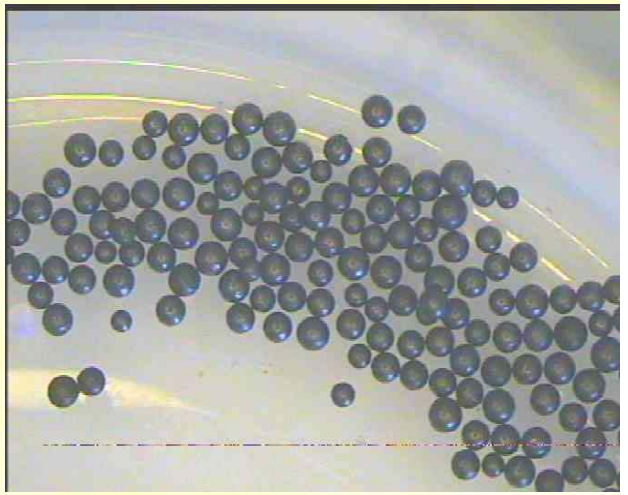
2. Support formats for SPOS

- 2.2.4. Grafted surfaces – pins
  - Any shape
  - Microtitre well format
  - Fast reaction rates
- 2.2.5. Irregular shapes – luck charms
  - Similar to beads
- 2.2.6. Discs
  - Similar to beads for chemistry
  - Similar to luck charms for handling

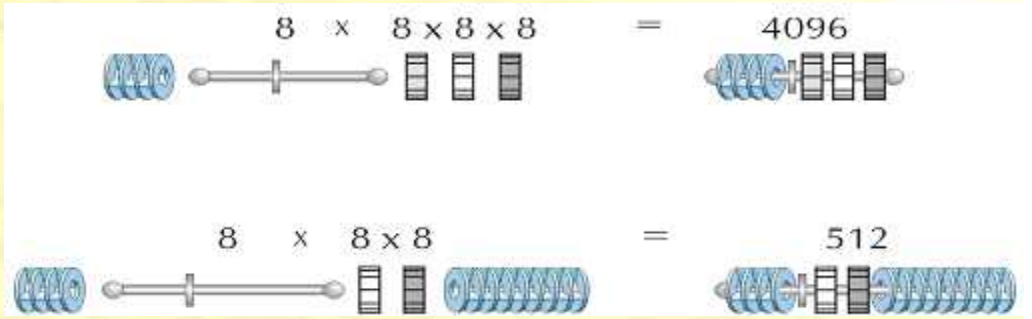
3. Tagging

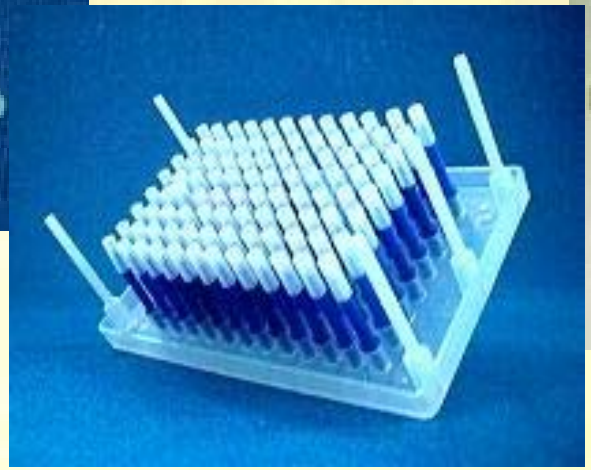
- **3.1. Chemical tagging**
  - Orthogonal
    - Isotopic encoding
    - Amino acid encoding
  - Genetic
    - Phage displays
  - Arylhalides
    - Levels of chlorine

3. Tagging



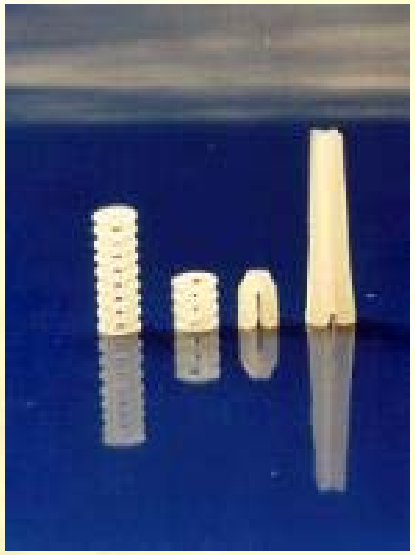
- **3.1. Physical tagging**
  - Single beads / pins etc.
  - Magnetic encoding
  - Radiofrequency tags
  - Colour coding

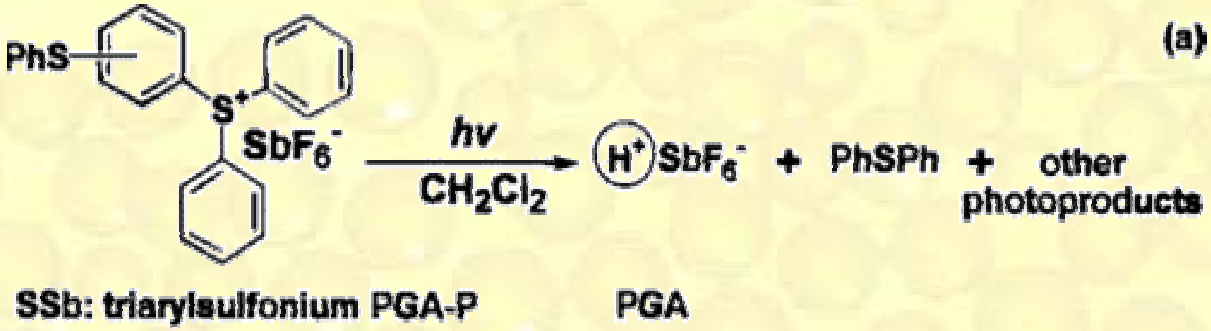


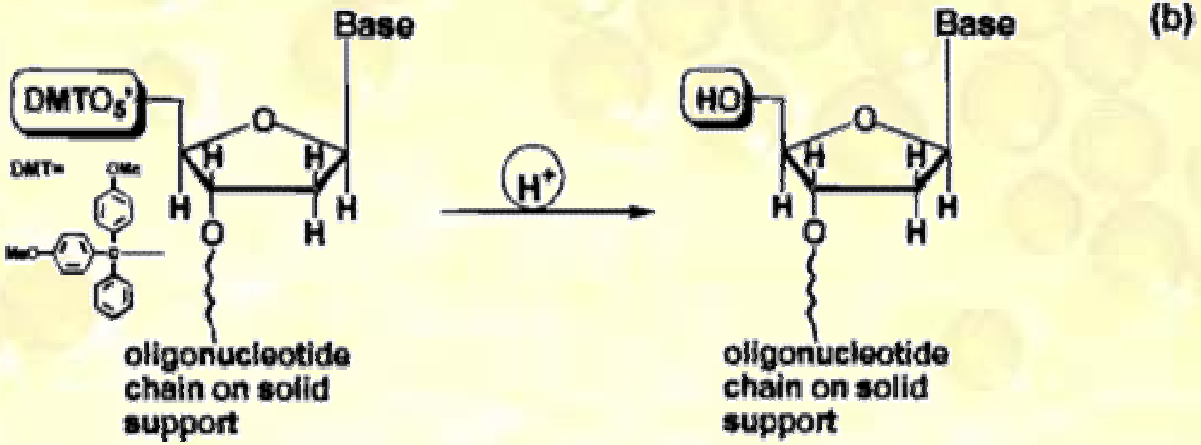


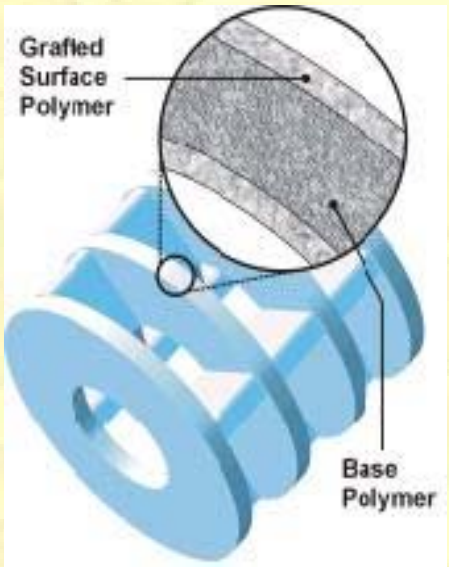
3. Tagging

- **3.1. Physical tagging**
  - Unique shapes
  - Spatially addressable



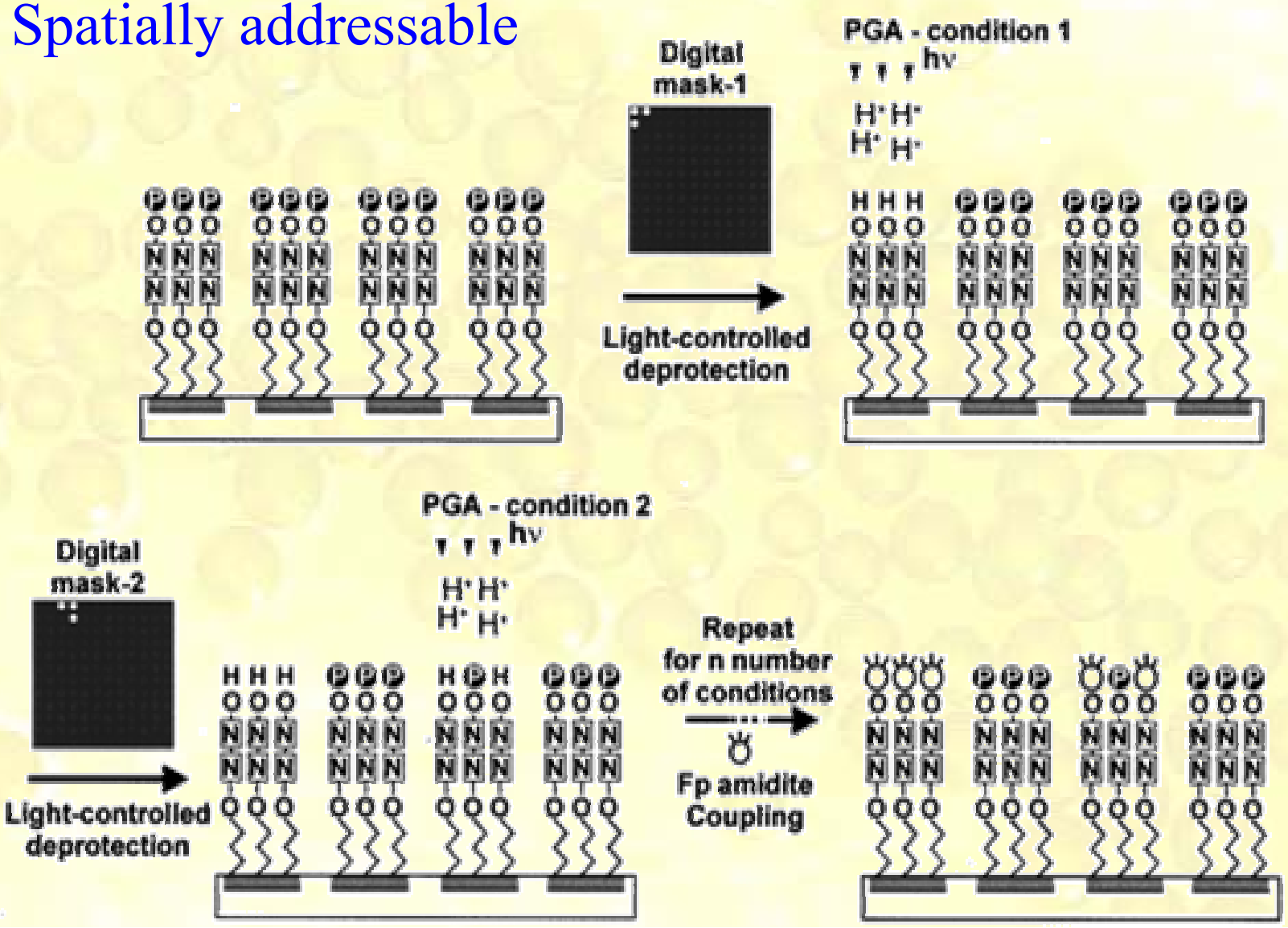






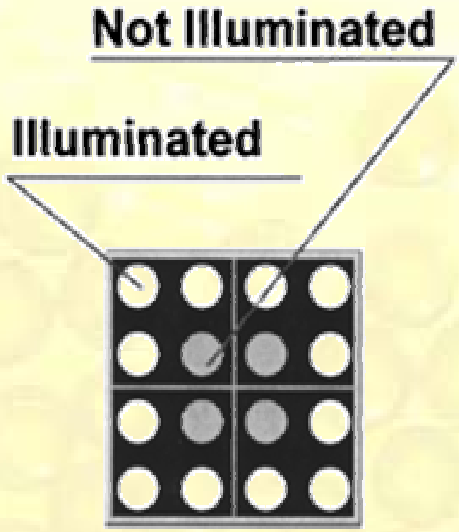
3. Tagging

- **3.1. Physical tagging**
  - Spatially addressable

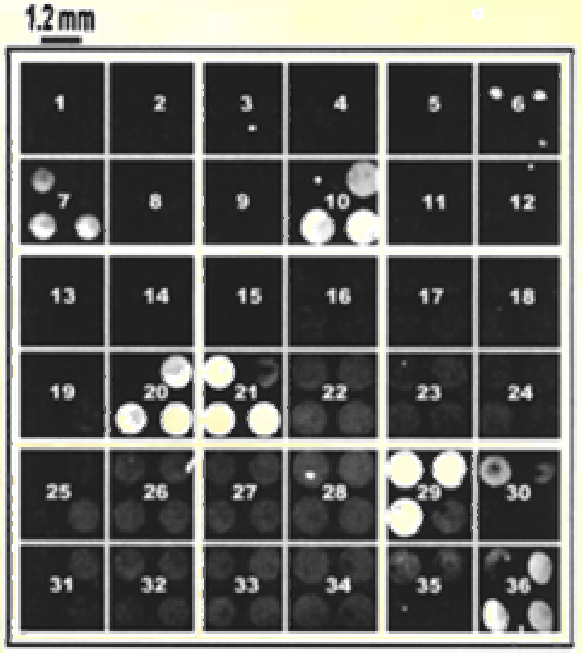


3. Tagging

- Spatially addressable

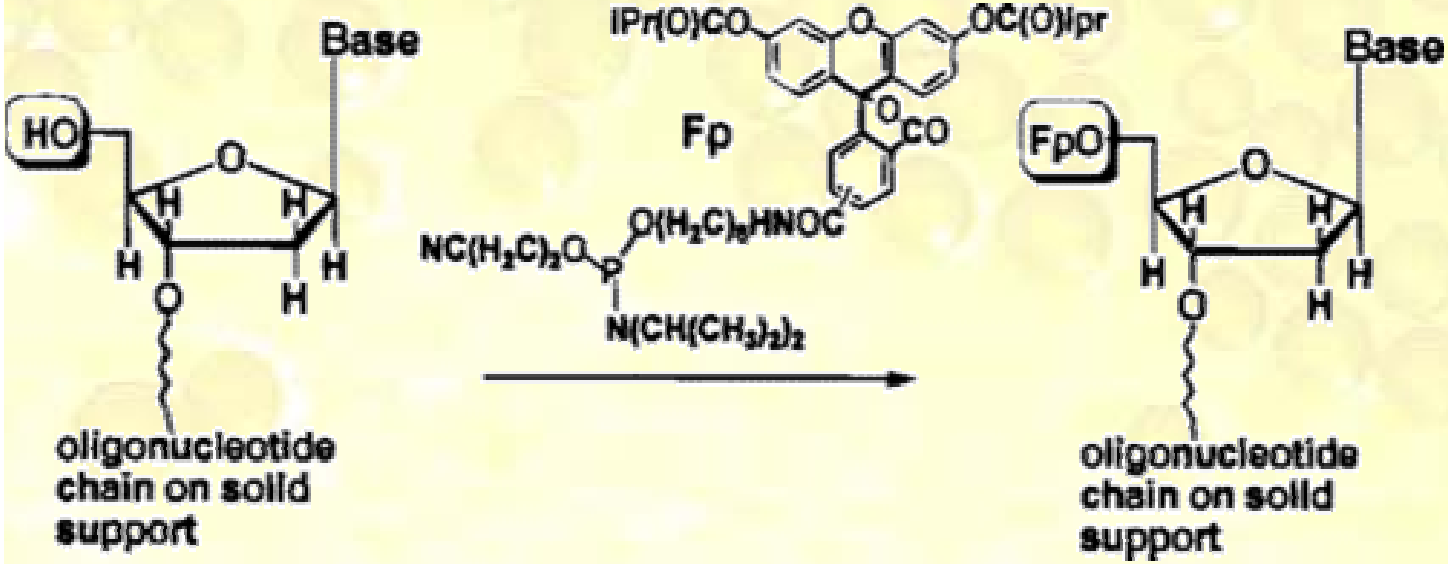


A panel of 4 PGA conditions



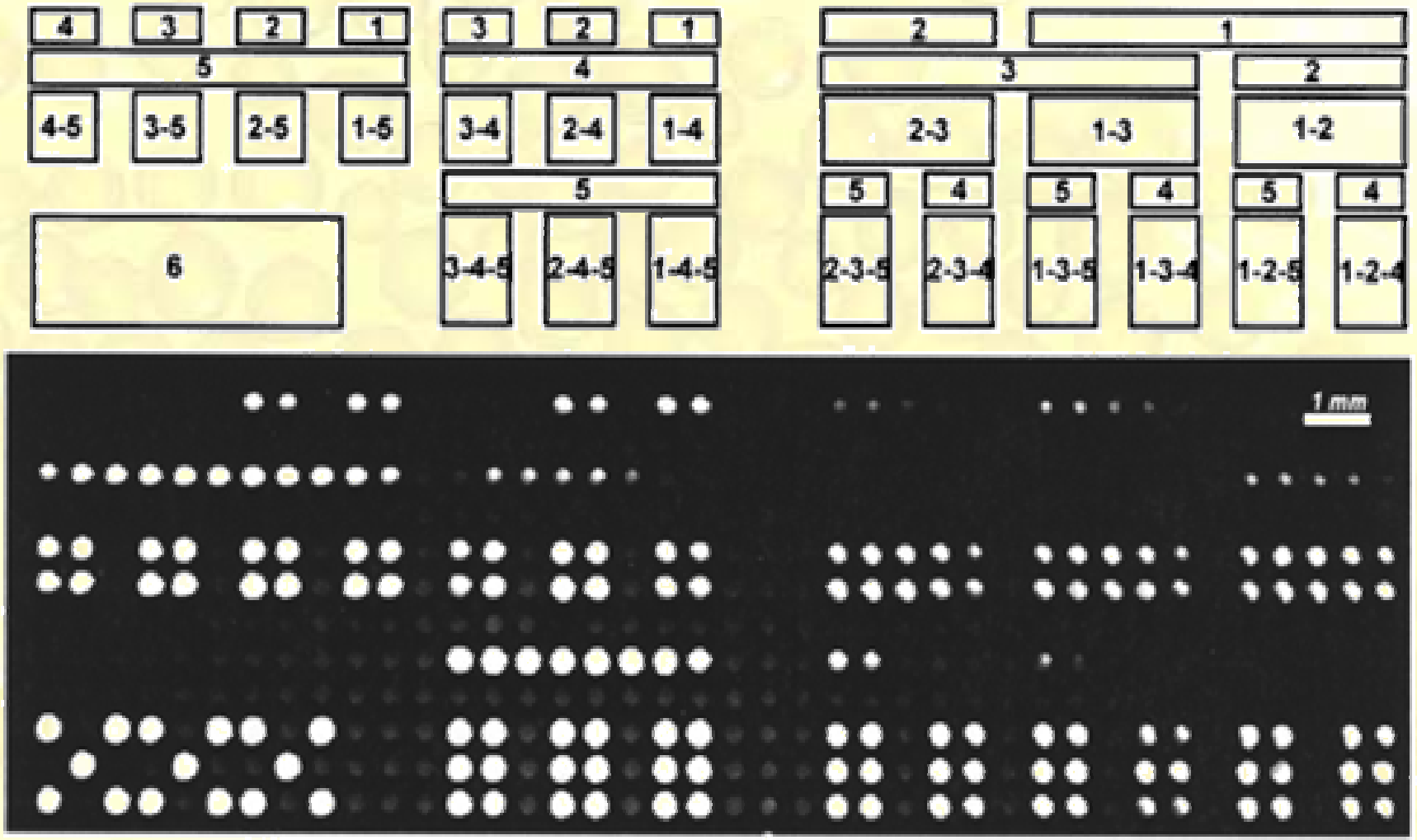
Intensity Ratio

#7	4.2±0.2	#21	6.6±0.5
#10	5.7±0.3	#29	6.3±0.5
#20	6.5±0.5	#36	4.4±0.3



3. Tagging

- Spatially addressable



4. Separation/Handling

- **4.1. Single beads/charms**
- **4.2. Pressure control**
- **4.3. Split and mix**
- **4.4. Tea bags**
- **4.5. Magnetic separation**
- **4.6. Irori tubes**
  - http://www.irori.com/Technology/directed_sorting_demo.html
- **4.7. Sheets**
- **4.8. Photolithographic masks**
- **4.9. Cotton Strips**

5. Solvent interactions

- **5.1. Swelling**
  - 5.1.1. Accessibility
    - Spacer length
  - 5.1.2. Reaction kinetics
    - Gel
    - Macroporous
    - Bead Size
    - Grafting

5. Solvent interactions

- Polyacrylamide
- CPS
- Poly(meth)acrylates
  - Gel vs Macroporous
- Tentagel
- Argogel

5. Solvent interactions

- Tentagel
- Argogel

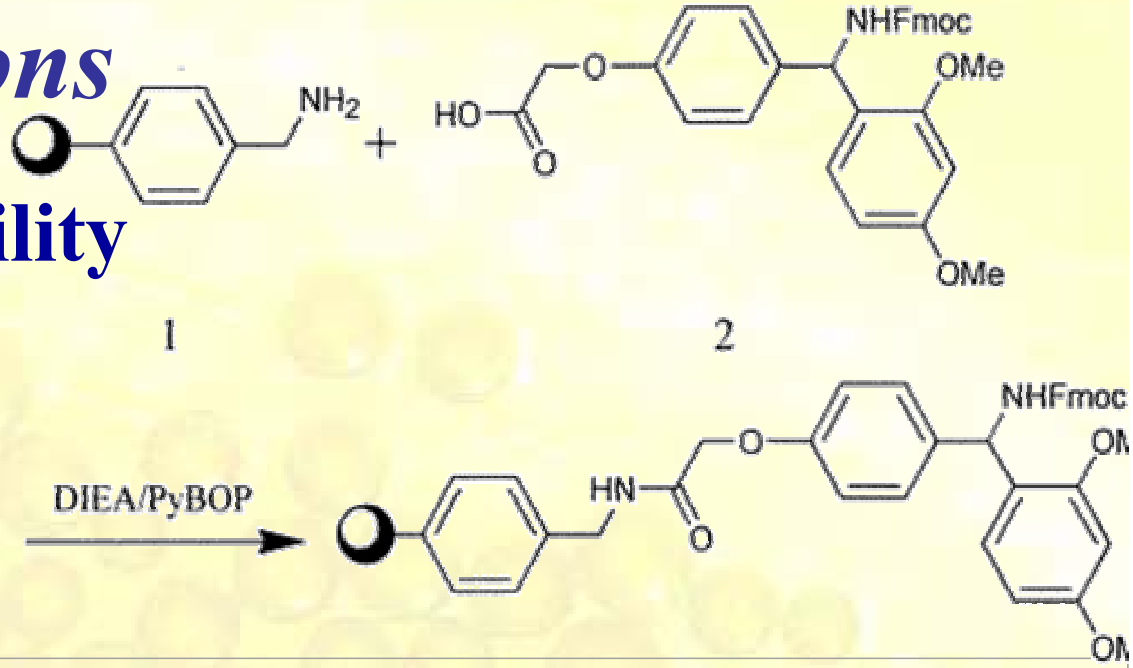
Table. Swelling Volume (mL/g) for Polystyrene and Various PS-PEG Graft Copolymers at 25 C (mL/g)

solvent	PS-NH2 a	TentaGel-OH b	ArgoGel-OH c	TentaGel-NH2 b	ArgoGel-NH2 c
toluene			5.2		6.2
THF	8.0	4.5	5.8	3.9	6.4
DCM	8.9	5.8	7.5	5.5	8.6
DMF	8.0	4.5	6.0	4.0	5.0
MeOH	2.8	3.8	4.7	3.0	4.9
water	2.1	3.8	3.9	3.0	4.0

a Obtained from Bachem.
b Obtained from Rapp Polymere.
c Obtained from Argonaut Technologies.

5. Solvent interactions

- **5.2. Solvent compatibility**
  - PE
  - PS
    - Gel vs Macroporous



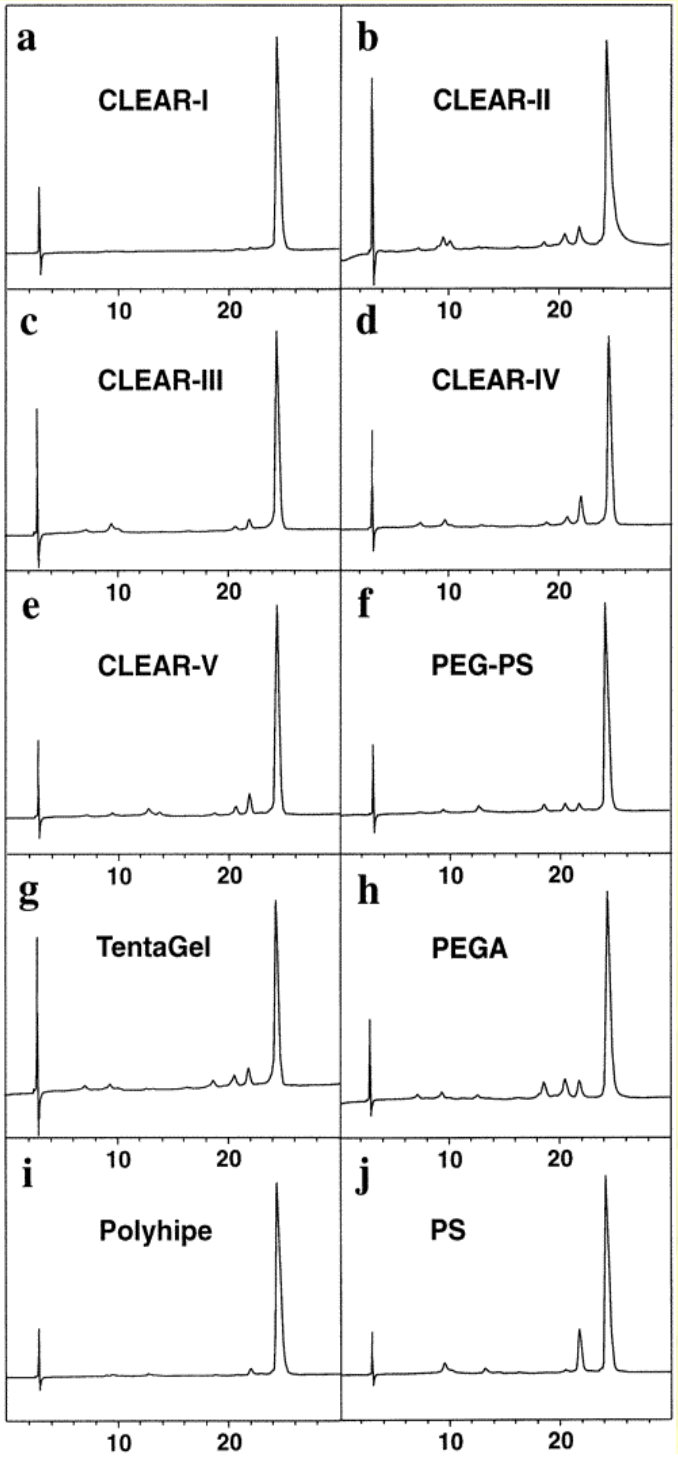
Kinetics of Knorr Formation Reaction on Various Resins a
resins (size)kobs (1/s)t1/2 (s)conversion (%)loading (mmol/g)b

PS (100-200 mesh)	PS (100-200 mesh) c	PS (200-400 mesh)	PS (70-90 mesh)	ArgoGel-AM (164 μm)	TentaGel-AM (130 μm)	Champion-1 (100-200 mesh) d	Polymer
2.1 × 10-2	7.9 × 10-3	ca. 8 × 10-2	3.9 × 10-3	ca. 7 × 10-2	ca. 6 × 10-2	ca. 4 × 10-1	k_{obs}
33	88	ca. 9	178	ca. 10	ca. 12	ca. 2	$t_{1/2}$
93	71	96	96	94	91	98	conversion
1.38	1.38	0.43	1.12	0.44	0.29	0.40	loading

a Experimental conditions: 0.2 M Knorr/0.4 M DIEA/0.2 M PyBOP in DCM at 25 C.
b Measured loading by Fmoc-Cl before Knorr formation (see Supporting Information for details).
c The same experimentalconditions used in previous entry but carried out in DMF instead of DCM.
d Champion-1, a type of PEG-AMPS resin that has 60% PEG content from Biosearch Technologies.8

5. Solvent interactions

- Poly(meth)acrylates
  - Gel vs Macroporous

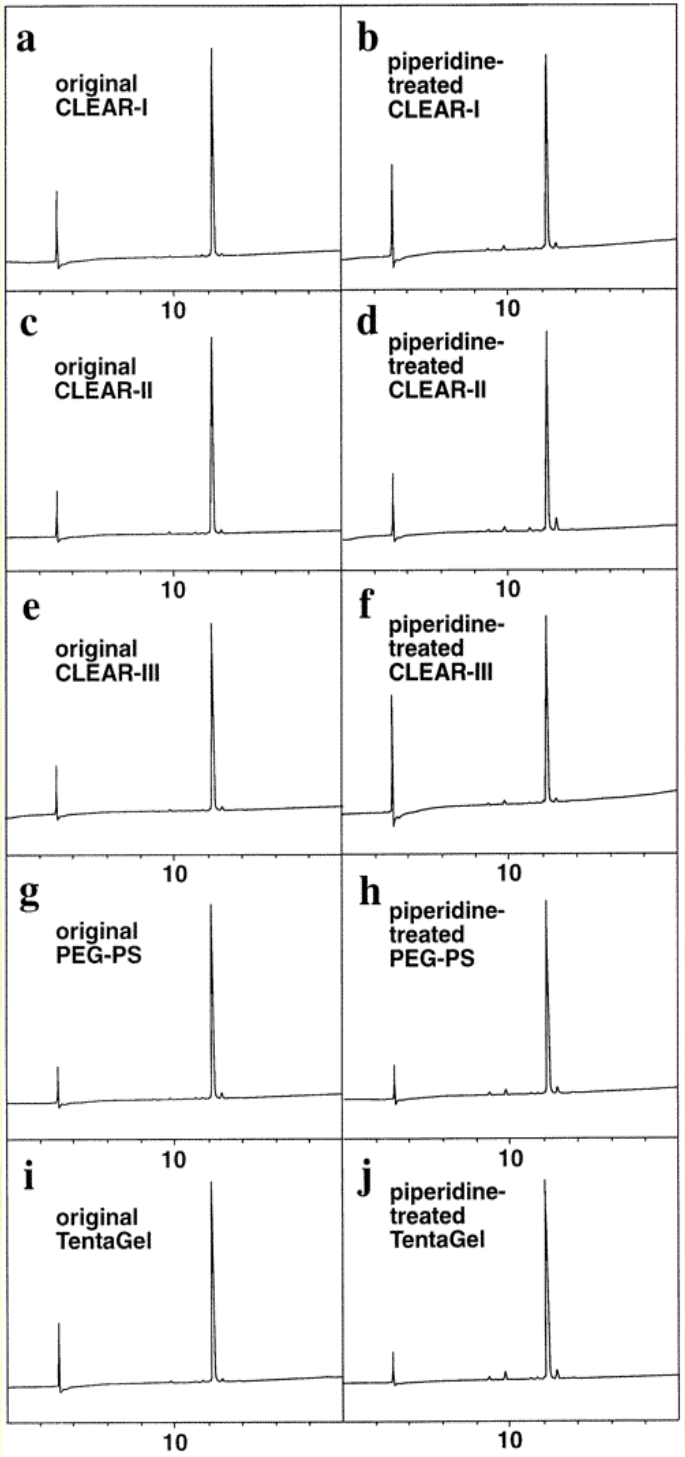


Analytical HPLC chromatogram of crude retro-ACP (74-65) amide, prepared by batchwise manual synthesis on (a) CLEAR-I; (b) CLEAR-II; (c) CLEAR-III; (d) CLEAR-IV; (e) CLEAR-V; (f) PEG-PS; (g) TentaGel; (h) PEGA; (i) Polyhipe; and (j) PS. Elutions at 1 mL/min with a linear gradient over 30 min from 17:3 to 3:1 of 0.1% aqueous TFA and 0.1% TFA in acetonitrile.

Peptides were detected at 220 nm (ordinates); time scale is in min (abscissa). The chromatogram shown in (b) was reproduced in the LC-MS mode, which indicated that the peaks preceding the major one were the des-Ile (9.4 min), des-Gln (20.5 min), and des-Asn (21.8 min) analogues of retro-ACP (74-65) amide.

5. Solvent interactions

- Poly(meth)acrylates



Analytical HPLC chromatogram of crude Leu-enkephalinamide, prepared by batchwise manual synthesis on (a) CLEAR-I (0.24 mmol/g); (b) CLEAR-I that had been treated with piperidine-DMF (1:4) for 9 days; (c) CLEAR-II (0.33 mmol/g); (d) CLEAR-II that had been treated with piperidine-DMF (1:4) for 9 days; (e) CLEAR-III (0.18 mmol/g); (f) CLEAR-III that had been treated with piperidine-DMF (1:4) for 9 days; (g) PEG-PS (0.18 mmol/g); (h) PEG-PS that had been treated with piperidine-DMF (1:4) for 9 days; (i) TentaGel (0.18 mmol/g); (j) TentaGel that had been treated with piperidine-DMF (1:4) for 9 days. Elutions at 0.8 mL/min with a linear gradient over 20 min from 19:1 to 2:3 of 0.1% aqueous TFA and 0.1% TFA in acetonitrile. Peptides were detected at 220 nm (ordinates); time scale is in min (abscissa).

5. Solvent interactions

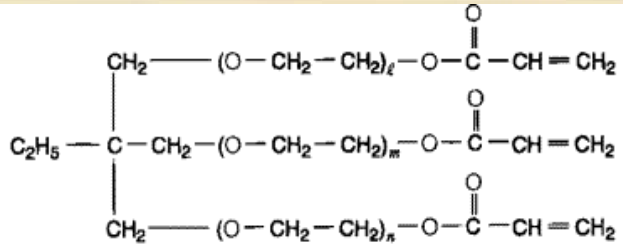
- **Preparation of CLEAR Supports**

SUPPORT monomer or crosslinker (mmol)	**CLEAR-I**	**CLEAR-II**	**CLEAR-III**	**CLEAR-IV**	**CLEAR-V**
1	**9.0**	**3.0**	**8.0**	**12.0**	**13.0**
2	**9.0**			**50.0**	**50.0**
3		**3.6**	**4.4**		
4		**7.0**			
5			**3.0**		
6				**3.0**	
solvent	c-hexanol	c-hexanol	c-hexanol	toluene b	toluene b
mL	17.5	16.0	20.0	12.7b	12.8b
loading a (mmol NH2/g)					
by AAA	0.26	0.30	0.30	0.17	0.13
by UV	0.29	0.25	0.27	0.23	0.20

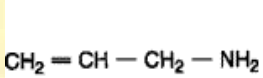
a The loadings varied slightly from batch to batch. Incorporation of components into the final polymers did not match the initial ratios; relevant elemental analysis data in Experimental Section.
b Volume reported for these suspension polymerizations refers to organic solvent. The volume of the aqueous phase was ~10× that of organic;. The amount of allylamine (2) used was high because it is soluble in both phases.

5. Solvent interactions

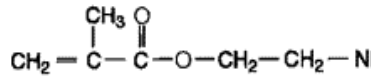
- **Swelling of CLEAR Supports**



1 $\ell + m + n \sim 14$



2



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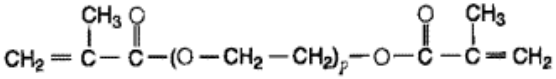
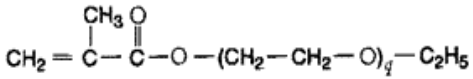
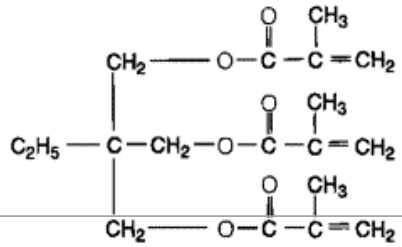


4 $p \sim 9$



5 $q \sim 3\text{-}5$



6

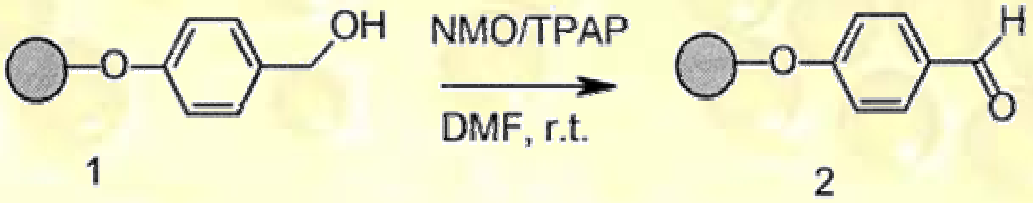
bed volume (mL) of 1 g polymer

solvent	DMF	CH_2Cl_2	CH_3CN	THF	MeOH	H_2O	toluene	EtOAc	t-BuOMe	hexane	TFA
CLEAR-I	8	10	6.5	6.5	7	8	5	5	3.5	3	12
CLEAR-II	5	7	4.5	4.5	5	5	4	4	4	3	7
CLEAR-III	5	7	5	5	5	5	5	4	4	3	8
CLEAR-IV	5.5	5.5	5	5	5	4	5	4.5	3	3	6.5
CLEAR-V	5	8	5	5	5	5	4	4.5	3	3	7.5

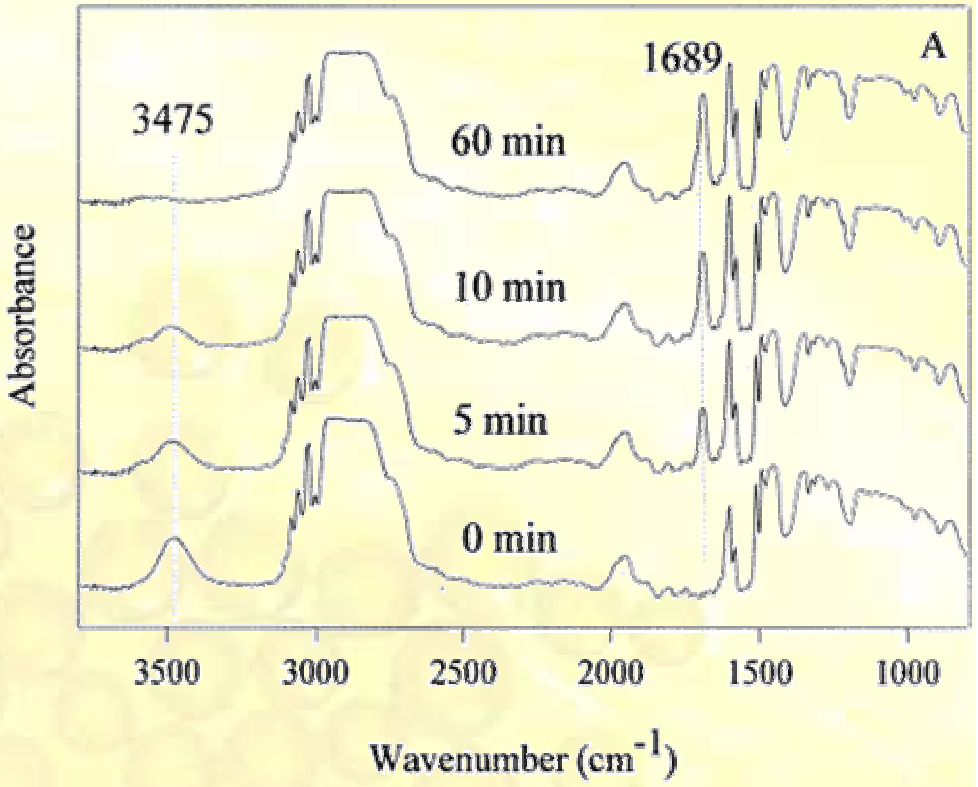
a For each set of swelling studies, the underivatized CLEAR support (0.1g) was placed in a 3-mL syringe fitted at the bottom with a porous frit. The support materials were washed 10× with the indicated solvent, and then allowed to stand for 5 min in that same solvent. Excess solvent was removed by brief suction, and the bed volume of the fully solvated support was noted. The CLEAR supports were then washed 10× with CH2Cl2 and dried [air-drying for volatile solvents; in vacuo overnight for H2O and DMF], and the procedure was repeated on the same resins with the next solvent.

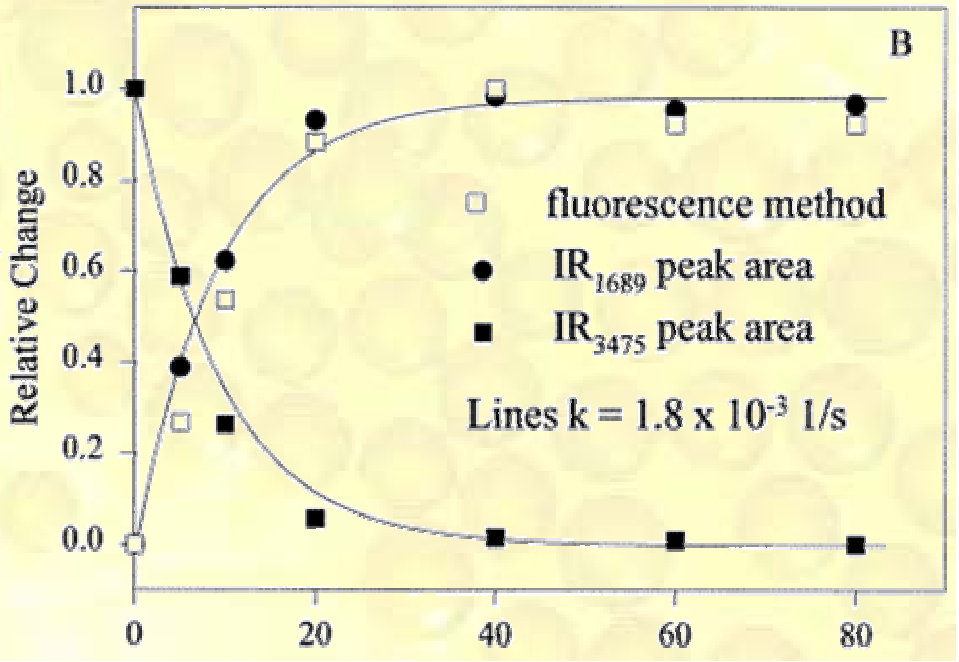
5. Solvent interactions

- PS vs Tentagel
  - Polymer represents a "solvent-like" phase
  - Choice of resin depends on the nature of the reaction
  - Choice of resin depends on polarity of the solvent



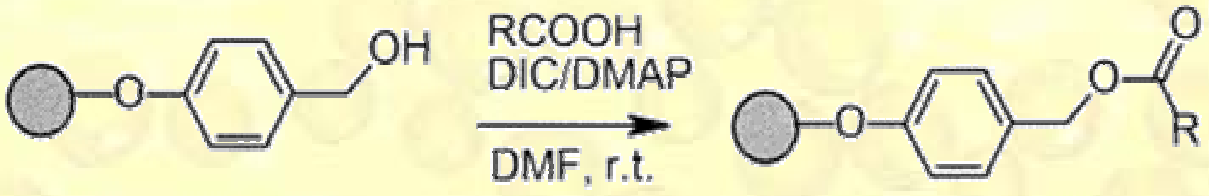
Reaction 1





5. Solvent interactions

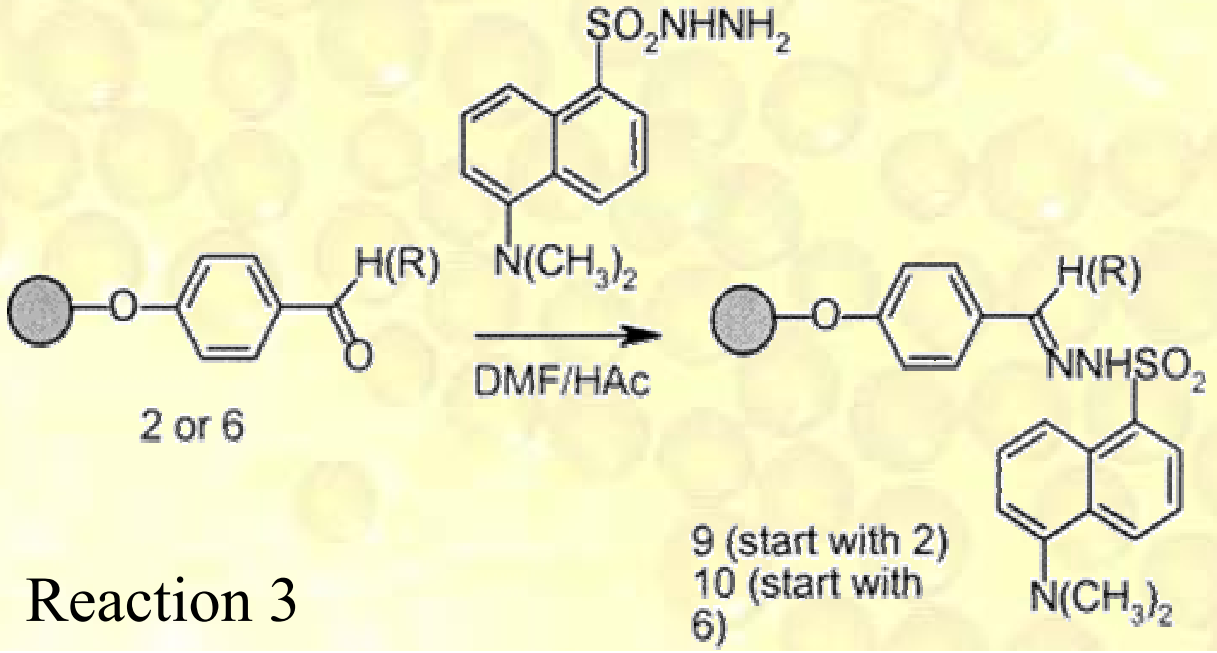
- PS vs Tentagel



1

Reagent		Product
3	R = $(CH_2)_3COCH_3$	6
4	CH_2Ph	7
5	CH_2CH_3	8

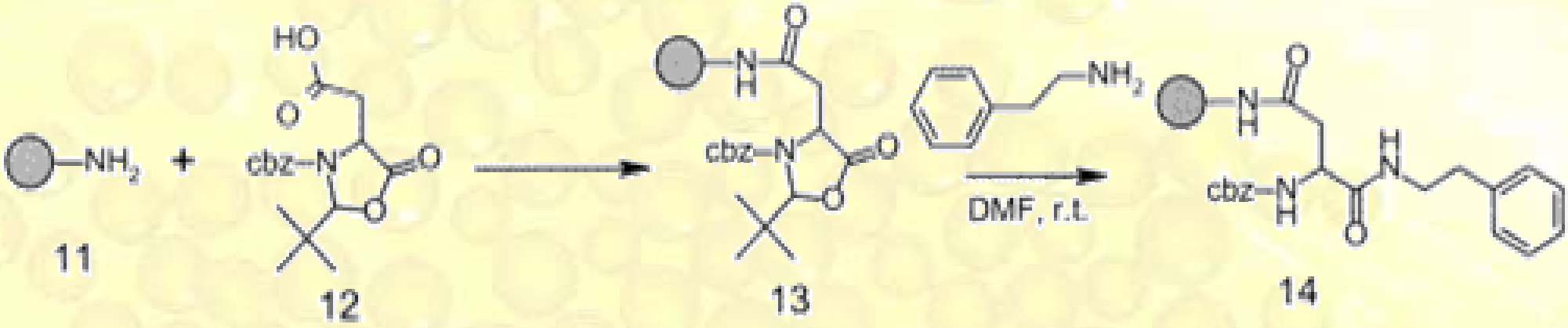
Reaction 2



Reaction 3

5. Solvent interactions

- PS vs Tentagel

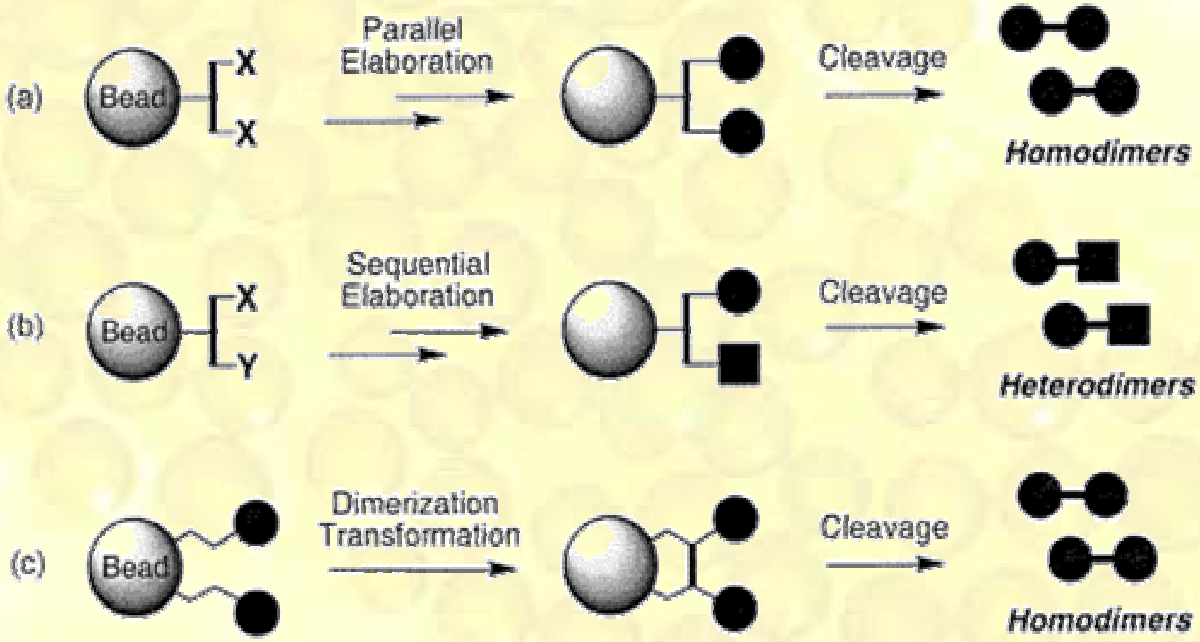


Reaction 4

Comparison of Reaction Rates on PS- and TG-Based Resins reaction scheme							
Reaction	**1**	**2 (R = 3)**	**2 (R = 4)**	**2 (R = 5)**	**3 (R = H)**	**3 (R = 3)**	**4 (step 2)**
kPS (1/s)	**4.6 × 10-4**	**2.2 × 10-4**	**4.8 × 10-4**	**2.0 × 10-4**	**3.1 × 10-3**	**4.1 × 10-4**	**1.13 × 10-4**
kTG (1/s)	**1.8 × 10-3**	**2.3 × 10-4**	**4.2 × 10-4**	**2.2 × 10-4**	**1.8 × 10-3**	**1.9 × 10-4**	**6.26 × 10-6**
kTG/kPS	**3.9**	**1.0**	**0.9**	**1.1**	**0.6**	**0.5**	**0.055**

6. Loading

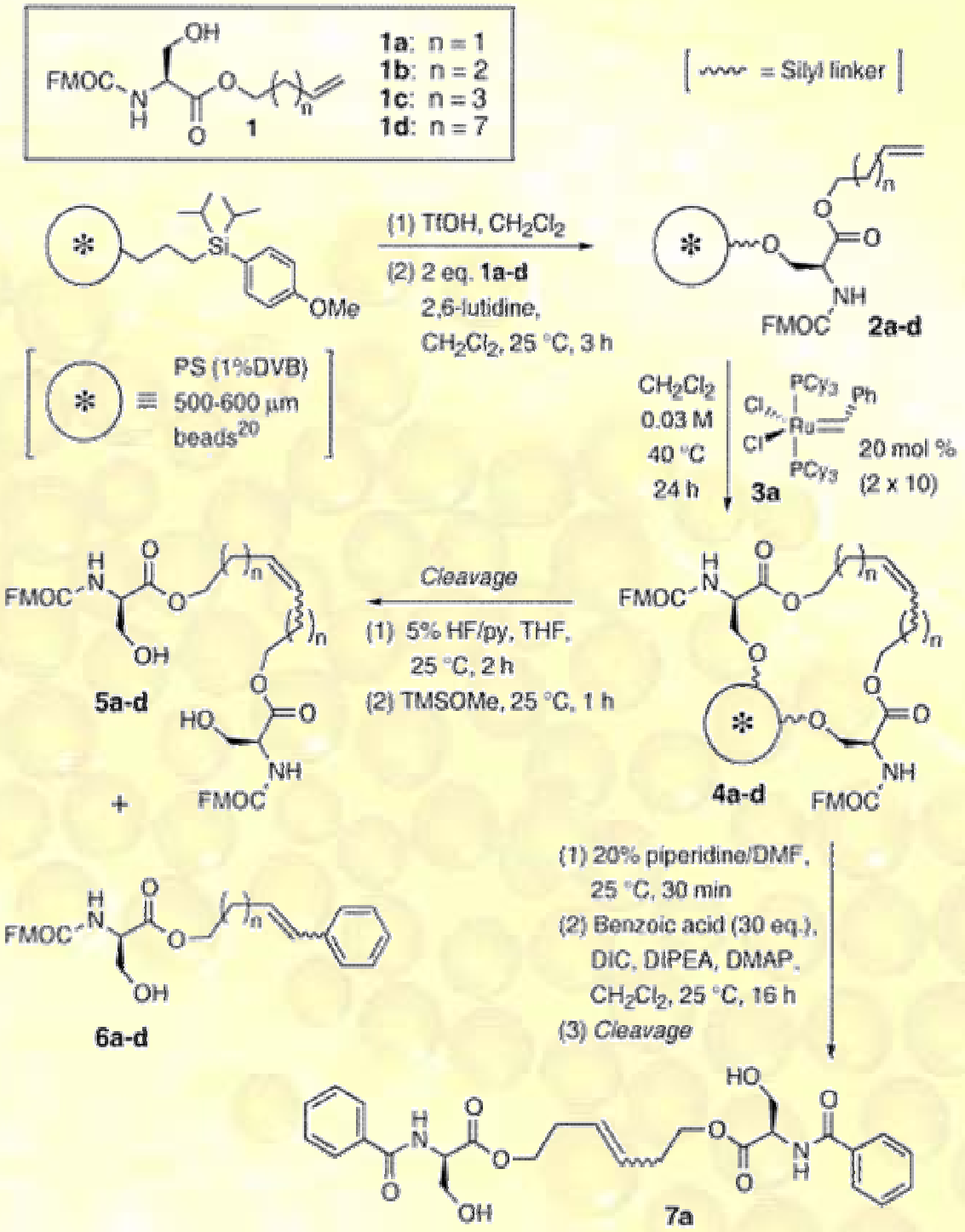
- **6.1. PS**
  - Gel
  - Macroporous
- **6.2. Tentagel**
- **6.3. Site isolation**
  - Physical meaning
    - Effect of loading levels
    - Effect of crosslinking
    - Effect of solvent
  - Examples
    - Cyclisation
    - Dimerisations
    - Kinetics
    - Catalysis
    - Enantioselectivity



High capacity (1-2 mmol/g), lightly cross-linked (1% DVB), 500-600 m polystyrene (PS) beads.

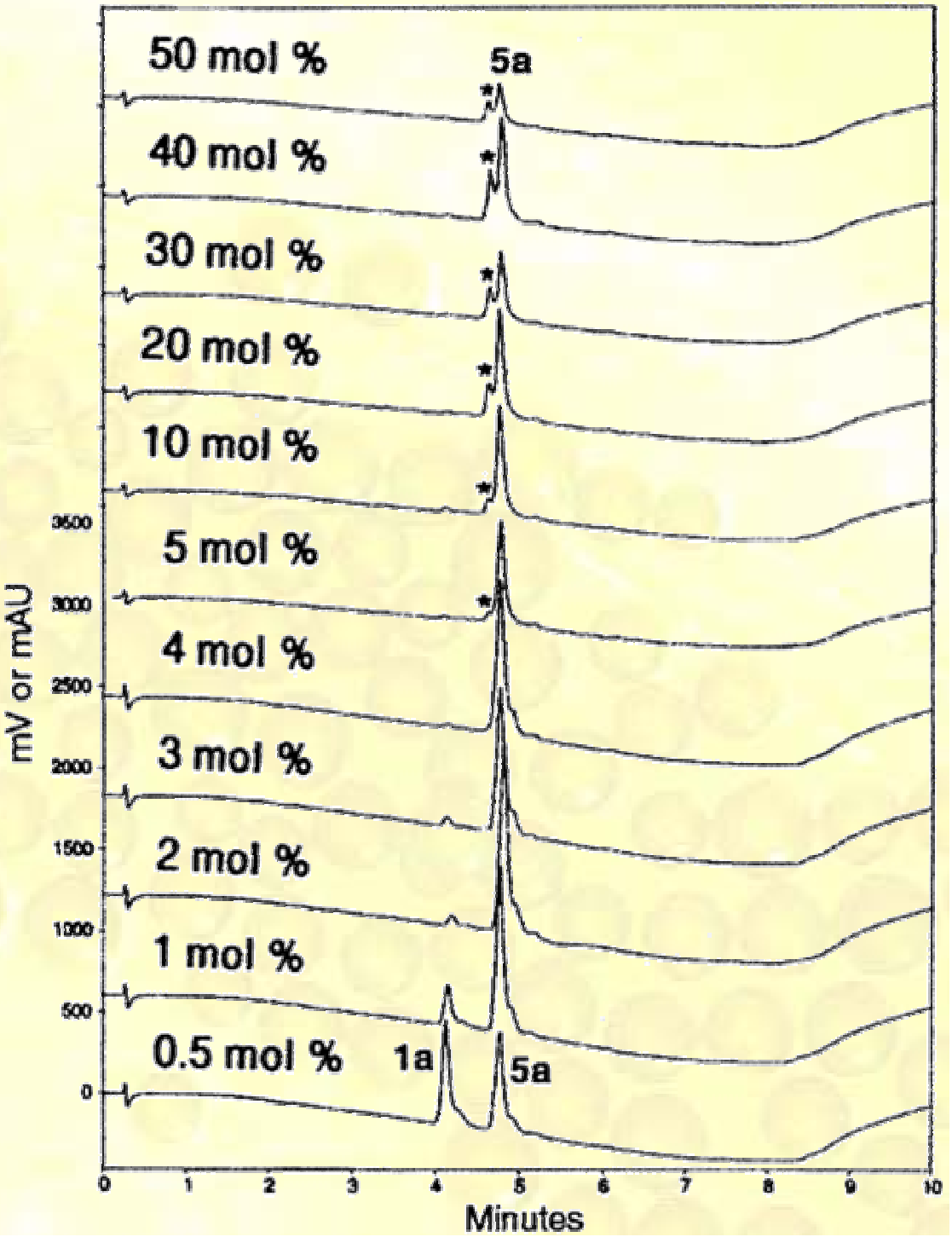
6. Loading

- Examples
  - Dimerisations



6. Loading

- Examples
  - Dimerisations



Reverse-phase HPLC traces for crude intra-site cross-metathesis reactions of resin-bound monomer 1a using various catalyst loadings of benzylidene 3a. The asterisk marks the peak corresponding to styrene adduct 6a.

6. Loading

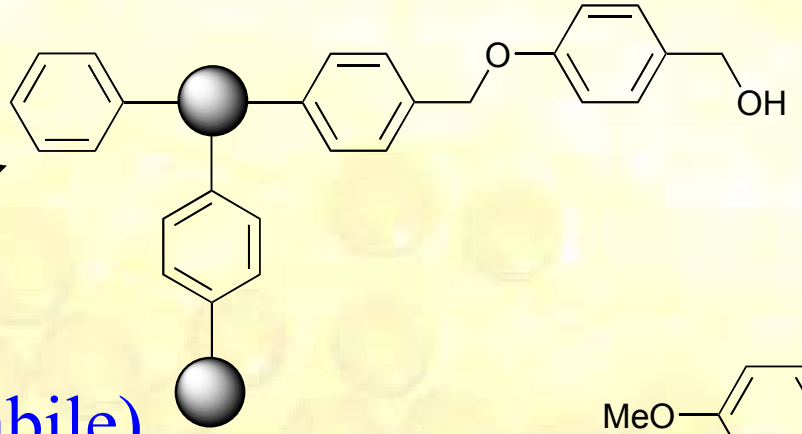
- Examples
  - Cyclisation
  - Dimerisations
  - Kinetics
  - Catalysis
  - Enantioselectivity

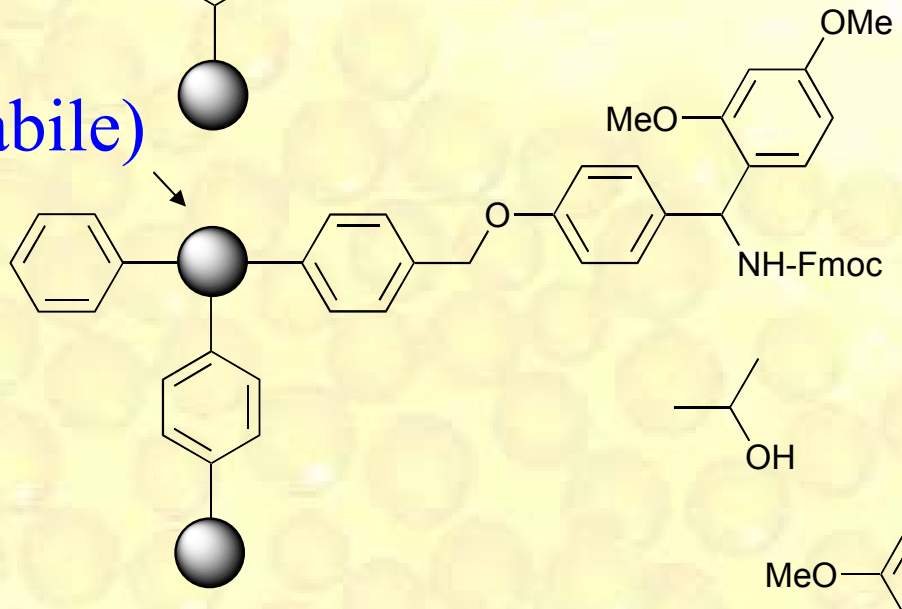
7. Stability

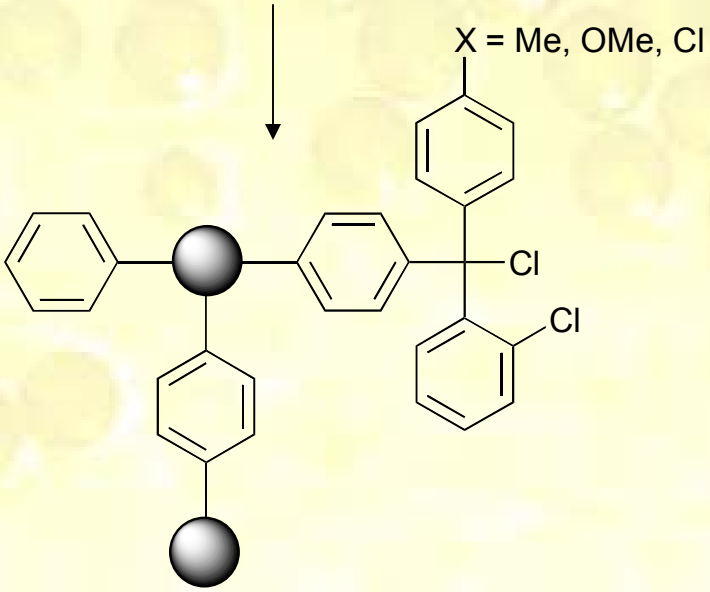
- **7.1. Physical**
- **7.2. Mechanical**
- **7.3. Chemical**
- **7.4. Comparison of supports**

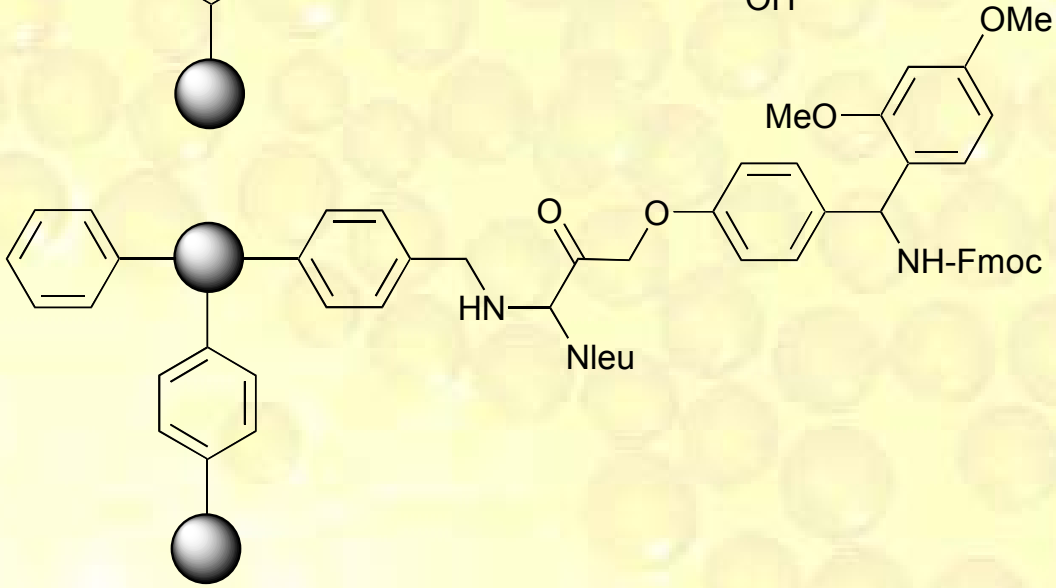
8. Linkers

- **8.1. Acid labile**
  - Wang (TFA)
  - Rink Amide (TFA)
    Rink Acid (very H+ labile)
  - Rink AM (95% TFA)
  - Trityl (2-chloro)



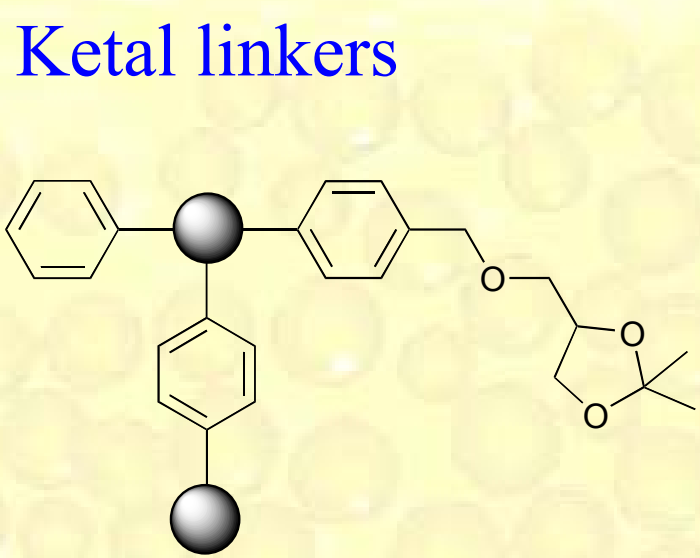


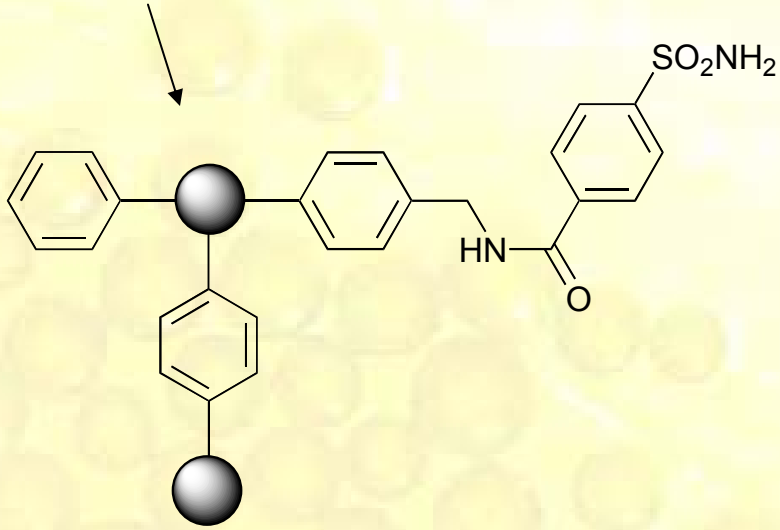




8. Linkers

- Sulfamylbenzoyl AM (highly base stable)
- Ketal linkers



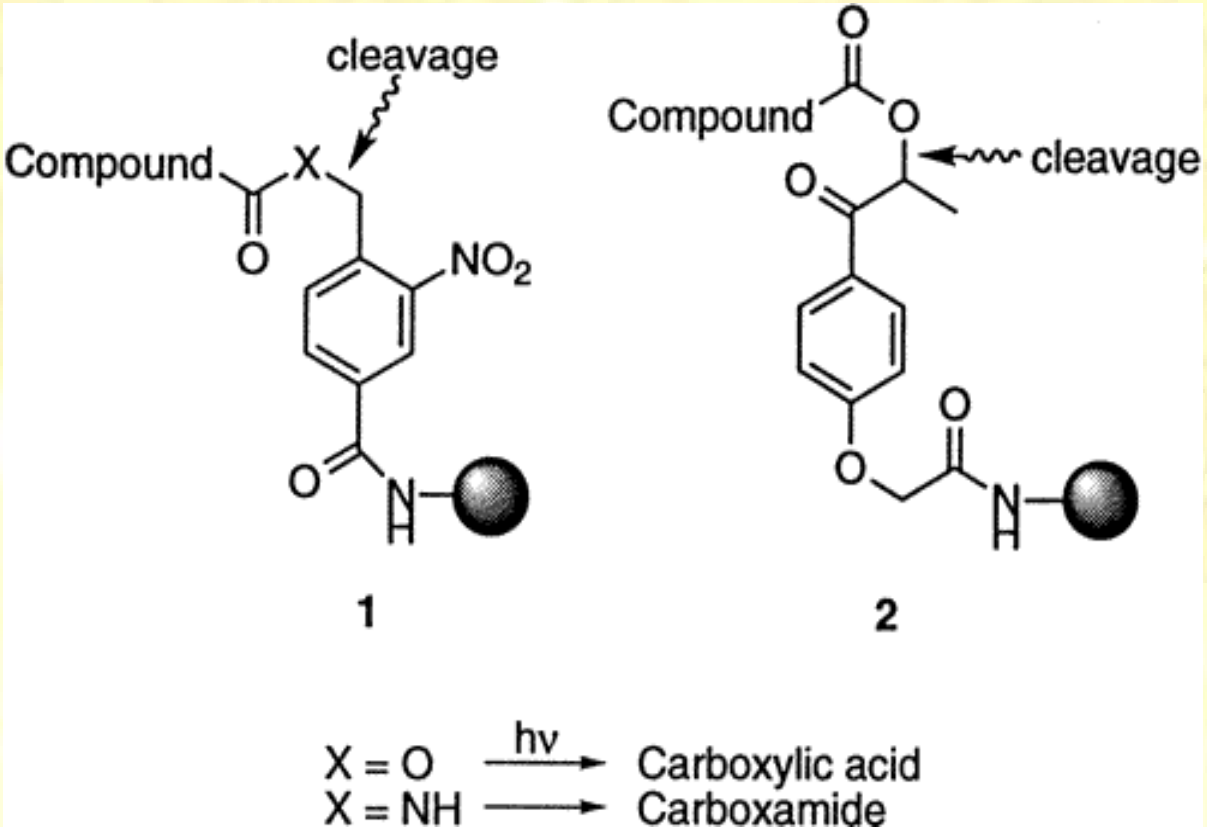


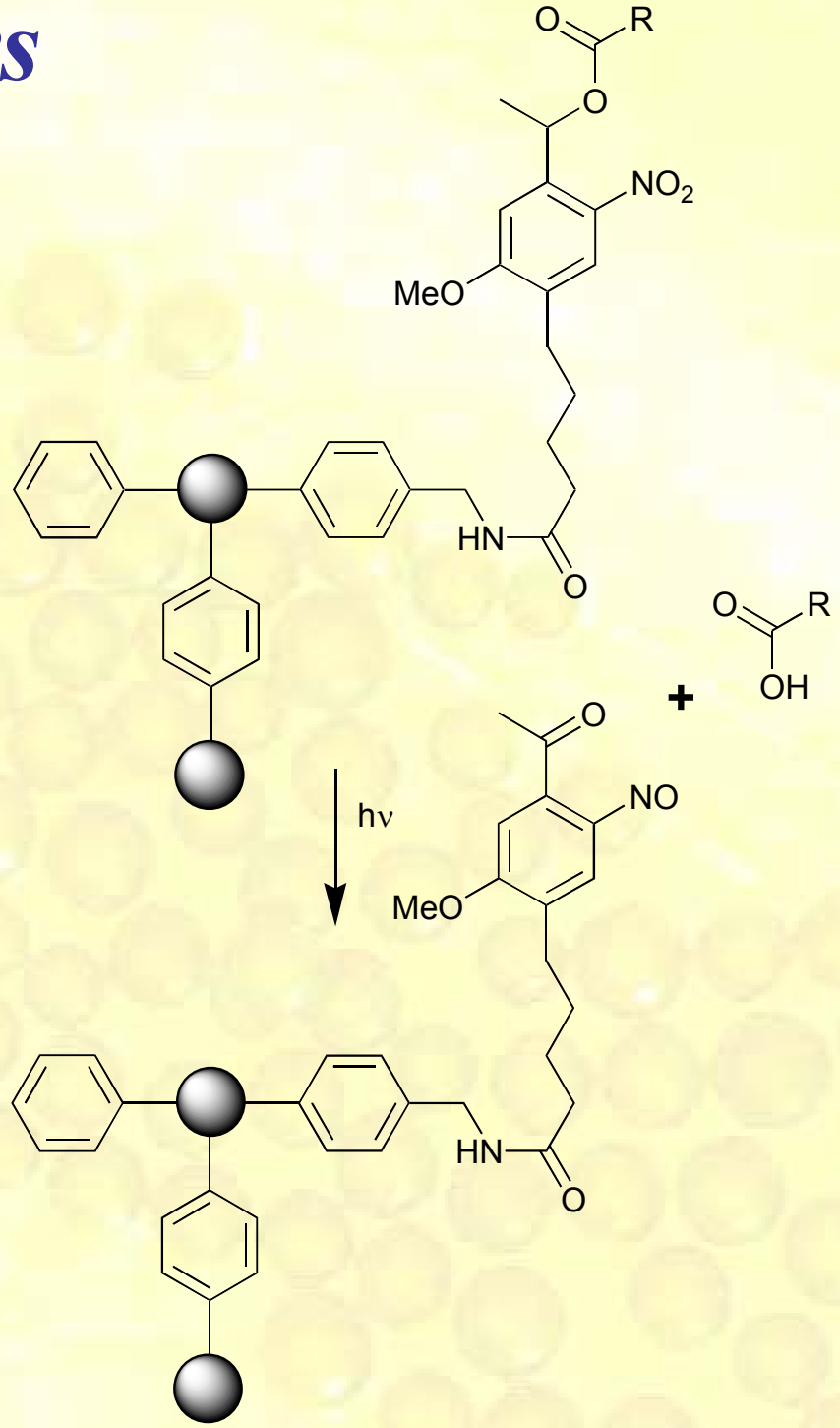
8. Linkers

- **8.2. Base labile**

8. Linkers

- **8.3. Photolabile**
  - Orthogonal synthesis (Affymetrix)





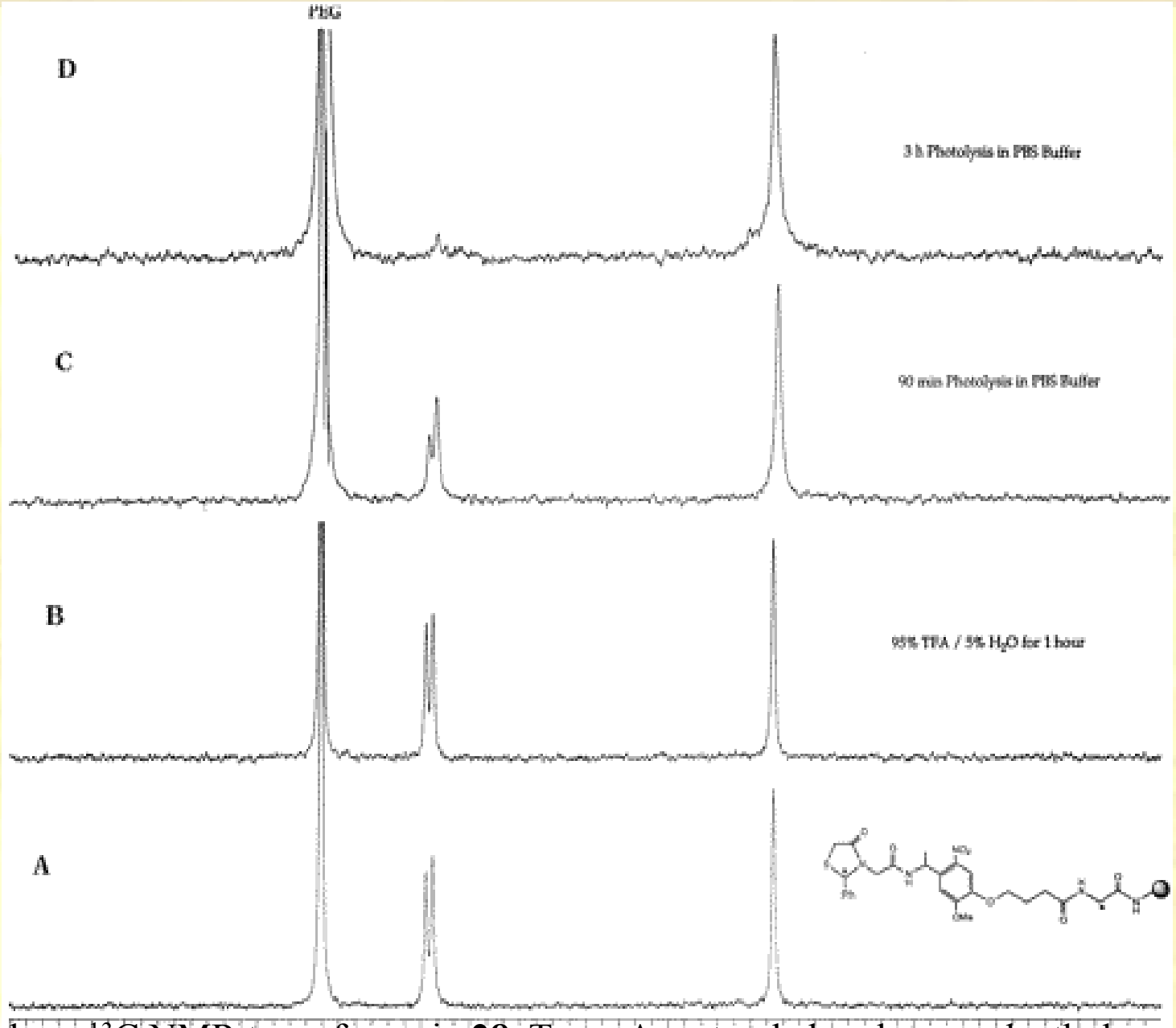
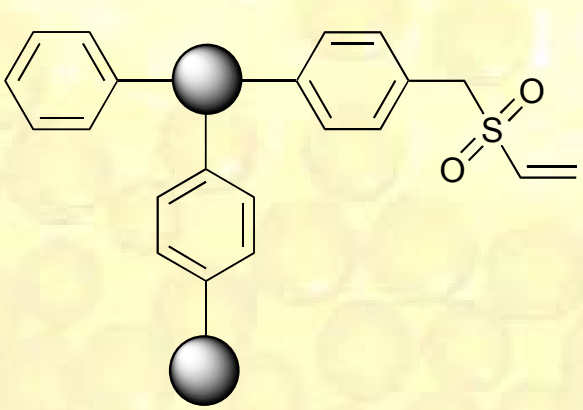


Figure 2 Gel phase ^{13}C NMR trace for resin **28**. Trace A: natural abundance polyethylene glycol (PEG) is at 71 ppm, ^{13}C-C_2 glycine appears at 44 ppm, and ^{13}C-C_2 of the thiazolidinone appears at 65 ppm. Trace B: resin **28** after exposure to TFA/H_2O) for 1 h. Trace C: resin **28** after irradiation at 365 nm for 1 h. Trace D: resin **28** after irradiation at 365 nm for 3 h.

8. Linkers

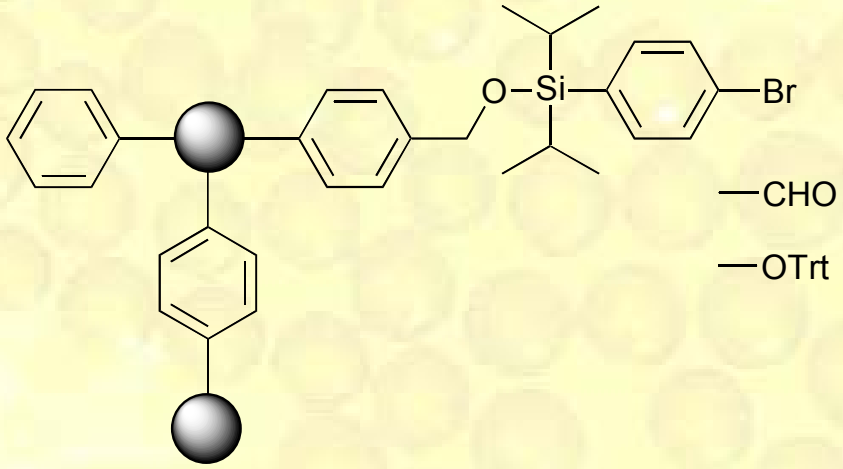
- **8.4. Traceless**
  - Vinylsulphonylmethyl



1. RNH2
2. Chemistry
3. Alkylation
4. Elimination

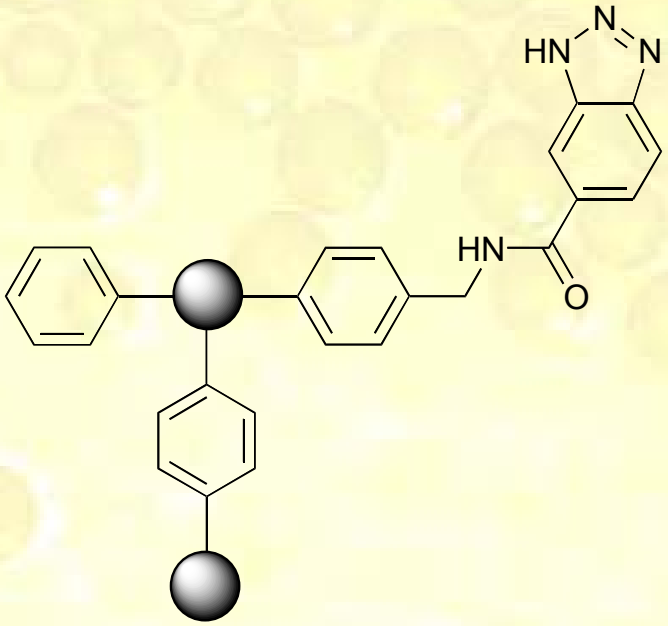
recycled

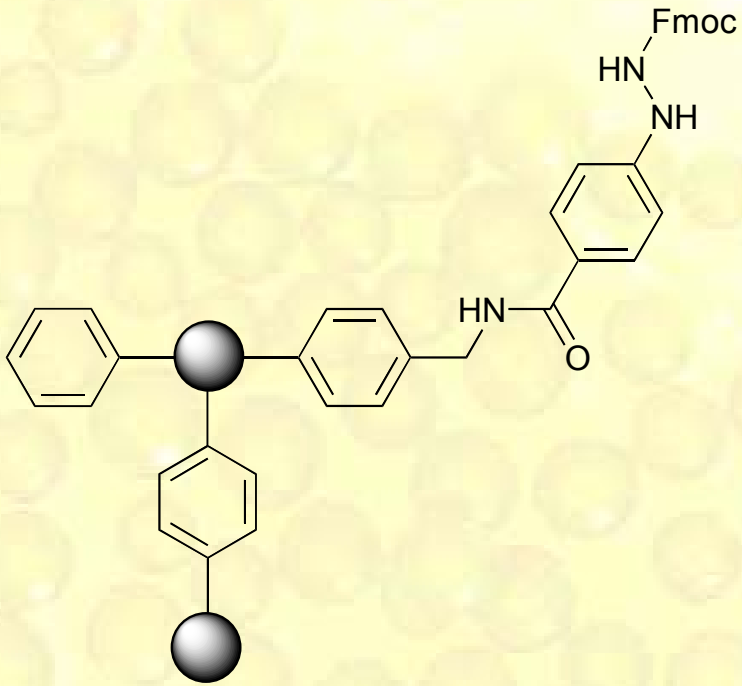
- **8.5. Specific reagents/catalysts**
  - Silyloxy
    BuLi and TFA stable
    not TBAF (THF)



8. Linkers

- **8.5. Special reagents/catalysts**
  - Oxidatively cleavable, Cu(II)acetate (diazene formation) TFA/piperidine stable
  - Hydride cleavage



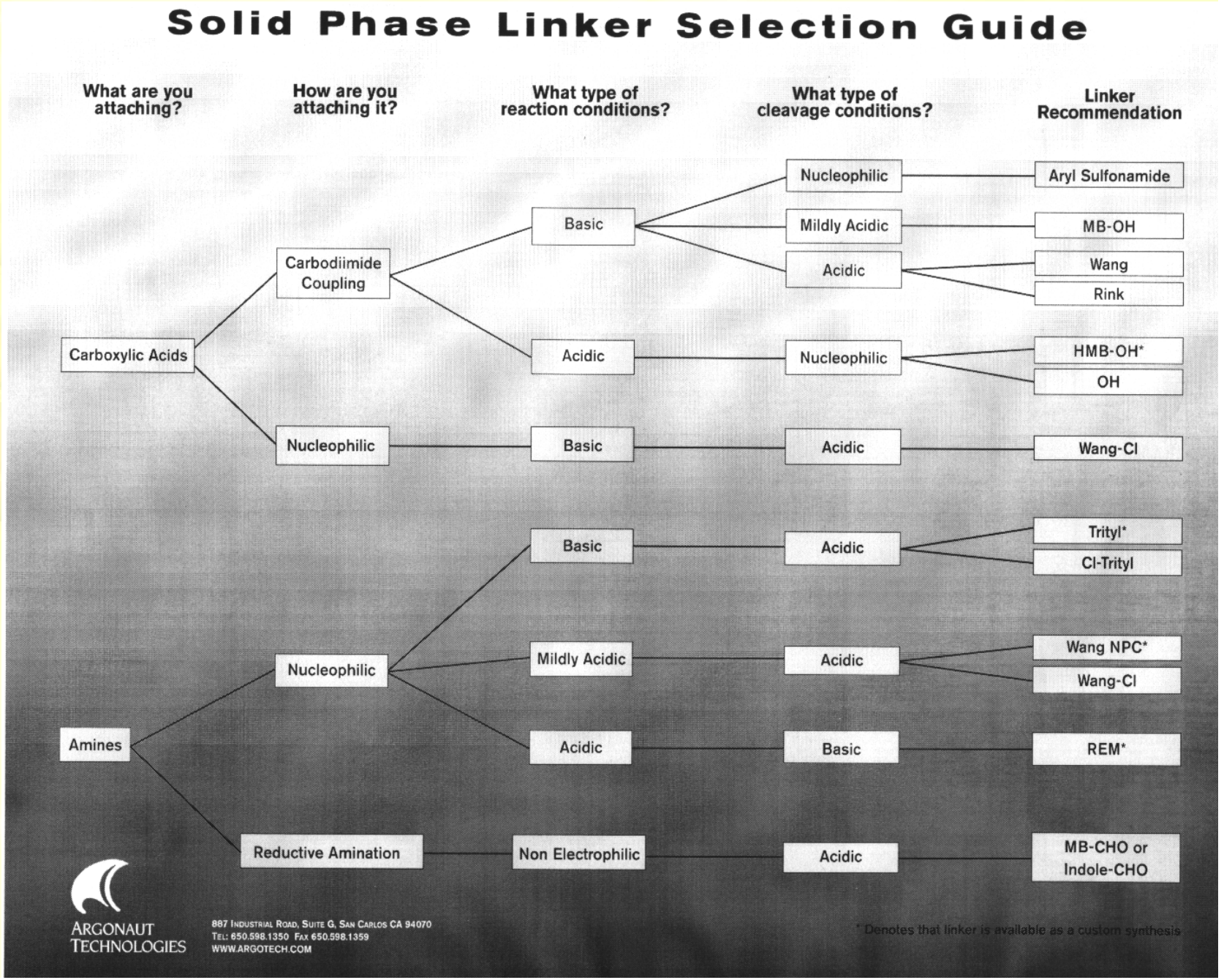


How to select the most appropriate…

- **Support**
  - Chemical compatibility
  - Swelling compatibility
  - Loading availability

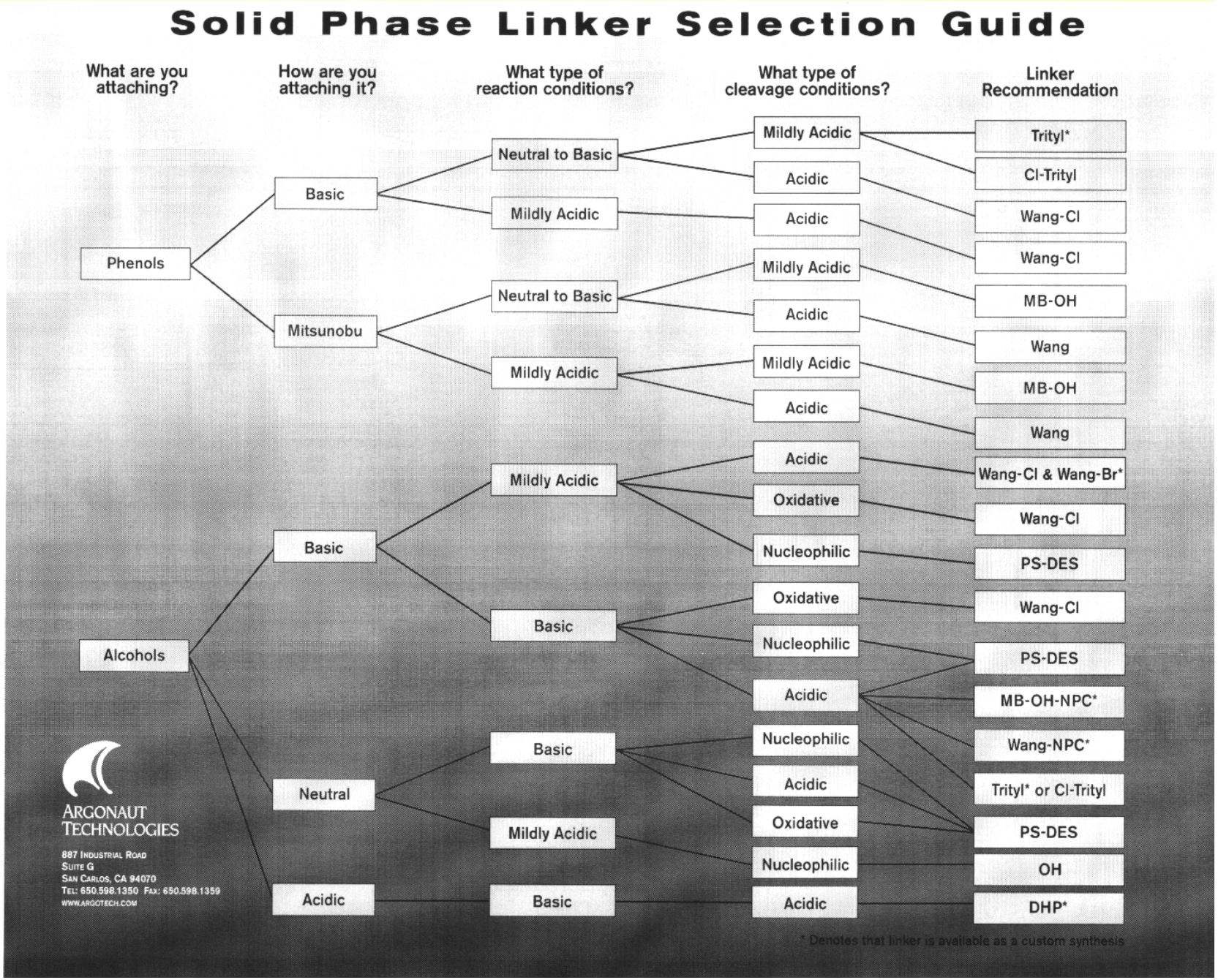
How to select the most appropriate…

- **Linker**



How to select the most appropriate…

- **Linker**



Lecture 4

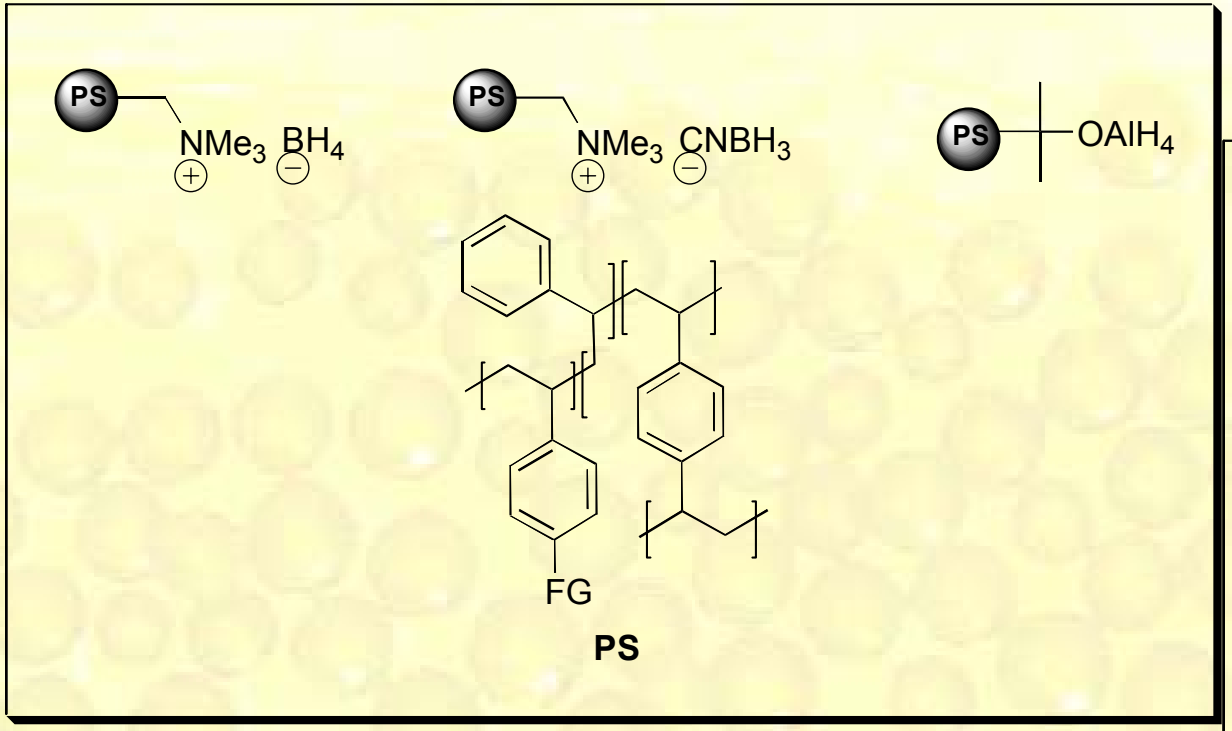
- **Polymer-assisted solution phase synthesis**

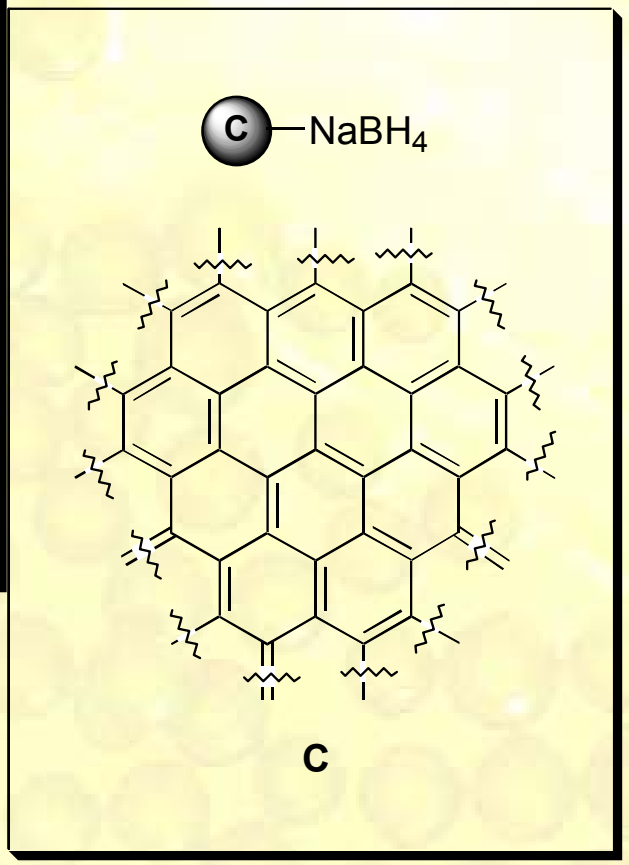
  Combines the advantages of solution-phase synthesis (analysis, readily available products) with those of solid-phase synthesis (separation by filtration, use of excess of reagents).

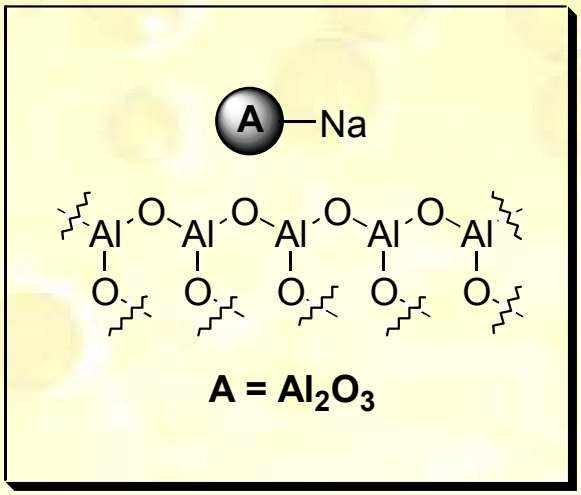
  No need of linkers and cleavage protocols.

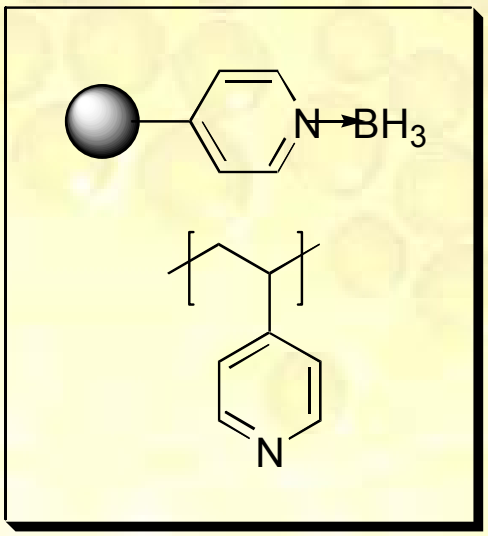
Polymers as reagents

Polymer supported reducing agents



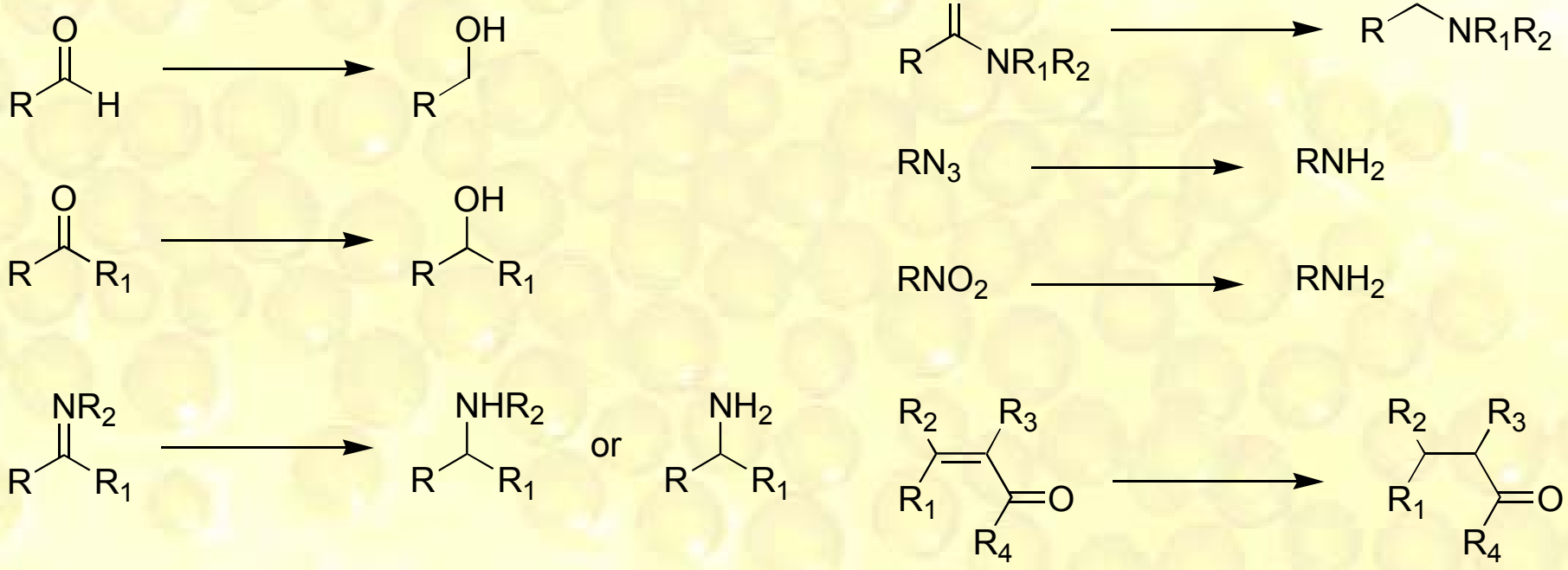






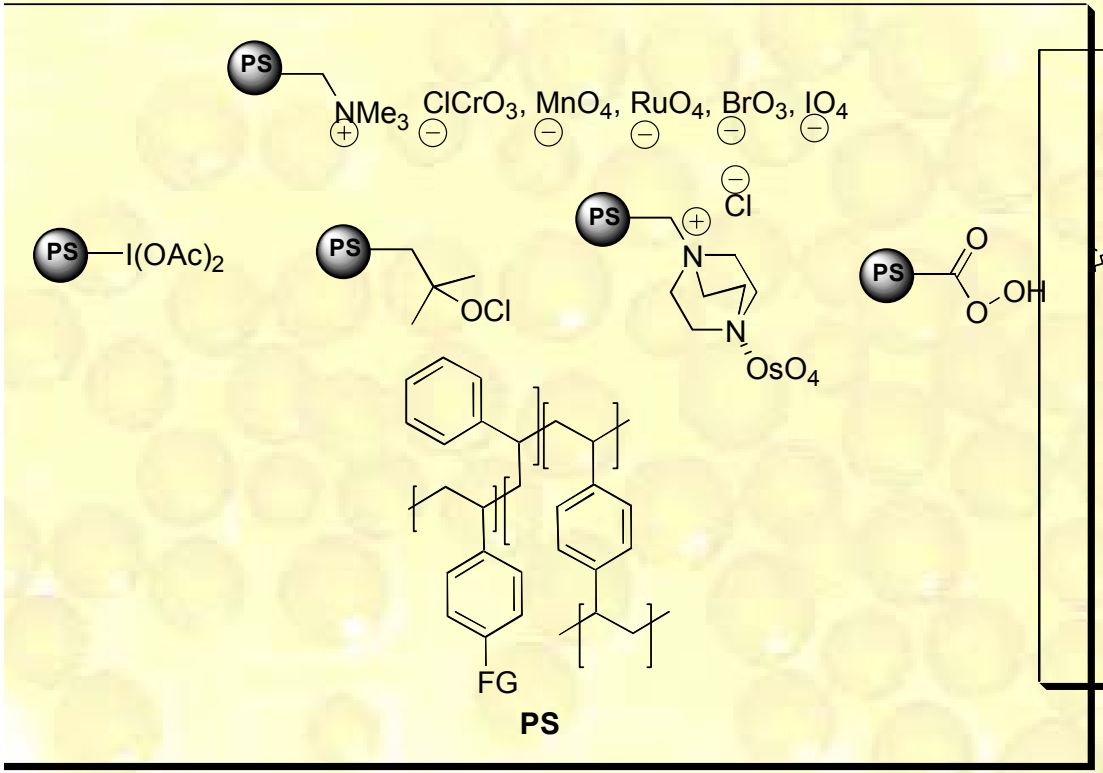
Polymers as reagents

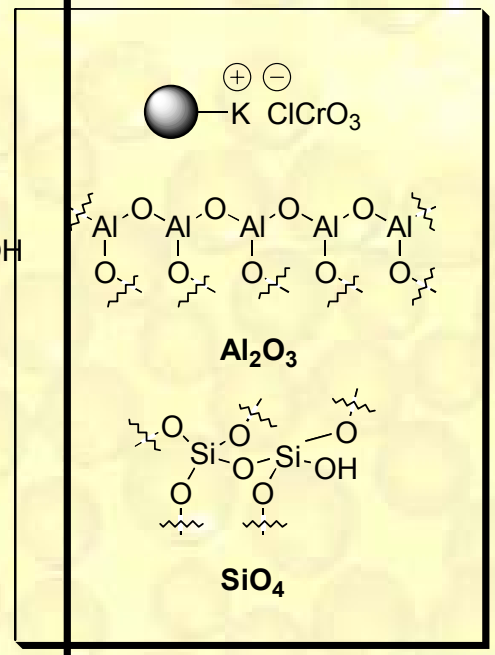
Polymer supported reducing agents

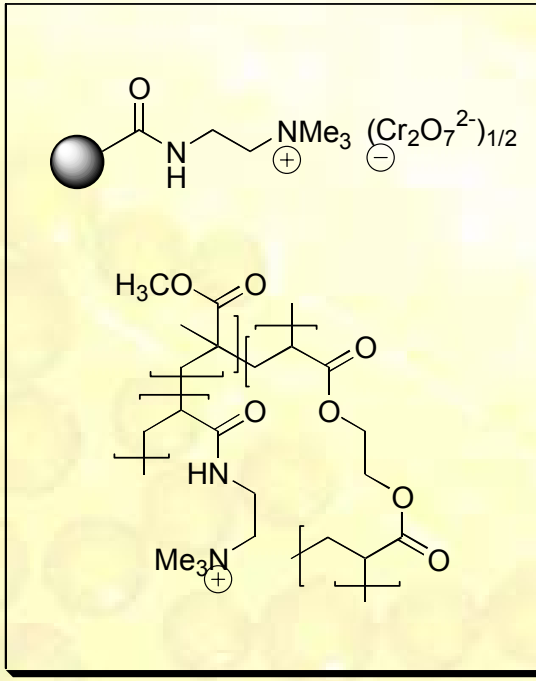


Polymers as reagents

Polymer supported oxidising agents

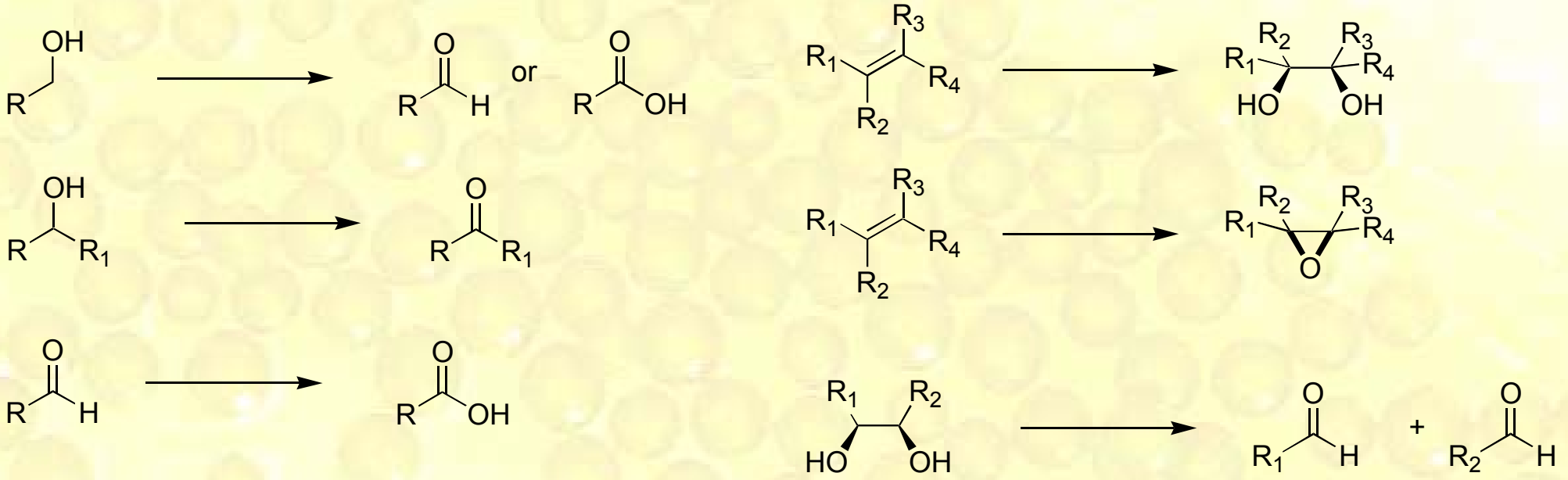






Polymers as reagents

Polymer supported oxidising agents



Polymers as reagents

Polymer supported reagents for C-C bond formation