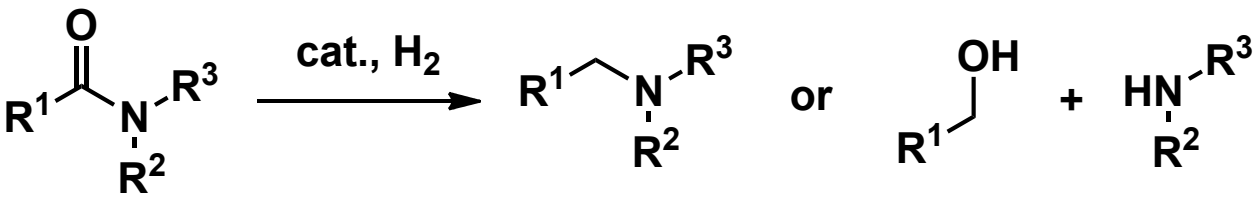
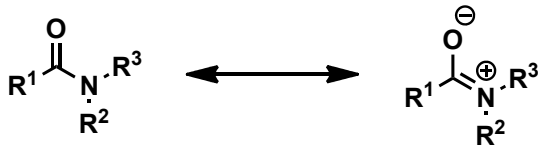
Catalytic Hydrogenation of Amides

2nd/Aug/2014 (Sat) Ozawa Jun (D1)



1. Introduction

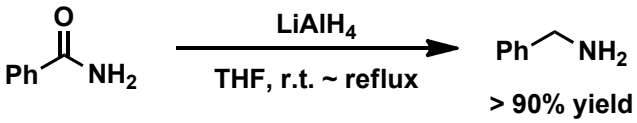
An amide, one of the most robust functional groups, is resistant to various chemical reactions such as nucleophilic attacks, redox reactions and acidic or basic decomposition.
The reason is clear: the resonance depicted below.



The resonance results in

1. a lower positive charge on the carbon atom than that in other carbonyl compounds
   → lower electrophilicity
2. lower electron density on the nitrogen atom
   → low basicity and coordinating ability, and high resistance toward oxidation of the nitrogen
3. planar nature due to the sp^2 hybridized orbital of the nitrogen
   → There is an energy barrier to rotation of the C-N bond (formamide: 75 ~ 80 kJ/mol).

Speaking of reduction of amides, $LiAlH_4$ is the most practical and reliable choice:

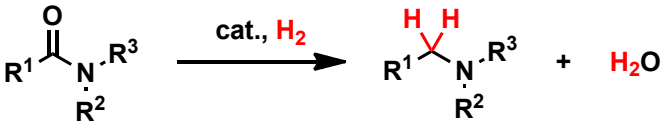


Other metal hydride agents (DIBAL, Red-Al, AlH_3, BH_3, $LiEt_3BH$, ...) are also effective ones.

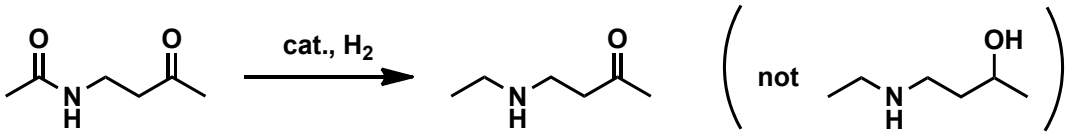
disadvantages:

1. coproduction of stoichiometric amounts of waste metal salts
   → complicated workup, poorly atom economical
2. incomplete chemoselectivity
   → Other functional groups such as ketones, nitro groups, some alkynes, will be reduced.
   → It's difficult to use such reagents at the late stage of the synthesis.

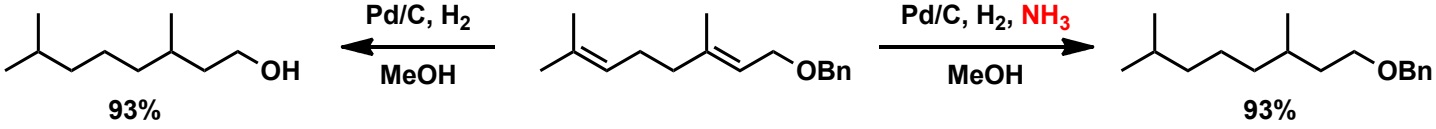
♥ a promising alternative: catalytic hydrogenation



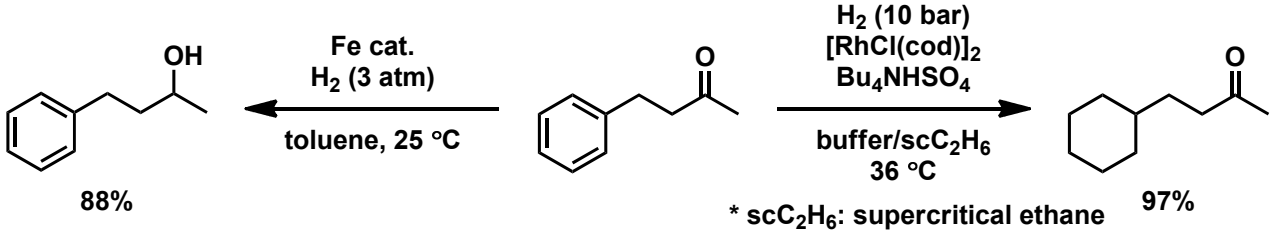
1. Water is the sole stoichiometric waste.
2. It is possible to control the chemoselectivity by modifying the catalysts:



cf. different catalyst system brings the different selectivity of hydrogenation



K. Hirota *Tetrahedron* 1998, *54*, 13981-13996.

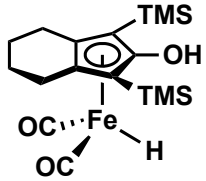


* scC_2H_6: supercritical ethane

C. P. Casey *JACS* 2007, *129*, 5816-5817.

P. G. Jessop *Chem. Commun.* 2000, 941-942.

Fe cat. =

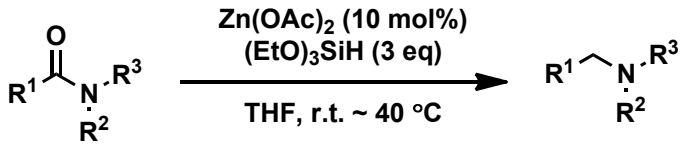


♥ other reduction reactions of amides

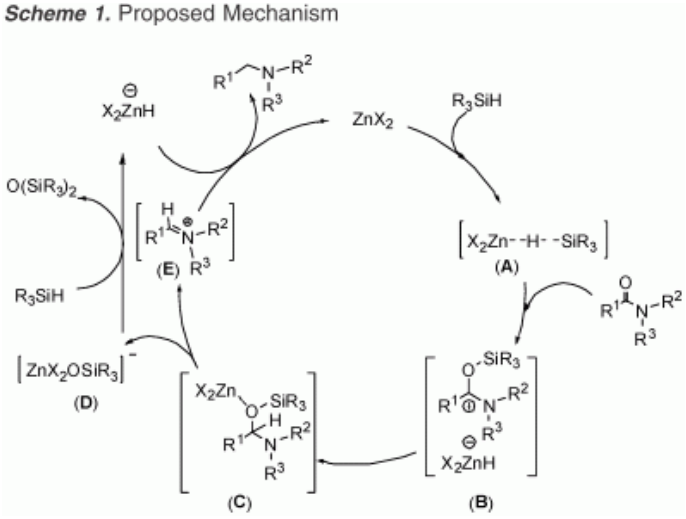
1. silane reduction

Stoichiometric silane reagents are needed, but metal catalysts are generally catalytic amount.
→ easier workup than when Al-H or B-H reagents are used

M. Beller *JACS* 2010, *132*, 1770-1771.



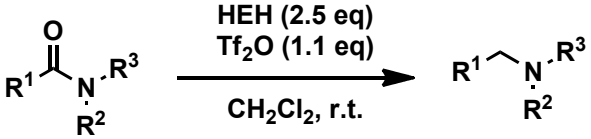
72 ~ 99%



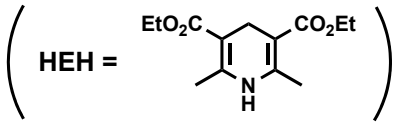
- **Only tertiary amides are applicable.**
- **Ketone, nitrile, nitro group, olefin, ester, diimide are tolerated.**

2. metal-free reduction using Hantzsch ester (HEH)

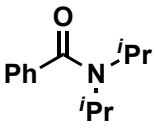
A. B. Charette *JACS* 2008, *130*, 18-19.



46 ~ 91%



- **Only tertiary amides are applicable.**
- **Ketone, nitrile, conjugated olefin, alkyne, ester, epoxide, are tolerated.**
- **Sterically hindered amides are difficult to reduce.**



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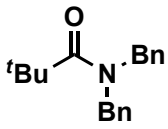

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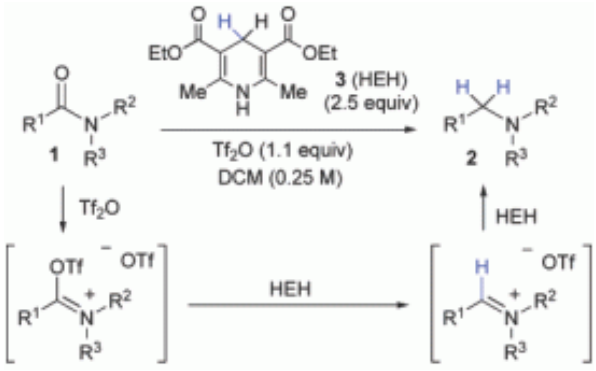


Mild and chemoselective reduction of amides into amines has been achieved, but the methods are still atom inefficient.

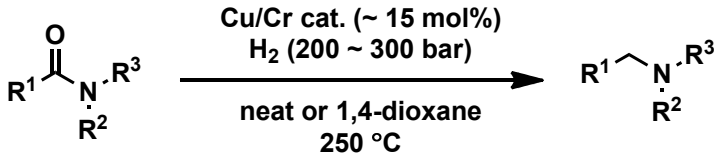
2. Hydrogenations with Heterogeneous Catalysts

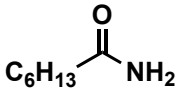
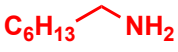
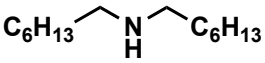
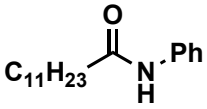
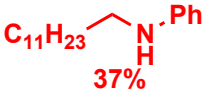
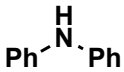
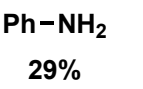
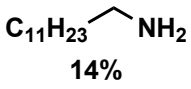
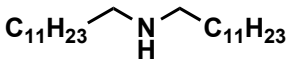
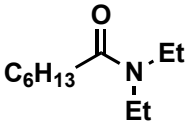
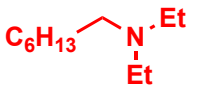
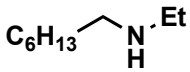
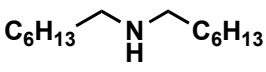
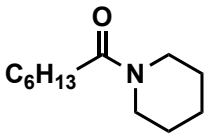
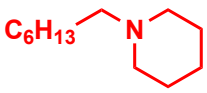
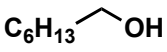
2-1. Early Development

pioneering work using Cu-Cr oxide catalysts by Adkins

H. Adkins *JACS* 1934, *56*, 247.
H. Adkins Patent US 2143751

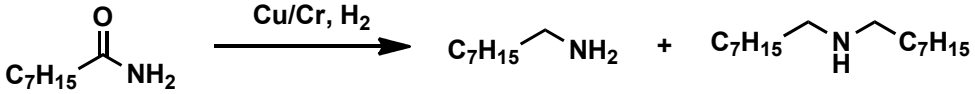
the preparation of the catalysts:
H. Adkins *JACS* 1932, *54*, 1138-1145.



Substrate (selected)	Products	
	 39%	 58%
	 37%  5%	 29%  14%  2%
	 4%	 64%  25%
	 92%	 5%

- Extremely high H_2 pressure (~ 300 bar) and reaction temperature (250 °C) were required.
- The target amines were obtained, but they were generally minor products.
- The solvent 1,4-dioxane was thought to dilute the water and minimize the hydrolysis of amides.

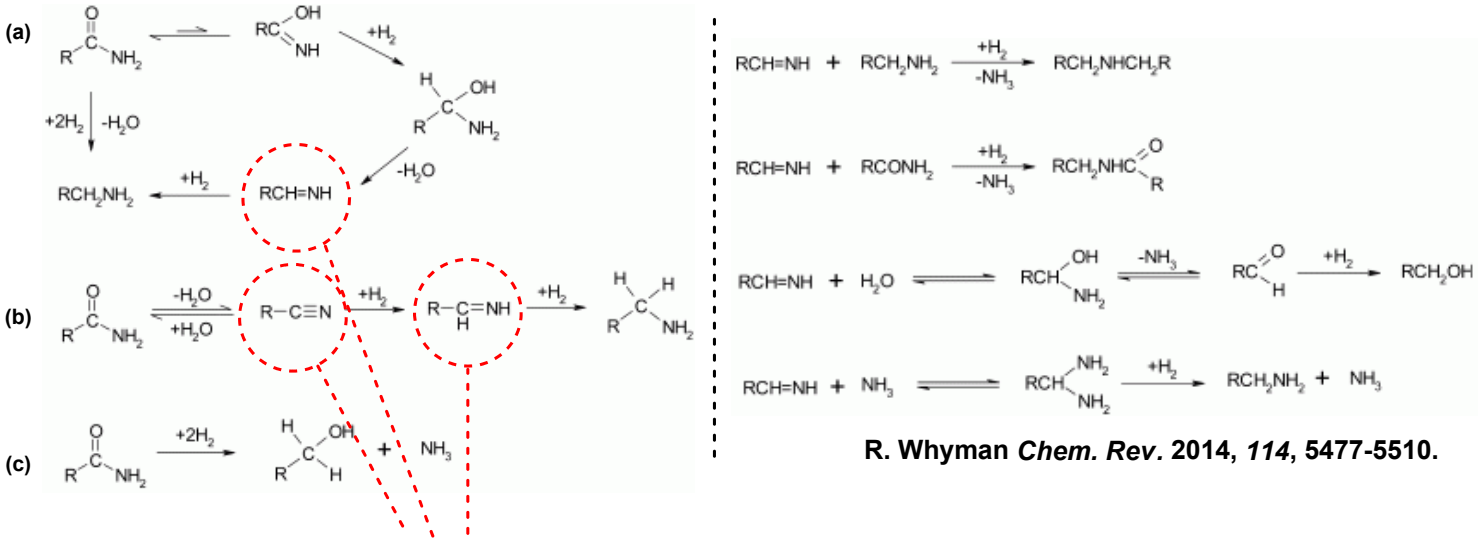
∗ Additives could improve the selectivity or reaction cocnditions
1. NH_3 effectively suppressed the formation of secondary amines in the hydrogenation of primary amines:



300 atm, 300 °C, w/o NH_3: 9% 83%
400 atm, 350 °C, w/ NH_3: 90% 10%

A. Guyer *Helv. Chim. Acta* 1955, *38*, 1649-1654.

♠ **the mechanism for the genaration of symmetric secondary amines**

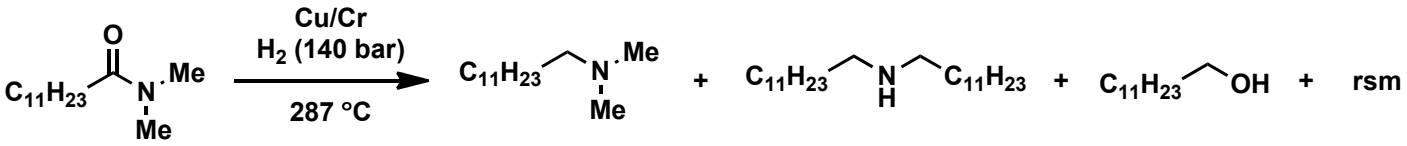


R. Whyman *Chem. Rev.* 2014, *114*, 5477-5510.

subject to nucleophilic attacks

- **the attack of the target amine → secondary amine**
- **the attack of NH_3 → no change (primary amine)**

2. A 4A zeolite enabled the hydrogenation as low as 140 bar and improved the selectivity.



w/o MS4A:	**17%**	**9%**	**1%**	**53%**
w/ MS4A:	**72%**	**9%**	**8%**	**8%**

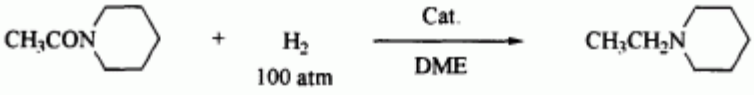
R. M. King Patent US 4448998

Additives could reduce the H_2 pressure, but the reaction temperature was still high (over 200 °C).

⇨ **The catalyst itself must be modified for higher catalytic property.**

2-2. Recent Progress

A landmark paper by T. Fuchikami (*TL* 1996, *37*, 6749-6752.) says,
"the bimetallic catalysts consisting of group 8 to 10, and group 6 or 7 metals show extremely potent reducing abilities in the hydrogenation of amides".
(One year before he reported that the same kind of bimetalic catalysts were also effective for the hydrogenation of carboxylic acids to alcohols. (*TL* 1995, *36*, 1059-1062.))



Entry	Cat. 1	Cat.2	Temp. (°C)	Conv. (%)	Yield (%)
1	$Rh_6(CO)_{16}$		160	24	19
2	$Ru_3(CO)_{12}$		160	1	1
3	$Re_2(CO)_{10}$		160	14	7
4	$Mo(CO)_6$		160	2	2
5	$W(CO)_6$		160	1	1
6	$Rh_6(CO)_{16}$	$Re_2(CO)_{10}$ [b]	160	100	96
7	$Rh_6(CO)_{16}$	$W(CO)_6$	160	51	50
8	$Rh_6(CO)_{16}$	$Mo(CO)_6$	160	100	98
9	$Ru_3(CO)_{12}$	$Re_2(CO)_{10}$	160	100	96
10	$Ru_3(CO)_{12}$	$Mo(CO)_6$	170	55	54
11	$Rh_6(CO)_{16}$	Re / C	170	83	82
12	Rh / C	Re / C	170	100	98
13	$Ru_3(CO)_{12}$	Re / Al_2O_3	170	100	94
14	Ru / Al_2O_3	Re / Al_2O_3	170	100	92

[a] All reactions were carried out with substrate (1.0 mmol) and catalyst (1 mol%) in DME (1.0 ml) at given temperatun for 16 h. [b] 0.5 mol% of Re was used.

	group
Cr	6
Cu	11
Rh	9
Ru	8
Re	7
Mo	6
W	6

→ **further investigation of the substrate scope**

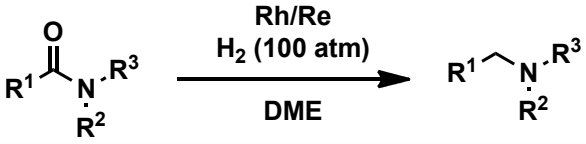
***Cat.1: Cat. 2 = 1:1, DME: 1,2-dimethoxyethane, bp 85 °C**

- **Monometallic catalysts were all ineffective (entry 1 to 5).**
- **The hydrogenation proceeded at 100 atm of H_2 at 160 °C, much milder than the conditions mentioned above.**

(see the next page)

- **Secondary and tertiary amides were hydrogenated smoothly to give the corresponding amines, and a primary amide was reduced to the primary amine with the help of Et_2NH that suppressed the formation of $(C_6H_{13})_2NH$.**
- **Benzene rings were unfortunately hydrogenated into cyclohexane rings (entry 6 and 7).**

***Rh(0) catalyzes benzene hydrogenation: R G. Finke *JACS* 1998, *120*, 5653-5666.**



Entry	Amide	Rh (mol%)	Re (mol%)	Temp. (°C)	Time (h)	Conv. (%)	Amine	Yield (%)
1	$HCON(CHMe_2)_2$	1	1	160	16	100	$MeN(CHMe_2)_2$	92
2	AcN⬡O	1	1	170	16	100	EtN⬡O	85
3	$EtCONEt_2$	3	3	160	36	75	$EtCH_2NEt_2$	62
4	$t\text{-}BuCONEt_2$	3	3	170	36	87	$t\text{-}BuCH_2NEt_2$	70
5	$AcNH(n\text{-}C_6H_{13})$	3	3	170	16	97	$EtNH(n\text{-}C_6H_{13})$	82
6	AcNHPh	3	3	170	16	100	EtNHCy[b]	90
7	$AcNHCH_2Ph$	3	3	180	16	100	$EtNHCH_2Cy$[b]	88
8	$n\text{-}C_5H_{11}CONH_2$[c]	3	6	180	8	100	$n\text{-}C_6H_{13}NH_2$	76
9		1	1	180	16	100		91
10		1	1	160	16	100		75
11		1	1	170	32	88		70
12		3	3	170	16	82		69

[a] All reactions were carried out with substrate (1.0 mmol) and catalysts (1-3 mol%) in DME (2.0 ml) at given temperature. [b] Cy: cyclohexyl group. [c] The reaction was carried out with 2 eq. of diethylamine under the diluted conditions (0.25 mol/l).

Bulky substituents didn't hinder the hydrogenation.

aromatic rings hydrogenated!!

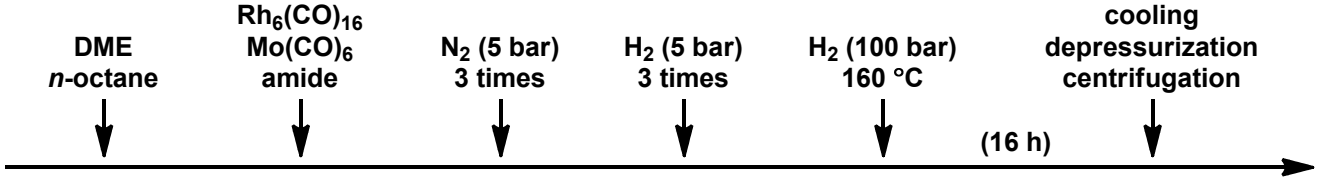
Et_2NH needed to suppress the generation of $(C_6H_{13})_2NH$.

♥ Whyman researched the properties of the bimetallic catalysts.
R. Whyman *J. Catal.* 2010, *269*, 93-102. (Rh/Mo)
R. Whyman *Adv. Synth. Catal.* 2010, *352*, 869-883. (Ru/Mo)
R. Whyman *J. Catal.* 2011, *278*, 228-238. (Ru/Re, Rh/Re)

Here only Rh/Mo catalyst system is put on the agenda.

Catalytic Procedures

$Rh_6(CO)_{16}$ (0.0165 g, 0.0930 mmol Rh), $Mo(CO)_6$ (0.0135 g, 0.0511 mmol Mo) and $CyCONH_2$ (0.235 g, 1.85 mmol) were added to a glass liner containing DME (30 mL), and *n*-octane (0.100 g) as an internal standard for GC analysis. The liner was placed in a ca. 300 mL capacity pressure vessel and the reaction mixture, under agitation, was purged (at 5 bar), 3 times with N_2 followed by 3 times with H_2. The autoclave was then pressurized to 100 bar with H_2 and heated to 160 °C for 16 h. After cooling and depressurization, a dark coloured colloidal suspension was recovered. This slowly settled to leave a colourless solution, and dark residue (ca. 15 mg), which was separated by centrifugation (2000 rpm, 20 min), washed several times with DME and dried as a fine black powder.



♠ **The ratio of Mo:Rh is an essential factor of high selectivity and onversion.**

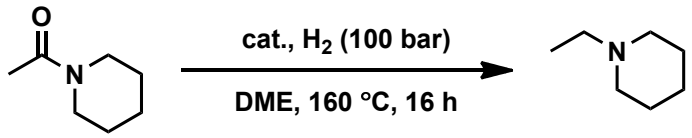


Table 1
N-acetylpiperidine (NAP) hydrogenation: conversion and product selectivity using bimetallic Rh/Mo and monometallic catalyst precursors.

Entry	Catalyst Precursor	Conversion (%)	Selectivity NEP	Piperidine
1	$Rh_6(CO)_{16}$	20	80	20
2	Rh/C	1	–	–
3	Rh_2O_3	1	–	–
4	$Mo(CO)_6$	2	–	–
5	Copper chromite	4	>90	–
6	$Rh_6(CO)_{16}/Mo(CO)_6$*	77	92	8
7	$Rh_6(CO)_{16}/Mo(CO)_6$**	94	95	5
8	Rh/MoO_3	7	71	28

Reaction conditions: 100 bar H_2, 160 °C, 16 h.
* Catalyst concentration: 1 mol% Rh, Rh:Mo atomic ratio: 1:1.
** Catalyst concentration: 1 mol% Rh, Rh:Mo atomic ratio: 1.5:1.

the highest when Mo/Rh = 0.67

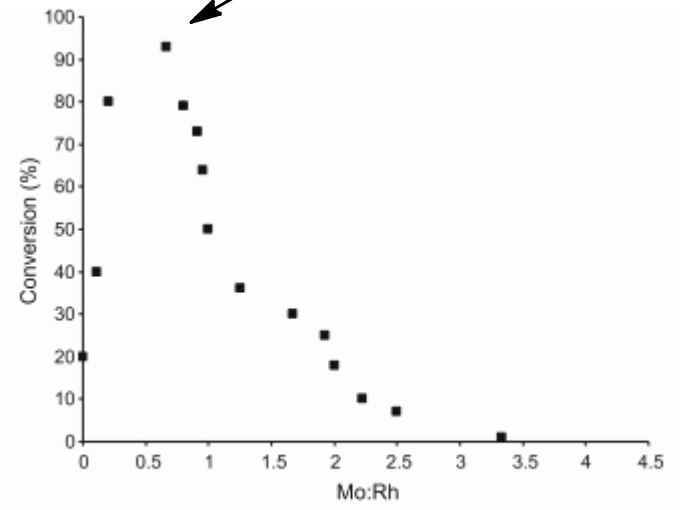
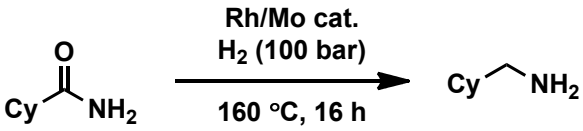


Fig. 1. NAP hydrogenation: conversion vs. Mo:Rh composition (100 bar H_2, 160 °C, 16 h, 1 mol% Rh).

The selectivity and conversion varied depending on the Mo:Rh ratio.

∗ **The best ratio of Mo:Rh varied dependig on the substrate.**



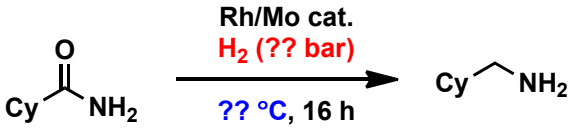
Mo:Rh	Conversion (%)	$CyCH_2NH_2$ (%)	$CyCH_2OH$ (%)	$(CyCH_2)_2NH$ (%)
0	20	68	24	4
0.16	91	89	8	2
0.55	100	87	10	0
1.01	100	77	11	8
1.39	100	58	22	15
1.53	100	47	27	24
1.90	89	43	36	16
2.37	22	0	21	78
3.40	24	0	34	62
4.03	29	0	33	64

excellent selectivity for the primary amine w/o additional NH_3 or other amines!

no primary amine

- **Best result (conversion and primary amine selectivity) was obtained when Mo/Rh was around 0.6.**
- **Significant decrease in the primary amine selectivity was observed at the ratio higher than 1.**
- **Above a Mo:Rh ratio of 2, the conversion dramatically decreased, with the secondary amine formed as the only amine product. (excess Mo is a catalyst poison?)**

♠ **Low temperature and pressure of H_2 resulted in low conversion and selectivity.**



T (°C)	H_2 (bar)	Conversion (%)	$CyCH_2NH_2$ (%)	$CyCH_2OH$ (%)	$(CyCH_2)_2NH$ (%)
160	100	100	87	10	0
140	100	97	79	7	12
130	100	95	53	19	23
120	100	9	0	75	20
160	50	100	83	8	14
160	20	63	66	10	17
160	10	41	56	26	20

The conversion dramatically decreased below 130 °C probably due to temperature dependent adsorption/desorption of reactants and products on the catalyst surface.

♠ **HP-FTIR analysis to monitor catalyst genesis during the *N*-acetyl piperidine hydrogenation**

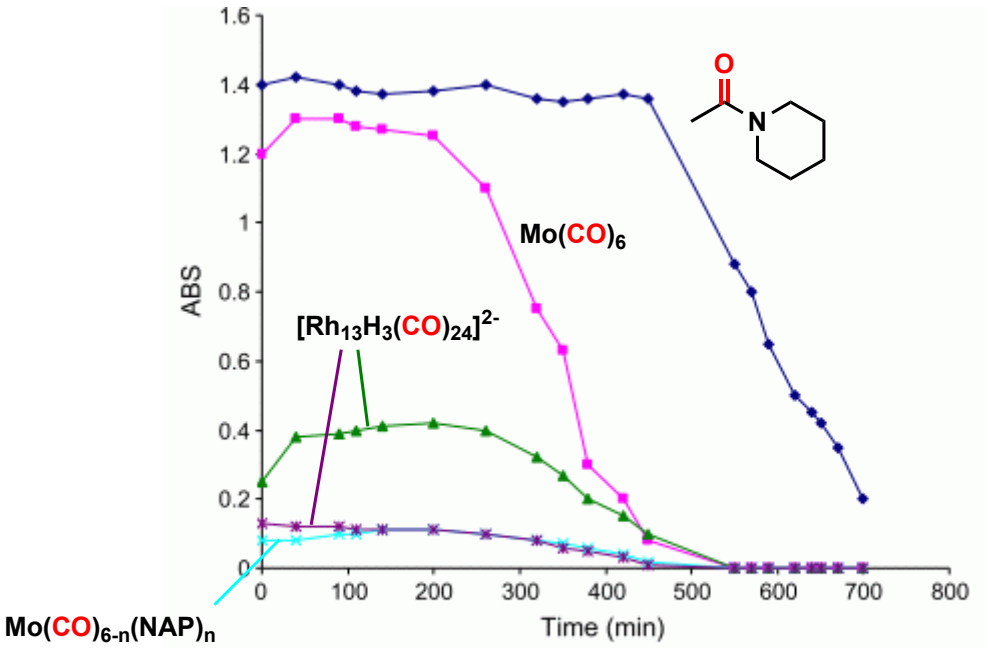


Fig. 2. In situ HPFTIR spectra (2100–1600 cm^{-1}) showing decay and disappearance of ν(CO) absorptions during catalyst genesis and initiation of hydrogenation. Key: NAP (1658 cm^{-1}), $Mo(CO)_6$ (1984 cm^{-1}), 2016 cm^{-1}, 1849 cm^{-1}, 1752 cm^{-1}.

***$Rh_6(CO)_{16}$ is insoluble to DME.**

- **$Rh_6(CO)_{16}$ and $Mo(CO)_6$ gradually change into the real catalyst *in situ*.**
- **NAP starts to be consumed just after the absorption of COs has disappeared; the induction period is about 8 h.**
- **2016 cm^{-1} and 1849 cm^{-1} are consistent with the reported peaks for $[Rh_{13}H_3(CO)_{24}]^{2-}$: ν(CO) in THF: 2020 and 1840 cm^{-1} (P. Chini *Chim. Ind. (Milan)* 1978, *60*, 989-997.)**

♠ X-ray Photoelectron Spectroscopy (XPS) of $Rh_6(CO)_{16}/Mo(CO)_6$ catalyst (Mo:Rh = 0.67)

Table 4
XPS data: Rh and Mo ($3d_{5/2}$) binding energies (eV) of Rh/Mo catalysts before and after use in NAP hydrogenation, and during Ar^+ (2–3 keV) sputter etching, including Rh and Mo standards.

Entry	Sample	Ar^+ sputter etching time	Rh (0)	Rh (III)	Mo (VI)	Mo (V)	Mo (IV)	Mo (0)
1	Rh foil	–	307.2	–	–	–	–	–
2	Rh_2O_3 powder	–	–	308.8	–	–	–	–
3	Mo foil	–	–	–	–	–	–	227.9
4	MoO_2 [25]	–	–	–	–	–	229.6	–
5	Mo_2O_5 [25]	–	–	–	–	231.0	–	–
6	MoO_3 powder	–	–	–	233.0	–	–	–
7	MoO_3 powder	8 min	–	–	232.7	–	229.1	–
8	MoO_3 powder	12 min	–	–	232.4	–	228.8	–
9	Rh/Mo catalyst, fresh	–	307.2	–	233.2	–	–	–
10	Rh/Mo fresh	8 min	307.2	–	–	–	228.6	–
11	Rh/Mo catalyst, used	–	307.3	–	233.0	–	–	–
12	Rh/Mo used	30 s	307.2	–	–	231.5	–	–
13	Rh/MoO_3 fresh	–	308.1	–	–	–	229.8	–
14	Rh/MoO_3 used	–	307.7	–	232.9	–	–	–
15	Rh/MoO_3 used	2 min	307.5	–	–	–	229.4	–

- **Rh is present in the metallic state throughout.**
- **Mo has various oxidation state ranging IV to VI; Mo(VI) is dominant on the catalyst surface, but Mo(IV) exists inside the catalyst (entry 9 and 10).**
- **After hydrogenation the catalyst surface is still covered with Mo(VI), but Mo(V) has generated inside, which is a clear contrast with the catalyst derived from Rh and MoO_3 (entry 11 to 15).**

∗ quantification of XPS profiles of the fresh Mo:Rh = 0.67 catalyst

Ar^+ sputter etching time [min]	0	1	2	4	8
Mo:Rh ratio	2.17	1.10	0.95	0.67	0.62

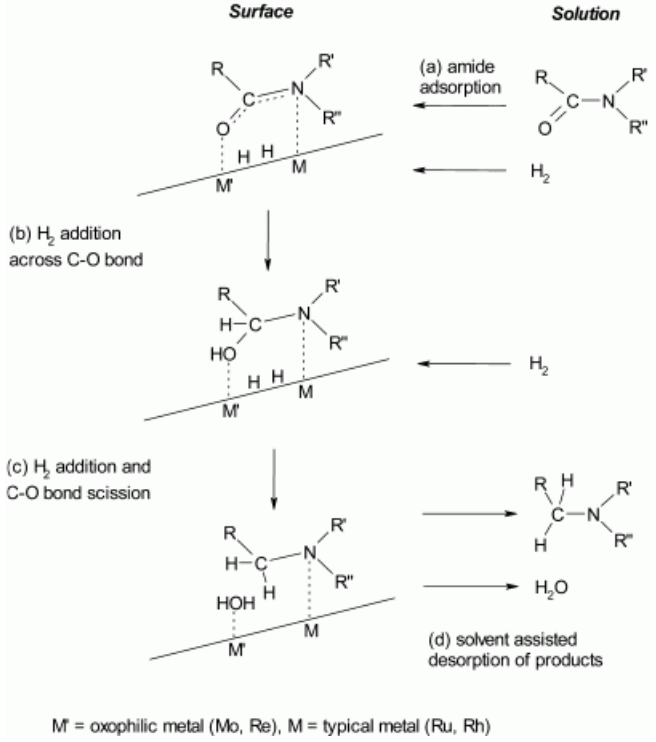
higher Mo content in the outer layer

⇨ **At high Mo:Rh levels excess Mo has the effect of coating the surface of Rh/Mo catalyst, blocking active sites, and thus leading to the observed poisoning of catalytic activity, and possibly influencing reaction selectivity via longer residence times.**

∗ MoO_2 has both acidic and metallic properties (J. W. Sobczak *Surf. Interface Anal.* 2002, *34*, 225-229.)

⇨ **The acidic Mo initially adsorbs the amide carbonyl group, which could lead to the promotion of overall rates of reduction at adjacent Rh centers.**

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

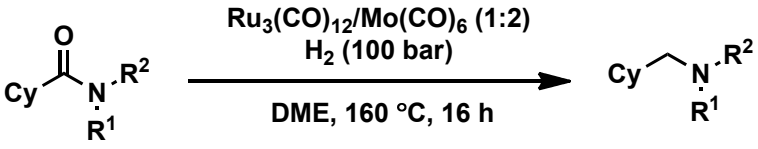


R. Whyman *Chem. Rev.* 2014, *114*, 5477-5510.

♥ Other aspects of the bimetallic catalysts

1. amide reduction reactivity ranking: Primary > Tertiary > Secondary (the position of Secondary is rather variable)

R. Whyman *Adv. Synth. Catal.* 2010, *352*, 869-883.



(R^1, R^2)	conv. [%]	yield [%]
(H, H)	100	85
(H, Me)	5	trace
(Me, Me)	30	22

a. Nitriles can be intermediates only for primary amides, which may be preferred to hydrogenation to hemiaminals.

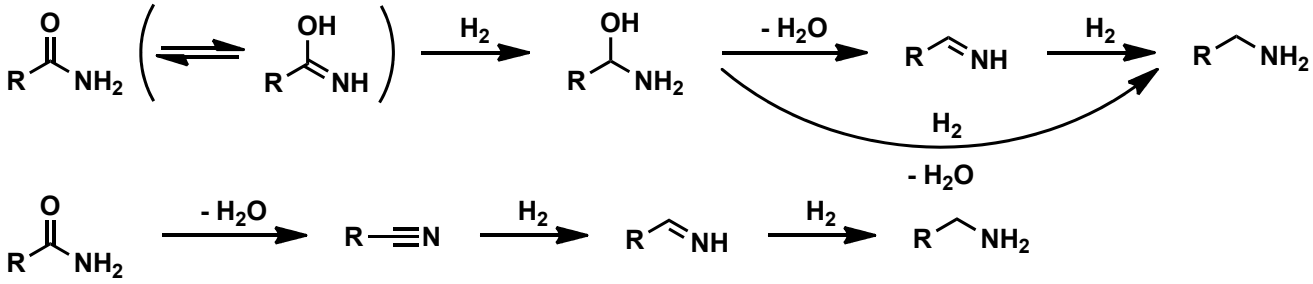


Table 8
Thermodynamic parameters relevant to amide hydrogenation.

R. Whyman *J. Catal.* 2011, *278*, 228-238.

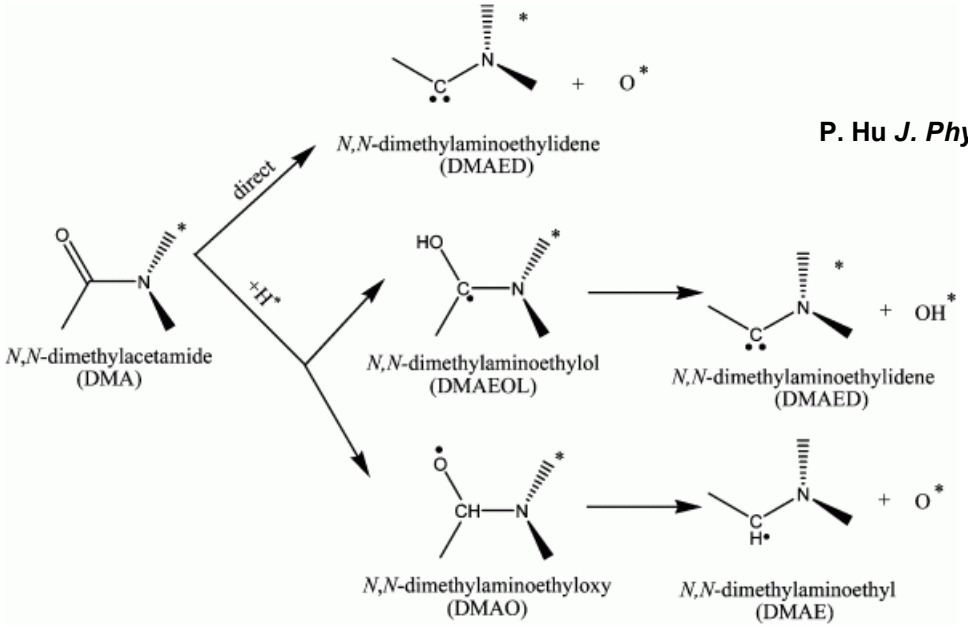
Entry	Reaction	$\Delta H°$ kJ mol^{-1}	$\Delta S°$ Jmol^{-1} K^{-1}	$\Delta G°_{298.15}$ kJ mol^{-1}
1	$CyCONH_2 + 2H_2 \rightarrow CyCH_2NH_2 + H_2O$	−49.8	−72.8	−28.1
2	$CyCONH_2 + H_2 \rightarrow CyCH(OH)NH_2$	51.5	−178.7	104.8
3	$CyCONH_2 + H_2 \rightarrow CyCH=NH + H_2O$	63.2	−21.1	69.5
4	$CyCONH_2 \rightarrow CyCN + H_2O$	73.2	156.5	26.5
5	$CyCN + H_2 \rightarrow CyCH=NH$	−10.0	−177.6	43.0
6	$CyCH=NH + H_2 \rightarrow CyCH_2NH_2$	−113.0	−51.7	−97.6
7	$CyCN + 2H_2 \rightarrow CyCH_2NH_2$	−123.0	−229.7	−54.6

*** This is an idealistic representation of the reaction pathways because the free energy values don't take account of the effect of the requirement for adsorption of the reactants and intermediates on the catalyst surface.**

b. For tertiary amides there is an alternative pathway to tertiary amines: direct cleavage of C=O bonds.

DFT calculation was performed to investigate the reaction mechanism of the cleavage of the carbonyl bond in *N*,*N*-dimethylacetamide on both flat and stepped Ru surface.

P. Hu *J. Phys. Chem. C* 2012, *116*, 18713-18721.



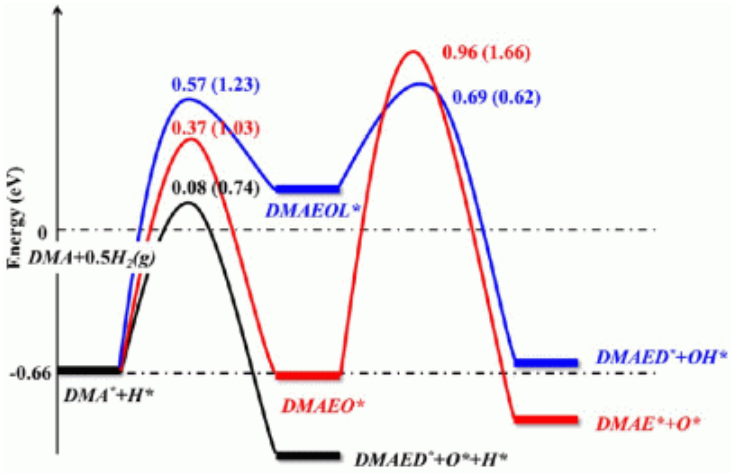


Figure 4. The reaction pathways over Ru(0001). Black line: The direct cleavage pathway. Blue line: O−H activation pathway. Red line: C−H activation pathway. The stabilities of the TSs with respect to absorbed DMA and H are listed (eV) and the energy barriers of the corresponding elementary steps are listed in parentheses (eV).

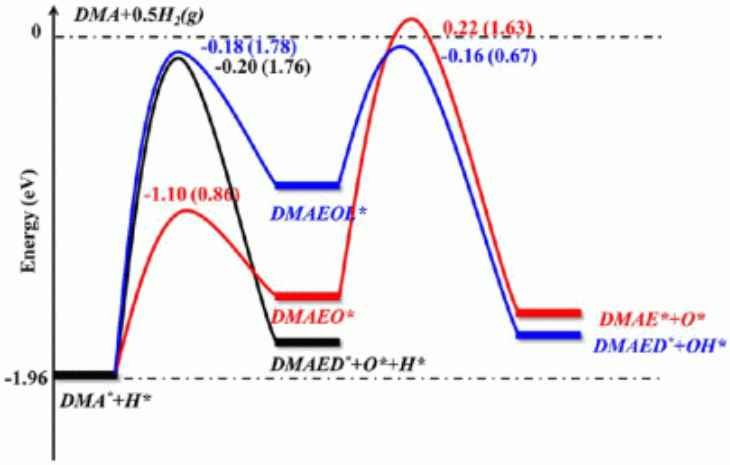
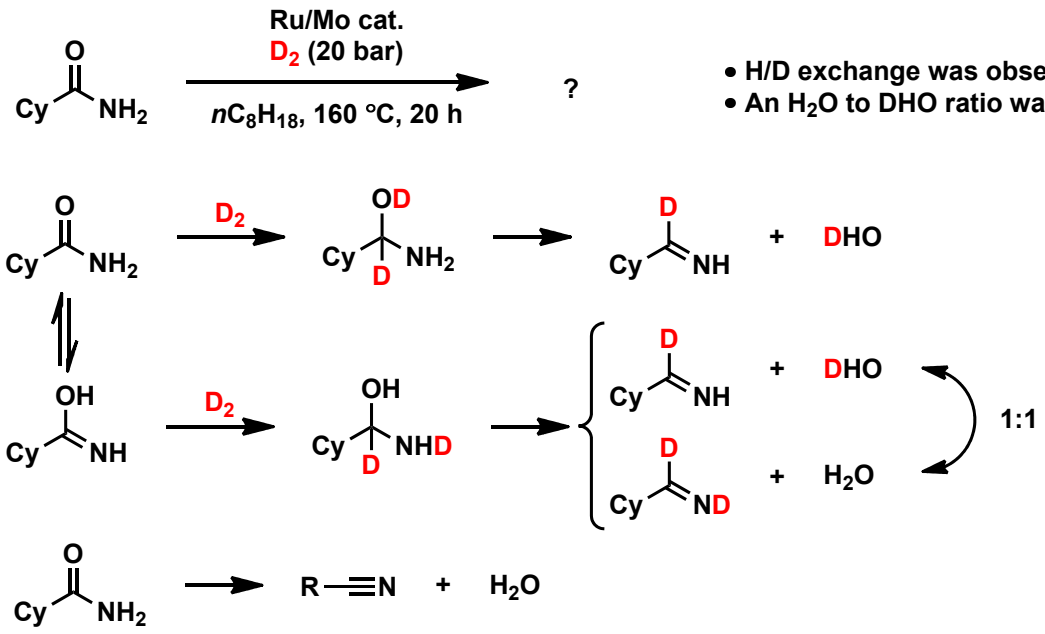


Figure 5. The reaction pathways over Ru(0001)-step. Black line: The direct cleavage pathway. Blue line: O−H activation pathway. Red line: C−H activation pathway. The stabilities of the TSs with respect to absorbed DMA and H are listed (eV) and the energy barriers of the corresponding elementary steps are listed in parentheses (eV).

In both cases direct C=O cleavage (DMA to DMAED) is preferred.

c. Hydrogenation using D_2 (A. M. Smith Ph.D. Thesis, University of Liverpool, 2006.)



d. Substituent(s) on N may be a steric bulk during amide adsorption onto the catalyst surface.
e. Hydrogen-bonded oligomer may also be an inhibiting factor for the adsorption onto the catalyst surface.

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2. the comparison among the catalysts of Ru/Mo, Rh/Mo, Ru/Re and Rh/Re

R. Whyman *J. Catal.* 2011, *278*, 228-238.

Table 7
Comparison between bimetallic catalysts for amide hydrogenation.

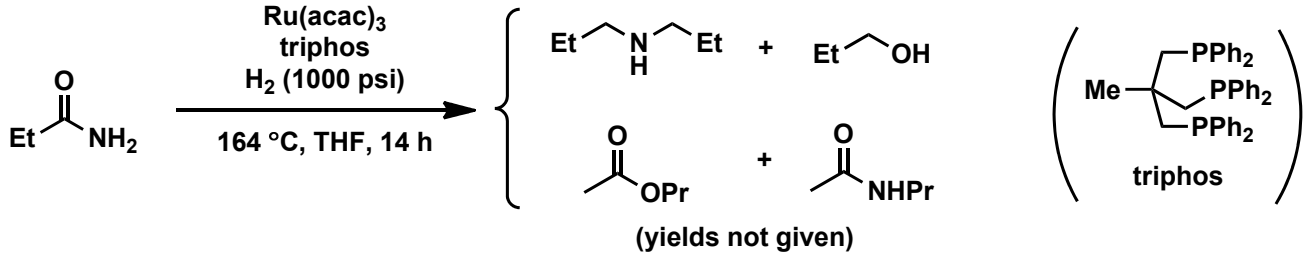
	Ru/Mo	Rh/Mo	Ru/Re	Rh/Re
Optimum Mo:M′/Re:M′	0.5	0.55	0.3–1.5	0.8
$CyCH_2NH_2$ selectivity (%)	85	85	95	90
H_2 pressure range (bar)	20–100	20–100	50–100	50–100
Minimum temperature (°C)	140	130	160	150
Nature of active catalyst	Ru/Mo and Mo oxides	Rh and Mo oxides	Ru/Re and Re oxides	Rh/Re and Re oxides

It cannot be determined which combination is the best for the hydrogenation of amides, mainly because there is no comprehensive data of substrate scope in the Whyman's papers.

3. Hydrogenations with Homogeneous Catalysts

There was only one report of the homogeneous hydrogenation of an amide before Cole-Hamilton's report.

S. P. Crabtree WO03/093208A1 (2003)



(yields not given)

much milder reaction conditions than that of Cu-Cr catalyst system, but no primary amine detected...

♥ Cole-Hamilton further researched the catalyst system.

D. J. Cole-Hamilton *Chem. Commun.* 2007, 3154-3156.

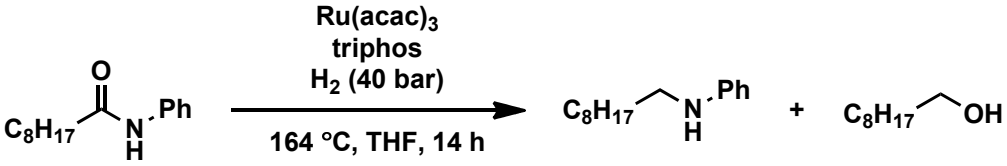


Table 1 Hydrogenation of *N*-phenylnonamide

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.

- **No reaction occurred in the absence of $Ru(acac)_3$ (entry 1 and 3).**
- **Lower conversion was observed in the absence of triphos (entry 2 and 4).**
- **Water was not essential for full conversion, but the catalyst was not stable in the absence of water (entry 5).**
- **Lower temperature than 140 °C resulted in lower conversion and secondary amine selectivity (entry 6 to 8).**
- **Additional aniline unfortunately reduced the catalyst stability and decreased the selectivity (entry 9), which is a strong contrast with heterogeneous catalyst system discussed above.**

∗ **Hydrogenation of butanamide**

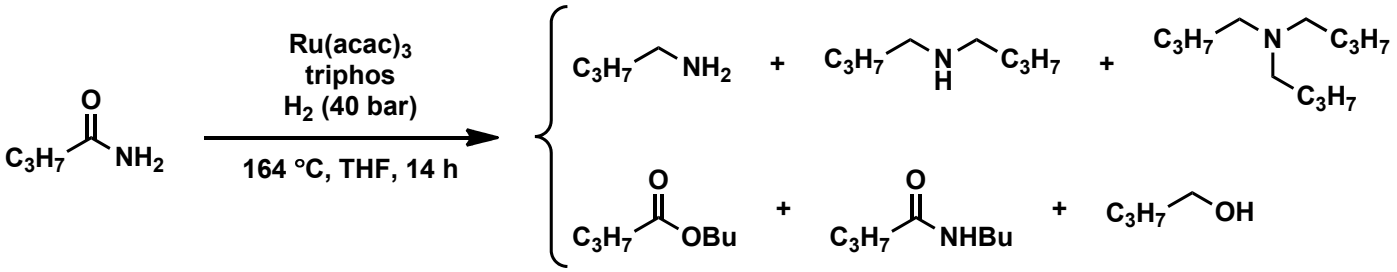


Table 2 Hydrogenation of butanamide

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 $[Ru_2(Triphos)_2Cl_3]Cl$

- **In this case addition of appropriate amount of NH_3 had an critical effect on the improvement of primary amine selectivity.**
- **Excess liquid NH_3 had a bad effect on conversion (entry 4)**
- **Excess aqueous NH_3 increased the concentration of water, leading to the hydrolysis and the alcohol production (entry 5 to 8).**
- **In fact, the work proved irreproducible at 164 °C; 200 °C was necessary for good reproducibility.**

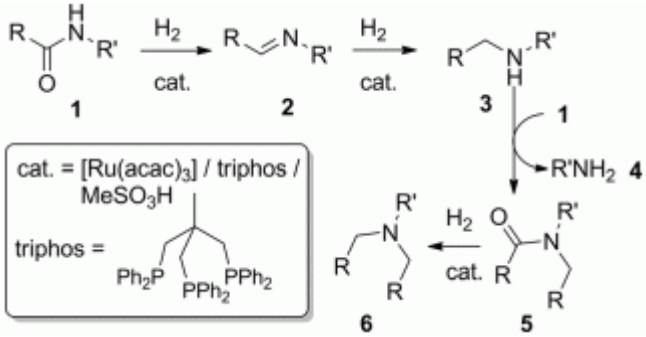
♥ **Further development by Cole-Hamilton**

D. J. Cole-Hamilton *Chem. Eur. J.* 2013, *19*, 11039-11050.

Table 1. Hydrogenations of benzanilide (**1**, R = R′ = Ph) with [Ru(acac)$_3$]/triphos and catalytic amounts of MSA.[a]

Entry	P_{H_2} [bar][b]	MSA [mol %]	t [h]	**2** [%]	**3** [%]	**4** [%]	**6** [%]	Conv. [%]	Sel. [%]
1	40	1	16	2	85	3	10	100	88
2	10	1	8	3	93	0	4	100	93
3	10	0.5	16	3	92	0	5	100	92
4[c]	10	10	16	<1	12	0	28	100	12
5	5	0.5	62	4	78	5	13	100	82
6[d]	10	1	16	ring hydrogenation products observed					
7[e]	10	1	16	2	91	0	7	100	91

[a] Conditions: amide (5 mmol), [Ru(acac)$_3$] (1 mol %), triphos (2 mol %), THF (10 mL), 220 °C, Hastelloy™ autoclave. Calculations based on GC-FID; selectivity is **3**/(**2**+**3**+**6**). [b] At RT. [c] *N*-Phenylpyrrolidine, benzylbenzamide and two other impurities are also formed, they are included as products in the calculation of selectivity. [d] Stainless steel autoclave. [e] Aniline (1 %) added.



- **MsOH as an additive enabled the hydrogenation at as low as 10 bar of H_2, accelerated the reaction, and improved the selectivity (entry 1 and 2).**
- **Too much MsOH resulted in relatively complicated reaction (entry 4).**
- **The reaction vessel had a strange effect on the reduction of the aromatic ring (entry 6).**

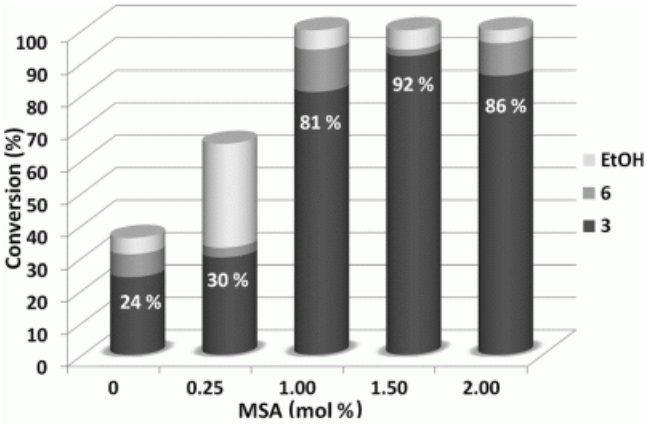
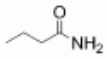
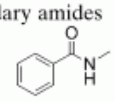
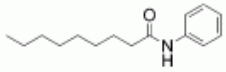
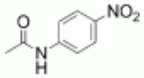
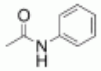
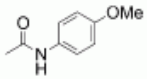
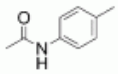
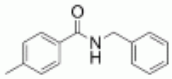
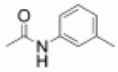
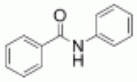
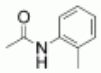
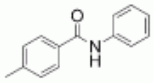
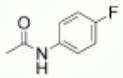
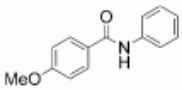
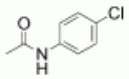
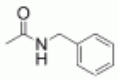
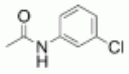
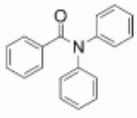
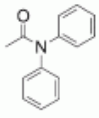
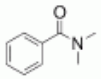
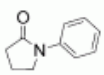
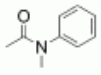


Figure 1. Effect of [MSA] on the products of *N*-phenylacetamide hydrogenation. *N*-phenylacetamide (**1**, R = Me; R′ = Ph, 5 mmol), [Ru(acac)$_3$] (1 mol %), triphos (2 mol %), 210 °C, H_2 (10 bar), THF, (10 mL), 16 h; for **6** and **3** R = Me and R′ = Ph.

The appropriate amount of MsOH dramatically improved the conversion and the selectivity in the hydrogenation of *N*-phenylacetamide.

Table 2. Substrate scope for amide hydrogenations with the [Ru(acac)$_3$]/triphos system.[a]

Entry	Substrate	MSA [mol %]	T [°C]	P_{H_2} [bar]	Conv. [%]	Sel. [%]	Entry	Substrate	MSA [mol %]	T [°C]	P_{H_2} [bar]	Conv. [%]	Sel. [%]
Primary amide[b]													
1		1.5	200	10	100	61							
Secondary amides													
2		1.5	200	10	82[c]	<5[c]	11		1.5	200	10	45	0
3		1.5	200	10	92[d]	92[d]	12		1.5	200	10	100	0
4		1.5	200	10	100[e]	92[e]	13		1.0	220	10	97	78
5		1.0	220	10	98	78	14		1.5	200	10	15[f]	<5[f]
6		1.5	200	10	100	79	15		1.0	220	10	100	92
7		1.5	200	10	100	90	16		1.5	200	10	100	94
8		1.0	220	10	99	77	17		1.5	200	10	92[c]	61[c]
9		1.5	200	10	64	28	18		1.5	220	10	100	<5
10		1.5	200	10	75	75							
Tertiary amides													
19		1.5	220	10	92	73	22		1.0	220	40	83	42
20		1.5	220	10	33[c]	7[c]	23		1.5	200	10	19	100
21		1.5	200	10	19	63	24		1.5	200	10	0	0

[a] Conditions: substrate (5 mmol), [Ru(acac)$_3$] (1 mol %), triphos (2 mol %), THF (10 mL), 16 h. Conversion and selectivity were calculated using NMR integration. [b] Reaction performed in the presence of aq. NH_3 (10 mL). [c] Based on uncalibrated GC-FID integration. [d] Ref. [6] reports 87 % conv. and 78 % sel. [e] Selectivity for different reactions with *N*-phenylacetamide under identical conditions varies between 86–92 %. In the presence of added mercury, 100 % conversion with 84 % selectivity was obtained. [f] Small amounts of mixed tertiary amines formed.

- **NH_3 was necessary for high primary amine selectivity (entry 1).**
- **Conversion and/or selectivity were low if there was not any aryl group on N (entry 2, 14, 18, 20, 24).**
- ***N*-Chorophenylamides yielded variable conv. and sel. depending on the position of Cl (entry 9 to 11).**
- **The benzene ring and the NO_2 group were reduced (entry 12).**
- **The yields for the hydrogenation of tertiary amides were generally poor.**

♥ **Mechanistic insight**

♠ **NMR studies showed that high temperature was required for the initial reduction of Ru^{III} to Ru^{II} and triphos coordination.**

$Ru(acac)_3$ (1 eq), triphos (2 eq) and MsOH (1.5 eq) were mixed and pressurised at 10 bar with H_2 in THF-d_8

- **at 130 °C (the max. probe temp.) : very little change on ^1H and ^{31}P NMR.**
- **after exposed to the typical reaction conditions: a number of species, including oxidized triphos, detected**

♠ **High temperature is also required for the turnover of the catalyst.**

Triphos-coordinated Ru^{II} catalyst (7 ~ 10) were tested if they showed catalytic activity, and 9 and 10 did display it.

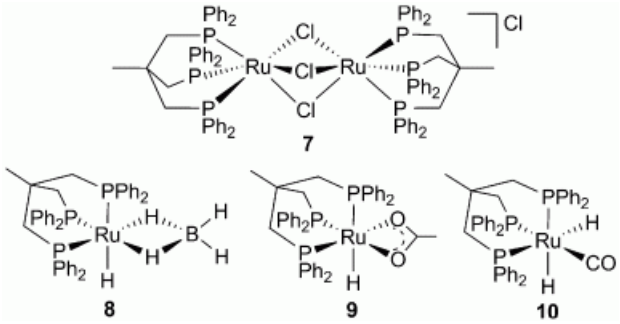


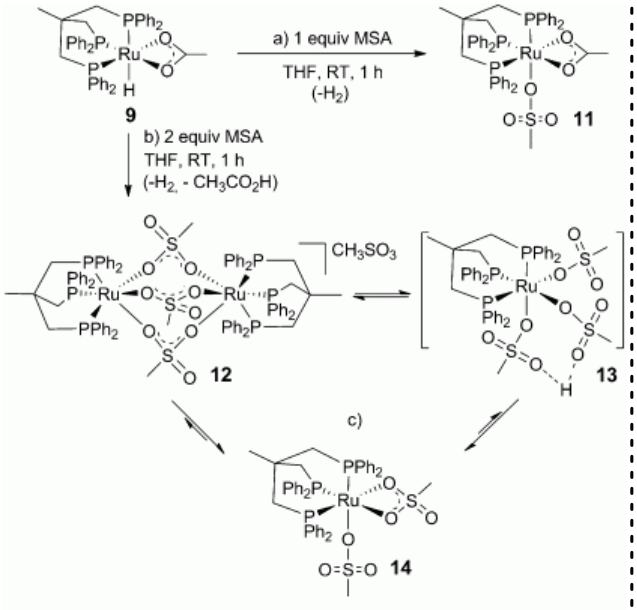
Table 4. Catalytic hydrogenation of *N*-phenylacetamide with **9** as precatalyst over a range of temperatures.[a]

Entry	*T* [°C]	**3** [%]	**6** [%]	EtOH [%]	Other [%]	Conv. [%]	Sel. [%]
1	120	0	0	1	26	27	0
2	150	0	0	1	99	100	0
3	200	75	23	0.4	1.6	100	75
4	210	78	11	0.5	10.5	100	78
5[b]	210	60	10	13	0	83	73

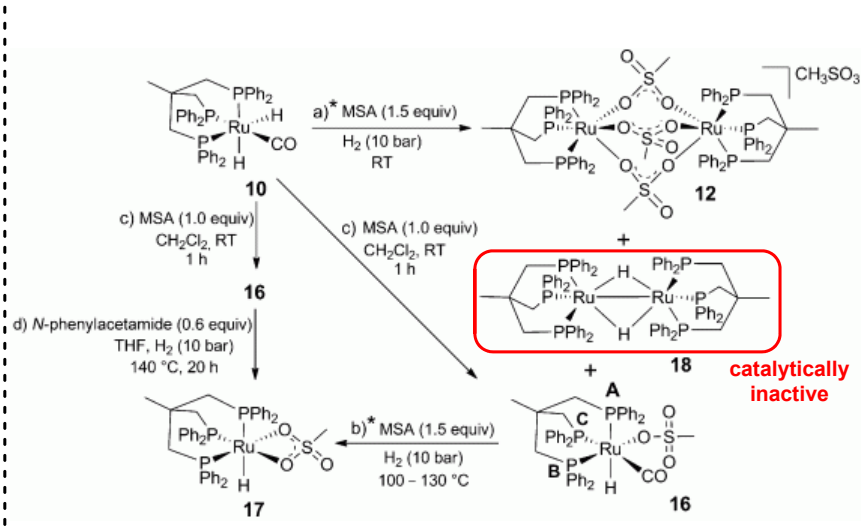
[a] Conditions: *N*-phenylacetamide (**1**, R = Me; R′ = Ph, 5 mmol), [RuH(OAc-κ²O,O′)(triphos)] (**9**, 1 mol %), MSA (1.5 mol %), THF (10 mL), H_2 (15 bar at RT), 16 h in a Hastelloy™ autoclave (250 mL); selectivity is **3**/(**3**+**6**+[EtOH]); for full product analysis see the Supporting Information. [b] Performed in the absence of added MSA.

∗ **10 was generated after the hydrogenation catalyzed by 9.**

♠ **In the presence of MsOH (> 1 eq.) 9 was converted to the mixture of 12 ~ 14, and 10 to 12, 16 ~ 18.**



Scheme 2. Reaction products observed when treating **9** with either: a) 1 equiv, or b) 2 equiv of MSA.



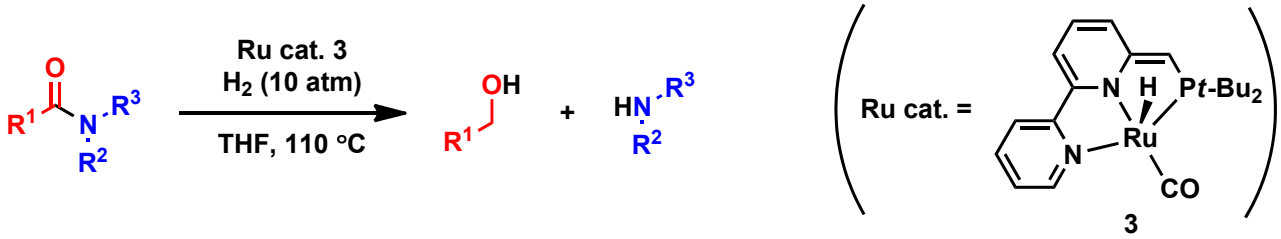
Cole-Hamilton proposed that

- **the role of MsOH would not only be to generate the active catalytic species, but also to control the protonation-deprotonation sequences required for efficient catalytic turnover;**
- **the equilibrium mixture of 12 ~ 14 would act as a pool for the $[(triphos)Ru]^{2+}$ fragment as the entry point into the actual catalytic cycle;**
- **the generation of 18 would be an important deactivation pathway.**

♥ Hydrogenation of amides to alcohols and amines ~C-N bond cleavage~

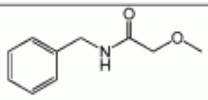
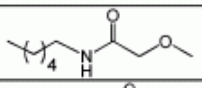
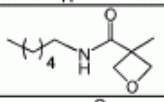
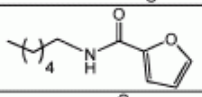
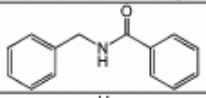
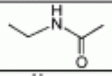
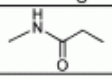
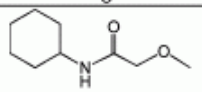
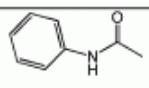
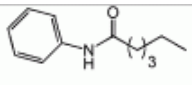
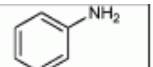
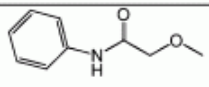
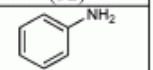
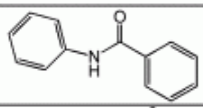
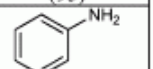
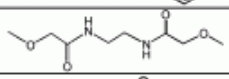
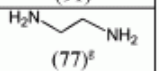
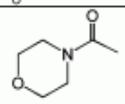
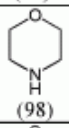
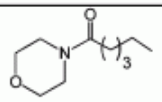
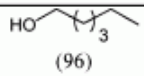
Milstein reported hydrogenation of amides with cleavage of the C-N bond.

D. Milstein *JACS* 2010, *132*, 16756-16758.



- **Although C-N bond cleavages and the generation of alcohols were mentioned in the previous papers, they were likely to be the result of hydrolysis of the amides to carboxylic acids, followed by hydrogenation.**
- **The reaction above was anhydrous, so direct C-N bond cleavage surely occurred.**
- **No hydrogenation on aromatic rings was observed (see the table below).**

Table 1. Hydrogenation of Amides to Alcohols and Amines Selectively Catalyzed by BPy-PNN-Ru(II) Pincer Complex **3**[a]

Entry	Amide	Products (yield [%])[b]	
		Alcohol	Amine
1		 Cat.**1**; (63)[a] Cat.**1**; (66)[c] Cat **2**; (0)[a] Cat.**3**; (89)[a] Cat.**4**; (80)[a,d]	 Cat.**1**; (62)[a] Cat. **1**; (67)[c] Cat. **2**; (0)[a] Cat.**3**; (90)[a] Cat.**4**; (82)[a,d]
2		 (91)	 (90)
3		 (74)	 (74)
4		 (69)	 (68)
5		 (57)	 (57)
6		EtOH (71)	$EtNH_2$[e]
7		 (68)	$MeNH_2$[e]
8		 (88)	 (87)
9		EtOH (94)	 (95)[f]
10		 (92)	 (92)
11		 (95)	 (95)
12		 (92)	 (91)
13		 (78)	 (77)[g]
14		EtOH (97)	 (98)
15		 (96)	(96)
16		(97)	(97)
17		MeOH (97)	(98)[h]

[a] Complex **1**, **2**, or **3** (0.01 mmol), amide (1 mmol), H_2 (10 atm), and dry THF (2 mL) were heated in a Fischer−Porter tube at 110 °C (bath temperature) for 48 h. [b] Yields of products were analyzed by GC (*m*-xylene as internal standard). [c] 1,4-Dioxane (2 mL) at 140 °C. [d] 1 equiv (relative to Ru) of base was used. [e] The amines ($EtNH_2$ and $MeNH_2$ for entries 6 and 7 respectively) were analyzed in the gas phase by GC-MS. [f] In the reactions involving anilide derivatives (entries 9−12), trace amounts of the corresponding secondary amines were detected by GC-MS. [g] 0.5 mmol of bis-amide was used. [h] Yield after 32 h.

*** No reaction occurred in the absence of base (entry 1, cat. 4).**

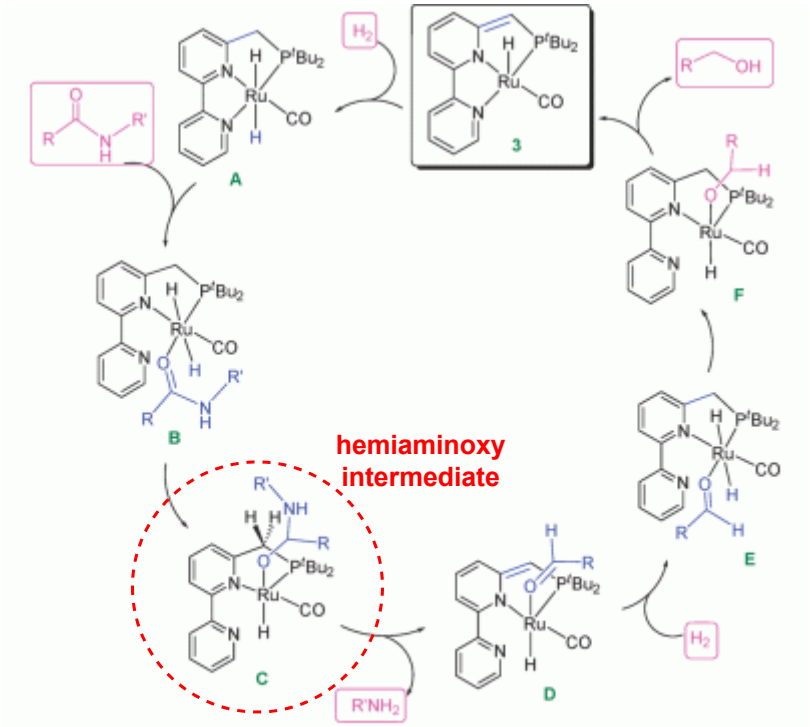
1

2

4

(the precursor of 3)

proposed mechanism by Milstein



Milstein postulated that key to the success of C-N cleavage is that it does not involve intermediacy of free hemiaminal, avoiding water elimination to give an imine.

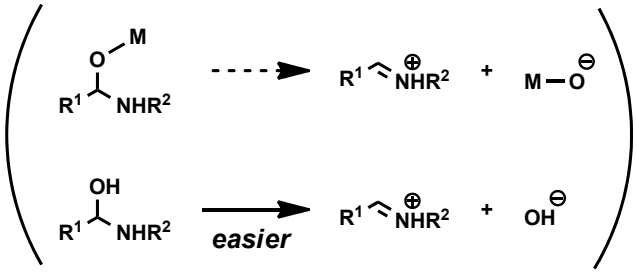


Figure 3. Postulated mechanism for hydrogenation of amides to amines and alcohols catalyzed by complex **3**.

♥ DFT analysis for the hydrogenation with Milstein's catalyst

D. Cantillo *Eur. J. Inorg. Chem.* 2011, 3008-3013.

***relative energies calculated at 298 K and 1 atm**

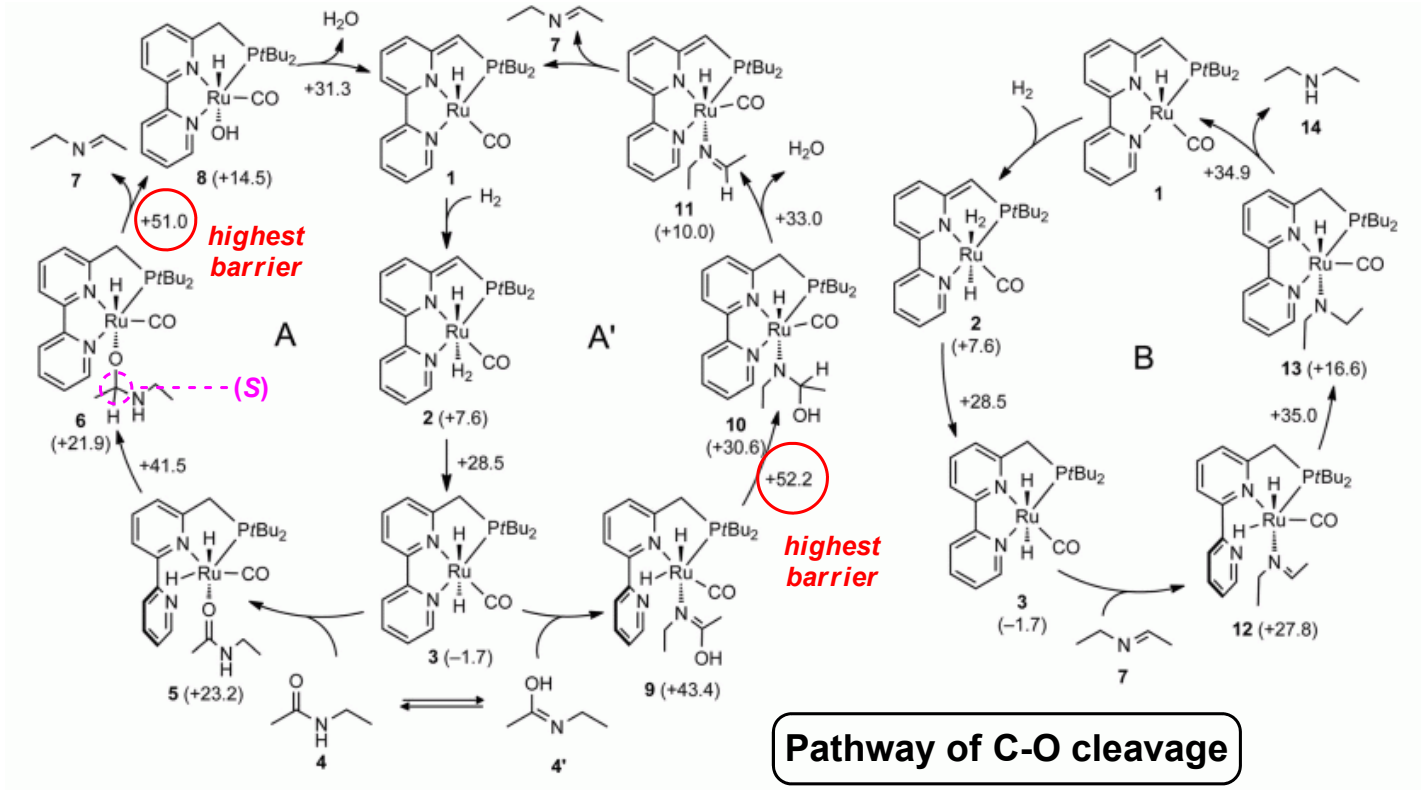
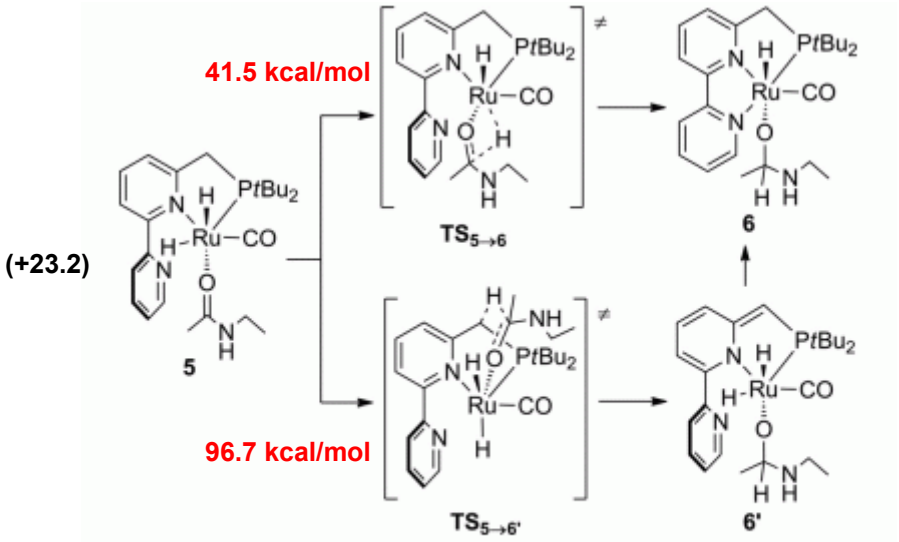


Figure 1. Proposed catalytic cycles for the hydrogenation of amides to secondary amines with C–O cleavage. In catalytic cycle A, imine **7** is released, and it is subsequently hydrogenated in catalytic cycle B. In catalytic cycle A′ addition of H_2 to **11** could give complex **12**, and thus cycles A′ and B could be depicted together. Relative free energies with respect to separate reactants (**1** + **4** + $2H_2$ = 0.0) for all the intermediates (in parentheses) and energy barriers (kcal mol^{-1}) are shown.

***equilibrium constant between 4 and 4': K ~ 10^{-8} (H. Sigel, R. B. Martin *Chem. Rev.* 1982, *82*, 385-426.)**

• **There are two possible pathways from 5 to 6:**



Scheme 2. Alternative pathways for the reduction of double bonds, exemplified by the reduction of intermediate **5**.

Dearomative hydride transfer to the carbonyl group cost higher energy.

↓

Hydride must come from Ru-H species.

Pathway of C-N cleavage

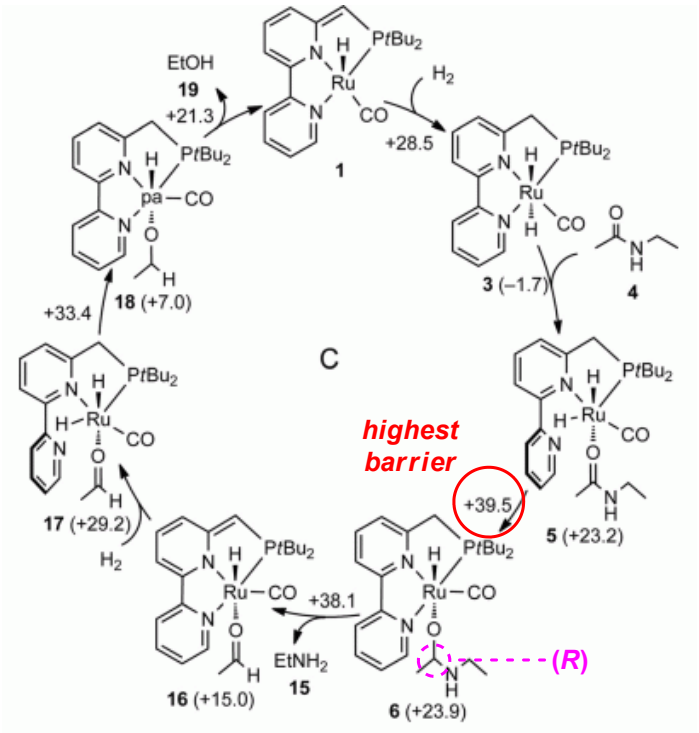


Figure 4. Catalytic cycle for the hydrogenation of amides to primary amines and alcohols with C–N cleavage proposed by Milstein and co-workers. Relative free energies with respect to separate reactants (**1** + **4** + 2H_2 = 0.0) for all the intermediates (in parentheses), and energy barriers (kcal mol^{-1}) are shown. The relative energies of **6** and the previous TS are different from those in catalytic cycle A, because cycles A and C follow different stereoisomeric pathways (see Supporting Information).

The highest energy barrier (39.5 kcal/mol) is lower than those in the catalytic cycles A and A' (51.0 and 52.2 kcal/mol, respectively).

↓

Pathway C is preferable during amide hydrogenation.

∗ Calculation at 110 °C and 10 atm gave the same order of the energy barriers for the pathway A, A' and C.

Table 1. Relative energies for the key transition structures involved in catalytic cycles A, A′, and C at the standard conditions and the experimental conditions employed by Milstein.[7]

	$\Delta G^{\neq}$ (kcal mol^{-1})	
	298 K, 1 atm	383 K, 10 atm
$TS_{6\to8}$	+51.0	+54.1
$TS_{9\to10}$	+52.2	+56.9
$TS_{5\to6}$	+39.5	+42.7

4. Summary

Various catalysts have been developed for hydrogenation of amides. Recent progress has enabled the hydrogenation under milder reaction conditions (160 °C, 100 bar) than primitive ones (250 °C, 300 bar), but they are still far from practical temperature and H_2 pressure (r.t. and 1 atm are ideal).

What revealed:

1. **Multimetallic catalysts, composed of oxophilic metal(s) and typical metal(s), are more effective than monometallic catalysts.**
2. **Some homogeneous catalysts can directly cleave the C-N bond in the amide moiety to give the corresponding alcohol and the amine.**
3. **DFT analysis by Cantillo discovered that hydride transfer to an amide or an iminol double bond had very high energy barrier (40 ~ 50 kcal/mol), likely being the rate-determining step.**

Remaining challenges:

1. **mild reaction conditions**
2. **substrate scope expansion**
3. **product selectivities (primary amides to primary amines, secondary amides to secondary amines, tertiary amides to tertiary amines)**
4. **functional group tolerance (aromatic rings must be tolerated; other carbonyl groups, unsaturated bonds, epoxides *etc.* should be tolerated)**
5. **cheap metal catalyst center**

reference:

R. Whyman *Chem. Rev*. 2014, *114*, 5477-5510. and the references therein

[EOF]