Medicinal Chemistry/ CHEM 458/658

Chapter 5 - Combinatorial Chemistry

Bela Torok

Department of Chemistry

University of Massachusetts Boston

Boston, MA

Introduction

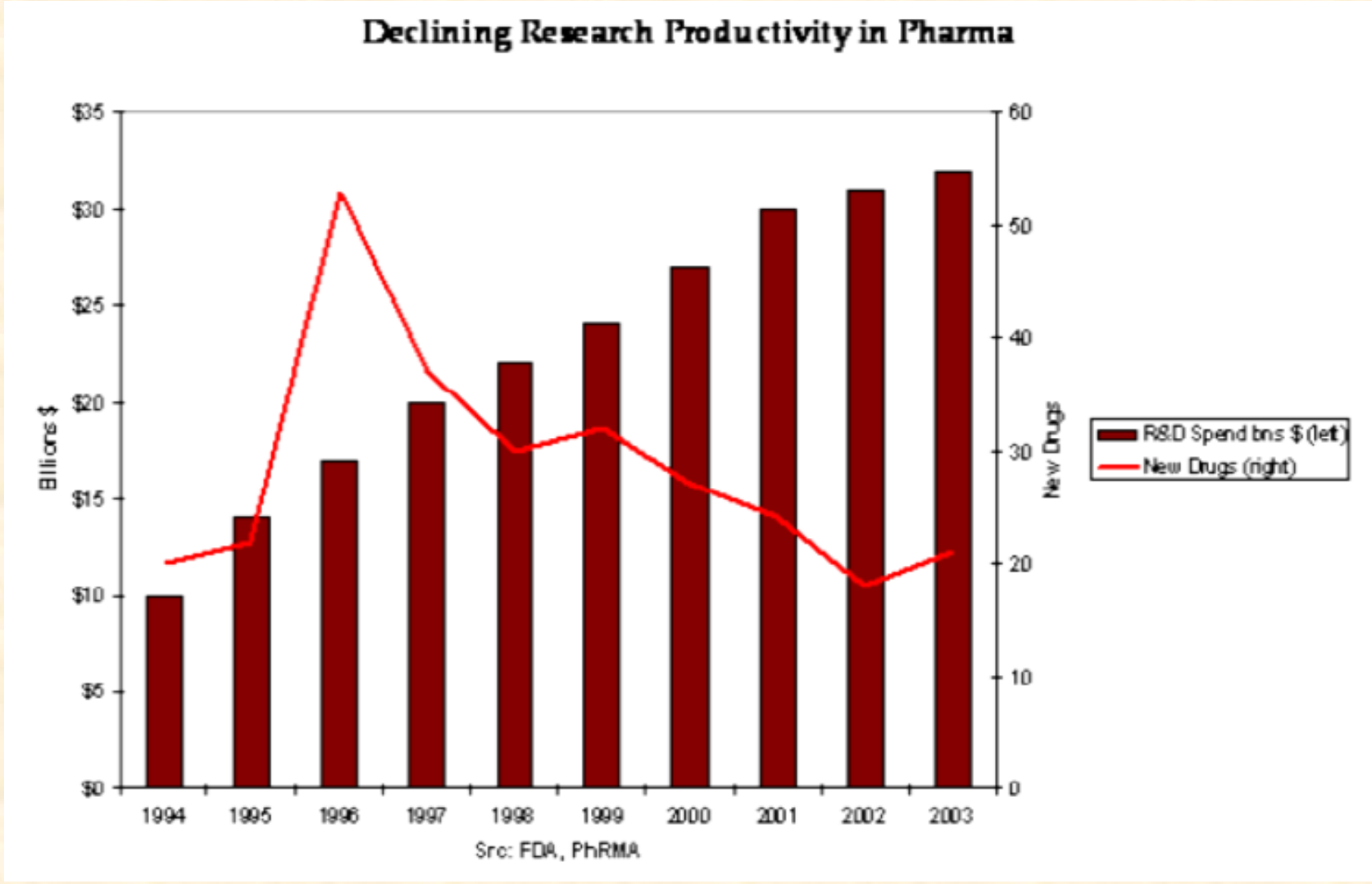
- Use a set of techniques for highly efficient synthesis of a large member of analog compounds (library).

- The compound libraries undergo high-throughput screening for a desired property.

- The pharmaceutical industry is the major user of combichem for drug discovery.

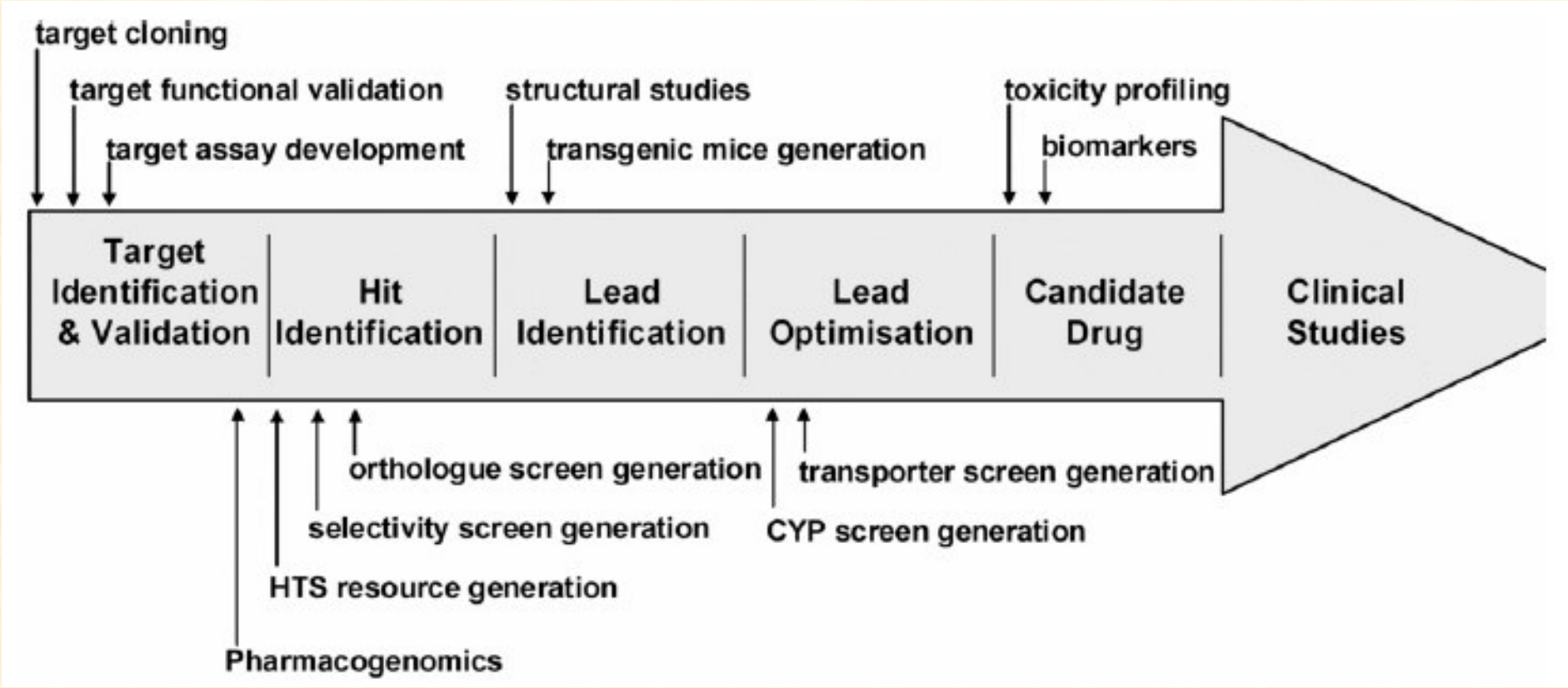
- Other applications of combichem include catalysis and materials science.

Introduction



Introduction

- It takes 12 to 15 years and costs $0.8 to 2 billions to develop a new drug!



Hit to lead steps

Introduction

Roots:

Bruce Merrifield (Rockefeller University) developed solid phase synthesis of peptides (SPPS).

The Nobel Prize in Chemistry 1984

Evolution

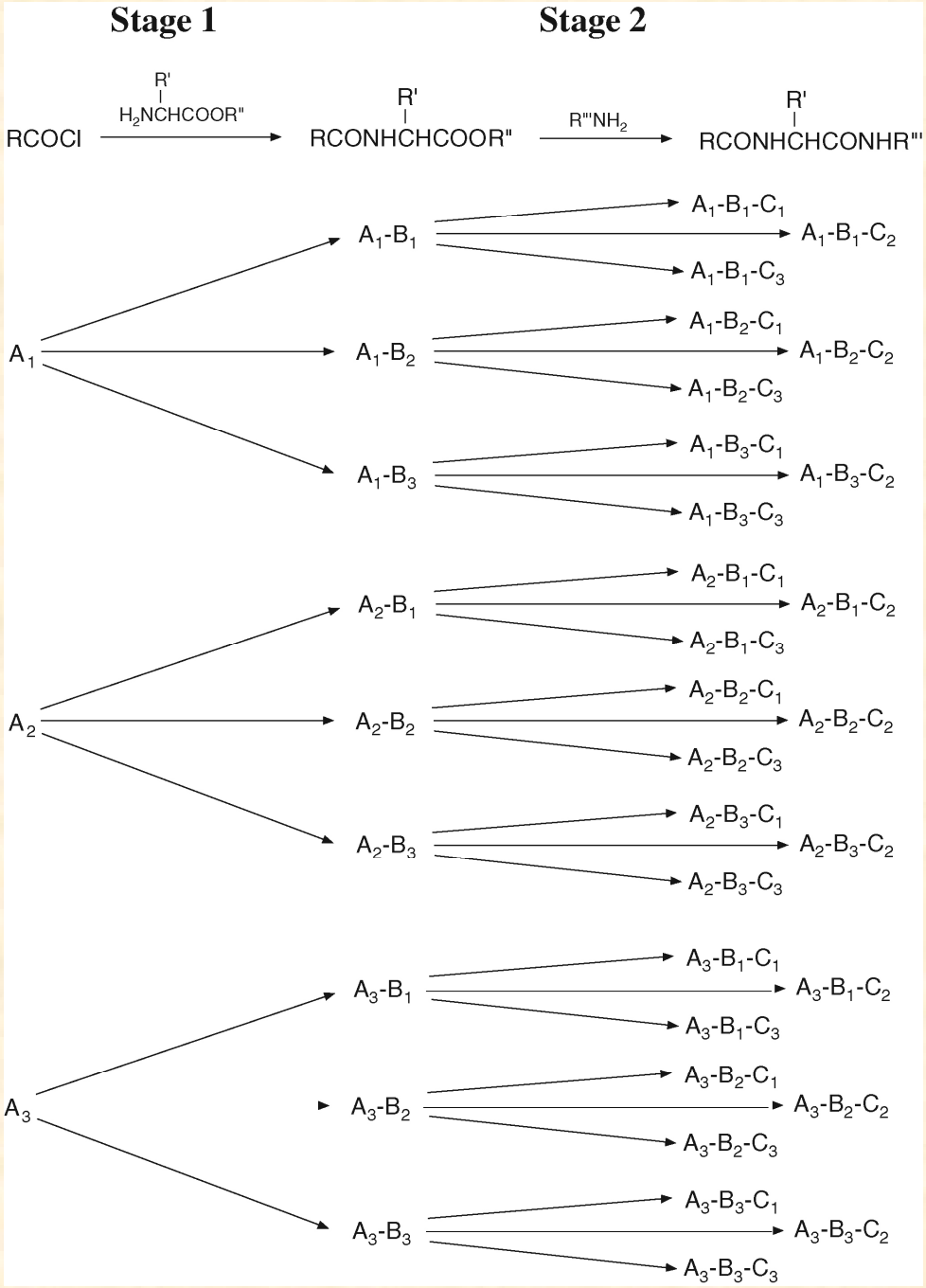
1st Phase (since early 1990s): The initial efforts in SPOS of a large set of compounds for biological screening. The compounds usually lack the structural complexity and are commonly found in literature.

The 2nd Phase (since late 1990s): It is not just about numbers; something was missing in compounds produced in a combinatorial fashion. Emphasis shifted towards quality (chemical diversity, compound purity) rather than quantity.

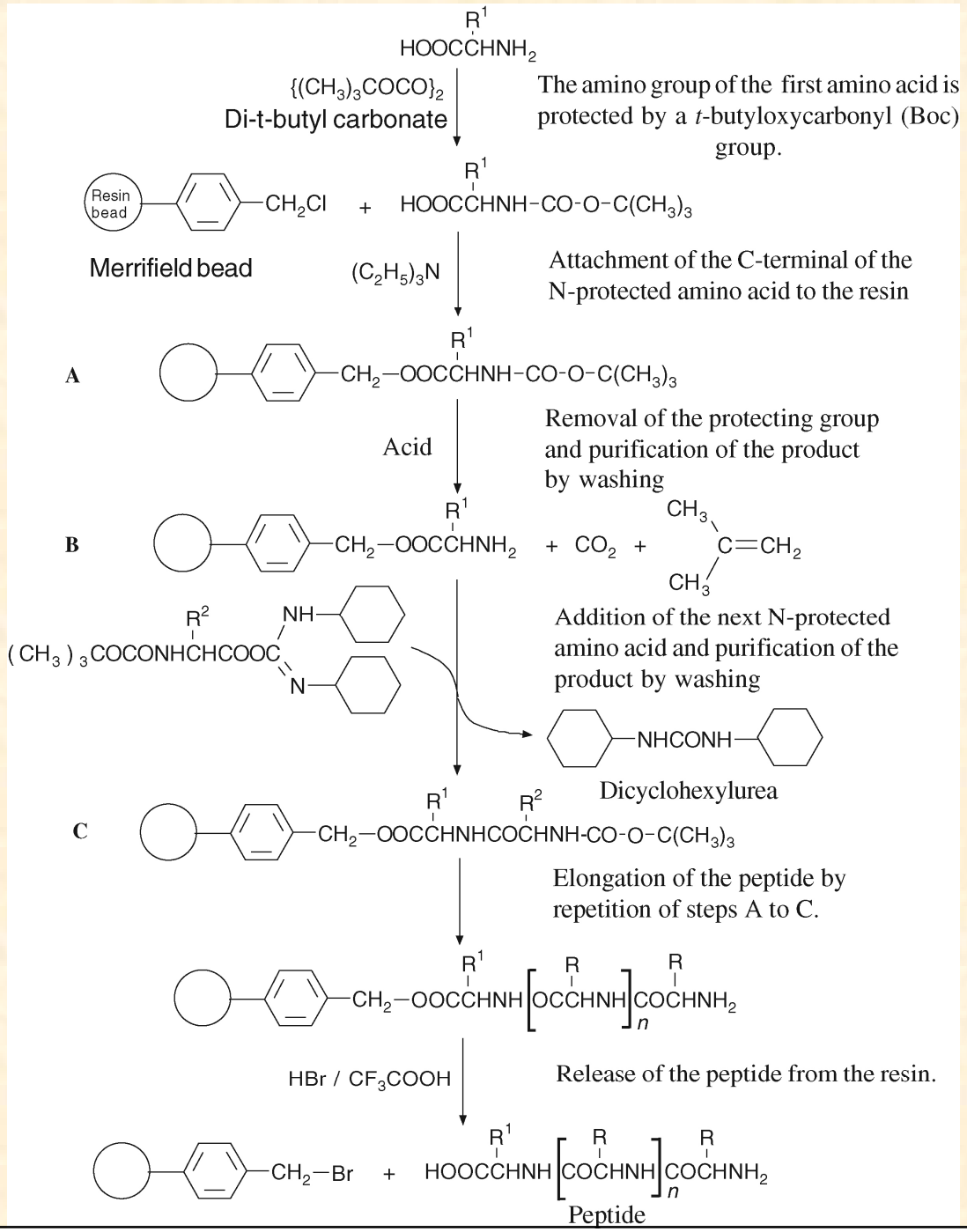
The 3rd Phase (since early 2000s): Post-genomic chemical biology age. To understand bio-macromolecular interactions and how small molecules could be utilized as useful chemical probes in systematic dissection of these interactions.

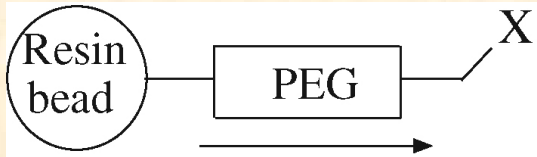
Basic Concept

- A, B, C are building blocks, they may produce a library of 27 compounds (in general, n^n)



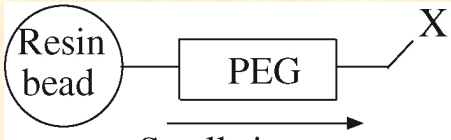
Basic Concept - SPOS



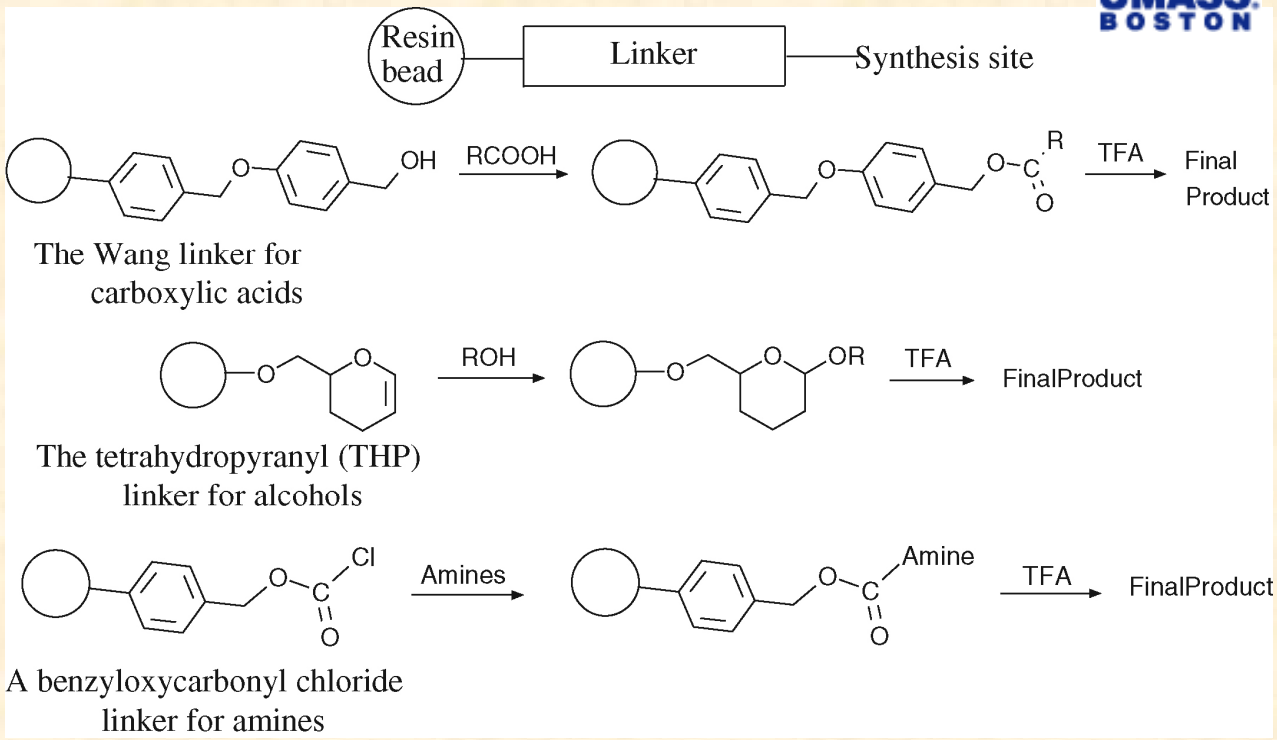


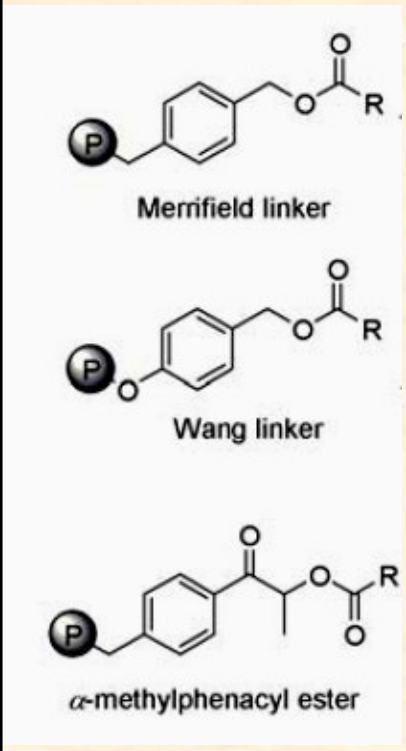
Key
X is
NH_2, OH, SH, Br or COOH

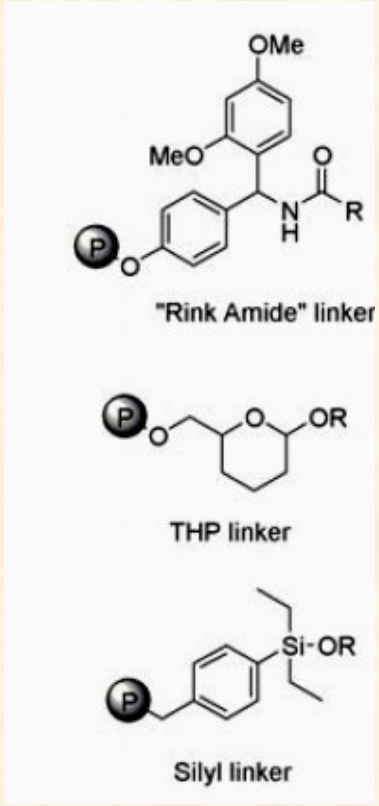
Basic Concept - SPOS



Key
X is
NH_2, OH, SH, Br or COOH







Basic Concept - SPOS

Solid Phase

- excess reagent can be used
- automation possible
- rapid purification
- fewer suitable reactions
- slower reactions
- scale-up is expensive
- not well documented
- special synthesis development

Solution Phase

- favorable reaction kinetics
- any organic reaction
- scale-up is easy, inexpensive
- well documented in literature
- purification could be difficult
- automation difficult
- easy intermediate analysis

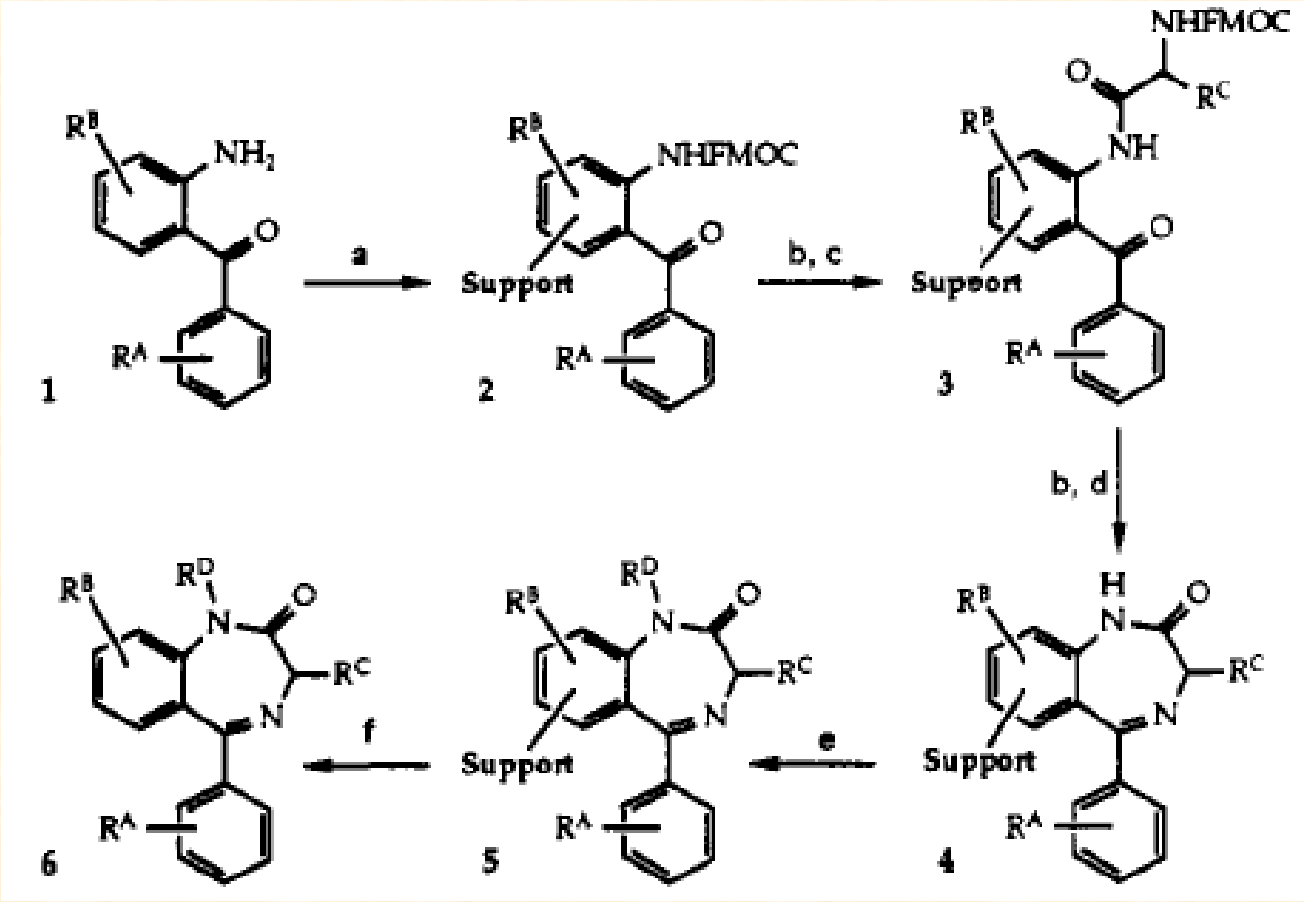
Methods of Combinatorial Chemistry

- Parallel synthesis

- Mixture Synthesis

Parallel Synthesis

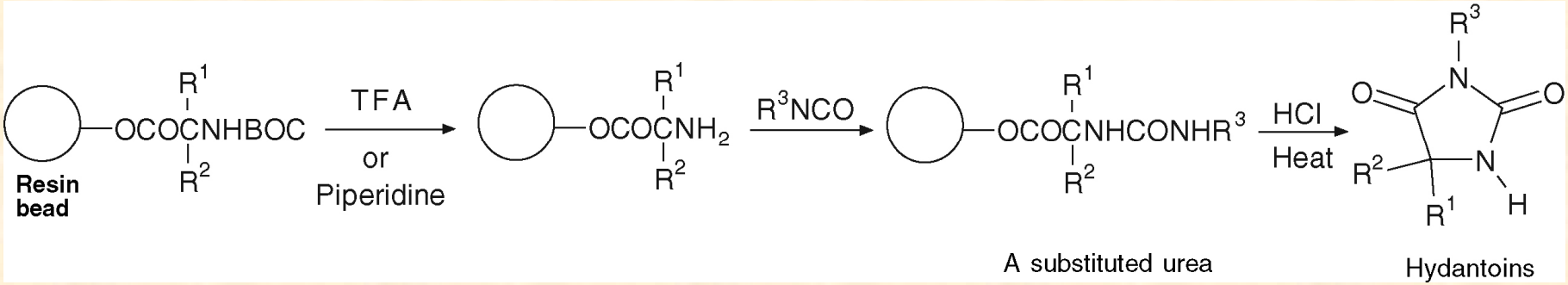
Ellman from UCLA introduced **solid-phase organic synthesis (SPOS)** techniques for **small molecules** (non-peptide). His 1992 paper was for parallel synthesis of 1,4-benzodiazepine-2-ones.



J. Am. Chem. Soc. **1992**, *114*, 10998

Parallel Synthesis

- Every reaction is done in separate vessels – in the same time



Parallel Synthesis

	A	B	C	D	E	F	G	H
1	X1	X2	X3	X4	X5	X6	X7	X8
2	X1	X2	X3	X4	X5	X6	X7	X8
3	X1	X2	X3	X4	X5	X6	X7	X8
4	X1	X2	X3	X4	X5	X6	X7	X8
5	X1	X2	X3	X4	X5	X6	X7	X8
6	X1	X2	X3	X4	X5	X6	X7	X8
7	X1	X2	X3	X4	X5	X6	X7	X8
8	X1	X2	X3	X4	X5	X6	X7	X8
9	X1	X2	X3	X4	X5	X6	X7	X8
10	X1	X2	X3	X4	X5	X6	X7	X8
11	X1	X2	X3	X4	X5	X6	X7	X8
12	X1	X2	X3	X4	X5	X6	X7	X8

(a) The placement of the first building blocks, the Boc protected amino acids X1 to X12 and their attachment to the resin

Deprotection of the amino acid

	A	B	C	D	E	F	G	H
1	X1-Y1	X2-Y1	X3-Y1	X4-Y1	X5-Y1	X6-Y1	X7-Y1	X8-Y1
2	X1-Y2	X2-Y2	X3-Y2	X4-Y2	X5-Y2	X6-Y2	X7-Y2	X8-Y2
3	X1-Y3	X2-Y3	X3-Y3	X4-Y3	X5-Y3	X6-Y3	X7-Y3	X8-Y3
4	X1-Y4	X2-Y4	X3-Y4	X4-Y4	X5-Y4	X6-Y4	X7-Y4	X8-Y4
5	X1-Y5	X2-Y5	X3-Y5	X4-Y5	X5-Y5	X6-Y5	X7-Y5	X8-Y5
6	X1-Y6	X2-Y6	X3-Y6	X4-Y6	X5-Y6	X6-Y6	X7-Y6	X8-Y6
7	X1-Y7	X2-Y7	X3-Y7	X4-Y7	X5-Y7	X6-Y7	X7-Y7	X8-Y7
8	X1-Y8	X2-Y8	X3-Y8	X4-Y8	X5-Y8	X6-Y8	X7-Y8	X8-Y8
9	X1-Y9	X2-Y9	X3-Y9	X4-Y9	X5-Y9	X6-Y9	X7-Y9	X8-Y9
10	X1-Y10	X2-Y10	X3-Y10	X4-Y10	X5-Y10	X6-Y10	X7-Y10	X8-Y10
11	X1-Y11	X2-Y11	X3-Y11	X4-Y11	X5-Y11	X6-Y11	X7-Y11	X8-Y11
12	X1-Y12	X2-Y12	X3-Y12	X4-Y12	X5-Y12	X6-Y12	X7-Y12	X8-Y12

(b) The placement of the isocyanate building blocks Y1 to Y8

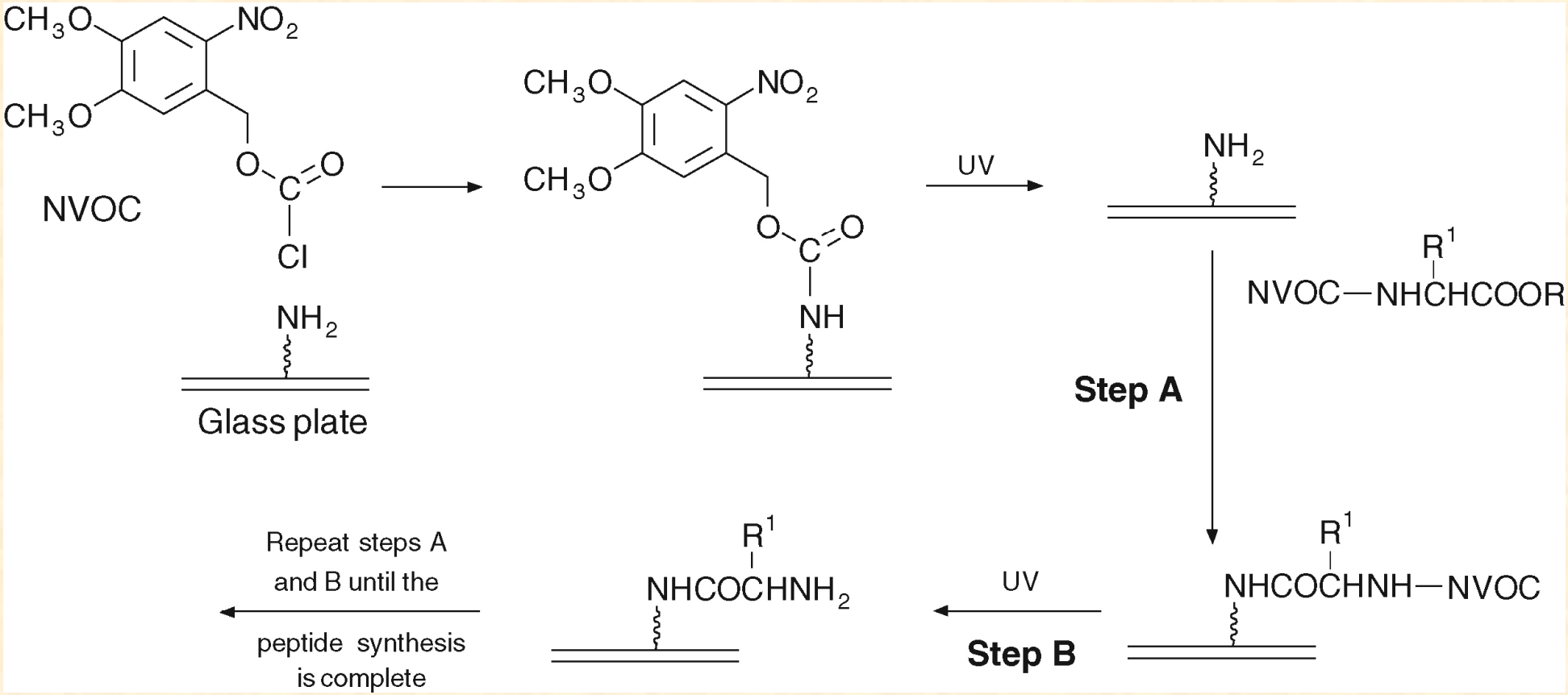
The hydantoins Z1 to Z96

	A	B	C	D	E	F	G	H
1	Z1	Z2	Z3	Z4	Z5	Z6	Z7	Z8
2	Z9	Z10	Z11	Z12	Z13	Z14	Z15	Z16
3	Z17	Z18	Z19	Z20	Z21	Z22	Z23	Z24
4	Z25	Z26	Z27	Z28	Z29	Z30	Z31	Z32
5	Z33	Z34	Z35	Z36	Z37	Z38	Z39	Z40
6	Z41	Z42	Z43	Z44	Z45	Z46	Z47	Z48
7	Z49	Z50	Z51	Z52	Z53	Z54	Z55	Z56
8	Z57	Z58	Z59	Z60	Z61	Z62	Z63	Z64
9	Z65	Z66	Z67	Z68	Z69	Z70	Z71	Z72
10	Z73	Z74	Z75	Z76	Z77	Z78	Z79	Z80
11	Z81	Z82	Z83	Z84	Z85	Z86	Z87	Z88
12	Z89	Z90	Z91	Z92	Z93	Z94	Z95	Z96

(c) Reaction, by placing the array in a suitable reaction environment, to form the substituted urea and subsequent treatment with hot 6M hydrochloric acid to form the hydantoins Z1 to Z96

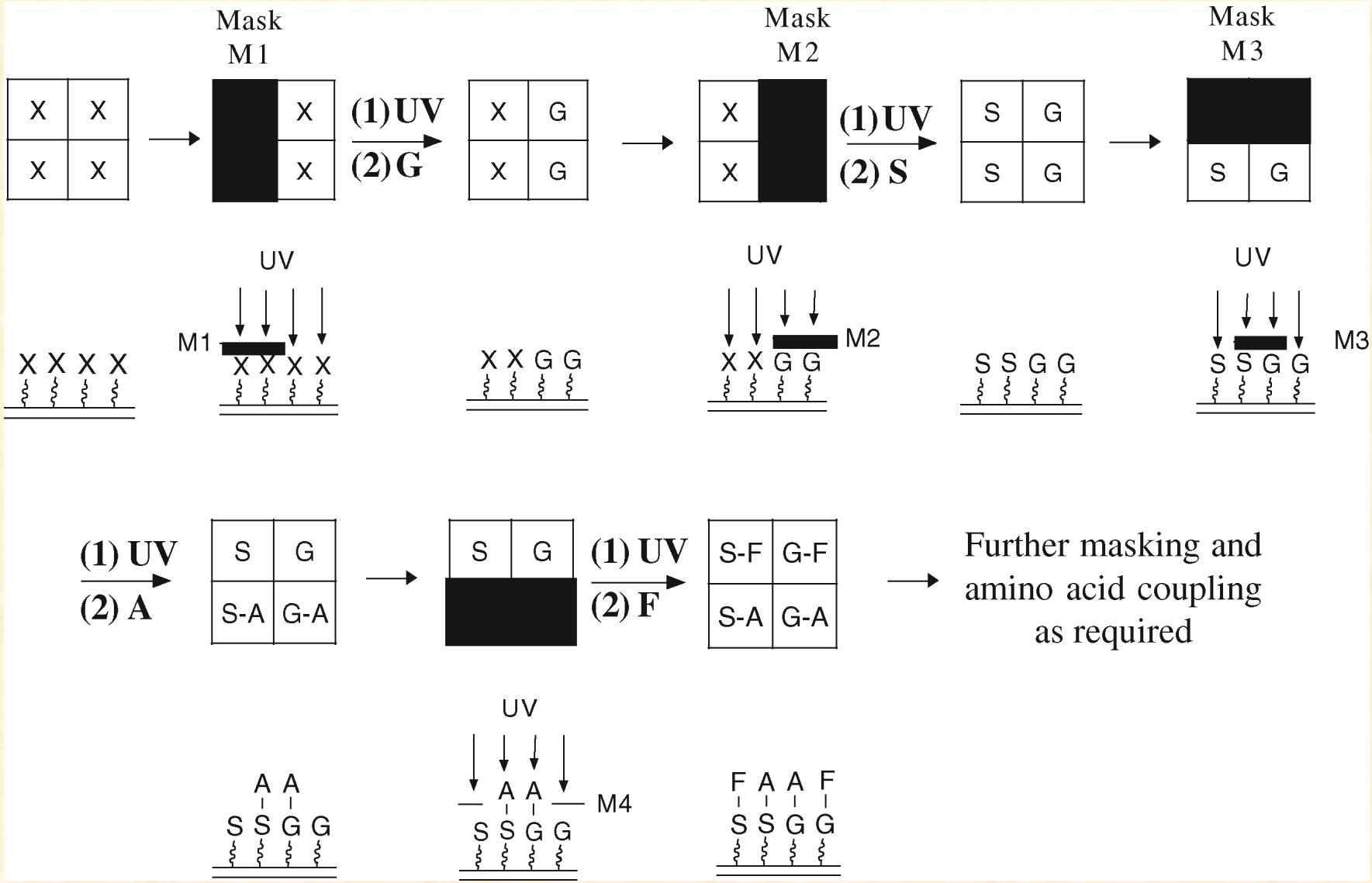
Parallel Synthesis

- Fodor's method



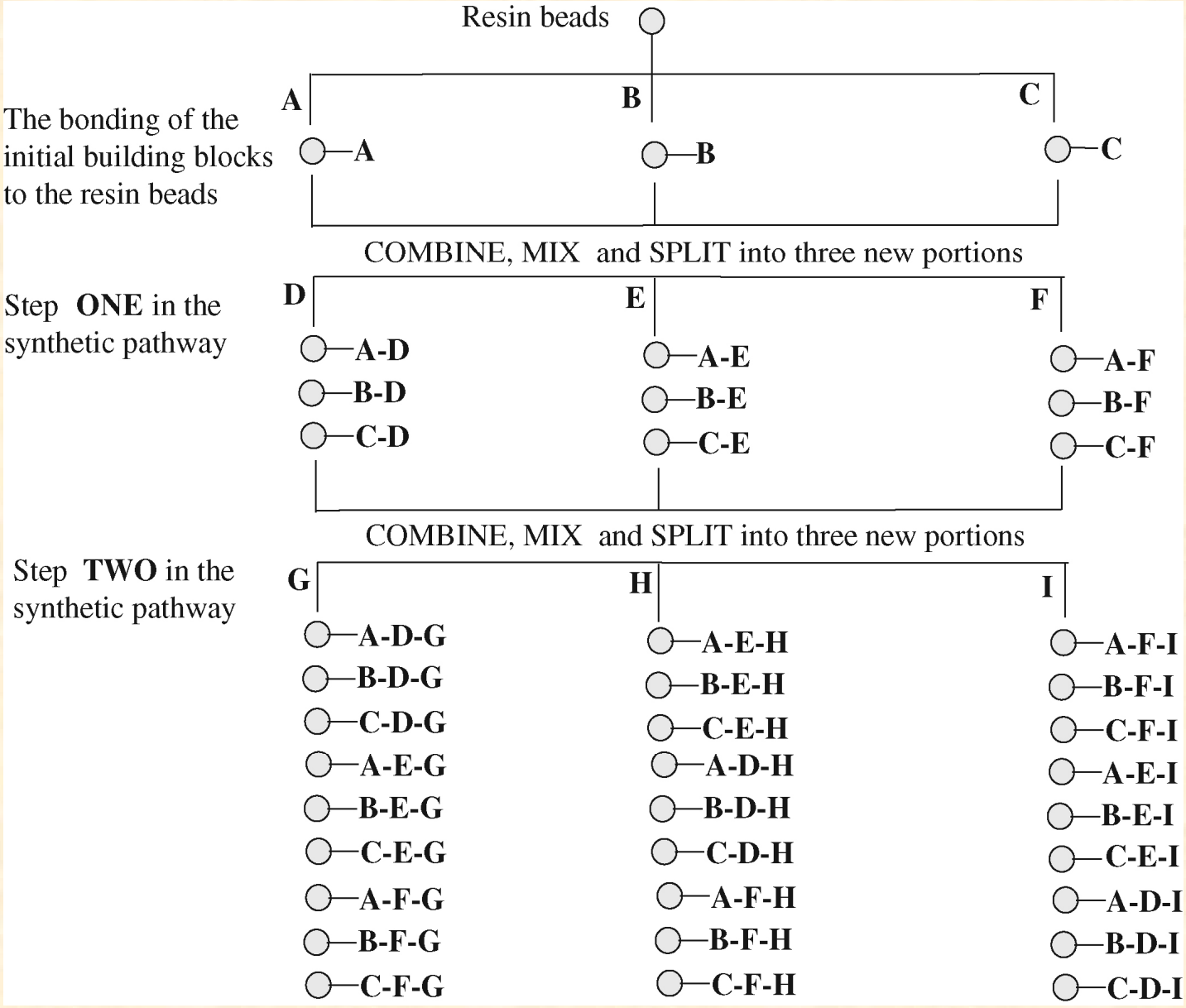
Parallel Synthesis

- Fodor's method



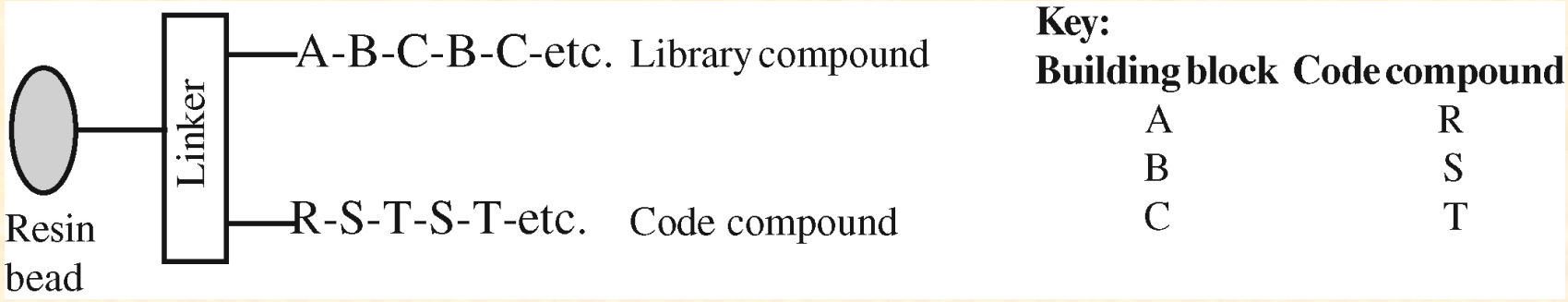
Mixture Synthesis

- Furka – Mix and Split method



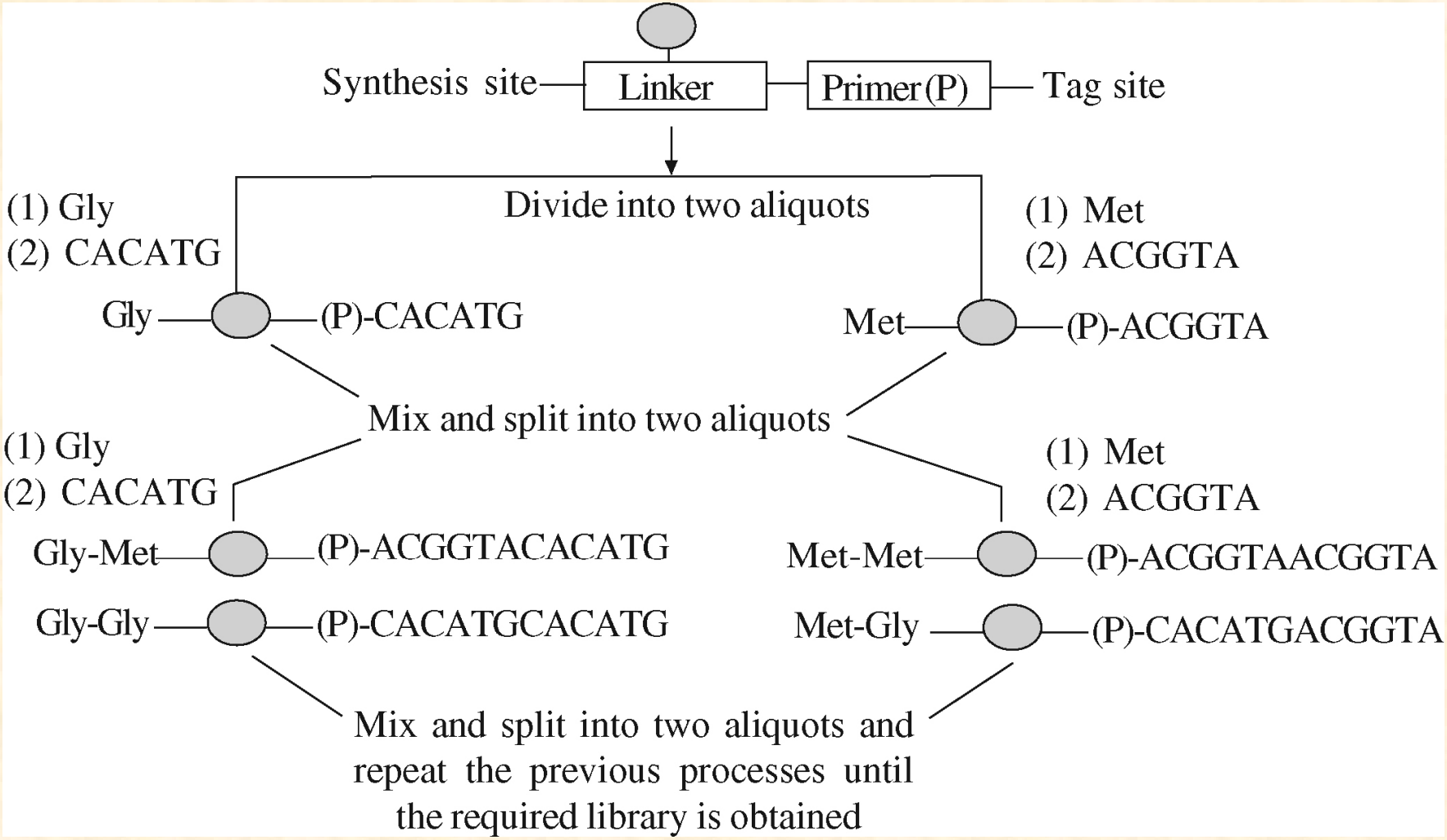
Encoding Methods

- Sequential Chemical Tagging



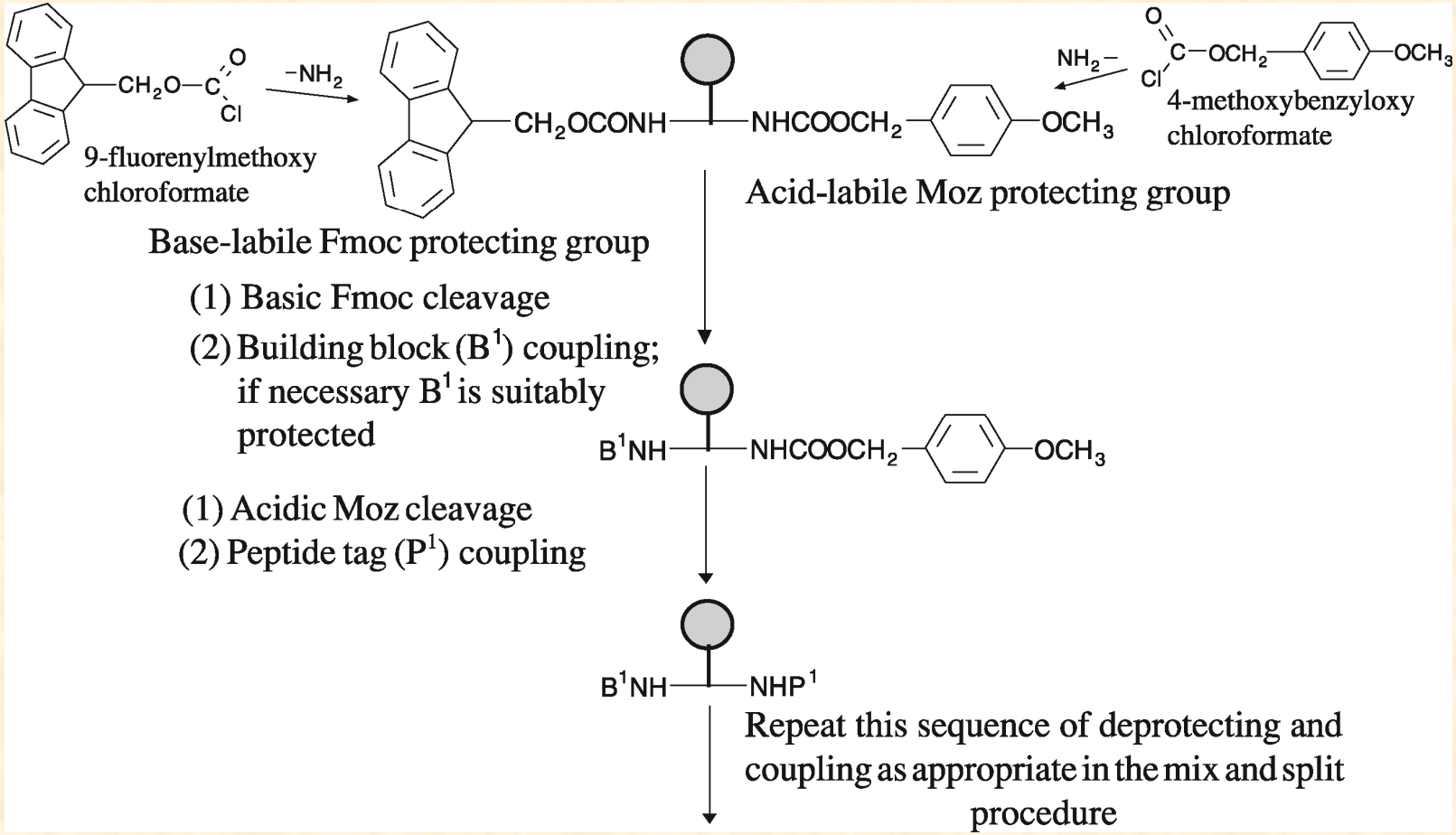
Encoding Methods

- Sequential Chemical Tagging



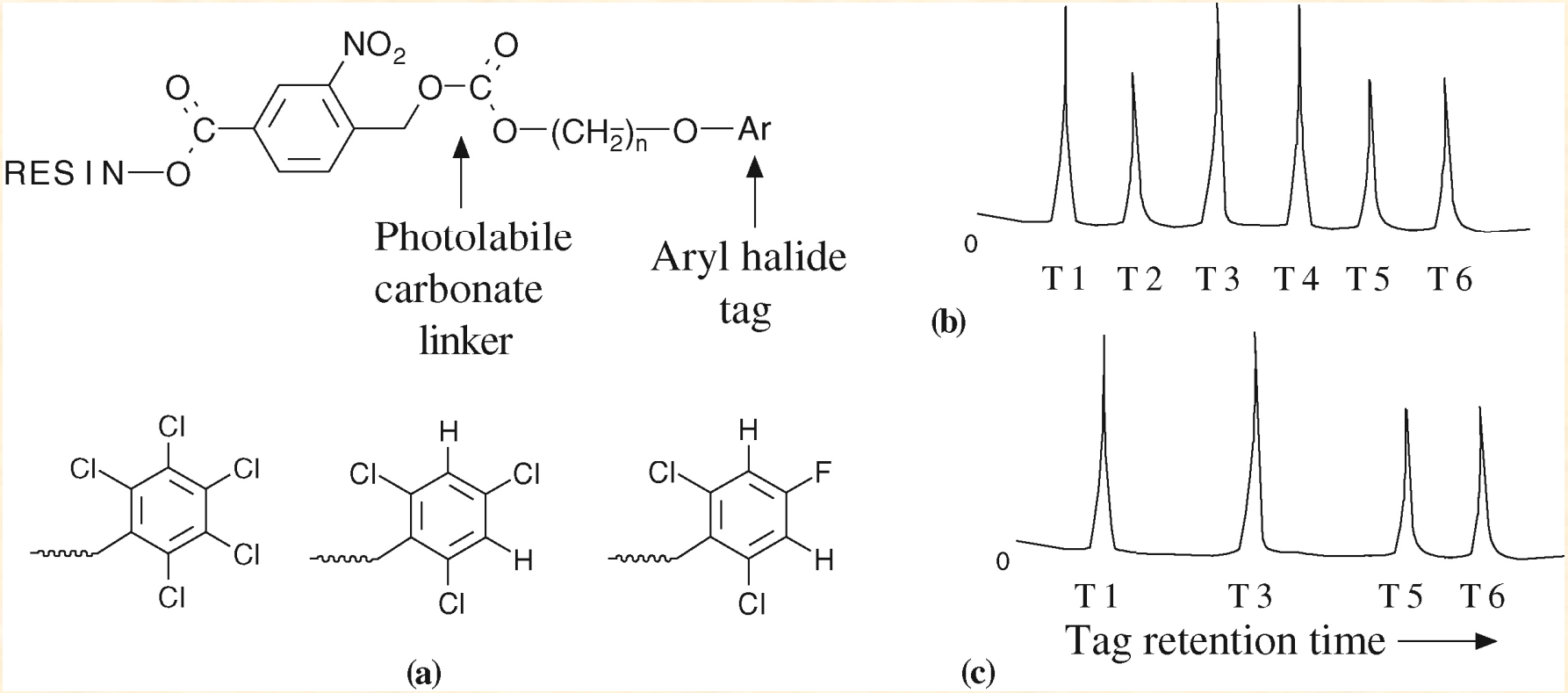
Encoding Methods

- Sequential Chemical Tagging



Encoding Methods

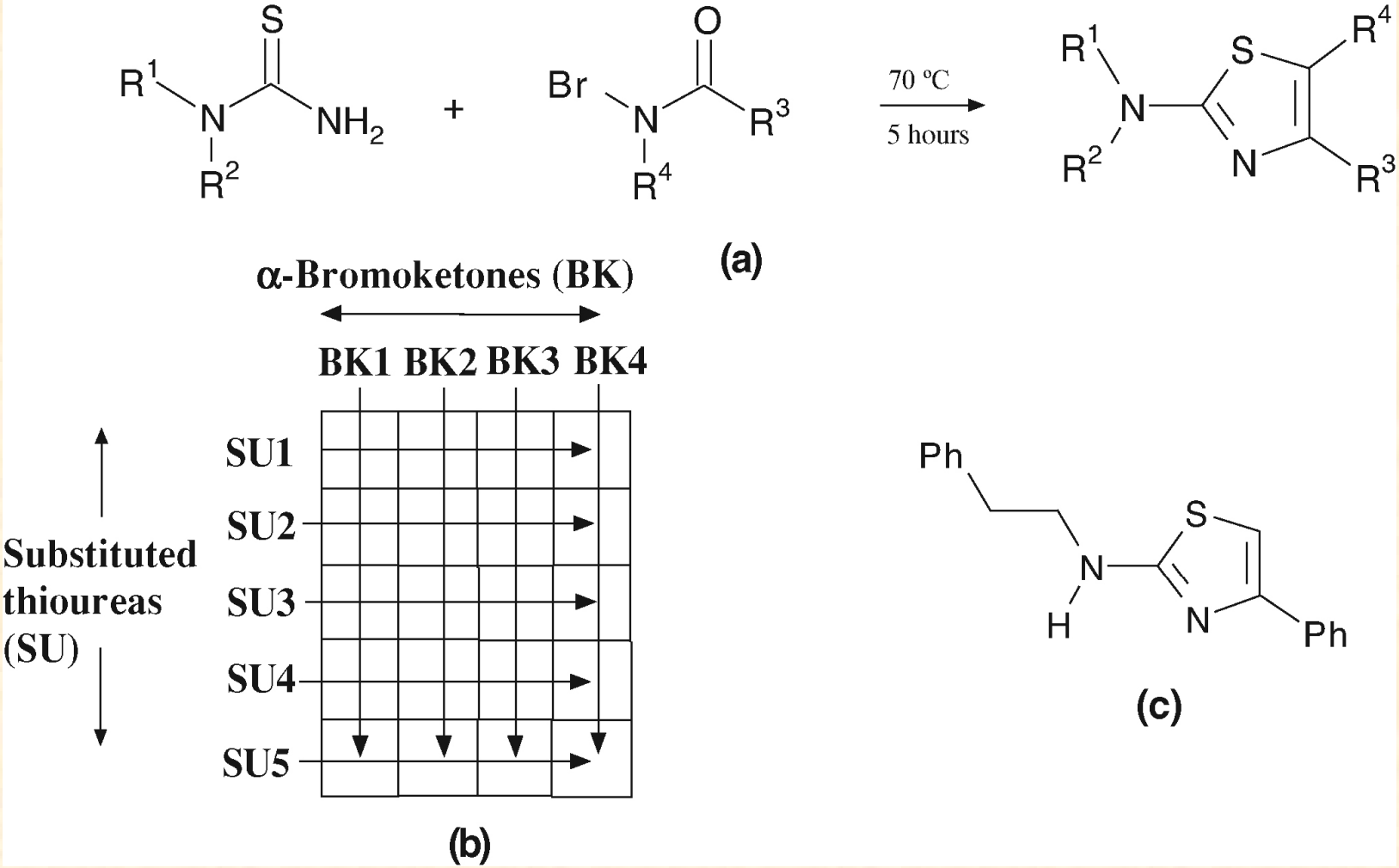
- Still's binary code tag system



Computerized tagging

Combinatorial Synthesis in Solution

Parallel synthesis in solution



Combinatorial Synthesis in Solution

The formation of libraries of mixtures

$$RCOCl + R'NH_2 \longrightarrow RCONHR' + Cl$$

The acid chloride-based set:

$A^1 + (B^1,B^2,B^3,B^4,B^5,B^6,B^7,B^8,B^9,B^{10}) \longrightarrow$ **Mixture 1** containing all the possible A^1—B compounds.

$A^2 + (B^1,B^2,B^3,B^4,B^5,B^6,B^7,B^8,B^9,B^{10}) \longrightarrow$ **Mixture 2** containing all the possible A^2—B compounds.

$A^5 + (B^1,B^2,B^3,B^4,B^5,B^6,B^7,B^8,B^9,B^{10}) \longrightarrow$ **Mixture 5** containing all the possible A^5—B compounds.

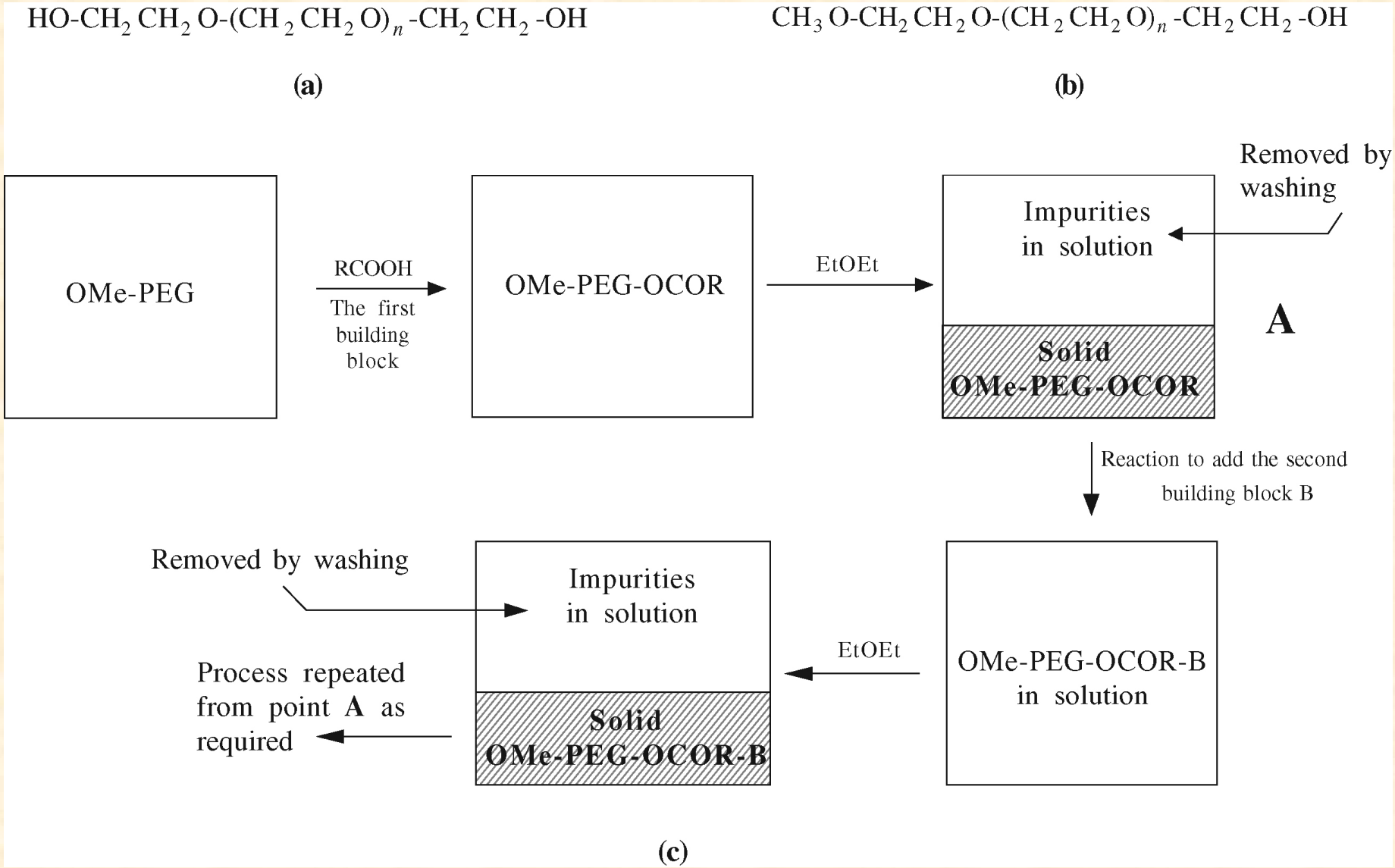
The amine-based set:

$B^1 + (A^1,A^2,A^3,A^4,A^5,) \longrightarrow$ **Mixture 6** containing all the possible B^1—A compounds.

$B^{10} + (A^1,A^2,A^3,A^4,A^5,) \longrightarrow$ **Mixture 15** containing all the possible B^1—A compounds.

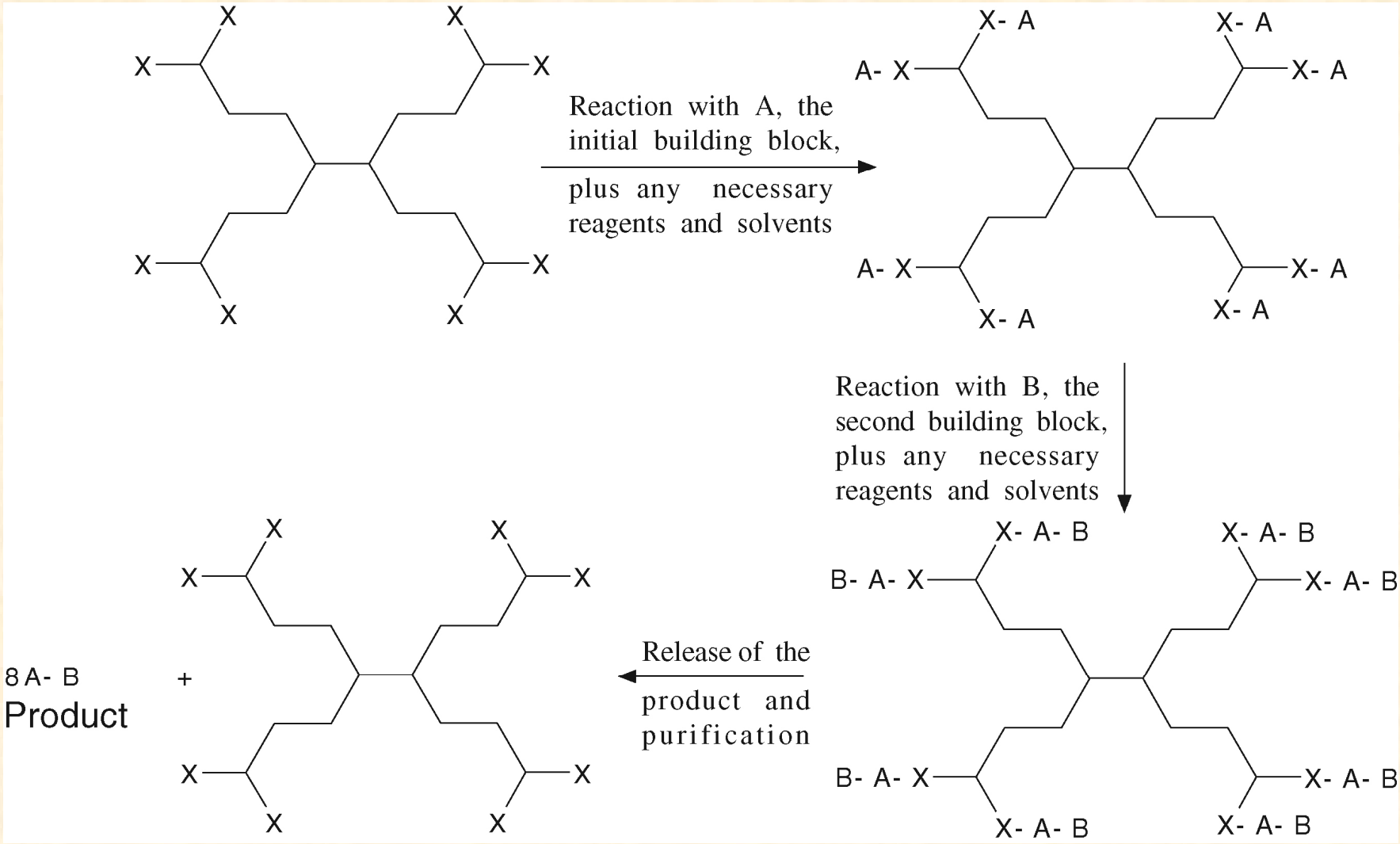
Combinatorial Synthesis in Solution

Libraries using OMe-PEG



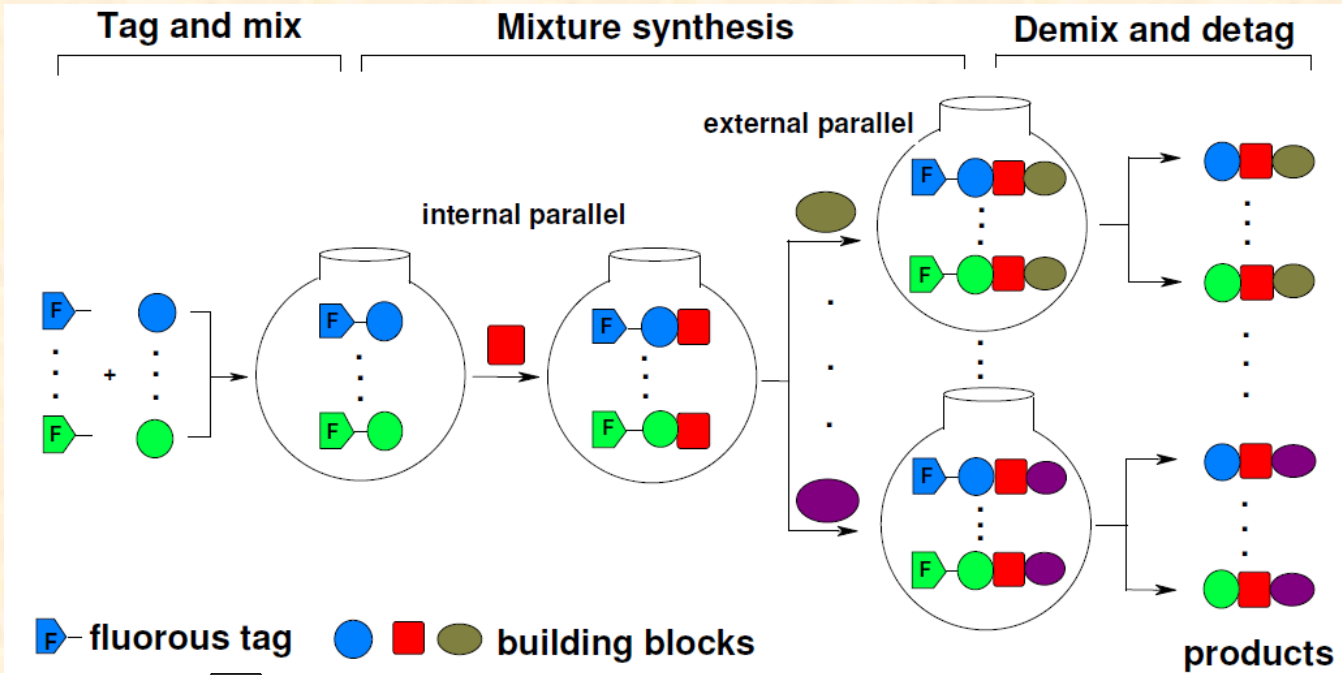
Combinatorial Synthesis in Solution

Libraries using dendrimers



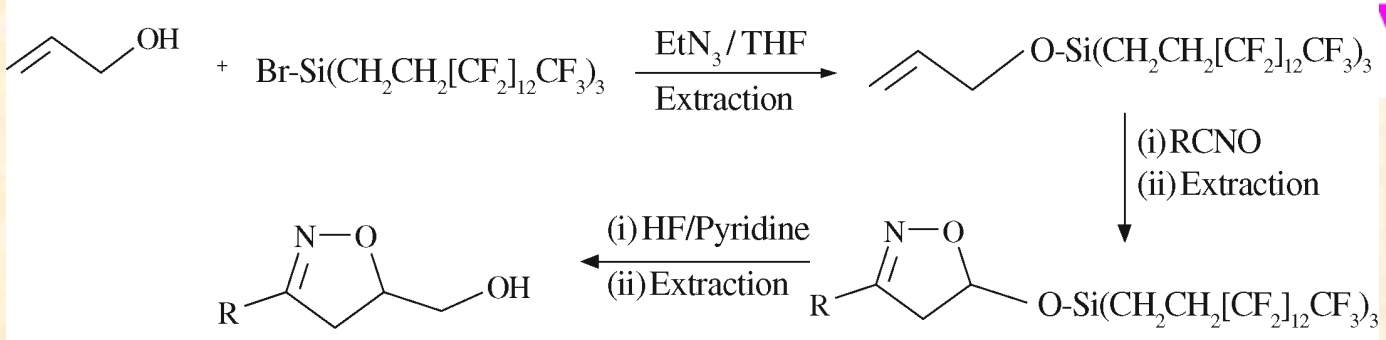
Combinatorial Synthesis in Solution

Fluorous Tagging

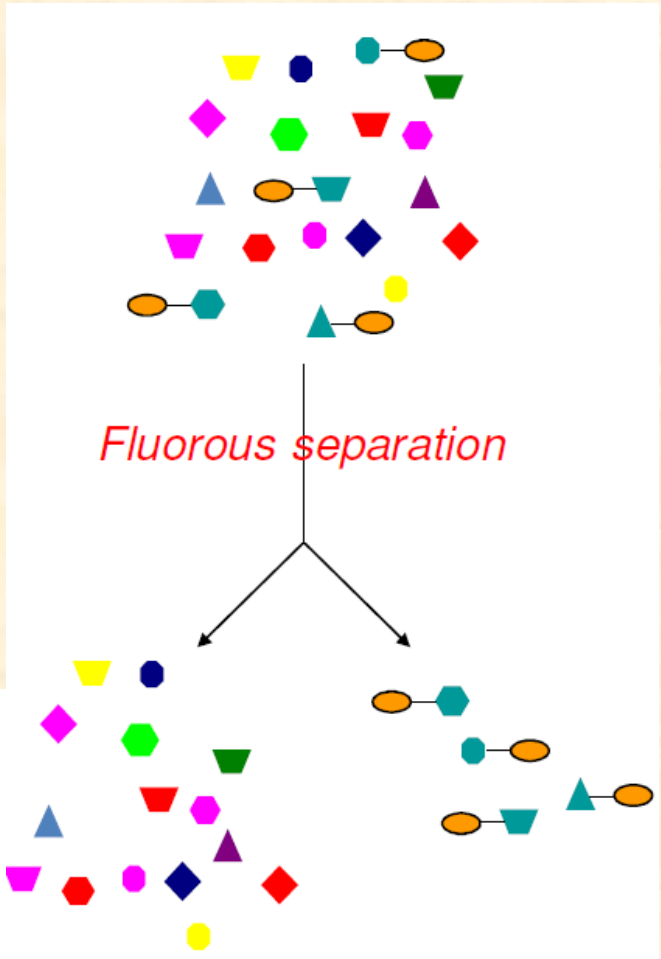


$CH_3O-Sn(CH_2CH_2[CF_2]_{12}CF_3)_3$ $\quad$ $Br\text{-}Si(CH_2CH_2[CF_2]_{12}CF_3)_3$

(a)

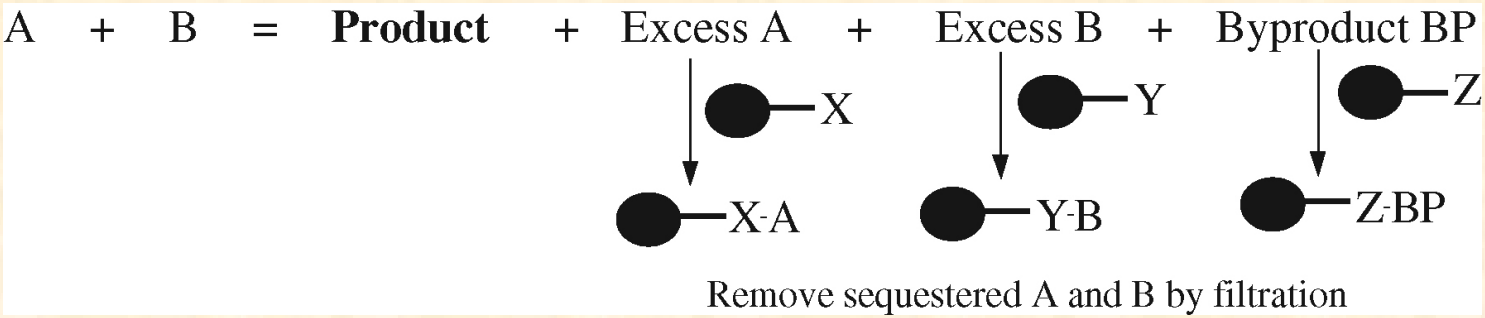


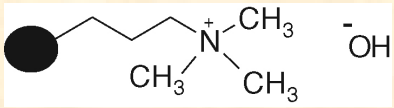
(b)

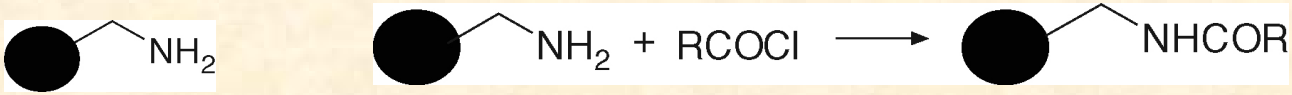


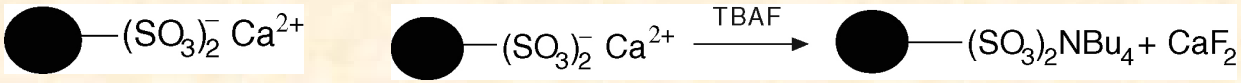
Combinatorial Synthesis in Solution

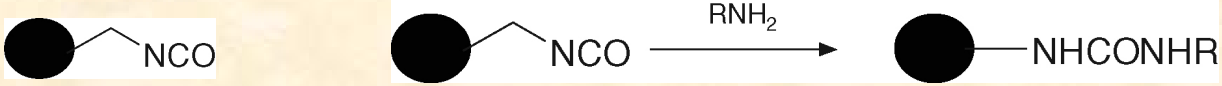
Libraries with resin-bound scavenging agents

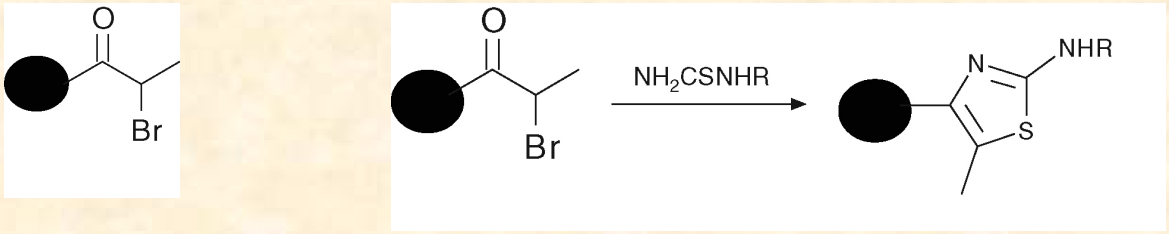






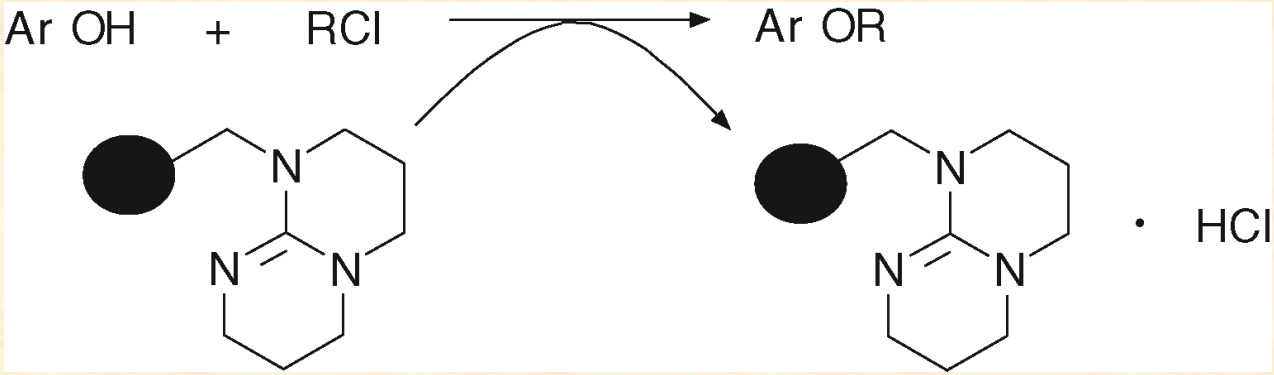






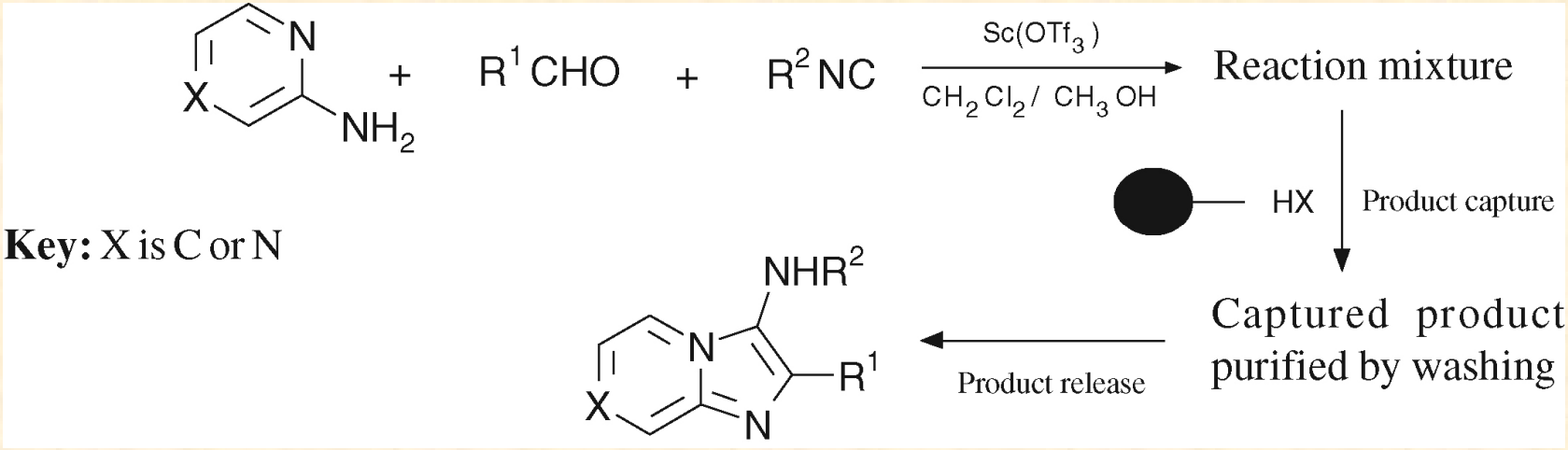
Combinatorial Synthesis in Solution

Libraries with resin-bound reagents



Combinatorial Synthesis in Solution

Resin capture of products



Deconvolution

Preparation of the original library	10	Ten amino acid reactants →	100	Ten amino acid reactants →	1000
The preparation of the first group of secondary libraries to find the first residue in the peptide	9	Nine amino acid reactants →	90	Ten amino acid reactants →	900
The preparation of the second group of secondary libraries to find the second residue in the peptide	10	Nine amino acid reactants →	90	Ten amino acid reactants →	900
The preparation of the third group of secondary libraries to find the third residue in the peptide	10	Ten amino acid reactants →	100	Nine amino acid reactants →	900