The synthesis of amines by the homogeneous hydrogenation of secondary and primary amides

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Amides can be hydrogenated to amines using a catalyst prepared *in situ* from [Ru(acac)$_3$] and 1,1,1-tris(diphenylphosphinomethyl)ethane; water is required to stabilize the catalyst and primary amines can only be formed (selectivity up to 85%) if ammonia is also present.

With a production of 100,000 t/a, amines are an important class of compounds in bulk chemistry, but they also high-value intermediates in organic synthesis. They are used in the manufacture of plastics, surfactants, textiles, dyes, drugs, agrochemicals and in the paper industry.[1] Hydrogenation of amides (which are available *via* aminocarbonylation)[2] would be a very attractive method for the synthesis of these high-value compounds. Hydrogenation of carboxylic acids and their derivatives is normally a difficult process which generally requires drastic conditions, *e.g.* heterogenous copper chromite at 250 °C and 300 bar of hydrogen.[3] In the particular case of amides a mixture of primary, secondary and tertiary amines has been obtained using copper chromite or Pd/Re/zeolite.[4] Ruthenium complexes of triphos (1,1,1-tris(diphenylphosphinomethyl)ethane) are excellent homogeneous systems[5] that catalyse the hydrogenation of esters under mild conditions (40 bar, 164 °C).[6] Recently some other homogeneous catalysts for the hydrogenation of carboxylic acids have been described.[7]

There has only been one report, of the homogeneous hydrogenation of an amide.[8] This also used ruthenium triphos and produced a mixture of alcohol, secondary amine, ester and amide from propanamide (see Fig. 1). None of the desired primary amine was formed.[8]

We now report the selective hydrogenation of amides to primary or secondary amines under relatively mild conditions catalysed by the ruthenium–triphos catalyst (Fig. 2).[6,8]† When *N*-phenylnonamide was used as substrate, in the absence of ruthenium precatalyst, no conversion was obtained (Table 1, entries 1 and 3). The use of [Ru(acac)$_3$] gave a moderate yield of 61% (Table 1, entry 2) while the combination of [Ru(acac)$_3$] and triphos gave full conversion and high selectivity (93%) to amine (**3**) (Table 1, entry 4). The corresponding alcohol, **6**, was obtained as a secondary product (7%). The origin of this alcohol (Fig. 3) is either from the hydrolysis of amide (**1**) to obtain the acid (**4**), or of imine (**2**) to obtain the aldehyde (**5**) followed by hydrogenation. In the absence of additional water, full conversion was obtained with only traces (1%) of alcohol (Table 1, entry 5). However, the catalyst was not stable under these conditions, so water was included in subsequent reactions.

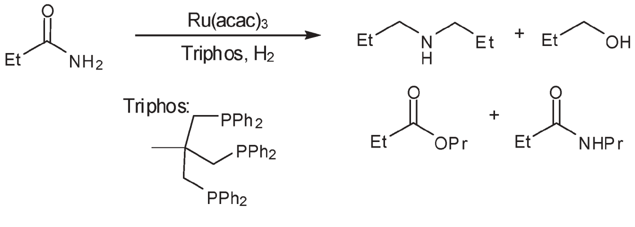

Fig. 1 Hydrogenation of a primary amide.[8]

The hydrogenation of amides could be carried out at 140 °C without any apparent difference from reactions at 164 °C (Table 1, entry 6) but reducing the temperature to 120 °C resulted in a loss of selectivity, giving more alcohol from the acid (**4**) or aldehyde (**5**), which is easier to reduce (Table 1, entry 7). Only alcohol (no amine) was produced at 100 °C (Table 1, entry 8). The addition of aniline reduced the stability of the catalyst, resulting in a loss of both yield and selectivity (Table 1, entry 9).

As indicated above,[8] a complex mixture of products (alcohol, secondary amine (**9**), secondary amide and ester but not the desired primary amine) was obtained by homogenous hydrogenation of propanamide (Fig. 1). According to the hypothetical mechanism proposed here (Fig. 3), primary amine (**3**) may react with the substrate, primary amide (**1**) giving secondary amide (**8**), or with the aldehyde (**5**) to generate imine (**7**). Both compounds (**8**) and (**7**) can then lead to the secondary amine (**9**) by hydrogenation

Under the conditions described but using butanamide as substrate,[8] we also observed no primary amine, but the main products were secondary and tertiary amines with traces of alcohol (Table 2, entry 1). The tertiary amine, **10**, presumably arises from reaction of **9** with **1** followed by hydrogenation. Reducing the concentration of water in the medium did not lead to significant changes (Table 2, entry 2).

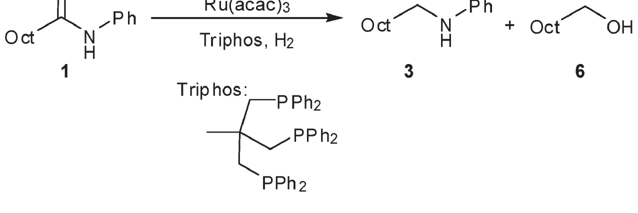

Fig. 2 Hydrogenation of the *N*-phenylnonamide catalysed by Ru/triphos.

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Table 1 Hydrogenation of *N*-phenylnonamide

Entry	Ru compound (%)	Triphos (%)	Solvent	*T*/°C	Water : Solvent ratio	Pressure/bar	*t*/h	Conversion (%)	Secondary amine (**3**) (%)	Alcohol (**6**) (%)
1	—	—	THF	164	0.1	40	14	0	0	0
2	$Ru(acac)_3$ (1%)	—	THF	164	0.1	40	14	61	57	4
3	—	2	THF	164	0.1	40	14	0	0	0
4	$Ru(acac)_3$ (1%)	2	THF	164	0.1	40	14	100	93	7
5	$Ru(acac)_3$ (1%)	2	THF	164	0	40	14	100	99	1
6	$Ru(acac)_3$ (1%)	2	THF	140	0.1	40	14	100	91	9
7	$Ru(acac)_3$ (1%)	2	THF	120	0.1	40	14	80	48	32
8	$Ru(acac)_3$ (1%)	2	THF	100	0.1	40	14	40	0	40
9[a]	$Ru(acac)_3$ (1%)	2	THF	164	0.1	40	14	92	71	21

[a] Aniline (1 equivalent) was added.

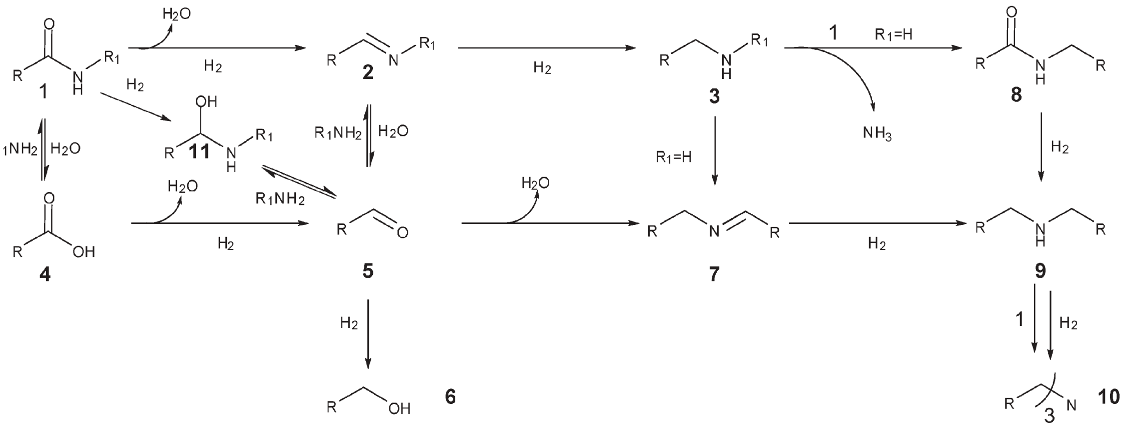

Fig. 3 Hypothetical mechanism of hydrogenation.

Table 2 Hydrogenation of butanamide

Entry	Water : Solvent ratio (v/v)	*P*(NH_3)/bar)	Aqueous ammonia : THF ratio (v/v)	Liquid NH_3 : THF ratio (v/v)	Conv. (%)	Primary amine (**2**) (%)	Secondary amine (**9**) (%)	Tertiary amine (**10**) (%)	Secondary ester (%)	Secondary amide (**8**) (%)	Alcohol (**6**) (%)
1[b]	0.1	—	—	—	100	0	46	53	Traces	Traces	Traces
2[b]	0.01	—	—	—	100	0	48	51	Traces	Traces	Traces
3	0.1	—	—	0.5	100	44	38	0	0	10	8
4	0.1	—	—	1	59	36	6	0	0	14	3
5	—	—	0.3	—	100	78	0	0	0	10	12
6	—	—	0.5	—	100	85	0	0	0	0	15
7	—	—	0.7	—	100	85	0	0	0	0	15
8	—	—	1	—	100	73	0	0	0	2	25
9	—	4	1	—	100	75	0	0	0	0	25

[a] *Conditions* (unless otherwise indicated): Butanamide (1 g, 11.4 mmol), $[Ru_2(Triphos)_2Cl_3]Cl$ (91 mg, 0.05 mmol), 164 °C, $p(H_2)$ = 40 bar, 14 h, THF (10 ml). [b] $Ru(acac)_3$ (45 mg, 0.1 mmol) and triphos (142 mg, 0.22 mmol) were used instead of $[Ru_2(Triphos)_2Cl_3]Cl$

As Fig. 3 shows, the hydrolysis of amide (**1**) and imine (**2**) as well as the loss of amine from the aminol (**11**) and transamidation of (**1**) by (**3**) to give secondary amide (**8**) all liberate ammonia (R^1 = H). This mechanism suggests that working in the presence of ammonia may reverse these three steps, and therefore direct the reaction towards producing the desired primary amine. The use of liquid ammonia gave a 100% conversion with a selectivity to primary amine of 44% (Table 2, entry 3). A higher concentration of liquid ammonia decreased the yield to 59% but increased the selectivity to the primary amine to 61% (Table 2, entry 4). Aqueous ammonia may also be used to increase the concentration of ammonia and therefore to increase the selectivity to the primary amine to as high as 85% (Table 2, entries 5 to 7). However a large excess of aqueous ammonia also increased the concentration of water, which increased the rate of hydrolysis of the amide and imine, resulting in a drop in selectivity to primary amine relative to

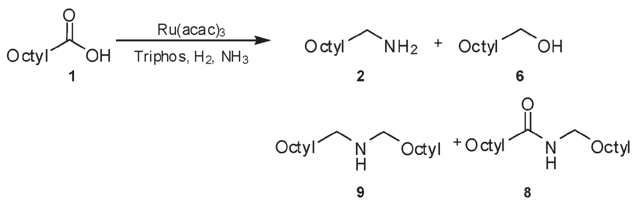

Fig. 4 Hydrogenation of nonanoic acid under an ammonium atmosphere.

Table 3 Hydrogenation of nonanoic under an ammonia atmosphere

Entry	Water : Solvent ratio	Aqueous ammonia : THF ratio	Liquid NH_3 : THF ratio	Conversion (%)	Primary amine (**2**) (%)	Secondary amine (**9**) (%)	Alcohol (**6**) (%)	Secondary amide (**8**) (%)
1	0.1	—	0.5	100	15	47	3	35
2	0.1	—	1	100	23	22	0	55
3	—	0.5	—	100	49	37	5	9
4	—	1	—	100	41	31	28	Traces

[a] *Conditions*: Nonanoic acid (1 ml, 5.7 mmol), $[Ru_2(triphos)_2Cl_3]Cl$ (45 mg, 0.03 mmol), 164 °C, $p(H_2)$ = 40 bar, 14 h, THF (10 ml).

butanol (Table 2, entry 8). The combination of ammonia gas and aqueous ammonia did not make a substantial difference (Table 2, entry 9).

Another approach to amine synthesis involved the hydrogenation of a carboxylic acid in the presence of ammonia. When liquid ammonia was used with nonanoic acid (Fig. 4), a mixture of primary amine (15%), secondary amine (47%), alcohol (3%) and secondary amide (35%) was obtained (Table 3, entries 1 and 2). The use of aqueous ammonia gave a moderate yield of primary amine (Table 3, entry 3). An excess of aqueous ammonia gave similar conversion and selectivity (41%) to the desired primary amine (Table 3, entry 4).

In conclusion, a careful analysis of the mechanism of formation of various products from the hydrogenation of primary and secondary amides has allowed conditions to be developed that allow the selective formation of primary and secondary amines by the ruthenium/triphos catalysed hydrogenation of amides or carboxylic acids in the presence of ammonia.

A patent covering these finding has been filed.[9]

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Notes and references

† *Experimental section*:

Hydrogenation of *N*-phenylnonamide: 1 g of *N*-phenylnonamide and $[Ru(acac)_3]$ (17 mg, 0.043 mmol) were placed in a 250 ml hasteloy autoclave, which was flushed three times with H_2. Triphos (54 mg, 0.086 mmol) was dissolved in THF (10 ml) and water (1 ml). The solution was transferred into the autoclave *via* cannula. The autoclave was pressurised with 40 bar of H_2 and heated to 164 °C for 14 h. The autoclave was then cooled and vented. The solution was analysed by GCFID. The isolation of the product was as follows: the solvent of the final solution was evaporated. The crude product was purified by column chromatography (hexane). Yield = 70%.

^{1}NMR (300 Hz):[10] 7.15 (t, 2 H, *J* = 8 Hz), 6.65 (t, 1 H, *J* = 8 Hz), 6.52 (d, 2 H, *J* = 8 Hz), 3.08 (t, 2 H, *J* = 7 Hz), 1.5–1.8 (m, 2 H), 1.4–1.5 (m, 11), 0.75–0.85 (m, 3 H),

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