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Amide Hydrogenation

Catalytic Hydrogenation of Amides to Amines under Mild Conditions**

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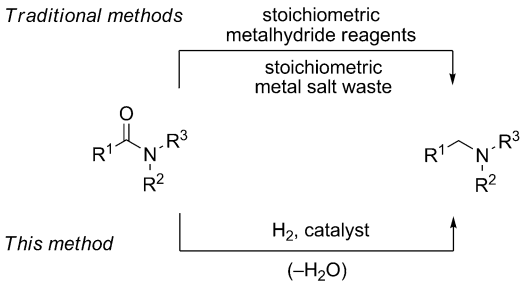
In 2005, a round table of pharmaceutical companies and the ACS Green Chemistry Institute generated a list of dream reactions that would have an important impact to make the future production of pharmaceuticals more economical, safe and environmentally benign.[1] Among the top candidates in this list was the catalytic hydrogenation of amides to furnish amines, a functional group present in almost any drug or drug candidate. In many cases, the amines are synthesized by the reduction of the corresponding amides, which is typically achieved by using a stoichiometric amount of a hydride reagent such as $LiAlH_4$, DIBAL, RedAl, borane, triethylsilane, or polymethylhydroxysilane.[2] Reactions with these reagents suffer from poor atom efficiency and issues regarding both the safety of operation and the removal of stoichiometric metal waste are not uncommon.[3] Conversely, catalytic hydrogenation with molecular hydrogen as reducing agent is ecologically and economically highly attractive with water being the only byproduct (Scheme 1).

Unfortunately, the catalytic reduction of carboxylic acids and their derivatives is highly challenging, with amides being the least reactive motifs.[4] Early efforts towards catalytic hydrogenation of amides with heterogeneous catalysts based on copper chromite,[5] rhenium,[6] and Raney catalysts[7] showed that the reaction is, in principle, feasible. However, harsh reaction conditions, with temperatures of 175–260 °C and high pressures of 100–990 bar, were required in all cases. Significant improvements were reported by Dobson, who employed a bimetallic catalyst of Pd and Re on high-surface-area graphite (HSAG) for the hydrogenation of propionamide at 200 °C and 260 bar with good conversion, but with poor chemoselectivity, furnishing mixtures of mono-, di-, and tripropylamine.[8] The groups of Fuchikami[9a] and Whyman[9b–d] have reported improved bimetallic catalysts based on combinations of Rh/Re, Rh/Mo, Ru/Re, and Ru/Mo, which allowed milder reaction conditions to be used. Intensive screening of a large bi- and trimetallic catalyst library by a research team from Avantium identified Pt/Re/In on silica (or carbon) as the best catalyst; this enabled mild conditions to be used in some cases, for example, 10 bar H_2 and 130 °C for the hydrogenation of a single amide substrate (*N*-acetylpyrrolidine).[10] A drawback of this method is the requirement for corrosive acetic acid as a solvent. A homogeneous catalyst formed in situ from $[Ru(acac)_3]$ and triphos was reported by Cole-Hamilton et al., which reduced amides at 164 °C and 40 bar of hydrogen.[11] Recently, Thompson et al. reported the catalytic hydrogenation of NMP with titania-supported Pt/Re catalysts.[12] Almost complete conversion was achieved at 120 °C and 20 bar H_2, with a 100 % selectivity for the desired *N*-methylpyrrolidine. Unfortunately, the use of *n*-hexane as solvent is crucial and, owing to the low solubility of amides in this solvent, problems might occur with other substrates. DFT calculations suggest that Re acts as a Lewis acid to render the C=O more electrophilic, whereas Pt acts as the hydrogenation catalyst.



Scheme 1. Hydrogenation of amides.

Alternative catalytic reductions of amides employing homogeneous Ru-catalysts have been developed by Milstein,[13] Bergens,[14] and Ikariya.[15] With these catalysts, amides are reduced under mild conditions with concomitant C–N bond cleavage to furnish an alcohol and an amine component. Deoxygenation of amides by catalytic hydrosilylation has been developed by the groups of Beller[16] and Brookhart.[17]

To date, there is no catalyst that is capable of hydrogenating a diverse range of amides under mild conditions. Herein, we report the hydrogenation of various tertiary and secondary amides at low temperatures and pressures using a graphite-supported bimetallic Pd/Re catalyst.

At the start of our work, we screened 43 different catalysts for activity in the catalytic hydrogenation of the model substrate *N*-acetylpiperidine (Table 1).[18] This could be done on a short timescale using a high pressure automation system with four autoclave blocks each containing ten reaction vessels. We included $[Ru(CO)_{12}]/[Mo(CO)_6]$, $[Ru_3(CO)_{12}]/[Re_2(CO)_{10}]$ (Entries 11 and 12), and $[Ru(acac)_3]$/triphos (Entry 7), which have been previously

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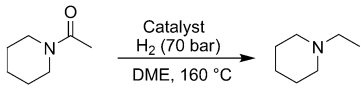
Table 1: Catalytic hydrogenation of *N*-acetylpiperidine in the presence of different catalysts.[a]



1 2

Entry	Catalyst (mol%)[b]	Conversion[c] [%]
1	–	–
2	RuO_2 (5.0)	–
3	4% Ru/C (5.0)	–
4	1% Ru/CDG (5.0)	–
5	$[Ru_2(CO)_{12}]$ (5.0)	–
6	$[Ru(NH_3)_5Cl]Cl_2$ (5.0)	–
7	$[Ru(acac)_3]$ (1.0)/triphos (2.0)	1
8	5% Rh/Al_2O_3 (5.0)	–
9	5% Rh/C (5.0)	–
10	[Rh(nbd)acac] (5.0)	–
11	$[Ru_3(CO)_{12}]$ (1.6)/$[Mo(CO)_6]$ (2.5)	92
12	$[Ru_3(CO)_{12}]$ (1.9)/$[Re_2(CO)_{10}]$ (0.7)	82
13	Ni (5.0)/Al (5.0)	–
14	2% Pd (1.7)/10% Re (5.0)/C	>99
15	1% Pt (0.5)/10% Re (5.0)/C	>99

[a] Reaction conditions: *N*-acetyl piperidine (1.0 mmol), DME (15 mL), 20 h. [b] Mol% values are based on the amount of metal used. [c] Determined by GC analysis. acac = acetylacetonate, CDG = chemically derived graphene, nbd = norbornadiene, triphos = bis(diphenylphosphinoethyl)phenylphosphine.

reported to be active hydrogenation catalysts.[9,11] As expected, most catalysts were inactive and no reaction occurred. The results of Whyman and co-workers were reproducible.[9] Unfortunately, the homogeneous Ru–triphos catalyst was not active for our chosen substrate.[19] We were delighted to observe that the bimetallic Pt/Re/graphite and Pd/Re/graphite catalysts gave full conversion and excellent selectivity for the desired amine (Entries 16 and 17).[18,20]

TEM images of the Pd/Re/graphite catalyst revealed homogeneously dispersed nanoparticles of 2–6 nm deposited on the graphite layers (Figure 1). The surface/volume ratio is therefore rather high, which might be the cause of the high reactivity of the catalyst.

Next we optimized the reaction parameters using both Pt/Re/graphite and Pd/Re/graphite as catalysts (Tables 2 and 3). The catalyst loading could be reduced to 4 mol% of Re without any loss of conversion. In contrast to the observations of Thompson et al.,[12] Pd/Re/graphite (catalyst **A**) showed a higher activity than Pt/Re/graphite (catalyst **B**; for example, Table 2, entries 3 and 8). Therefore, we decided to focus on Pd/Re/graphite as the catalyst for further investigations. The reactivity was independent of the substrate concentration in the range of 0.07–1M (Table 2, entries 2, 10, and 11). For practical reasons we used a concentration of 0.2M for further experiments. Furthermore, it was found that molecular sieves (MS) have a beneficial effect on the reactivity (Table 2, entries 15–21). The hydrogenation of **1** occurred within 20 h at 120°C and 10 bar H_2 with 85% conversion, and with no other byproducts observed (Table 2, entry 19). To the best of our knowledge, these are the mildest conditions thus far reported for amide hydrogenation. At 160°C and with a higher catalyst loading, we were able to further reduce the hydrogen pressure to 5 bar (Table 2, entry 21). Alternative solvents were 1,4-dioxane, diglyme, and cyclohexane.[18]

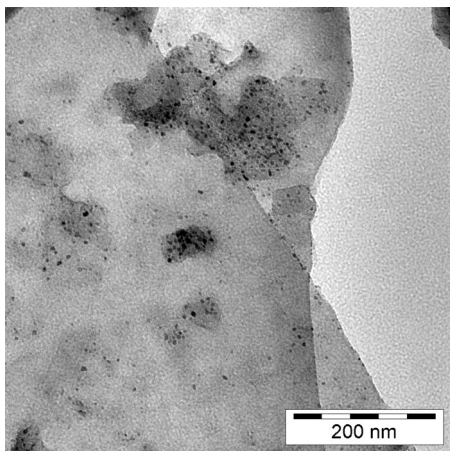
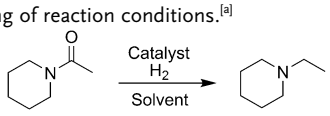


Figure 1. TEM image of Pd/Re/graphite.

Next, we examined the substrate scope and limitations for the catalytic hydrogenation with Pd/Re/graphite. As general conditions, we chose 160°C and 30 bar H_2 for the hydrogenation of 108 different amides.[18] A representative selection of the results is shown in Table 3. Out of the 108 amides tested, 90 showed conversions of greater than 50%, and 69 showed more than 90%. In 79 examples, the selectivity for the desired amine was 90% or higher. When the alkyl residue next to the carbonyl function of the amide became longer, the conversion slightly decreased, from 100% for methyl substitution to 60% for octyl substitution, whereas the selectivity remained perfect (Table 3, entries 1–4). In many cases, the

Table 2: Screening of reaction conditions.[a]

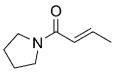
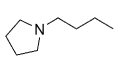
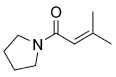
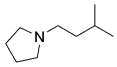
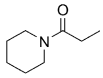
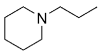
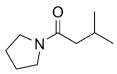
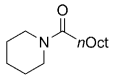
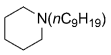
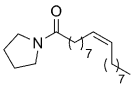
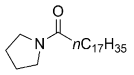
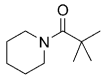
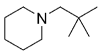
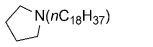
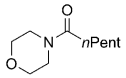
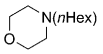
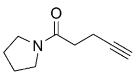
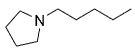
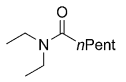
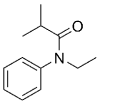
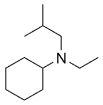
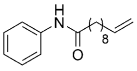
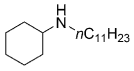
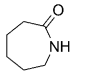
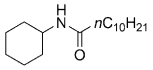
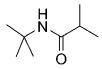
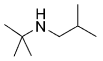
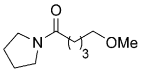
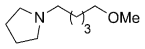
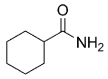
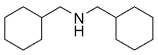


1 2

Entry	Cat.[b]	Conc. [M]	*T* [°C]	*p* [bar]	4 Å MS	Conv. of **2**[c] [%]
1	**A**	0.07	160	70	no	>99
2	**A**	0.07	140	70	no	>99
3	**A**	0.07	120	70	no	59
4	**A**	0.07	100	70	no	10
6	**B**	0.07	160	70	no	>99
7	**B**	0.07	140	70	no	>99
8	**B**	0.07	120	70	no	45
9	**B**	0.07	100	70	no	4
10	**A**	0.20	140	70	no	>99
11	**A**	1.00	140	70	no	>99
12	**A**	0.20	140	50	no	>99
13	**A**	0.20	140	30	no	81
14	**A**	0.20	140	10	no	59
15	**A**	0.20	140	30	yes	>99
16	**A**	0.20	120	30	yes	95
17	**A**	0.20	100	30	yes	84
18	**A**	0.20	120	20	yes	86
19	**A**	0.20	120	10	yes	85
20	**A**	0.20	120	5	yes	21
21[d]	**A**	0.10	160	5	yes	90

[a] Reaction conditions: *N*-acetylpiperidine (1.0 mmol), catalyst (4 mol% Re), DME, 20 h. [b] Catalyst **A**: 2% Pd/10% Re/graphite, catalyst **B**: 1% Pt/10% Re/graphite. [c] Determined by GC analysis. [d] Loading of Re was 10 mol%. MS = molecular sieves.

Table 3: Representative examples of the substrate scope for catalytic hydrogenation with Pd/Re/graphite.[a]

Entry	Substrate	Conv.[b] [%]	Products	Selectivity [%][b]	Entry	Substrate	Conv.[b] [%]	Products	Selectivity [%][b]
1		>99 (93)[c]		100	12		>99		100
2		>99 (95)[c]		100	13		>99		96
3		72		100					4
4		60		100	14		>99		36
5		10		100					32
6		71		100	15		>99		100
7		89		100	16		>99		100
8		>99		100	17		>99		63[f]
9		>99 (88)[c]		100					29[f]
10		9 (>99)[d]		100 (92)[c]	18		>99		100
11		21 (35)[e]		100					

[a] Reaction conditions: substrate (1.0 mmol, 2% Pd/10% Re/graphite (4 mol% Re), DME (0.2 M), 4 Å MS, H_2 (30 bar), 160 °C, 20 h. [b] Determined by GC, GC/MS, and/or ^{1}H NMR analysis. [c] Values in parentheses are the yield of isolated product after precipitation as a hydrochloride salt. [d] Values in parentheses are for reactions conducted at 200 °C for 72 h. [e] 35% conversion was obtained when montmorillonite K-10 added. [f] Yield of isolated product.

conversion dropped when the substituent on the amide carbonyl was more sterically demanding, with *N*-pivaloylpiperidine giving only 10% conversion under the standard conditions (Table 3, entry 5). Changes in the nitrogen substituents did not clearly affect the reactivity, as shown for different caproic acid amides (Table 3, entries 6 and 7). The reactivity trends were the same for both tertiary and secondary amides.[18]

The effectiveness of the method on a 10 mmol scale was demonstrated with *N*-acetylpiperidine and *N*-acetylpyrrolidine. In both cases the corresponding amines could be isolated as hydrochloride salts with yields above 90% (Table 3, entries 1 and 2).

To our delight, secondary and tertiary lactams were readily hydrogenated with high selectivities for the desired cyclic amines. (Table 3, entries 8 and 9). For ε-caprolactam, the reaction performed on a 10 mmol scale produced quantitative conversion, and the corresponding hydrochloride salt of the azepan was isolated in 88% yield.[18]

For very bulky carboxylic acid amides the conversion was rather low in most cases, with *N*-*tert*-butyl-isobutyramide giving only 9% conversion (Table 3, entry 10). At a temperature of 180 °C and with a longer reaction time, the conversion increased to 55%, whereas at 200 °C the bulky amide was hydrogenated with full conversion and 92% yield. This demonstrates that it is possible to reduce very unreactive amides simply by increasing the temperature and reaction time.

Unfortunately, the hydrogenation of primary amides was problematic. In these cases, secondary amines were obtained as the major products (Table 3, entry 11).

As expected, alkene and alkyne functions were rapidly hydrogenated (Table 3, entries 12–15 and 17). Even a trisubstituted double bond does not withstand the active hydrogenation catalyst and is readily converted into the corresponding alkane (Table 3, entry 13). Also, aromatic rings were hydrogenated prior to amide reduction (Table 3, entries 16 and 17). Various attempts were made to suppress this without success. However, amides with ether substituents were hydrogenated without problems (Table 3, entry 18).

We were also interested in the recyclability of the Pd/Re/graphite catalyst, the heterogeneous nature of which makes it easy to separate by simple filtration. After the reduction of *N*-acetyl piperidine to *N*-ethyl piperidine, we filtered the catalyst and directly submitted the residue to another hydrogenation under the same reaction conditions. With this procedure, we obtained 80% conversion from the second run and 70% from the third run. Other recycling techniques,

such as drying and recalcination, preforming the catalyst, or the addition of new substrate after the reaction, did not improve the results.

In conclusion, we have developed the first general catalytic hydrogenation of secondary and tertiary amides to secondary and tertiary amines employing a highly reactive bimetallic Pd/Re/graphite catalyst. This catalyst displays the highest activity reported to date. The generality of this method was demonstrated by the hydrogenation of 108 different amides. Depending on the steric hindrance of the substrate, the reaction rate can be adjusted by varying the temperature, thus allowing even very hindered substrates to be hydrogenated in high yields. Simple filtration liberates the desired amine without significant impurities and allows reisolation of the catalyst, which could be recycled and used in two subsequent runs. This makes this method an environmentally benign, easy, and reliable tool for the preparation of amines from amides.

Experimental Section

General procedure for the hydrogenation of amides: A 30 mL headspace vial containing a stir bar was charged with 2% Pd/10% Re/graphite (74 mg, 4 mol% Re, 1.4 mol% Pd). The amide (1 mmol) was dissolved in 1,2-dimethoxyethane (DME; 5 mL) and added. The vial was closed with a septum and transferred under argon atmosphere to a parallel autoclave block capable of performing ten reactions in parallel. After purging with argon, the parallel autoclave was pressurized with H_2 (30 bar). The mixture was stirred for 20 h at 160 °C. After cooling to room temperature, the pressure was released and the reaction mixture was filtered. The conversion and yield was determined from the clear filtrate by GC analysis by comparison with representative samples.

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