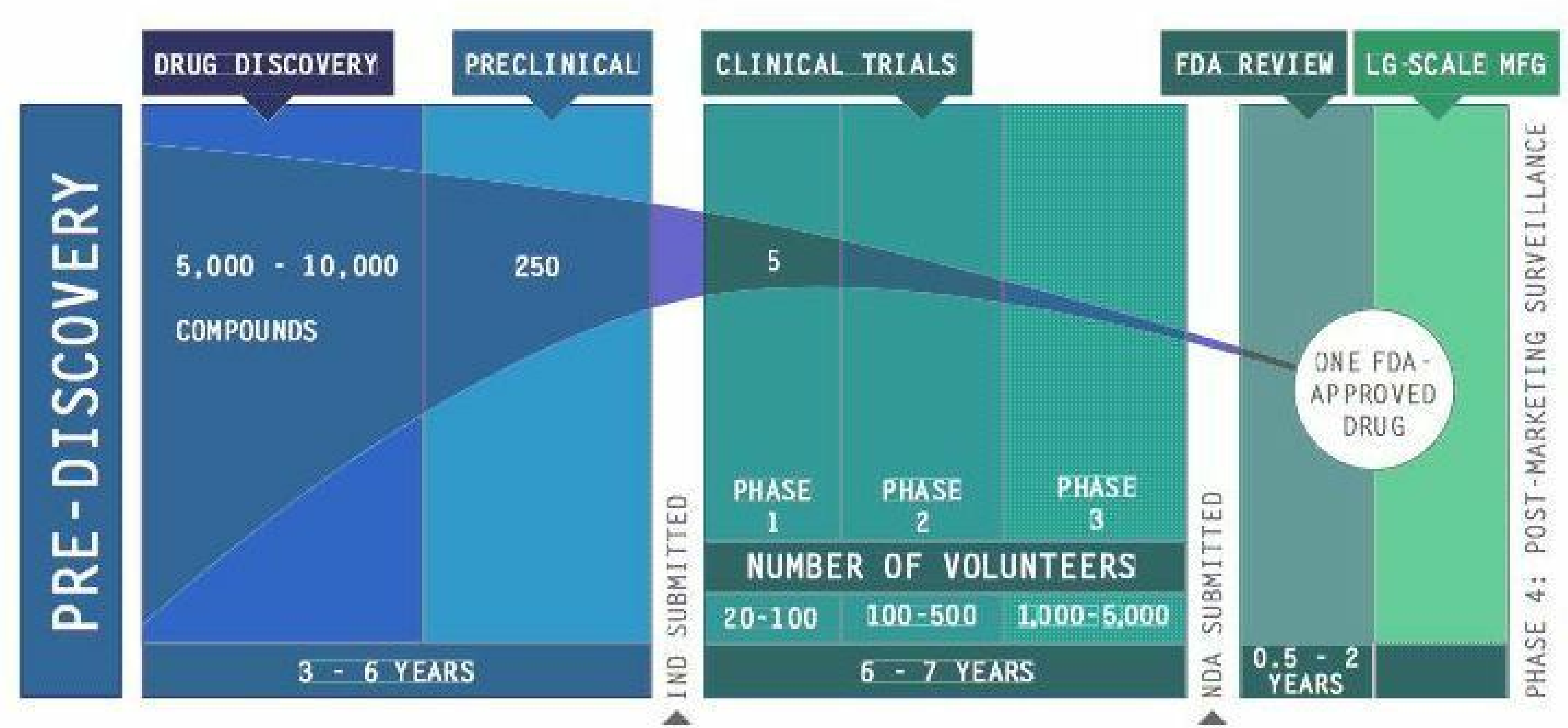
Green chemistry applied to process chemistry: from milligrams to tons in a sustainable way

Luciano Lattuada

BRACCO
LIFE FROM INSIDE

New drug timeline

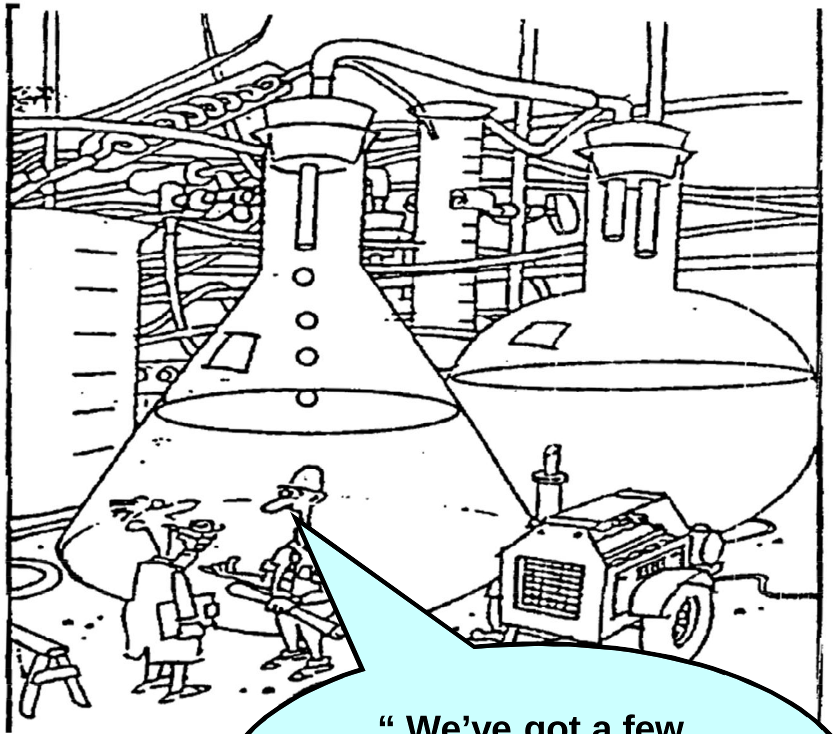
Usually multi kg of drug substance are required in preclinical and clinical phase



Scale-up

Scale-up is not just a matter of increasing the size of the equipment

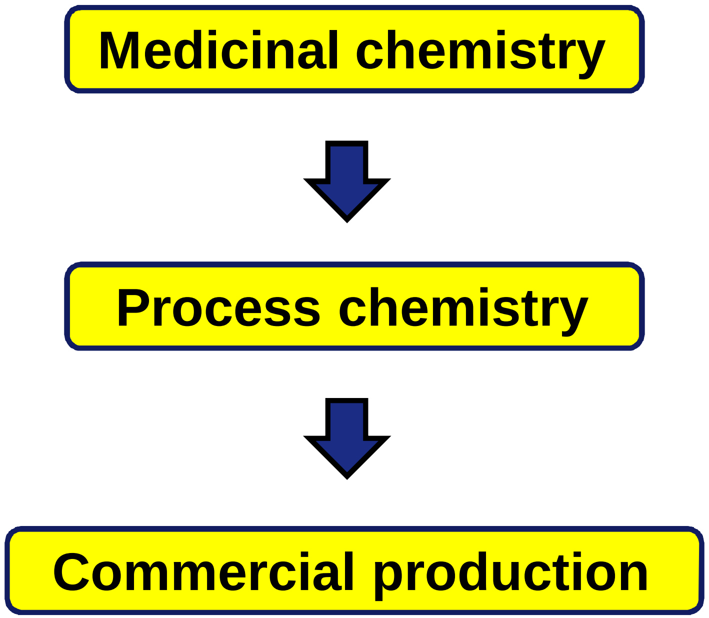
Scale-up?



“ We’ve got a few problems going from lab scale to full-scale commercial “

Process Chemistry

"Process Chemistry generally refers to the design and development of synthetic routes for the ultimate goal of manufacturing fine chemicals or pharmaceuticals at commercial scale."



Zhang, T. Y. Chem. Rev. **2006**, *106*, 2583

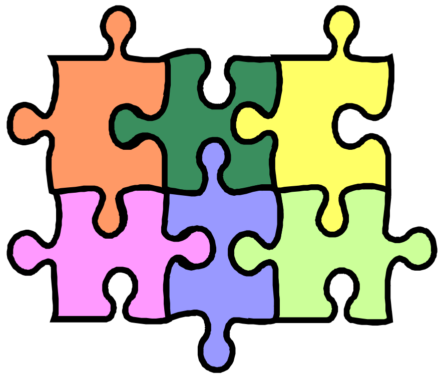
Process Chemistry

Organic synthesis

Chemical engineering

Analytical science

Intellectual property



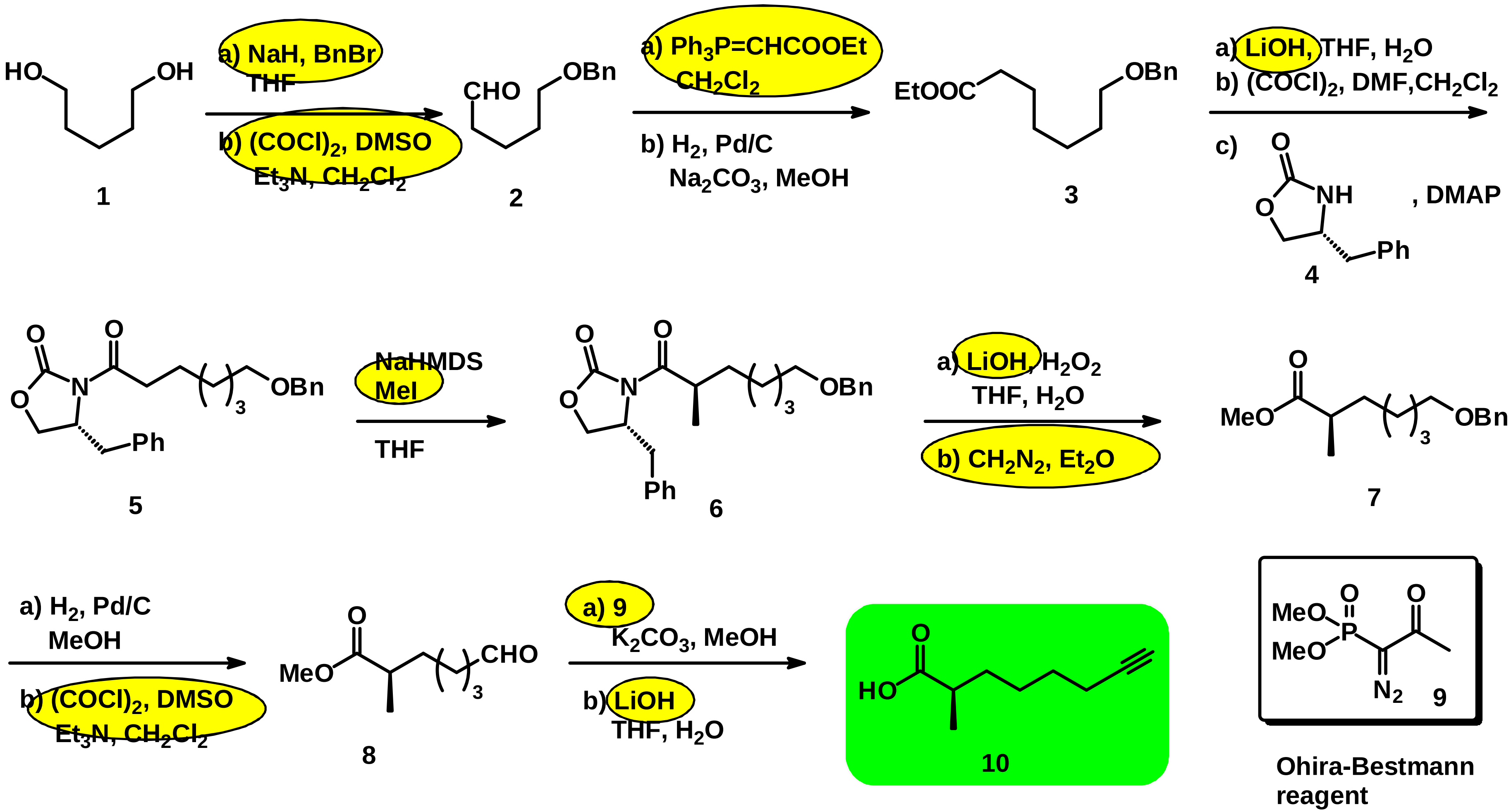
Separation techniques

Regulatory science

Environmental science

Pharmaceutical engineering

Improving a synthetic route



Purification: flash chromatography

Chen, H. *et al.* *Tetrahedron* **2005**, *61*, 11132

Improving a synthetic route: the yield

Step	70%	80%	85%	90%	95%
1	70	80	85	90	95
2	49	64	72	81	90
3	34	51	61	73	86
4	24	41	52	66	81
5	17	33	44	59	77
6	12	26	38	53	74
7	8	21	32	48	70
8	6	17	27	43	66
9	4	13	23	39	63
10	3	11	20	35	60
11	2	9	17	31	57
12	1.4	7	14	28	54
13	1	5	12	25	51

Improving a synthetic route: the yield

Single step yield	70%	80%	85%	90%	95%
Overall yield	1	5	12	25	51
Staring material to make 1 kg of final product	69.7	12.3	5.6	2.7	1.3
Total weight of reagents to make 1 kg of final product	1138	284	159	96	62

To make 1 kg of final product with the yields of the paper:

4 kg of diol, 2.7 kg benzyl bromide, 9.5 kg of phosphorane, 10 kg MeI,

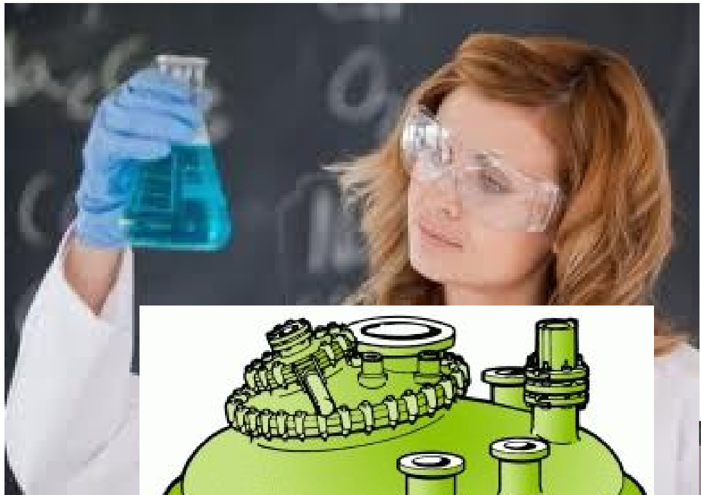
21 kg oxalyl chloride, 9 kg Ohira-Bestmann reagent, **119 kg total reagents!**

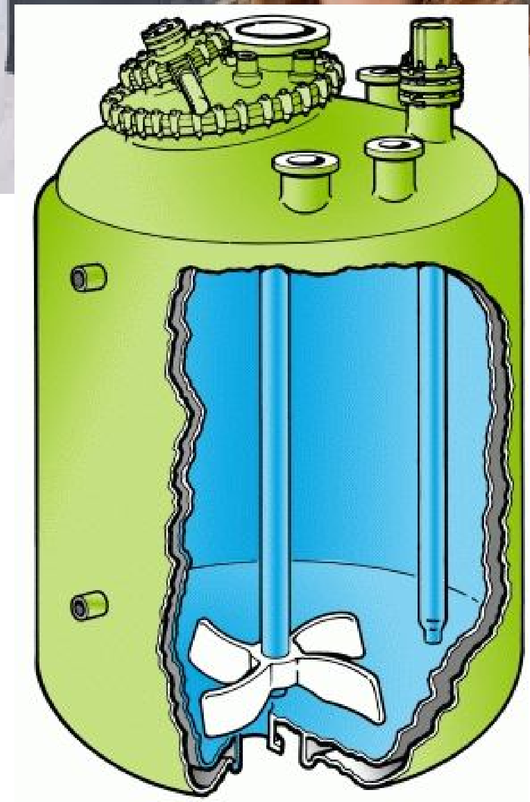
Improving a synthetic route: useful advices

- Design convergent syntheses
- Reduce number of steps as much as possible
- Run low yielding steps early in the synthesis
- Use cheap raw materials early in the synthesis
- Use expensive raw materials late in the synthesis
- Minimise the number of C-C bond forming steps
- Run concentrate reactions if possible
- Look beyond yield and number of steps:

  - separation/isolation
  - waste
  - solvent
  - time
  - sourcing

Some important differences between lab and plant





Some important differences between lab and plant

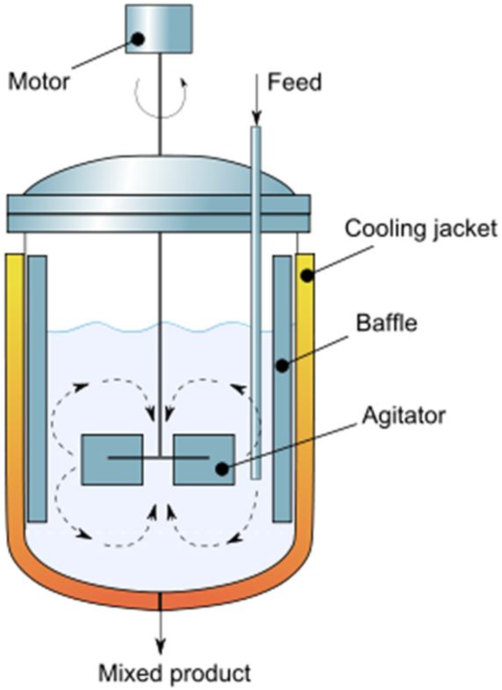
- **Heat transfer**
- **Agitation**
- **Mass transfer**
- **Visibility**
- **Separation**
- **Time**
- **Off-gas treatment**
- **Evaporation to low volume**
- **Cleaning**
- **Charging systems**

Example: heat loss (time taken for 1°C temperature drop at 80°C)

Vessel size	Time
10 mL test tube	11 sec
100 mL beaker	17 sec
1 L flask	2 min
2500 L reactor	21 min
5000 L reactor	43 min
12.700 L reactor	59min
25.000 L reactor	233 min
1 L glass Dewar	62 min

Some important differences between lab and plant

- **Rate of heat generation** $Q_r = Z\ e^{-E/RT}$
- **Rate of heat removal** $Q_c = U\ A\ (T - T_c)$



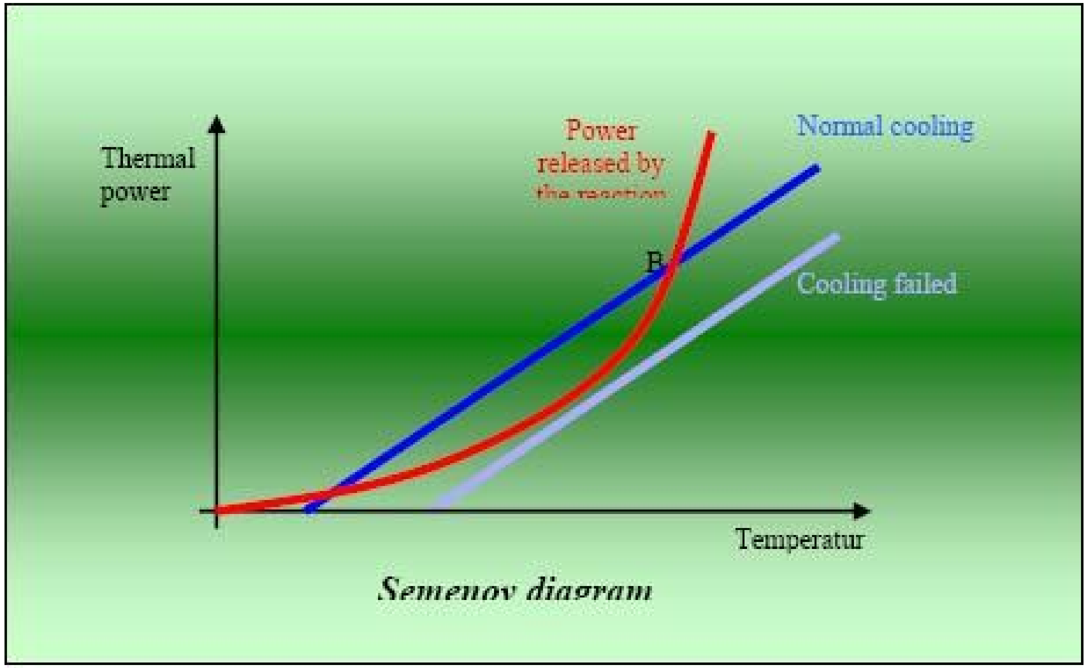
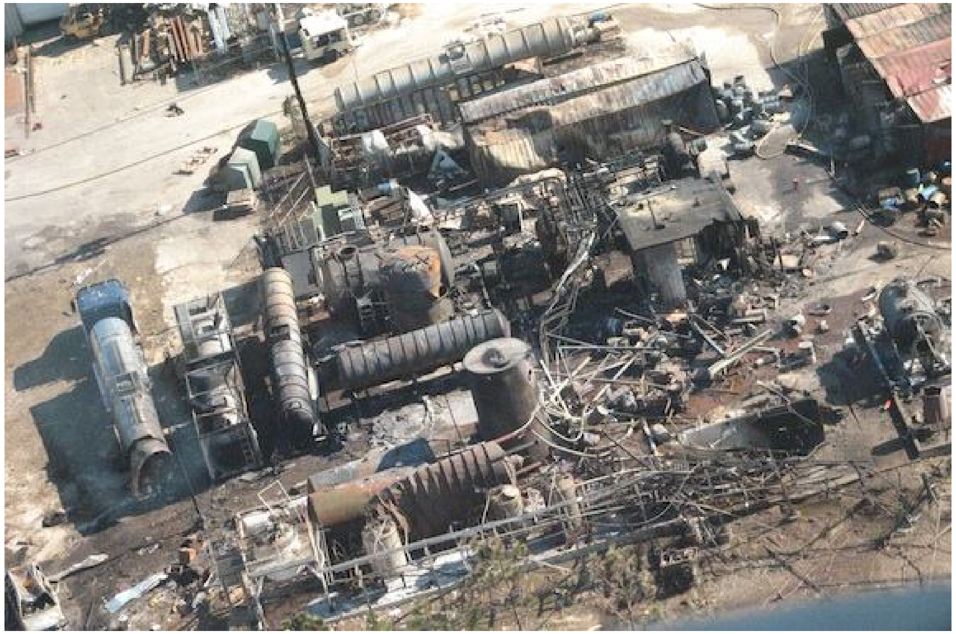


Fig. 1

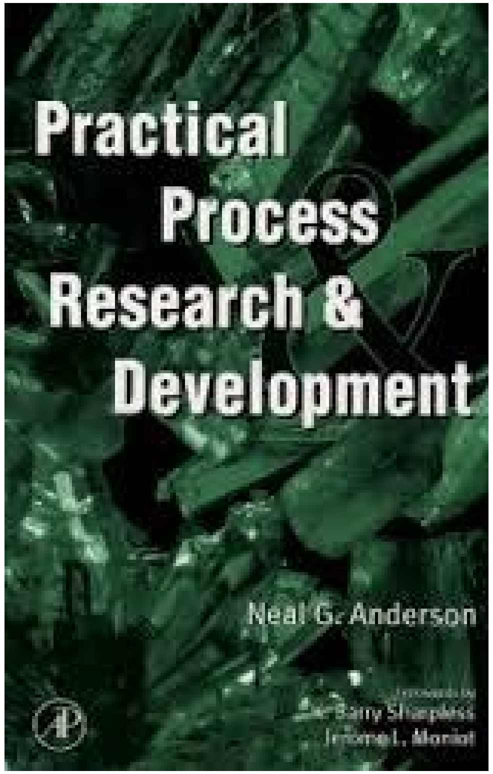
Runaway reaction

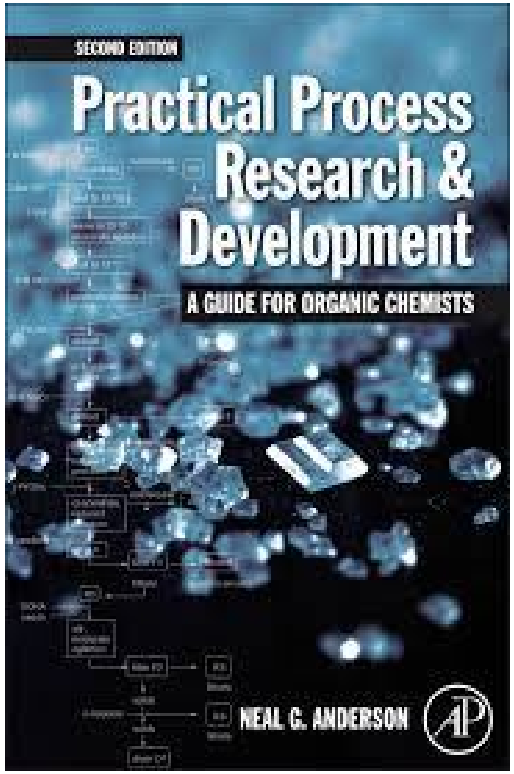
T2 Laboratories explosion and fire (19 December 2007, Jacksonville, Florida)
Four people killed and fourteen injured!



To avoid this….. safety first!

Safety first!





1st Edition 2000
Chapter 1: Introduction
Chapter 2: Route selection

2nd Edition 2012
Chapter 1: Introduction
Chapter 2: Process Safety

Improving a synthetic route: the SELECT criteria

Centro Ricerche Bracco

- **S afety** **(explosions, toxic or carcinogenic compounds)**
- **E nvironmental** **(quantity, toxicity and variety of wastes)**
- **L egal** **(patent infringement)**
- **E conomics** **(expensive materials)**
- **C ontrol** **(specifications, GMP requierements)**
- **T hroughput** **(time, availability of raw materials)**

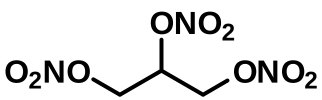
Butters, M. *et al.* *Chem. Rev.* **2006**, *106*, 3002

Highly energetic functional groups

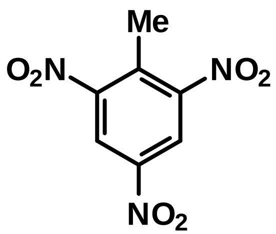
Name (structure)	Range of decomposition energies (kJ mol^{-1})
Alkenes ($R_2C=CR_2$)	50-90
Alkynes (R-C≡C-R)	120-170
Epoxides	70-100
Peroxides/hydroperoxides (R-O-O-R / R-O-O-H)	230-360
Peracids (RCO-O-O-H)	240-290
Sulphoxides ($R_2S=O$)	40-70
Sulphonyl chloride (RSO_2Cl)	50-70
Hydrazines (R-NH-NH-R)	70-90
Diazo/diazonium (R-N=N-R / R-N≡N^+)	100-180
Azides ($R-N_3$)	200-240
Oximes ($R_2C=N-OH$)	110-140
N-oxides ($R_2N=O$)	100-130
Nitroso ($R_2CH-N=O$)	150-290
Isocyanate (R-N=C=O)	50-75
Nitro (R_3C-NO_2)	310-360
N-Nitro (R_2N-NO_2)	400-430
Acyl nitrates ($RCO-ONO_2$)	400-480

Rowe, S.M. *Org. Process Res. Dev.* **2002**, *6*, 877

A rule of thumb: the oxygen balance



Nitroglycerine
OB = +3.5



TNT
OB = -74

Oxygen Balance = -1600[2x+(y/2)-z] / M

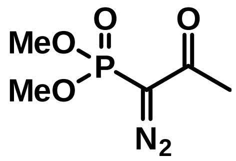
M = molecular weight

x = no. of carbon atoms

y = no. of hydrogen atoms

z = no. of oxygen atoms

(other heteroatoms are ignored)



OB = -87

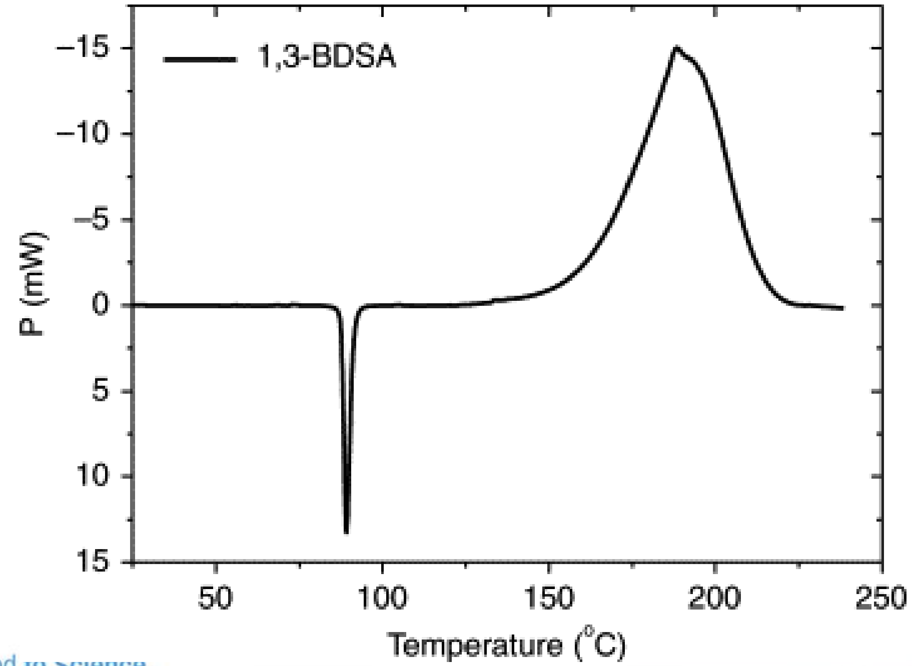
CO_2; H_2O
OB: 0
Highly explosive??

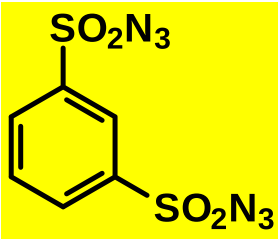
Hazard potential

Oxygen balance

Thermal stability tests

- DTA (Differential thermal analysis)
- DSC (Differential scanning calorimetry)
- TGA (Thermogravimetric analysis)
- ARC (Accelerating Rate Calorimetry)
- Reaction Calorimetry





OB = -55.5

DSC curve of 1,3-benzene disulfonylazide
Heating rate of 20°C/min
(*Polymer*, **2005**, *46*, 12073)

Amery, G. *Aldrichimica Acta* **2001**, *34*, 61 and references

Reactions having a high hazard potential

Reaction	Example of concern
Curtius rearrangements	Use of acyl azides, nitrous acid or hydrazine
Decarboxylations	CO_2 evolution, possible pressure hazard
Diazotizations	Especially if followed by reduction to the hydrazine
Displacements	Oxalyl chloride to displace -OH (CO_2, CO, HCl generated)
Epoxidations	Epoxides are high energy strained rings
Esterifications	When using oxalyl chloride
Friedel-Crafts	Reactions and quenches due to use of $AlCl_3$, BCl_3, H_2SO_4, HF
Grignard reactions	Highly exothermic, activation period required
Hydrolysis	When using H_2O_2 (e.g. from cyano to amide)
Metallations	Use of *n*-BuLi, *t*-BuLi, LDA, NaHMDS
Nitrations	Very exothermic, hazard of explosion for thermal runaway
Oxidations	$K_2Cr_2O_7$, O_3, H_2O_2, $KMnO_4$, $NaIO_4$
Peptide formation	Use of HOBT
Quenches	Water quench when PCl_5 or $POCl_3$ have been used previously
Reductions	Use of hydrogen, hydrazine, $NaBH_4$ in MeOH
Sulfonations	Sulfonation of an amine to form sulfonamide

Leggett, D. *J. Hazard. Mater.* **2004**, *115*, 63

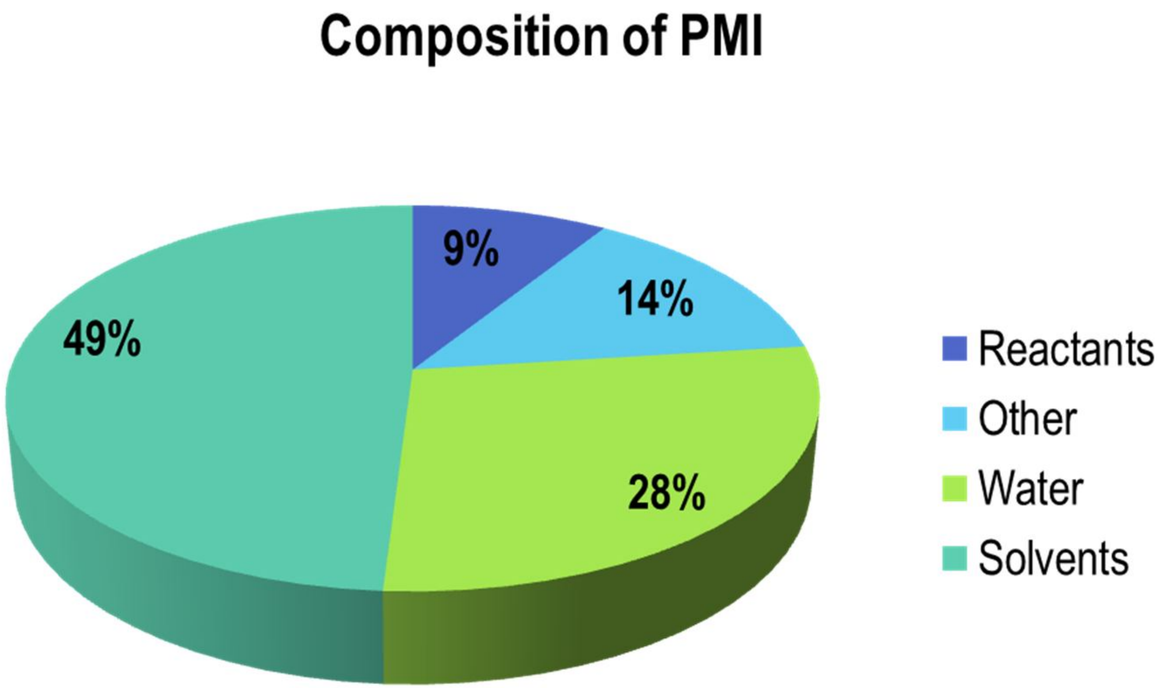
Alternatives to hazardous reagents

Reagent	Alternatives
Diazomethane	Trimethylsilyl diazomethane
Sodium azide	DPPA, TMG azide, tetrabutylammonium azide
DEAD	DIAD, DMEAD[1]
Hydrogen	Transfer hydrogenation
HOBT	HOPy[2]
Dess Martin/ IBX	Polymer supported IBX
Alkyl lithiums, LDA	NaOH/phase transfer catalysis
$LiAlH_4$	$NaAlH_2(OCH_2CH_2OCH_3)_2$ (Vitride®, Red-Al®)
$COCl_2$	Triphosgene
CrO_3	TEMPO/NaOCl

DPPA: diphenylphosphonic azide
DEAD: diethyl azodicarboxylate
DMEAD: di-2-methoxyethyl azodicarboxylate
HOPy: 2-hydroxypyridine
LDA: lithium diisopropylamide
TMG: tetramethylguanidinium
DIAD: diisopropyl azodicarboxylate
HOBT: 1-hydroxybenzotriazole
IBX: 2-iodoxybenzoic acid
TEMPO: 2,2,6,6-tetramethylpiperidine 1-oxyl

[1]Hagiya, K. et al. *Tetrahedron* **2009**, *65*, 6109; [2]Bright, R. et al. *Org. Process Res. Dev.* **2004**, *8*, 1054

Importance of solvents in pharmaceutical industry



$$\text{Process mass intensity} = \frac{\text{Quantity of raw materials input (kg)}}{\text{Quantity of bulk API out (kg)}}$$

http://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/solvent-selection-guide.pdf

Simple solvent selection guide

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	TBME	Dichloromethane
Ethyl Acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-MeTHF	NMP
MEK	THF	DMF
1-Butanol	Xylenes	DMAc
t-Butanol	DMSO	Pyridine
	Acetic Acid	Dioxane
	Ethylene Glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

Alfonsi, K. et al. *Green Chem.* **2008**, *10*, 31

Undesirable solvents

Pentane	very low flash point, highly flammable
Hexane(s)	toxic
Di-isopropyl ether	very powerful peroxide former
Diethyl ether	very low flash point, highly flammable
Dichloroethane	carcinogen
Chloroform	carcinogen
NMP	reprotoxic
DMF	reprotoxic
DMAc	reprotoxic
Pyridine	carcinogen
Dioxane	cancer suspect agent
Dimethoxyethane	teratogenic
Benzene	carcinogen, use regulated by EU
Carbon tetrachloride	carcinogen, ozone depleter, banned

Alfonsi, K. et al. *Green Chem.* **2008**, *10*, 31

Alternatives to undesirable solvents

Pentane	Heptane
Hexane(s)	Heptane
Di-isopropyl ether	2-MeTHF, MTBE
Diethyl ether	2-MeTHF, MTBE, CPME
Dichloroethane	Dichloromethane
Chloroform	Dichloromethane
NMP	Acetonitrile
DMF	Acetonitrile
DMAc	Acetonitrile
Pyridine	Et_3N
Dioxane	2-MeTHF, MTBE, Diethoxymethane
Dimethoxyethane	2-MeTHF, MTBE, Diethoxymethane
Benzene	Toluene
Carbon tetrachloride	Dichloromethane

MTBE: methyl *t*-butyl ether; CPME: cyclopentyl methyl ether

Alfonsi, K. et al. *Green Chem.* **2008**, *10*, 31

The twelve principles of Green Chemistry

1. **Waste prevention instead of remediation**
2. **Atom Economy or Atom Efficiency (AE)**
3. **Less hazardous/toxic chemicals**
4. **Designing safer chemicals**
5. **Safer solvents and auxiliaries**
6. **Energy efficiency**
7. **Use of renewable raw materials**
8. **Shorter synthesis and minimal derivatization**
9. **Catalytic rather than stoichiometric reagents**
10. **Design products for degradation**
11. **Real-time analyses for pollution prevention**
12. **Inherently safer processes**

Prof. Paul Anastas
Yale University

Anastas, P. and Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301

Atom economy and E factor: two faces of the same coin

$$\text{Atom Economy} = \frac{\text{MW product}}{\sum \text{MW of reagents}}$$

(Trost *Science* **1991**, *254*,1471)

$$3\ PhCH(OH)CH_3 + 2\ CrO_3 + 3\ H_2SO_4 \longrightarrow 3\ PhCOCH_3 + Cr_2(SO_4)_3 + 6\ H_2O$$

Atom Economy = 360/860 = 42% **E factor = 500/360 = 1.39**

$$PhCH(OH)CH_3 + \tfrac{1}{2}\ O_2 \xrightarrow{\text{Catalyst}} PhCOCH_3 + H_2O$$

Atom Economy = 120/138 = 87% **E factor = 18/120 = 0.15**

(Sheldon *Chem. Ind.* **1992**,903)

$$\text{E factor} = \frac{\text{kg waste}}{\text{kg product}}$$

Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273

Atom economy and E factor: two faces of the same coin

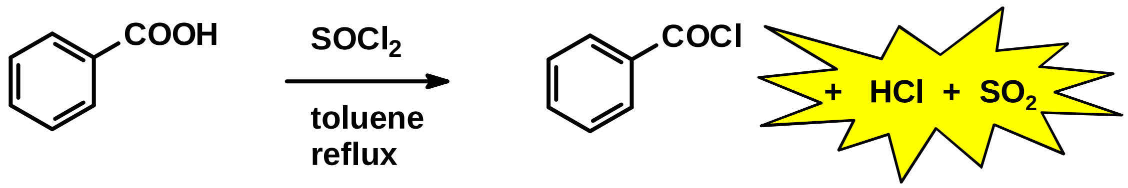
Atom economic reactions	Atom un-economic reactions
Rearrangement	Substitution
Addition	Elimination
Diels-Alder	Wittig
Other concerted reactions	Grignard

Industry segment	Production (ton/y)	E factor
Oil refining	10^6-10^8	<0.1
Bulk chemicals	10^4-10^6	<1-5
Fine chemicals	10^2-10^4	5-50
Pharmaceuticals	10 -10^3	25-100

Lancaster, M. *Green Chemistry* **2002**, RSC, Cambridge; Sheldon, R.A. *Pure Appl. Chem.* **2000**, *72*, 1233

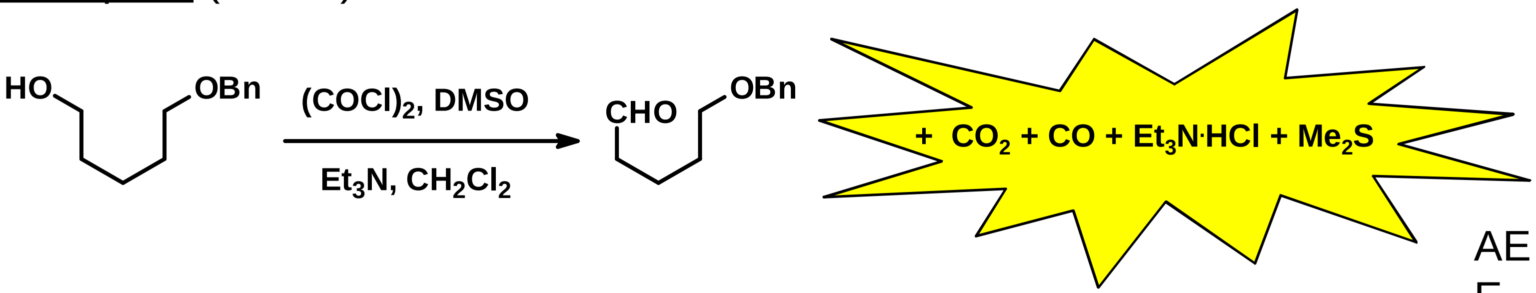
Importance of the full stoichiometry

Example 1



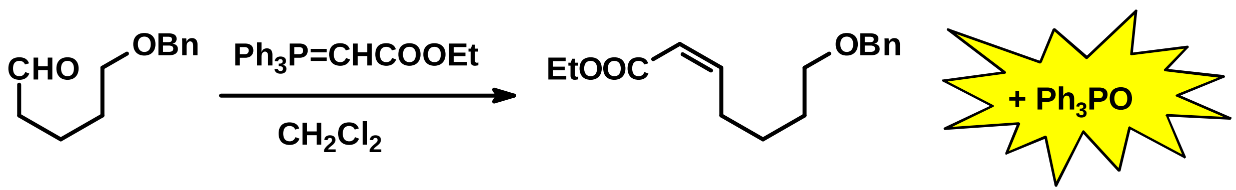
AE = 59%
E_{factor} = 0.72

Example 2 (Swern)



AE = 38%
E_{factor} = 1.41

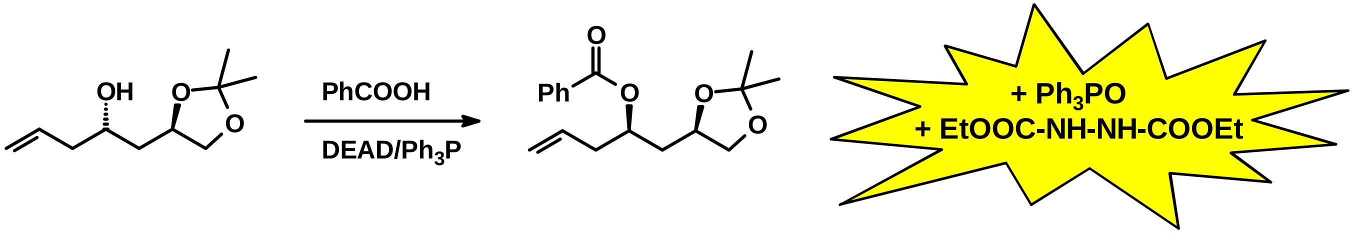
Example 3 (Wittig)



AE = 49%
E_{factor} = 1.06

Importance of the full stoichiometry

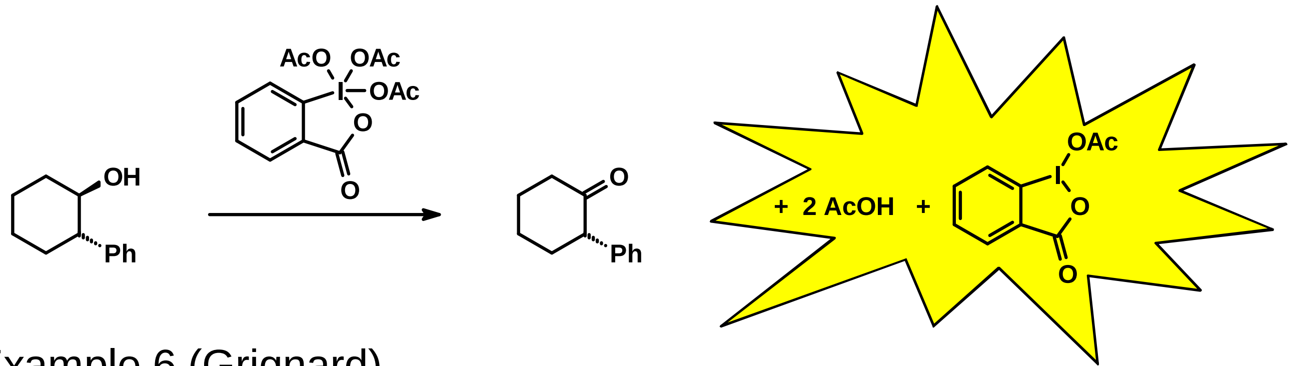
Example 4 (Mitsunobu)



AE = 47%

E_{factor} = 1.57

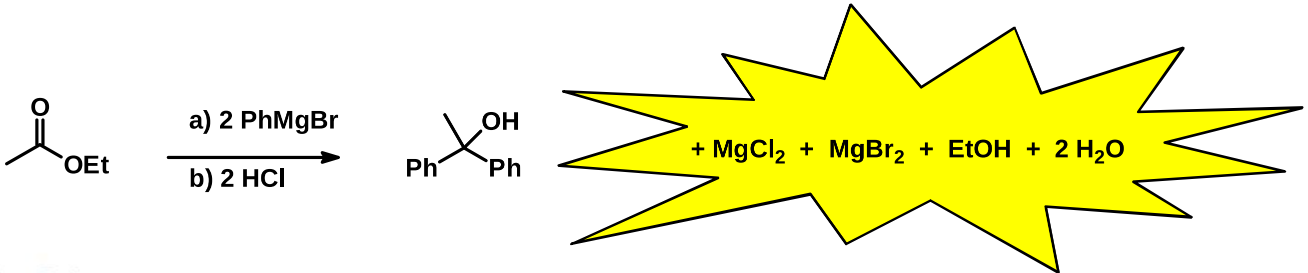
Example 5 (Dess-Martin)



AE = 15%

E_{factor} = 3.5

Example 6 (Grignard)



AE = 38%

E_{factor} = 1.82

General considerations for Process Chemistry

Design convergent syntheses

Minimize number of steps

Avoid protecting groups

Take advantage of catalysis

Avoid solvent with flash point <15°C (*e.g.* ether, hexane, DCM)

Avoid mixture of solvents

Avoid reagents accumulation

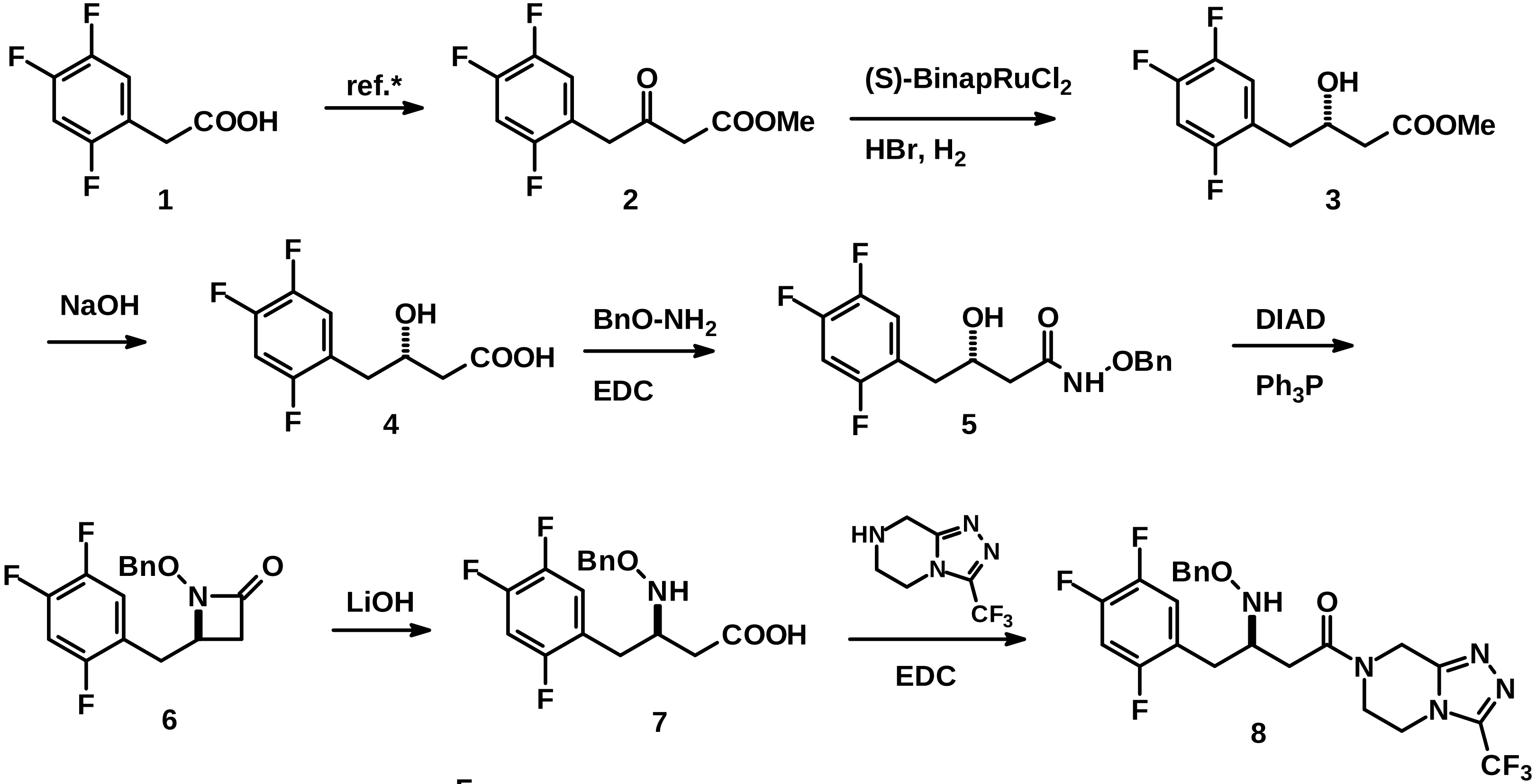
Temperature range -40°C to 120°C

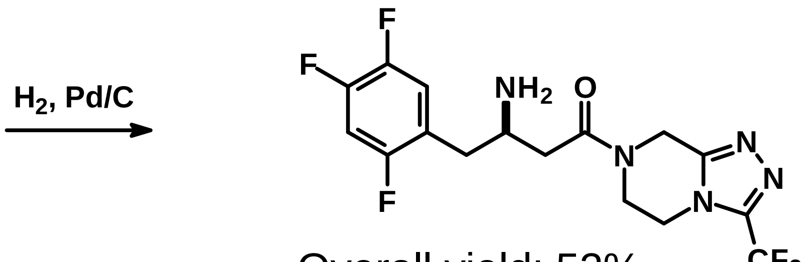
Avoid dessicants, use azeotropes

Avoid column chromatography

Seeding helps crystallization

Sitagliptin example (1)





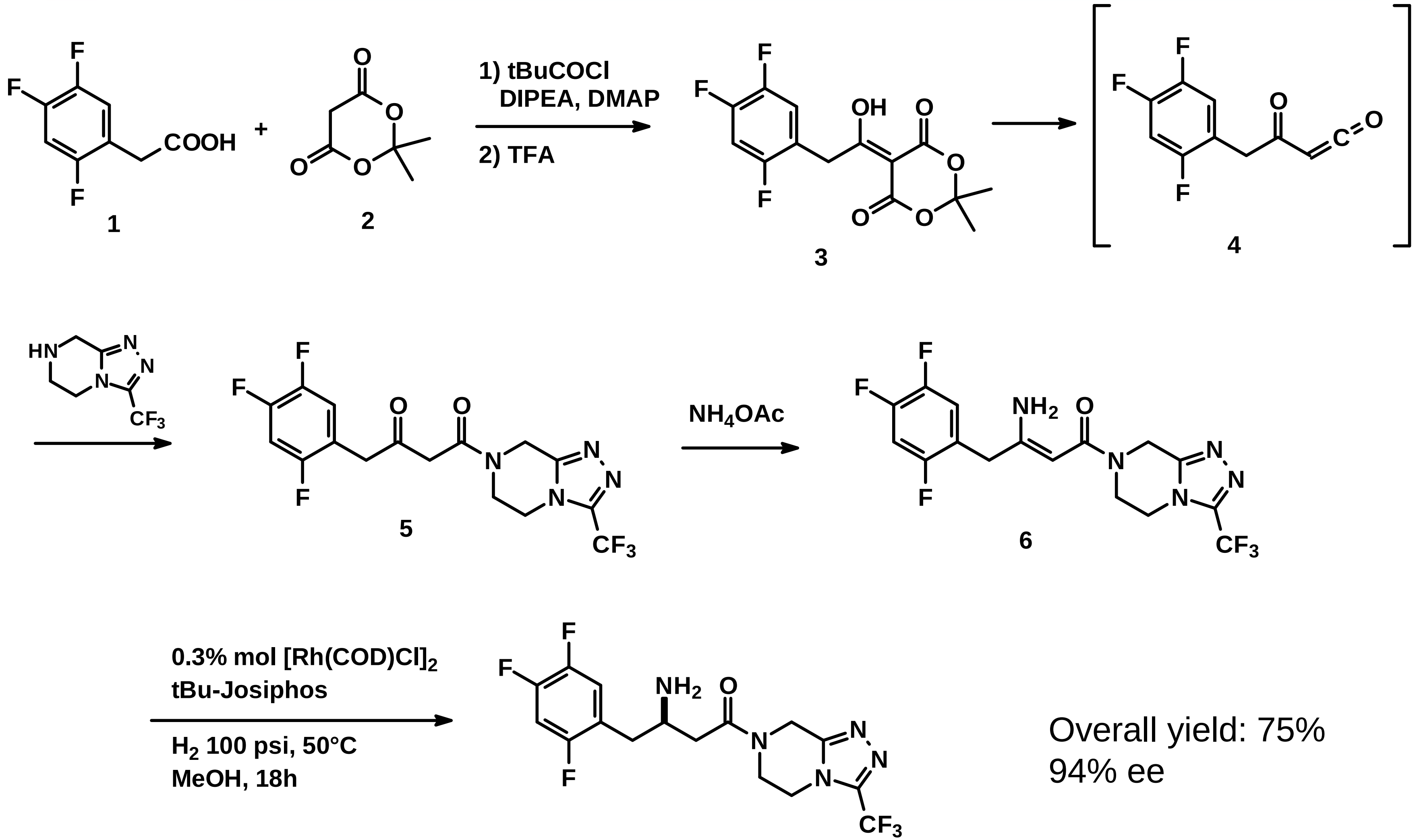
Overall yield: 52%

Sitagliptin is a dipeptidyl peptidase IV inhibitor for the treatment of diabetes.

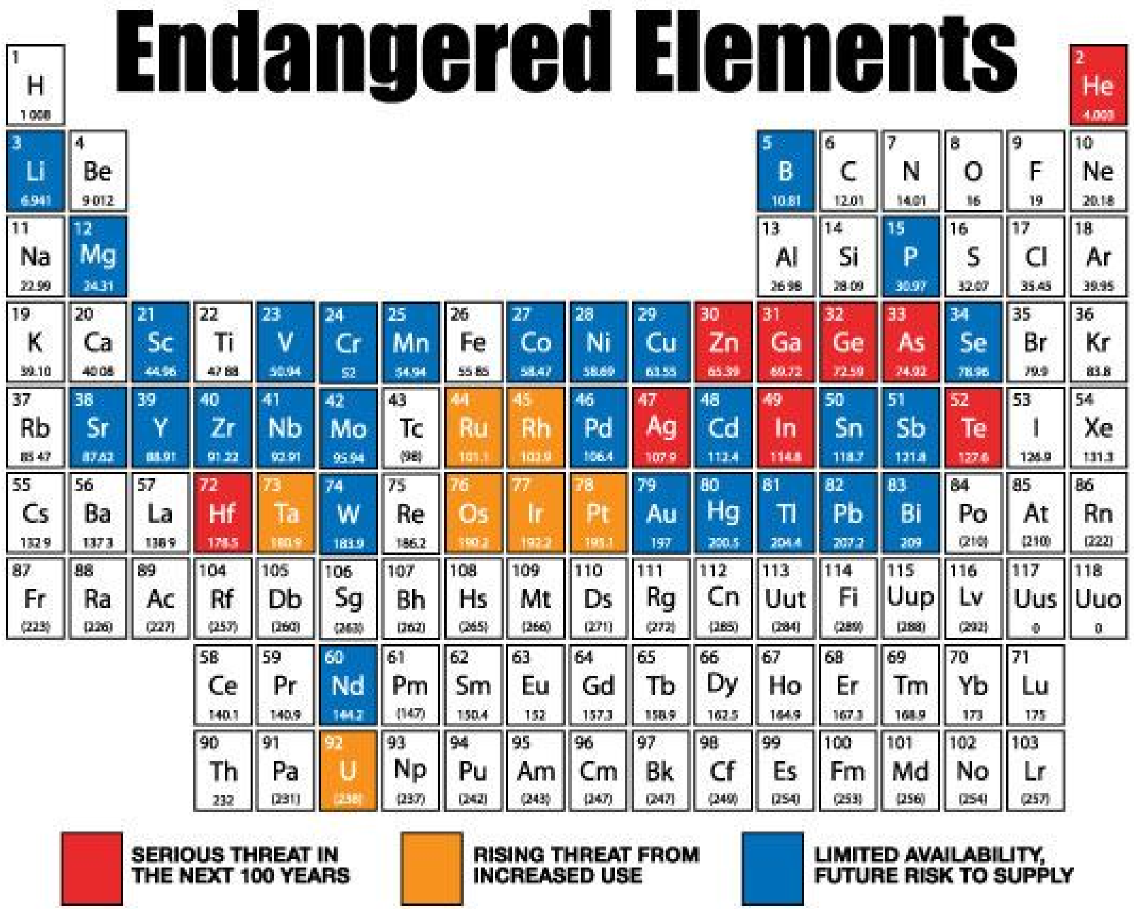
It is the API of Januvia® (Merck & Co.).

Hansen, K.B. et al. *Org. Process Res. Dev.* **2005**, *9*, 634

Sitagliptin example (2)



Overall yield: 75%
94% ee



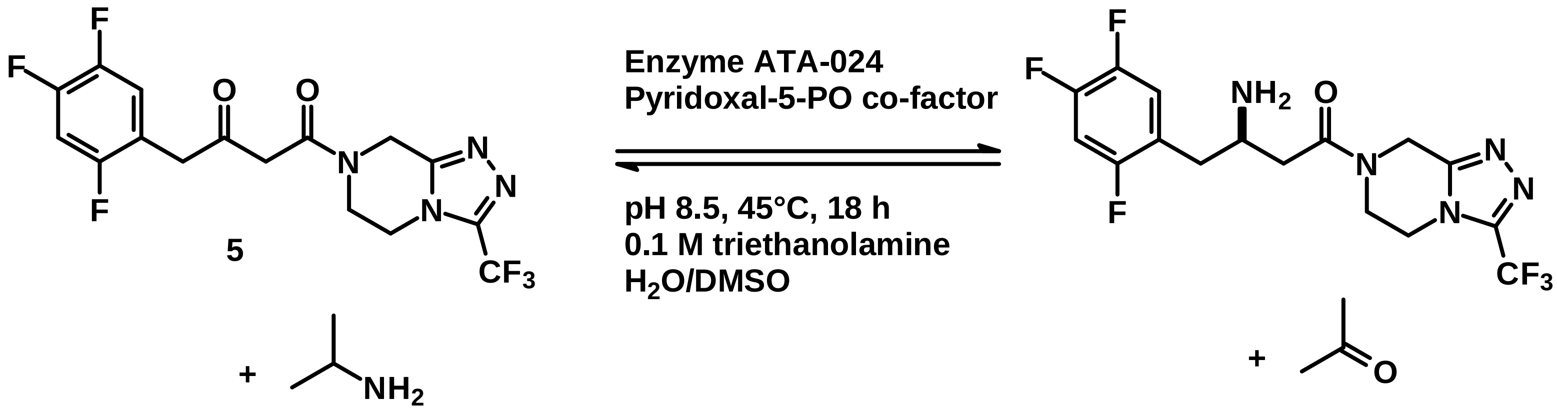
SOURCE: CHEMISTRY INNOVATION KNOWLEDGE TRANSFER NETWORK

ACS Chemistry for Life®

AMERICAN CHEMICAL SOCIETY

ACS Green Chemistry Institute®

Sitagliptin example (3)



Yield: 94%
>99.99% ee

The enzyme is a mutated R-selective transaminase developed in collaboration with Codexis

Benefits of the new process:

- No high-pressure hydrogenation
- No metals
- No wasteful purification step

Savile, C.K. et al. *Science* **2010**, *329*, 305; Desai, A.A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1974

The ideal synthesis

- Safe
- Simple
- One step
- 100% yield
- Economical
- Robust
- Environmentally acceptable
- Resource efficient
- Renewable raw materials
- Efficient throughput
- Minimal plant footprint

Next generations

Planet Earth

THANK YOU

Other useful references

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	Chem. Soc. Rev. 2012, 41, 1452
	RSC Adv. 2015, 5, 26686
Solvents	Green Chem. 2014, 16, 4060
	Org. Process Res. Dev. 2013, 17, 1517
	Green Chem. 2011, 13, 854
Reagent selection	Green Chem. 2013, 15, 1542
Oxidations	Org. Process Res. Dev. 2016, 20, 129
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Reductions	Org. Process Res. Dev. 2012, 16, 1156
Phase Transfer Catalysis	Org. Process Res. Dev. 2015, 19, 1731
Coupling reagents	Chem. Rev. 2011, 111, 6557
Enzymes	Chem. Soc. Rev. 2012, 41, 1585
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	Green Chem. 2011, 13, 226
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	Chem. Rev. 2006, 106, 2794
Continuous processes	Org. Process Res. Dev. 2012, 16, 852