



Direct Amide Formation: The Issues, The Art, The Industrial Application.

- Why amides are important
- What is wrong with the current technology
- Catalytic technologies
- Insights into «uncatalysed» reactions

Syngenta is an Agribusiness

Crop Protection



Selective herbicides

Non-selective herbicides

Fungicides

Insecticides

Seed care

Seeds



Corn & Soybean

Diverse Field Crops

Vegetables

Lawn & Garden



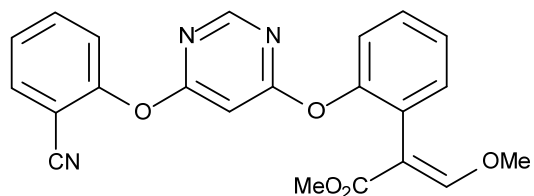
Flowers

Growing Media

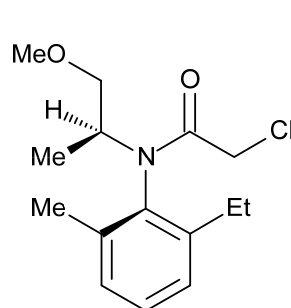
Chemical Controls

Turf & Ornamentals

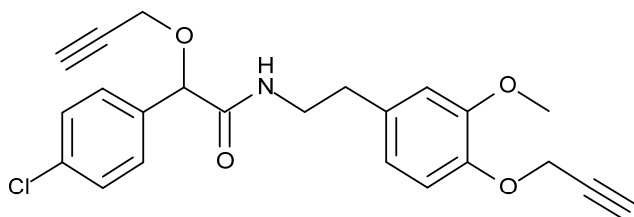
Syngenta manufactures over 400 active substances & intermediates



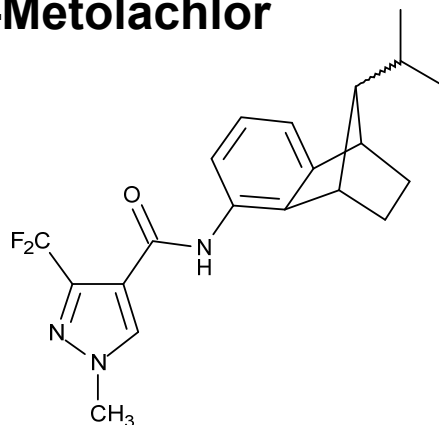
Azoxystrobin



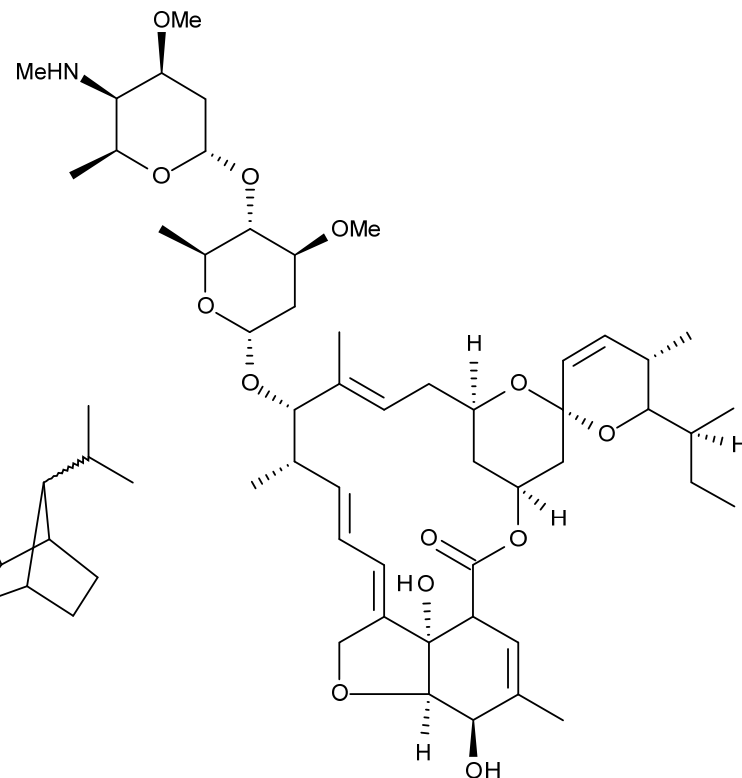
S-Metolachlor



Mandipropamid



Isopyrazam



Emamectin

Approximately 20% of our products are amides

The scale of manufacture is 20-100,000 tpa

	tpa
Oil Refining	10^6 - 10^8
Bulk Chemical	10^4 - 10^6
Fine Chemical	10^2-10^4
Pharma	10 - 10^3



Syngenta manufactures around the world

Raw
Materials



Energy



Water



Cost
Regulation

PRODUCTS



Waste

Solids

Liquids

Gases

5 to 50:1

Increasing environmental issues for manufacture are

- **Water** – quantity used, recycling, quality of release to the environment.
- **Energy** – strongly regulated use, higher cost, more efficiency, more sophisticated thinking.
- **Gas emissions** – Green-house gases (CO_2 , CH_4 , NO_x), Ozone depleters, Volatile Organics (VOC's), destruction.
- **Solid & liquid waste** – improved destruction methods; thermal & biological.
- **Metals** in waste.
- **Soil contamination** – decontamination & remediation.

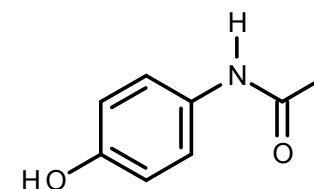
Amides are important in society

- Polypeptides

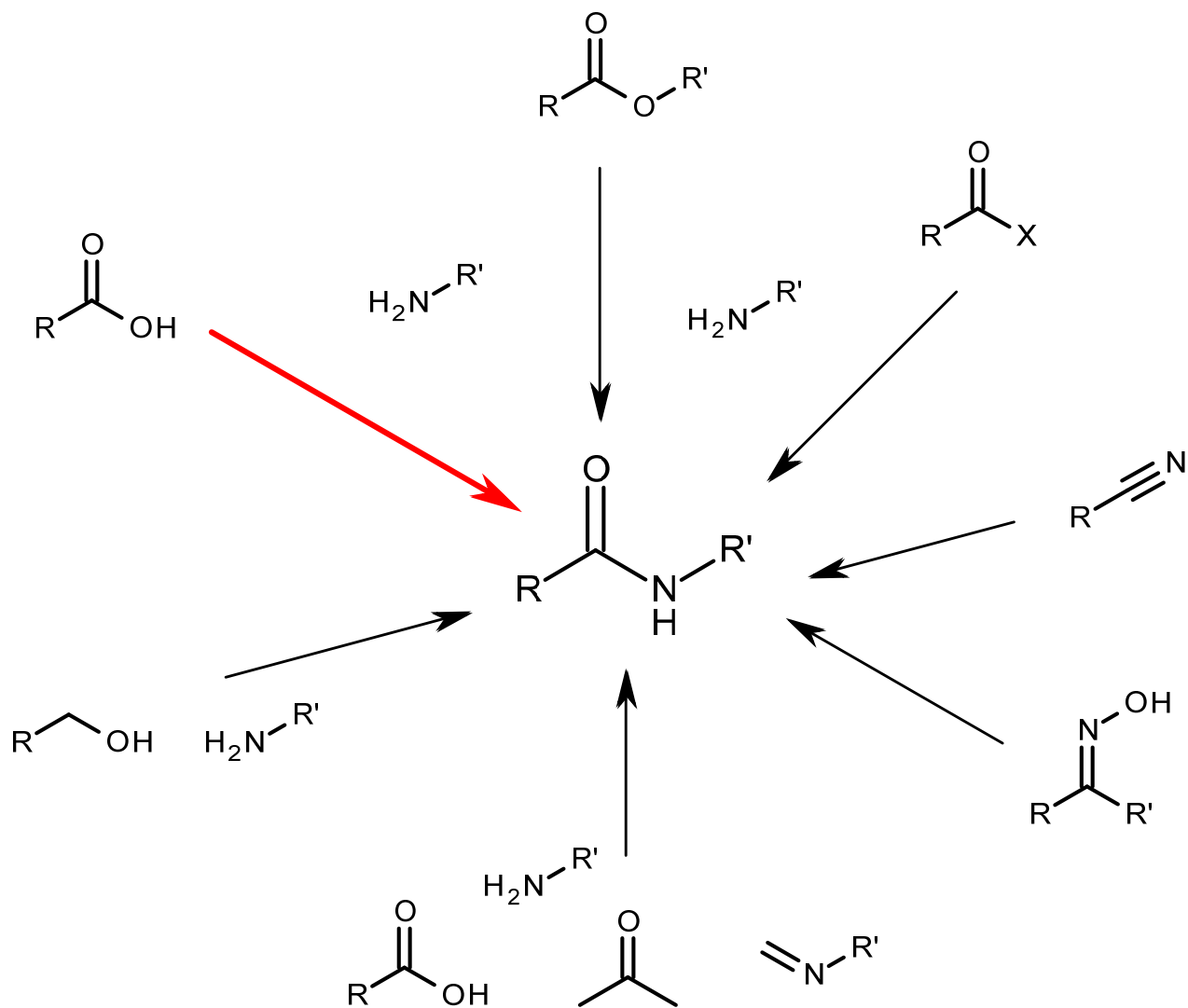
- Beef 58Mt in 2013 (USDA)
- Pork 100Mt
- Nylon 6 & 6,6 8Mt/a

- Chemicals

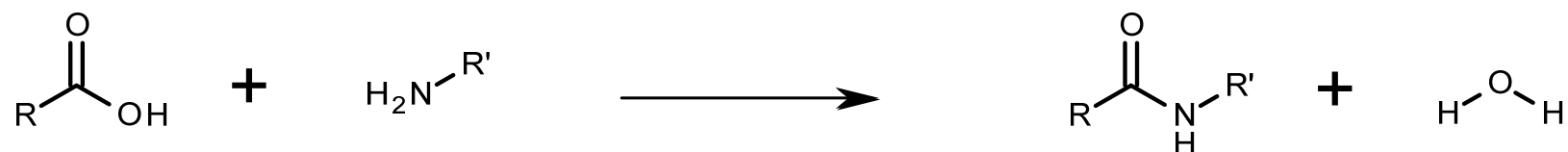
- N,N-Dimethylacetamide >100kt/a
- Fatty acid amides >10kt/a
- Paracetamol >50kt/a
- S-Metolachlor >30kt/a



Amides can be synthesised by many routes

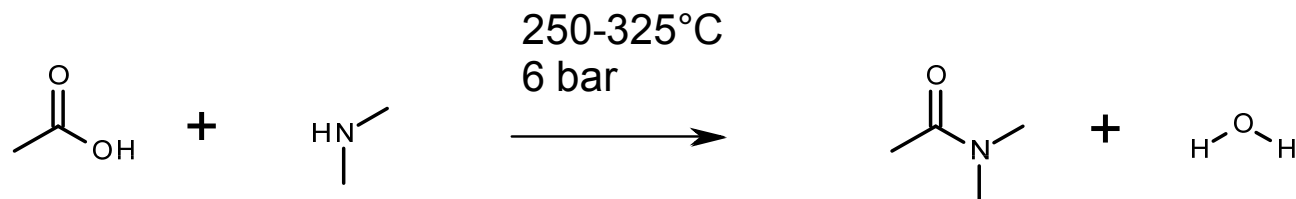


Direct amide formation is generally quite difficult



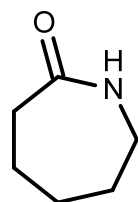
- ΔG +20-30kJ/mole (depending on the state)
- Salt formation
- Thermolysis (230 °C) of alkylammonium salts under pressure, 5-6 h (*Hofmann, Ber. 1882, 15, 977*)
- Overcome by acid activation – acid chlorides, anhydrides, e.t.c.

High temperatures are used industrially

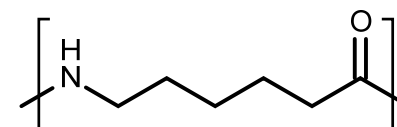


Downing US 366751 (1954)

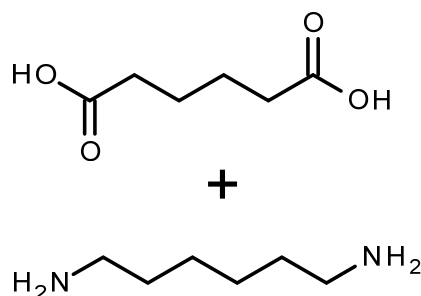
Campbell US 3006956 (1961)



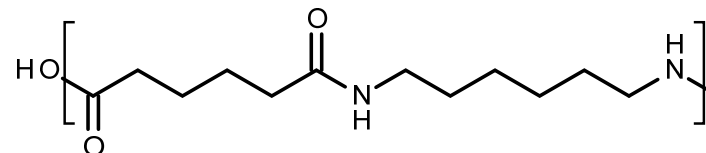
$>200^\circ\text{C}$



Nylon 6

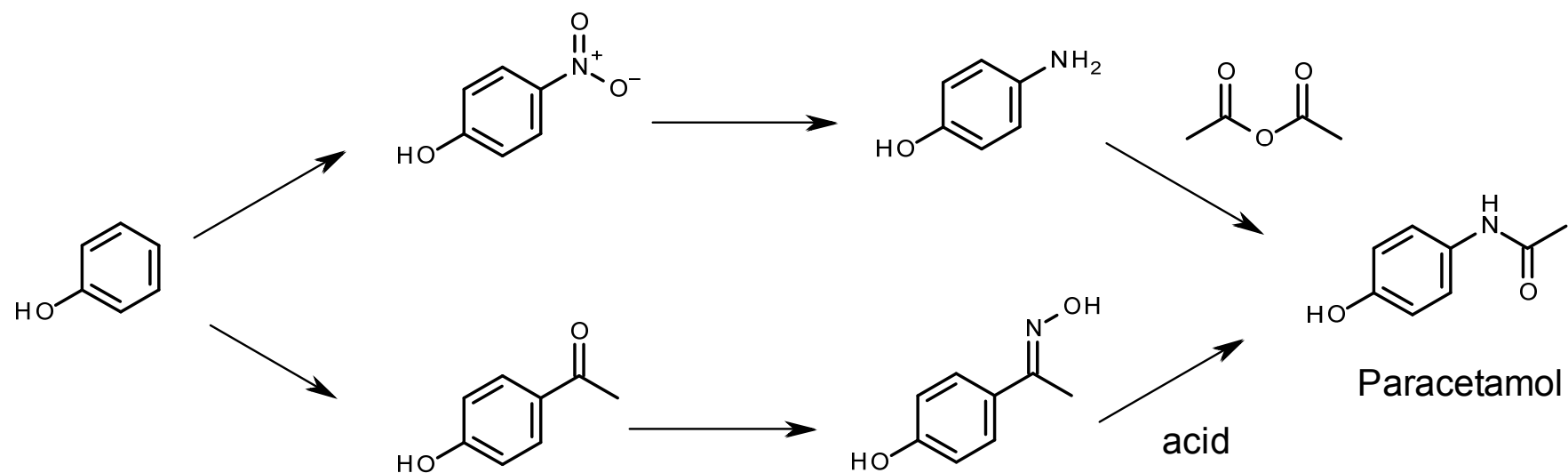


1) salt formation in water
2) drying
3) continuous thermolysis
250-300°C, 300 bar

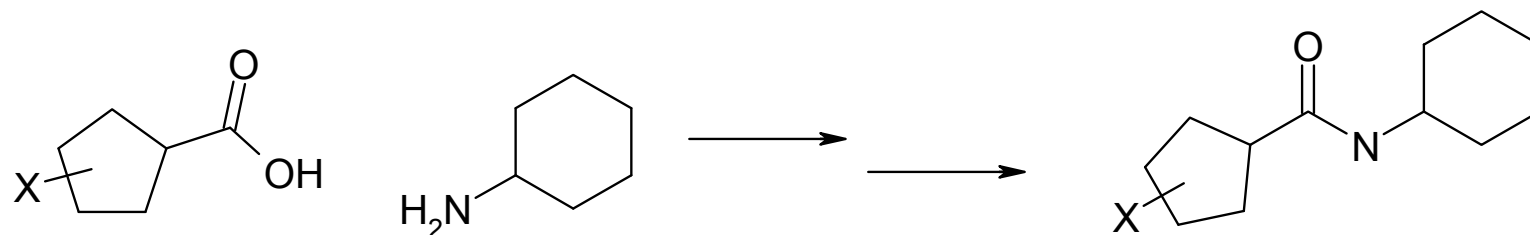


Nylon 6,6

Industry is sometimes flexible



Simple but dirty transformations....



Theory: loss of water equivalent to 0.1 waste/t product

1) COCl_2 or SOCl_2 in solvent

Wash acid gases

2) Amination, auxiliary base

3) Aq. Work-up

Waste as tonnes per annum/1000tpa product

- Yield 95%, loss 50tpa
- Chlorinator (CO_2 , SO_2) 250tpa
- NaCl waste ($\text{NaOH} + \text{HCl} \rightarrow \text{NaCl}$) 600tpa
- Auxiliary base recycle 25tpa
- Solvent 4000tpa (50tpa after recycle)
- Water 5000tpa (\rightarrow bio treatment)

Challenges for global agriculture

- Huge rise in demand
- Limited farmland
- Limited water supplies
- Need to continue raising yields

Grow more with less in an environmentally sustainable way



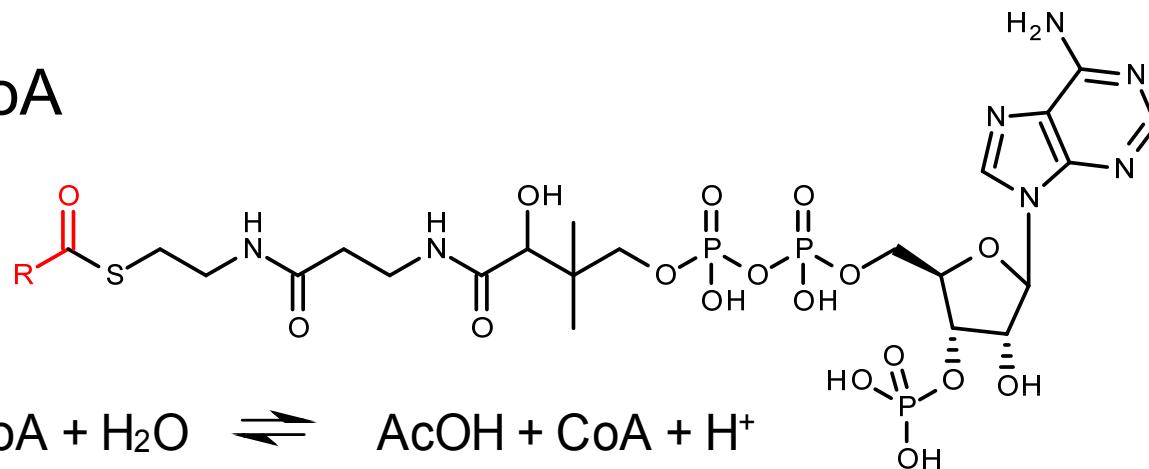
This also includes manufacture



What about amides !!!

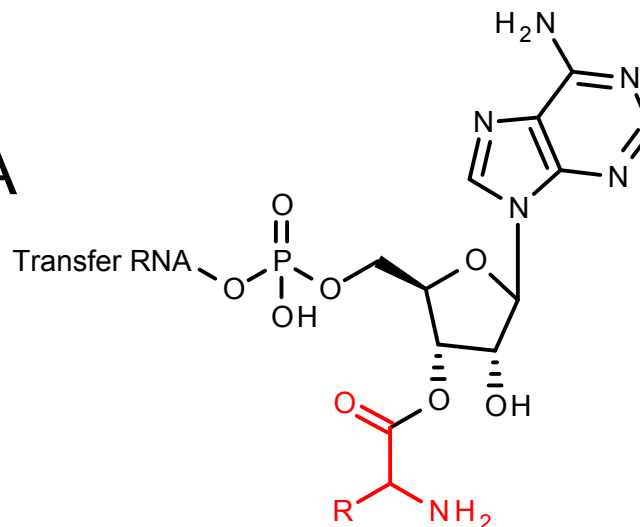
Nature does it by acyl activation

Acyl CoA

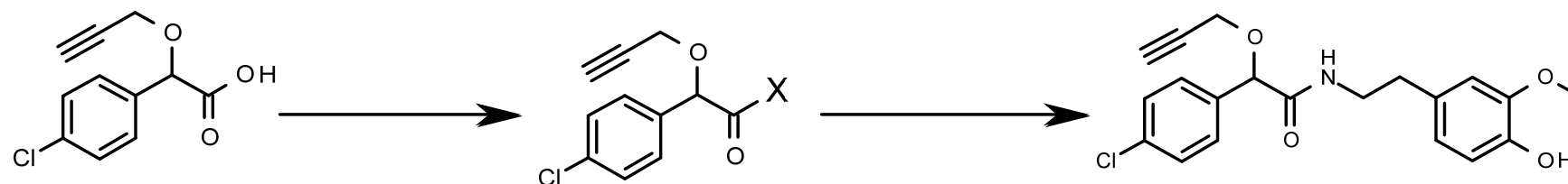


$$\Delta G = -31 \text{ kJ/mole}$$

Aminoacetyl-transfer-RNA



Mandipropamid uses activation



- Two steps
- Activating group cannot be recycled
- Martin Bowden & Alexander Saint-Dizier (2006) – How can we do this in a single step with a minimum of reagents, solvents and energy?

There are basically 3 types of catalysis for direct amide formation

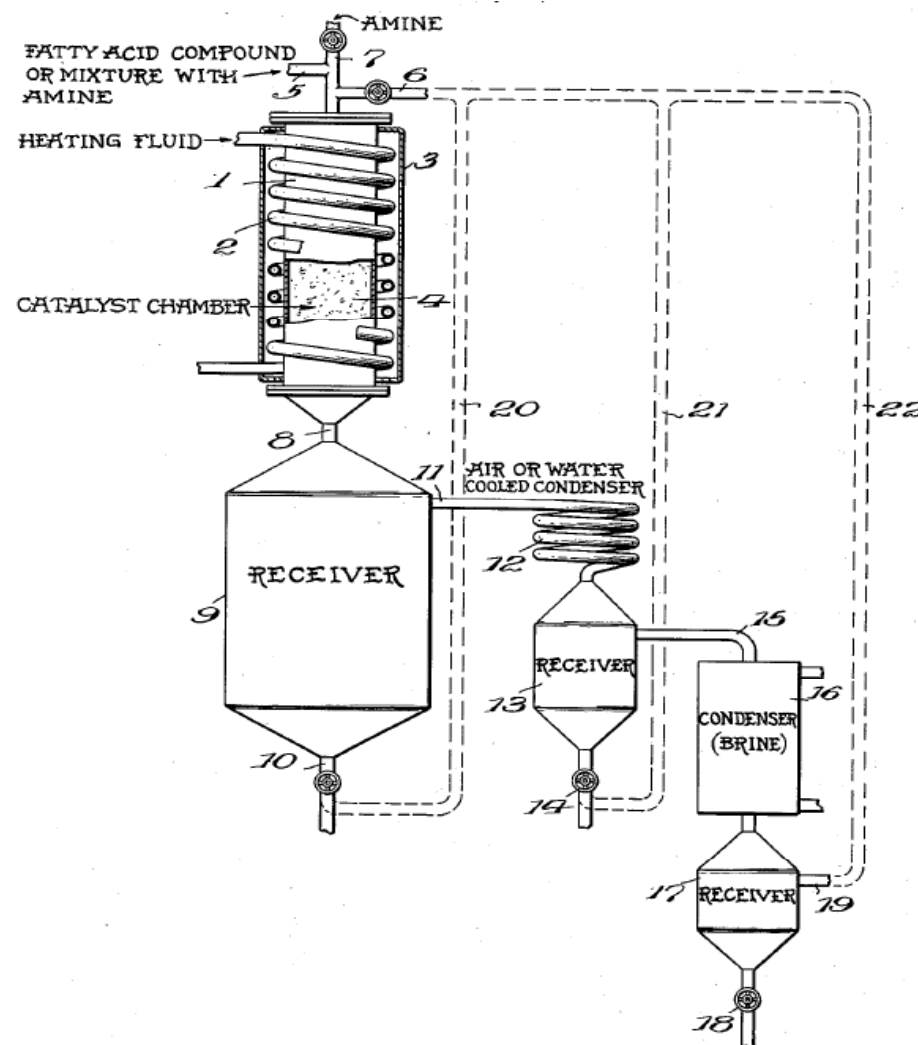
- Acid catalysis: e.g. Lewis acids, metal salts, zeolites
- Activated acyl formed in-situ: e.g borates
- Biocatalysis

Acid catalysis: Was described in 1932

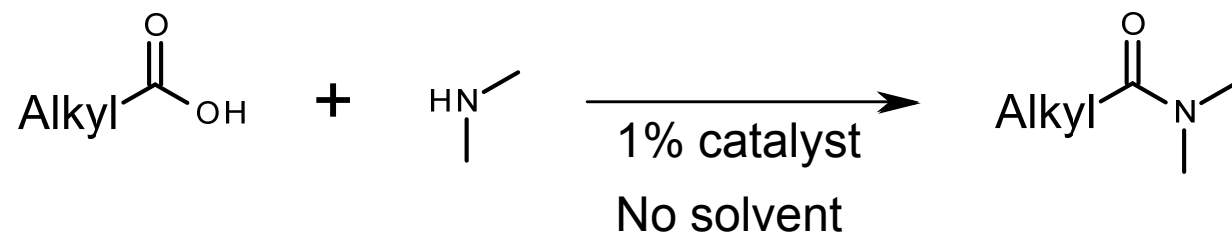
Oleic acid + Aniline
Over Alumina at 500°C
Continuous process

Ralston, US1991956 (1935)

I.G. Farben, US 2013208 (1932)



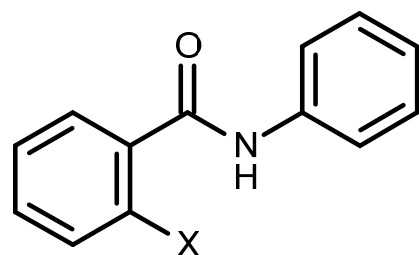
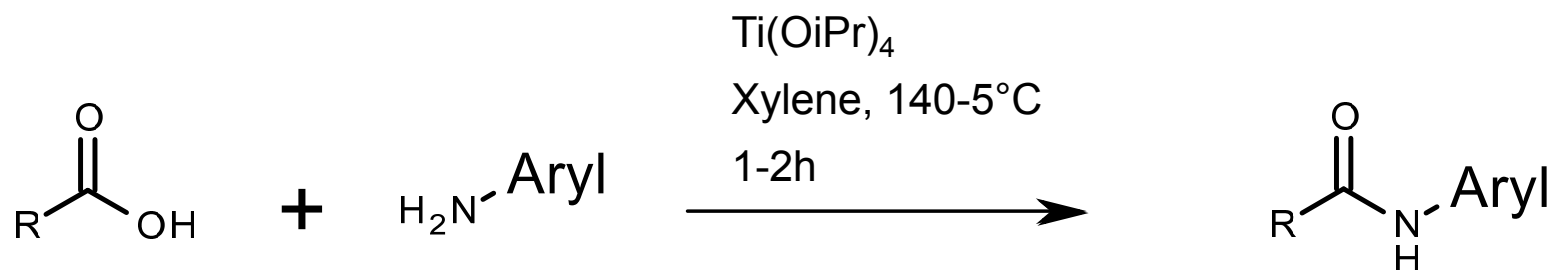
Use of metal derivatives in 1974: Zr, Ti



Acid	Catalyst	°C	h	% Yield
Oleic	Zr(OiPr) ₄	195	5	98.5
Oleic	Zr(OiPr) ₄	150	12	97.7
Oleic	Ti(OiPr) ₄	195	5	99.4
Myristic	Zr(OiPr) ₄	195	6	99.4
Oleic	Alumina	195	10	98.5
Oleic	H ₃ BO ₃	195	9	97.3

Weiderhausen, US 3801610 (1971), Henkel

Greater synthetic diversity is demonstrated

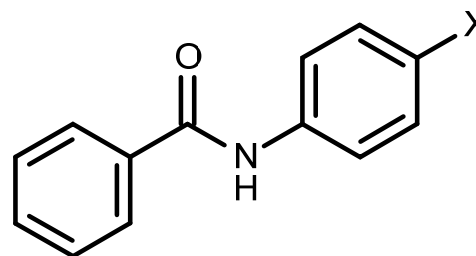


X =

H 85%

Br 98%

OMe 18%



X =

H 85%

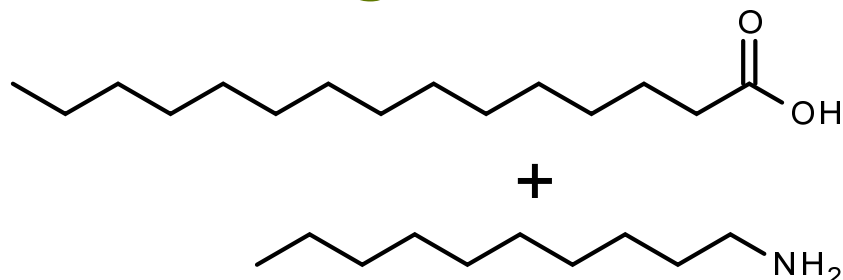
NO₂ 25%


OMe 69%

Shteinberg Zh Org Chim (1988) 1968 & (1989) 1945.

Lactams: Maddar, Tet Lett., (1988) 3049

A wide range of metals have been tested




 Mesitylene (0.15M)
 Reflux, - Azeo
 Catalyst (0.12 eq)

Amide

Catalyst	% Yield after 6h	% Yield after 24h
None	20	20
ZnCl ₂	80	90
CuCl ₂	50	70
NiCl ₂	75	90
CoCl ₂	65	85
MnCl ₃	70	95
CrCl ₃	60	80
ZrOCl ₂	50	65
InCl ₃	40	50
AlCl ₃	25	65
FeCl₃	80	95

Also:

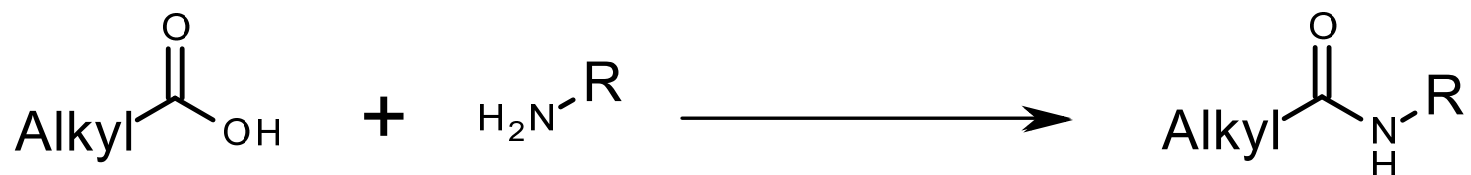
- Benzene, toluene, xylene
- Counter ions
- Chain lengths

Terada, Synthesis (2008) 2318.

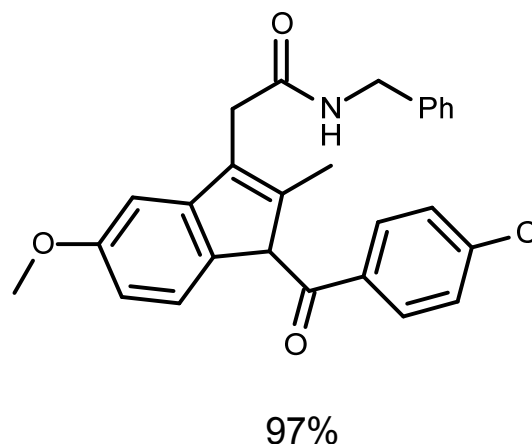
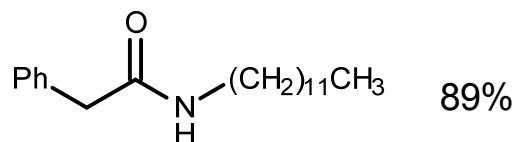
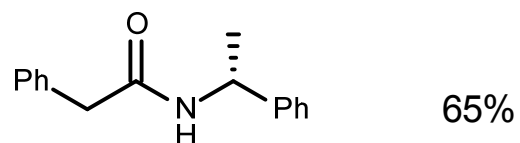
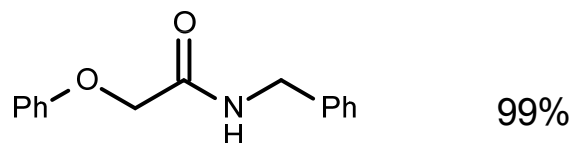
Do not forget about azeotropes

	Boiling Point °C	Boiling Point of Azeotrope °C	Water in Azeotrope
THF	67	64	5%
Benzene	80	69	91%
Toluene	110	84	80%
Chlorobenzene	132	90	30%
M-Xylene	139	94	40%
Mesitylene	165	97	<50% ?

Use of ZrCl_4 in THF



0.4M in THF, catalyst 5-10 mole%, 4A mol-sieves (500g/mole), sealed tube at 70°C, 24h.



Adolfsson, Chem Eur J, (2012) 3822

Ti(OiPr)₄: Adolfsson, Synlett, (2012) 2201

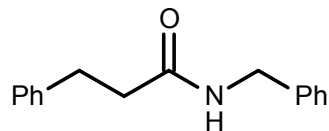
Also tested: $\text{Zr}(\text{OEt})_4$, $\text{Zr}(\text{OtBu})_4$

No cat: no/little conversion

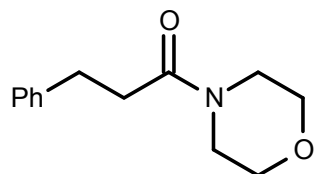
No MS: no/little conversion

Use of Zr in toluene

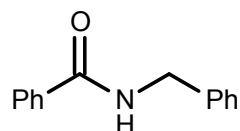
1M in toluene, catalyst 5 mole%, sealed tube at reflux !!?.



ZrCl₄ 5h 100%

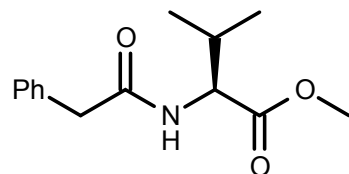


Zr Cp₂Cl₂ 24h 100%

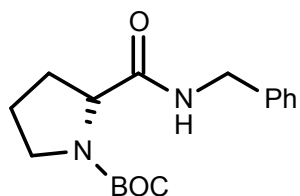


ZrCl₄ 25h <50%

Zr Cp₂Cl₂ 22h 83%



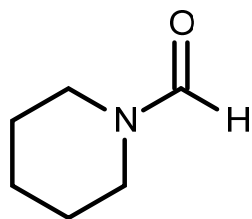
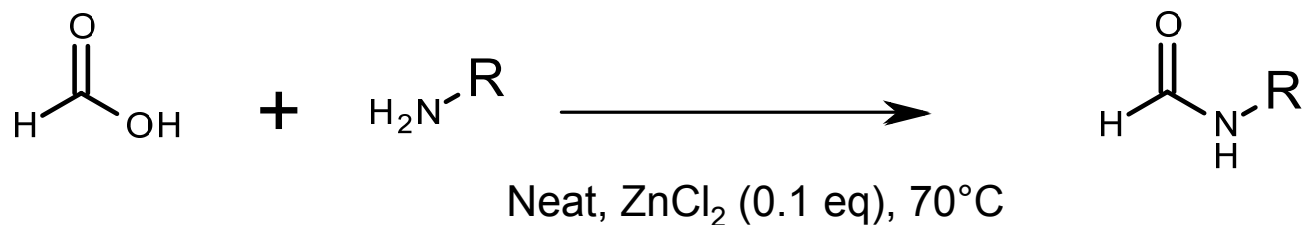
ZrCl₄ 12h 100%



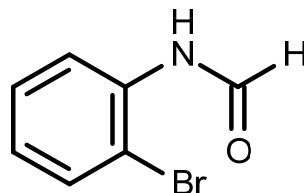
ZrCl₄ 22h 64% (99% ee)

Williams, Chem Com. (2012) 666

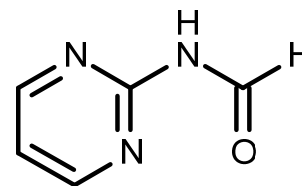
Formylations are also possible



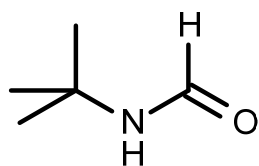
4h, 80%



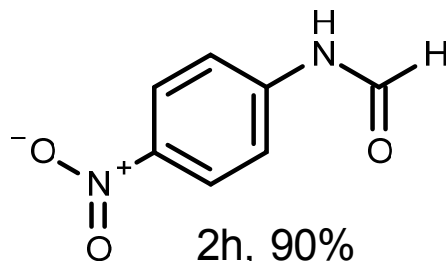
1.5h 80%



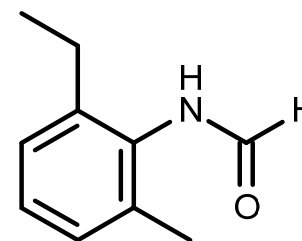
0.5h, 96%



1h, 60%



2h, 90%

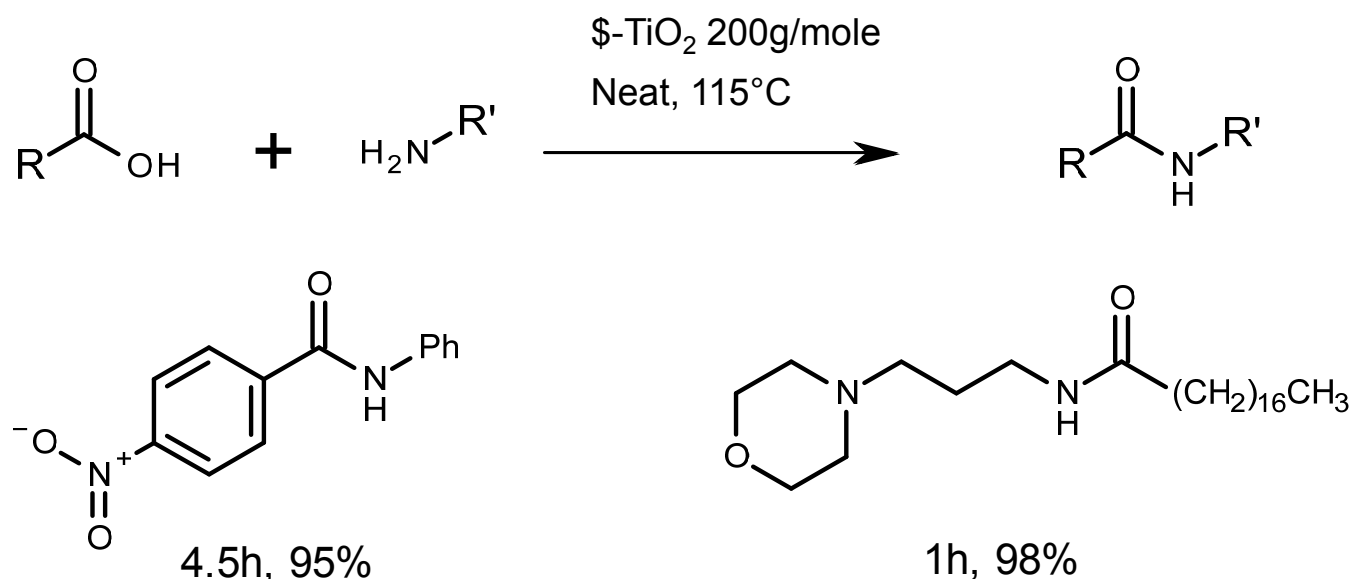
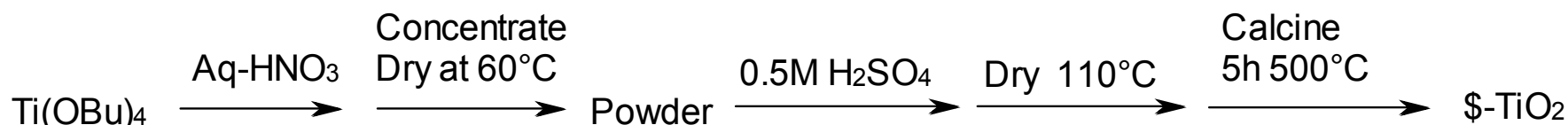


1h, 80%

Shekhar, Tet Letts., (2009) 7099

Solid separable catalysts are demonstrated

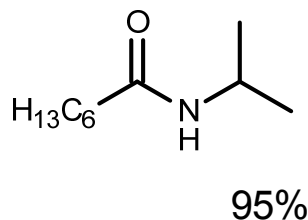
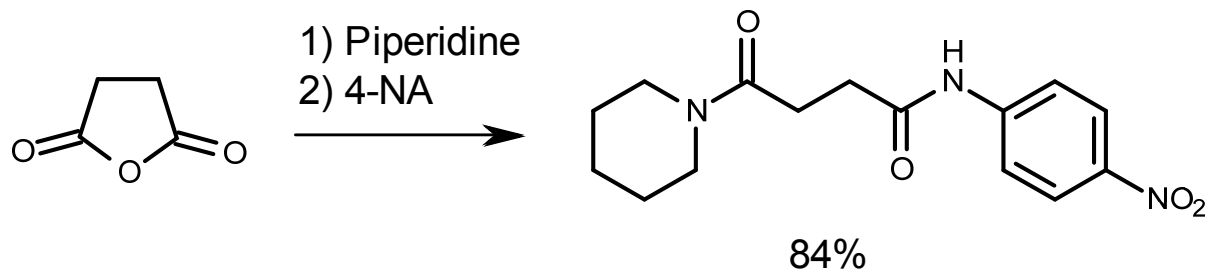
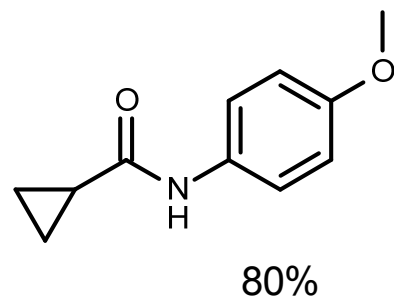
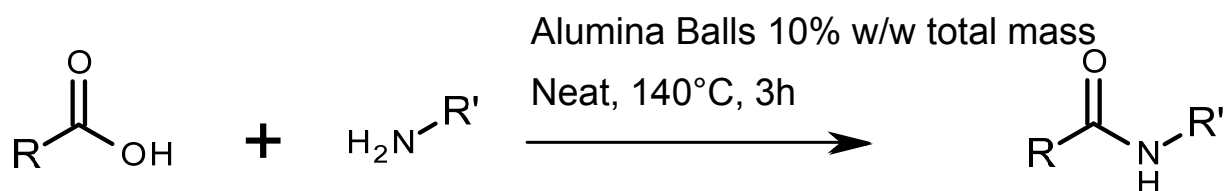
Nanosized sulphated titania (sol-gel, 218m²/g)



Hosseini-Sarvari, J. Org. Chem., (2011) 2853.

Solvents were detrimental to rate

Solid catalysts – Alumina Balls



Mukhopadhyay, Green Chem., (2012) 3220

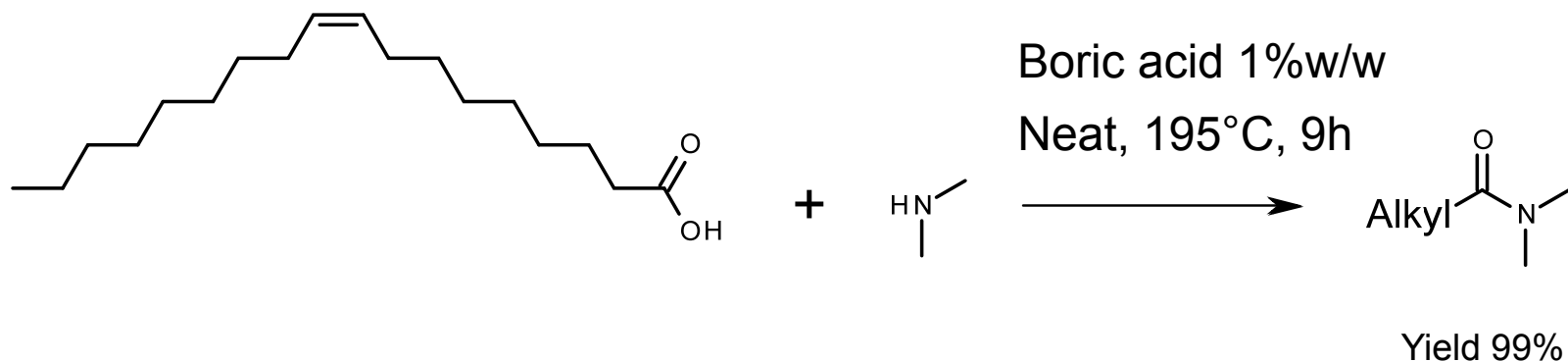
See also:

Silica: Clark, Chem Comm., (2009) 2562

Zeolites: Kulkarni, Green Chem., (2006) 368

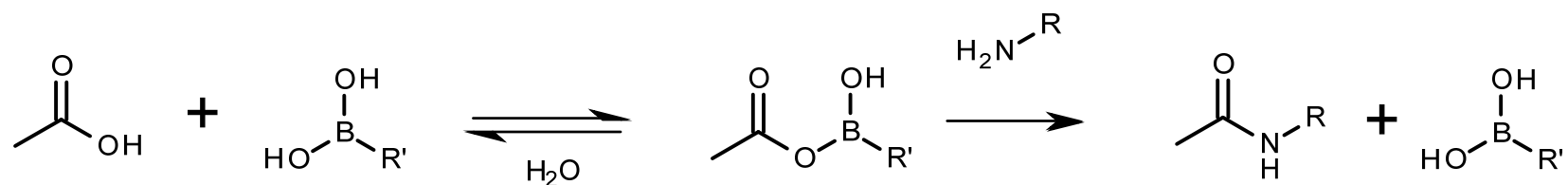
Borates:

Boric acid has been used for over 40 years



Weiderhausen, US 3801610 (1971), Henkel

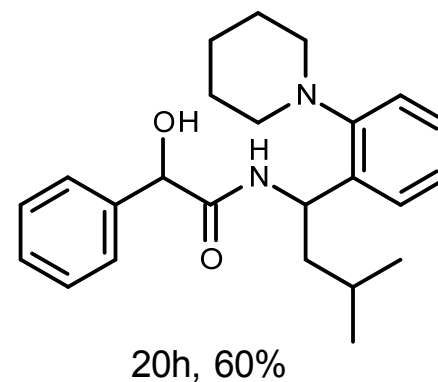
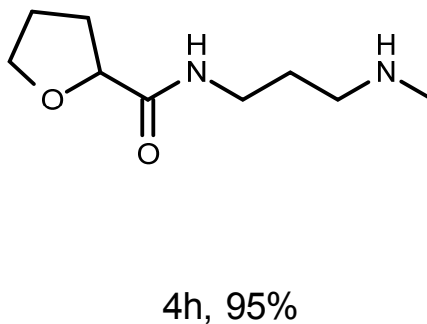
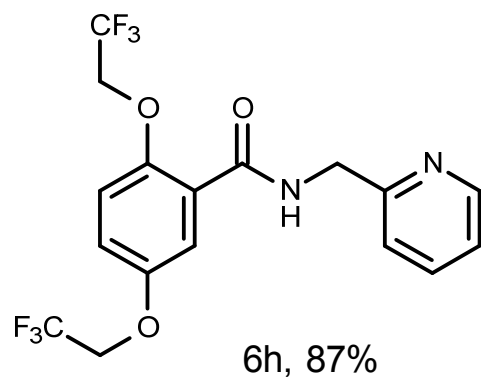
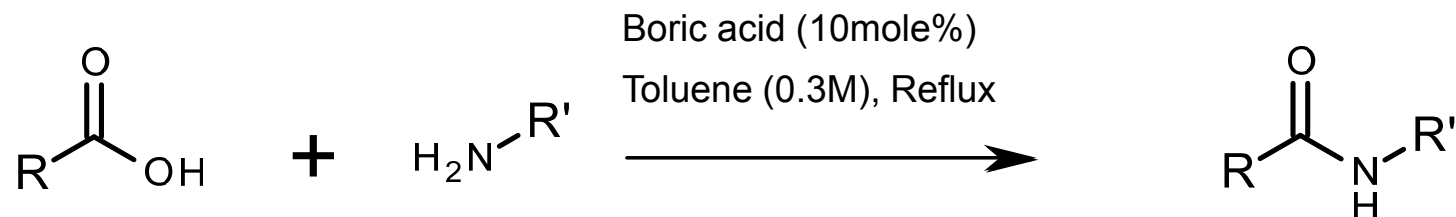
Borates probably work by acyl activation



$\text{R}' = \text{OH, Alkyl, Aryl}$

For a discussion of mechanisms see: Charville, Chem. Commun., (2010) 1813

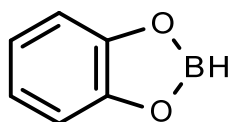
Boric acid is now more popular



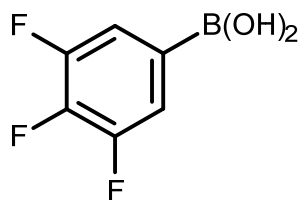
Kumar, OPRD., (2007) 1065

Improvement in boron reagents

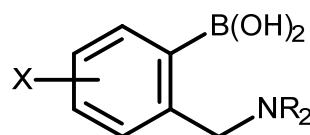
Pelter, Ganem, Yamamoto, Ishihara, Whiting, Hall, and many others



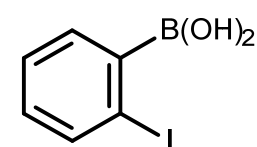
1978



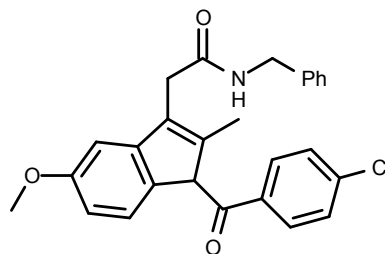
1996



2006



2008

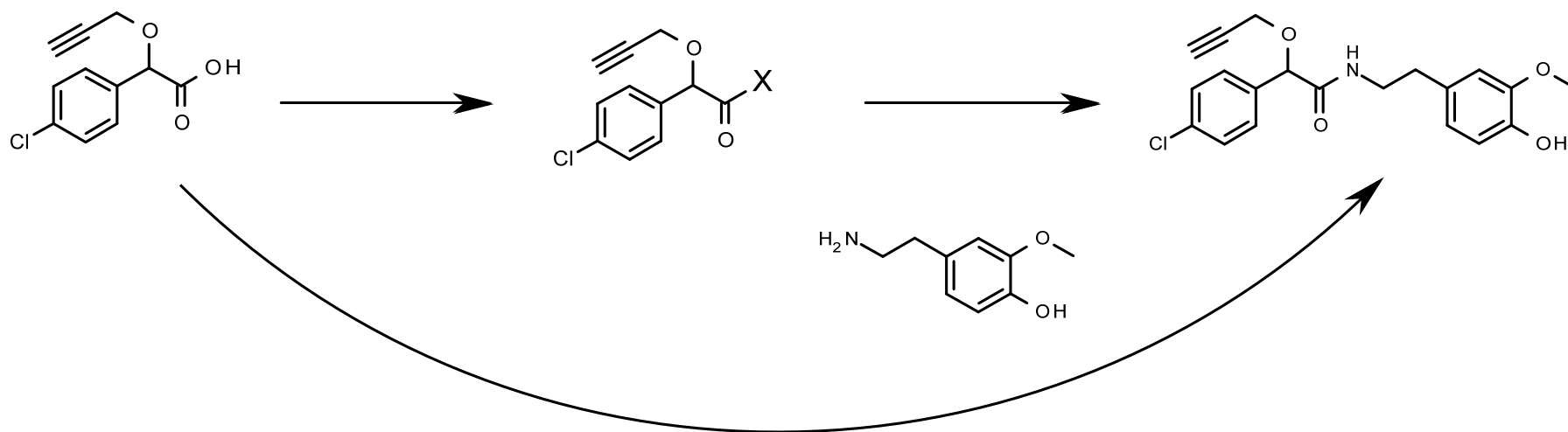


Hall (2008): 2-I-PhB(OH)₂ (0.1eq), 4A-MS, CH₂Cl₂ (0.07M), 25°C, 48h, yield 93%

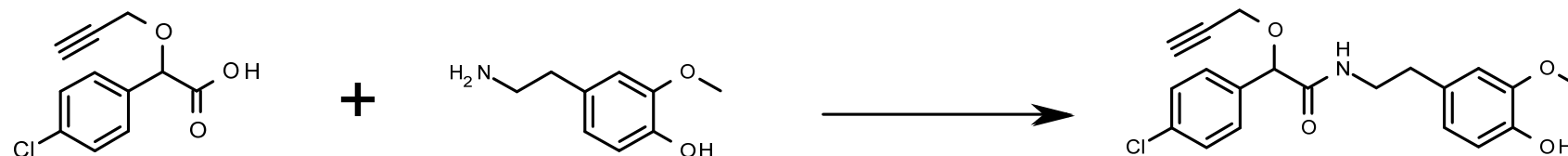
Adolfsson (2012): ZrCl₄ (0.1eq), 4A-MS, THF (0.4M), 70°C, 24h, yield 97%

Charville, Chem. Comm., (2010) 1813

We have applied this learning to identify new processes for manufacture



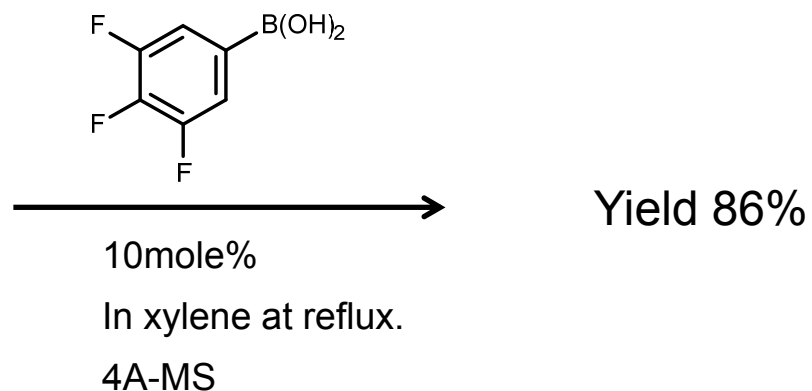
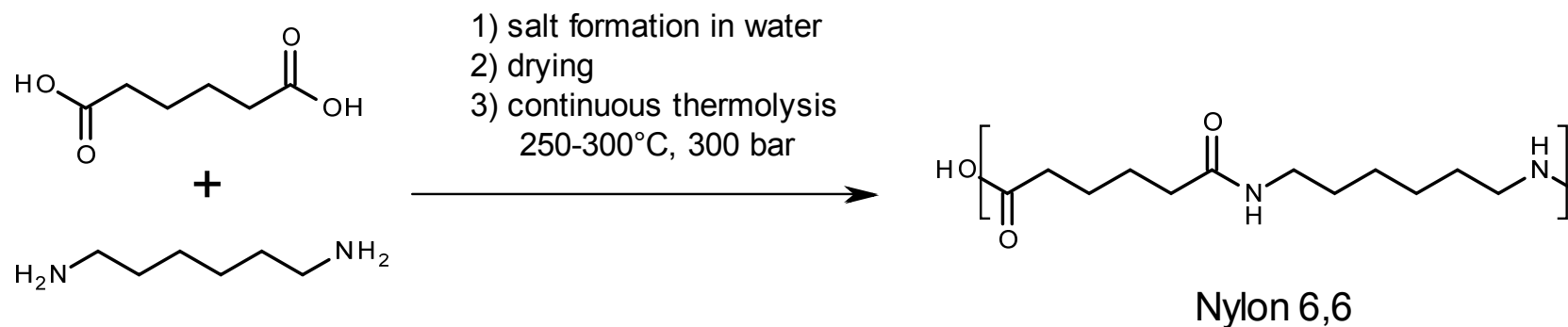
We have found interesting reactions



	Catalyst	3A-Mol-sieves	h	% Yield
Cl-Benzene	PhB(OH) ₂	Yes	6	32
Xylene	PhB(OH) ₂	Yes	1	96
Xylene	PhB(OH) ₂	none	6	85
Xylene	Boric acid	none	6	14
Xylene	none	Yes	4	83

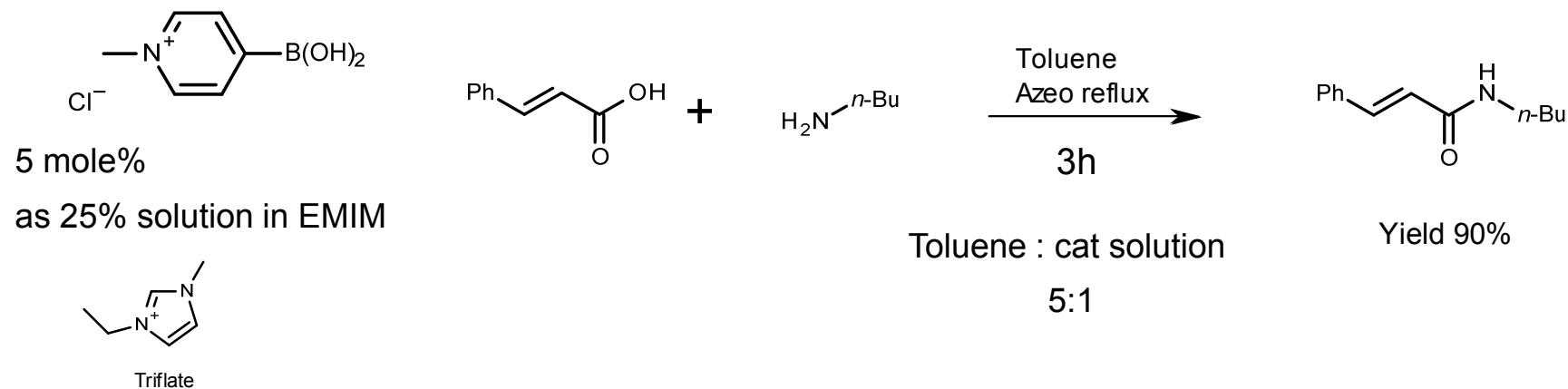
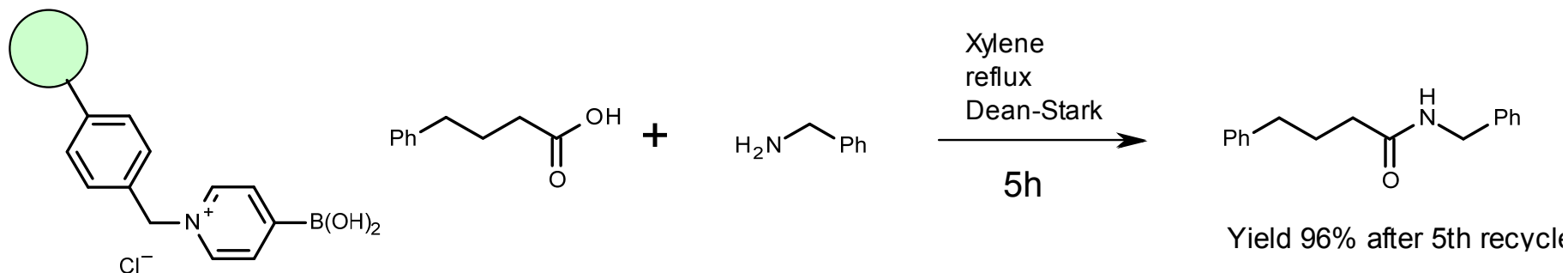
Bowden, WO 138372 (2009), Syngenta

Catalysis for nylon production



Yamamoto, Macromolecules (2000) 3511.

Recyclable boron catalysts are also known

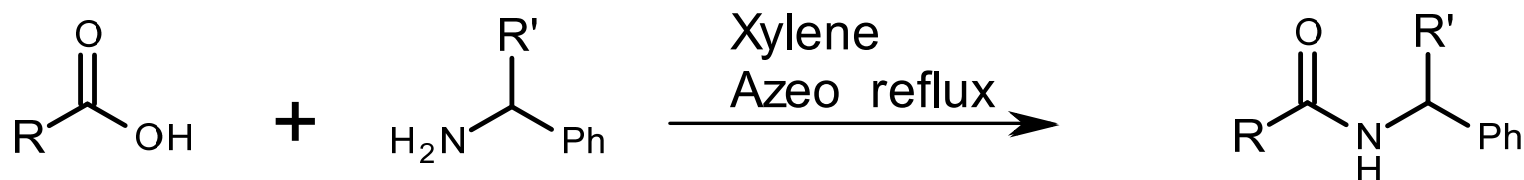


Yamamoto, Org Lett (2005) 5043.

Ishihara, Tetrahedron (2009) 1085.

Why do we need catalysis?:

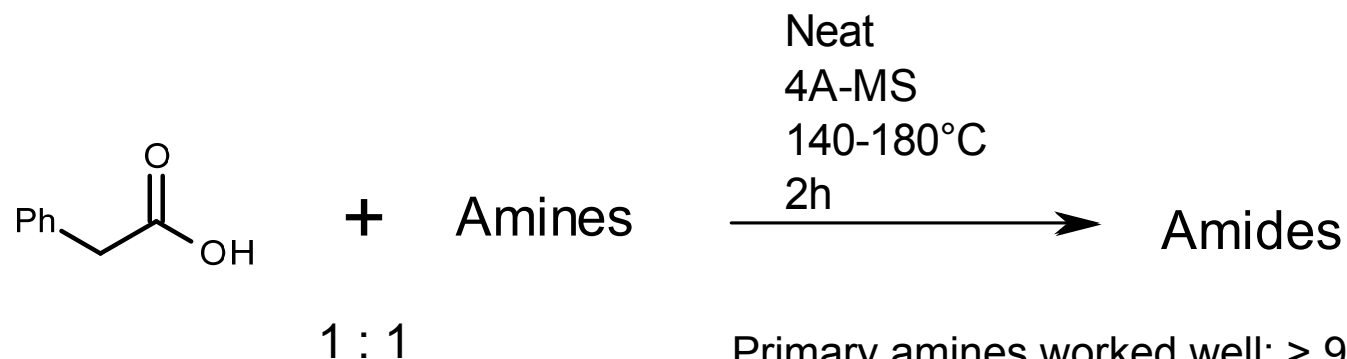
There are some surprisingly easy reactions



Acid	R'	h	% Yield
Isostearic	C ₅ H ₁₁	55	83
Linoleic	C ₁₅ H ₃₁	40	79
Arachidonic	C ₁₀ H ₂₁	58	74
Linoleic	C ₅ H ₁₁ (d)	55	85
Linoleic	C ₅ H ₁₁ (l)	55	86

Suzuki, US 3950057 (1971), Sumitomo.

First studies



Primary amines worked well: > 90% yield.

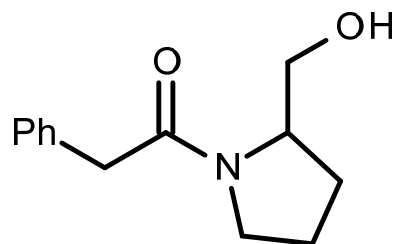
Morpholine failed.

Pyrrolidine 98% yield

Anilines were moderate

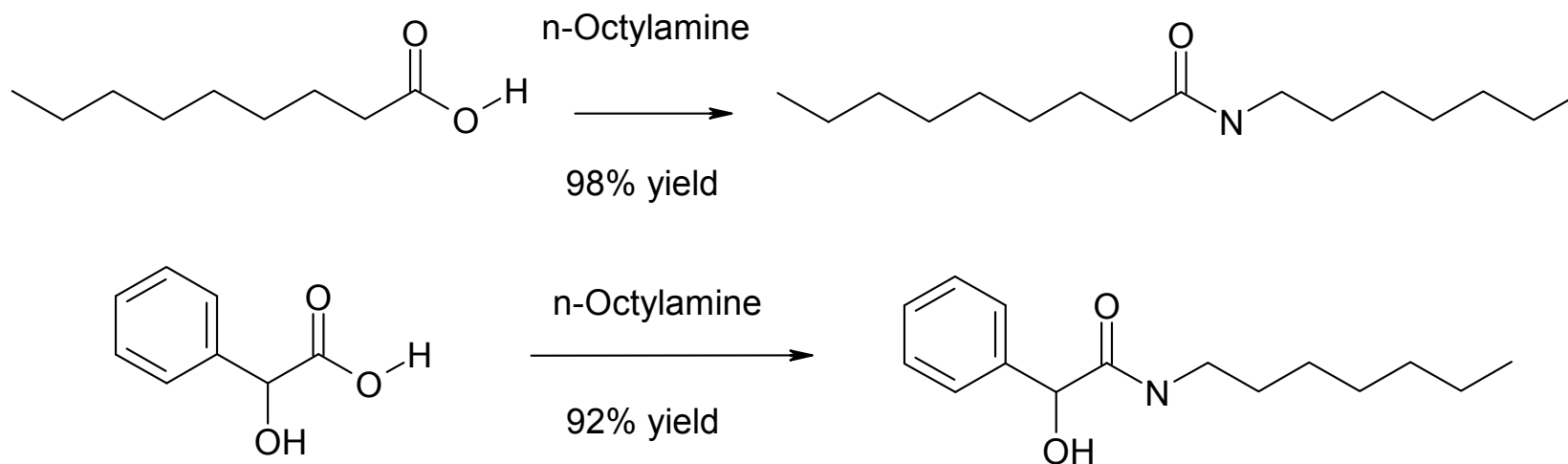
Amino-alcohols >90% yield

Acids – not many examples



Cossy, Tet Lett., (1989) 2771.

Simple heating of acid + amine ...

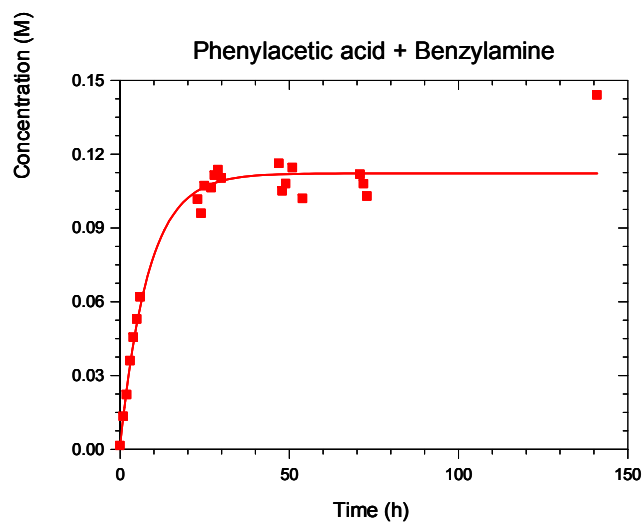
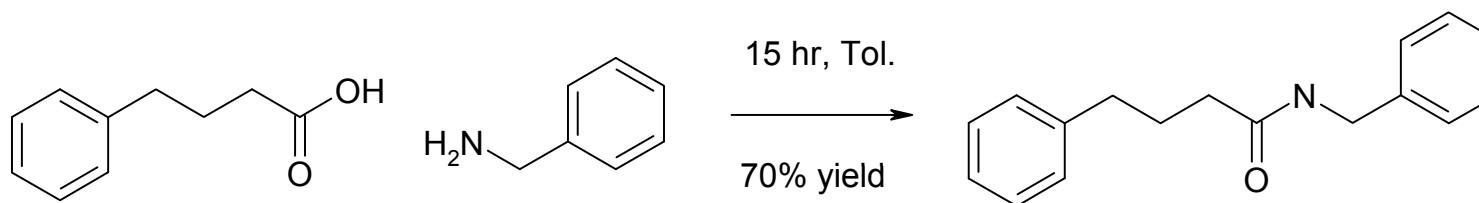


160-180 °C, 10-30 mins., water removal essential

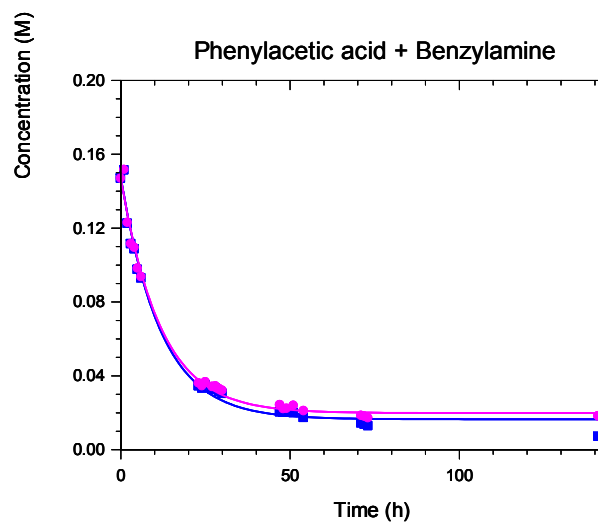
Not all amides can be made this way → decomposition, tar

Jursic, *Synth. Commun.*, (1993) 2761.

A surprisingly easy reaction – why ??



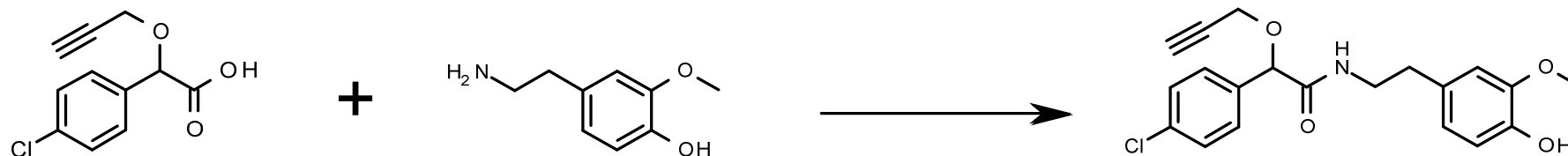
Amide Final LC yield = 97 %
Isolated yield = 82%



Benzylamine
Phenylacetic acid
 $k = 0.0857 \text{ h}^{-1}$

Whiting, Adv. Synth. & Cat., (2006) 813

We also noted



	Catalyst	3A-Mol-sieves	h	% Yield
Cl-Benzene	PhB(OH) ₂	Yes	6	32
Xylene	PhB(OH) ₂	Yes	1	96
Xylene	PhB(OH) ₂	none	6	85
Xylene	Boric acid	none	6	14
Xylene	none	Yes	4	83

Bowden, WO 138372 (2009), Syngenta

Later: 3A-MS, Goosen, Synthesis (2009) 160.

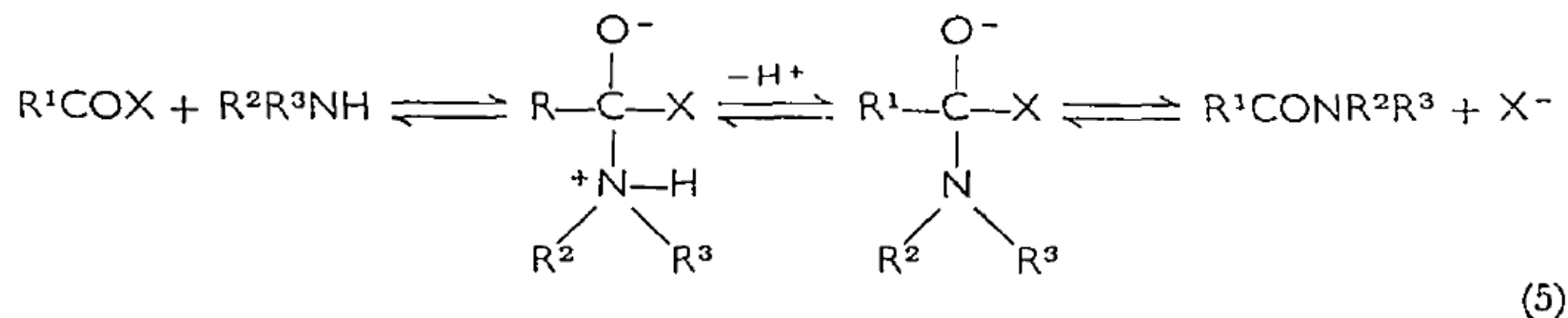
Neat, Williams, Chem. Commun. (2012) 666.

We looked for explanations

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A. L. J. Beckwith

acylation, mechanism (3) must include a step involving loss of a proton from nitrogen and then is most simply represented as equation (5).

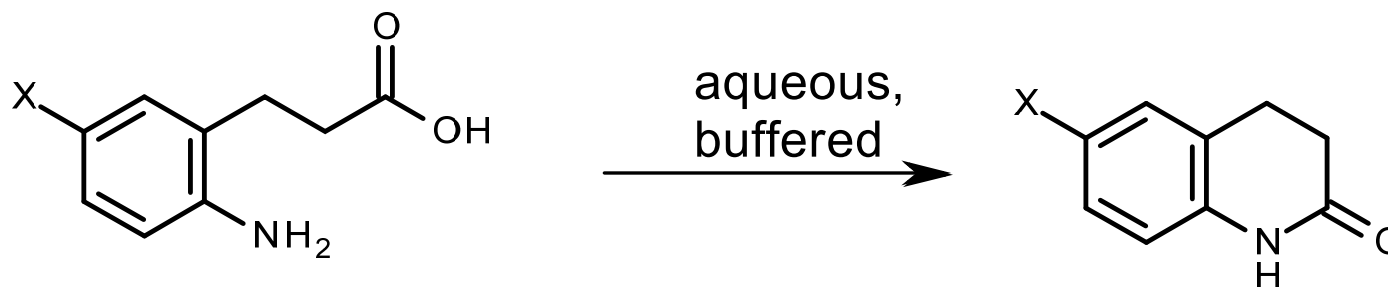


The Chemistry of amides

Edited by Jacob Zabicky

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Later studies of lactams clarified requirement for nucleophile & electrophile



X = H, Me, OMe, Cl

«requires significant [NH₂] and [CO₂H] or [CO₂H⁺]
..... requires similar pK_a of –NH₂ and –COOH»

Kirby, J. Chem. Soc. P1 (1979) 1610 & 1617.

Direct Amide formation – refluxing toluene, removal of azeotrope, 48h

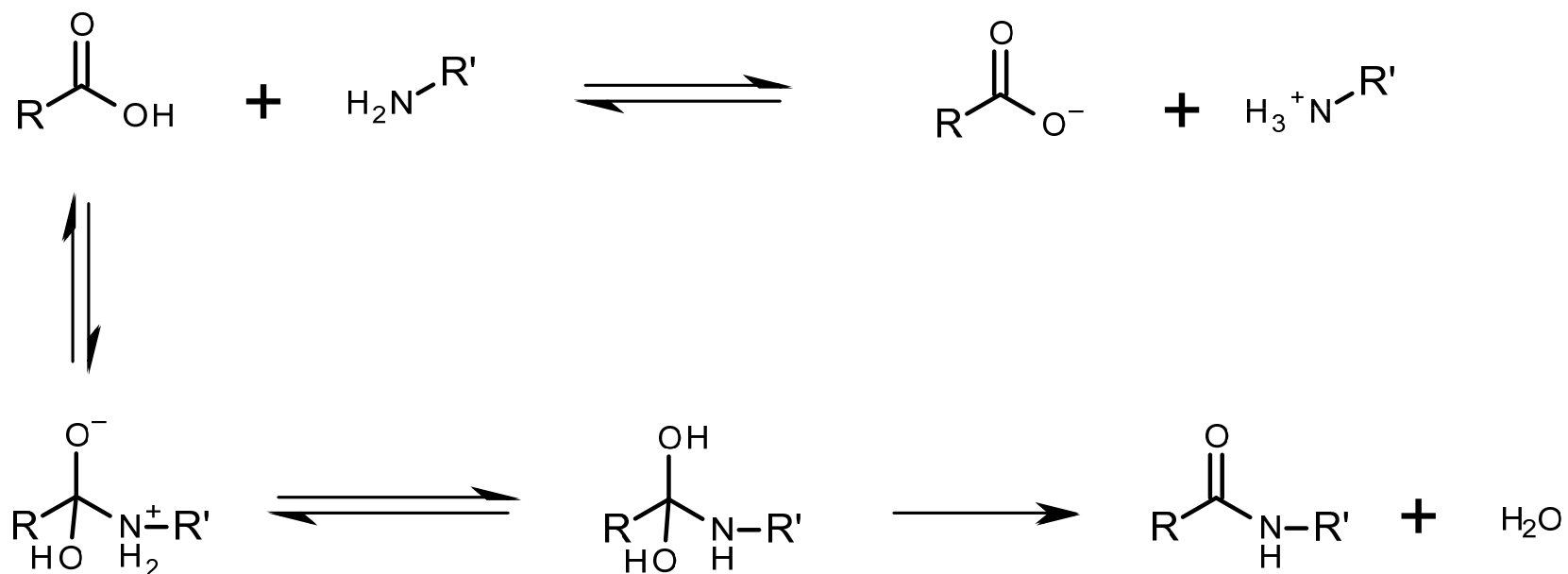
Carboxylic acid (pK _a)	Amine	Yield (%)		
		pK _a	Uncat.	H ₃ BO ₃
Bromoacetic acid (2.69)	Benzylamine	9.33	0	0
	<i>t</i> -Butylamine	10.83	0	0
	2- methoxyethylamine	9.89	0	0
	Piperidine	11.12	0	0
	Aniline	4.63	0	0
Phenylbutyric acid (4.76)	Benzylamine	9.33	64	89
	<i>t</i> -Butylamine	10.83	< 1	3
	2-Methoxyethylamine	9.89	54	70
	Piperidine	11.12	24	80
	Aniline	4.63	4	74
Benzoic acid (4.18)	Benzylamine	9.33	14	86
	<i>t</i> -Butylamine	10.83	0	0
	2-Methoxyethylamine	9.89	5	24
	Piperidine	11.12	10	49
	Aniline	4.63	0	35

Charville, Eu. J. Org. Chem., (2011) 5981.

Some of our observations for reactions without an added catalyst

- Need an apolar solvent
- Water must be removed
- Sometimes does not go to completion
- Product amide does not inhibit reaction
- <20% Rate enhancement from excess amine or acid
- Complete salt formation blocks the reaction
- Addition of Na-carboxylate slows the reaction

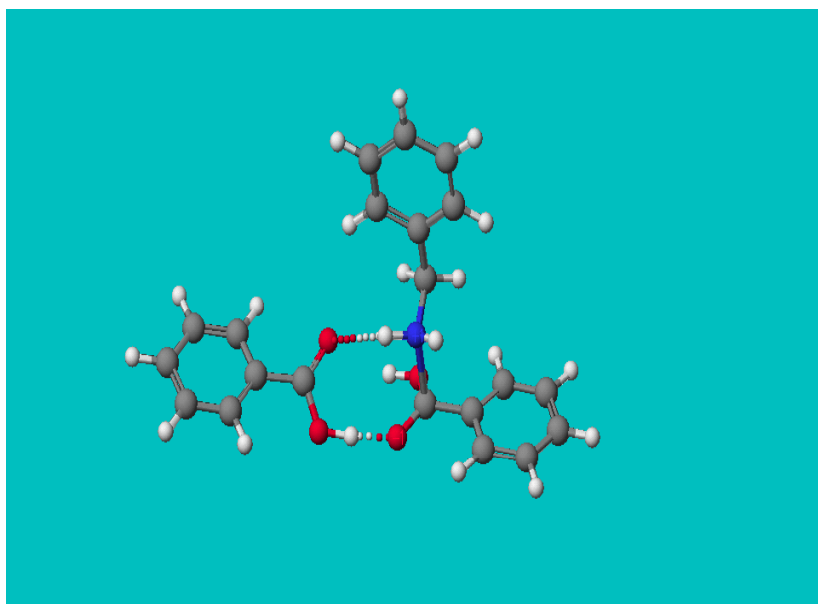
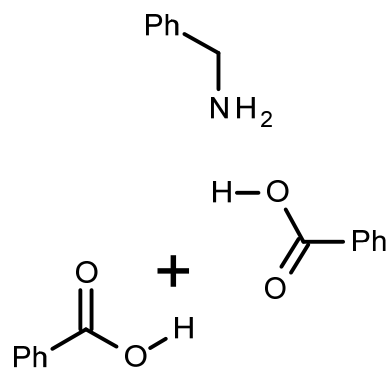
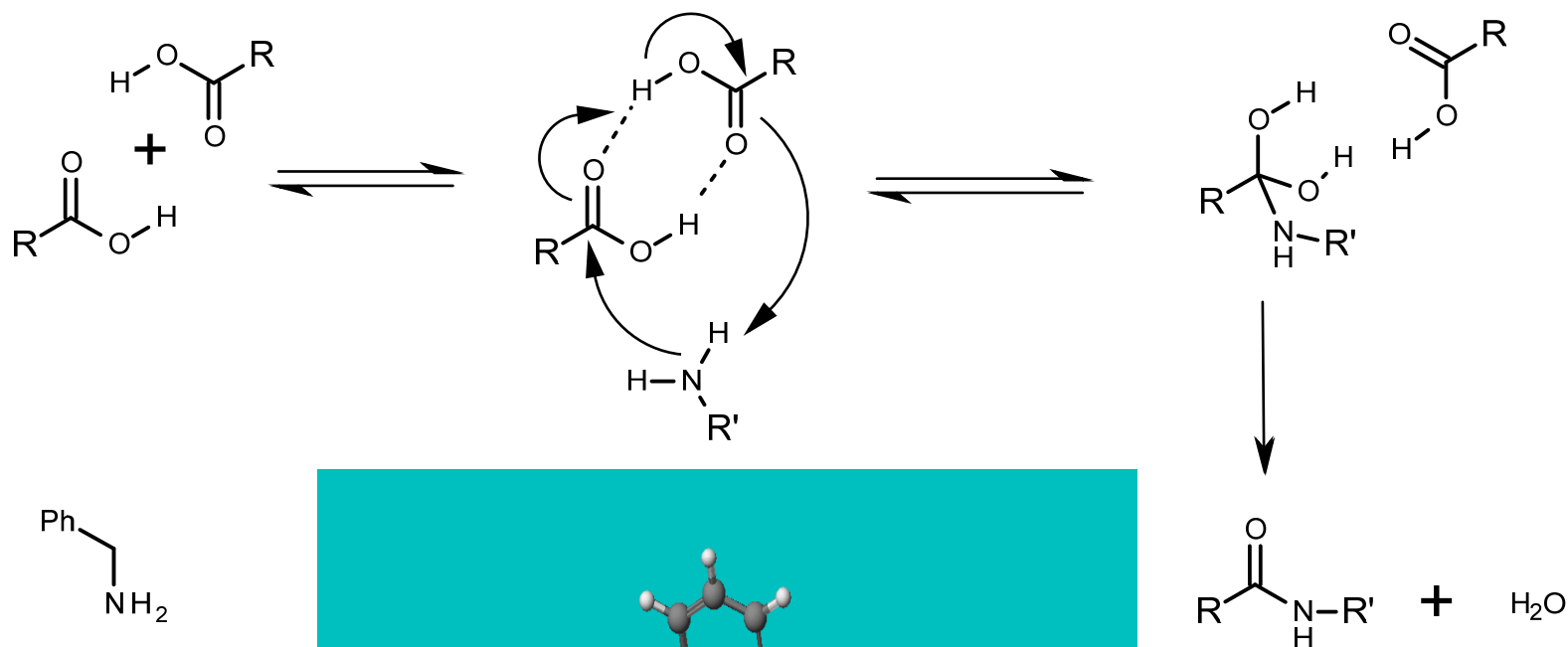
Problem of higher energy zwitterion



DFT calculations: zwitterion unstable v acid + amine (Mark Wilson, Durham).

Amino-diol is stable relative to acid/amine.

Is there an uncharged pathway?



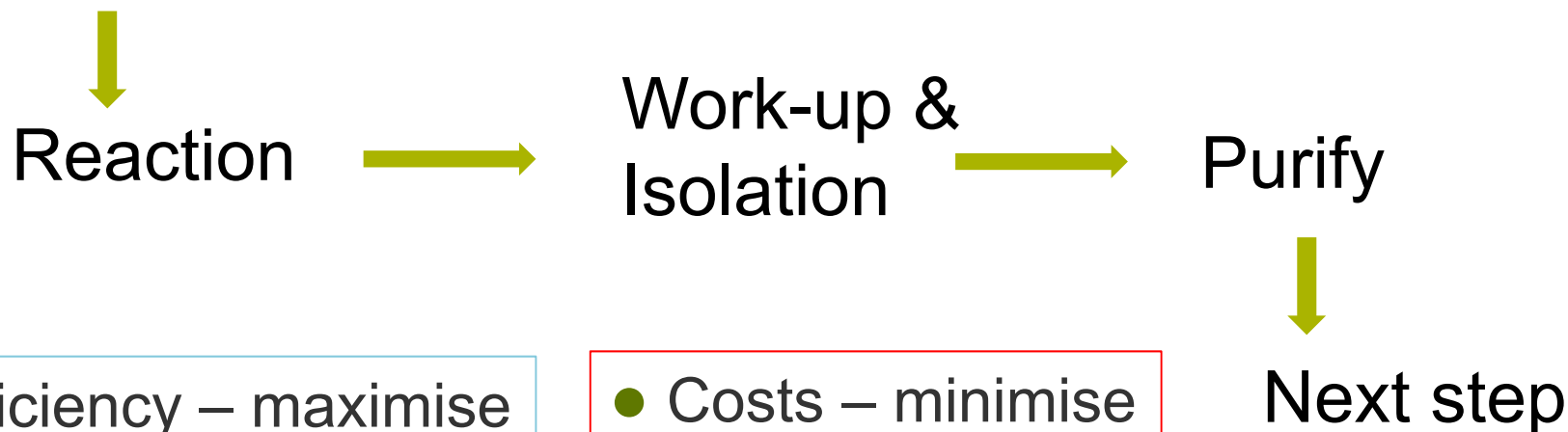
Charville, Eu. J. Org. Chem., (2011) 5981.

For the catalyst free reaction

- Need appreciable concentration of free acid and free amine
- Best in an environment that facilitates activation of the carbonyl by hydrogen bonding
 - E.g. Neat, toluene
- Needs elevated temperatures to achieve acceptable rate $>100^{\circ}\text{C}$ (?)
- Must remove water
 - It is not because water is in equilibrium with the amide/acid/amine
 - Water probably destroys the desired hydrogen bonding (?)
 - Azeotrope for large scale or molecular sieves in lab
- Overall: some catalysis takes place, best to choose the most appropriate holistic system

Route & Technology Selection – be holistic

Prior step



- Efficiency – maximise

- Selectivity
- Reaction & work-up concentration
- Reaction rates
- Safety

- Costs – minimise

- Time
- Waste
- Purification
- Corrosion
- Material handling

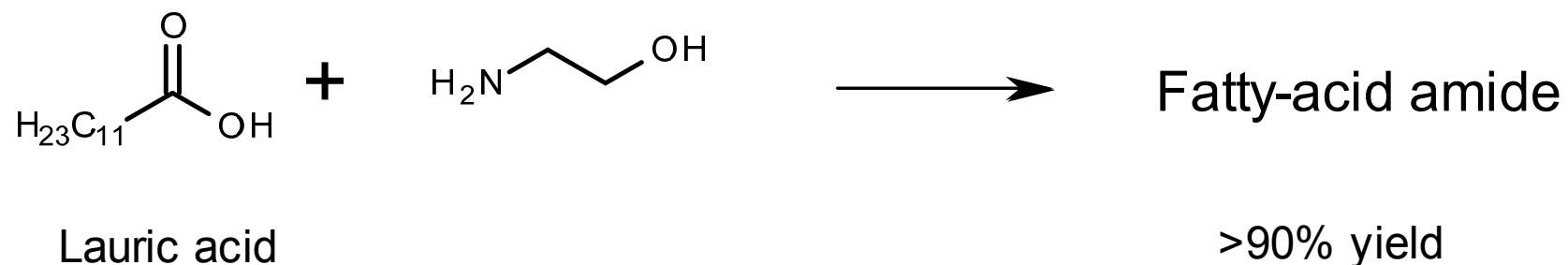
This is how I would approach a new process for amide formation...

1. Check the neat reaction without catalysts (1mole/mole acid:amine)
2. Test the same with toluene and azeotropic removal of water
3. If no success reach for boric acid and iron(III)chloride
4. Next try the zirconium tetrachloride and titanium tetra-alkoxides
5. Then more complex metal salts
6. Then the complex aryl or alkyl boronic acid derivatives
7. Then look for alternative catalytic technologies: biocatalysis, redox processes.
8. finally stoichiometric acid activation

Catalysis still needs improvement

- What we need are catalyst systems that
 - Have faster reaction rates
 - At lower temperatures
 - Are compatible with a range of functionality and solvents
 - Cheap or recoverable
 - Have a good Health, Safety & Environmental profile
 - Function without the need to continuously remove water

Biocatalysis is improving. For example...



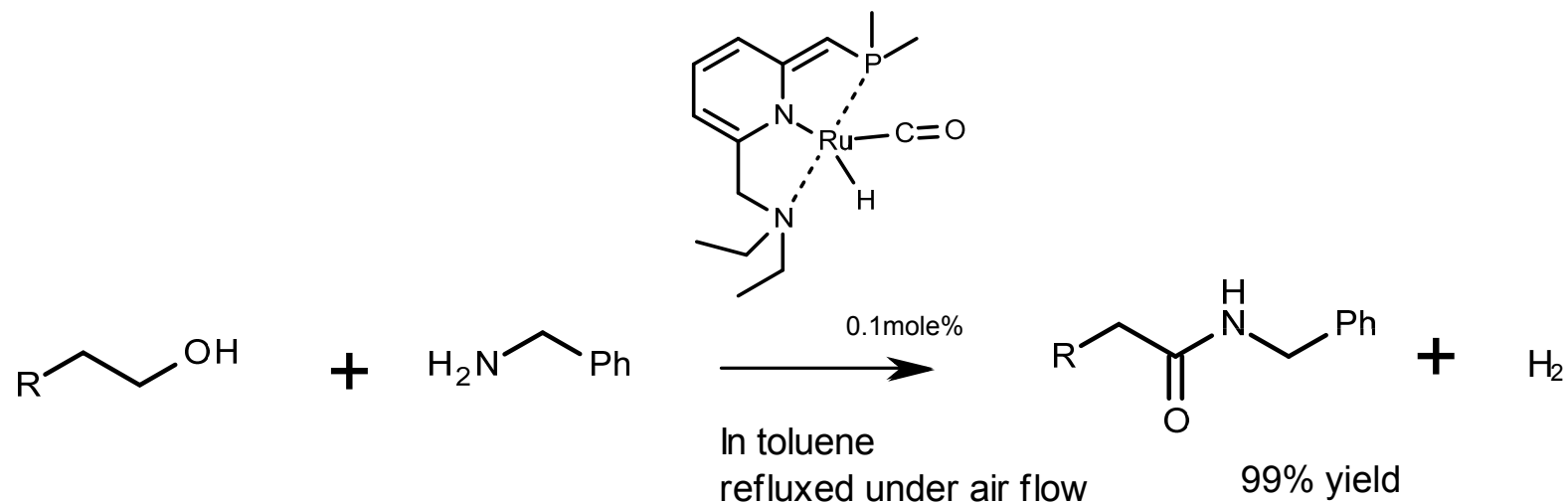
Novozyme 435 (125g/mole) in dioxane, hexane or MeCN at 40°C.

Ferrandez-Perez, Enzy. Microbiol. Tech., (2001) 527

Novozyme 435 (10g/mole), neat at 90°C with vacuum distillation of water.

Tuffvesson, Biotech. Bioeng., (2007) 447

And there is always something new..



R= Propyl, Butyl, MeO

Milstein, Science (2007) 790

Acknowledgements

- Martin Bowden, Alexander Saint-Dizier, George Hodges (Syngenta)
- Andrew Whiting & Hayley Charville (Durham University, UK)
- Reviews:
 - Ishihara, Tetrahedron, (2009) 1085
 - Charville, Chem. Commun., (2010) 1813
 - Adolfsson, Chem. Soc. Rev., (2014) 2714
- Thanks to the organisers
- Thank you for your attention