Combinatorial Chemistry Technology

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Combinatorial Diversity in Nature

20 natural amino acids yield

- **400 dipeptides**
- **8,000 tripeptides ...**
- **64,000,000 hexapeptides and, in principle,**
- **10^{400} proteins with MW ≈ 30 kD**

100 chemically modified amino acids yield

- **e.g. 1,000,000,000,000 hexapeptides,**

and ... 4 nucleic bases encode all organisms !

Number of organic molecules with MW < 500 (C, H, O, N, P, S, F, Cl, Br, I)

1 000 000 000 000 000 000 000 000 000 000
000 000 000 000 000 000 000 000 000 000
000 000 000 000 000 000 000 000 000 000
000 000 000 000 000 000 000 000 000 000

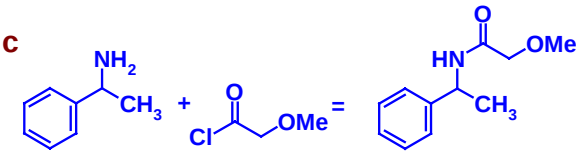
or more or less ....

Principles of Combinatorial Chemistry

Combinatorial Chemistry generates a multitude of chemically related (”congeneric”) compounds, so-called ”combinatorial libraries"

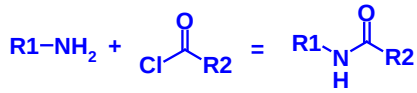
In the last years, combinatorial chemistry in drug research changed more and more to automated parallel synthesis and parallel purification.

Classical organic synthesis:



1 educt x 1 educt = 1 product

Combinatorial synthesis:



e.g. 50 educts x 20 educts = 1,000 products

Multistep combinatorial synthesis: **e.g. 50 x 20 x 20 educts = 20,000 products**

Multicomponent reaction (e.g. Ugi reaction):

R1-NH_2 + R2-CHO + R3-NC + R4-COOH =

e.g. 50 x 20 x 5 x 200 educts = 1 million products

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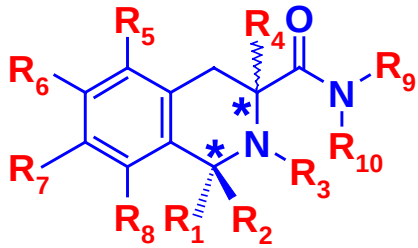
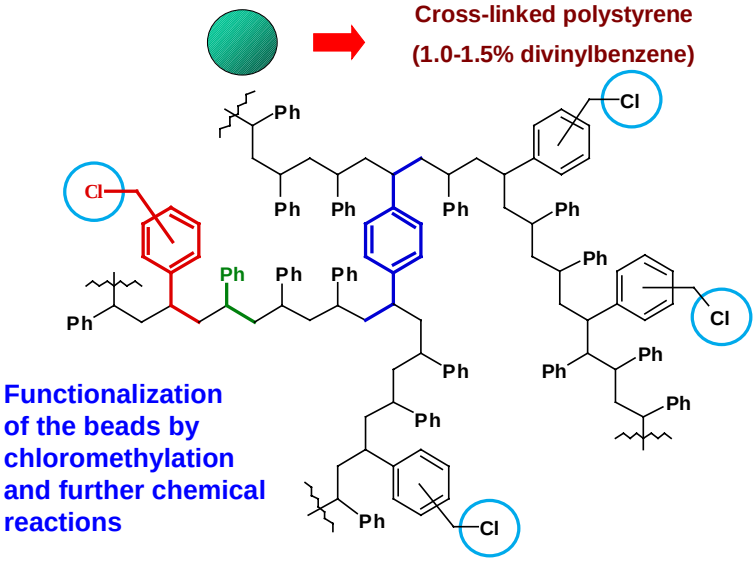
Combinatorial Library

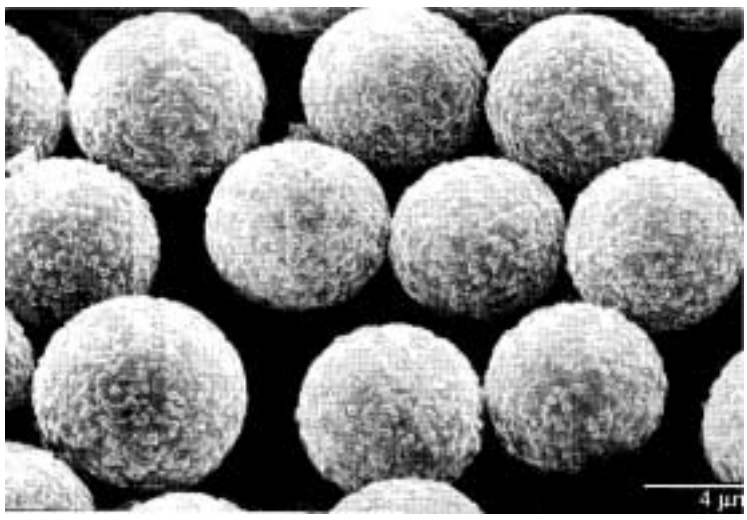


Building blocks with 68 different residues in 10 positions (R_1 - R_{10} are 5, 10, 10, 4, 2, 5, 5, 2, 5, and 20 residues) generate a library of 20 million different compounds. Consideration of both steric centers (*) increases this number by a factor of four, i.e. to 80 million different compounds.

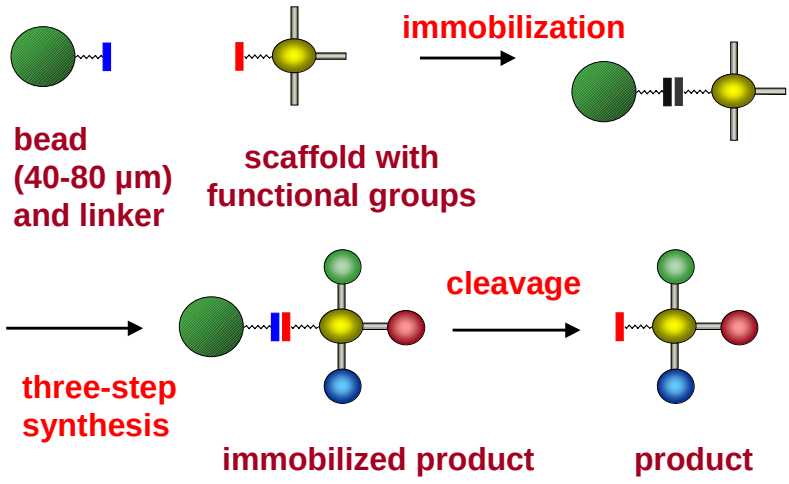
Solid Phase Synthesis: Beads



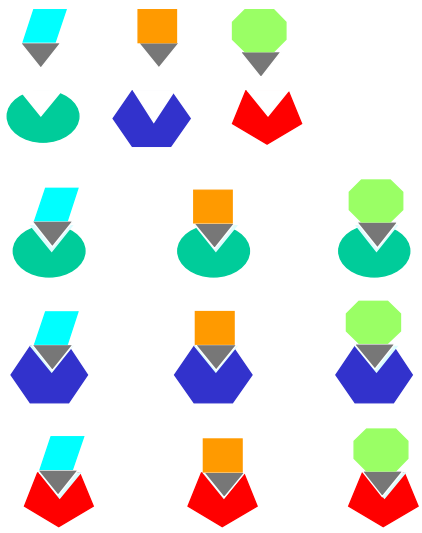
Tentagel Beads (Polystyrene, Grafted with Polyoxyethylene), Rapp Polymers, Tübingen, Germany



The Principle of Solid Phase Synthesis



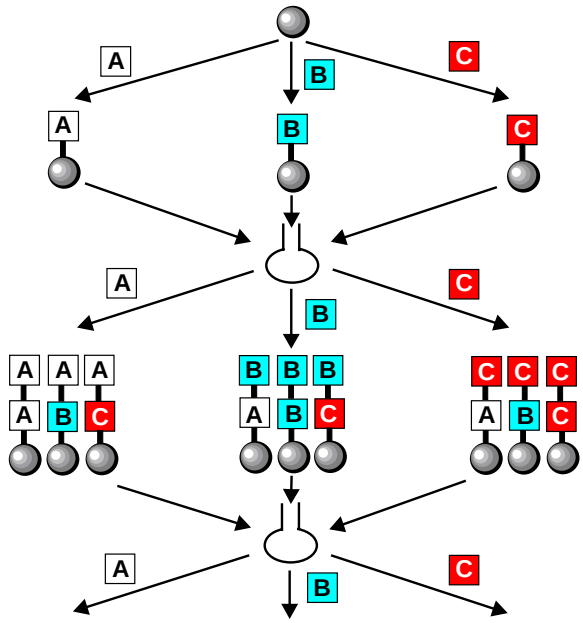
The Combination of Scaffolds and Building Blocks



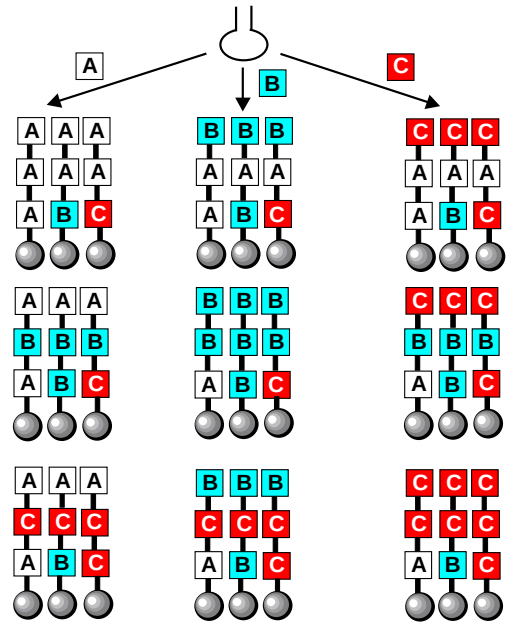
3 building blocks A_1-A_3
and
3 building blocks B_1-B_3

yield 9 products
A_1B_1 – A_3B_3 .

In the same manner,
10 x 10 x 10 building
blocks yield 1,000
products $A_1B_1C_1$ –
$A_{10}B_{10}C_{10}$.

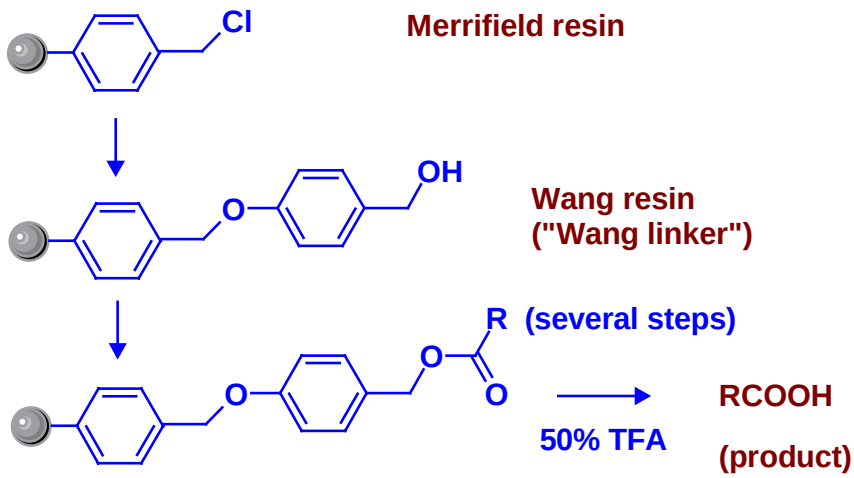


"*Split and Combine*" Method for Library Synthesis

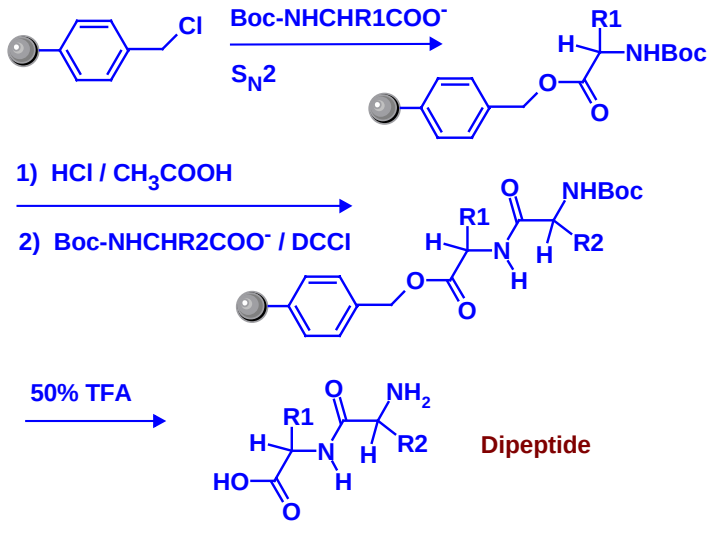


3 Mixtures with 9 different compounds in each reaction vessel

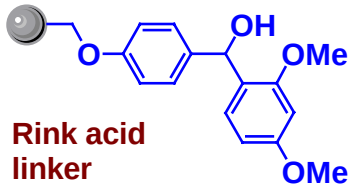
Linkers: Merrifield and Wang linkers



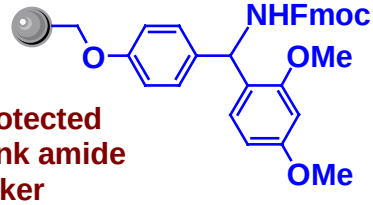
Linkers: a) Merrifield Peptide Synthesis



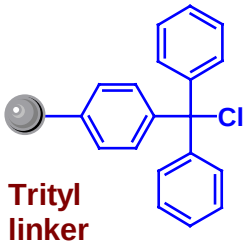
Other linkers



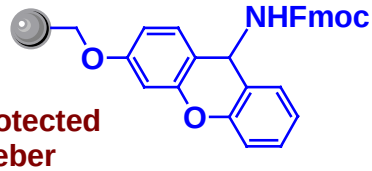
Rink acid linker



protected Rink amide linker

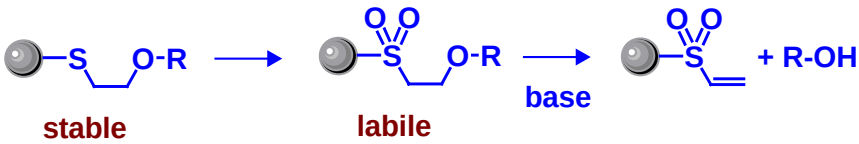


Trityl linker

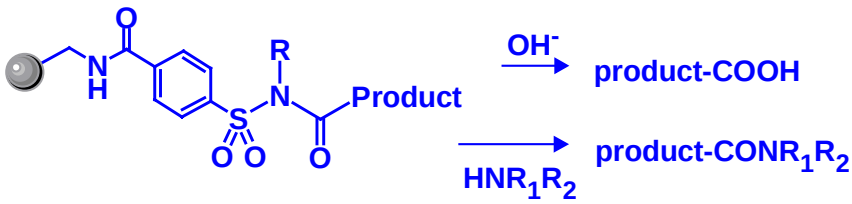


protected Sieber linker

Safety catch linkers



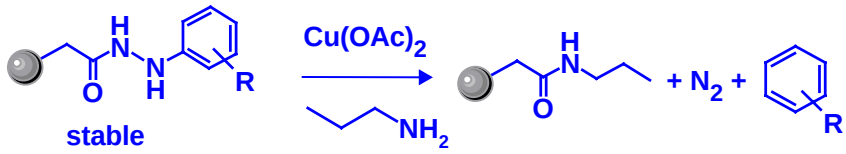
stable labile



R = H: stable

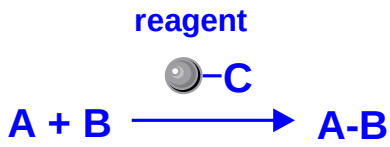
+ CH_2N_2 → R = CH_3: labile

Traceless (safety catch) linker

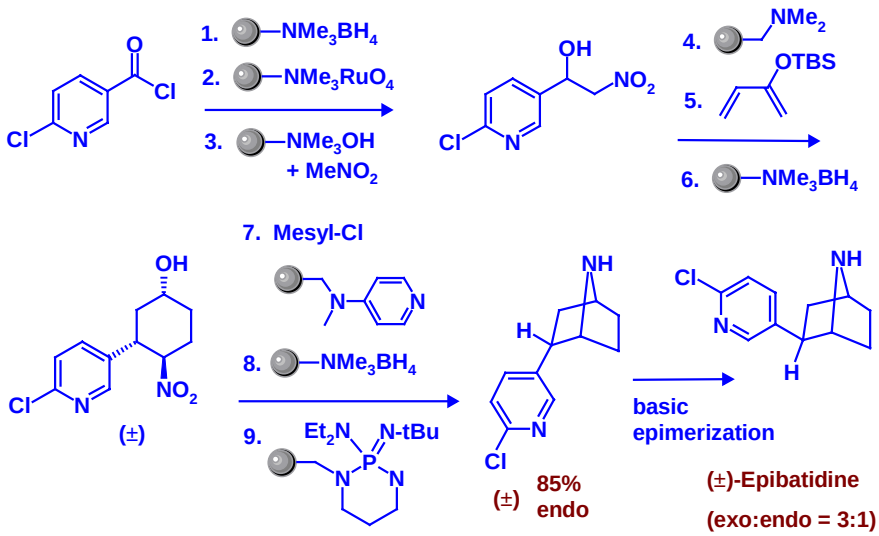


Polymer-supported solution phase syntheses

Polymeric reagents

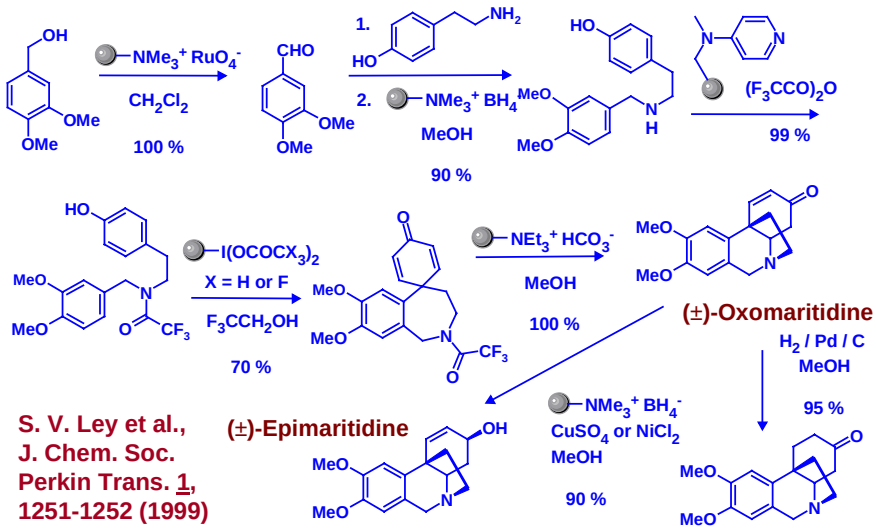


Solid Phase-Supported Synthesis of (±)-Epibatidine



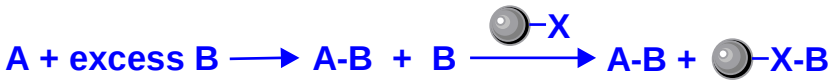
R. J. Booth and J. C. Hodges, J. Am. Chem. Soc. 119, 4882-4886 (1997)

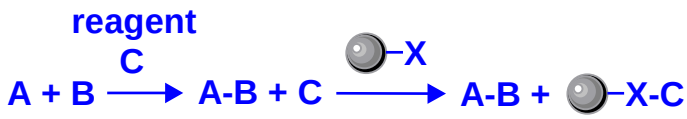
Solid Phase-Supported Synthesis of (±)-Oxomaritidine and (±)-Epimaritidine

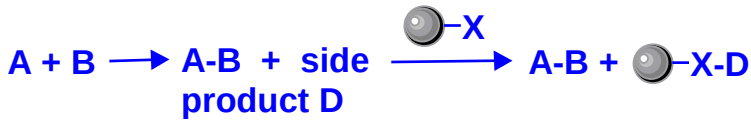


S. V. Ley et al., J. Chem. Soc. Perkin Trans. 1, 1251-1252 (1999)

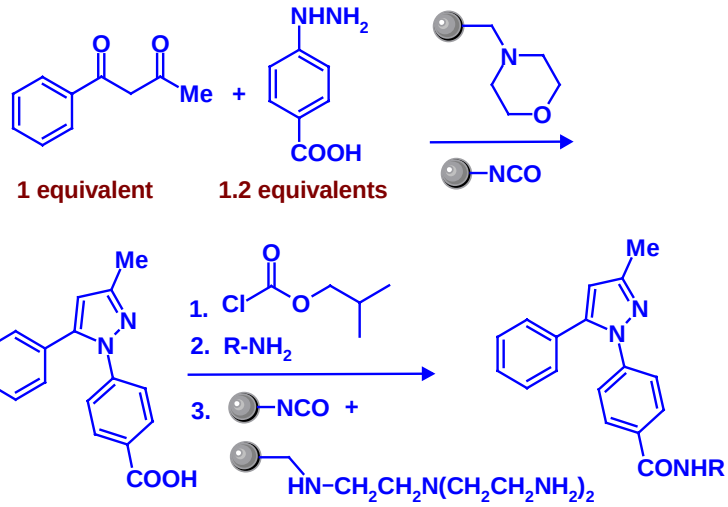
Polymeric scavengers for building blocks, side products and reagents



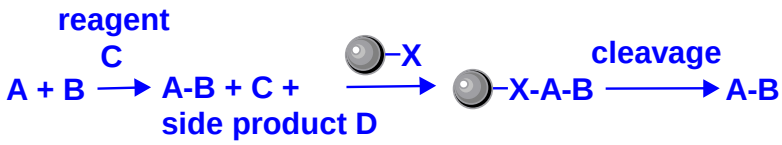




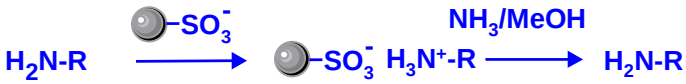
Scavenger Reagents: Ion Exchange Resins, Polymeric Acids and Bases, Isocyanates, etc.



Resin capture strategy

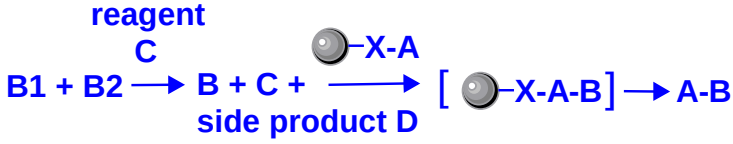


Resin capture with an ion exchange resin

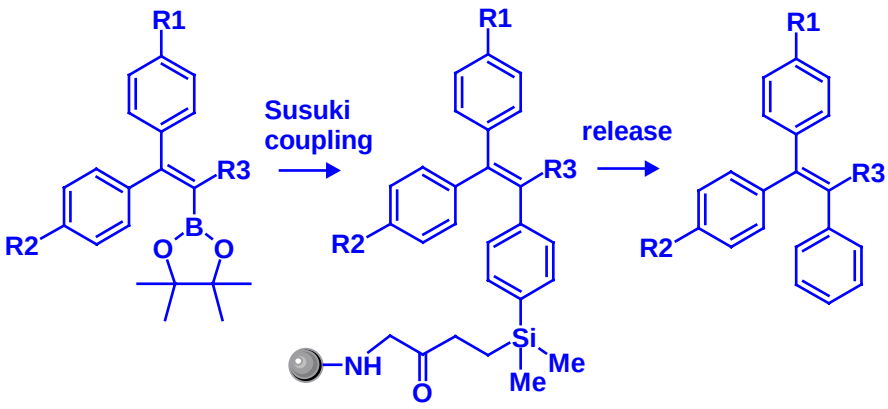


(Amberlite ion exchange resin)

Catch and release strategy

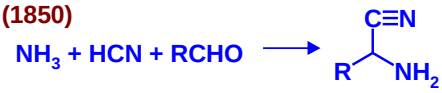


Catch and release strategy, using a traceless linker

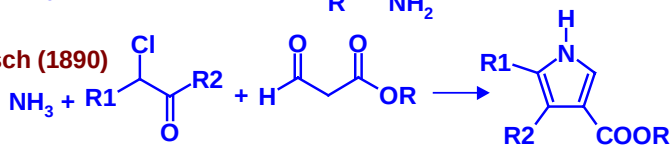


Milestones in the History of Multicomponent Reactions

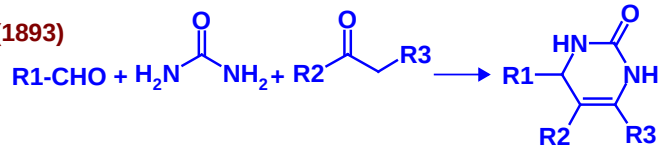
A. Strecker (1850)



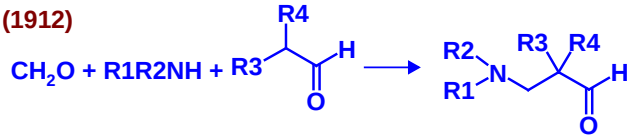
A. R. Hantzsch (1890)



P. Biginelli (1893)

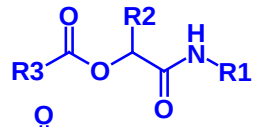


C. Mannich (1912)



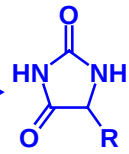
M. Passerini (1921)

R1NC + R2CHO + R3COOH →



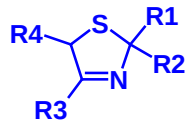
H. T. Bucherer (1934)

HCN + NH_3 + CO_2 + RCHO →



F. Asinger (1958)

NH_3 + R1(C=O)R2 + R3(C=O)R4(SH) →



I. Ugi (1959)

$R1NH_2$ + R2CHO + R3NC + R4COOH →

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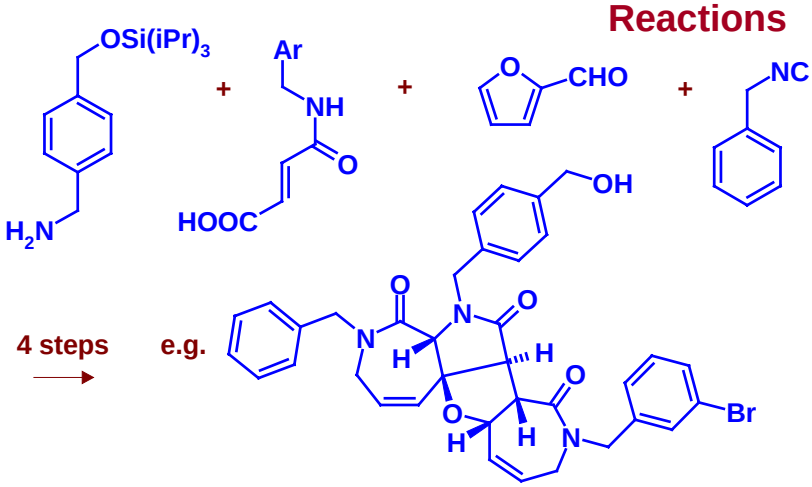
Complex Molecules from Multicomponent Reactions



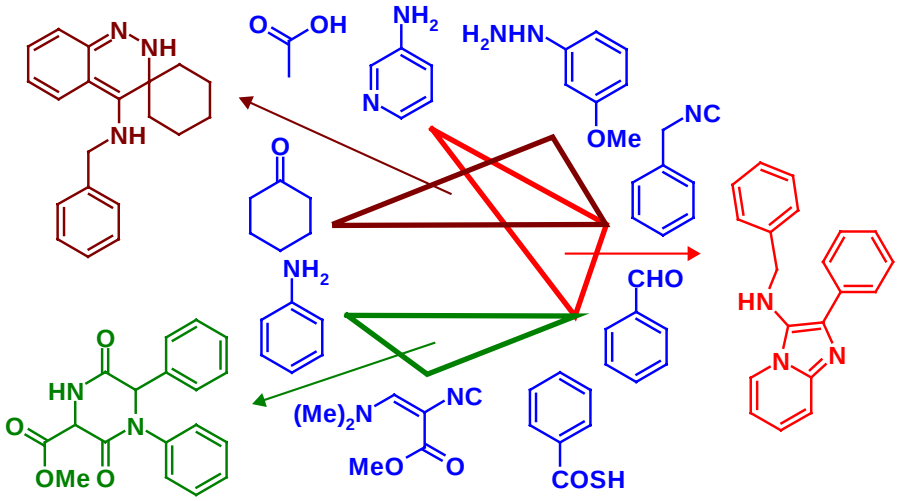
4 steps →

e.g.

S. L. Schreiber, Science 287, 1964-1969 (2000)

L. Weber, Drug Discov. today 7, 143-147 (2002)

The Generation of Scaffold Diversity



L. Weber, Drug Discov. today 7, 143-147 (2002)

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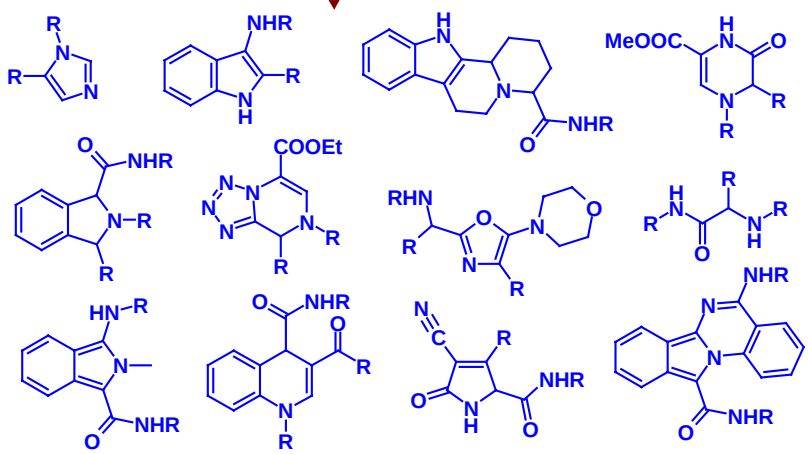
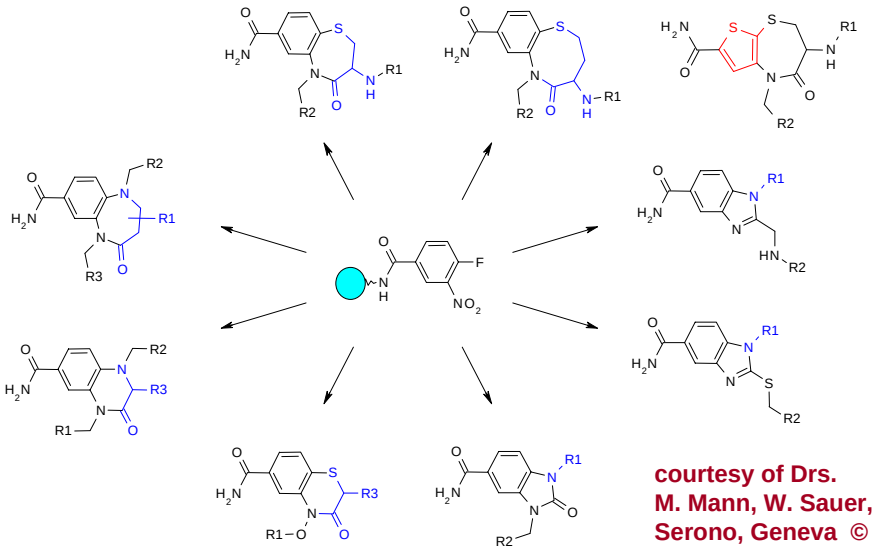
The Generation of Scaffold Diversity

Three component
Ugi reaction



L. Weber, QSAR Comb. Sci. 24, 809-823 (2005)

Increasing Diversity of Combinatorial Libraries



courtesy of Drs.
M. Mann, W. Sauer,
Serono, Geneva ©

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