Catalysis within DSM: Enabling, Improving, and Changing Chemicals Manufacture

Paul Alsters
DSM Pharma Products
paul.alsters@dsm.com

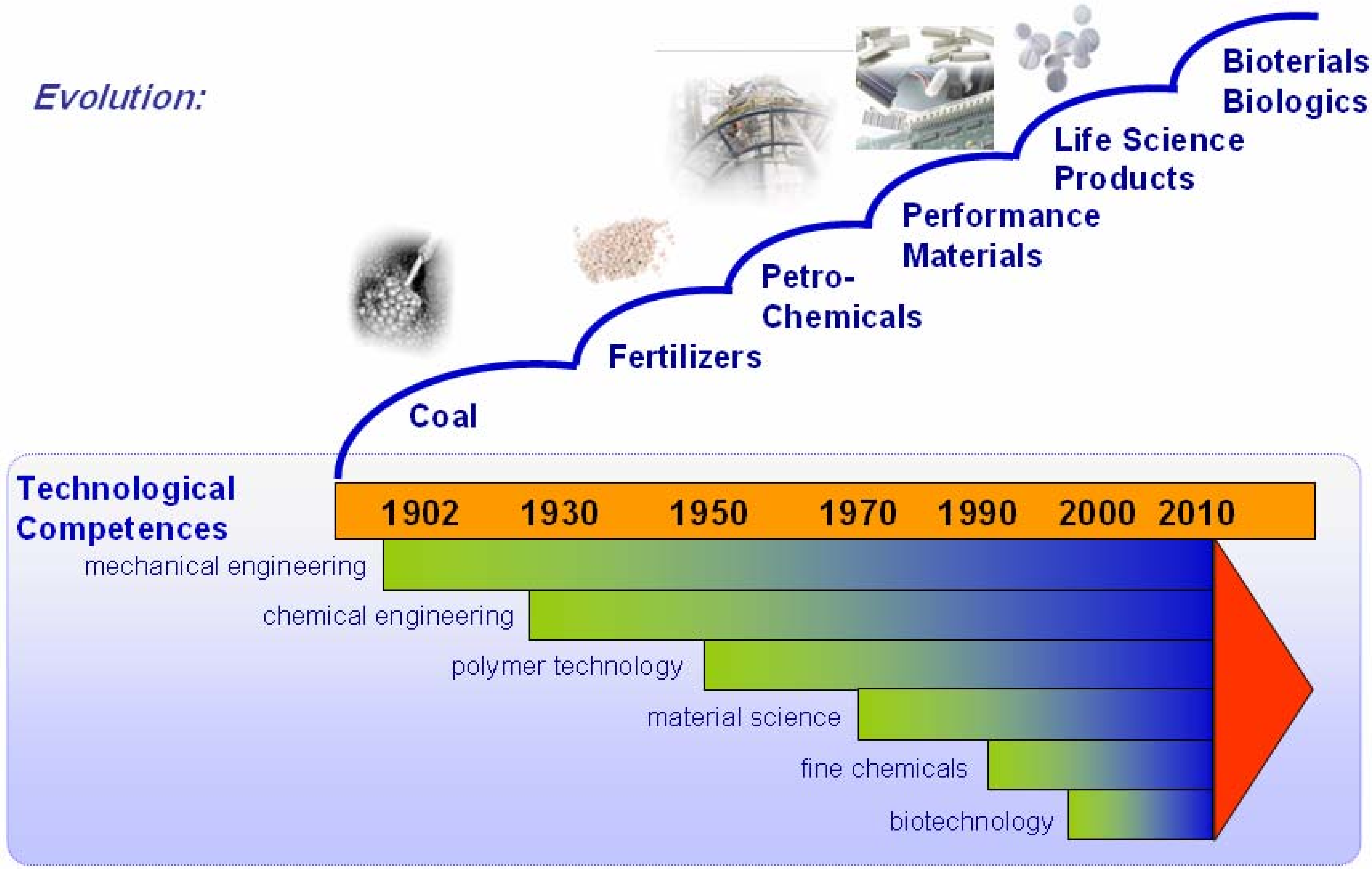
Royal Society of Chemistry Symposium:
"Catalysts for Change" (ChemSpec)
Barcelona, 17-18 June, 2009

DSM is everywhere

Unlimited. DSM

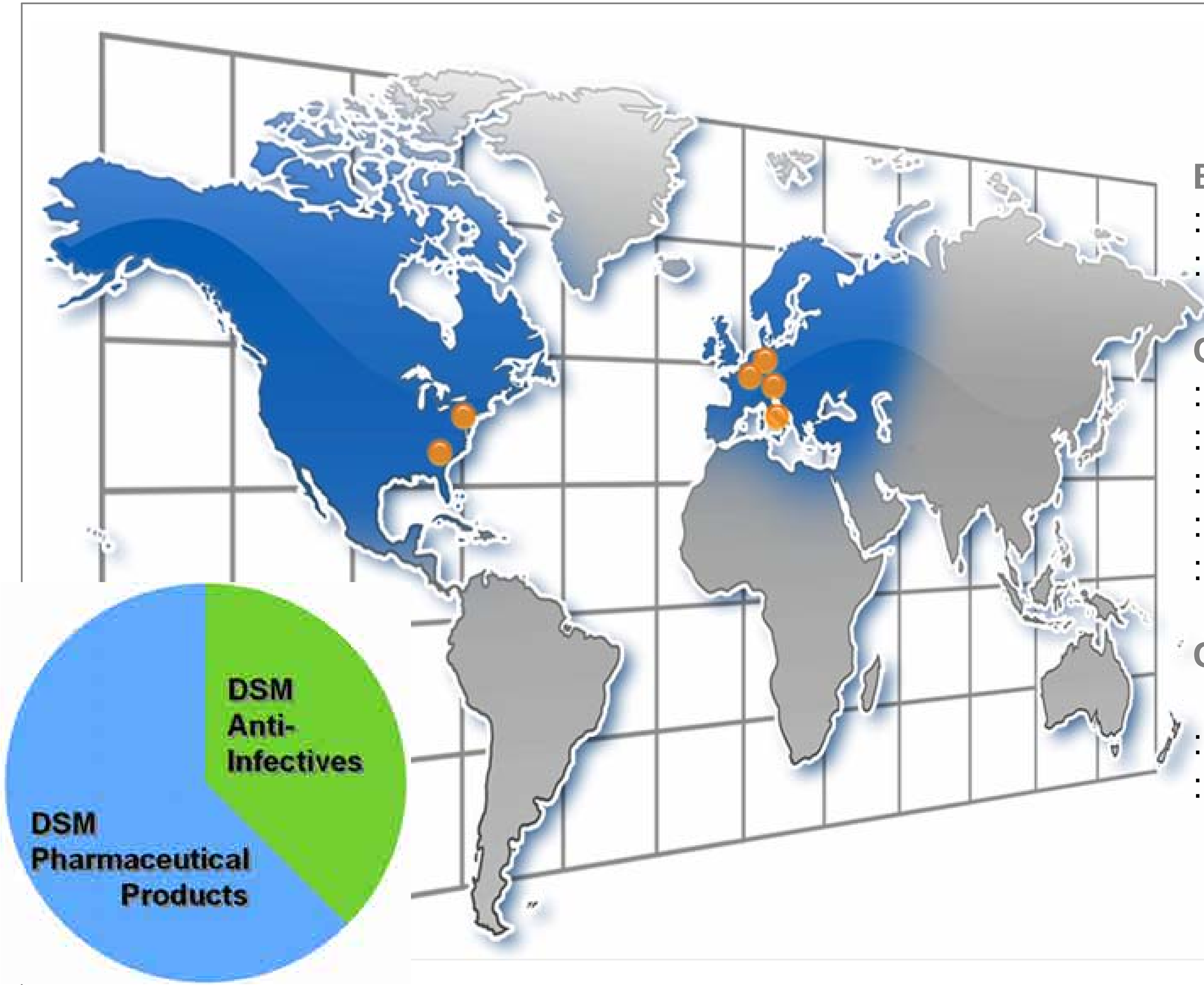
Unlimited.DSM: Ability to change

100 years of successful transformations



Unlimited. DSM

DSM Pharma:
Global sites; ~ € 1 bn. sales (12% of total DSM)



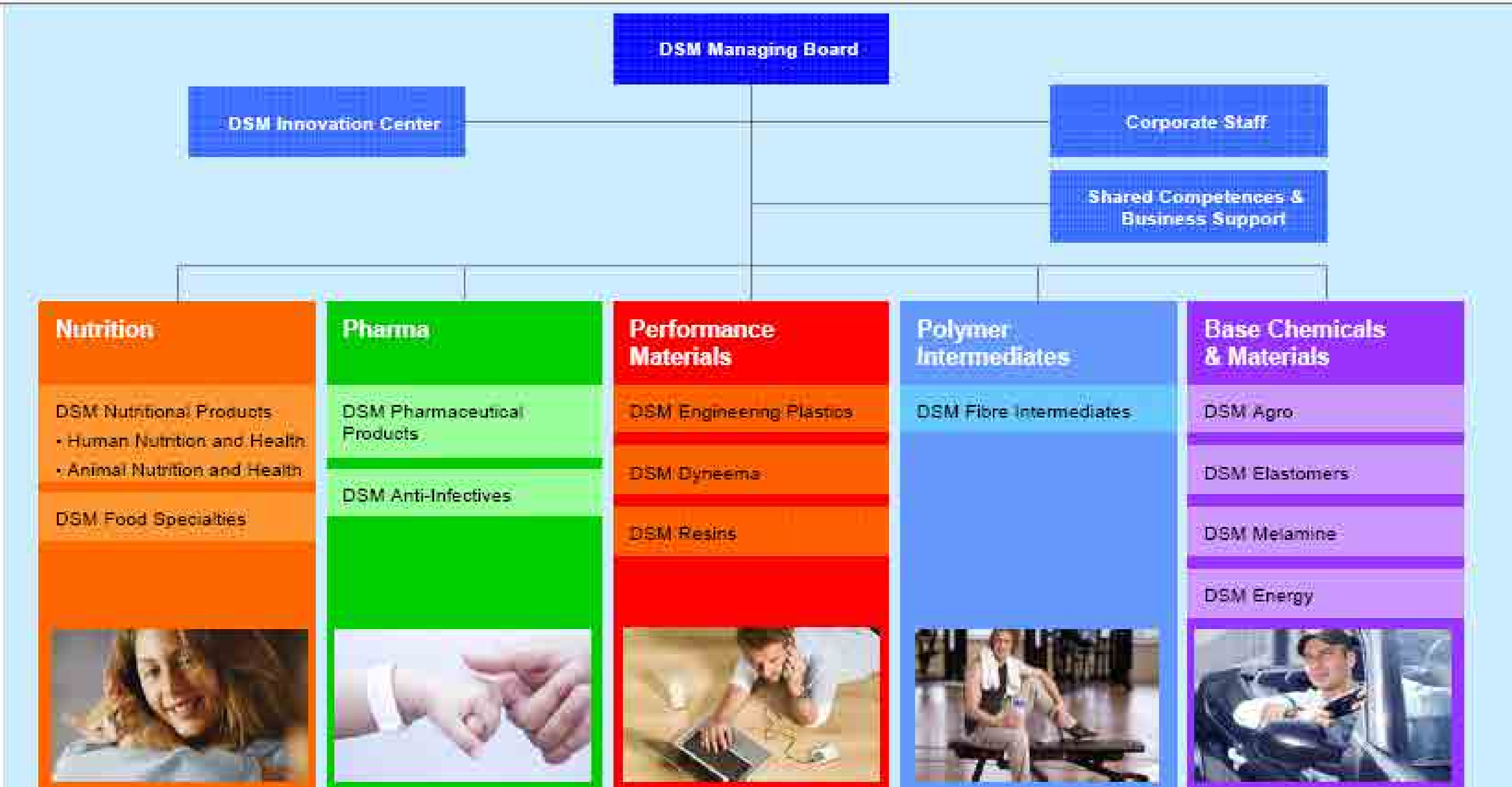
Biologics:
:: Groningen, Netherlands
:: Capua, Italy

Chemical:
:: Linz, Austria
:: Venlo, Netherlands
:: Regensburg, Germany
:: Geleen, Netherlands
:: Vienna, Austria

Corporate & Secondary Manufacturing:
:: Parsippany, USA
:: Greenville, USA

Unlimited. DSM

Organization chart



Where is catalysis applied within DSM?

Analyzing the title

Catalysis within DSM:
Enabling, Improving, and Changing Chemicals Manufacture

Improving:
Catalysis improves a process based on the same starting material
- stoichiometric hydride reduction ➔ catalytic hydrogenation
- protection/deprotection ➔ enzymatic step without protective groups
- 50% yield resolution ➔ 100% yield enantioselective step

Changing:
Catalysis changes a process to allow a more attractive starting material
- stoichiometric multi-step sequence ➔ shorter catalytic route

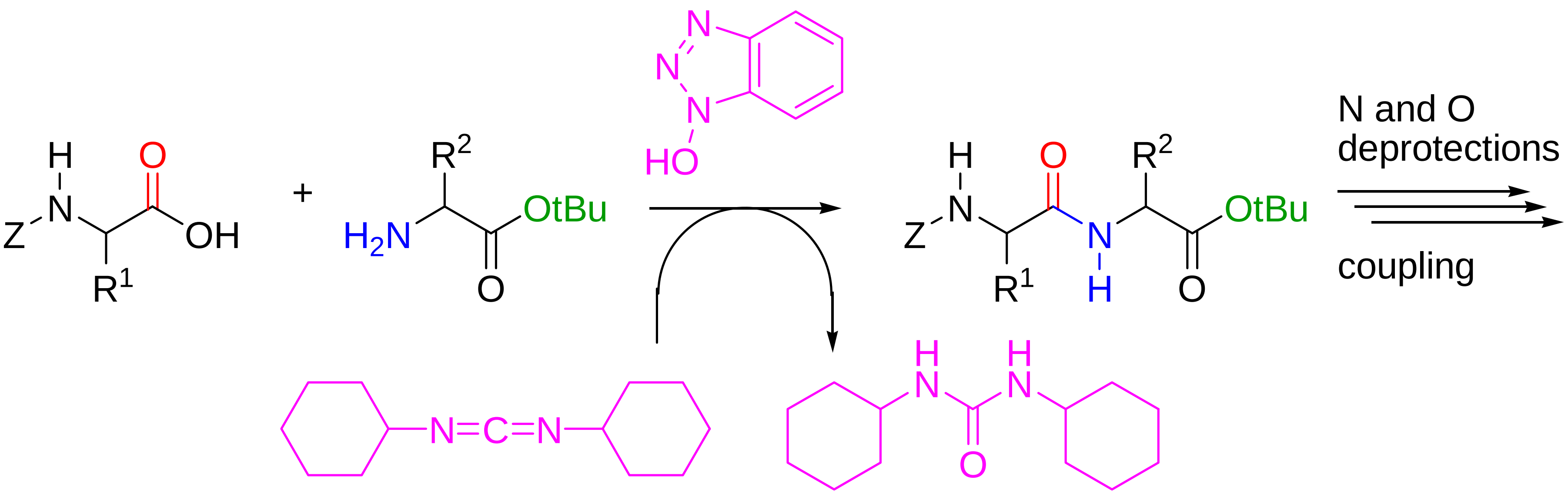
Enabling:
Catalysis enables commercial production; no viable process without catalysis
- med chem route based on stoichiometric lab reagents is far too expensive
- stoichiometric approach requires infrastructure not available on large scale

Improving peptide synthesis

Increased interest in **large scale production** of peptides for food and pharma

But:

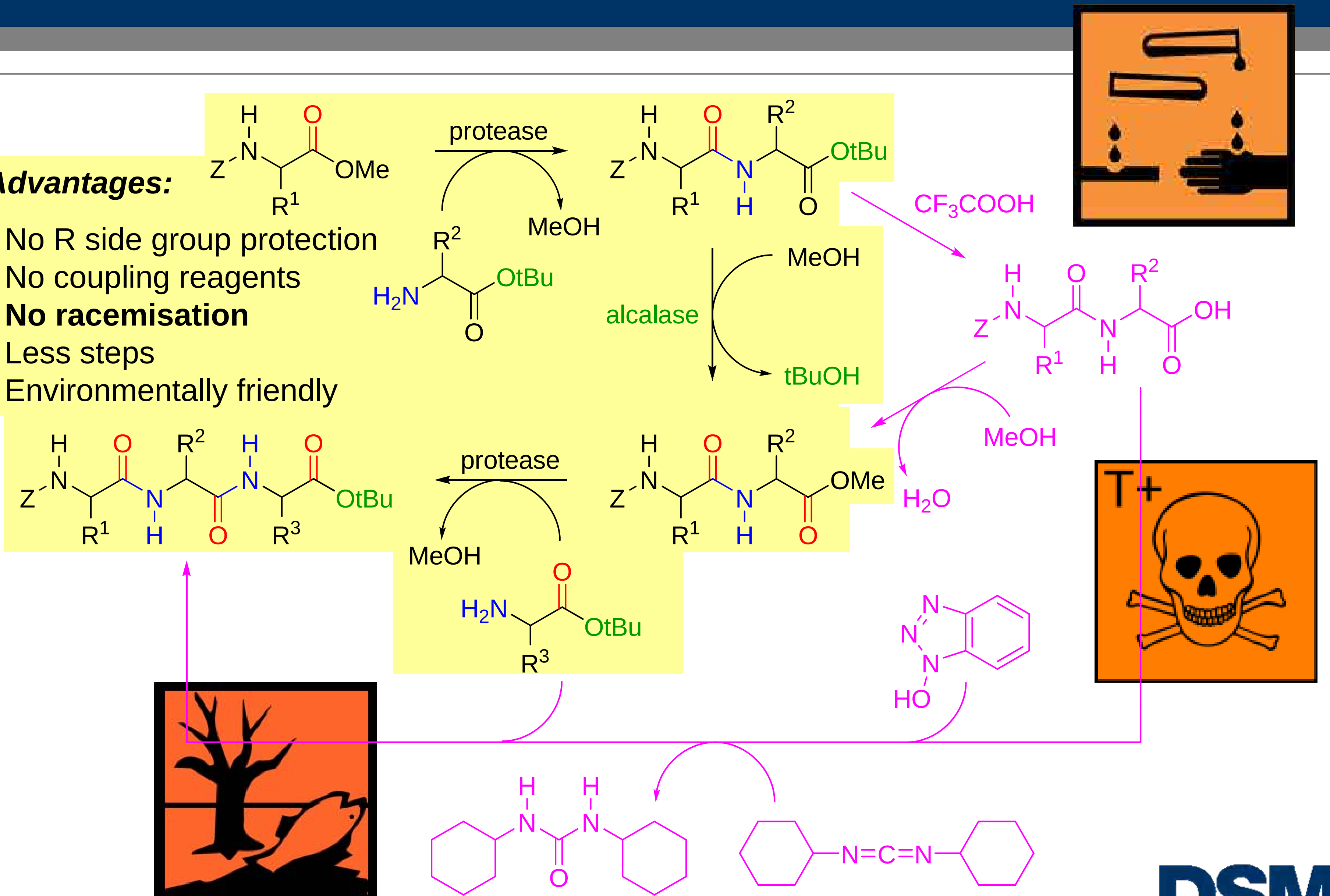
Large scale *chemical* synthesis is costly, waste generating, and time consuming...



DSM's chemoenzymatic peptide coupling

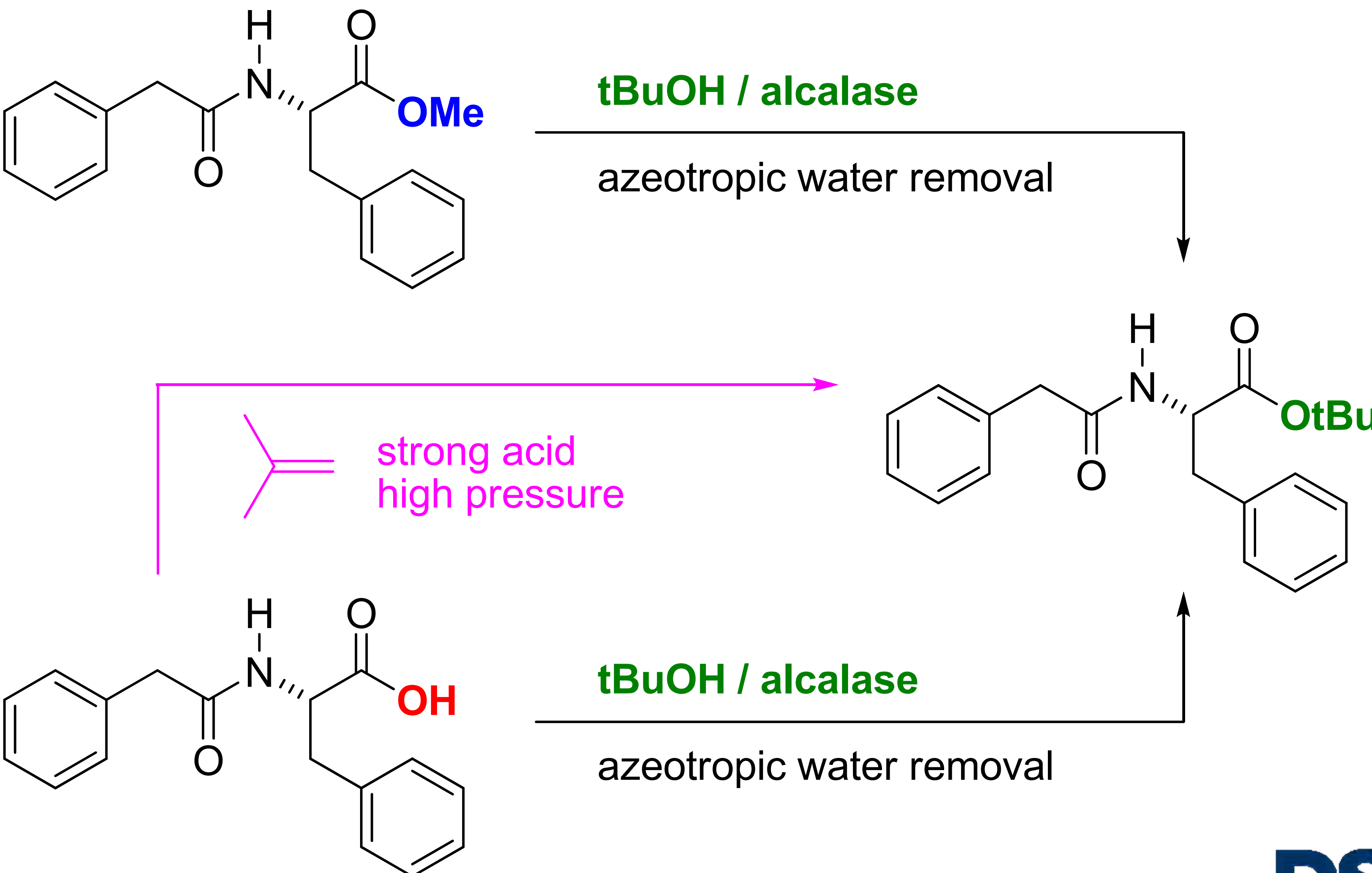
Advantages:

- No R side group protection
- No coupling reagents
- **No racemisation**
- Less steps
- Environmentally friendly



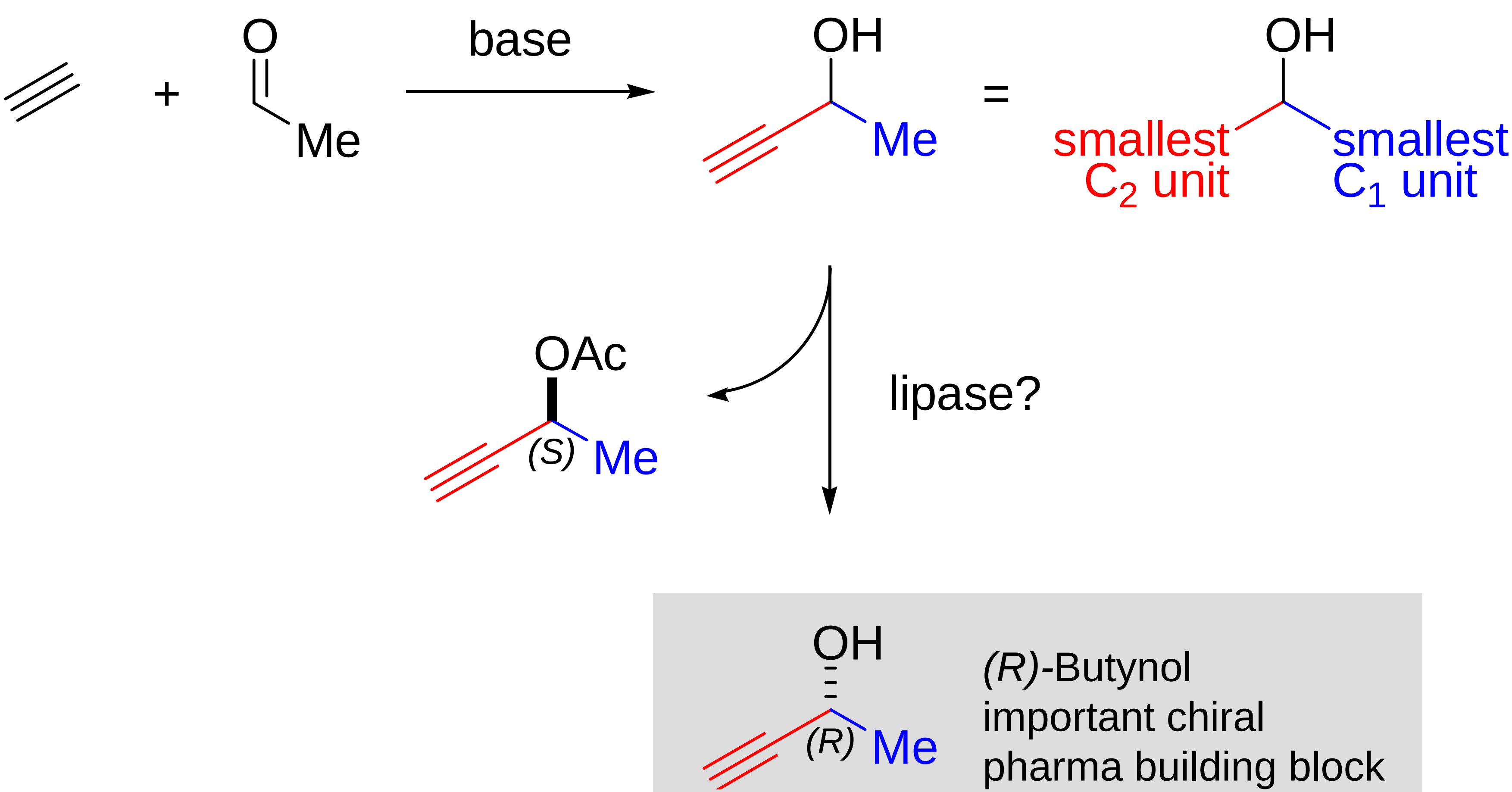
Using alcalase the other way round:

Synthesis of tBu esters



Improved synthesis of a challenging chiral alcohol[10]

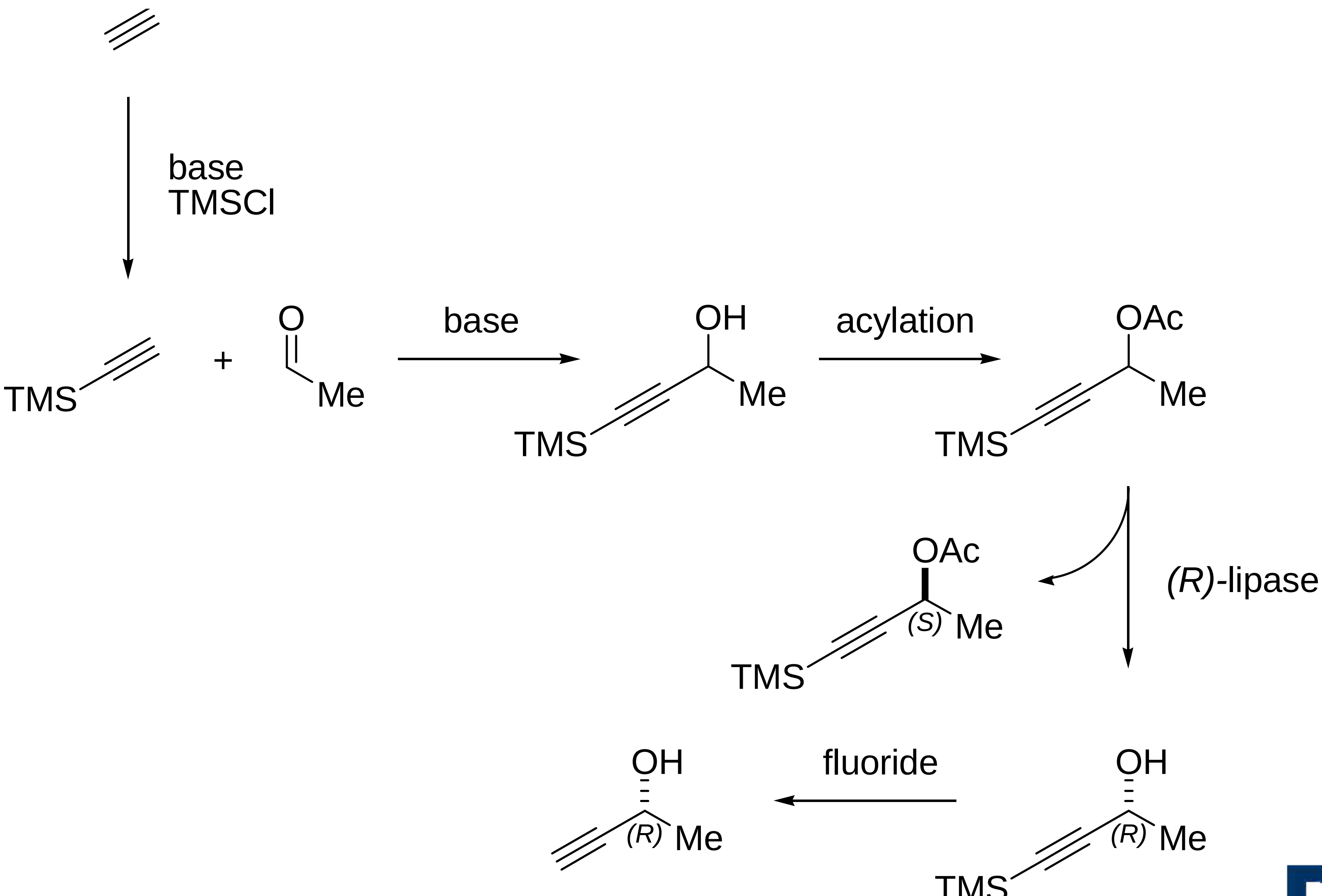
An obvious approach



(R)-Butynol
important chiral
pharma building block

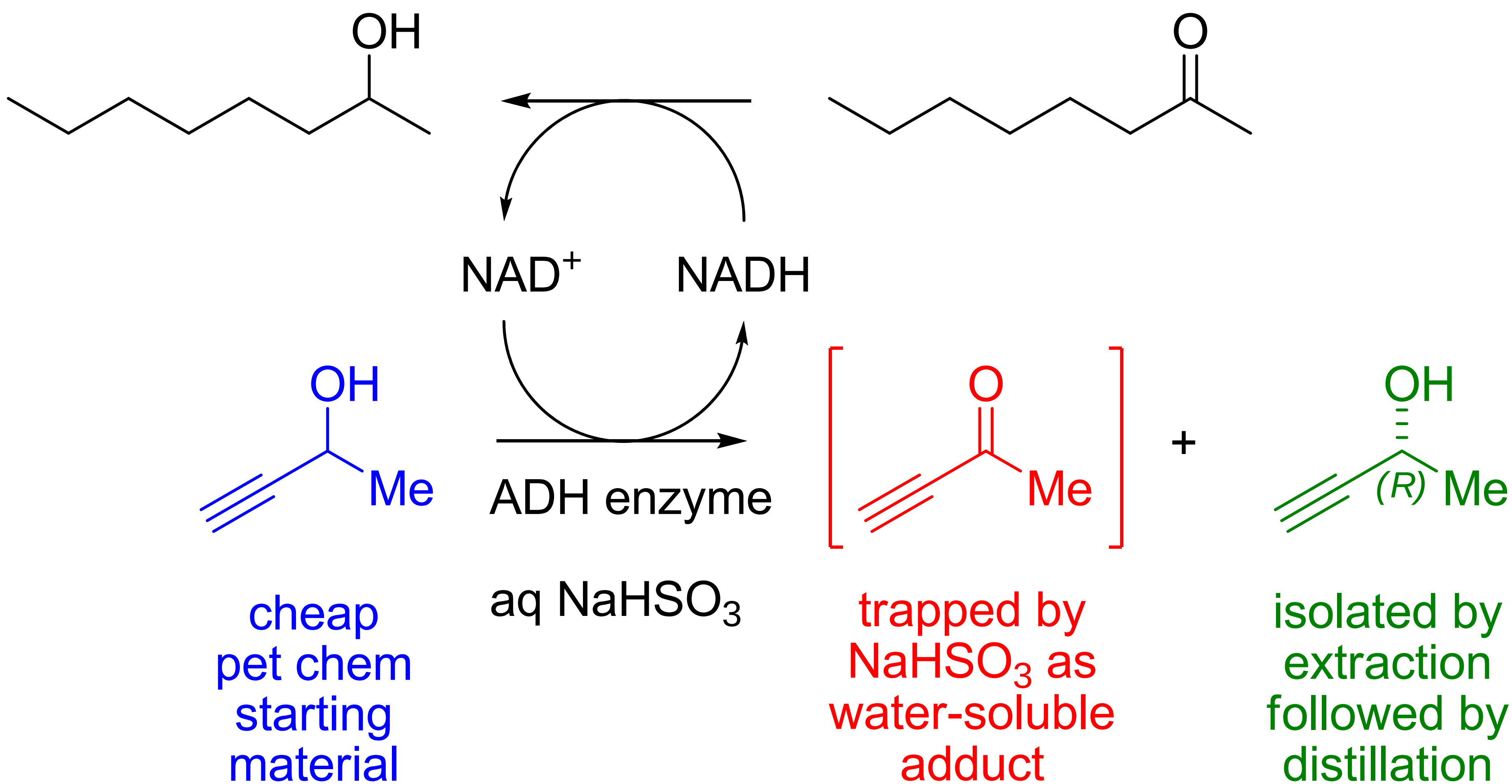
The conventional solution to achieve high ee

Increasing steric bulk by substrate modification



The DSM approach

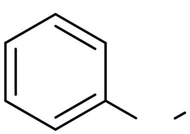
1 Step resolution via ADH catalyzed *(S)*-oxidation

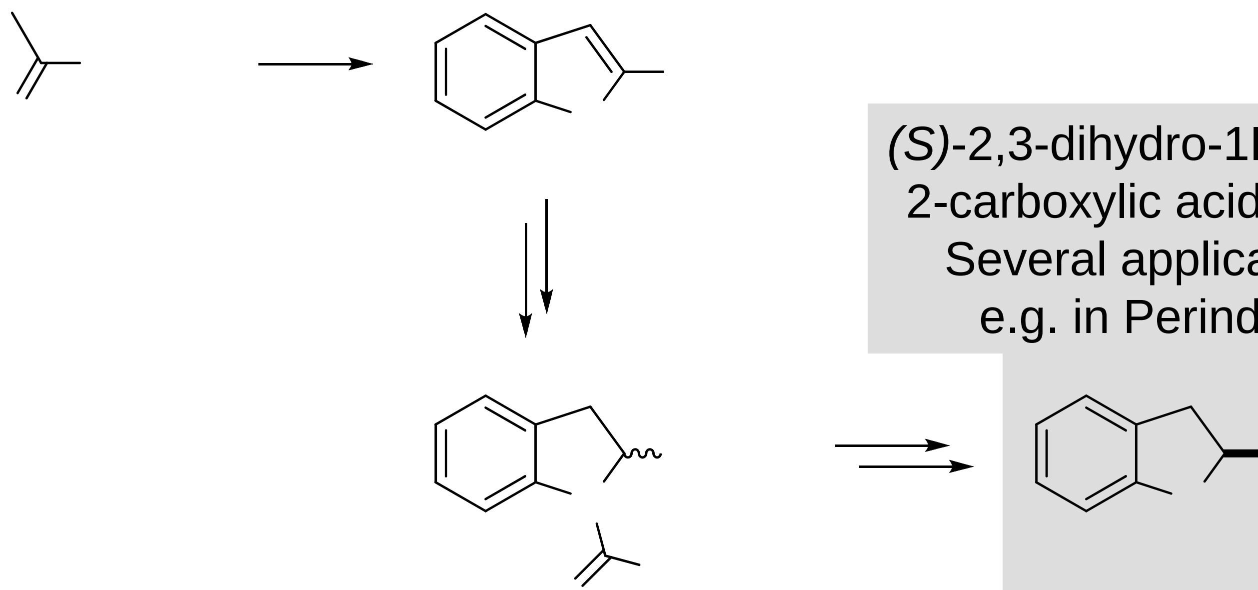


Changing production of a pharma intermediate

Old non-enantioselective 5 step route

Fischer indole + classical resolution





(*S*)-2,3-dihydro-1H-indole-2-carboxylic acid (Indac)
Several applications,
e.g. in Perindopril

CO_2Et

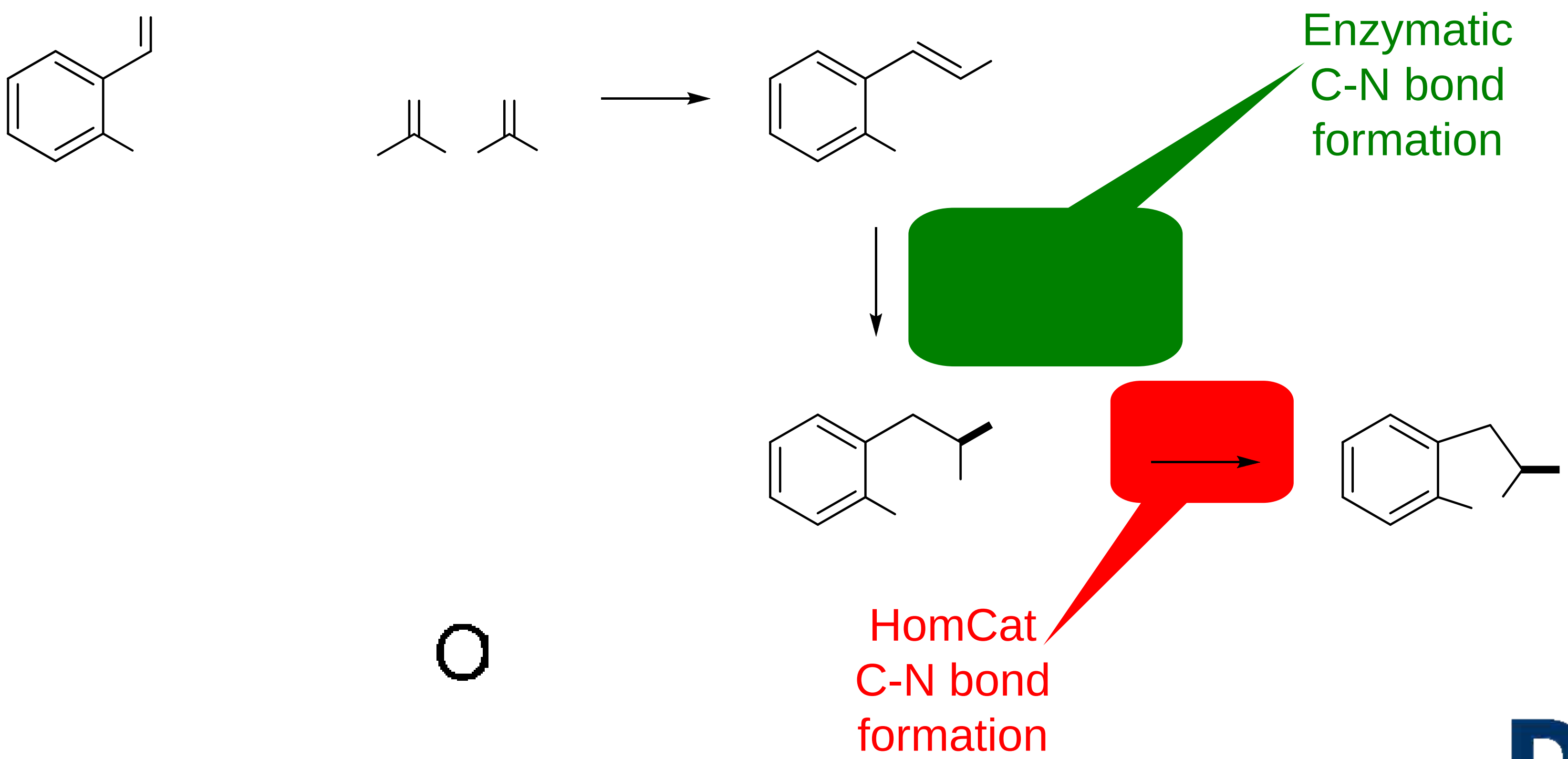
NH_2

Unlimited. DSM

DSM approach based on double C-N formation

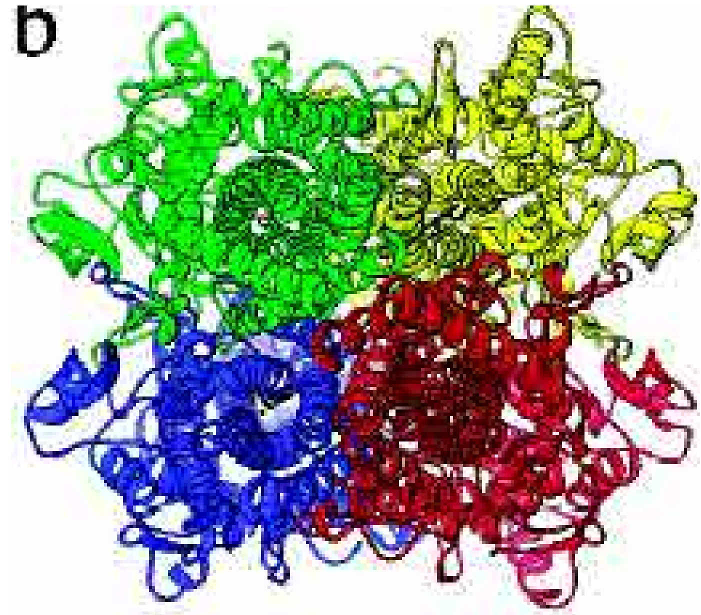
DSM enantioselective 3 step route

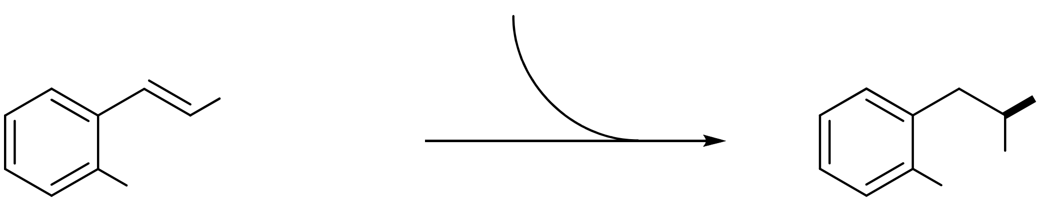
Shortcut via combined bio- and homogeneous catalysis



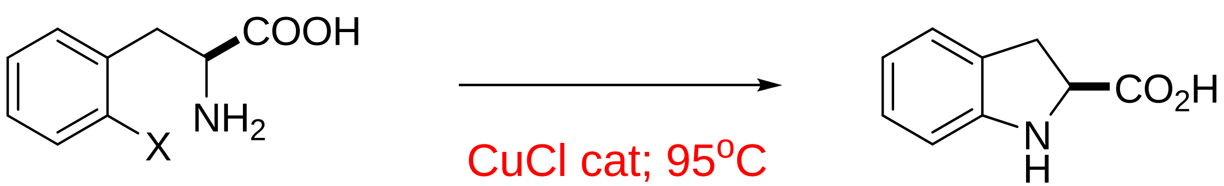
Phenylalanine Ammonia Lyase (PAL)

- Phenylalanine Ammonia Lyases are well known for Phe
- Structure of *R. glutinis* PAL is known, Calabrese *et al*., 2004
- No cofactor required
- *(S)*-specific
- "Standard" literature conditions:
  10% NH_3, pH 10.
- Broad substrate scope





Cu-catalyzed ring closure

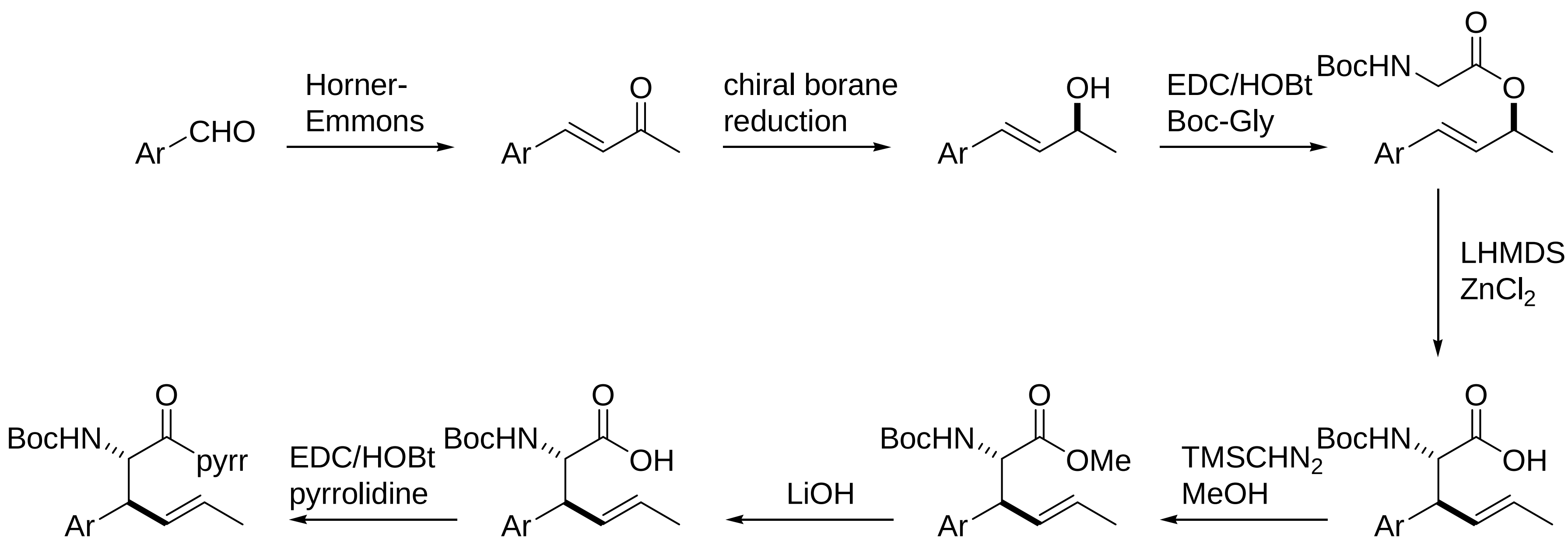


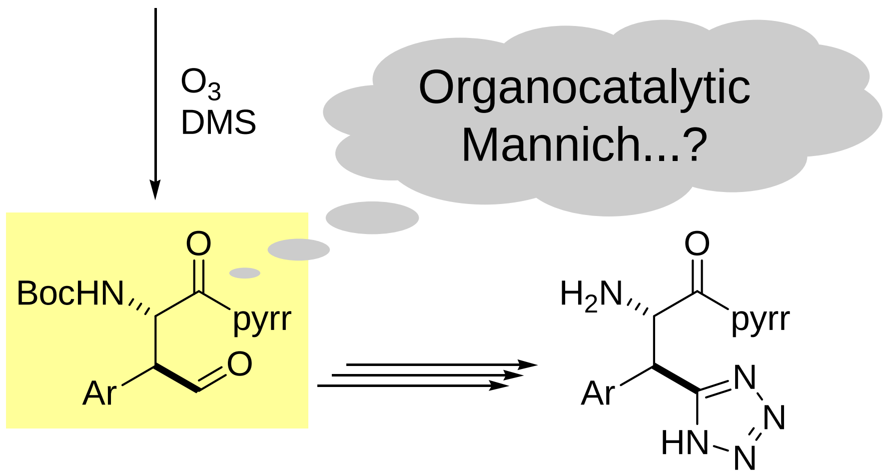
CuCl cat; 95^{o}C
1 eq K_2CO_3
water solvent

X = Br: 95% yield after 5 h@0.01 mol% Cu
X = Cl: 76% yield after 2 h@4.00 mol% Cu

Changing synthesis of a DPP-IV inhibitor

Stoichiometric med chem Merck route to DPP-IV inhibitors



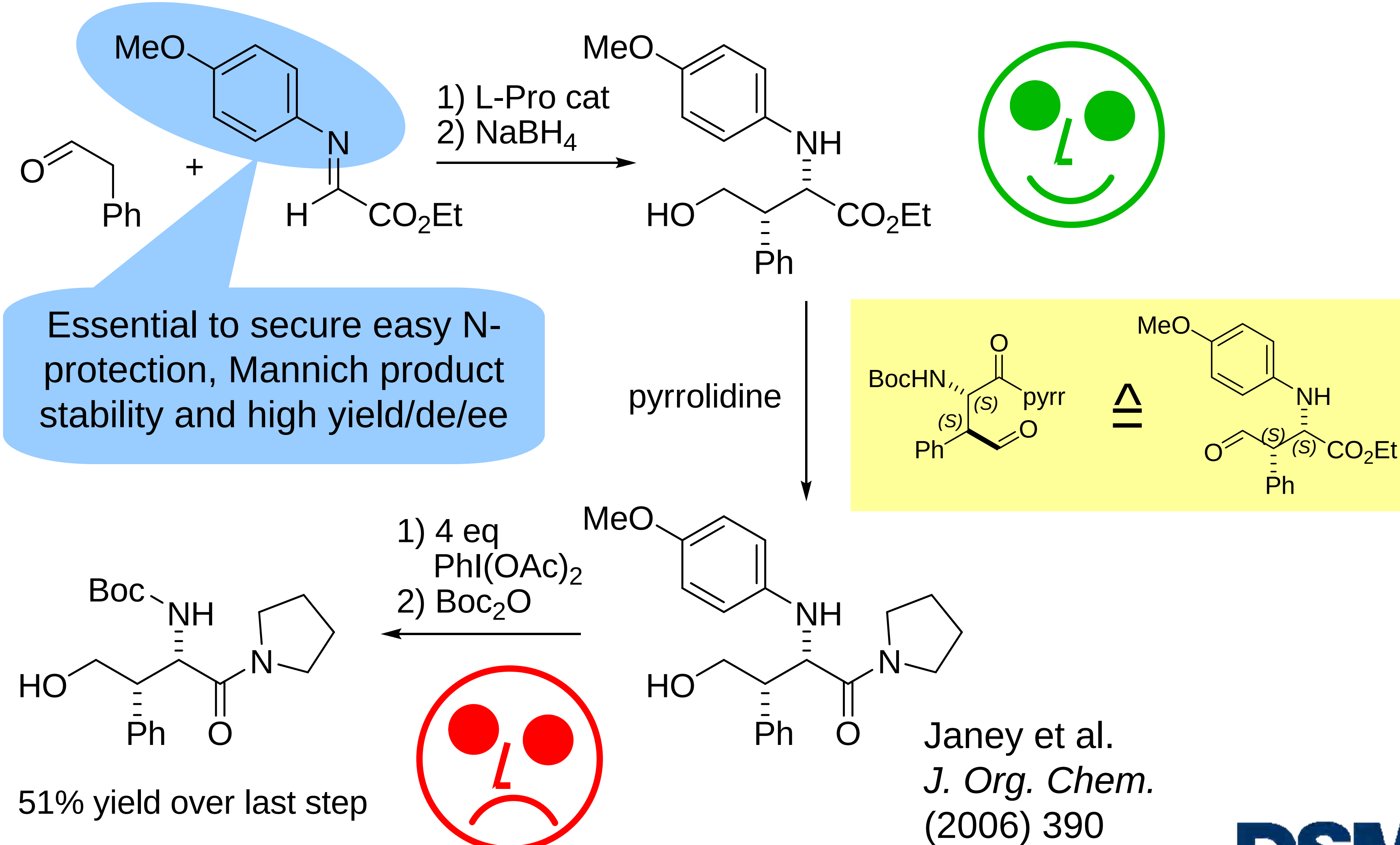


Preparation of DPP-IV inhibitors
with substituted Ar and pyrr groups

Edmondson et al.
Bioorg.Med.Chem. Lett.
(2005) 3048

Organocatalytic alternative to DPP-IV Inhibitors

Proline-Catalyzed, Asymmetric Mannich Reaction (Merck)



Essential to secure easy N-protection, Mannich product stability and high yield/de/ee

51% yield over last step

Janey et al.
J. Org. Chem.
(2006) 390

Methods for PMP removal

How to make PMP-based (organo)catalysis scalable?

N-PMP → N-H

- Excess CAN (ceric ammonium nitrate)

  Classical method most commonly applied

- Excess $PhI(OAc)_2$

  Hoveyda et al. *J. Am. Chem. Soc.* (2001) 10409

- Electrochemical

  Mioskowski et al. *J. Org. Chem.* (2005) 10592

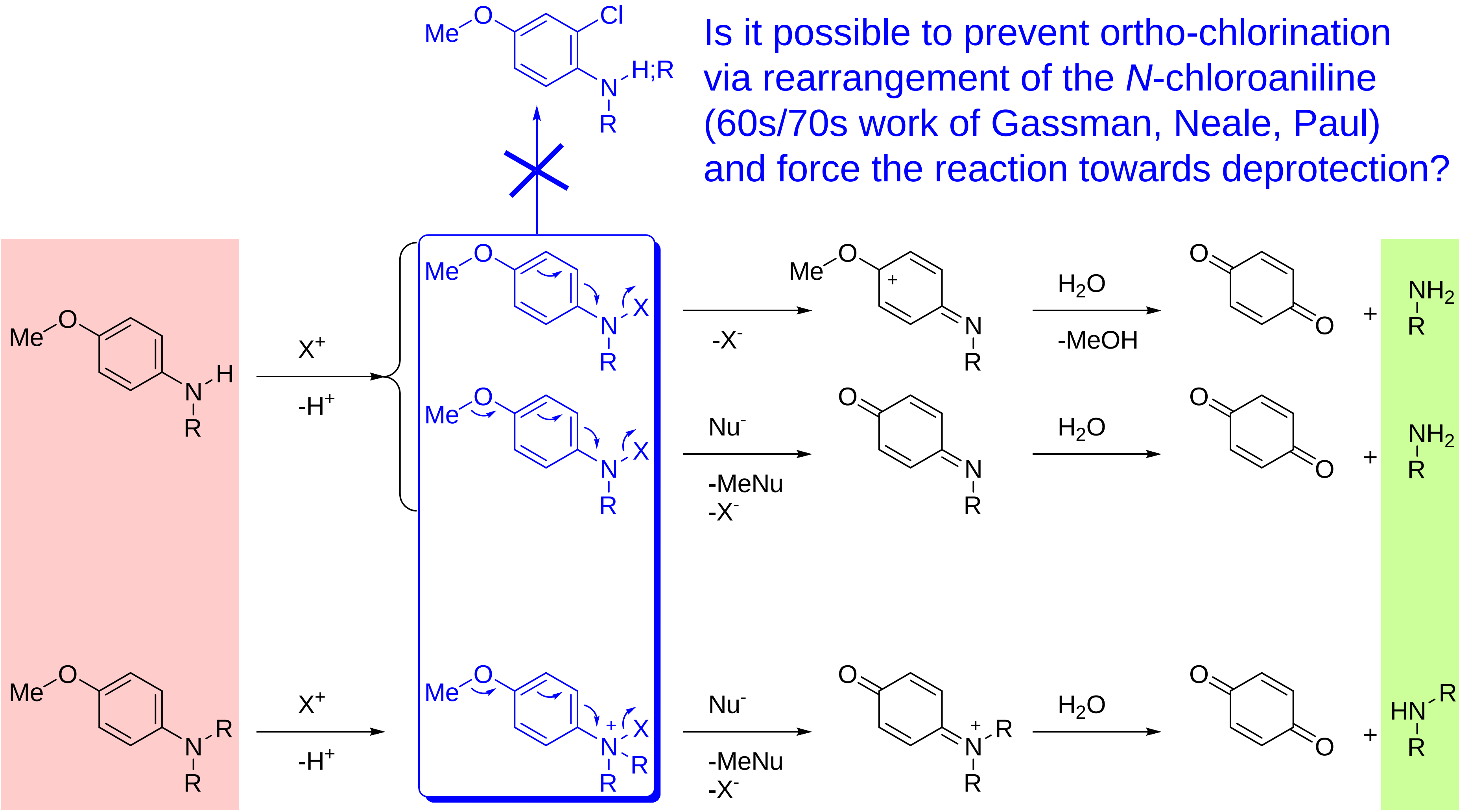
Clear need for a broadly applicable, inexpensive and scalable PMP deprotection method

Unlimited. DSM

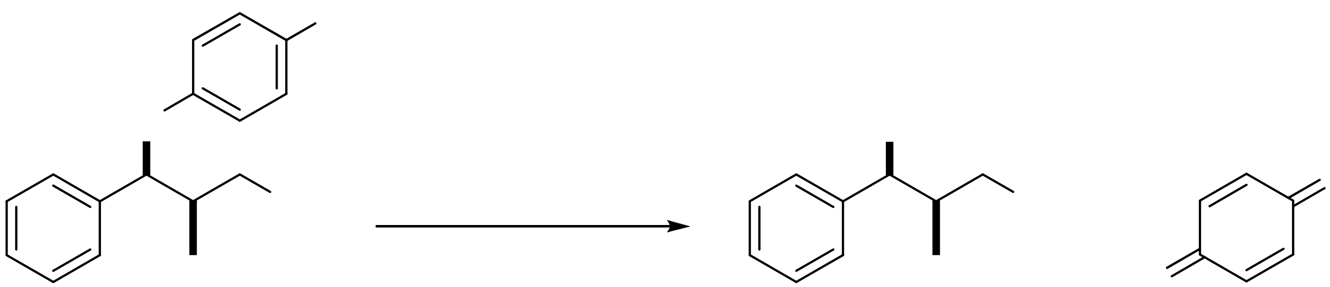
How about positive halogen reagents?

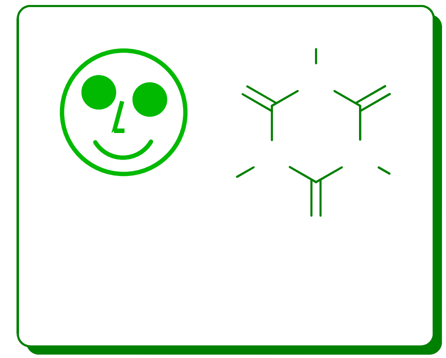
From 1 electron Ce(IV) to 2 electron X^{n+} oxidation

Is it possible to prevent ortho-chlorination via rearrangement of the *N*-chloroaniline (60s/70s work of Gassman, Neale, Paul) and force the reaction towards deprotection?



Testing various X^{n+} oxidants: it works!





Entry	Oxidant	Equivalents	Yield (%)	Entry	Oxidant	Equivalents	Yield (%)
1	CAN	1	34 (20 h)	15	NCS	1	41 (8 h)
2	CAN	4	42 (20 h)	16	NCS	4	81 (8 h)
3	$PhI(OAc)_2$	1	47 (20 h)	17	NBS	1	77 (8 h)
4	$PhI(OAc)_2$	4	64 (20 h)	18	NBS	4	75 (8 h)
5	Dess-Martin	1	48 (20 h)	19	NIS	1	57 (8 h)
6	Dess Martin	4	67 (20 h)	20	NIS	4	80 (8 h)
7	TCCA	1	82 (20 h)	21	HOCl	1	41 (20 h)
8	TCCA	4	0 (20 h)	22	HOCl	4	81 (20 h)
9	H_5IO_6	1	87 (20 h)	23	$pyH^+Br_3^-$	1	60 (20 h)
10	H_5IO_6	4	75 (20 h)	24	H_2O_2	4	<5 (8 h)
11	Br_2	1	50 (8 h)	25	$KMnO_4$	4	15 (8 h)
12	Br_2	4	50 (8 h)	26	$NaBO_3 \cdot 4H_2O$	4	0 (8 h)
13	I_2	1	53 (8 h)	27	$Na_2CO_3 \cdot 1.5H_2O_2$	4	0 (8 h)
14	I_2	4	55 (8 h)	28	$K_2Cr_2O_7$	4	0 (8 h)

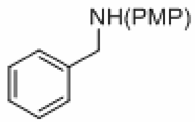
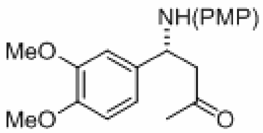
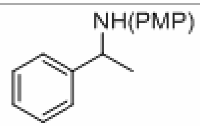
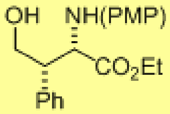
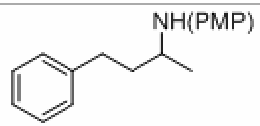
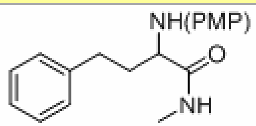
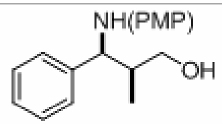
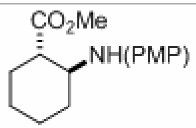
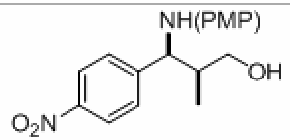
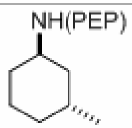
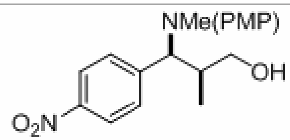
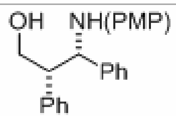
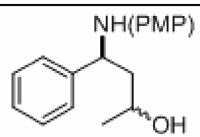
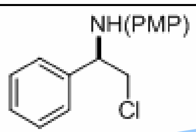
Unlimited. DSM

Scope and synthetic applications

Savings on oxidant:

mass ratio 0.5-0.7 eq TCCA / 4 eq $PhI(OAc)_2$ = 0.09-0.13 ⇒ 91-87% reduction of oxidant

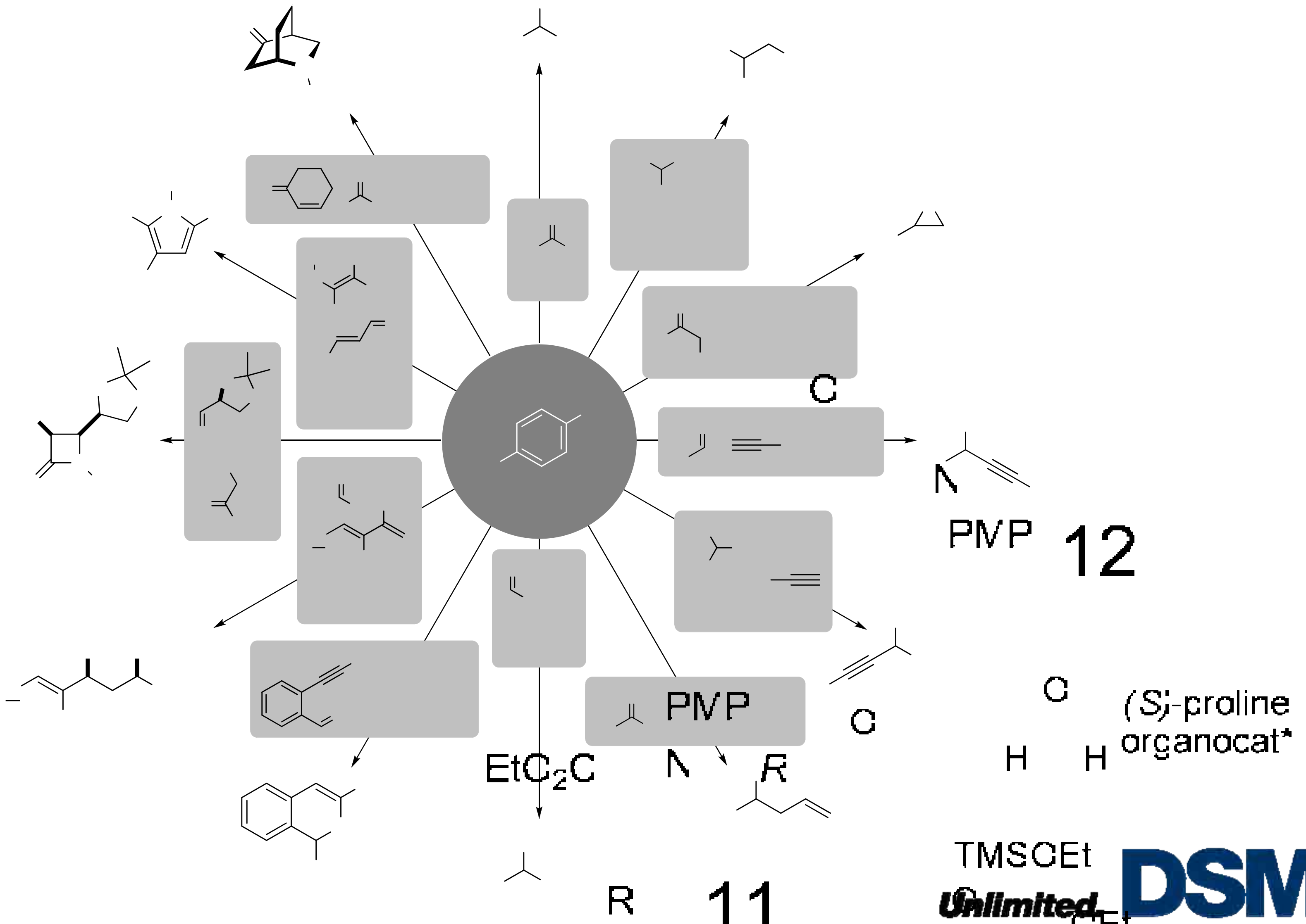
Table 1. Preparative scale examples of N-PMP deprotection with TCCA or H_5IO_6.

Entry	Substrate	Yield (Oxidant)	Ref	Entry	Substrate	Yield (Oxidant)	Reference
1		73% (TCCA) <5% (H_5IO_6)	Rutjes et al. *Tetrahedron Lett.* **2006**, *47*, 8109	8		49% (H_5IO_6) unstable product	Rutjes et al. *J. Org. Chem.* **2009**, *74*, 3207
2		99% (TCCA) 89% (H_5IO_6)	Rutjes et al. *Tetrahedron Lett.* **2006**, *47*, 8109	9		90% (TCCA)	Rutjes et al. *unpublished result*
3		73% (TCCA) 80% (H_5IO_6)	Rutjes et al. *Tetrahedron Lett.* **2006**, *47*, 8109	10		88% (TCCA)	Li et al. *Angew. Chem. Int. Ed* **2008**, *47*, 7075
4		80% (TCCA) 99% (H_5IO_6)	Rutjes et al. *Tetrahedron Lett.* **2006**, *47*, 8109	11		51% (H_5IO_6) (over 2 steps)	Hamada et al. *Tetrahedron. Asymm.* **2008**, *19*, 1751
5		99% (TCCA) 95% (H_5IO_6)	Rutjes et al. *Tetrahedron Lett.* **2006**, *47*, 8109	12		90% (H_5IO_6)	List et al. *Synlett* **2007**, *13*, 2037
6		77% (TCCA) 66% (H_5IO_6)	Rutjes et al. *Tetrahedron Lett.* **2006**, *47*, 8109	13		NR (TCCA)	Malkov et al. *Chem. Eur. J.* **2008**, *14*, 8082
7		81% (TCCA) 95% (H_5IO_6)	Rutjes et al. *Tetrahedron Lett.* **2006**, *47*, 8109	14		NR (TCCA)	Malkov et al. *Angew. Chem. Int. Ed* **2007**, *46*, 3722

It is pertinent to note that for the deprotection of the nitrogen atom, use of TCCA proved to be superior to the known methods that employ Ce^{IV} or $PhI(OAc)_2$, which gave intractable mixtures.

Synthetic versatility of N-PMP

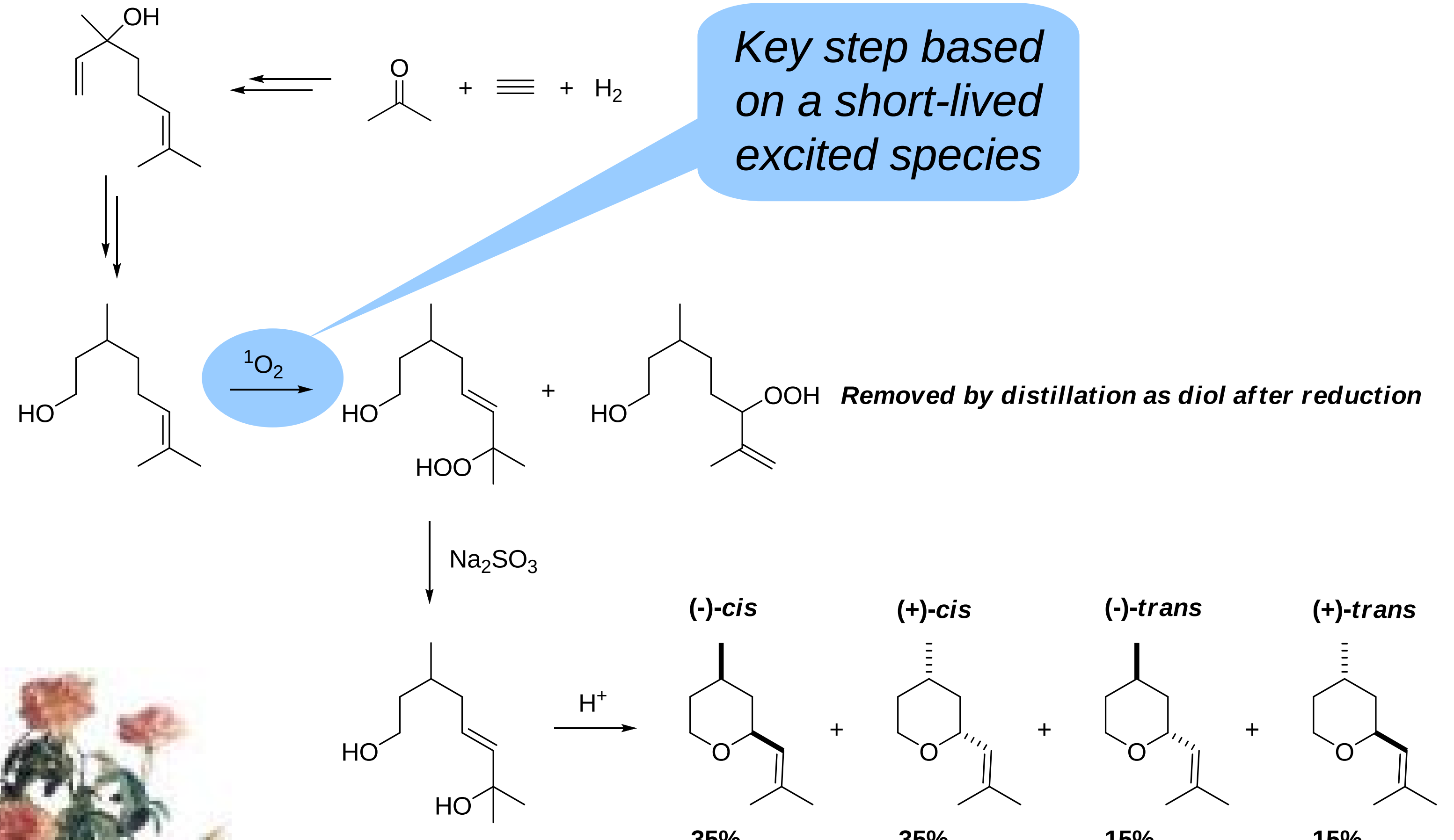
Uses in stoichiometric synthesis and catalysis



Unlimited. DSM

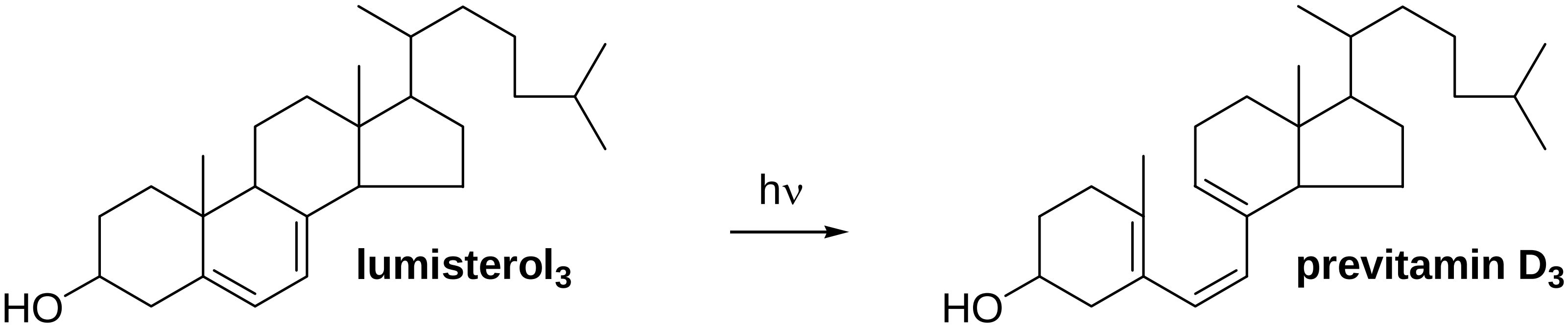
Enabling production of an F&F compound

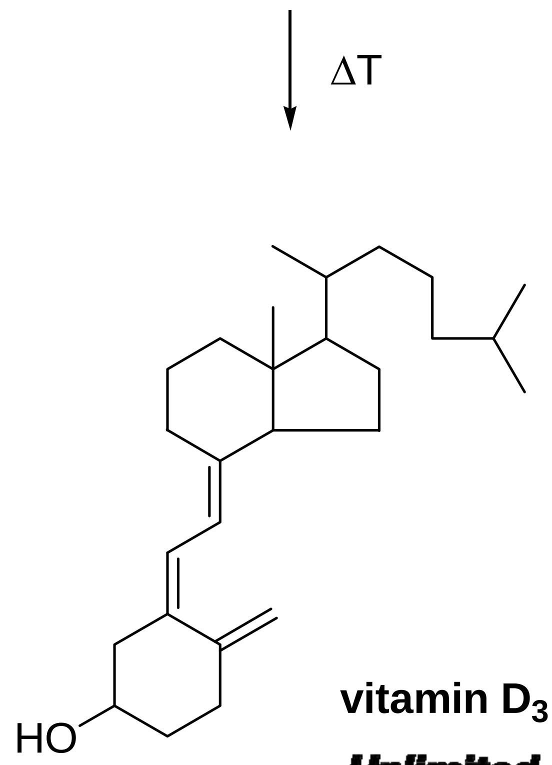
Rose Oxide from Citronellol via Linalool



5000 kg rose flowers yield 1 kg rose oil

Rose Oxide via singlet oxygenation:
Can we do photochemistry within DSM...?





...but not for "dark" singlet oxygenation...

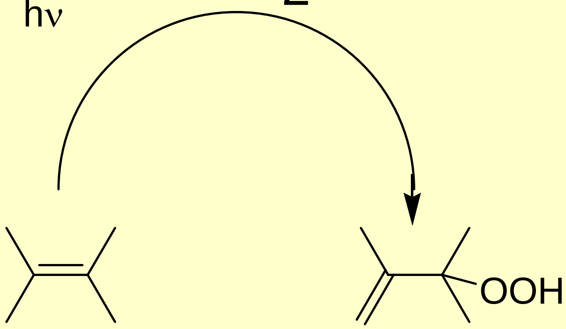
Too much €€€ for investment in proper $^1O_2$ photoreactor...

DSM Unlimited.

Generating singlet oxygen:
Photo- vs. "dark" singlet oxygenation (DSO)

Photo-singlet oxygenation:

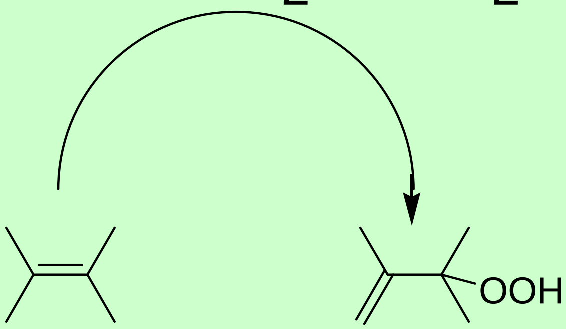
$$^{3}O_2 \xrightarrow[h\nu]{\text{sensitizer}} {}^{1}O_2$$



Requires dedicated bubble column photo-reactors

“Dark” singlet oxygenation:

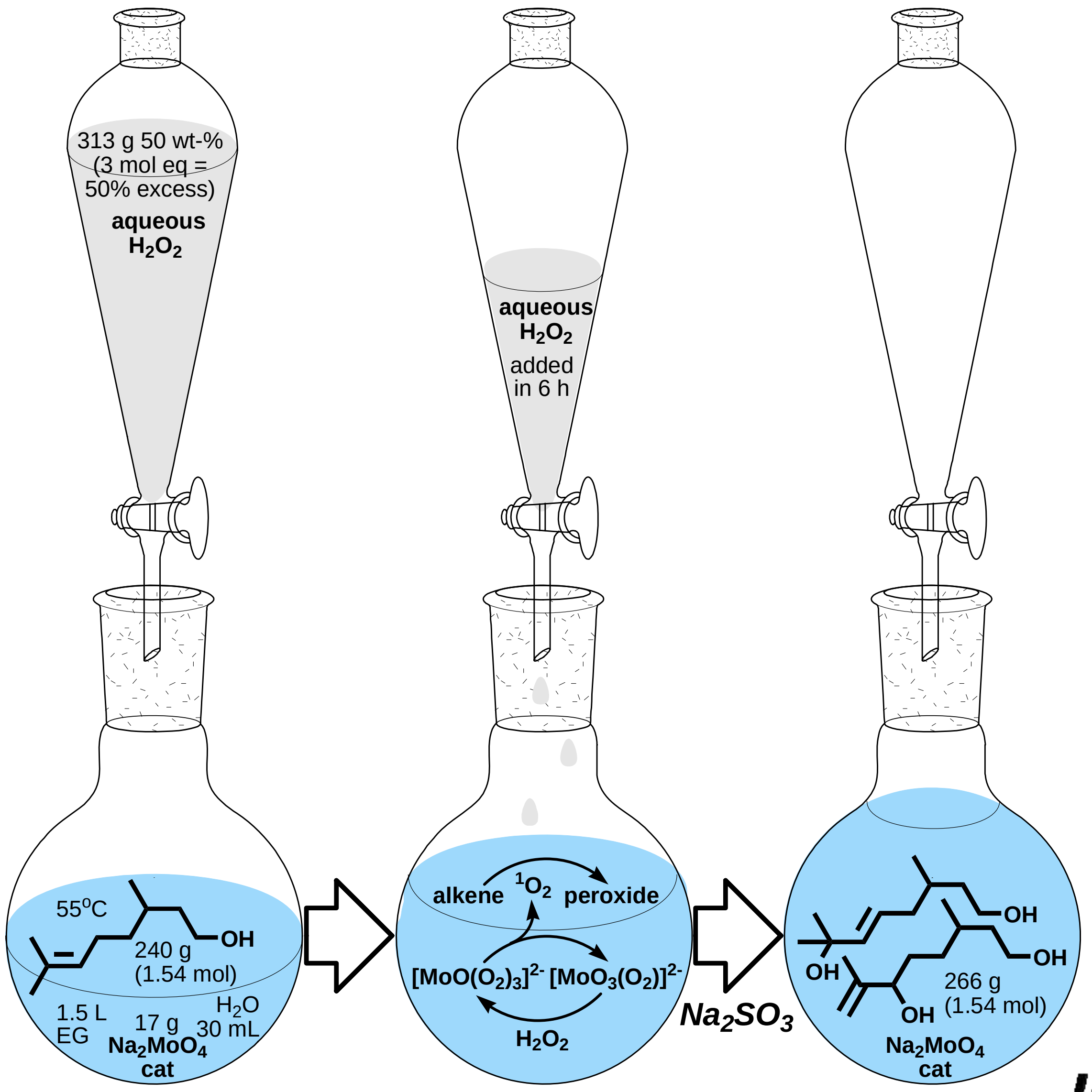
$$2\ H_2O_2 \xrightarrow{\text{catalyst}} {}^{1}O_2 + 2\ H_2O$$



Suitable for multi-purpose plant stirred-tank reactors

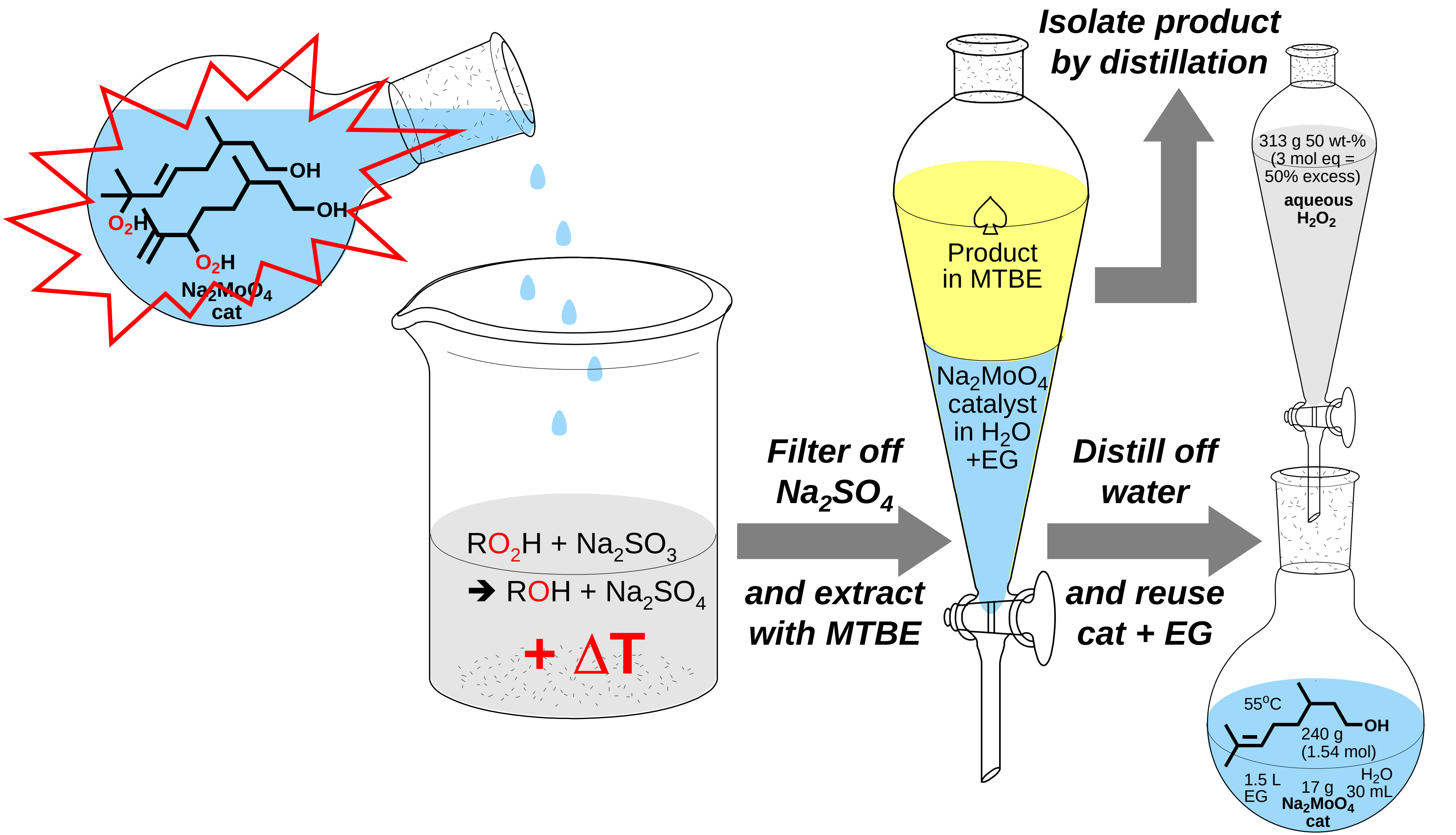
DSO of citronellol in Ethylene Glycol (EG)

Catalysis enables production in normal CSTR



Unlimited. DSM

Product isolation and catalyst recycling

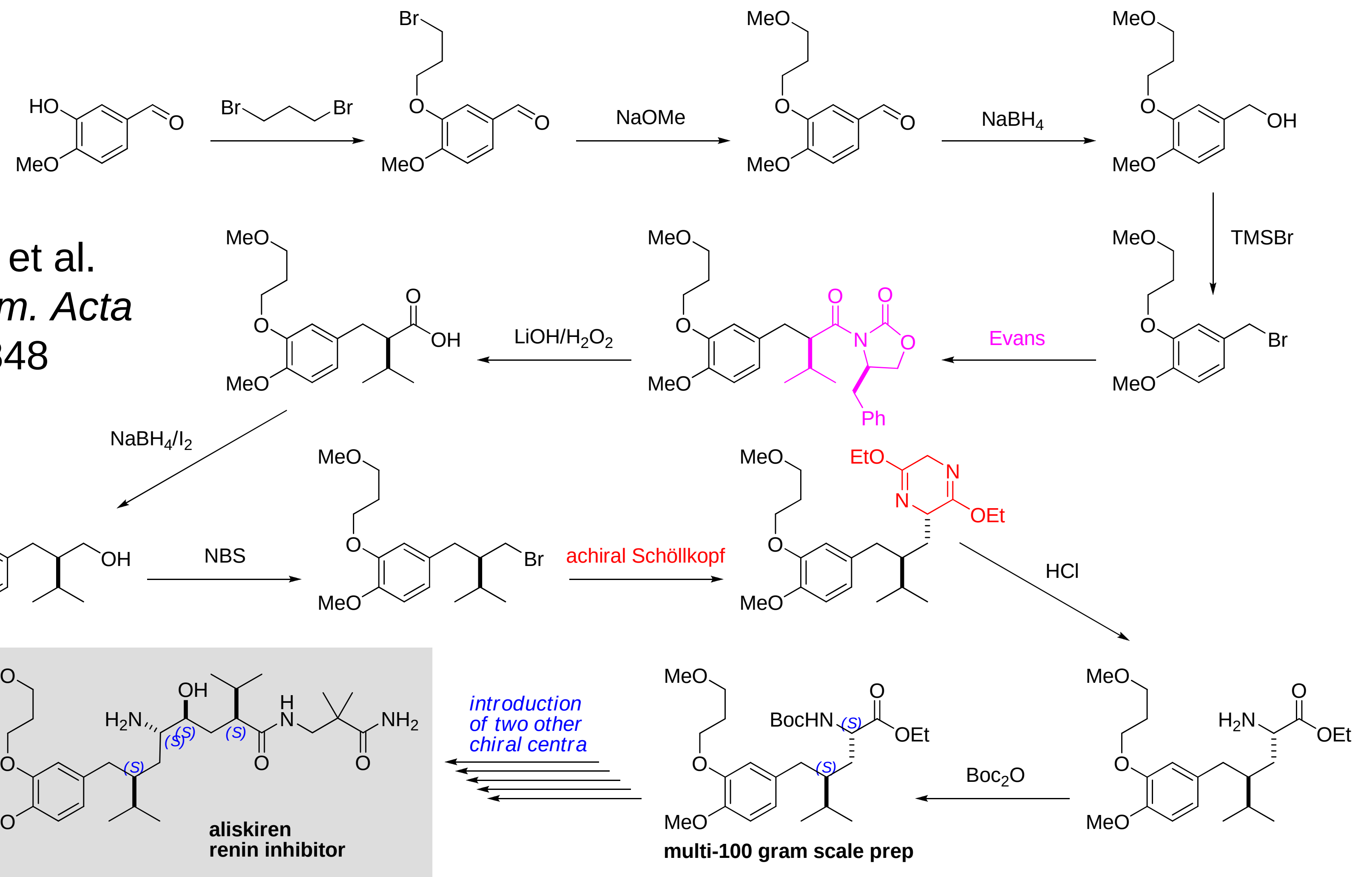


Unlimited. DSM

Enabling production of a pharma intermediate

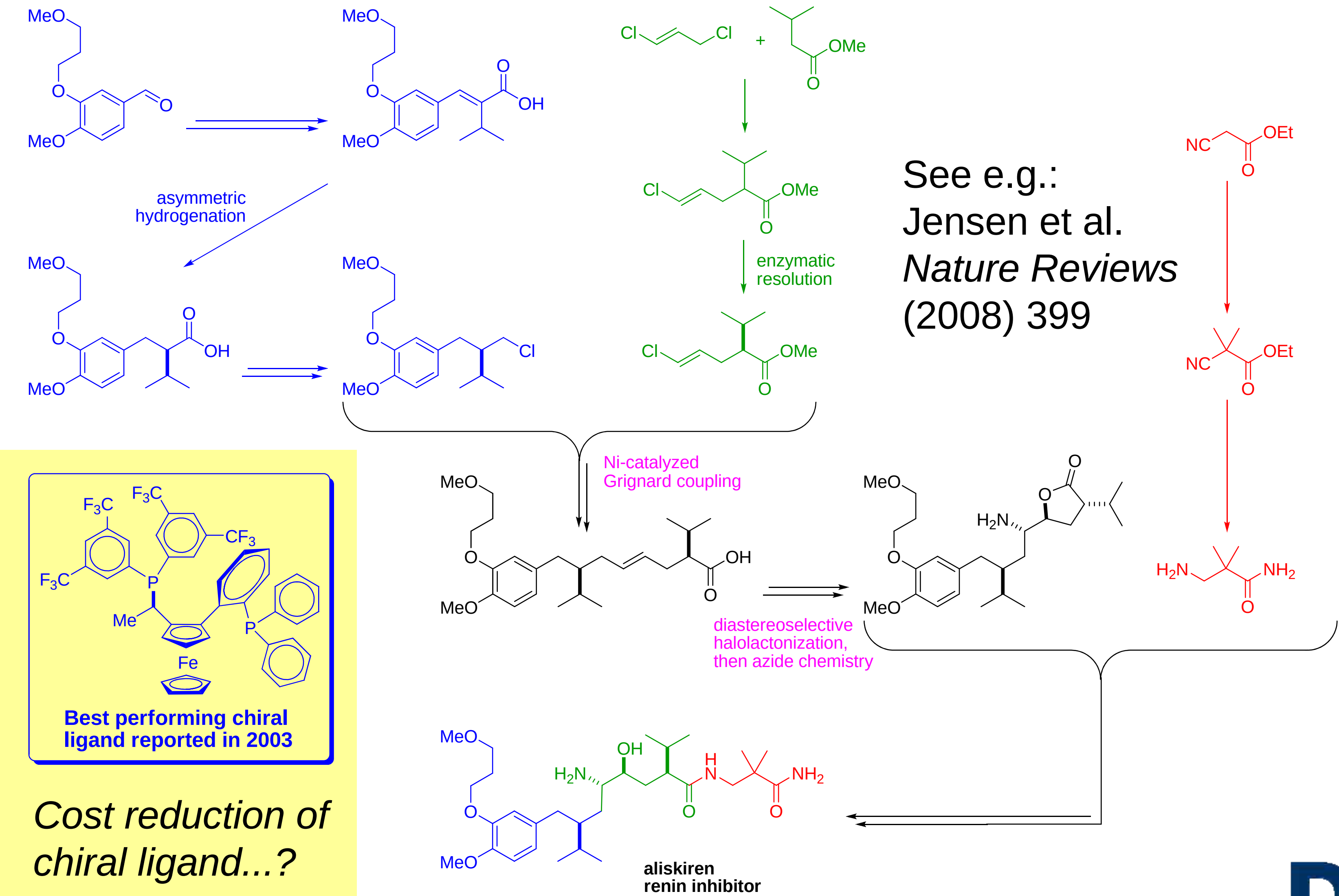
Stoichiometric med chem Novartis route to aliskiren

Maibaum et al.
Helv. Chim. Acta
(2003) 2848



Speedel's convergent synthon A, B, C approach

Shortcuts via combined bio- and homogeneous catalysis

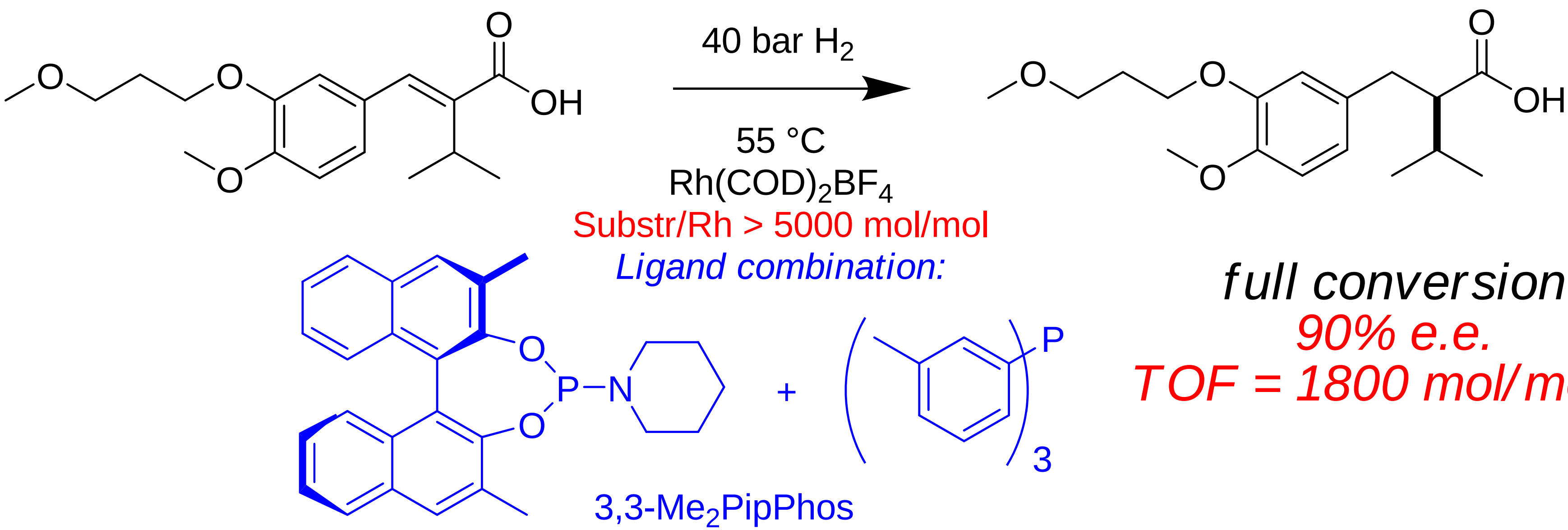


See e.g.:
Jensen et al.
Nature Reviews
(2008) 399

Cost reduction of chiral ligand...?

Cheap 3,3-Me_2PipPhos made it in the DSM plant!

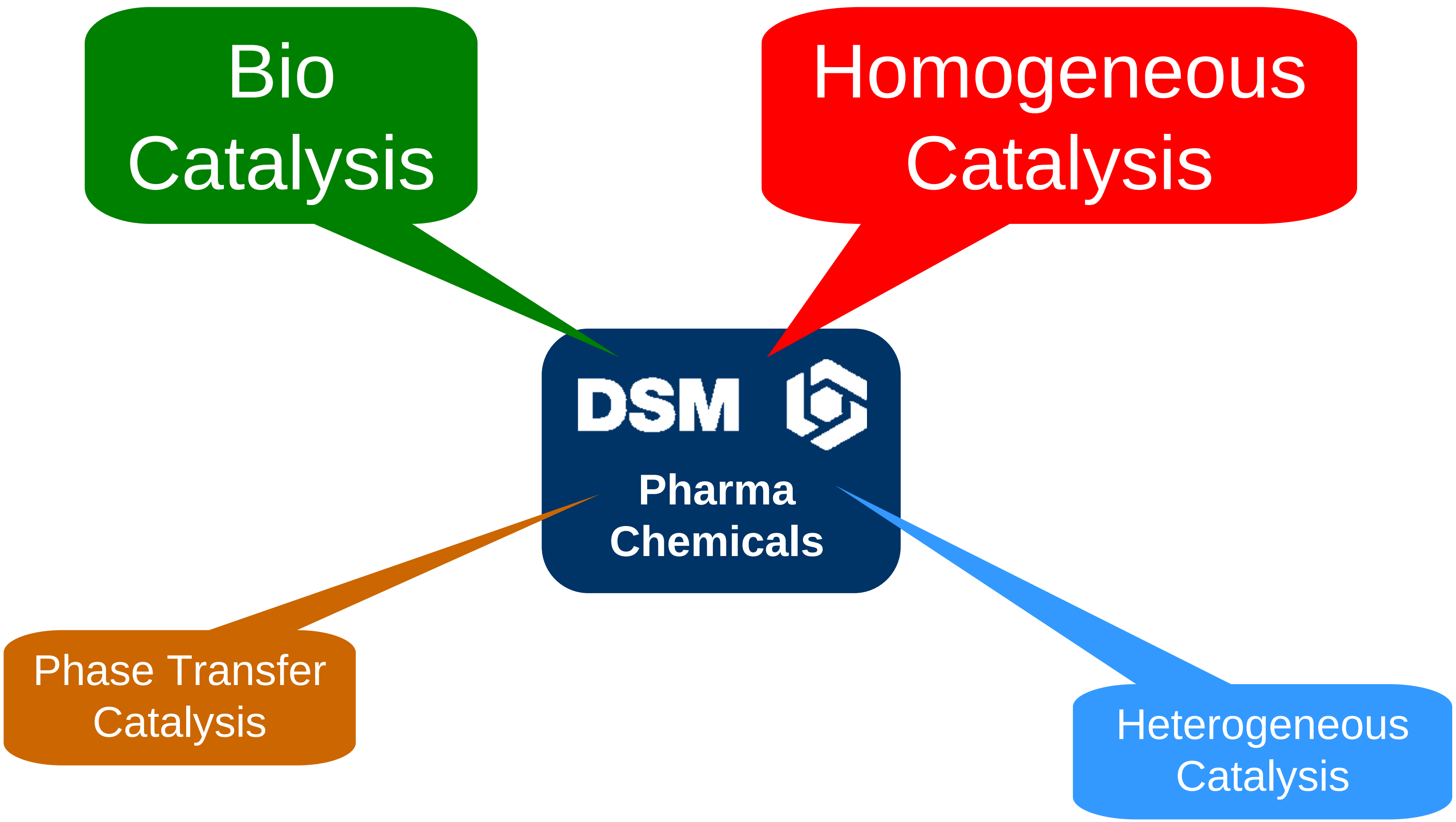
Thanks to support from a non-chiral phosphine



full conversion
90% e.e.
TOF = 1800 mol/mol/h

Catalyst system derived *in situ* from $Rh(COD)_2BF_4$, 3,3-dimethyl-PipPhos, and non-chiral phosphine applied at multi ton scale.

Catalysis within DSM Pharma Chemicals:
Enabler for economic, safe, and green processing



Acknowledgement

DSM:

Linz (Austria):

- Walther Jary
- Ruth Müllner
- Peter Pöchlauer
- Marion Wagner
- Ulfried Felfer
- Martina Kotthaus
- Wolfgang Skranc

Geleen (Netherlands):

- Peter Quaedflieg
- Claudia Cusan
- Timo Nuijens
- Harold Moody
- Friso van Assema
- Natascha Sereinig
- Stefaan de Wildeman
- Harrie Straatman
- Peter Maas
- Ben de Lange

DSM Geleen (Netherlands) continued:

- Jeroen Boogers
- Laurent Lefort
- André de Vries
- Hans de Vries

Univ. Groningen (Netherlands):

- Prof. Ben Feringa

Univ. Nijmegen (Netherlands):

- Jorge Verkade
- Lieke van Hemert
- Floris van Delft
- Floris Rutjes

Univ. Lille (France):

- Prof Jean-Marie Aubry
- Prof Véronique Nardello

European Union (Sustox project)

Royal Society of Chemistry

Thank you!

Unlimited. DSM