Polymer Supports for Combinatorial Chemistry

The Ins and Outs

Literature

- **Combinatorial chemistry : synthesis and application / edited by Stephen R. Wilson, Anthony W. Czarnik. New York ; Chichester : Wiley, c1997.**
- Combinatorial chemistry and molecular diversity in drug discovery / edited by Eric M. Gordon and James F. Kerwin. New York ; Chichester : Wiley, 1998.
- Combinatorial chemistry : a practical approach / edited by Willi Bannwarth and Eduard Felder. Weinheim ; Cambridge : Wiley-VCH, 2000.
- Combinatorial chemistry : a practical approach / edited by Hicham Fenniri. Oxford : Oxford University Press, 2000.
- Combinatorial strategies in biology and chemistry / Annette Beck-Sickinger, Peter Weber, translated by Michael Soderman and Allan Wier. New York : Wiley, c2002.
- A practical guide to combinatorial chemistry / Anthony W. Czarnik, editor, Sheila H. Dewitt, editor. Washington, DC : American Chemical Society, c1997.
- **Combinatorial chemistry / Nicholas K. Terrett. Oxford : Oxford University Press, 1998.**
- Combinatorial chemistry : synthesis, analysis, screening / edited by Günther Jung. Weinheim ; Cambridge : Wiley-VCH, 1999.
- Combinatorial organic chemistry : an educational approach / Sherif El-Basil. Huntington, NY : Nova Science Publishers, 1999.
- Experimental design for combinatorial and high throughput materials development / James N. Cawse. New York, Chichester : Wiley, 2002.

Literature

- **Barrett, A. G. M., B. T. Hopkins, et al. (2002). "ROMPgel reagents in parallel synthesis." Chemical Reviews 102(10): 3301-3323.**
- Boyle, N. A. and K. D. Janda (2002). "Formats for combinatorial synthesis: solid-phase, liquid-phase and surface." Current Opinion in Chemical Biology 6(3): 339-346.
- Delgado, M. and K. D. Janda (2002). "Polymeric supports for solid phase organic synthesis." Current Organic Chemistry 6(12): 1031-1043.
- Dickerson, T. J., N. N. Reed, et al. (2002). "Soluble polymers as scaffolds for recoverable catalysts and reagents." Chemical Reviews 102(10): 3325-3343.
- **Hudson, D. (1999). "Matrix assisted synthetic transformations: a mosaic of diverse contributions. I. The pattern emerges." Journal of Combinatorial Chemistry 1(5): 333-360.**
- **Hudson, D. (1999). "Matrix assisted synthetic transformations: A mosaic of diverse contributions. II. The pattern is completed." Journal of Combinatorial Chemistry 1(6): 403-457.**
- Kempe, M. and G. Barany (1996). "CLEAR: A novel family of highly

Literature

- Maier, W. F., G. Kirsten, et al. (2001). "Combinatorial chemistry of materials, polymers and catalysts." Macromol. Symp. 165, 1.
- McNamara, C. A., M. J. Dixon, et al. (2002). "Recoverable catalysts and reagents using recyclable polystyrene-based supports." Chemical Reviews 102(10): 3275-3299.
- Meldal, M. (1992). "PEGA - a Flow Stable Polyethylene-Glycol Dimethyl Acrylamide Copolymer for Solid-Phase Synthesis." Tetrahedron Letters 33(21): 3077-3080.
- Meldal, M. (1997). Properties of solid supports. Solid-Phase Peptide Synthesis. San Diego, Academic Press Inc. 289: 83-104.
- Renil, M. and M. Meldal (1996). "POEPOP and POEPS: inert polyethylene glycol crosslinked polymeric supports for solid synthesis." Tetrahedron Lett. 37(34): 6185-6188.
- **Sherrington, D. C. (2001). "Polymer-supported reagents, catalysts, and sorbents: Evolution and exploitation - A personalized view." Journal of Polymer Science Part a-Polymer Chemistry 39(14): 2364-2377.**

Literature

- **Vaino, A. R. and K. D. Janda (2000). "Solid-phase organic synthesis: A critical understanding of the resin." Journal of Combinatorial Chemistry 2(6): 579-596.**
- van Heerbeek, R., P. C. J. Kamer, et al. (2002). "Dendrimers as support for recoverable catalysts and reagents." Chemical Reviews 102(10): 3717-3756.
- Wennemers, H. (2001). "Combinatorial chemistry: A tool for the discovery of new catalysts." Combinatorial Chemistry and High Throughput Screening 4(3): 273-285.
- Yu, Z. R. and M. Bradley (2002). "Solid supports for combinatorial chemistry." Current Opinion in Chemical Biology 6(3): 347-352.

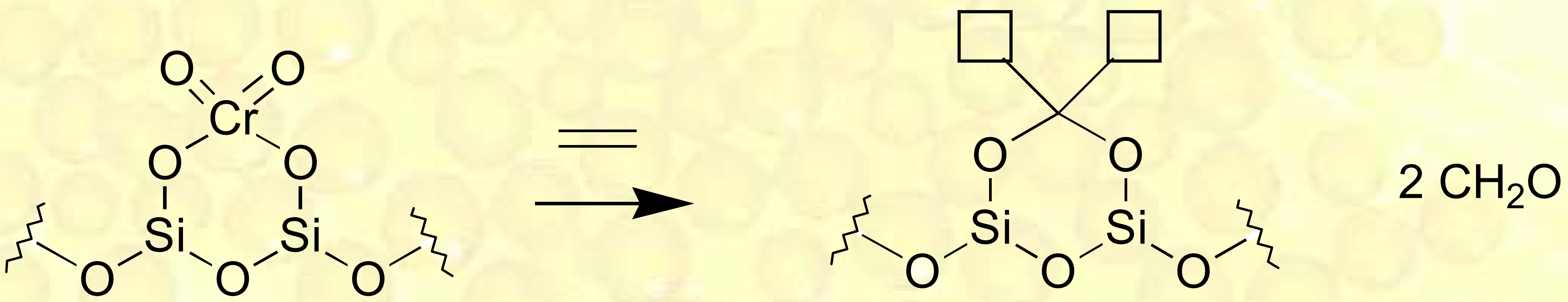
Lecture 1

- **Introduction – General Background**
  1. Historical Development
     1.1-1.7 Polymer Supports
  2. Solid Phase Synthesis – Examples
     2.1 SPOS
     2.2 SPMS

1. Historical Development

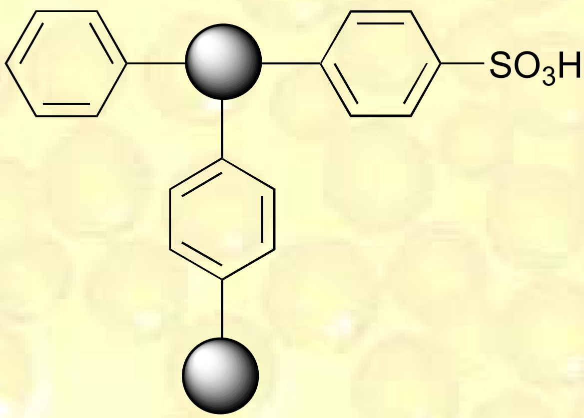
- **1.1. Silica**

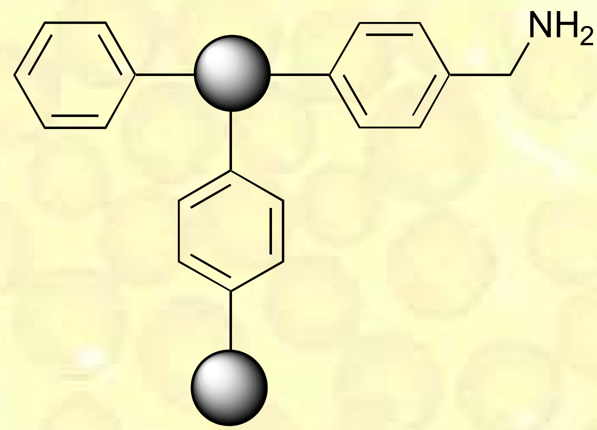
  1.1.1. Heterogeneous Catalysis

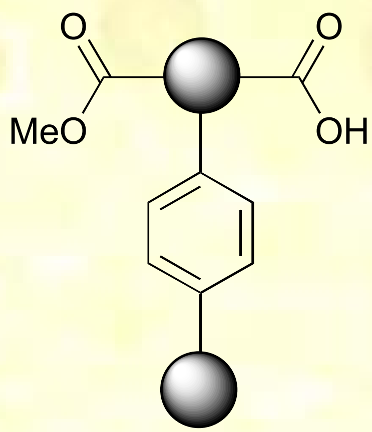


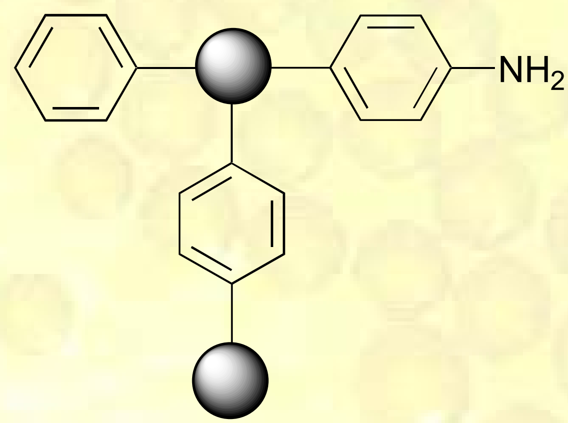
Historical Development

- **1.2. Crosslinked polystyrene**
  - 1.2.1. Weak and strong acid catalysts
  - 1.2.2. Weak and strong base catalysts





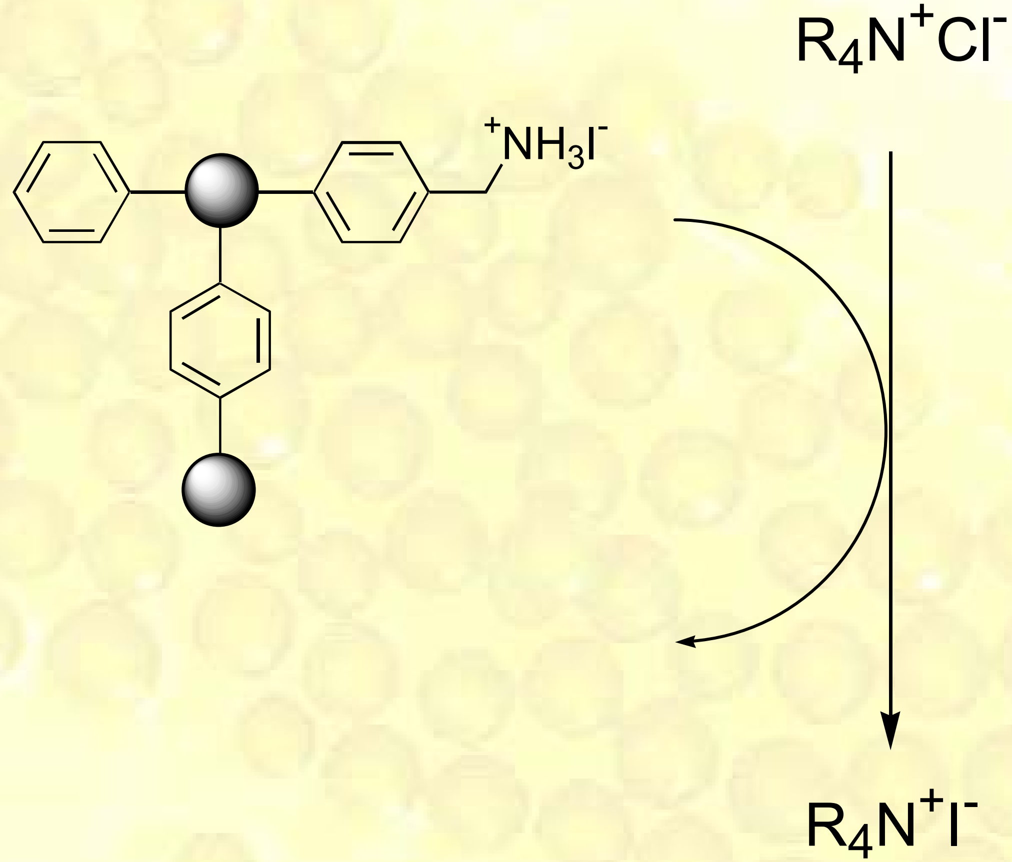




Historical Development

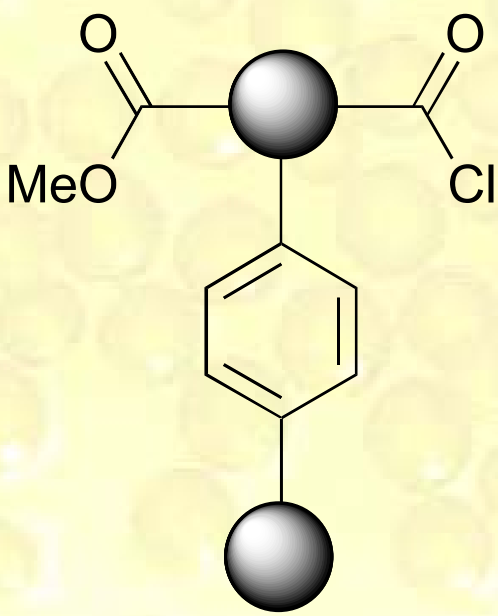
1.2.3. Ion exchange

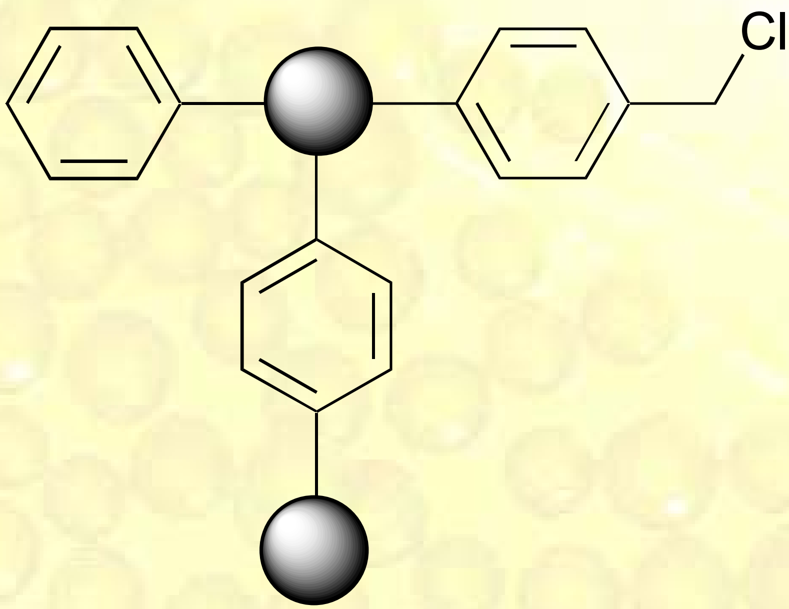
- 1.2.3.1. Purification
- 1.2.3.2. Synthetic uses



Historical Development

1.2.4. Merrifield Resins

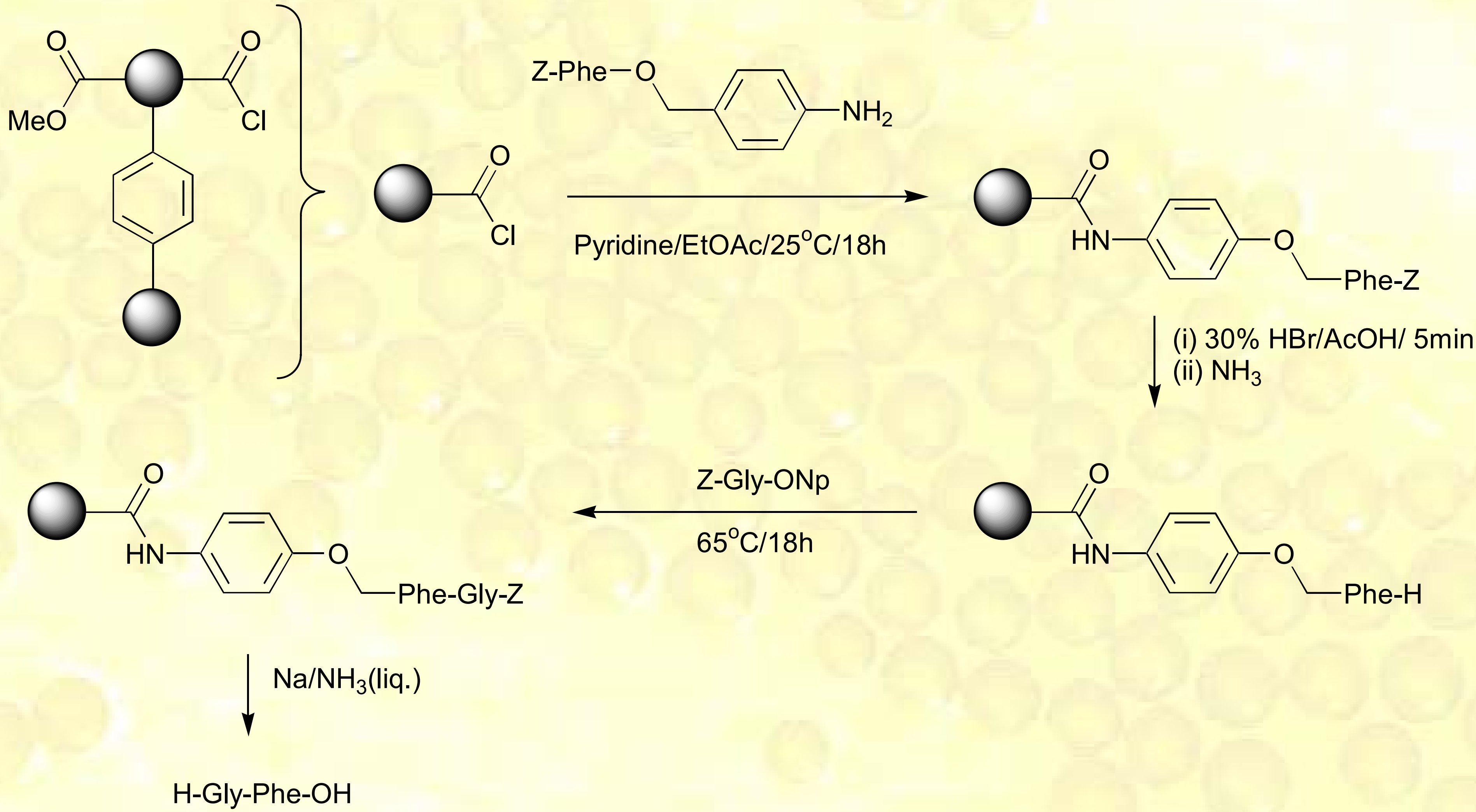




Synthesis of ribonuclease A and ribonuclease S

Merrifield Resins

1.2.4.1. Polypeptide synthesis



Merrifield Resins

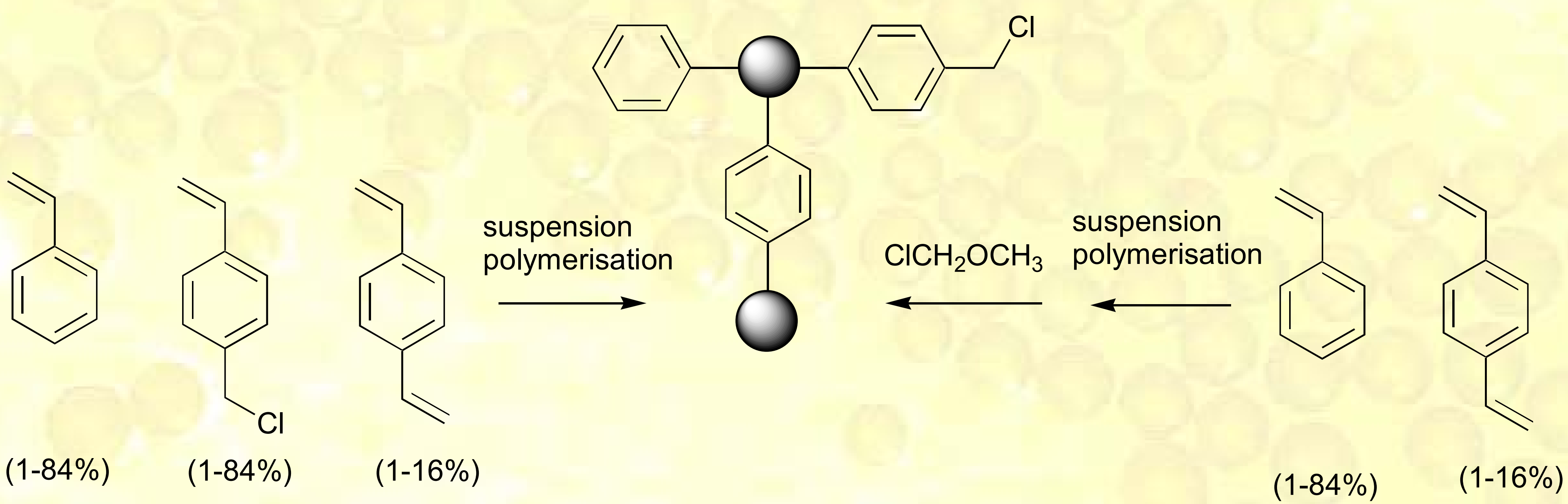
1.2.4.2. General features

1.2.4.2.A. Synthesis

1.2.4.2.B. Chloromethylation

1.2.4.2.C. Crosslink density

1.2.4.2.D. Loading



Merrifield Resins

1.2.4.2.E. Stability - Limitations

- Benzylether linkage / Lewis acids
- Aromatic “backbone” / Friedel-Crafts Chemistry

1.2.4.2.F. Handling

- Controllable bead size
- Controllable bead size distribution

Merrifield Resins

1.2.4.3. Merrifield and Polymer Supports

- Cellulose – Chromatography of enzymes
  - Peptide chemistry insufficiently developed
- Poly(vinyl alcohol)
  - Water soluble / 40% dialysable (5 kDa cut-off)
- Poly(MMA(94%)-co-DVB(6%) /Amberlite IRC-50
  - Saponified resin
    - Titration/Accessibility (COOH: 94% Rohm and Haas / 97.5% Merrifield)
  - 0.003% COOH (outside) / 99.997% COOH (inside)
  - Loading 0.0003 mmol/g (surface) / 10 mmol/g (total)
  - Actual loading used: 0.3 mmol/g
  - Dipeptide synthesised / Tetrapeptide unsuccessful

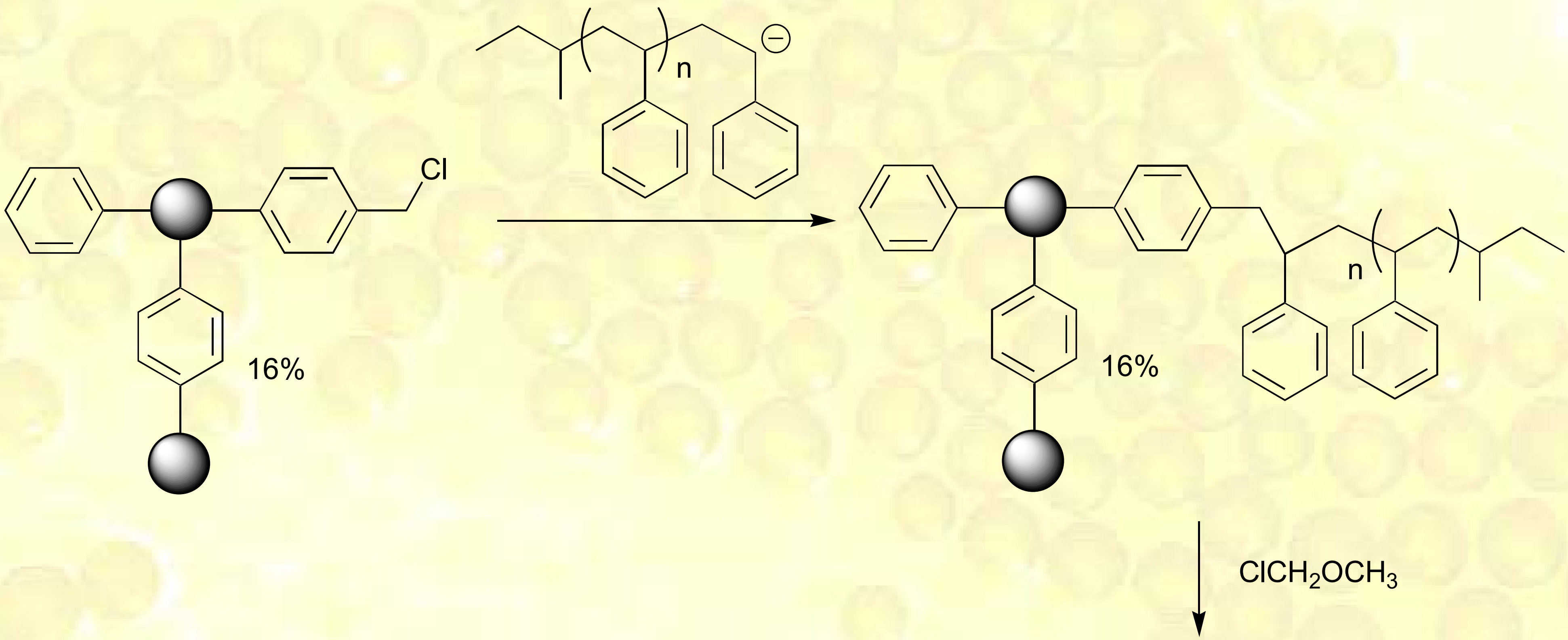
Merrifield Resins

- Poly(S-co-DVB) / Dowex 50
  - 4% or 16% crosslinked later dropped to 2%
  - Chloromethylation ($SnCl_4$ / 60^{o}C / 1h)
  - Kinetics and accessibility to be improved
  - Smaller beads allow faster diffusion and are more stable towards mechanical stress and shear.

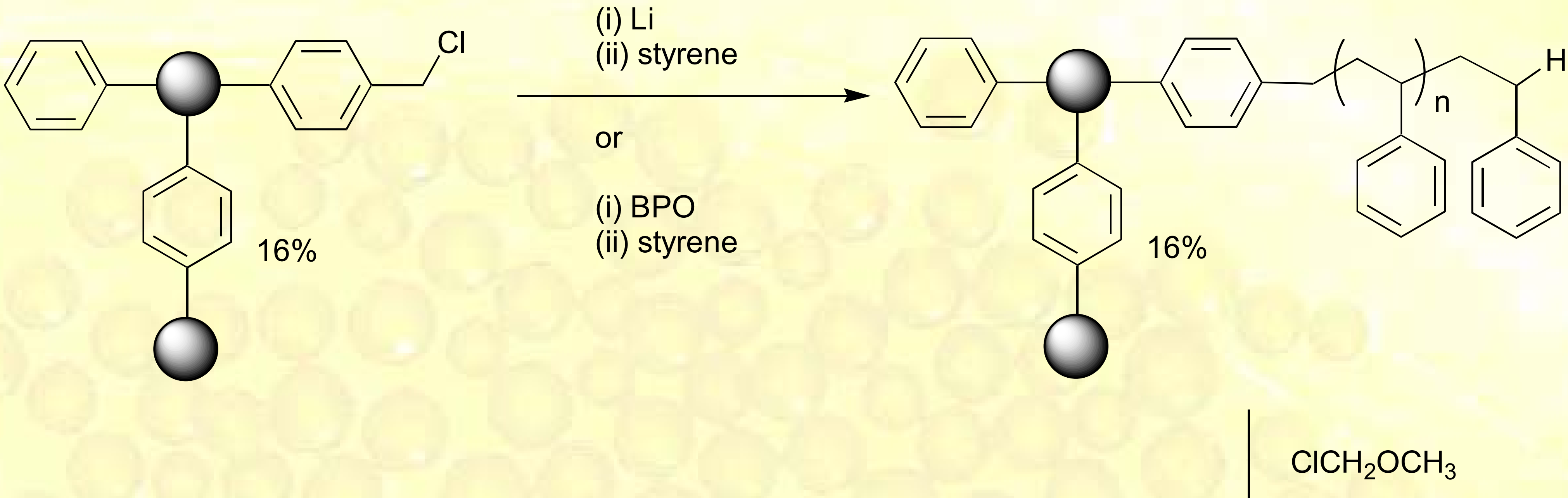
- Macroreticular (Macroporous) poly(S-co-DVB)
  - Kunin (Rohm and Haas)
  - Millar (Permutite, U.K.)
  - 25-75% crosslinked (DVB)
  - Permanent porosity – high internal surface area
  - Never better than Merrifield gels

Merrifield Resins

- Graft copolymers – "Whiskers"
  - Increase accessibility
  - Increase chain mobility



Merrifield Resins

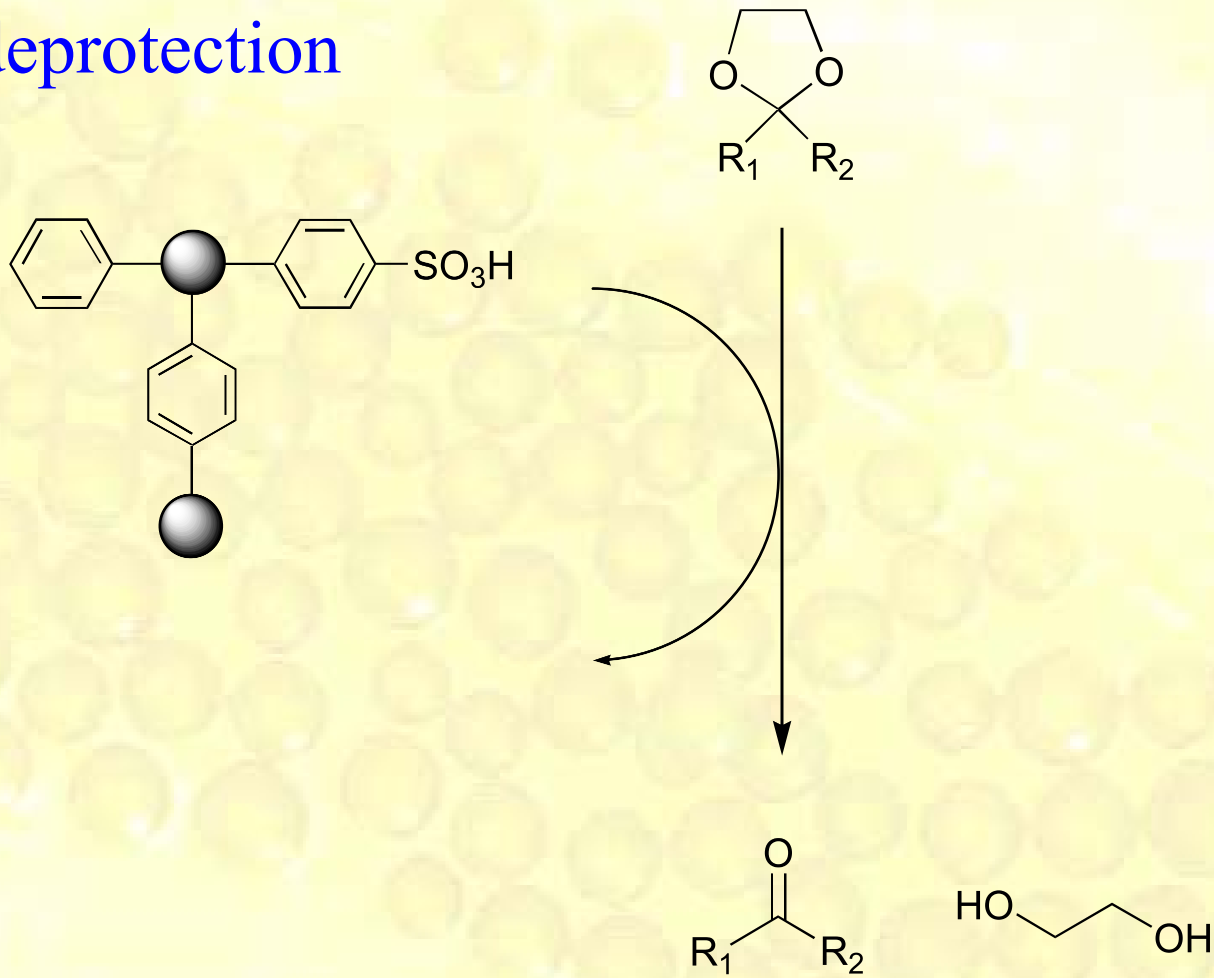


- Copolymerisation (always) preferred to postmodification
- Polymer chain mobility is high in Merrifield resins despite crosslinks.
- Merrifield explored the synthesis of peptide libraries in the 1970s but without much success.

Historical Development

1.2.4.4. Supported catalysts

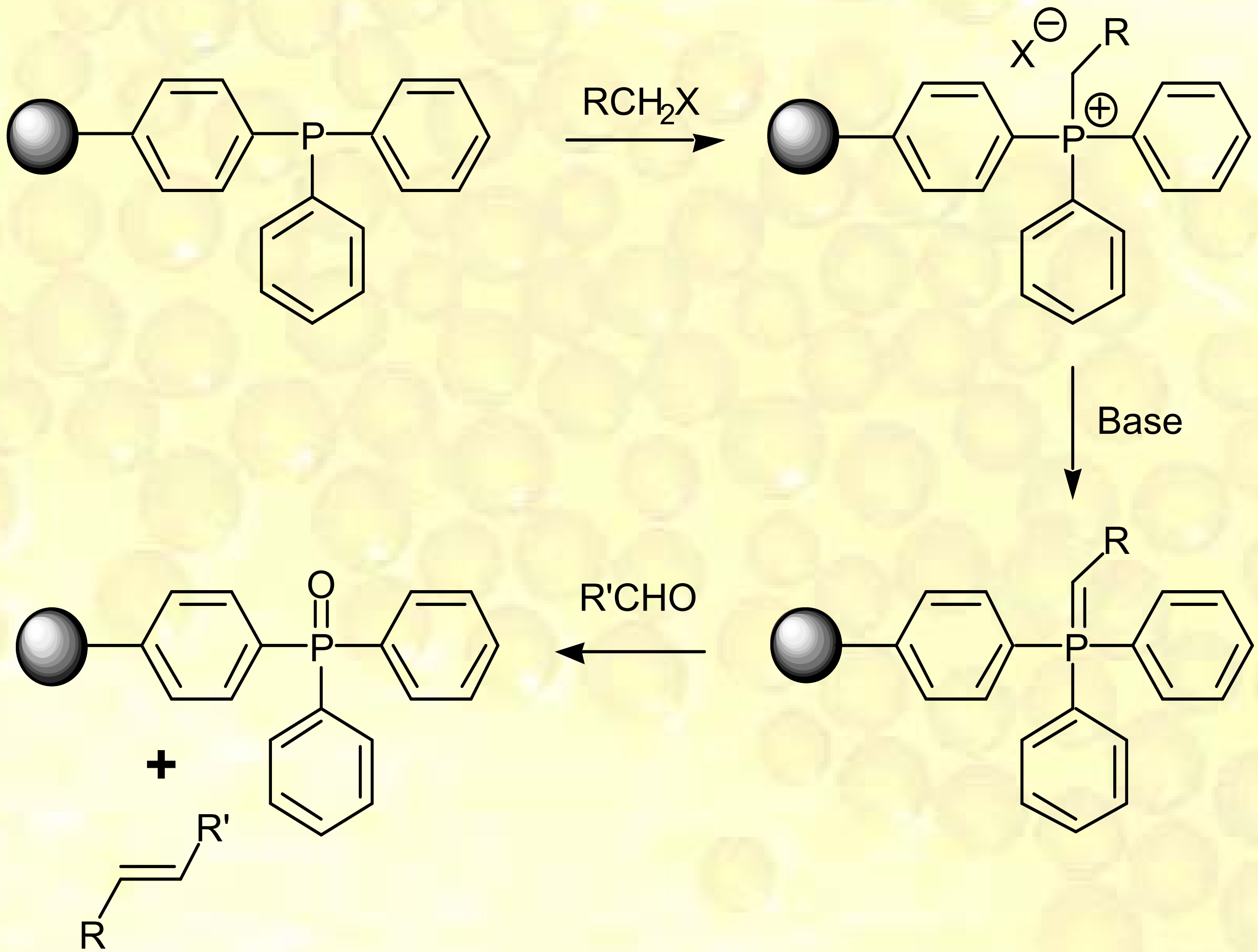
1.2.4.4.A. Acetal deprotection



Historical Development

1.2.4.5. Supported reagents

1.2.4.5.A. Wittig reaction



Historical Development

1.3. Cellulose

1.3.1. Polypeptide synthesis

(see Merrifield)

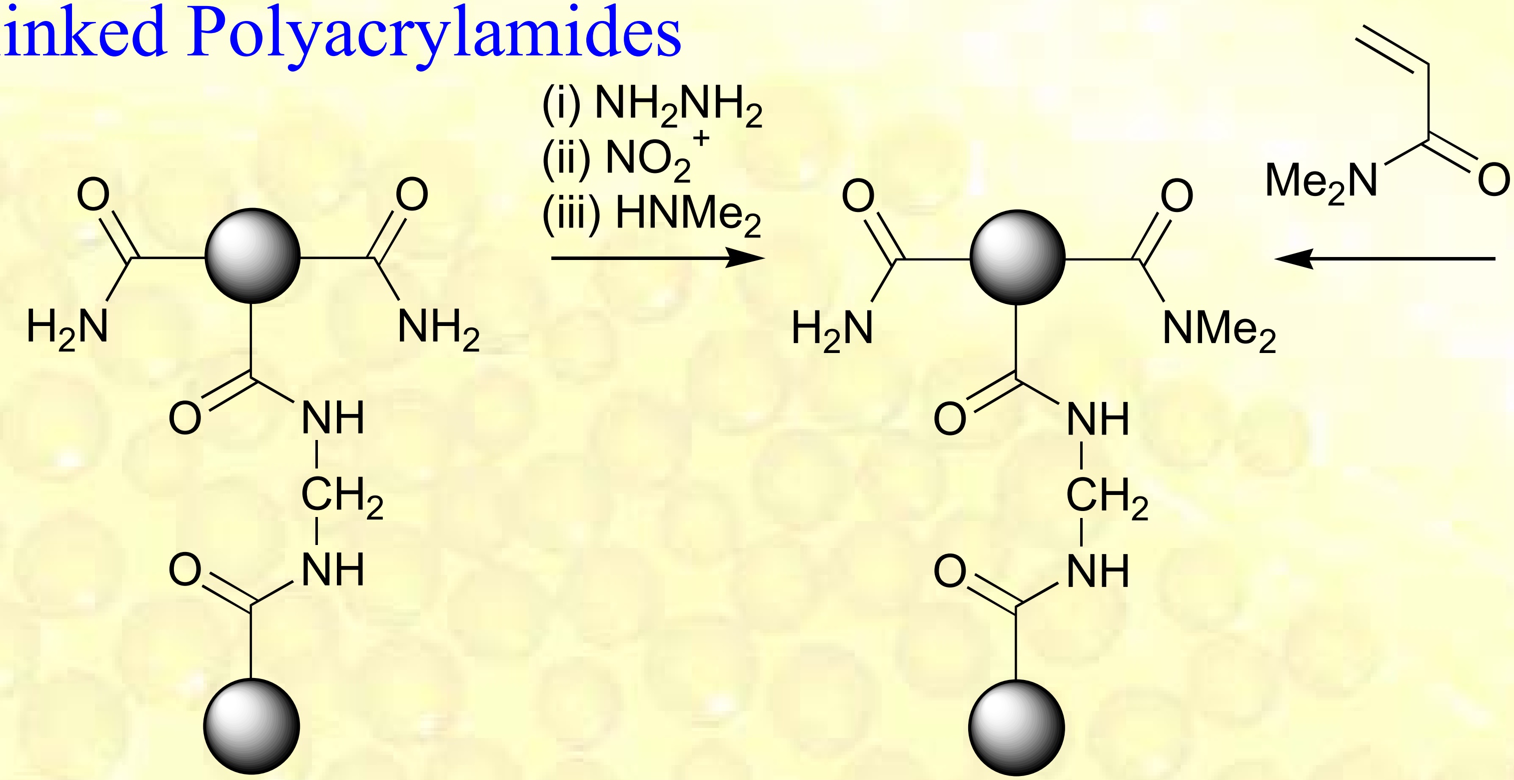
1.3.2. Sephadex

Crosslinked cellulose

Ubiquitous separation medium

Historical Development

1.4. Crosslinked Polyacrylamides

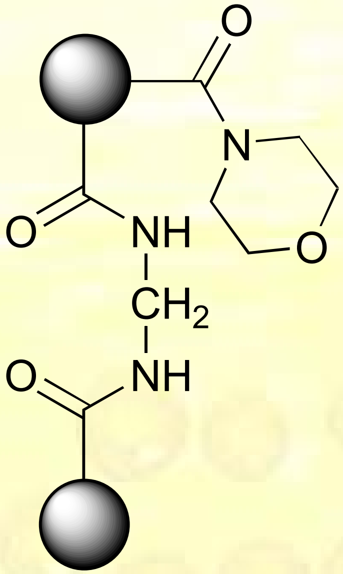


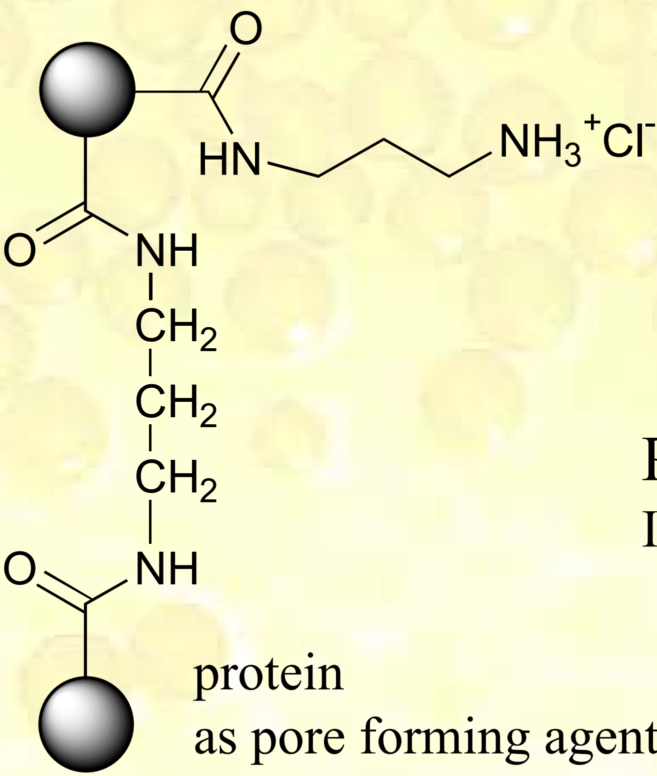
Pepsyn

1.4.1. Features/Properties

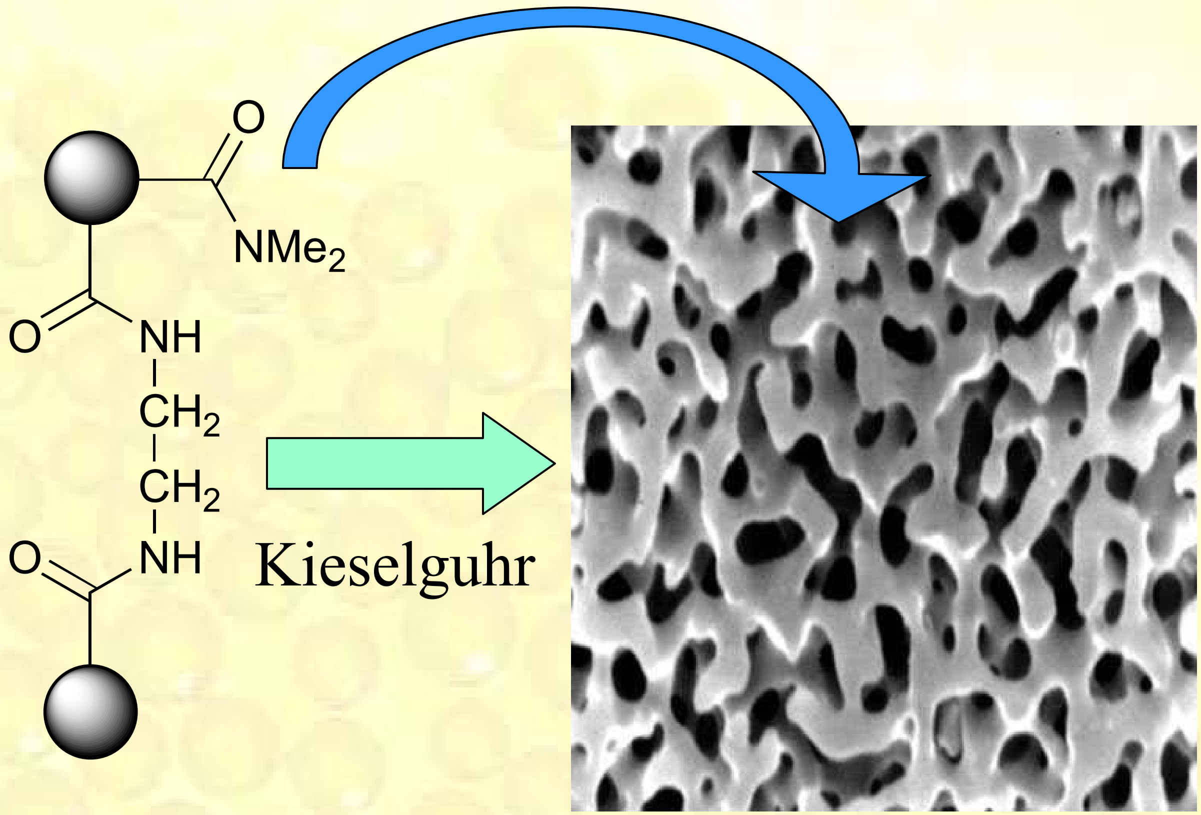
- Compatible with hydrophilic solvents (DMF)
- Improved performance in polypeptide synthesis
- Enhanced solubility for protected peptides and polar reagents/substrates
- Otherwise similar to Merrifield resins

Historical Development





protein
as pore forming agent



Pepsyn S
Improved hydrolytic stability

Pepsyn K
Pressure stable

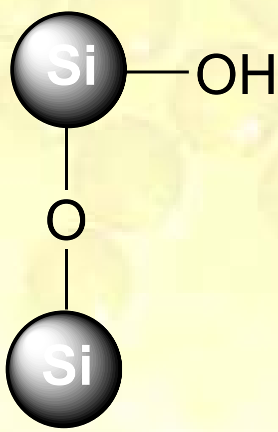
Historical Development

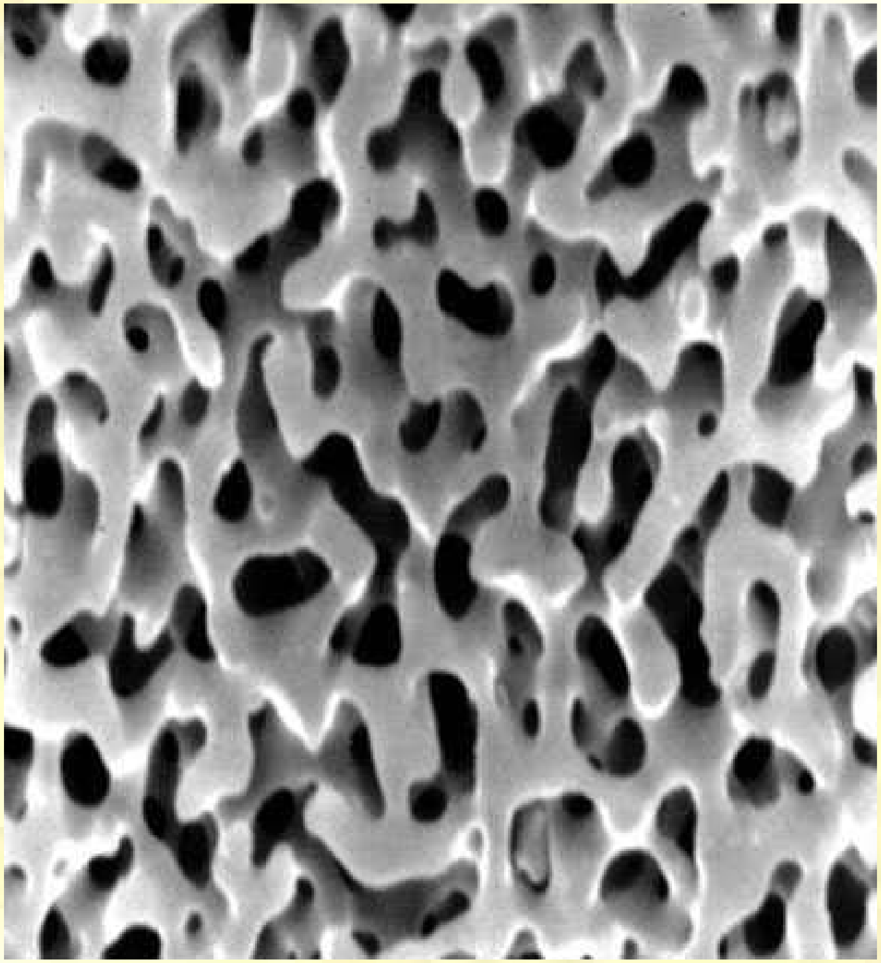
1.5. Controlled Pore Glass

Essentially zero swelling

Pore size control (10-1000 nm)

DNA and RNA synthesis





Historical Development

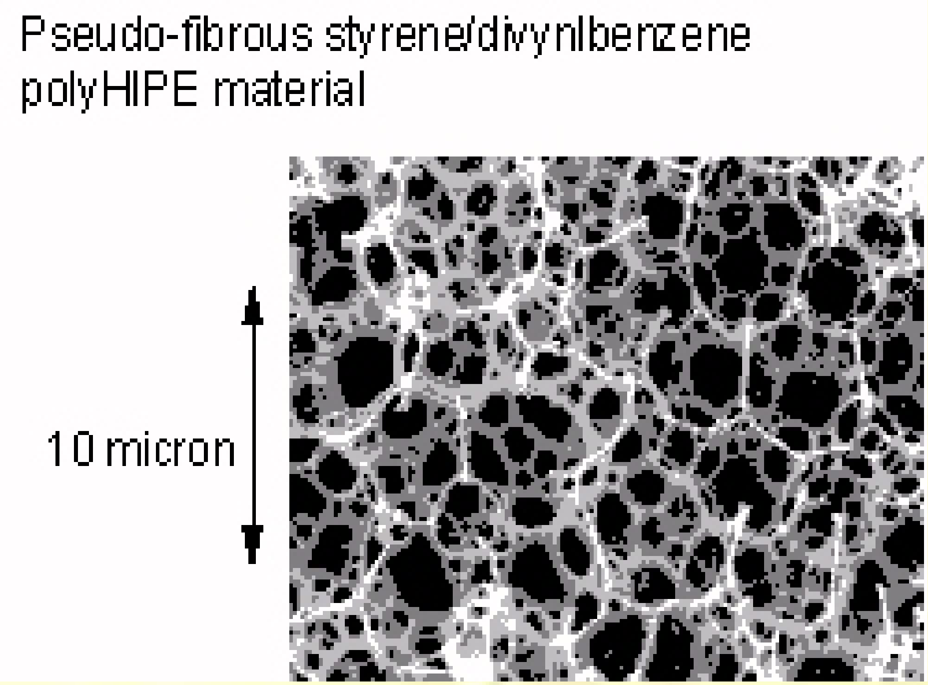
1.6. PolyHIPE

High Internal Phase Imulsion

Open pore structure

Excellent diffusion properties

Merrifield and other resin chemistries possible



Historical Development

1.7. Tentagel and Derivatives

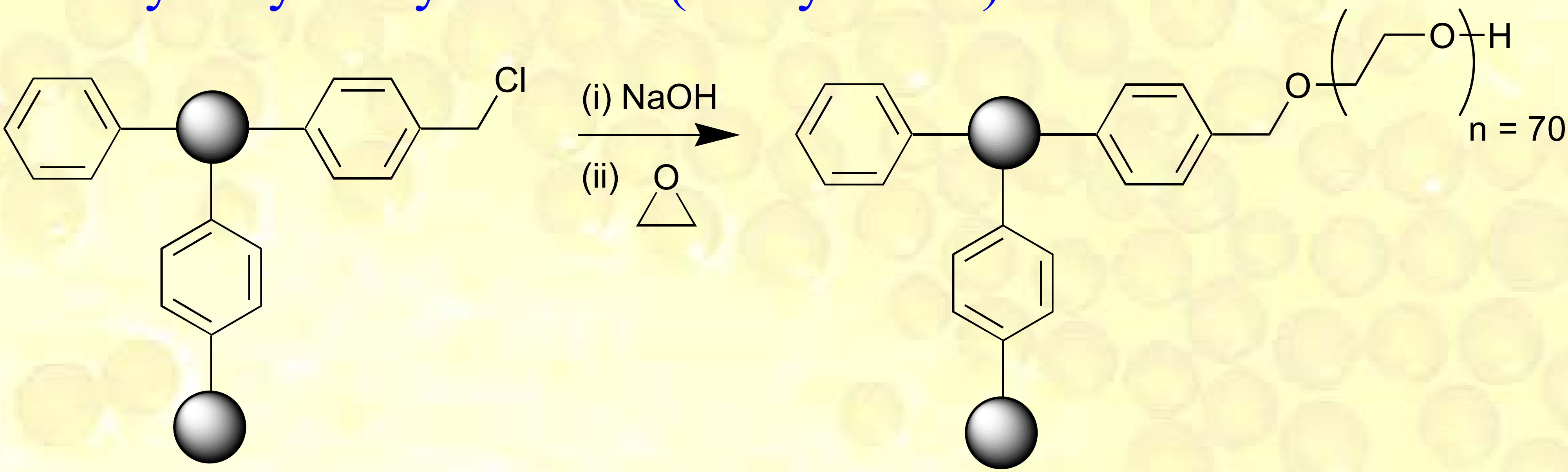
1.7.1. Synthesis/Features/Properties

Extended solvent compatibility (incl. H_2O)

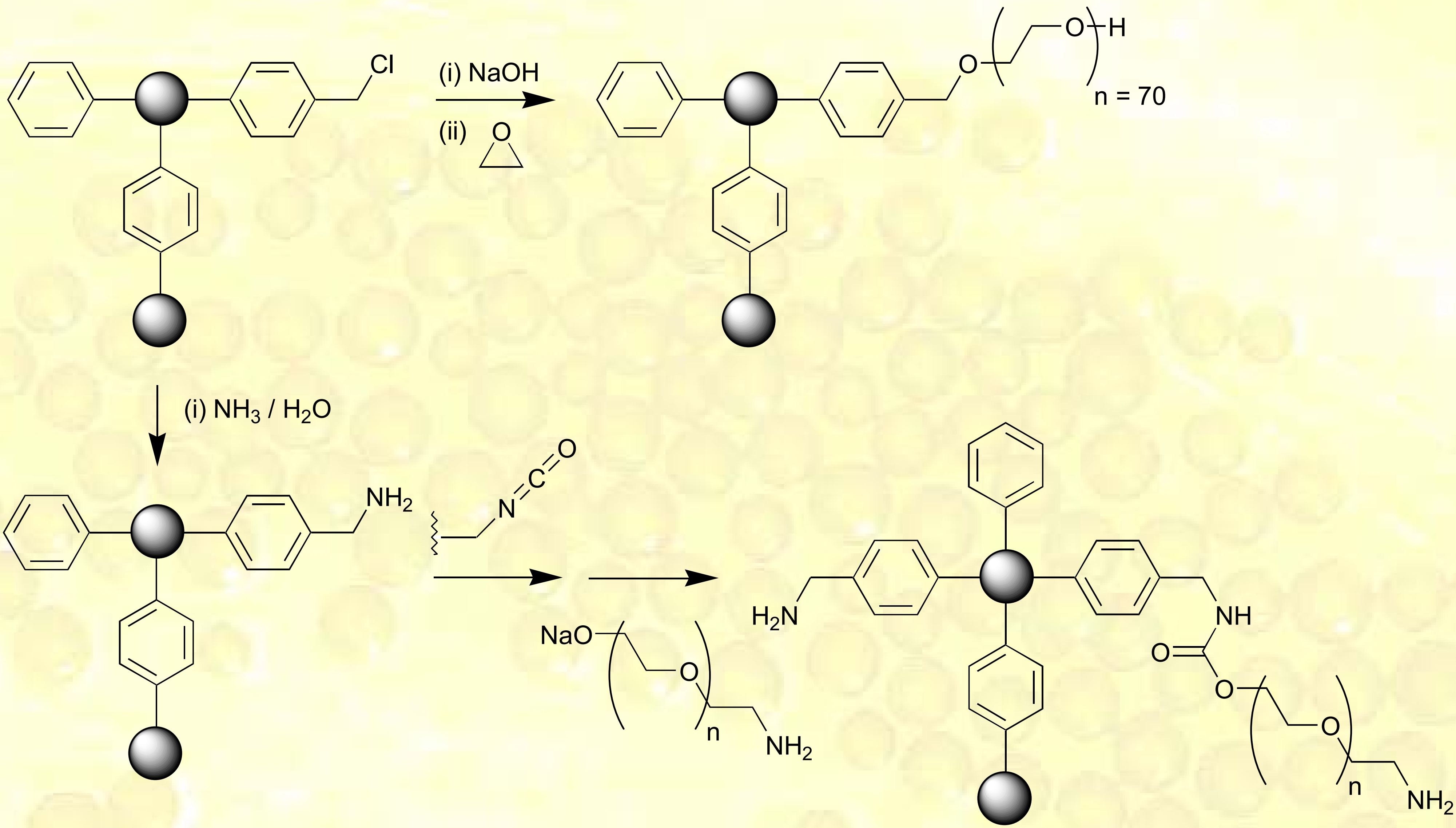
Higher degrees of swelling and faster kinetics (than PS)

Low loading but good pressure stability

Hydrolytically unstable (benzylethers)

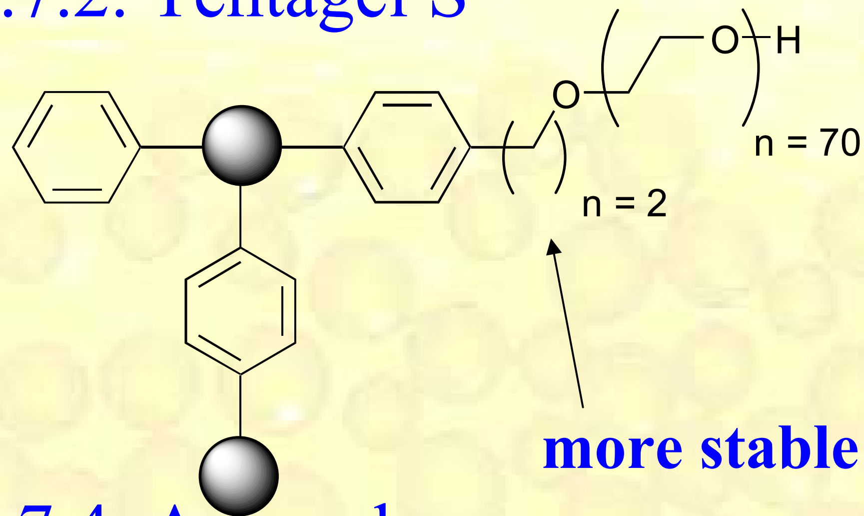


Historical Development



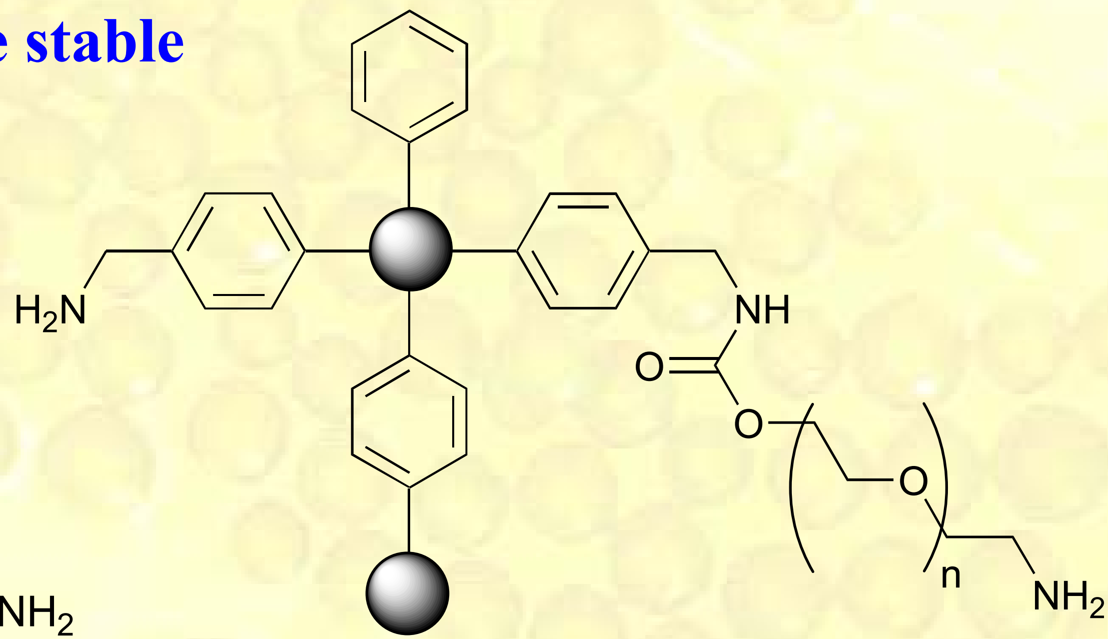
Historical Development

1.7.2. Tentagel S

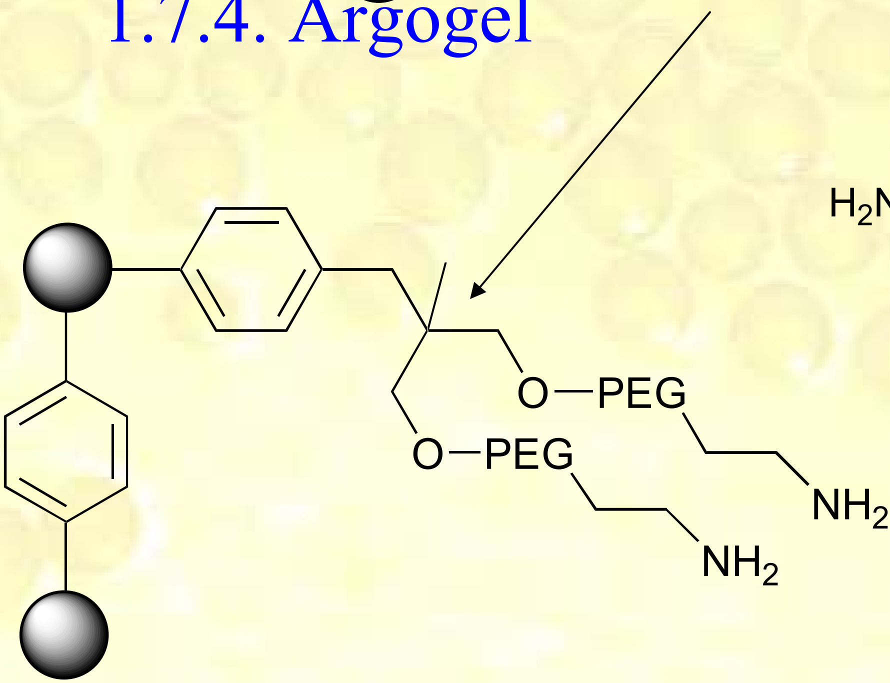


more stable

1.7.3. Novagel



1.7.4. Argogel



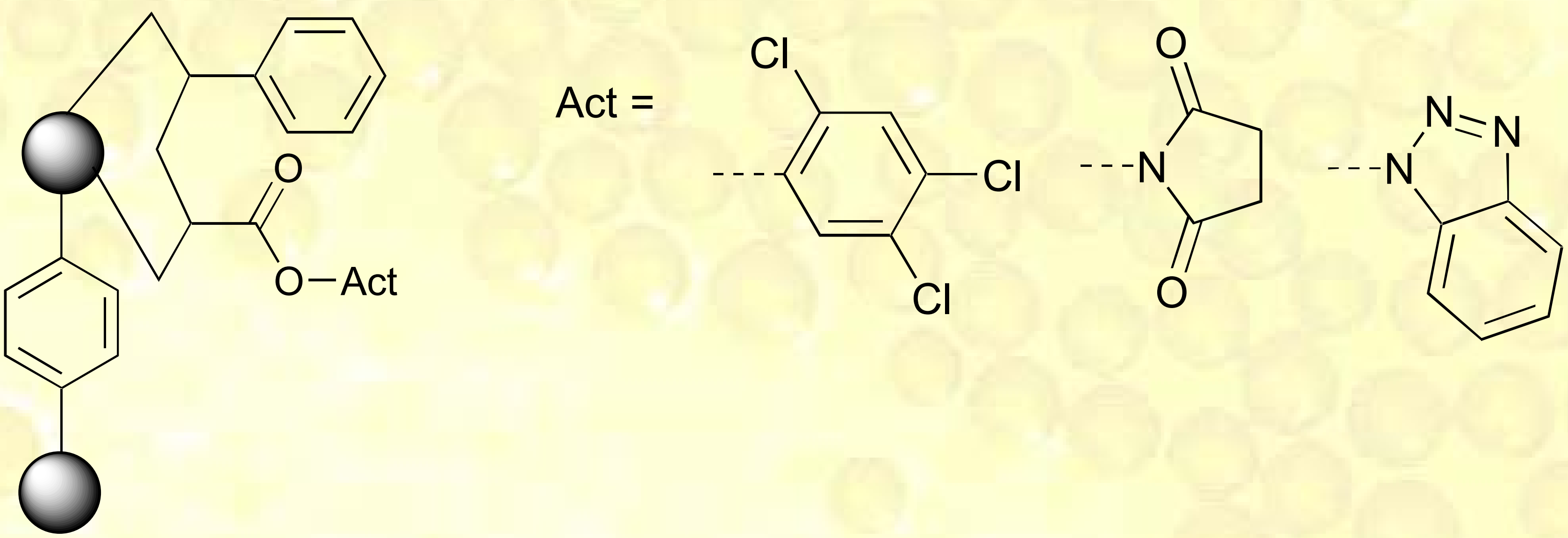
Historical Development

1.8. Alternating PS-co-PAAmides

1.8.1. Synthesis/Features/Properties

Traditional polyacrylamide supports perform poorly with hydrophobic amino acid sidechains

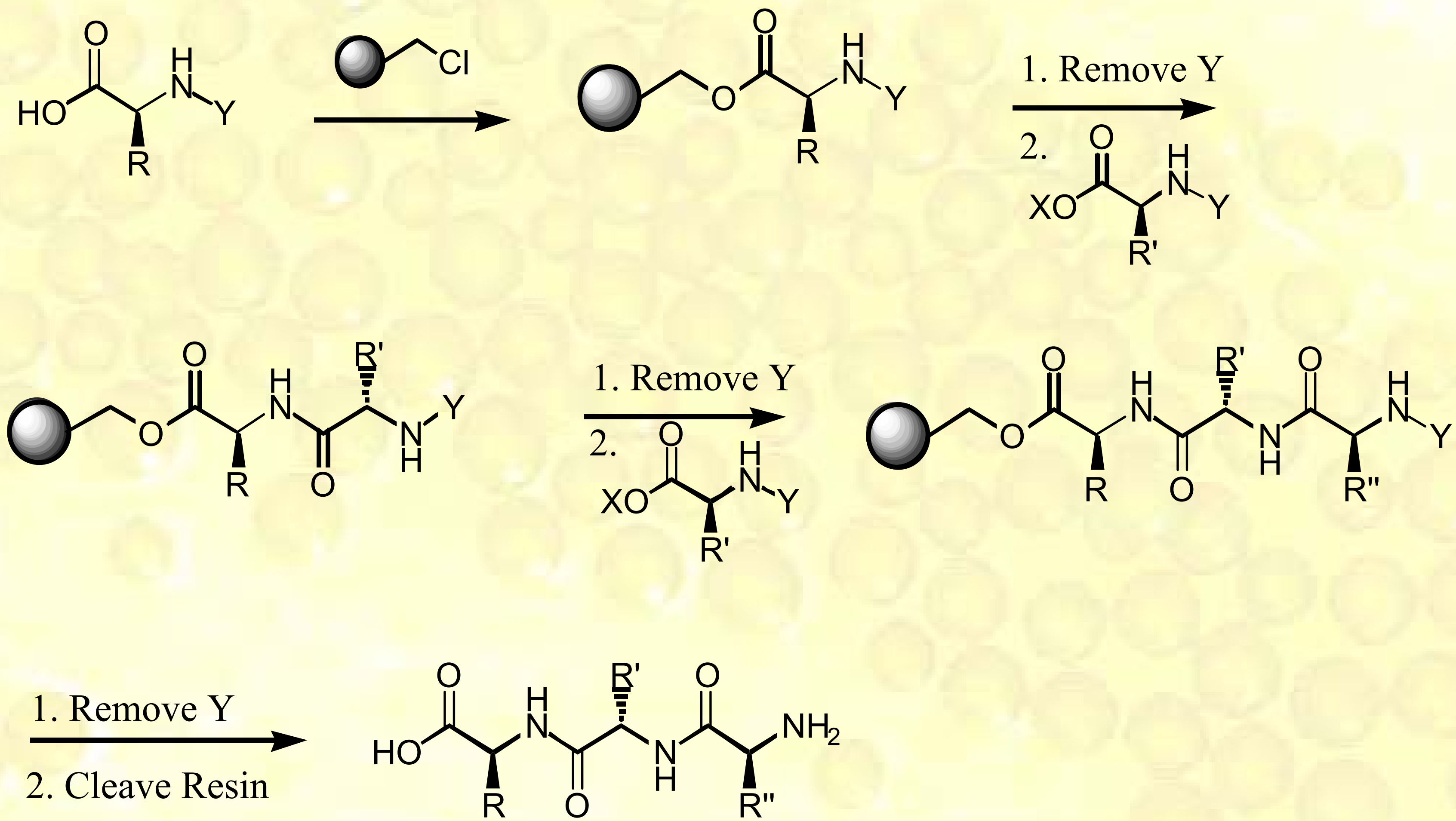
Improved swelling/solvent compatibility behaviour



2. Solid Phase Synthesis - Examples

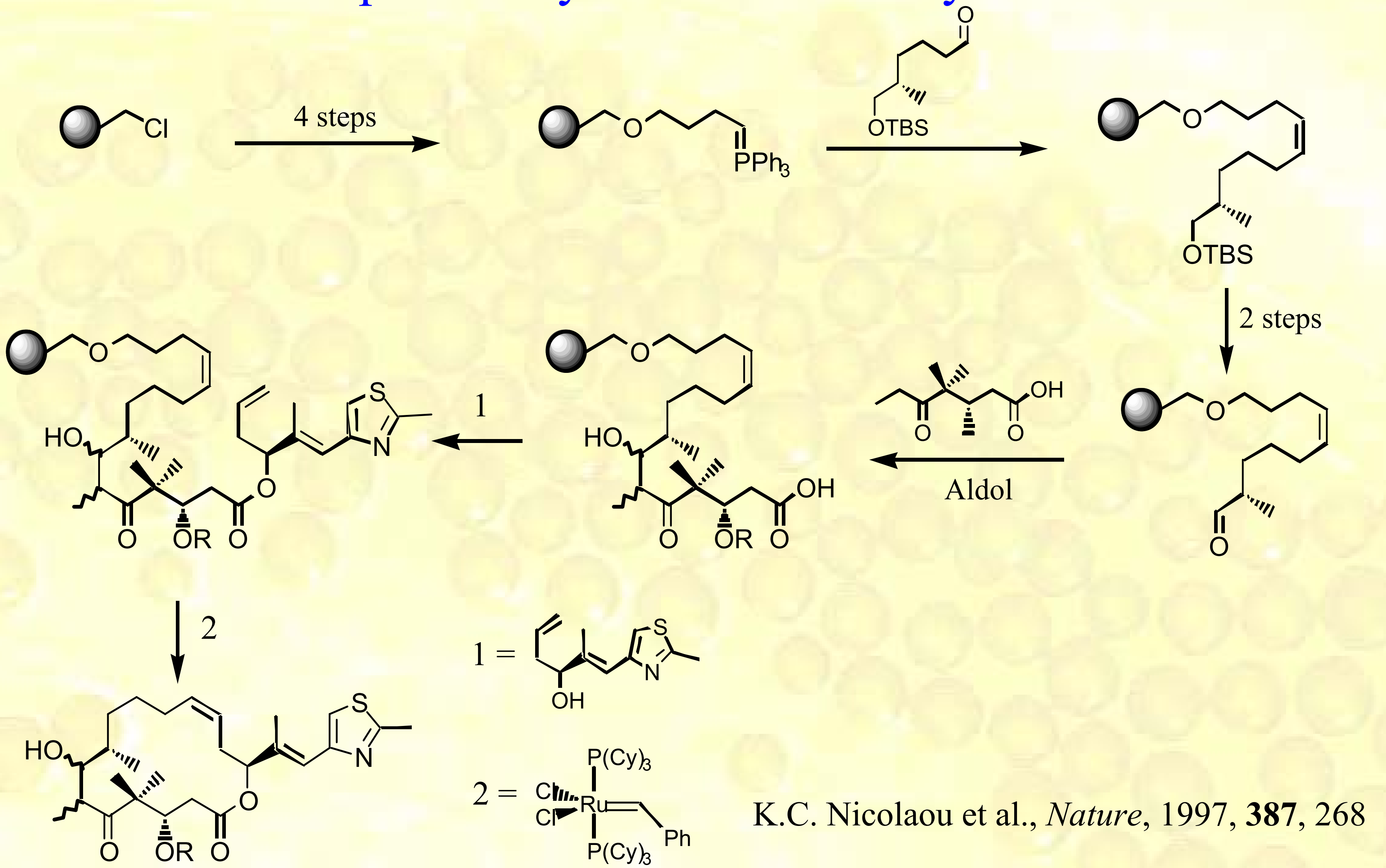
- **2.1. Solid phase organic synthesis (SPOS)**

  2.1.1. Peptides/Peptoides



Solid Phase Synthesis - Examples

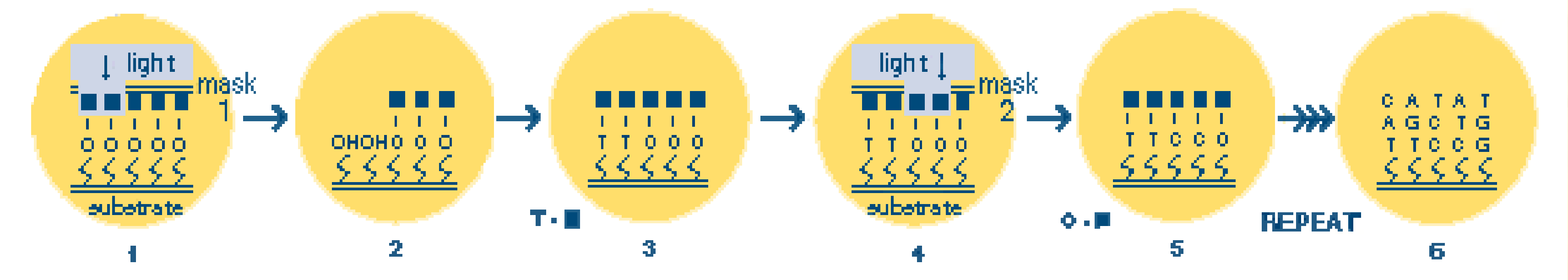
2.1.2. Natural product synthesis - Macrocyclisation



K.C. Nicolaou et al., *Nature*, 1997, **387**, 268

Solid Phase Synthesis - Examples

2.1.3. Light-directed spatial synthesis



Solid Phase Synthesis - Examples

2.2. Solid phase materials synthesis

2.2.1. Organic and Biomaterials

Polyhydroxyalkanoates

Polymeric enzyme mimetics

D.J. Schaefer et al., *Angew. Chem. Int. Ed.* 1999, **38**, 2495

Solid Phase Synthesis - Examples

2.2.2. Inorganic materials

Superconductors

Magnetoresistive materials

Ferroelectrics

Dielectrics

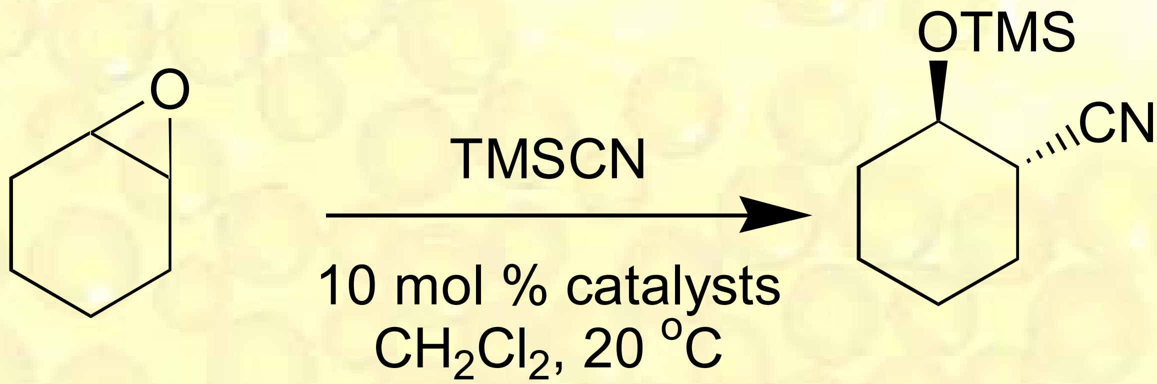
Au Nanoclusters

Luminescent materials

X.-D. Xiang, *Biotechnol. Bioeng.* 1998, **61**, 227

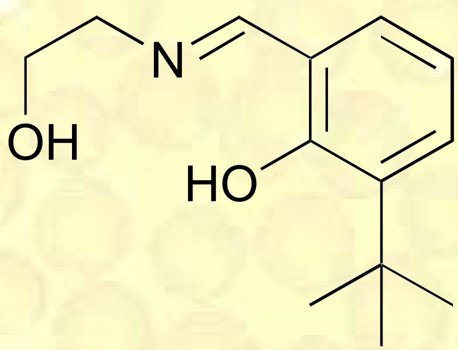
Solid Phase Synthesis - Examples

2.2.4. Catalysts



catalysts: $Ti(OiPr)_4$, $Ti(OiPr)_4$ +

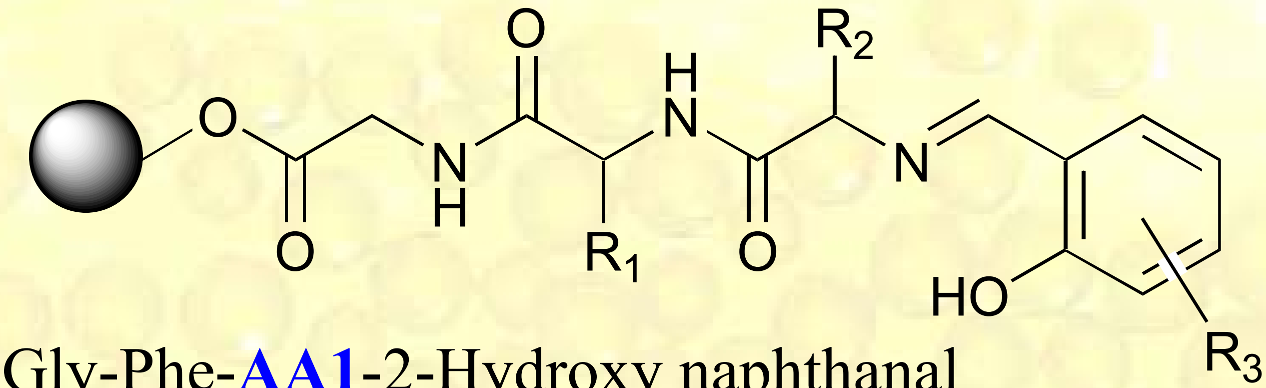
12% 80%



Hoveyda et al. *Angew. Chem. Int. Ed. Engl.* 1996, **35**, 1668

Solid Phase Synthesis - Examples

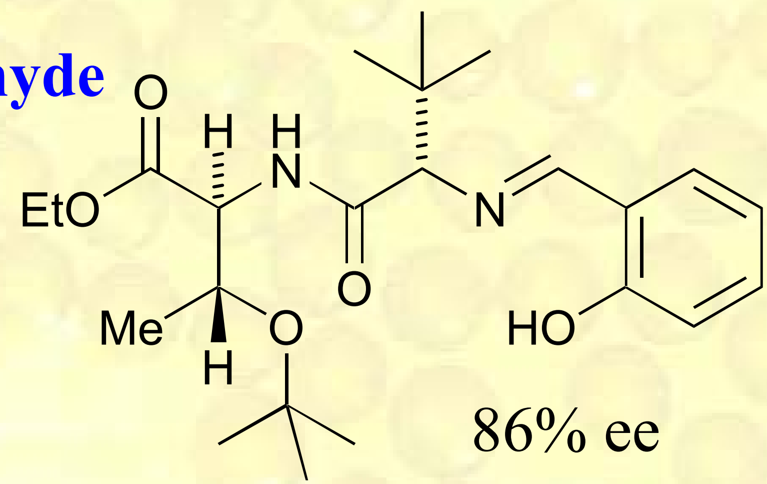
- **Screening – Solution phase**



MeO-Gly-Phe-**AA1**-2-Hydroxy naphthanal

MeO-Gly-**AA2**-t-Leu -2-Hydroxy naphthanal

MeO-Gly-Thr(t-Bu)-t-Leu-**Aromatic Aldehyde**



86% ee

Historical Development

- **Polymer support design features**

  Chemical stability

  Loading

  Solvent compatibility – Swelling

  Hydrophobic and hydrophilic nature

  Physical stability (automation)

  Recyclability

  Availability of monomers

  Good performance with excess amounts of reagents

  Good performance with equimolar amounts of reagents

  Different morphologies accessible (gel, bead, macroporous)

Lecture 2 and 3

The Ins and Outs

1. **Polymer supports for SPOS**
2. **Support formats for SPOS**
3. **Tagging**
4. **Separation/Handling**
5. **Solvent interactions**
6. **Loading**
7. **Stability**
8. **Linkers**

1. Polymer supports for SPOS

1.1. PS

1.2. Polyacrylamides

1.3. Poly(meth)acrylates

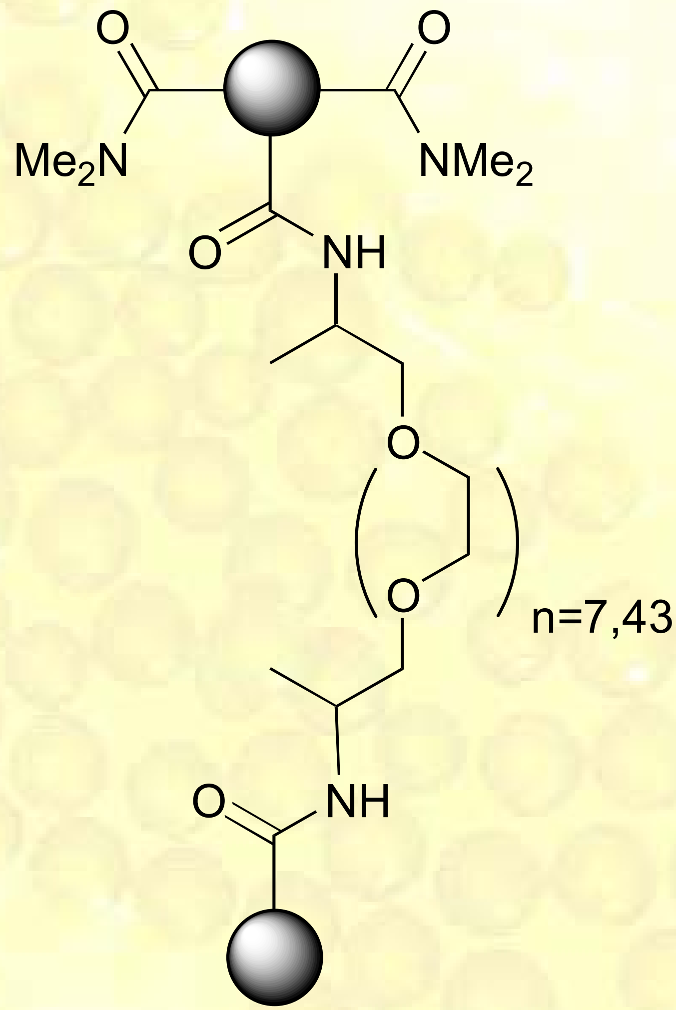
1.4. PEGA

1.5. CPG

1.6. PS-g-PEG

1.7. PE

1.8. PP



2. Support formats for SPOS

- **2.1. Intrinsic formats**
  - 2.1.1. Gel
    - Chain mobility comparable to linear polymer
    - Diffusion slow
    - Size and diffusion depending on swelling
  - 2.1.2. Macroporous
    - Restricted chain motion
    - Diffusion fast
    - Swelling has little influence
  - 2.1.3. Bulk surface
    - No chain motion
    - Diffusion fast (no inner surface)
    - No swelling (low loading levels)

2. Support formats for SPOS

2.2. Shape formats

- 2.2.1. Beads
  - Standard format
  - Narrow particle size important for screening
  - Easy handling
- 2.2.2. Sheets
  - Easy handling
  - Cut to size (and loading)
  - Diffusion always high
- 2.2.3. Membranes
  - Easy handling
  - Cut to size
  - Fast reaction rates (flow)