

Recently, Whyman and coworkers reported a similar series of bimetallic heterogeneous catalysts using combinations of Rh/Mo [14], Ru/Mo [15], Rh/Re, and Ru/Re [16]. A detailed study was carried out on each of these systems employing the primary amide, cyclohexane carboxamide **14**, as the test substrate (Scheme 1-11) to give cyclohexylmethanamine **15** in good yields. Minimum operating conditions were found to be either 100 bar and 130 °C, or 50 bar and 160 °C in the case of Rh/Mo. At lower temperatures and pressures, lower conversions, higher amounts of alcohol, and unwanted amine products were observed.

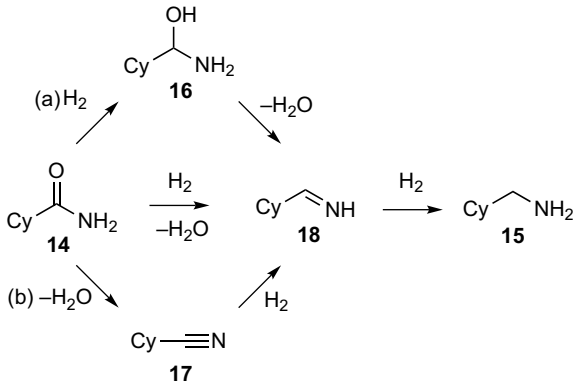
Using the Ru/Mo catalyst system at 100 bar and 160 °C, primary amides were readily hydrogenated to the desired primary amines. Although benzamide gave 83% primary amine (accompanied by16% of the alcohol), the phenyl ring was also reduced. In comparison, the hydrogenation of butanamide and 2,2-dimethypropanamide gave 77% and 40% primary amine, respectively, with the remainder attributable to alcohol. Conversely, the two secondary amides tested, *N*-methyl benzamide and *N*-methyl cyclohexamide, were only hydrogenated to the corresponding amines in trace amounts. In contrast, reductions of tertiary aliphatic amides proceeded much more smoothly, with up to



SCHEME 1-10. Hydrogenation of *N*-acetylpyrrolidine **12** to *N*-ethylpyrrolidine **13**.



SCHEME 1-11. Hydrogenation of cyclohexane carboxamide **14** to cyclohexylmethanamine **15**.



SCHEME 1-12. Potential amide hydrogenation pathways: (a) proceeds via the hemiaminal **16**; (b) proceeds via the nitrile **17**.

100% conversion for *N*,*N*-diethylpropanamide. Higher conversions and selectivities were also achieved with the Re-based catalysts, although the operating temperatures were also higher.

The same authors also conducted a study of the mechanism by examining thermochemical data for the hydrogenation of **14**. They proposed that the amide hydrogenation could proceed via two pathways: the first is through the hemiaminal **16** followed by a second hydrogenation, with a concerted loss of water (Scheme 1-12, route a). The second pathway could proceed, in the case of primary amides, through the nitrile **17** (dehydration), which is then hydrogenated to give the amine (Scheme 1-12, route b).

The calculated free energy $\Delta G^{\circ}_{298.15}$ of the formation of the hemiaminal is much greater than that of the dehydration reaction (104.8 kJ mol^{-1} vs. 26.5 kJ mol^{-1}, respectively) [16], suggesting that the formation of the nitrile intermediate may be more favorable. Pathway (b) should also be more selective for the formation of the amine, as water is eliminated, reducing the likelihood of alcohol formation (from **16**). The authors proposed that nitrile formation is rate limiting, and under the adopted reaction conditions, the two routes may be competitive processes, accounting for the difference in observed reactivity (primary > tertiary $\gg$ secondary).

1.5 HOMOGENEOUS AMIDE HYDROGENATION

The first report of a homogeneous catalytic amide reduction was described in a patent by Crabtree and coworkers at Davy Process Technology, using a triphosphine ligand,

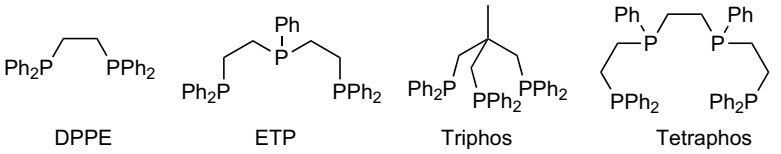
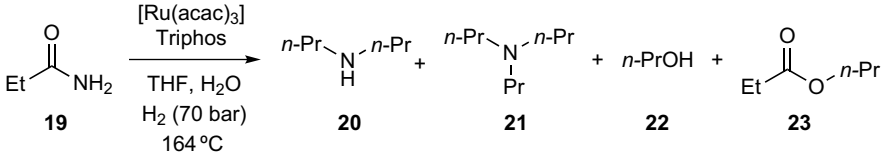


FIGURE 1-1. Selection of the ligands tested in hydrogenation of dimethyl oxalate [18].



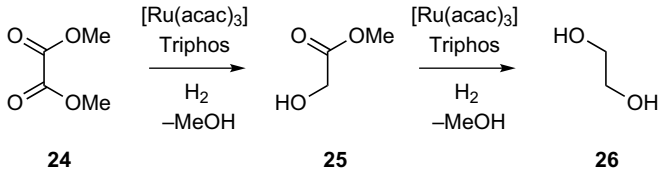
SCHEME 1-13. Hydrogenation of propanamide **19**.

1,1,1-tris(diphenylphosphinomethyl)ethane (Triphos, Figure 1-1), in a ruthenium-catalyzed reaction [17]. Examination of product mixtures revealed that the hydrogenation of propanamide **19** did not result in the expected propylamine, but a mixture of dipropylamine **20**, tripropylamine **21**, propanol **22**, and propyl propanoate **23** (Scheme 1-13).

The use of Triphos was not unfounded, as it had previously been found to be a useful ligand for the hydrogenation of carboxylic acid derivatives by Elsevier and coworkers in 1997 [18,19]. Used in conjunction with $[Ru(acac)_3]$, the hydrogenation of dimethyl oxalate **24** proceeded smoothly to ethylene glycol **26** (Scheme 1-14). The addition of Zn as a cocatalyst was found to increase the yield of ethylene glycol—it is thought to have a dual role in the process: (a) acts as a reducing agent for the Ru(III) precatalyst and (b) the resultant Zn(II) acts as a Lewis acid to activate the ester group toward attack by the Ru catalyst.

In a later study by the same authors, a series of ligands was screened, including mono-, bi-, tri-, and tetradentate phosphines (Figure 1-1), as well as arsines and amines. Of those tested, PPh_3, DPPE, ETP, and Tetraphos showed conversion to **21** in 36, 11, 67, and 85% yields, respectively. Among these, Triphos was the only ligand that can effect the second reduction of **25** to give the diol **26** [20]. The TON for Triphos was also high (160, four times greater than that afforded by ETP and Tetraphos).

The success of the Triphos ligand is attributed to its ability to only adopt a *facial* (*fac*-) geometry around the metal center, which is catalytically more active than the other tridentate ligand, ETP, which can form facial and meridional (*mer*-) isomers (Figure 1-2). A similar effect is observed in the hydrogenation of 2-cyclohexen-1-one, where Triphos



SCHEME 1-14. Hydrogenation of dimethyl oxalate **24** to ethylene glycol **26** via methyl glycolate **25**. Conditions: MeOH, H_2 (80 bar), 120 °C, 16 h, Zn (0.3 mol%).

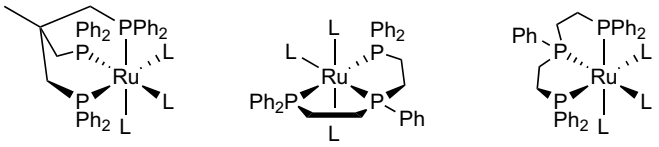


FIGURE 1-2. Coordination geometries of tridentate ligands.

reacts twice as fast as ETP [21]. This could also explain the reduced performance of the tetradentate ligand, Tetraphos, as this can also form a number of geometric isomers that can have different catalytic activities [22]. Another distinct advantage of the Triphos ligand over other phosphine ligands is the fact that it is an air-stable solid.

Since this initial study, a variety of other homogeneous catalysts has been applied to the hydrogenation of esters, and these will be discussed in the following chapter.

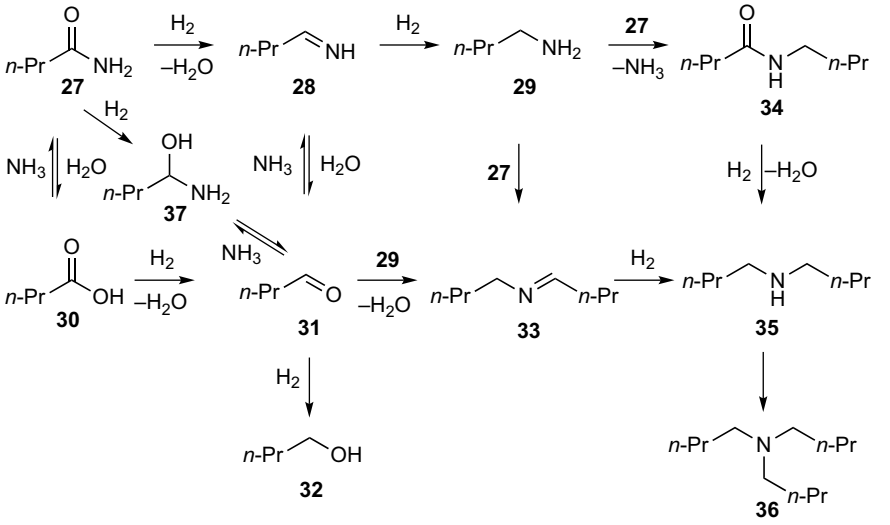
1.5.1 Hydrogenation of Primary Amides

Following the work of Crabtree and coworkers [17], Cole-Hamilton and coworkers [23] reported their initial results on some hydrogenation studies, where 100% conversion of butanamide **27** to dibutylamine **35** and tributylamine **36** can be achieved in ca. 50:50 ratio, with no observed formation of butylamine **29** (Table 1-1, entries 1 and 2, and Scheme 1-15). In order to obtain **29**, butanamide **27** must first undergo hydrogenation with the loss of water to give the imine **28**; this is then hydrogenated to give the desired primary amine. However, the reaction does not stop here, and **29** can undergo transamidation with the amide **27** to afford secondary amide **34**, or it can form an imine **33** with the aldehyde **31** (generated from **27**). Both of these observed intermediates are then readily hydrogenated to the secondary amine **35**. This cycle can then be repeated to give the tertiary amine **36**.

TABLE 1-1. Hydrogenation of Butanamide 27[a] (Scheme 1-15) [23]

Entry	H_2O: THF[b]	NH_3(aq): THF[b]	NH_3(l): THF[b]	1° Amine **29** (%)	Alcohol **32** (%)	2° Amide **34** (%)	2° Amine **35** (%)	3° Amine **36** (%)	Conversion (%)
1[c]	0.1	–	–	0	Trace	Trace	46	53	100
2[c]	0.01	–	–	0	Trace	Trace	48	51	100
3	0.1	–	0.5	44	8	10	38	0	100
4	0.1	–	1	36	3	14	6	0	59
5	–	0.3	–	78	12	10	0	0	100
6	–	0.5	–	85	15	0	0	0	100
7	–	0.7	–	85	15	0	0	0	100
8	–	1	–	73	25	2	0	0	100
9[d]	–	1	–	75	25	0	0	0	100

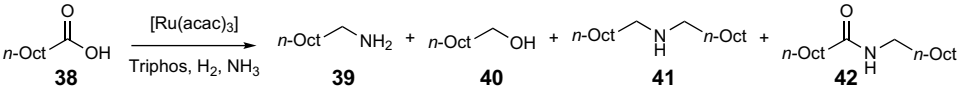
[a]Conditions (unless otherwise indicated): Butanamide **27** (1 g, 11.4 mmol), $[Ru_2(Triphos)_2Cl_3]Cl$ (91 mg, 0.05 mmol), 164°C (external), 220°C (internal), H_2 (40 bar), 14 h, THF (10 ml), Hastelloy autoclave.
[b]v/v.
[c]$[Ru(acac)_3]$ (45 mg, 0.1 mmol) and Triphos (142 mg, 0.22 mmol) were used instead of $[Ru_2(Triphos)_2Cl_3]Cl$.
[d]NH_3 (4 bar).



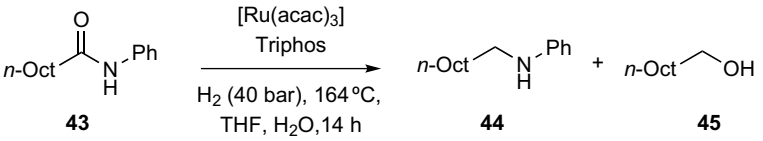
SCHEME 1-15. Proposed mechanism of amide reduction indicating possible intermediates and routes to side products [23].

The initial processes involve the formation of many unwanted side reactions, that is, hydrolysis of amide **27** and imine **28**, liberation of amine from the aminal **37**, and transamidation of **29** with **27**, all proceeding with the liberation of ammonia. However, the proposed mechanism suggests that these processes may be reversed or suppressed by working in the presence of ammonia. Indeed, the introduction of liquid ammonia increased the selectivity for primary amine **29** to 44%, while the formation of the tertiary amine **36** was sequestered (entry 3). A higher concentration of liquid ammonia increased the selectivity of the primary amine to 61% (entry 4), although this somewhat suppressed the yield to 59%. The use of aqueous ammonia was more fruitful, and a selectivity of 85% toward primary amine could be achieved while complete conversion was maintained (entries 6–7). The downside to using aqueous ammonia is the inevitable accumulation of water in the reaction, which leads to the formation of a higher amount of alcohol **32** (entry 8). By the same token, a combination of aqueous ammonia and ammonia gas also did not lead to any improvement. Nevertheless, this reaction represents the first example of the homogeneously catalyzed hydrogenation of a primary amide to a primary amine using only molecular hydrogen, with a high level of selectivity.

The protocol may be adapted for the hydrogenation of nonanoic acid **38**, which proceeds in the presence of ammonia to produce nonylamine **39** with 49% selectivity (the other products obtained are shown in Scheme 1-16) [23].



SCHEME 1-16. The production of nonylamine **39** by the hydrogenation of nonanoic acid **38** in the presence of ammonia [23].



SCHEME 1-17. Hydrogenation of *N*-phenylnonanamide [23].

1.5.2 Hydrogenation of Secondary Amides

Secondary amides are challenging substrates as they may potentially undergo further reaction to give tertiary amines, rather than the desired secondary amines. To date, the only example of homogeneous hydrogenation of secondary amides was reported by Cole-Hamilton and coworkers. In the original communication on amide hydrogenation [23], the reaction temperature was "set" at 164 °C using collar-type heaters used for heating the autoclaves. Subsequently, by using an autoclave fitted with a thermocouple pocket, the internal temperatures were in fact found to be some 60 °C higher (the temperatures quoted in the current chapter are actual reaction temperatures).

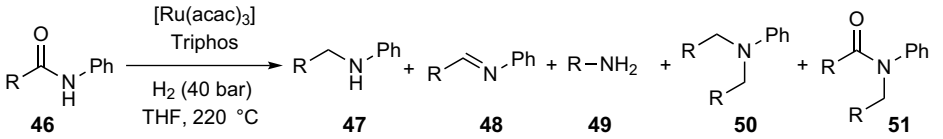
Choosing *N*-phenylnonanamide **43** as a test substrate, the reduction furnished a mixture of the corresponding secondary amine, *N*-phenylnonylamine **44** and nonanol **45**, where the selectivities are dependent upon the reaction conditions employed. The alcohol is thought to originate either from the hydrolysis of the amide to the acid or from the hydrolysis of the imine to the aldehyde. Subsequent hydrogenation of these intermediates leads to the alcohol (see Scheme 1-17).

The optimum reaction conditions for the hydrogenation of **43** were reported to be 220 °C at 40 bar hydrogen pressure in THF for 14 h. The reaction requires both [$Ru(acac)_3$] and Triphos in order to proceed (Table 1-2, entries 1–3). In the absence of Triphos, a lower conversion is observed (entry 2). The addition of water appears to have a detrimental effect on the selectivity (entries 4 and 5). However, water is thought to also have a stabilizing effect on the catalyst. The reaction still gives full conversion at 220 °C, with only a slight loss in selectivity. Below this temperature, the conversion drops dramatically with a significant loss in selectivity. In fact, only alcohol is observed at 160 °C, as a result of C−N cleavage, which was also reported by Milstein and coworkers [24].

TABLE 1-2. Hydrogenation of *N*-Phenylnonanamide 43[a] (Scheme 1-17) [23]

Entry	[$Ru(acac)_3$] (%)	Triphos (%)	T (°C)[b]	Amine **44** (%)	**45** (%)	Conversion (%)
1	–	–	220	0	0	0
2	1	–	220	57	4	61
3	–	2	220	0	0	0
4	1	2	220	93	7	100
5[c]	1	2	220	99	1	100
6	1	2	200	91	9	100
7	1	2	180	48	32	80
8	1	2	160	0	40	40

[a]Conditions (unless otherwise indicated): *N*-phenylnonanamide **43** (4.3 mmol), H_2 (40 bar), 14 h, THF (10 ml), H_2O (1 ml), Hastelloy autoclave.
[b]Internal temperature, external autoclave temperature actually around 60 °C lower.
[c]No water added.



SCHEME 1-18. Hydrogenation of benzanilide (R = Ph) and acetanilide (R = Me), showing the products and side products obtained.

By studying a variety of substrates, it was found that the presence of an aryl group on the nitrogen atom is a key requirement for the amide substrate. Conversely, the reaction was less sensitive to changes of substituents on the C=O, where both aromatic and aliphatic groups are tolerated. Thus, benzanilide and acetanilide (**46**, R = Ph and Me, respectively) were chosen as model substrates for further optimization (Scheme 1-18).

The first area of optimization was the pressure, which, at 40 bar, was too high for widespread application in the pharmaceutical industry (Table 1-3). Subsequently, it was found that the reaction could be performed at 10 bar with no loss of conversion, and a rather unexpected improvement in selectivity (entries 1 and 2). Lowering the pressure to 5 bar (entry 3) further improved the selectivity, but a concurrent loss of conversion was also observed. By extending the reaction time, it was possible to obtain 89% conversion, but with reduced selectivity (entry 4).

Previously, the hydrogenation reactions could be run at 200 °C without any detrimental effects on conversion or selectivity. In the present system, a decrease in both was observed by lowering the temperature to 200 °C (entry 5). Further decrease to 180 °C led to the formation of only a trace of the desired product, the main product being aniline. By running the reaction at lower temperatures and pressures simultaneously (10 bar, 200 °C), 80% conversion can be achieved after an extended reaction period of 63 h.

Shortly after its publication, several research groups reported problems with reproducing the results reported in the original paper (M. Beller and coworkers, private communication). By a process of elimination, the purity of the ligand was found to exert an important effect on the reaction outcome. Several batches were tested, alongside purified samples stored under an inert atmosphere, but each showed a much reduced activity. It was

TABLE 1-3. Optimization of the Hydrogenation of Benzanilide (46, R = Ph)[a]

					2°			3°		
Entry	pH_2	T (°C)	*t* (h)	Amide **46** (%)	Amine **47** (%)	Imine **48** (%)	Aniline **49** (%)	Amine **50** (%)	Conversion (%)	Selectivity (%)
1	40	220	16	8	62	2	26	2	92	67
2	10	220	16	8	71	1	17	2	92	78
3	5	220	16	29	64	3	3	1	71	90
4	5	220	66	11	58	2	26	3	89	66
5	40	200	16	27	38	1	34	0	73	52
6	40	180	16	42	<1	0	58	0	58	<1
7	10	200	16	51	33	1	15	<1	49	67
8	10	200	63	20	55	1	22	1	80	69

[a]Conditions: Benzanilide (5 mmol), $[Ru(acac)_3]$ (1 mol%), Triphos (2 mol%), THF (10 ml), Hastelloy autoclave. Product distribution calculated based on GC-FID.

TABLE 1-4. Hydrogenations of Benzanilide (46, R = Ph) Employing Catalytic Amounts of MSA[a]

Entry	pH_2 (bar)	MSA (%)	t (h)	2° Amine **47** (%)	Imine **48** (%)	Aniline **49** (%)	3° Amine **50** (%)	Other (%)	Conversion (%)	Selectivity (%)
1	10	1	16	84	3	3	10		100	84
2	10	0.5	16	91	4	0	5		100	91
3	10	10	16	12	<1	0	28	53[b]	100	12
4	5	0.5	62	76	6	5	13		100	76
6[c]	10	1	16	Ring hydrogenation occurred						
7[d]	10	1	16	89	3	0	7		100	89
8	10	1	8	92	4	0	4	0	100	92

[a]Conditions (unless otherwise indicated): Benzanilide (5 mmol), [$Ru(acac)_3$] (1 mol%), Triphos (2 mol%), 220 °C, THF (10 ml), Hastelloy autoclave, product distribution calculated based on GC-FID.
[b]*N*-phenylpyrrolidine, tertiary amide, and two other impurities.
[c]Stainless steel autoclave.
[d]Aniline (1%) added.

subsequently discovered that the catalytic activity and the selectivity of the reaction could be restored by adding a catalytic amount of acid, specifically, methanesulfonic acid (MSA), see Table 1-4 [25]. The addition of 1% MSA (1:1, MSA:Ru) resulted in full conversion of benzanilide with excellent selectivity for the secondary amine (entry 1) [25]. Interestingly, the product distribution also changed. In the absence of acid, aniline **49** was found to be the major side product, whereas the corresponding tertiary amine, *N*,*N*-dibenzylaniline **50**, was produced as the major side product in the presence of acid, which presumably arises from the transamidation of the starting benzanilide **46** with product *N*-benzylaniline **47**, followed by hydrogenation of the tertiary amide **51**.

The amount of acid added is also vital, as too much (10% MSA) leads to the formation of *N*-phenylpyrrolidine, derived from a reaction of the solvent THF with aniline, as well as tertiary amide **51** (entry 3). The optimum MSA for this reaction appears to be between 0.5 and 1%, although 1.5% is found to be optimal for the hydrogenation of acetanilide. Under 5 bar of H_2 pressure, the reaction proceeded with full conversion (entry 4) and a respectable selectivity of 76% after 62 h. Last but not the least, the reaction is sensitive to the type of autoclave used, and the best results are achieved in Hastelloy C-276,[1] as opposed to stainless steel, which was found to promote the formation of alcohol and hydrogenation of the phenyl ring (entry 6). Under optimized conditions, the best selectivity of 92% can be achieved in 8 h, with only 4% of the tertiary amine as side product (entry 8).

The optimized reaction conditions were subsequently applied to the hydrogenation of a series of *para*-substituted acetanilides (Table 1-5), where it was found that 98–100% conversion can be achieved with methoxy-, methyl-, and fluoro-substituted acetanilides (entries 1, 2, and 4), which was comparable to acetanilide itself (entry 3). The selectivity, however, was lower at 60–68%, compared with 85% for acetanilide. Conversely, the hydrogenation of more electron-withdrawing substituents did not proceed cleanly (entries 6 and 7); an insoluble precipitate was obtained from the CF_3-substituted acetanilide. While the nitro-substituted substrate showed some reactivity, there was evidence of alcohol hydrogenation and phenyl ring hydrogenation.

[1] Nickel-based alloy incorporating chromium and molybdenum.

TABLE 1-5. Study of *para*-Substituted Acetanilides, Incorporating Electron-Withdrawing and -Donating Groups[a]

Entry	*p*-Subst.	Amide (%)	2° Amine (%)	Imine (%)	Aniline (%)	3° Amine (%)	Pyrrolidine (%)	Conversion (%)	Selectivity (%)
1	OMe	3	66	1	6	24	0	98	66
2	Me	1	68	0	6	22	4	99	68
3	H	0	86	0	4	8	3	100	86
4	F	1	60	1	4	23	10	99	60
5	CF_3	Insoluble precipitate, reaction outcome unclear							
6	NO_2	Side reactions of ring hydrogenation and alcohol hydrogenation							

[a]Conditions: *p*-substituted acetanilide (5 mmol), $[Ru(acac)_3]$ (1 mol%), Triphos (2 mol%), MSA (1%), 220 °C, 16 h, THF (10 ml), Hastelloy autoclave, product distribution calculated based on GC-FID.

1.5.3 Tertiary Amides

The observation of tertiary amine as a side product in the above system indicates that the system should also be active for the hydrogenation of tertiary amides, such as PhC(O) NBzPh, formed from the transamidation of the starting benzanilide with the product *N*-benzylaniline. Thus, the hydrogenation of the tertiary amine, *N*,*N*-diphenylacetanilide, was carried out in the presence of MSA (Table 1-6) [25]. In this case, a much higher conversion was achieved at 40 bar, compared with 10 bar (85% vs. 47%). In both cases, the selectivity was around 50%; a large proportion of diphenylamine was also present.

1.5.4 Scope of Ru/Triphos Amide Hydrogenation

Accordingly, full conversion to hydrogenation products can be obtained with a primary amide substrate, such as butanamide, if MSA is added to the reaction mixture [25]. As was observed in the initial findings [23], secondary amines are the major products unless ammonia is added, in which case the selectivity for the primary amine can be as high as 80%.

The general scope of the hydrogenation of amines using Ru/Triphos in the presence of MSA is outlined in Figure 1-3.

1.5.5 Hydrogenation of Diacids in the Presence of Amines

Building on previous results (Section 1.5.1), the hydrogenation of dicarboxylic acids and esters was also attempted in the presence of amines. For long-chain diesters such as dimethyl 1,19-nonadecanedioate, reduction in the presence of aniline produces an oligoamide (nylon 19) [26]. Intermediate-chain length diacids such as 1,8-octanedioic acid

TABLE 1-6. Hydrogenation of *N*,*N*-Diphenylacetanilide[a]

Entry	pH_2 (bar)	Ph_2NH (%)	Amine (%)	Amide (%)	Conversion (%)	Selectivity (%)
1	10	24	23	53	47	49
2	40	46	38	15	85	45

[a]Conditions: *N*,*N*-diphenylacetanilide (5 mmol), $[Ru(acac)_3]$ (1 mol%), Triphos (2 mol%), MSA (1%), 220 °C, 16 h, THF (10 ml), Hastelloy autoclave, product distribution calculated based on GC-FID.

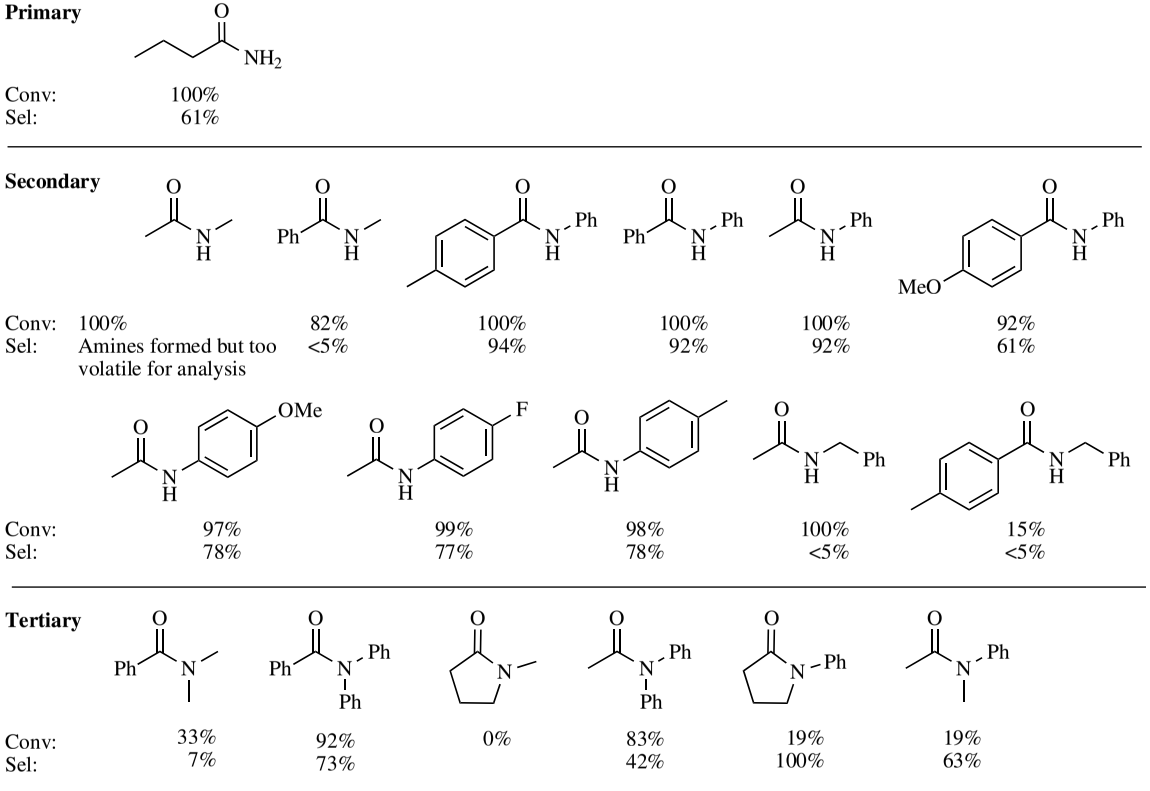
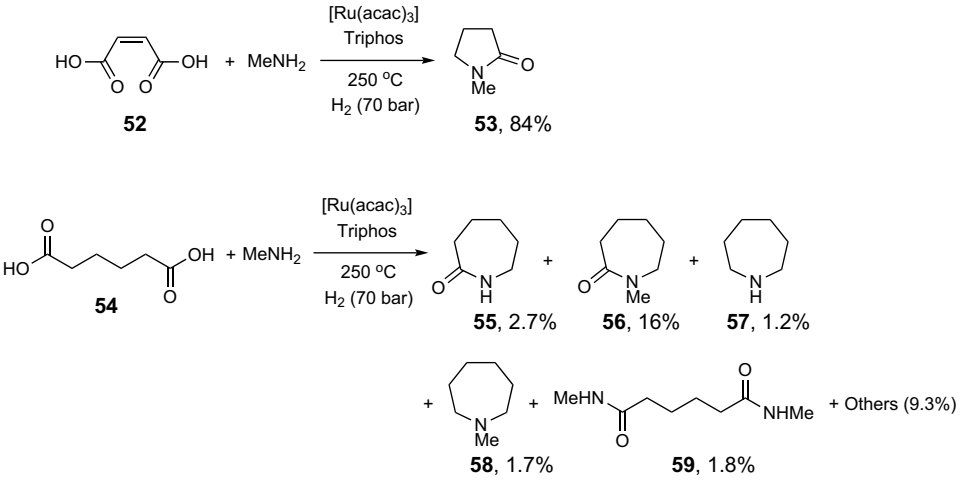


FIGURE 1-3. Substrate scope for the hydrogenation of amides catalyzed by [Ru(acac)$_3$]/Triphos/MSA. Substrate (5 mmol), [Ru(acac)$_3$] (0.05 mmol, 1 mol%), Triphos (0.10 mmol), MSA (3 μl), 1.5 mol%), 220°C, H_2 (10–40 bar), THF (16 h) [25].

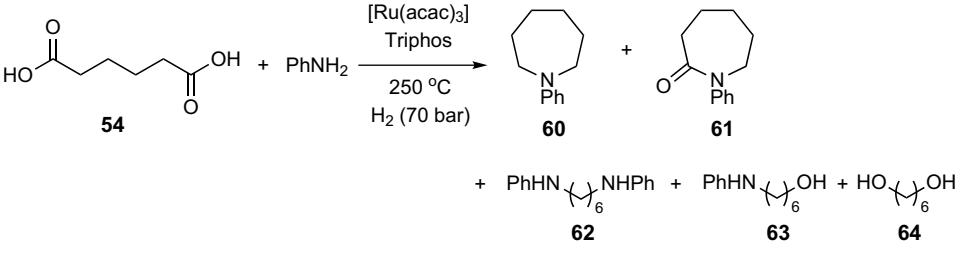


SCHEME 1-19. Catalytic formation of cyclic lactams from the hydrogenation of diacids. The product distribution obtained from the reaction with adipic acid **54** was derived from the integration of GC peak areas (TCD) [28].

give linear α,ω-amino alcohols and diamines [27], while shorter-chain diacids give heterocyclic molecules [27].

Earlier, Crabtree and coworkers had reported that the hydrogenation of maleic acid **52** or adipic acid **54** in the presence of water and methylamine (at 250 °C and 70 bar) gave the corresponding cyclic lactam (**53** and **56,** respectively) with selectivity up to 83.5% [28]. The fact that *N*-methylpyrrolidone is also produced from *N*-methylsuccinimide under similar conditions without any methylamine suggests that it might be an intermediate in the reaction (Scheme 1-19).

More recently, these reactions were reexamined [27] using aniline as the amine substrate, which were shown to give a variety of products (Scheme 1-20, Figure 1-4), which do not change with extended reaction time. However, if MSA is added, the major product is the heterocyclic *N*-phenyl hexahydroazepine **60**. Hence, five- to eight-membered heterocycles are obtained by varying the chain length, but longer chain diacids give amino alcohols. The reaction also works when ammonia or benzylamine was employed, but less selectively.



SCHEME 1-20. Products obtained from the hydrogenation of adipic acid **54** in the presence of aniline, $[Ru(acac)_3]$, Triphos, and optionally MSA [27].

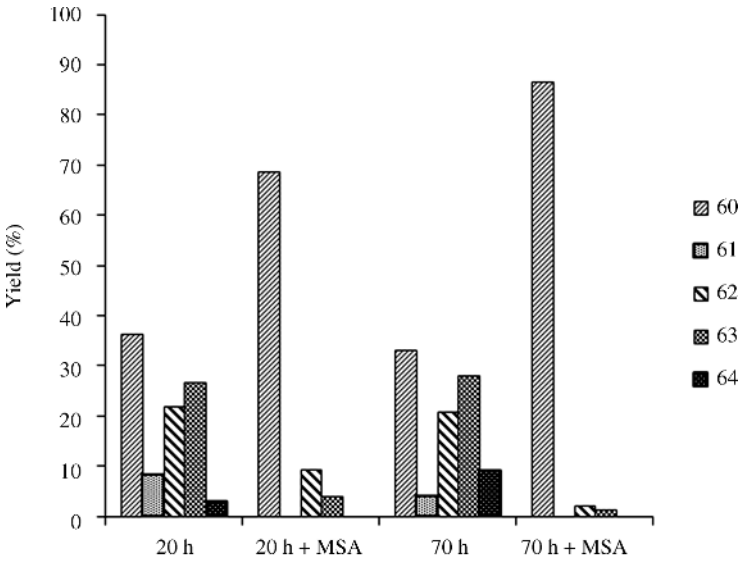


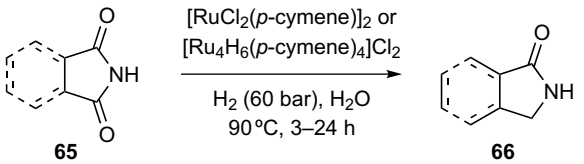
FIGURE 1-4. Product distribution obtained from the hydrogenation of adipic acid **54** in the presence of aniline, [Ru(acac)$_3$], Triphos, and optionally MSA [27].

Since heterocyclic moieties are important in many pharmaceutical compounds, this low-waste route from readily available diacids may prove to be important for future applications.

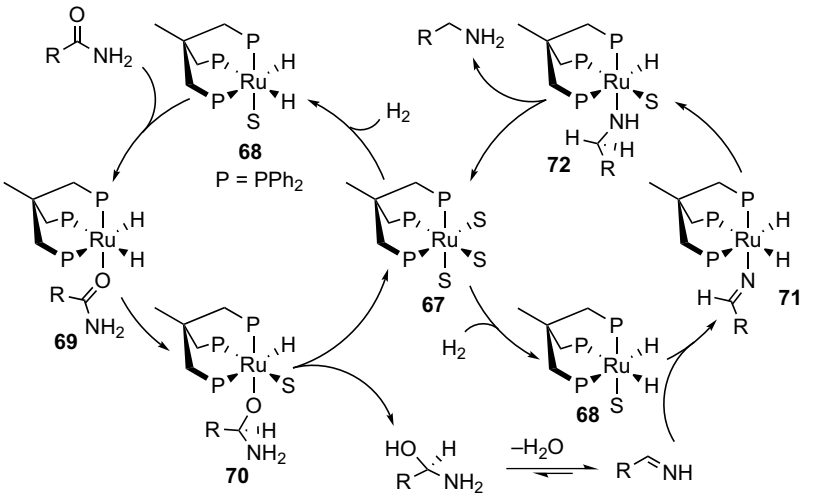
In a related reaction, Bruneau and coworkers reported the hydrogenation of cyclic imides to lactams, employing [$RuCl_2$(*p*-cymene)]$_2$ and [Ru_4H_6(*p*-cymene)$_4$]Cl_2 as catalyst precursors at 60 bar H_2 and 90 °C [29]. The use of water as the solvent further improves the green credentials of this reaction. A series of substrates was tested, and excellent conversions (full conversion in many cases) were achieved. Succinimide and phthalimide (**65**, Scheme 1-21) were both successfully mono-reduced in yields of 87% and 78%, respectively. One drawback with this method, however, is that unsaturated moieties such as alkenes and aromatic rings were also hydrogenated under these conditions.

1.5.6 Homogeneous Amide Hydrogenation Mechanism

The proposed mechanism is based on one described by Milstein and coworkers for the hydrogenation of esters (Scheme 1-22) [30]. The two reduction steps are thought to



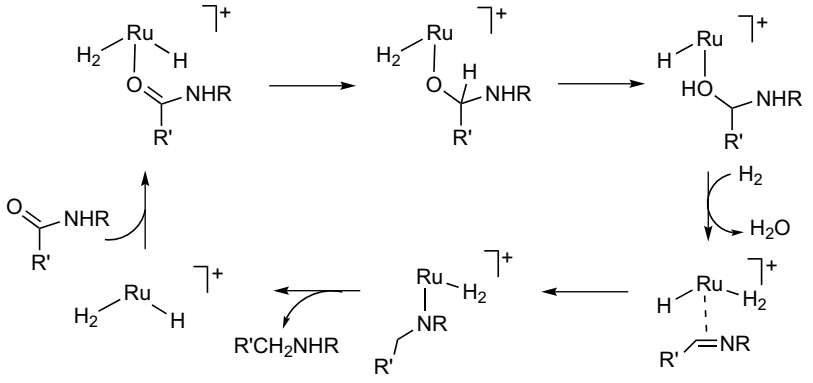
SCHEME 1-21. Monoreduction of succinimide and phthalimide (**65**, without and with fused benzo ring, respectively) [29].



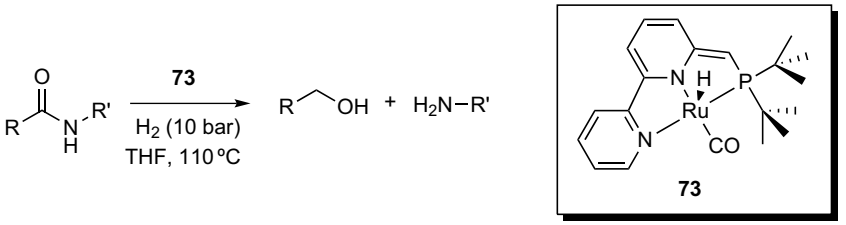
SCHEME 1-22. Tentative mechanism for the Ru-catalyzed hydrogenation of amides, based on a similar ester hydrogenation mechanism proposed by Milstein (S = coordinating solvent) [30].

proceed through a common catalytic precursor, **67**, which first undergoes oxidative addition with hydrogen to give **68**. Next, coordination of the amide (**69**) is followed by its hydrogenation. Finally, reductive elimination of the intermediate **70** generates the uncoordinated hemiaminal, which is highly unstable and rapidly eliminates water to give the imine. The imine can then enter the second catalytic cycle by coordination to the dihydride species **68**. Hydrogenation of **71** followed by reductive elimination of **72** gives the expected amine.

It is not clear yet what role the tridentate ligand plays, other than restricting the geometry in a *facial* fashion. It is also not clear what the nature of the moieties occupying the other coordination sites is. Additionally, tripodal ligands have been shown to exhibit hemilability [31]. Leitner and coworkers [32] have reported calculations relating to the mechanism of hydrogenation of itaconic acid and levulinic acid using the same catalyst system [33]. Proposing that protonated (cationic) complexes may be important in the mechanism of hydrogenation [32], they demonstrated that activation barriers obtained for the reaction are consistent with those obtained from the calculations using protonated intermediates, although a neutral cycle could not be ruled out. Adapting their mechanism to amide hydrogenation would give the mechanism shown in Scheme 1-23. An alternative pathway involving a loss of amine from the 1,1-aminoalcohol to give aldehyde, followed by Schiff base condensation, seems less likely since, as the reaction proceeds, Schiff base formation with the product amine would be favored. This would be expected to lead to the formation of tertiary amines in the case of secondary amide substrates. However, these products are usually only formed in low yield and may arise from transamidation of the product amine with the substrate amide. Furthermore, this mechanism could not operate for *N,N*-disubstituted (tertiary) amides, since it is not possible to eliminate water from 1,1-aminoalcohol. If they have enolizable α-hydrogens, they could proceed through the vinyl amine, but this is not possible for a substrate such as *N,N′*-diphenylbenzamide.



SCHEME 1-23. Possible mechanism for the hydrogenation of primary (R = H) and secondary amides based on that proposed by Leitner and coworkers [32] for the hydrogenation of carboxylic acids. Three coordination sites are always occupied by the Triphos ligand.

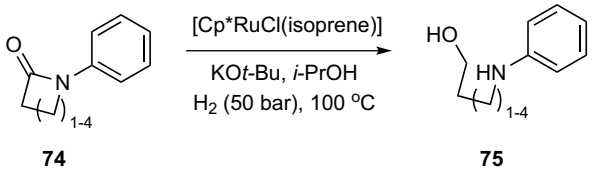


SCHEME 1-24. Ru-catalyzed C−N cleavage of amides employing pincer complex **73**.

1.5.7 Amide C−N Cleavage by Hydrogenation

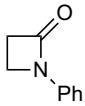
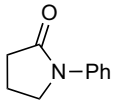
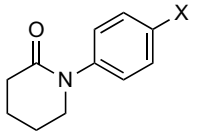
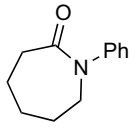
Using a ruthenium complex **73** containing the 6-di-*tert*-butylphosphinomethyl-2,2′-bipyridine (BPy-*t*-PNN) ligand, secondary amides undergo hydrogenation to alcohols and primary amines at 10 bar and 110 °C (Scheme 1-24) [24]. This reaction also occurs under anhydrous conditions, so it is not thought to be a result of hydrolytic cleavage of the amide. It is not an atom efficient route to the desired amine as 1 equiv. of the corresponding alcohol is generated, which must be removed from the reaction mixture. In addition, the amine formed in this way is generally less valuable than the starting amide.

Similar findings were reported by Ikariya and coworkers where a series of lactams **74** underwent hydrogenation via C−N cleavage to give linear amino alcohols **75** (Scheme 1-25) [34].



SCHEME 1-25. Hydrogenation of lactams **74** to linear amino alcohols **75**.

TABLE 1-7. C−N Cleavage of Lactams via Ru-Catalyzed Hydrogenation (Scheme 1-25) [34][a]

Entry	Substrate		*t* (h)	Conversion (%)	Yield (%)[b]
1			24	>99	83
2			24	84	73
3		X = H	24	>99	96
4		$X = CF_3$	24	>99	90
5		X = OMe	24	88	78
6			72	60	60[c]

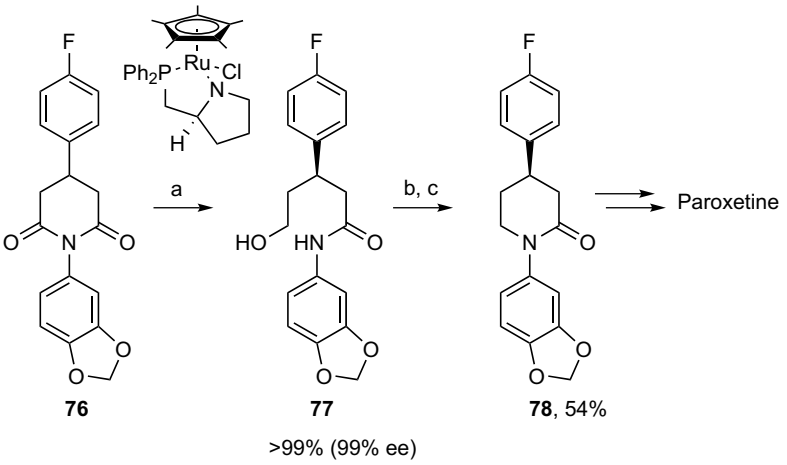
[a]Conditions: lactam (1.0 M in 2-propanol), [Cp∗RuCl(isoprene)] (10 mol%), KO*t*-Bu (25 mol%), 100°C, pH_2 (50 bar).
[b]Isolated yield.
[c]Product yield determined by ^1H NMR spectroscopy, using triphenylmethane as an internal standard.

Table 1-7 summarizes the hydrogenation of a series of heterocycles. Maximum conversion is obtained with heterocycles containing four- and six-membered rings (entries 1 and 3). A lower conversion of 84% was obtained in the case of the five-membered ring (entry 2), and only 60% for the seven-membered ring, even after an extended reaction period (entry 6). Electronic influences were also investigated (entries 3–5) and an electron-donating substituent (*p*-OMe) had a detrimental effect on the conversion. No such effect was observed with an electron-withdrawing substituent (p-CF_3). The reduction was investigated for a series of *N*-protected pyrrolidones, and the reactivity was found to increase in the following order: $CBz < Boc \approx Ts < CO_2CH_3 < Ms$.

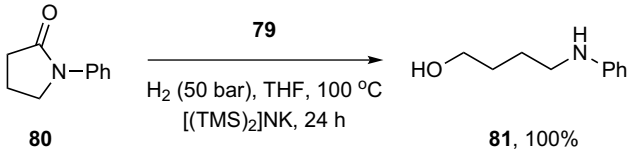
The procedure was applied to the asymmetric synthesis of paroxetine (Scheme 1-26) [35], whereby the imide **76** was desymmetrized to give optical active **77** as a result of C−N cleavage. Excellent enantioselectivity was achieved (>99% ee), which was maintained throughout subsequent steps toward paroxetine precursor **78**.

John and Bergens have reported similar findings employing a similar Ru complex, $[Ru(Ph_2P(CH_2)_2NH_2)_2(\eta^3\text{-}C_3H_5)]BF_4$ **79**, to hydrogenate lactams and tertiary amines to their C−N cleavage products [36]. Scheme 1-27 shows the hydrogenation of *N*-phenylpyrrolidin-2-one **80** to the linear amino alcohol **81**, which proceeds in 100% conversion and a TON of 1000.

The analogous six-membered lactam was also hydrogenated with full conversion as were a number of acyclic tertiary amides. The TON was found to increase to ca. 7000 when $[(TMS)_2]NK$ is replaced with NaOMe. The proposed mechanism of this system



SCHEME 1-26. Asymmetric synthesis of paroxetine by amide reduction: (a) H_2 (30 bar), KO*t*-Bu, 60 °C, 18 h; (b) CBr_4, PPh_3; (c) NaH.



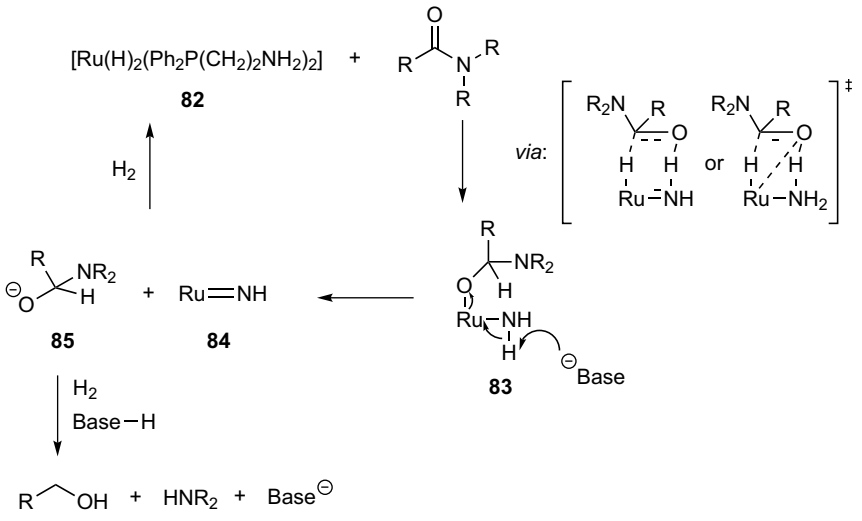
SCHEME 1-27. Hydrogenation of *N*-phenylpyrrolidin-2-one **80** to 4-(phenylamino)butan-1-ol **81**.

(Scheme 1-28) involves the bifunctional-type addition to the dihydride species **82**, resulting in ruthenium hemiaminal **83**. Base-assisted elimination generates the free hemiaminal **85** and "ruthenium amide" **84**. The hemiaminal eliminates aldehyde that undergoes hydrogenation to give the alcohol and the amine products. The dihydride **82** is regenerated following the addition of H_2 to **84**.

1.6 HYDROSILATION

The use of silanes as a hydride source in amide reductions has received a lot of interest in recent years. It has proven to be highly effective and tolerant to a variety of functional groups. It should be noted, however, that there are hazards associated with the use of triethoxysilane and Lewis acids, as there is the potential for highly pyrophoric and toxic silane gas (SiH_4) to form [37]. Methyldiethoxysilane [38] or polymethylhydrosiloxane (PMHS), which do not lead to the formation of silane, are safer alternatives, particularly for larger scale syntheses [39].

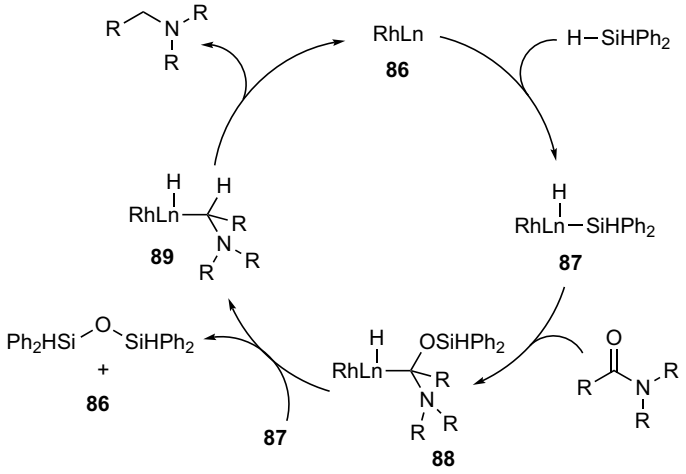
Igarashi and Fuchikami [40] reported a series of metal-catalyzed amide reductions by employing group 7–10 transition metals (Mn, Re, Ru, Os, Rh, Ir, Pd, Pt) and trisubstituted silanes. Other cocatalysts such as ethyl iodide and diethylamine were required in some cases to achieve good yields.



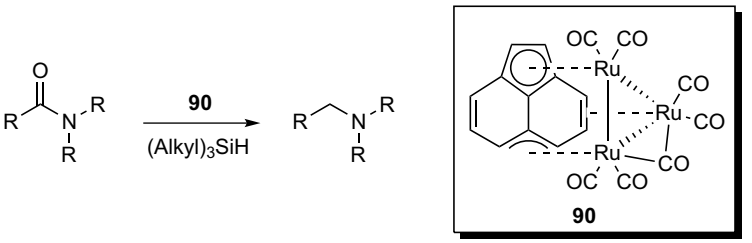
SCHEME 1-28. Proposed mechanism for amide hydrogenation [36].

1.6.1 Rhodium-Catalyzed Reduction of Amides Using Silanes

Used in conjunction with Ph_2SiH_2, $[RhH(CO)(PPh_3)_3]$ was found to be the most effective for the reduction of tertiary amides to amines, where yields of 65–98% were achieved at room temperature over periods of 0.5–48 h [41]. Notably, ester and epoxide functionalities remained inert under these reaction conditions. A catalytic cycle was proposed (Scheme 1-29), where the first step is thought to involve the oxidative addition of hydrosilane to the rhodium complex **86**, generating the activated hydrido silane complex **87**. The amide is then believed to insert into the Rh−Si bond, leading to



SCHEME 1-29. Proposed mechanism for Rh-catalyzed reduction of amides [41].



SCHEME 1-30. [(μ_3, η^2; η^3; η^5-acenaphthylene)$Ru_3(CO)_7$] (**90**)-catalyzed silane-mediated reduction of amides.

species **88**. Hydride transfer from activated silane complex **87** then allows selective C−O cleavage, siloxane formation, and regeneration of the catalyst **86**. The resultant amino complex **89** then reductively eliminates the product amine.

1.6.2 Ruthenium-Catalyzed Reduction of Amides Using Silanes

Nagashima and coworkers [42] first reported the use of a ruthenium cluster catalyst, [(μ_3, η^2; η^3; η^5-acenaphthylene)$Ru_3(CO)_7$] (**90**), in silane-mediated amide reduction in 2002 (Scheme 1-30). Three tertiary amides were reduced in 90–100% conversion, employing $EtMe_2SiH$ at 20 °C for 30 min.

They also addressed the problem of lengthy and wasteful workup procedures by encapsulating the catalyst within a polymer [43]. Using PMHS as the reducing agent, gel formation occurs as the reaction proceeds, as the oxygen molecules produced aid crosslinking of the polymer. At the end of the reaction, the products are easily separated from the catalyst, which is encapsulated within the gel. ICP-mass analysis indicated that $<$15 ppm of ruthenium was present in the amine (compared with ca. 10% when acid–base workup is used). Additionally, the encapsulated catalyst remains active and can be recycled. This is an excellent example of a green approach to waste disposal, and removing the need for acid–base workups.

The ruthenium cluster **90** is also able to reduce the more challenging secondary amides in $>$99% conversion under optimized reaction conditions by employing a disiloxane, $(H(Me)_2Si)_2O$ [44].

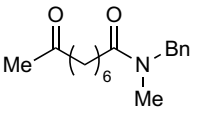
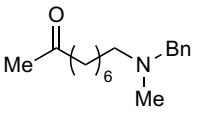
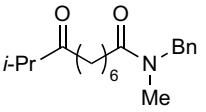
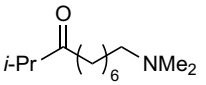
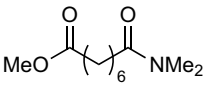
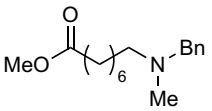
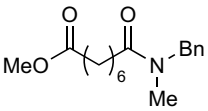
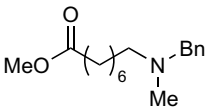
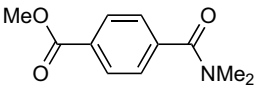
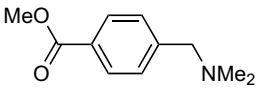
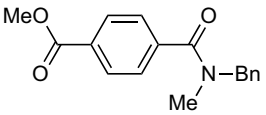
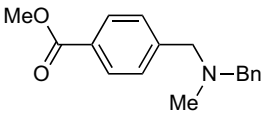
Using the same catalyst, selective reduction of amides can also be achieved in the presence of ketones and esters (Table 1-8) [45]. The presence of an amine, NEt_3, poisons the catalyst toward ketone and ester reduction, resulting in selective reduction of amides (entries 1 and 2). In many cases, it was found that the addition of an amine was not necessary as the amino groups produced during the reaction were sufficient to poison the catalytic activity (entries 3–6).

An interesting observation was made when the reduction of a primary amide **91** was attempted with this system, where dehydration to the nitrile **92** was observed with the evolution of hydrogen gas, rather than the expected reduction (Scheme 1-31) [46].

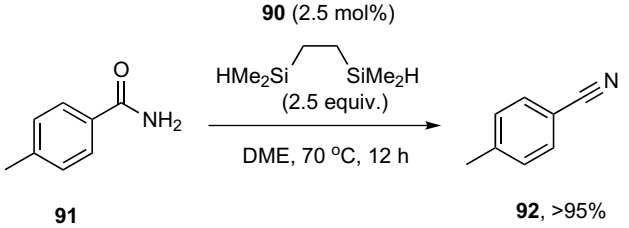
1.6.3 Platinum-Catalyzed Reduction of Amides Using Silanes

Nagashima and coworkers also applied their self-encapsulation strategy to platinum-catalyzed silane reduction of tertiary amides [47,48]. The most effective system involved

TABLE 1-8. Reduction of Tertiary Amides in the Presence of Ketones and Esters[a]

Entry	Substrate	Si−H (equiv.)	*t* (h)	Product	Yield (%)[b]	Selectivity (%)[c]
1		2.5	1		91	>99
2[d]		2.5	1.5		94	>99
3[e]		3.0	1.5		91	>99
4[e]		3.0	0.5		96	>99
5[e]		3.0	3.5		81	>99
6[e]		3.5	18		88	>99

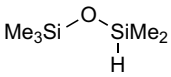
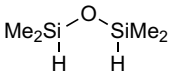
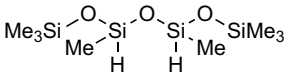
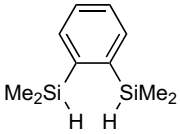
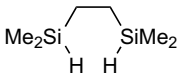
[a]Conditions (unless otherwise indicated): Amide (1 mmol), **90** (0.01 mmol), $PhMe_2SiH$ (2.5–3.5 mmol), NEt_3 (1 mmol), rt.
[b]Isolated yield (determined by ^1H NMR).
[c]Determined by ^1H NMR spectroscopy of crude reaction mixtures.
[d]0.5 mmol substrate, 0.005 mmol catalyst.
[e]In the absence of NEt_3.



SCHEME 1-31. Dehydration of primary amide **91** to nitrile **92**.

$H_2PtCl_6{\cdot}H_2O$ and PMHS, which formed a gel to encapsulate the platinum catalyst. After purification on a short Al_2O_3 column, amines were obtained with <1 ppm of Pt residue. The Pt-containing resin was still active, and could be recycled, although the conversion was somewhat diminished (first: 100%, second: 84%, third: 76%).

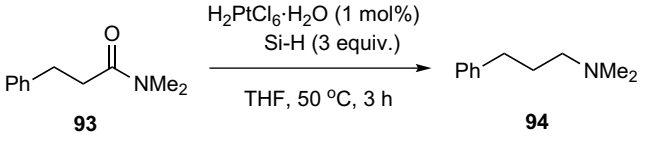
TABLE 1-9. Structural Effect of Hydrosilanes on the Reduction of *N*,*N*-Dimethyl-3-Phenylpropanamide[a]

Entry	Hydrosilane	Yield (%)[b]	Entry	Hydrosilane	Yield (%)[b]
1	$PhMe_2SiH$	<1	6		>98 (90)[c]
2	$EtMe_2SiH$	<1	7[d]		>98 (63)[c]
3	$(EtO)_3SiH$	<1	8[e,f]		>98
4	Ph_2SiH_2	<1	9[f]		<1
5		<1			

[a]Conditions (unless otherwise indicated): Amide (1 mmol), $H_2PtCl_6{\cdot}H_2O$ (0.01 mmol), silane (3 equiv.), 50°C, 3 h.
[b]Determined by ^1H NMR.
[c]Isolated yield after alumina column chromatography.
[d]10 h.
[e]8 h.
[f]4 equiv. silane.

More recently in 2009, the "dual Si−H effect" was described with respect to platinum-catalyzed hydrosilation [48]. A series of mono- and disilanes and siloxanes was tested (Table 1-9) with varying numbers of Si−H and proximate Si−H bonds in the hydrogenation of *N*,*N*-dimethyl-3-phenylpropanamide **93** to amine **94** (Scheme 1-32). Silanes and siloxanes containing one or two Si−H bonds gave <1% conversion (Table 1-9, entries 1–5). In comparison, siloxanes with two proximal Si−H units resulted in >98% yield (entries 6–8), whereas the related disilane (entry 9) showed no conversion.

From this study, 1,1,3,3-tetramethyldisiloxane (TMDS) was chosen as the optimal reductant due to its commercial availability and low cost. It was used in 5 equiv. to reduce a variety of tertiary amides in excellent yields of up to 96%, in the presence of sensitive functional groups including nitro, nitrile, ester, ether, and di- and trisubstituted alkenes. Selected secondary amides were also reduced, although higher catalyst and silane loadings were required (3 mol% and 10 equiv., respectively).



SCHEME 1-32. Pt-catalyzed reduction of *N*,*N*-dimethyl-3-phenylpropanamide **93** to amine **94**.

95 **96**

SCHEME 1-33. Mo-catalyzed reduction of 1-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)ethanone **95**.

1.6.4 Molybdenum-Catalyzed Reduction of Amides Using Silanes

Fernandes and Romão [49] reported MoO_2Cl_2-catalyzed reductions of secondary and tertiary amides in yields of 40–78% and 81–87%, respectively. The silane $PhSiH_3$ was chosen, in combination with 10 mol% of the catalyst, to reduce the amide **95** to **96** in very high yields (Scheme 1-33), for example. The mechanism is thought to proceed via the imine, as confirmed by deuterium studies.

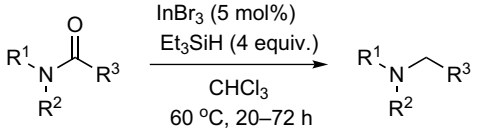
1.6.5 Indium Bromide-Catalyzed Reduction of Amides Using Silanes

A system for amide reduction described by Sakai et al. [50] employs indium bromide in conjunction with triethylsilane (Scheme 1-34).

This system has been shown to reduce a series of tertiary amides with yields of up to 94% in the case of *N*-benzoyl morpholine. Aliphatic amides gave much lower yields, as did secondary amides, where acetanilide and benzanilide gave yields of 45% and 72%, respectively. Some functional group tolerance was also observed as the reaction proceeded in the presence of a nitrile group (85%).

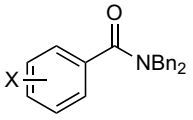
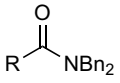
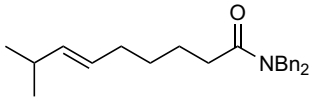
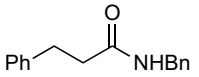
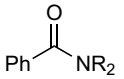
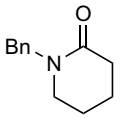
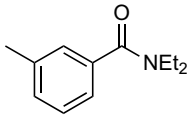
1.6.6 Iron-Catalyzed Reduction of Amides Using Silanes

In 2009, two groups, Beller and coworkers [51] and Nagashima [52], simultaneously and independently reported the catalyzed hydrosilane reduction of tertiary amides catalyzed by iron. Beller and coworkers reported a system using $[Fe_3(CO)_{12}]$ with 4 equiv. of PMHS at 100 °C for 24 h (Table 1-10). Most substrates based on *N*,*N*-dibenzylbenzamide were reduced with excellent yields (>90%), which included a variety of functional groups such as halides, ethers, cyclopropane, and alkenes (entries 1–9, 11–17). The only exception was an ester-substituted amide (entry 10), which gave a rather low yield of 58%. The presence of sterically demanding groups requires further equivalents of silane to achieve good conversions, for example, substrates with a *tert*-butyl on the C=O or *i*-propyl groups on nitrogen required 8 equiv. of silane (entries 17 and 22). The conditions for this reaction are fairly mild, as they were conducted at ambient pressure at 100 °C.

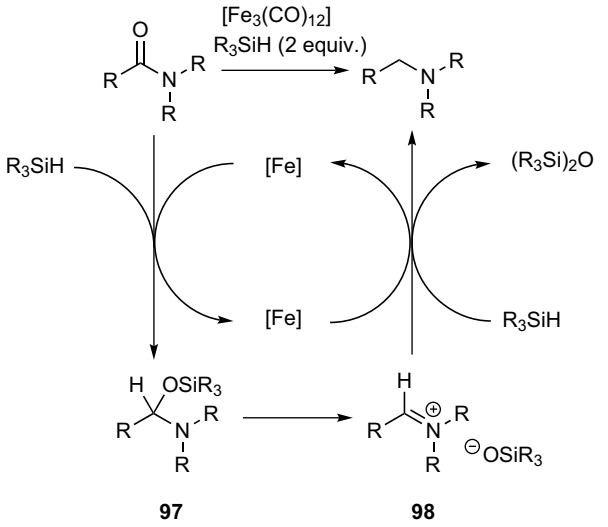


SCHEME 1-34. In-catalyzed reduction of tertiary amides.

TABLE 1-10. Iron-Catalyzed Reduction of Tertiary Amides in the Presence of Silanes[a]

Entry	Amide	Cat. (%)	Si−H (equiv.)	Yield (%)[b]
1	 X = H	4	4	89
2	X = *p*-Me	4	4	93
3	X = *m*-Me	4	4	93
4	X = *o*-Me	8	4	94
5	X = *p*-OMe	4	4	93
6	X = *p*-CF_3	4	4	84
7	X = *p*-Cl	4	4	95
8	X = *p*-Br	4	4	92
9[c]	X = *p*-I	4	4	83
10[d]	X = *p*-CO_2Me	4	4	58
11[d]	 R = Me	4	4	89
12	R = 1-naphthalene	4	4	77
13	R = 2-naphthalene	4	4	84
14	R = 2-furan	10	8	82
15	R = 2-thiophene	10	8	84
16	R = Cyclopropane	6	6	82
17	R = *t*-Bu	8	8	98
18[d]		4	4	76
19[c]		4	4	63
20	 R = $-(CH_2)_5-$	3	4	94
21	R = $-(CH_2)_2O(CH_2)_2-$	3	4	80
22	R = *i*-Pr	10	8	59
23	R = Me, Ph	4	4	81
24	R = Ph	4	4	50
25[d]	R = Me, H	2.5[e]	99[f]	
26[d]		3	4	90
27[d,g]		2	PMHS (4)	85

[a]Conditions (unless otherwise indicated): Amide (1 mmol), [$Fe_3(CO)_{12}$] (2–10 mol%), PMHS (4–8 mmol), *n*-Bu_2O (5 ml), 100°C, 24 h.
[b]Isolated yield.
[c]Contained 10% tribenzylamine.
[d]Toluene.
[e]$PhSiH_3$.
[f]Determined by GC.
[g]100 mmol scale.



SCHEME 1-35. Proposed mechanism for Fe-catalyzed hydrosilation of tertiary amides.

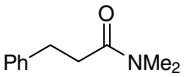
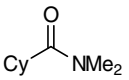
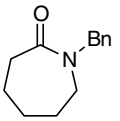
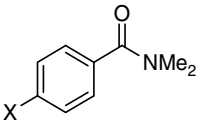
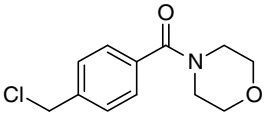
Beller and coworkers proposed a mechanism based on that previously described by Nagashima for the ruthenium-catalyzed reaction (Scheme 1-35). This proceeds through the *O*-silylated intermediate **97**, a result of the reaction of the amide with an activated iron/silane species, which was transformed to the iminium species **98**. A second equivalent of the activated iron species is then required to regenerate the catalyst, release the newly formed amine, and generate 1 equiv. of siloxane. This mechanism is supported by deuteration studies employing Ph_2SiD_2, which showed the incorporation of two deuterium atoms in place of the carbonyl moiety.

On the other hand, Nagashima and coworkers found that $[Fe(CO)_5]$ and $[Fe_3(CO)_{12}]$ were both suitable catalyst precursors for this reaction under similar conditions to that adopted by Beller (100 °C, 24 h, toluene, TMDS). Furthermore, the reduction of a series of tertiary amides could also be achieved at room temperature under photoassisted conditions. The utility of the thermal and photochemical reactions was compared (Table 1-11). Overall, good-to-high yields were achieved with all the substrates tested, including another reducible carbonyl (entry 7), halogens (entries 5 and 6) and a cyclic amide (entry 3). In contrast, a benzyl chloride substrate resulted in a dehalogenated side product in the thermal reaction, but then proceeded to the desired amine product under photoassisted conditions (entry 8).

As described earlier in the Ru and Pt examples, it is also possible to conduct the reaction using PMHS, using the encapsulation technique to remove residual iron from the sample.

Nagashima also noted that the iron-catalyzed reactions behaved differently toward nitro groups. In contrast to ruthenium and platinum systems reported previously, nitroarenes were readily reduced instead of amides, which remained intact even with an excess of silane. It was thought that aniline products effectively inhibit the catalyst, preventing further reaction with the amide.

TABLE 1-11. Thermal and Photoassisted Iron-Catalyzed Silane Reductions of Tertiary Amides[a]

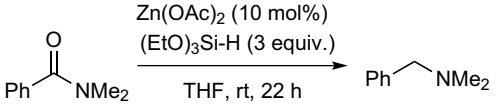
			Thermal Reduction[b]		Photoassisted Reduction[c]	
Entry	Amide		$[Fe(CO)_5]$ (%)	$[Fe_3(CO)_{12}]$ (%)	$[Fe(CO)_5]$ (%)	$[Fe_3(CO)_{12}]$ (%)
1			86	85	94	73
2			67	81	69	68
3			95	84	81	81
4		X = OMe	81	82	82	93
5		X = Cl	66	85	78	90
6		X = Br	98	96	77	95
7		$X = CO_2Me$	88	84	79	94
8			–	21[d]	–	84

[a]Conditions (unless otherwise indicated): Amide (1 mmol), iron catalyst (0.1 mmol), TMDS (2.2 mmol, Si−H = 4.4 mmol), toluene (0.5 ml).
[b]100°C, 24 h.
[c]rt, 9 h, 400 W high-pressure Hg lamp.
[d]Dehalogenated product formed in 68% yield.

1.6.7 Zinc-Catalyzed Reduction of Amides Using Silanes

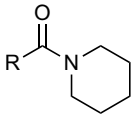
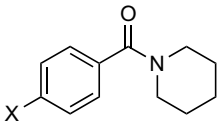
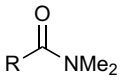
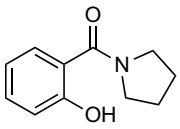
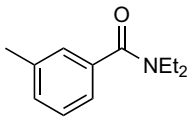
Zinc-catalyzed reductions of tertiary amide in the presence of silanes were reported by Beller and coworkers in 2010 [38]. By employing zinc acetate in the presence of silanes such as $PhSiH_3$, Ph_2SiH_2, $(EtO)_2MeSiH$, and $(EtO)_3SiH$, amides could be reduced to amines, even at room temperature in the case of $(EtO)_3SiH$ (Scheme 1-36).

A variety of substituted tertiary amides were tested, and excellent yields (73–99%) were obtained (Table 1-12). Steric and electronic effects of piperidinyl-substituted amides were investigated, where it was found that aromatic, aliphatic, and heterocyclic amides can be



SCHEME 1-36. Zinc acetate-catalyzed reduction of *N,N*-dimethylbenzamide.

TABLE 1-12. Zinc Acetate-Catalyzed Reduction of Tertiary Amides[a]

Entry	Amide		Yield (%)
1		R = Ph	85
2		R = Cy	86
3		R = 2-naphthalene	99
4		R = 2-thiophene	82
5[b,c]		R = 2-furan	73
6[d]		R = CH_2CH_2Ph	73
7		X = *p*-F	92
8		X = *p*-Br	97
9[d]		X = *p*-OMe	80
10[e]		R = Me	96
11[e]		R = Ph	97
12		R = Ph-*o*-Cl	87
13			87
14[b,c]			75

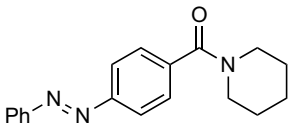
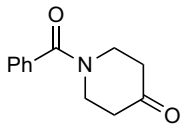
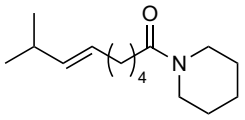
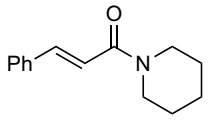
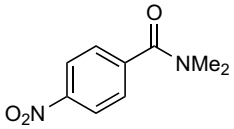
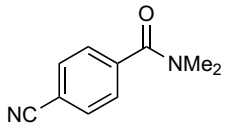
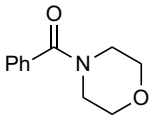
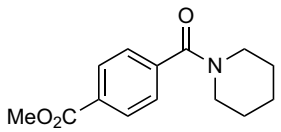
[a]Conditions (unless otherwise indicated): Amide (1 mmol), $Zn(OAc)_2$ (10 mol%), $(EtO)_3SiH$ (3 mmol), rt or 40 °C, 22 h, THF (3 ml), yields were isolated.
[b]3 mmol scale.
[c]Purified by distillation.
[d]Purified by column chromatography.
[e]Not isolated yield.

successfully reduced (entries 1–6), including the naphthyl-substituted amide in 99% yield (entry 3). Electron-donating aromatic groups were found to give poorer yields than electron-withdrawing groups (compare entries 7–9).

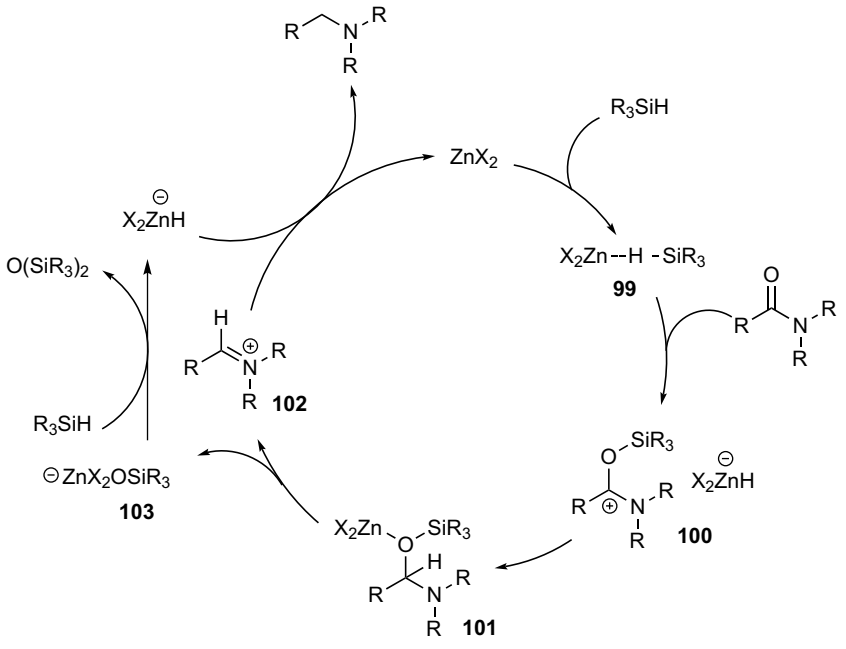
The reaction also showed excellent functional group tolerance (Table 1-13); amide reduction proceeded with >99% selectivity in the presence of azo, alkene, nitro, ketone, benzyl, nitrile, and ester groups.

Zinc acetate was found to activate the silane as opposed to the carbonyl of the amide. This was confirmed by IR studies of the carbonyl stretch (which showed no change) and ^{29}Si NMR spectroscopy (which indicated the formation of a new species). The proposed mechanism of the reduction is shown below (Scheme 1-37), beginning with reaction of the silane with the zinc to generate the activated species **99**. Next, coordination of the amide occurs at the metal center in **99**, which results in the hemiaminal species **101** (via **100**). An imine species, **102**, is then liberated from the release of the anionic zinc siloxide, **103**. A second equivalent of silane is then required to convert the imine to the amine, producing siloxane and regenerating the catalyst.

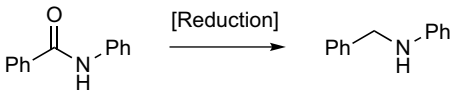
TABLE 1-13. Zinc Acetate-Catalyzed Reduction of Tertiary Amides to Demonstrate Functional Group Tolerance[a]

Entry	Amide	Yield (%)	Entry	Amide	Yield (%)
1		91	5		83
2		87	6[b]		78
3		85	7[b]		72
4		84	8[b]		65

[a]Conditions: Amide (1.0 mmol), $Zn(OAc)_2$ (0.1 mmol), $(EtO)_3SiH$ (3.0 mmol), rt, 22 h, THF (3 ml).
[b]Purified by column chromatography.



SCHEME 1-37. Proposed mechanism of Zn-catalyzed hydrosilation of amides [38].



104 **105**

SCHEME 1-38. Reduction of benzanilide **104** to phenyl benzylamine **105**.

TABLE 1-14. Comparison of Different Amide Reduction Methods

Method	Advantages	Disadvantages	AE[a]	E[b]
Homogeneous hydrogenation (Ru/Triphos)	The only by-product is water 1°, 2° and 3° amides Low pressures Excellent selectivity of 1° and 2° amides	High temperatures Need specialist equipment	91	0
Heterogeneous hydrogenation (bimetallic)	Simple catalyst separation Excellent substrate scope (1°, 2°, 3° amides) Recyclability	High temperatures and pressures Incompatible with aromatics Need specialist equipment	91	0
Heterogeneous hydrogenation (copper chromite)	Simple catalyst separation	Harsh reaction conditions Poor selectivity Low functional group tolerance	91	0
Homogeneous hydrosilation (e.g., Zn or Fe)	Mild conditions Excellent functional group tolerance	Excess silane required Potential for SiH_4 formation Mainly 3° amides	35	1.9
B_2H_6 (stoichiometric)	Efficient Good functional group tolerance	Difficult to handle Low atom economy Waste disposal Complex workup procedure	68	0.5
$LiAlH_4$ (stoichiometric)	Efficient	Difficult to handle Low atom economy Waste disposal Complex workup procedure Low functional group tolerance Low reactivity toward 1° amides	46	1.2

[a] AE = atom economy = (mass product/mass starting materials), based on theoretical (100% yield) hydrogenation of benzanilide to phenylbenzylamine.

[b] E = environmental factor = mass of waste products/mass of desired product, based on 100% theoretical yield, does not take into account solvents or workup.

1.7 CONCLUSIONS AND FUTURE PERSPECTIVES

The homogeneous hydrogenation of amides is still in its infancy; however, great strides are being made toward milder reaction conditions, improved selectivity, and functional group tolerance. It is possible to hydrogenate primary, secondary, and tertiary amides, in the presence of sensitive functional groups, but there are still some trade-offs to be made. Currently, heterogeneous bimetallic catalysts afford excellent conversions of a variety of substrates with straightforward catalyst removal, but there are problems associated with the overreduction of aromatic groups and the relatively harsh operating conditions. In contrast, metal-catalyzed reductions with silanes offer relatively mild transformations of tertiary amides to tertiary amines with excellent functional group tolerance, but the additional waste disposal and safety implications associated with stoichiometric amounts of silanes are undesirable. Homogeneous hydrogenation with molecular hydrogen represents a truly green approach, as water is generated as the only by-product. However, current advances still require relatively harsh reaction conditions. Nevertheless, it is possible to hydrogenate primary and secondary amides to give primary and secondary amines with excellent conversions and selectivities. Selective reduction of tertiary amides remains a challenge in this area.

The green credentials of different methods for the reduction of amides to amines are compared in terms of AE and E (environmental) factor (Scheme 1-38 and Table 1-14) [53] based on the theoretical reduction of benzanilide **104** to the desired product **105** in 100% conversion (and does not take into account workup procedures and solvents).

Future challenges include hydrogenation reactions that can be conducted at much lower temperatures and pressures, and preferably without the need of specialist equipment. For widespread application, particularly in the pharmaceutical industry, the reaction must also have excellent selectivity and functional group tolerance. Although this has been achieved to some extent in the case of tertiary amides employing hydrosilation technology, an entirely green solution is some way off. With an ever-increasing interest in this area and further investments, more breakthroughs are sure to follow.

REFERENCES

1. Salvatore RN, Yoon CH, Jung KW (2001). Synthesis of secondary amines. *Tetrahedron* 57, 7785–7811.
2. Constable DJC, Dunn PJ, Hayler JD, Humphrey GR, Leazer, Jr., JL, Linderman RJ, Lorenz K, Manley J, Pearlman BA, Wells A, Zaks A, Zhang TY (2007). Key green chemistry research areas—a perspective from pharmaceutical manufacturers. *Green Chem.* 9, 411–420.
3. Carey JS, Laffan D, Thomson C, Williams MT (2006). Analysis of the reactions used for the preparation of drug candidate molecules. *Org. Biomol. Chem.* 4, 2337–2347.
4. Gill CD, Greenhalgh DA, Simpkins NS (2003). Application of the chiral base desymmetrisation of imides to the synthesis of the alkaloid jamtine and the antidepressant paroxetine. *Tetrahedron* 59, 9213–9230.
5. Andersson PG, Schink HE, Osterlund K (1998). Asymmetric total synthesis of (+)-tolterodine, a new muscarinic receptor antagonist, via copper-assisted asymmetric conjugate addition of aryl Grignard reagents to 3-phenyl-prop-2-enoyl-oxazolidinones. *J. Org. Chem.* 63, 8067–8070.
6. Gant TG, inventor; Auspex Pharmaceuticals Inc, assignee. Substituted benzamide modulators of dopamine receptor. US Patent US2010/0105755. April 29, 2010.

7. Giles ME, Thomson C, Eyley SC, Cole AJ, Goodwin CJ, Hurved PA, Morlin AJG, Tornos J, Atkinson S, Just C, Dean JC, Singleton JT, Longton AJ, Woodland I, Teasdale A, Gregertsen B, Else H, Athwal MS, Tatterton S, Knott JM, Thompson N, Smith SJ (2004). Development of a manufacturing process for sibenadet hydrochloride, the active ingredient of viozan. *Org. Process Res. Dev.* 8, 628–642.
8. Bannister RM, Brookes MH, Evans GR, Katz RB, Tyrrell ND (2000). A scaleable route to the pure enantiomers of verapamil. *Org. Process Res. Dev.* 4, 467–472.
9. Nakazato A, Ohta K, Sekiguchi Y, Okuyama S, Chaki S, Kawashima Y, Hatayama K (1999). Design, synthesis, structure-activity relationships, and biological characterization of novel arylalkoxyphenylalkylamine sigma ligands as potential antipsychotic drugs. *J. Med. Chem.* 42, 1076–1087.
10. Adkins H, Wojcik B (1934). Catalytic hydrogenation of amides to amines. *J. Am. Chem. Soc.* 56, 2419–2422.
11. King RM, inventor; The Proctor & Gamble Company, assignee. Catalytic hydrogenation of *N*,*N*-disubstituted amides to amines. US Patent 4,448,998. May 15, 1984.
12. Hirosawa C, Wakasa N, Fuchikami T (1996). Hydrogenation of amides by the use of bimetallic catalysts consisting of group 8 to 10, and group 6 or 7 metals. *Tetrahedron Lett*. 37, 6749–6752.
13. Smith AA, Dani P, Higginson PD, Pettman AJ, inventors; Avantium International B.V., assignee. Bimetallic and trimetallic non-alloy catalysts for the hydrogenation of amides into amines under mild reaction conditions. World Patent WO2005/066112. July 21, 2005.
14. Beamson G, Papworth AJ, Philipps C, Smith AM, Whyman R (2010). Selective hydrogenation of amides using Rh/Mo catalysts. *J. Catal.* 269, 93–102.
15. Beamson G, Papworth AJ, Philipps C, Smith AM, Whyman R (2010). Selective hydrogenation of amides using ruthenium/molybdenum catalysts. *Adv. Synth. Catal.* 352, 869–883.
16. Beamson G, Papworth AJ, Philipps C, Smith AM, Whyman R (2011). Selective hydrogenation of amides using bimetallic Ru/Re and Rh/Re catalysts. *J. Catal.* 278, 228–238.
17. Kilner M, Tyers DV, Crabtree SP, Wood MA, inventors; Davy Process Technology, assignee. Homogenous process for the hydrogenation of carboxylic acids and derivatives thereof. World Patent WO2003/093208. November 13, 2003.
18. Teunissen HT, Elsevier CJ (1997). Ruthenium catalyzed hydrogenation of dimethyl oxalate to ethylene glycol. *Chem. Commun.* 667–668.
19. Teunissen HT, Elsevier CJ (1998). Homogeneous ruthenium catalyzed hydrogenation of esters to alcohols. *Chem. Commun.* 1367–1368.
20. van Engelen MC, Teunissen HT, de Vries JG, Elsevier CJ (2003). Suitable ligands for homogeneous ruthenium-catalyzed hydrogenolysis of esters. *J. Mol. Catal. A: Chem.* 206, 185–192.
21. Sung KM, Huh S, Jun MJ (1999). Syntheses of ruthenium(II) complexes containing polyphosphine ligands and their applications in the homogeneous hydrogenation. *Polyhedron* 18, 469–479.
22. Bautista MT, Earl KA, Maltby PA, Morris RH, Schweitzer CT (1994). New dihydrogen complexes—the synthesis and spectroscopic properties of iron(II), ruthenium(II), and osmium(II) complexes containing the meso-tetraphos-1 ligand. *Can. J. Chem.* 72, 547–560.
23. Nùnez-Magro AA, Eastham GR, Cole-Hamilton DJ (2007). The synthesis of amines by the homogeneous hydrogenation of secondary and primary amides. *Chem. Commun.* 3154–3156.
24. Balaraman E, Gnanaprakasam B, Shimon LJW, Milstein D (2010). Direct hydrogenation of amides to alcohols and amines under mild conditions. *J. Am. Chem. Soc.* 132, 16756–16758.
25. (a) Dodds DL, Coetzee J, Brosinski S, Klankermeyer J, Leitner W, Cole-Hamilton DJ (2011). Published as an addition to reference 24: http://www.rsc.org/suppdata/cc/b7/b706635j/addition.htm. (b) Dodds DL, Coetzee J. Brosinski S, Klankermeyer J, Leitner W, Cole-Hamilton DJ. Upon the hydrogenation of amides to amines. *Chemistry. Eur. J*. Submitted.

26. Furst MRL, le Goff R, Quinzler D, Mecking S, Cole-Hamilton DJ (2012). Polymer precursors from catalytic reactions of natural oils. *Green Chem.* 14, 472–477.
27. Baxter EF, Lim K, Harvie M, Charkovskiy A, Pogorzelec PJ, Cole-Hamilton DJ. A new route to nitrogen heterocycles. Manuscript in preparation.
28. Crabtree SP, Tyers DV, Sharif, M, inventors; Davy process Technology, assignee. Process for the production of lactams. World Patent WO2005/051907. June 9, 2005.
29. Aoun R, Renaud JL, Dixneuf PH, Bruneau C (2005). Concomitant monoreduction and hydrogenation of unsaturated cyclic imides to lactams catalyzed by ruthenium compounds. *Angew. Chem., Int. Ed.* 44, 2021–2023.
30. Zhang J, Leitus G, Ben-David Y, Milstein D (2006). Efficient homogeneous catalytic hydrogenation of esters to alcohols. *Angew. Chem., Int. Ed.* 45, 1113–1115.
31. Landgrafe C, Sheldrick WS, Sudfeld H (1998). Fluxionality and phosphane arm-off reactions of octahedral ruthenium(II) complexes with the tripodal polyphosphane $MeC(CH_2PPh_2)_3$. *Eur. J. Inorg. Chem.* 407–414.
32. Geilen FMA, Engendahl B, Holscher M, Klankermayer J, Leitner W (2011). Selective homogeneous hydrogenation of biogenic carboxylic acids with $[Ru(TriPhos)H]^+$—a mechanistic study. *J. Am. Chem. Soc.* 133, 14349–14358.
33. Geilen FMA, Engendahl B, Harwardt A, Marquardt W, Klankermayer J, Leitner W (2010). Selective and flexible transformation of biomass-derived platform chemicals by a multifunctional catalytic system. *Angew. Chem., Int. Ed.* 49, 5510–5514.
34. (a) Ito M, Ootsuka T, Watari R, Shiibashi A, Himizu A, Ikariya T (2011). Catalytic hydrogenation of carboxamides and esters by well-defined Cp^*Ru complexes bearing a protic amine ligand. *J. Am. Chem. Soc.* 133, 4240–4242. (b) Ito M, Koo LW, Himizu A, Kobayashi C, Sakaguchi A, Ikariya T (2009). Hydrogenation of *N*-acylcarbamates and *N*-acylsulfonamides catalyzed by a bifunctional $[Cp^*Ru(PN)]$ complex. *Angew. Chem.*, *Int. Ed.* 48, 1324–1327.
35. Ito M, Sakaguchi A, Kobayashi C, Ikariya T (2007). Chemoselective hydrogenation of imides catalyzed by $Cp^*Ru(PN)$ complexes and its application to the asymmetric synthesis of paroxetine. *J. Am. Chem. Soc.* 129, 290–291.
36. John JM, Bergens SH (2011). A highly active catalyst for the hydrogenation of amides to alcohols and amines. *Angew. Chem., Int. Ed.* 50, 10377–10380.
37. Wells AS (2010). On the perils of unexpected silane generation. *Org. Process Res. Dev.* 14, 484.
38. Das S, Addis D, Zhou S, Junge K, Beller M (2010). Zinc-catalyzed reduction of amides: unprecedented selectivity and functional group tolerance. *J. Am. Chem. Soc.* 132, 1770–1771.
39. Lawrence NJ, Drew MD, Bushell SM (1999). Polymethylhydrosiloxane: a versatile reducing agent for organic synthesis. *J. Chem. Soc., Perkin Trans. 1* 3381–3391.
40. Igarashi M, Fuchikami T (2001). Transition-metal complex-catalyzed reduction of amides with hydrosilanes: a facile transformation of amides to amines. *Tetrahedron Lett*. 42, 1945–1947.
41. Kuwano R, Takahashi M, Ito Y (1998). Reduction of amides to amines via catalytic hydrosilylation by a rhodium complex. *Tetrahedron Lett*. 39, 1017–1020.
42. Matsubara K, Iura T, Maki T, Nagashima H (2002). A triruthenium carbonyl cluster bearing a bridging acenaphthylene ligand: an efficient catalyst for reduction of esters, carboxylic acids, and amides by trialkylsilanes. *J. Org. Chem.* 67, 4985–4988.
43. Motoyama Y, Mitsui K, Ishida T, Nagashima H (2005). Self-encapsulation of homogeneous catalyst species into polymer gel leading to a facile and efficient separation system of amine products in the Ru-catalyzed reduction of carboxamides with polymethylhydrosiloxane (PMHS). *J. Am. Chem. Soc.* 127, 13150–13151.
44. Hanada S, Ishida T, Motoyama Y, Nagashima H (2007). The ruthenium-catalyzed reduction and reductive *n*-alkylation of secondary amides with hydrosilanes: practical synthesis

of secondary and tertiary amines by judicious choice of hydrosilanes. *J. Org. Chem.* 72, 7551–7599.

45. Sasakuma H, Motoyama Y, Nagashima H (2007). Functional group-selective poisoning of molecular catalysts: a ruthenium cluster-catalyzed highly amide-selective silane reduction that does not affect ketones or esters. *Chem. Commun.* 4916–4918.
46. Hanada S, Motoyama Y, Nagashima H (2008). Hydrosilanes are not always reducing agents for carbonyl compounds but can also induce dehydration: a ruthenium-catalyzed conversion of primary amides to nitriles. *Eur. J. Org. Chem.* 4097–4100.
47. Hanada S, Motoyama Y, Nagashima H (2006). Dual Si−H effects in platinum-catalyzed silane reduction of carboxamides leading to a practical synthetic process of tertiary-amines involving self-encapsulation of the catalyst species into the insoluble silicone resin formed. *Tetrahedron Lett*. 47, 6173–6177.
48. Hanada S, Tsutsumi E, Motoyama Y, Nagashima H (2009). Practical access to amines by platinum-catalyzed reduction of carboxamides with hydrosilanes: synergy of dual Si−H groups leads to high efficiency and selectivity. *J. Am. Chem. Soc.* 131, 15032–15040.
49. Fernandes AC, Romão CC (2007). Reduction of amides with silanes catalyzed by MoO_2Cl_2. *J. Mol. Catal. A: Chem.* 272, 60–63.
50. Sakai N, Fujii K, Konakahara T (2008). One-step conversion to tertiary amines: $InBr_3/Et_3SiH$-mediated reductive deoxygenation of tertiary amides. *Tetrahedron Lett*. 49, 6873–6875.
51. Zhou S, Junge K, Addis D, Das S, Beller M (2009). A convenient and general iron-catalyzed reduction of amides to amines. *Angew. Chem., Int. Ed.* 48, 9507–9510.
52. Sunada Y, Kawakami H, Imaoka T, Motoyama Y, Nagashima H (2009). Hydrosilane reduction of tertiary carboxamides by iron carbonyl catalysts. *Angew. Chem., Int. Ed.* 48, 9511–9514.
53. Constable DJC, Curzons AD, Cunningham VL (2002). Metrics to 'green' chemistry—which are the best? *Green Chem*. 4, 521–527.