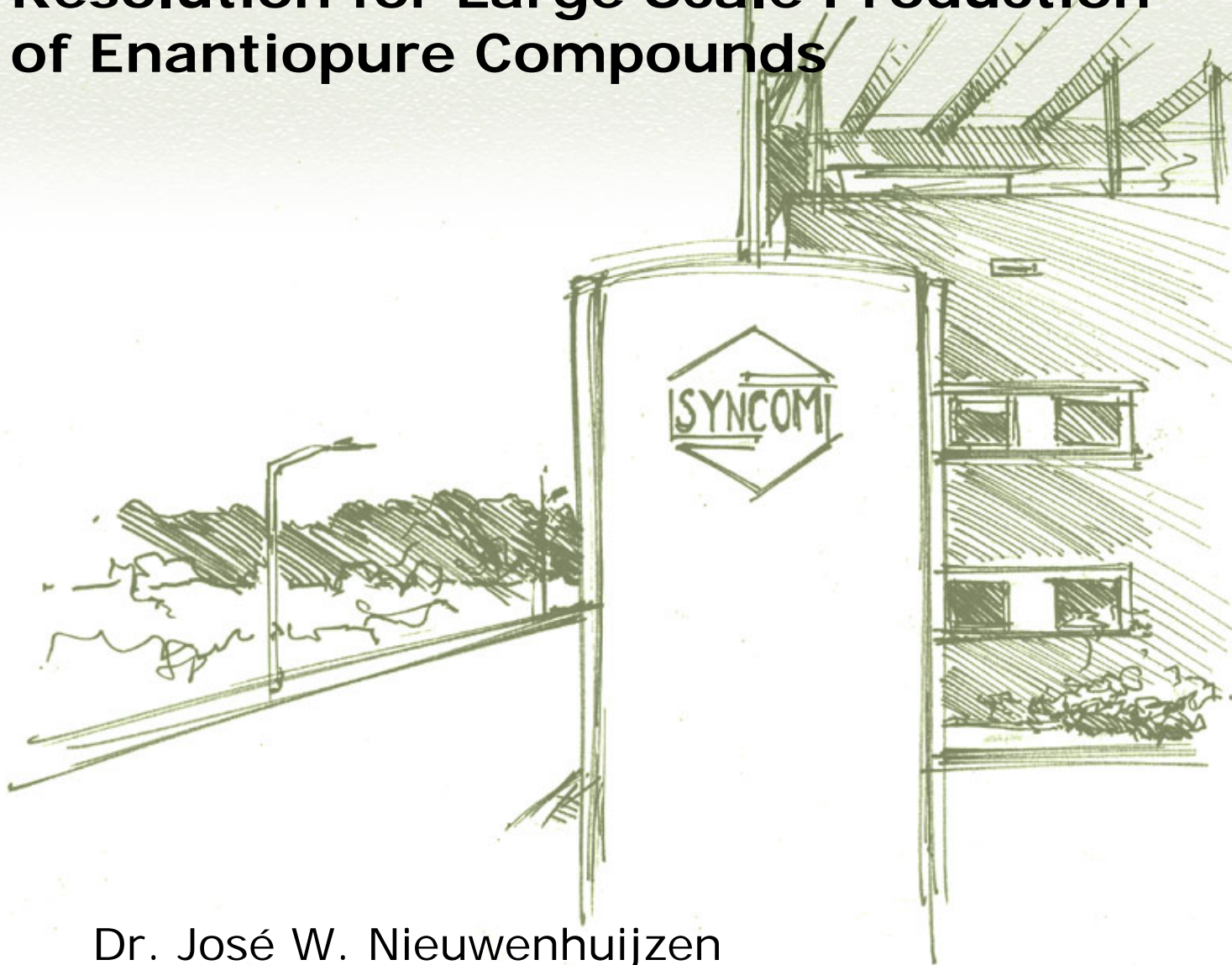


Use of (Second Generation) Dutch Resolution for Large Scale Production of Enantiopure Compounds



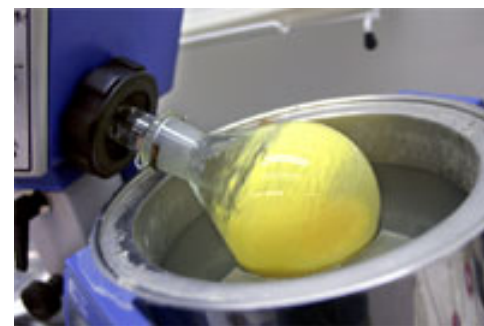
Dr. José W. Nieuwenhuijzen

23 June 2004

Syncom



- Syncom is a *contract research organization* (CRO) specialized in organic synthesis



Market share world wide (CROs)

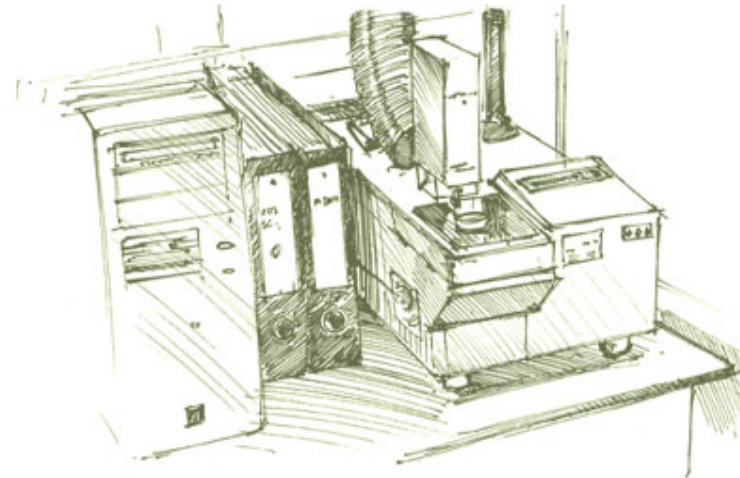


- Market \$ 250 million; share Syncom 2%
- About 3000 chemists; share Syncom 2%
- Synthetic organic portion; share Syncom >5%

Employees



- Employees 84
77 chemists
(43 Ph.D, 9 Masters, 25 Engineers)



Employers



- Synthetic Organic Chemistry chiefly for two industries:
 - Pharmaceutical industry **90%**
 - Organic materials **10%**



Clients

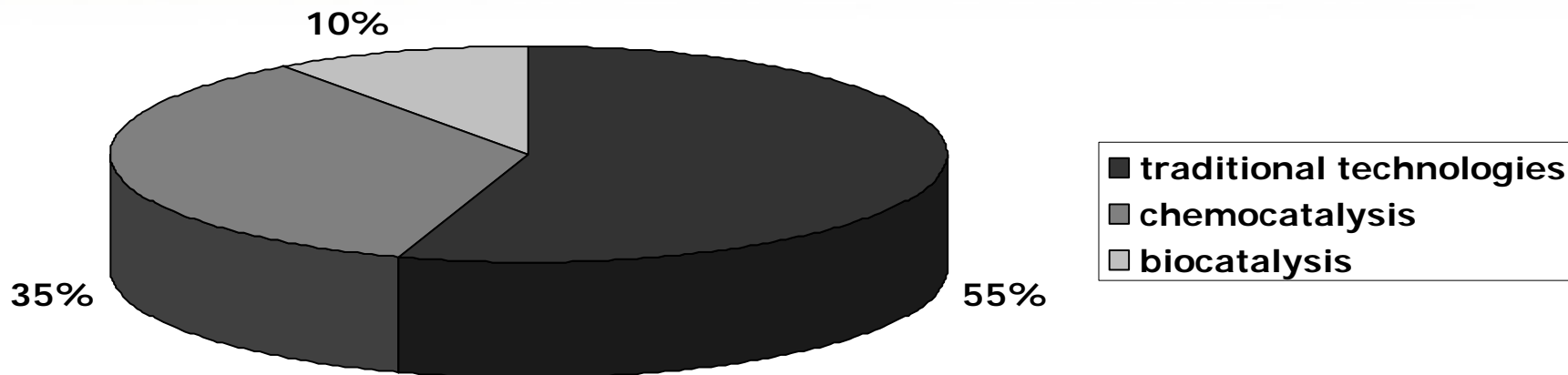


Our clients include major pharmaceutical and chemical companies:

Altana Pharma (D)
Aventis (USA)
DSM Pharma Chemicals (NL)
Eli Lilly & Co. (USA)
Fuji Photo Film (JP)
Organon NV (NL)
Pfizer Inc. (USA)
Philips Research Laboratories (NL)
Solvay Pharmaceuticals (NL / D)
Wyeth (USA)



Sales of enantiopure drugs



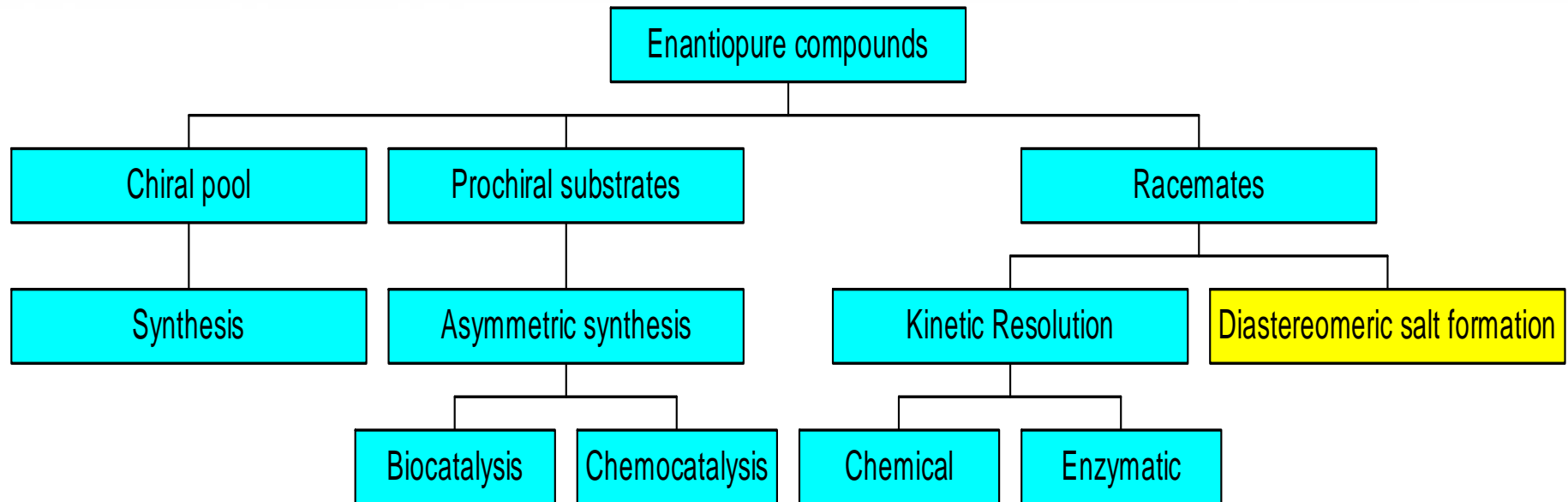
\$7 billion (**2002**)

\$9.5 billion (**2005**): 49% traditional, 36% chemocatalysis, 15% biocatalysis

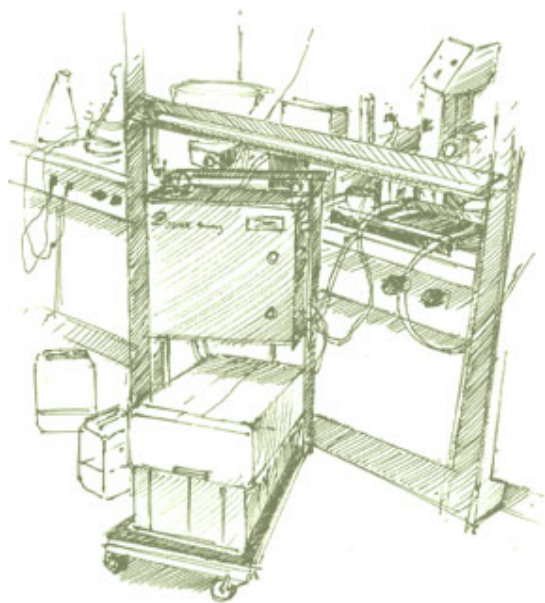
Rouhi, M.A. *Chem. Eng. News* **2004**, June 14, 47-62.



Methods for obtainment of enantiopure drugs



Classical Resolution



- Trial-and-error approach with 20-25% chance of success¹
- Solution would be a faster screening method with a higher success rate
- Time tested technology
- Still the most prevalent method for separation of enantiomers in industry

¹ Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates and Resolutions*, Wiley, New York, **1981**.

Dutch Resolution

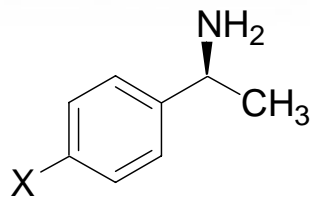
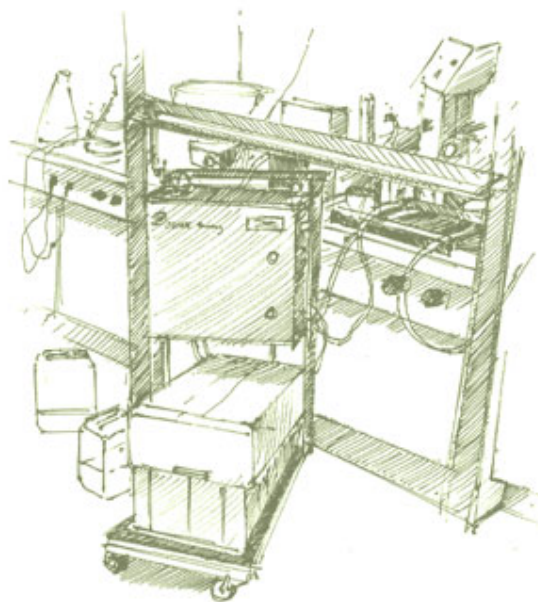


- Use of a mixture of resolving agents results in:
 - higher enantiomeric excess
- Resulting crystals display a non-stoichiometric ratio of resolving agents
- A family of resolving agents has structural similarity and is stereogenically homogeneous

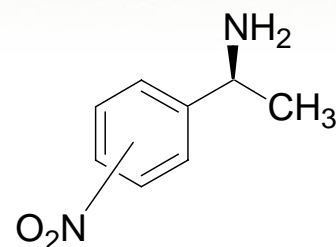
Vries, T.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R.M.; Broxterman, Q.B.; Minnaard, A.; Kaptein, B.; van der Sluis, S.; Hulshof, L.A.; Kooistra, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2349



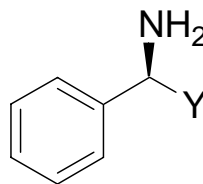
Families of basic resolving agents



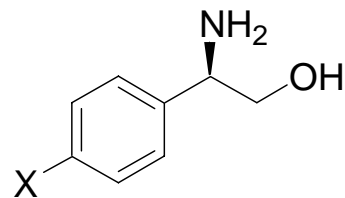
X = Cl, Br, Me
PE-I-mix



PE-II-mix



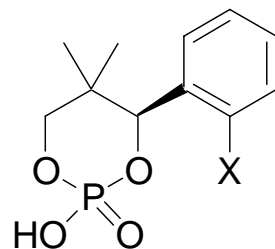
Y = Me, Et, *i*-Pr
PE-III-mix



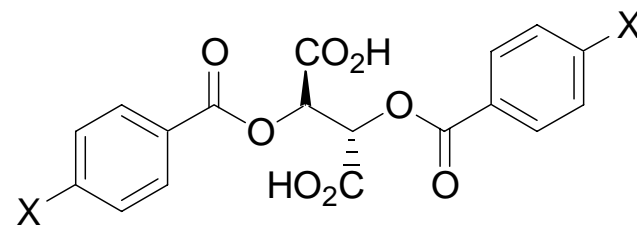
X = H, Me, OMe
PG-mix

Kellogg, R.M.; Nieuwenhuijzen, J.W.; Pouter, K.; Vries, T.R.; Broxterman, Q.B.; Grimbergen, R.F.P.; Kaptein, B.; La Crois, R.M.; de Wever, E.; Zwaagstra, K.; van der Laan, A.C. *Synthesis* **2003**, 1626.

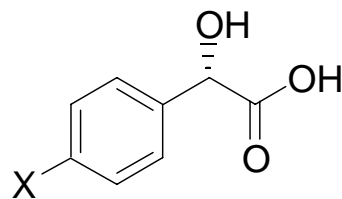
Families of acidic resolving agents



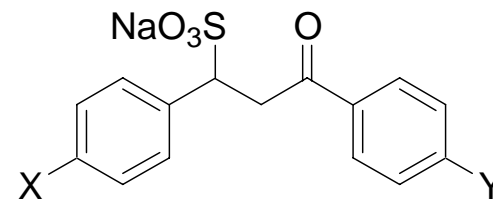
X = H, Cl, OMe
P-mix



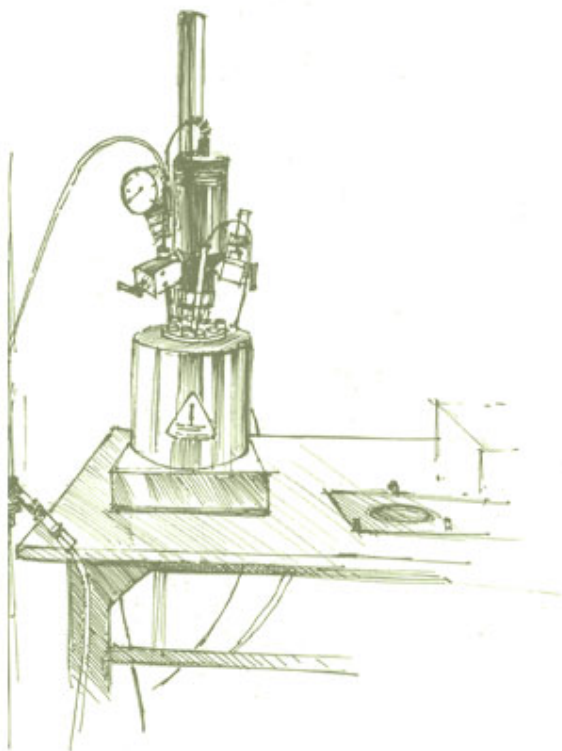
X = H, Me, OMe
T-mix



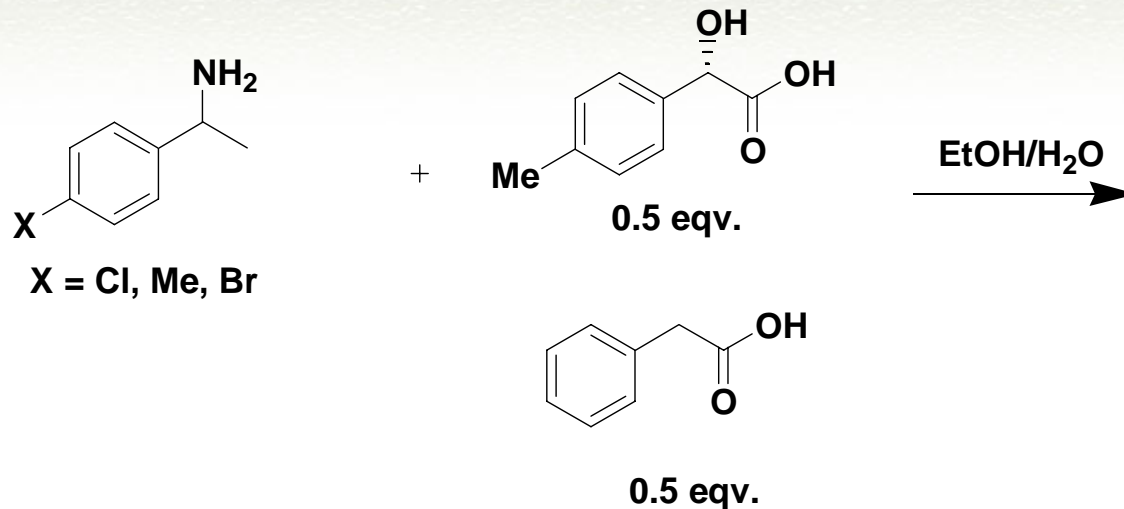
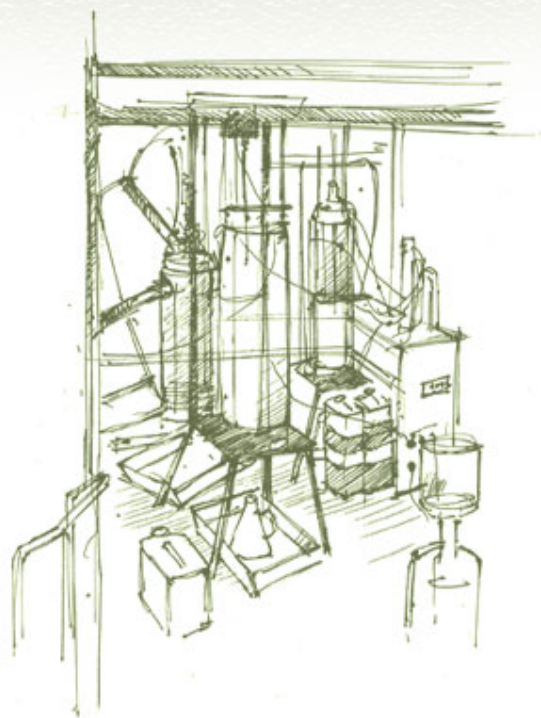
X = H, Me, Br
M-mix



J-mix

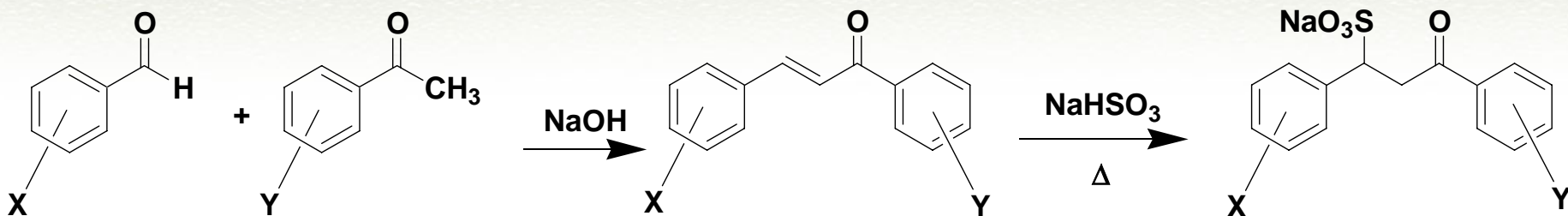


Example I: Resolution of PEA-family



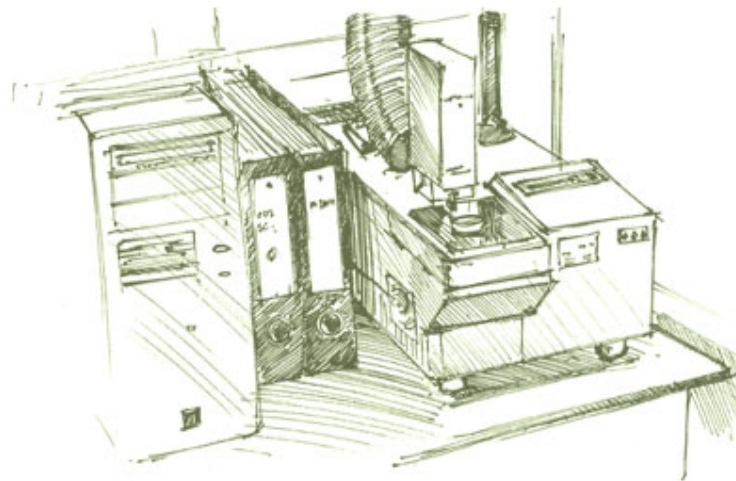
- Peachy-Pope resolution on 2 mole scale
- Yield 28%, 98% ee in first salt
- GC: ratio phenylethylamines 1:1:1

Example II: chiral sulphonic acids

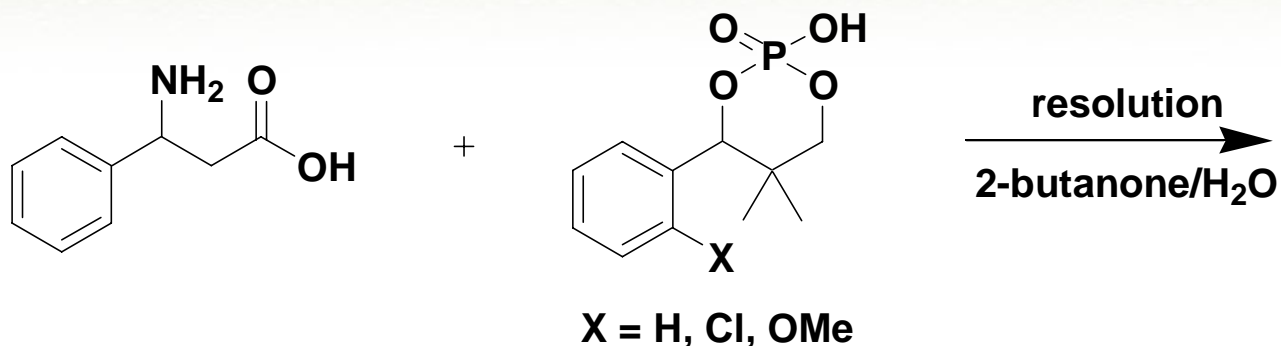


- Overall yields 86-96% over 2 steps; product separates from reaction mixture in both steps.
- Resolution with L-Leu on 2.1 mol scale furnished (+)-isomer in 99+% ee in 34% yield.
- Resolution of mixtures of racemic sulphonic acids possible

Wynberg, H.; Pouwer, K.; Nieuwenhuijzen, J.W.; Vries, T.R. *PCT Int. Appl.* WO 01/014327 **2001** to DSM



Example III: β -aminophenylpropionic acid

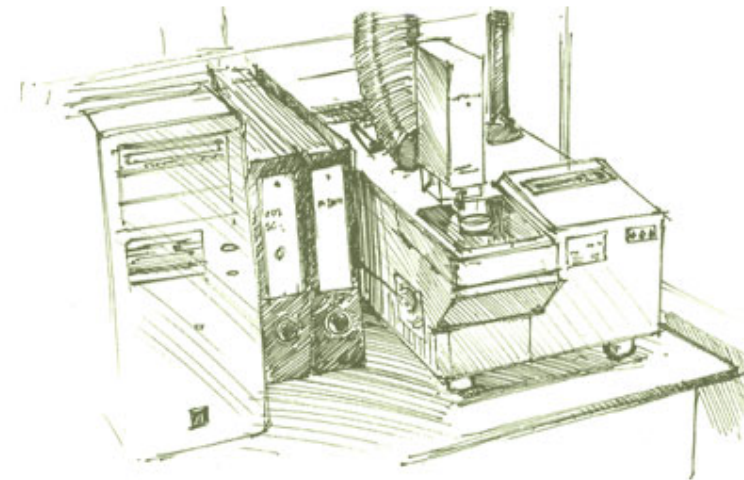


- Screening of resolution : best result with P-mix
- On 6 mmol scale 20% yield and 82% *ee*
- Single resolving agents gave salts with *ee* < 10%
- Later on kg scale with tartaric acid

Dutch Resolution on large scale



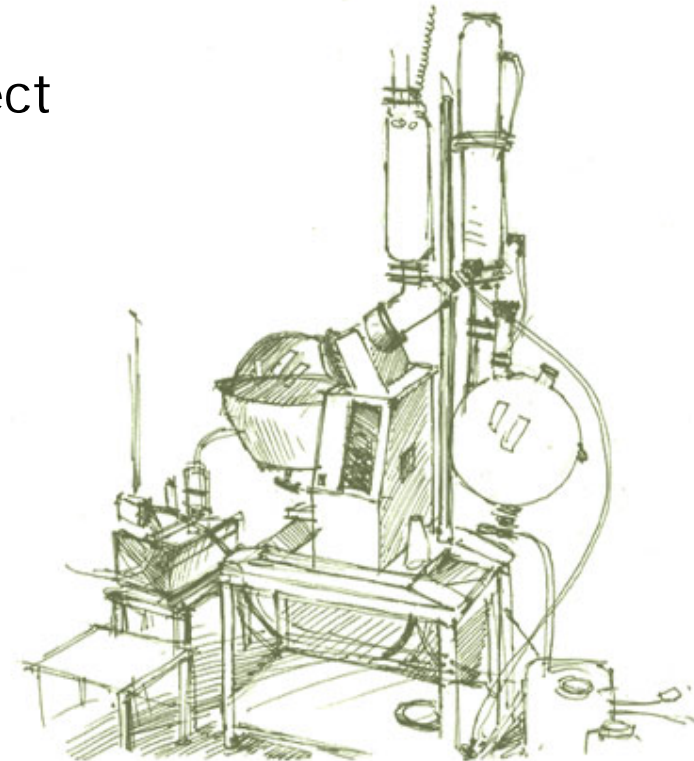
- Mixture of resolving agents:
- Expensive
- Difficult to recycle (ratio)
- Limited use
- Screening method



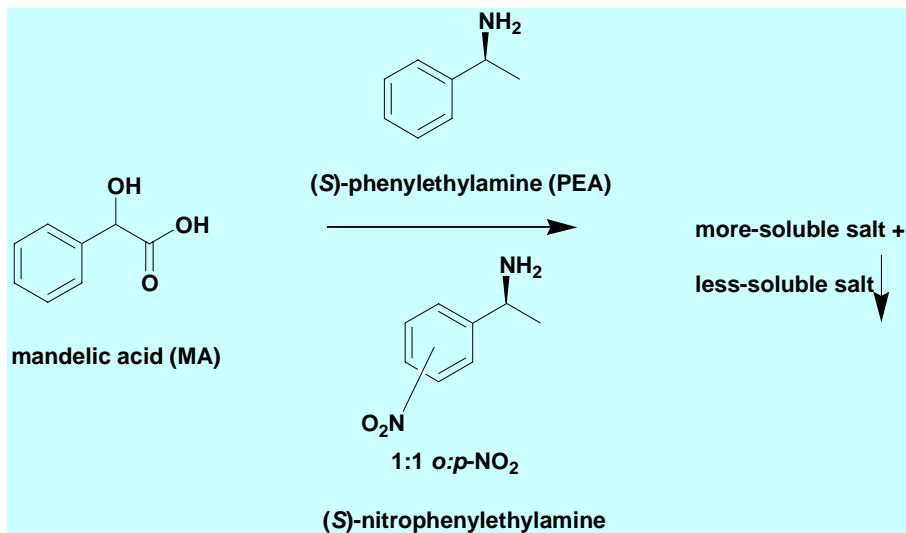
Understanding Dutch Resolution



- Some family members are not or only poorly incorporated
(ratios in Angewandte article)
- Not-incorporated family member: effect on resolution
- “The dog that didn’t bark”? (Sherlock Holmes)



First experiment

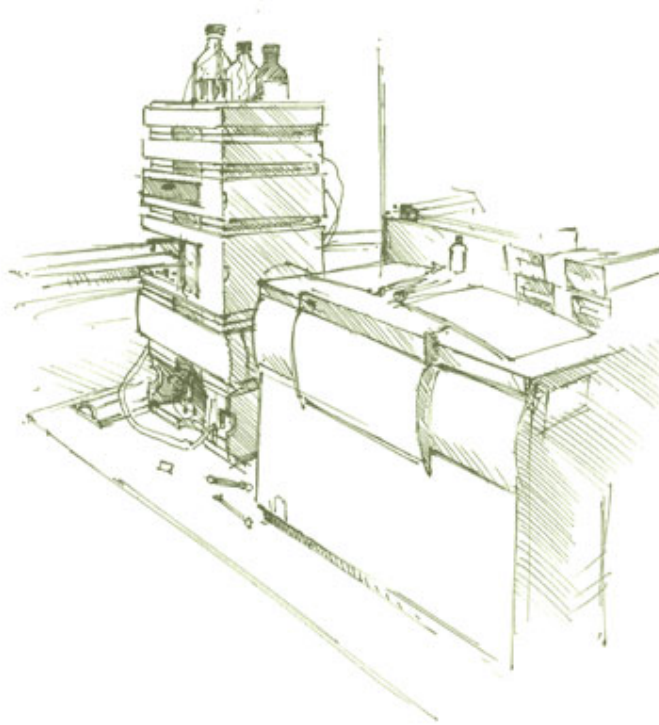


- PE-II-mix: *o,p*-nitroPEA + PEA: Nitro-PEA often not incorporated

- Resolution of MA with PEA in the presence of 10% 1:1 *o,p*-NO₂PEA

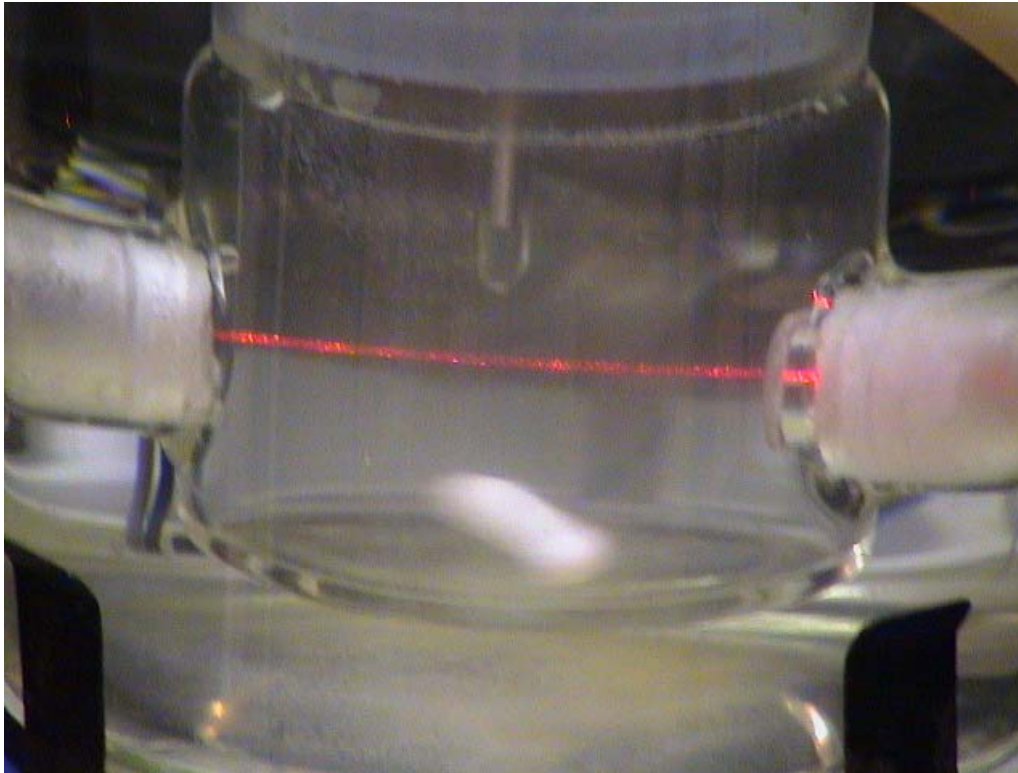
Entry	Additive	Yield (%)	ee (%)	S-factor
1	-	68	14	0.19
2	1:1 <i>o,p</i> -NO ₂ PEA	37	55	0.41

Turbidity measurements



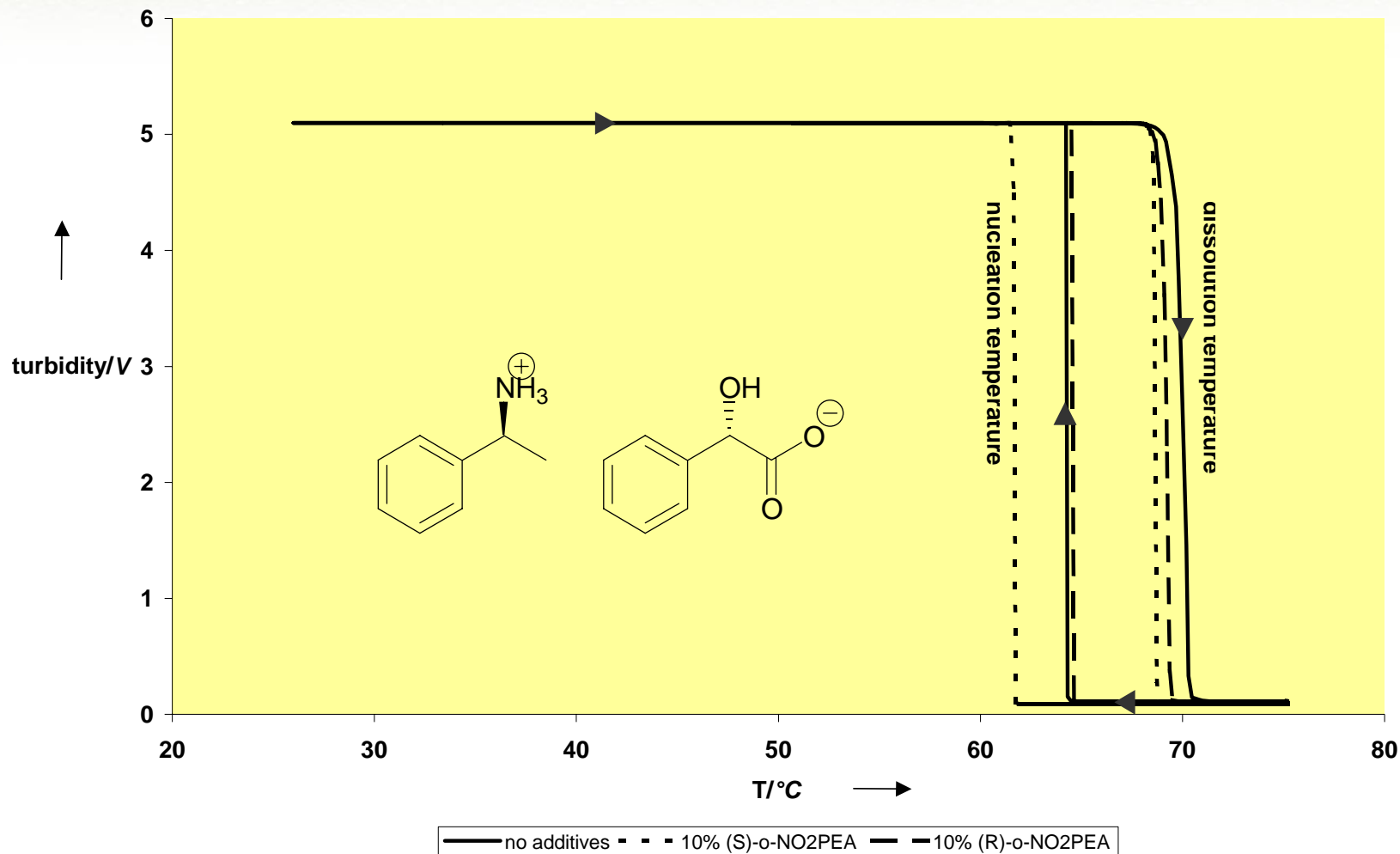
- Indications that kinetic factors play a role
- Observation that resolution with additive precipitates at lower temperature

Experimental set-up

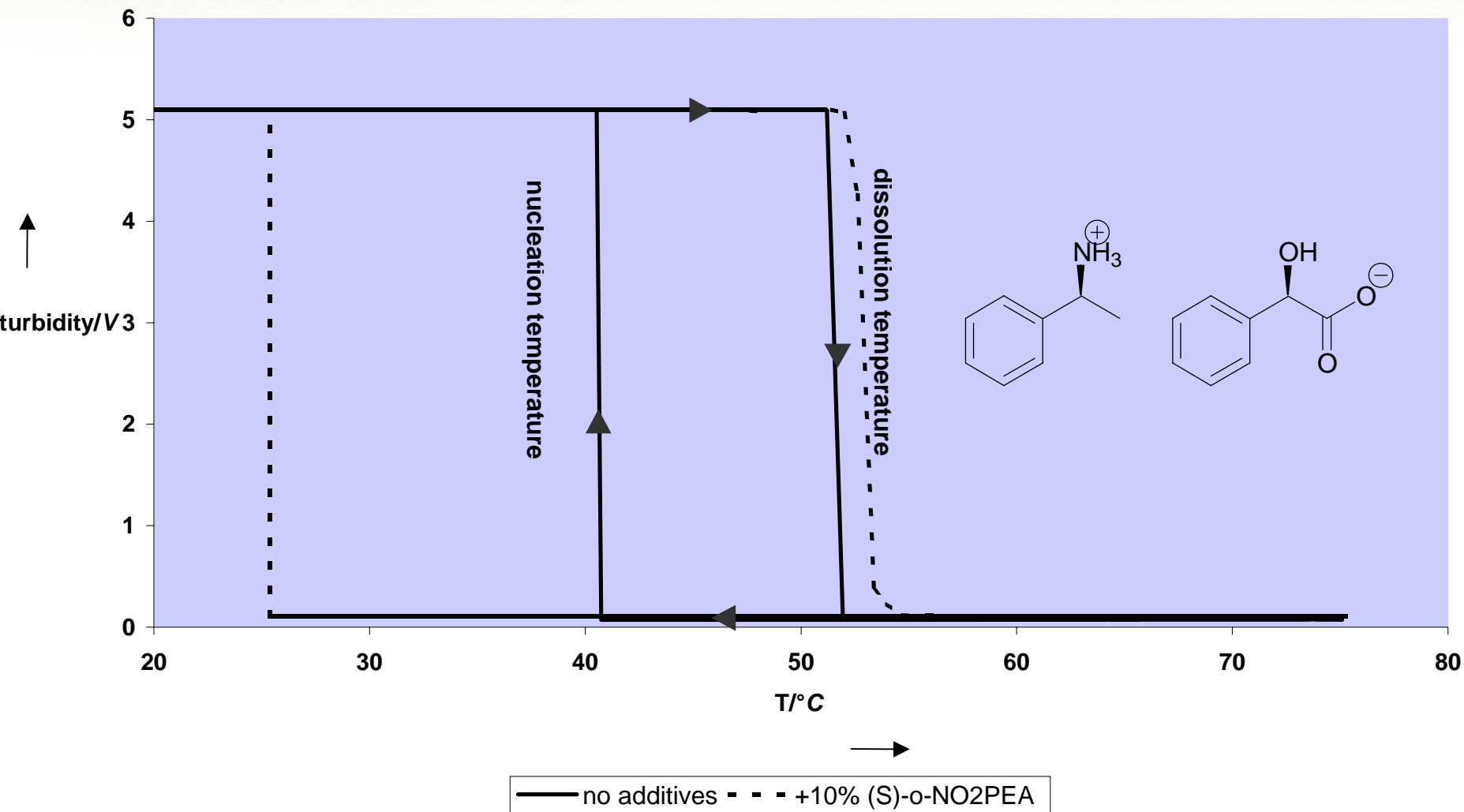


- Computer detects temperature and turbidity versus time
- Vessel is connected to programmed water bath

Less soluble salt (S)MA(S)PEA



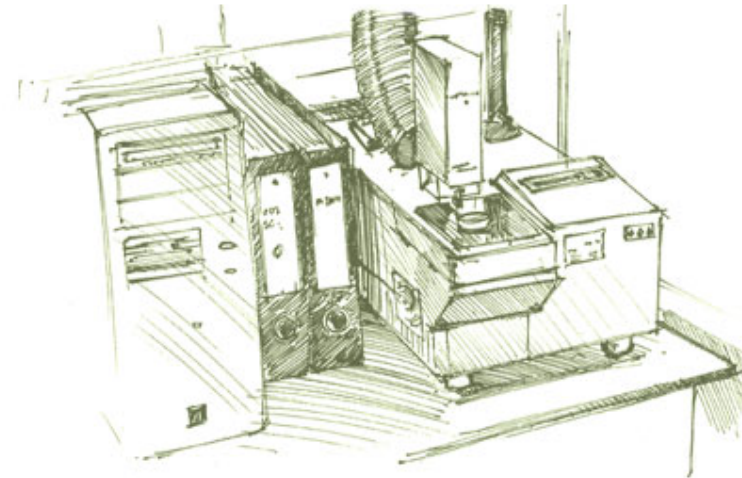
More soluble salt (*R*)MA(*S*)PEA



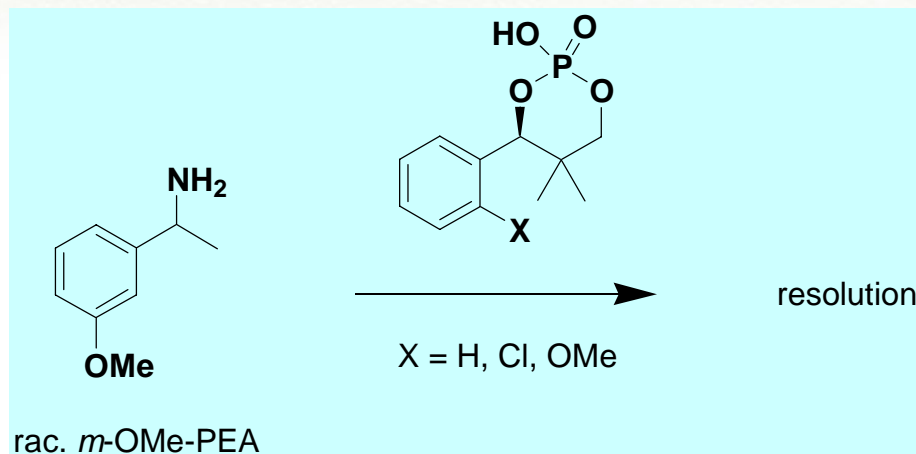
Does it work?



- Screening for known difficult resolutions
- Angewandte article: ratios
- Several resolving agents and additives:
 - Phosphoric acids
 - Phenylethylamines



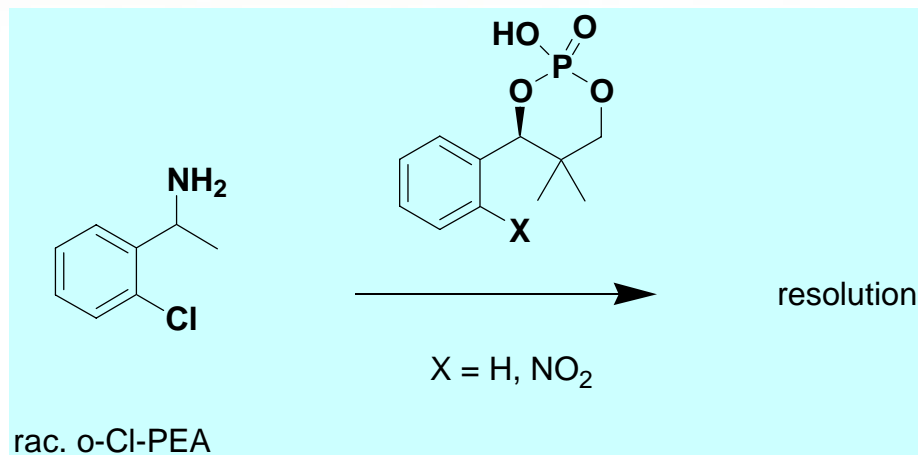
Phosphoric acids (I)



- Resolution of *m*-methoxyphenylethylamine with phencyphos
- 10% chlocyphos or anicyphos as additive

Entry	Additive	Yield (%)	ee (%)	S-factor
1	-	41	14	0.11
2	10% chlocyphos	29	53	0.31
3	10% anicyphos	33	28	0.18

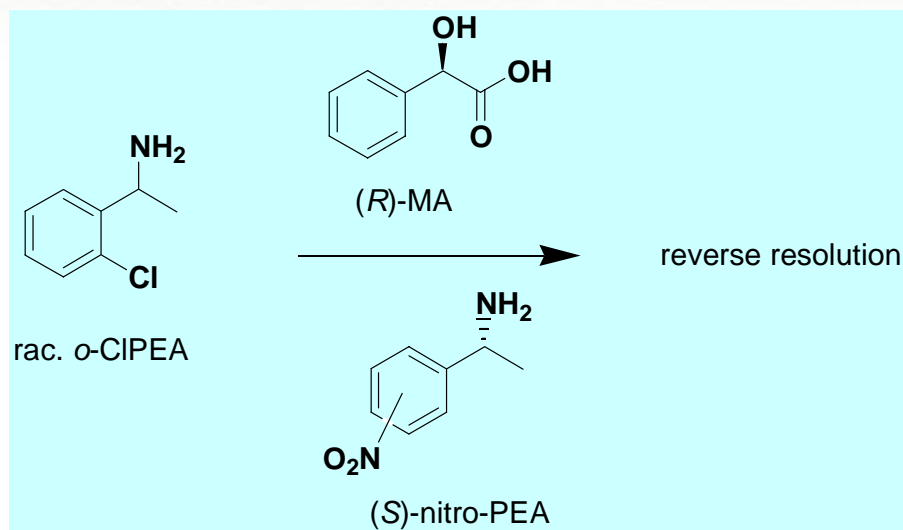
Phosphoric acids (II)



- Resolution of *o*-chlorophenylethylamine with phencyphos
- 10% nitrocyphos as additive
- No nitrocyphos found in the salts!

Entry	Additive	Yield (%)	ee (%)	S-factor
1	-	58	22	0.26
2	10% nitrocyphos	36	86	0.62

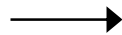
Phenylethylamines (I)



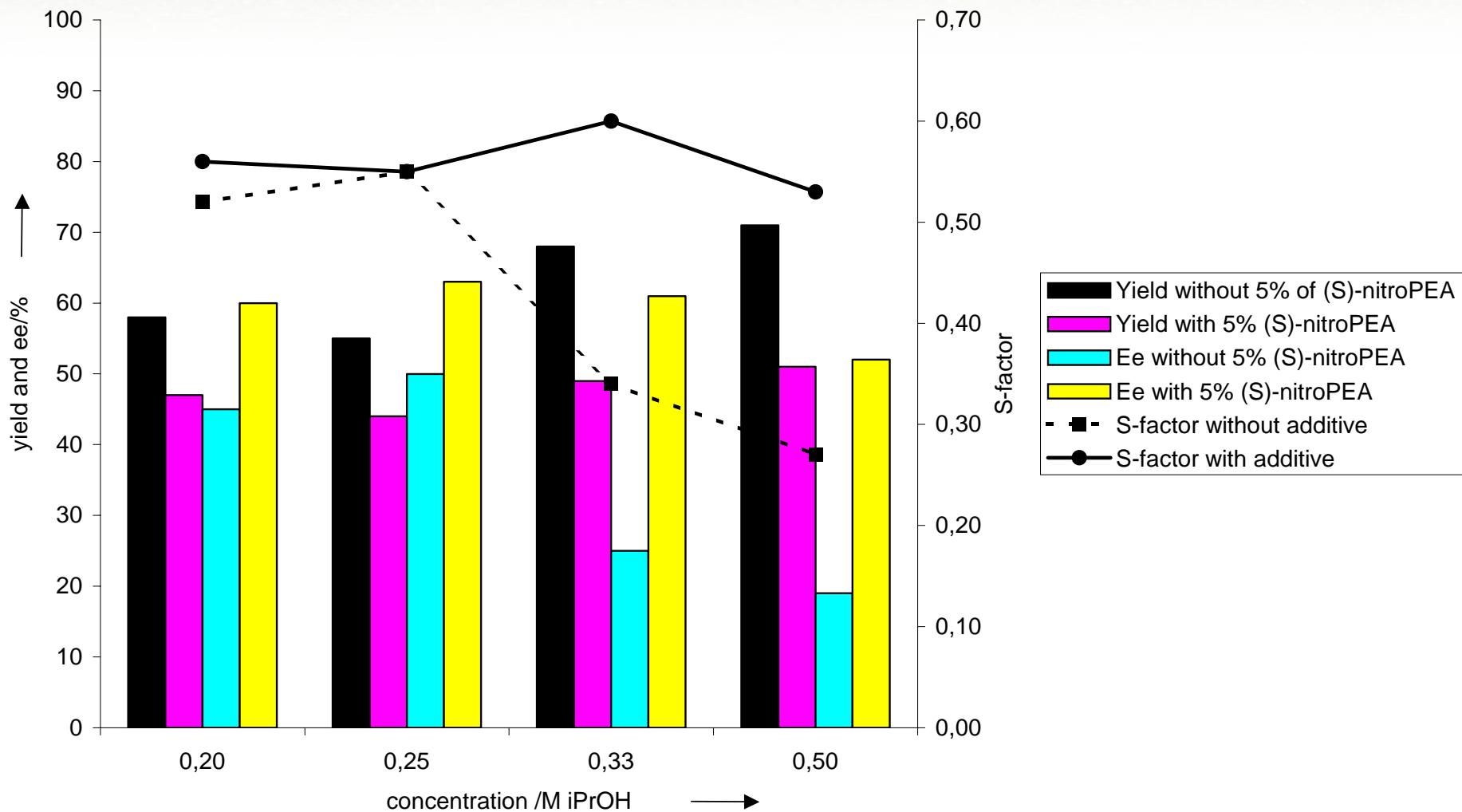
- Reverse resolution of *o*-chlorophenylethylamine with mandelic acid
- Addition of 5 or 10% nitro-PEA
- No nitro-PEA found in the salts!

Entry	Additive	Yield(%)	ee (%)	S-factor
1	-	39	44	0.34
2	5% (<i>S</i>)-nitro-PEA	16	62	0.20
3	10% (<i>S</i>)-nitro-PEA	10	87	0.17

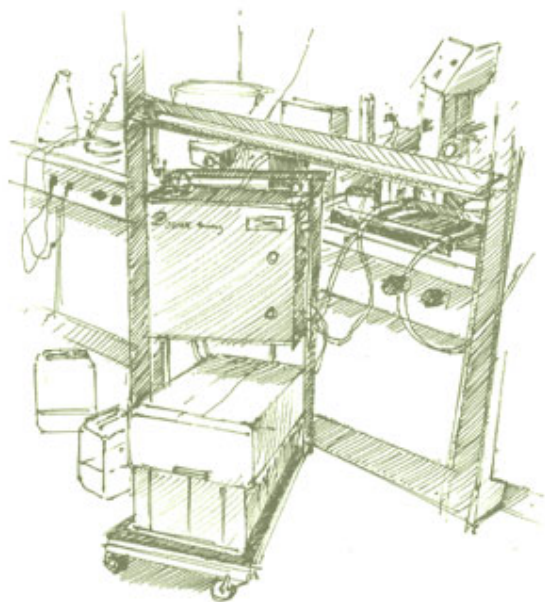
Phenylethylamines (II)



Resolution at different concentrations



Application in large scale resolutions



- If additive is not incorporated in the salt, then easy recovery of resolving agent from the salt
- The mother liquor with resolving agent and additive can be re-used
- It is cheaper to use only a few percent of an additive instead of three expensive resolving agents
- Resolutions can be performed at higher concentrations

Nieuwenhuijzen, J.W.; Grimbergen, R.F.P.; Koopman, C.; Kellogg, R.M.; Vries, T.R.; Pouwer, K.; van Echten, E.; Kaptein, B.; Hulshof, L.A.; Broxterman, Q.B. *Angew. Chem. Int. Ed.* **2002**, *41*, 4281.

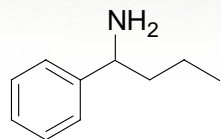
Conclusions



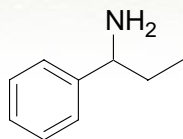
- Dog that didn't bark is important
- 10% additive results in higher ee and sometimes higher S-factor (Second generation Dutch Resolution)
- DR is a useful screening method for nucleation inhibitors
- Some inhibitors are not incorporated
- What are criteria for a good nucleation inhibitor?
- Prediction of nucleation inhibitor?



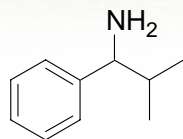
Screening for nucleation inhibitors (I)



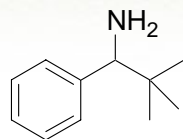
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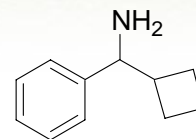
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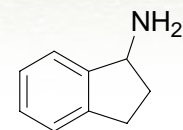
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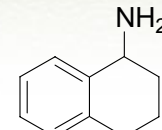
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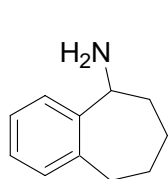
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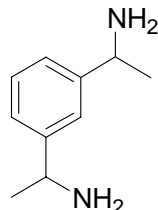
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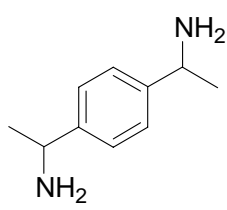
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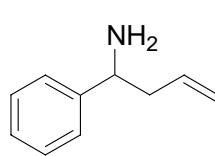
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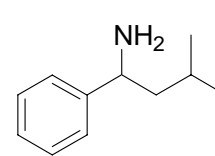
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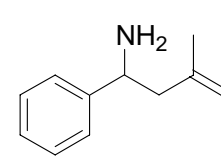
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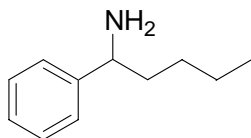
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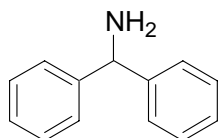
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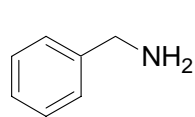
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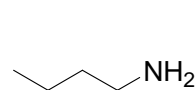
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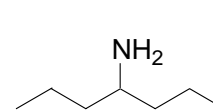
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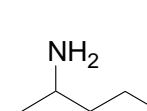
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17

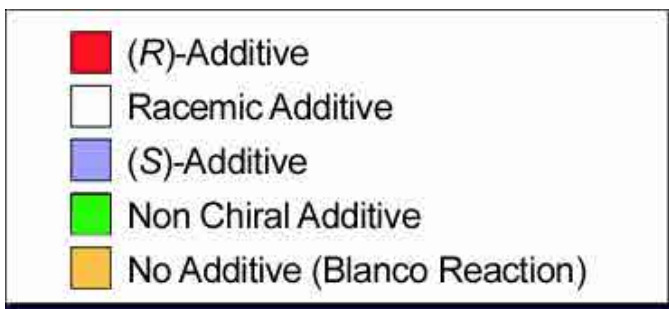
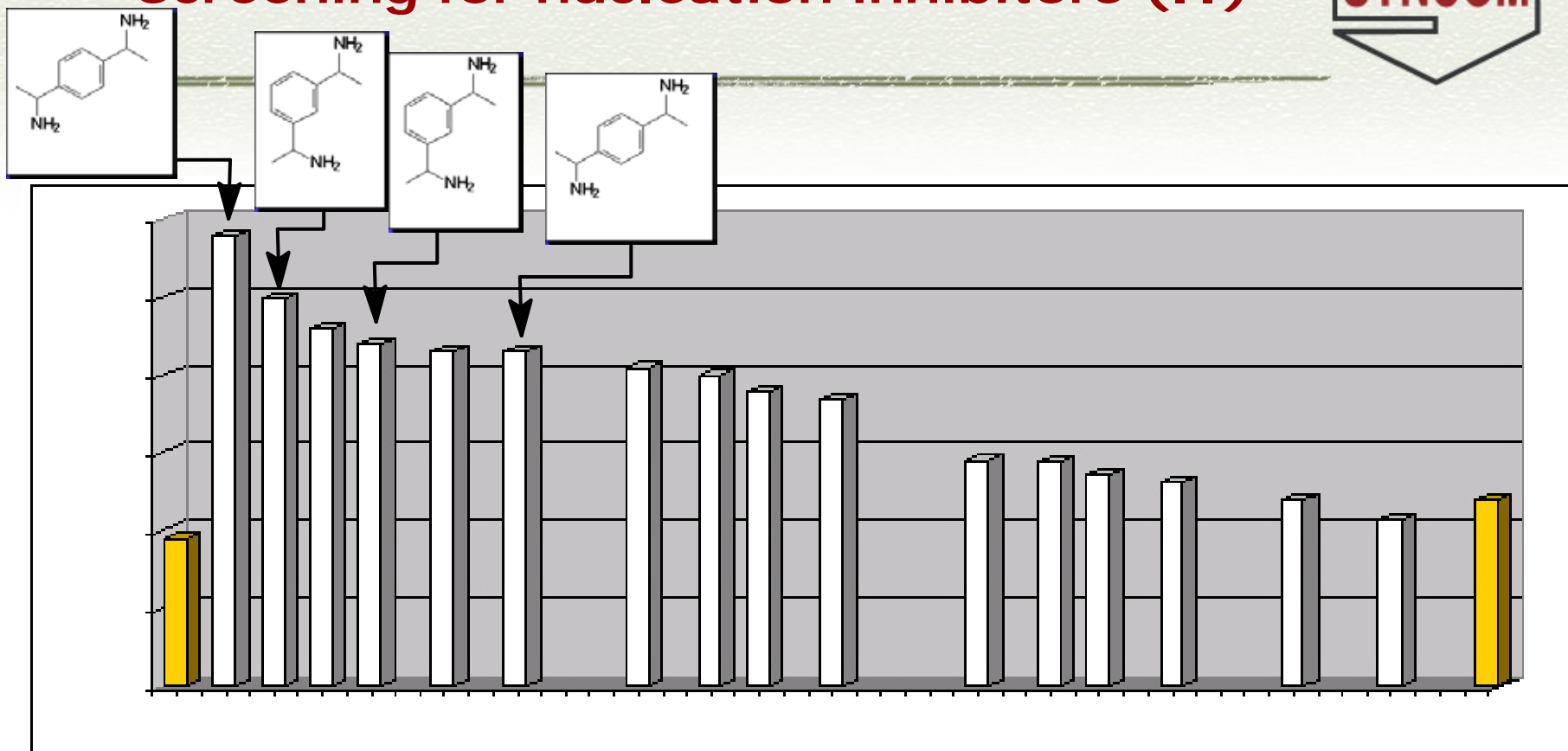


18



19

Screening for nucleation inhibitors (II)



Acknowledgements



- Prof. Wijnberg
- Prof. Kellogg
- Ton Vries
- Kees Pouwer
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- Jan Dalmolen
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Weizmann Institute of Science



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- Carla Koopman
- Bernard Kaptein
- Rinus Broxterman
- Bert Hulshof

Prof. Lahav

