Lecture 9: Step-by-Step Approaches I: Polypeptide Synthesis: Examples from Biology, Step-by-Step Approaches II: Dendrimers, Traditional Convergent and Divergent Routes, New "One Pot" Approaches to Hyperbranched Species
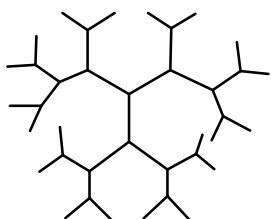
Building Macromolecules Step by Step

Step growth advantages:
      - systematically build well-defined structures
      - two examples:

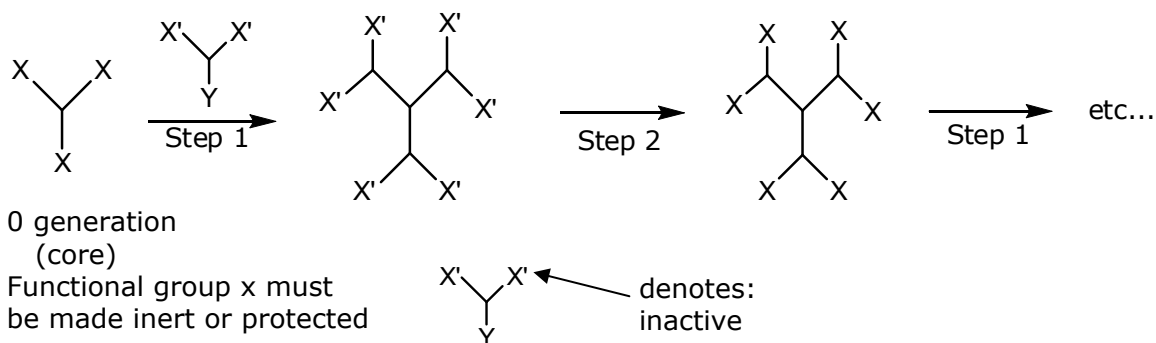## Dendrimers: regularly multibranched polymers with a common core

root for "tree"

- grow with core + func $\geq$ 2
- each incremental increase yields an exponential increase in MW, # of end groups "generation" $\rightarrow$ increment
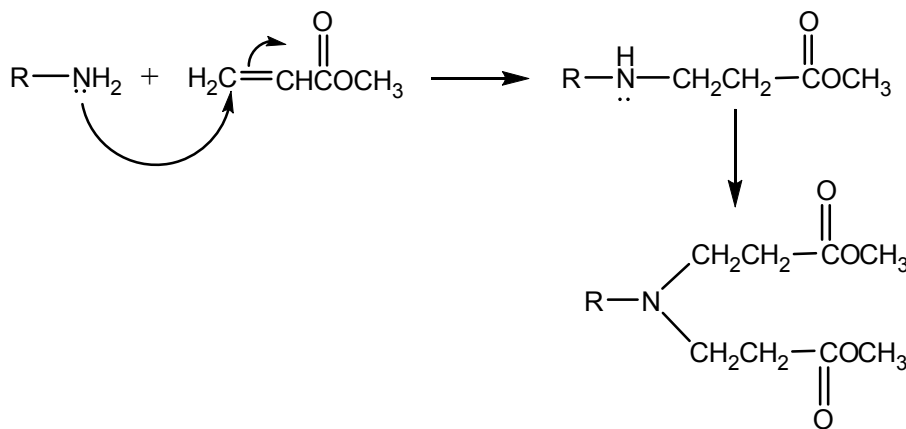
Two approaches to making dendrimers:
      1. Convergent synthesis
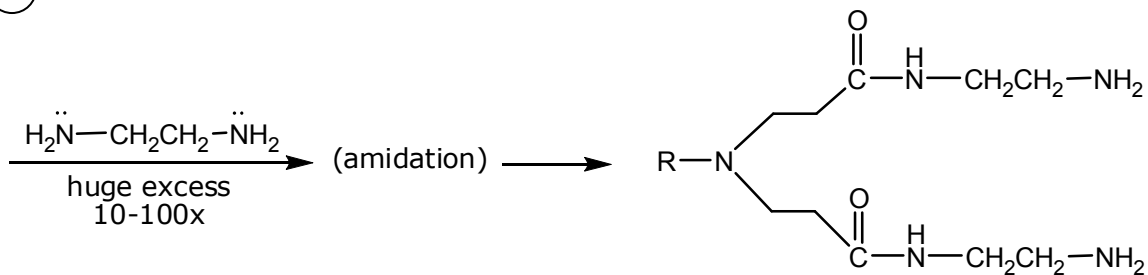   2. Divergent synthesis

Dendrimer Divergent Synthesis

0 generation
  (core)
Functional group x must
be made inert or protected

denotes:
inactive

Polyamidoamine dendrimers:

(1) Michael addition:

$$R-NH_2 \ + \ H_2C{=}CHCOCH_3 \xrightarrow{\hspace{1cm}} R-\overset{H}{\underset{..}{N}}-CH_2CH_2-COCH_3$$

(with $C{=}O$ groups on the acrylate and product)

$$\downarrow$$

$$R-N \begin{cases} CH_2CH_2-COCH_3 \\ CH_2CH_2-COCH_3 \end{cases}$$

(2)

$$\underset{\substack{\text{huge excess} \\ \text{10-100x}}}{\overset{H_2\overset{..}{N}-CH_2CH_2-\overset{..}{N}H_2}{\xrightarrow{\hspace{2cm}}}} \text{(amidation)} \xrightarrow{\hspace{1cm}} R-N \begin{cases} CH_2CH_2-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-CH_2CH_2-NH_2 \\ CH_2CH_2-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-CH_2CH_2-NH_2 \end{cases}$$

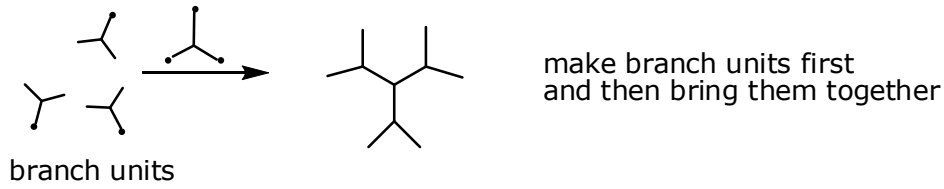Repeat (1) and (2) for each new generation.

Need core molecule:

> Tomalia:
> NH_3 (trifunctional core)
> or
> $NH_2\text{-}CH_2CH_2CH_2$ (tetrafunctional core)

• can convert end group to other group to suit application

Dendrimer Convergent Approach

make branch units first
and then bring them together

branch units

①

surface group

reactive group

c reacts with fr

protected version of fr

②

deprotect
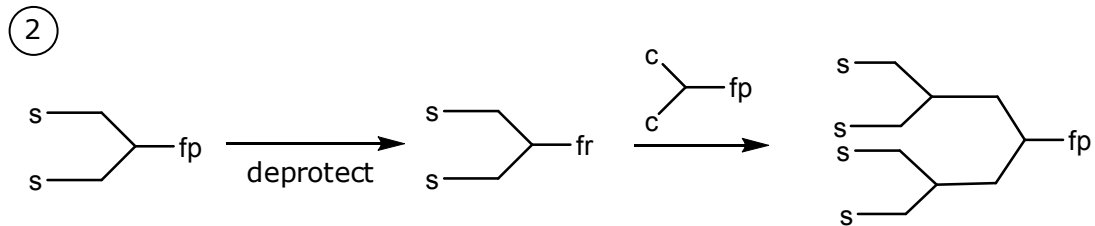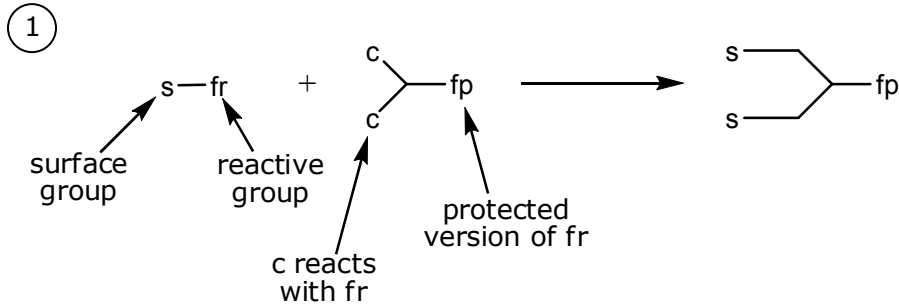
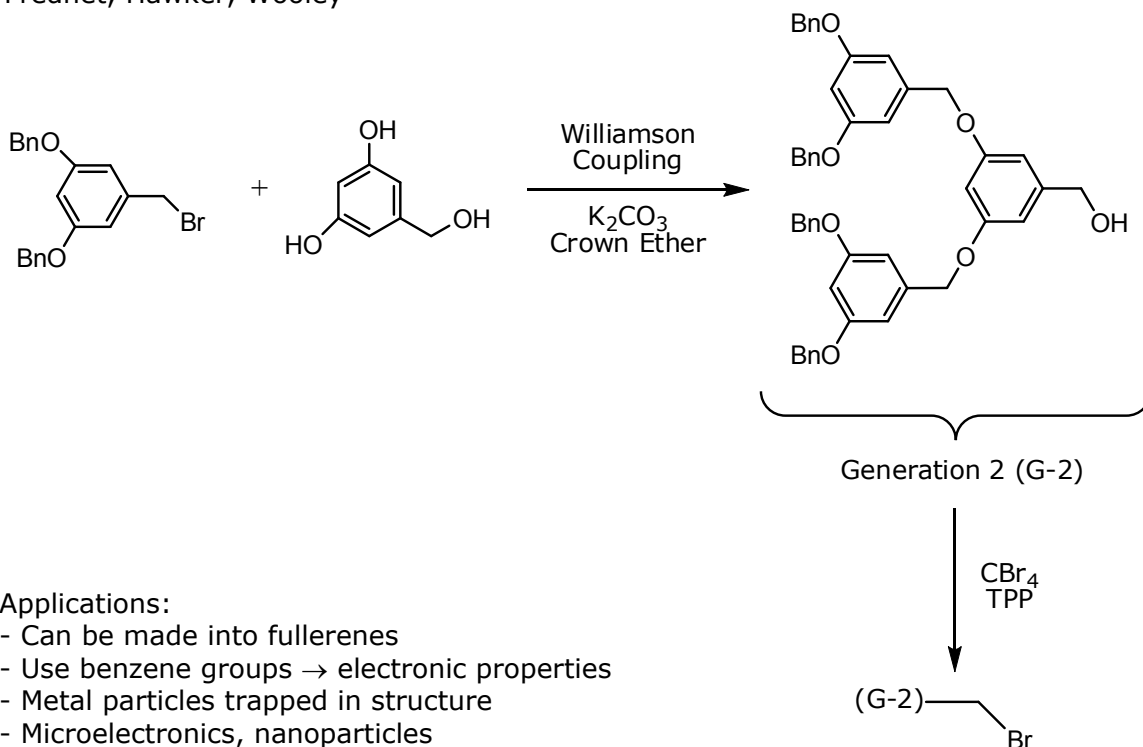Repeat ① and ② to build dendron (branch).

③ After reaching desired dendron generation:

central core

dendron
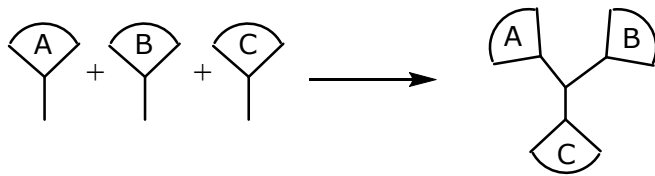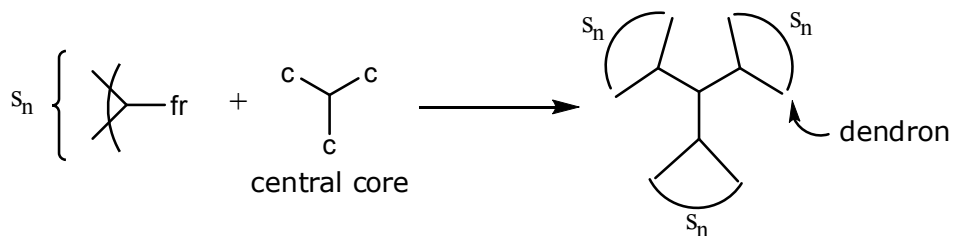
Convergent
+ block copolymers easily
+ purify between steps more easily

Divergent
- difficulty in purification
- potential for more defects due to stoichiometry
+ more readily adapted to commercial batch process

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Frednet, Hawker, Wooley

Williamson Coupling

K_2CO_3
Crown Ether

Generation 2 (G-2)

CBr_4
TPP

(G-2)——Br
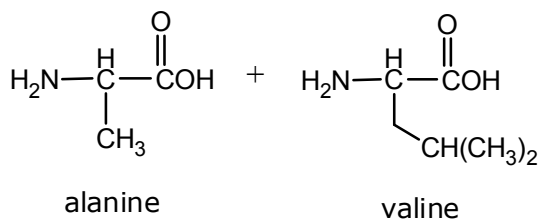
Applications:
- Can be made into fullerenes
- Use benzene groups → electronic properties
- Metal particles trapped in structure
- Microelectronics, nanoparticles
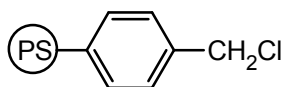
Polypeptides: one step at a time

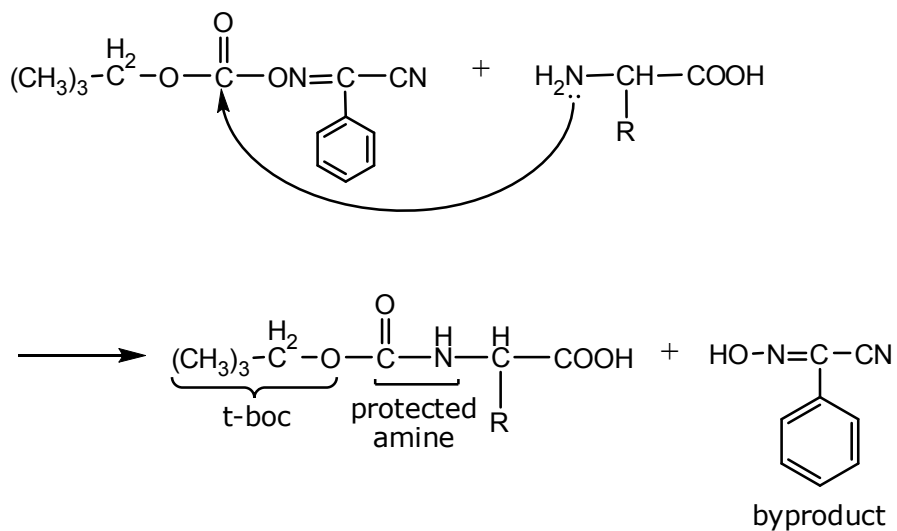Build specific sequence:

alanine   valine

Sequence order is important.

R.B. Merrifield:
• Use of a solid support + protection group
• Polymer solid support: polystyrene in latex bead form (PS)

PS—⬡—CH₂Cl

(1) Protection of amino terminus:
    t-butoxy carbonyl (t-boc)

$$(CH_3)_3-\overset{H_2}{C}-O-\overset{O}{\overset{\|}{C}}-O-N=C-CN \quad + \quad H_2\ddot{N}-\underset{R}{CH}-COOH$$

(with phenyl ring attached to the N=C)

$$\longrightarrow \quad \underbrace{(CH_3)_3-\overset{H_2}{C}-O}_{t\text{-boc}}-\underbrace{\overset{O}{\overset{\|}{C}}-\overset{H}{N}}_{\substack{\text{protected} \\ \text{amine}}}-\underset{R}{\overset{H}{C}}-COOH \quad + \quad HO-N=C-CN$$

byproduct

For deprotection:
    Use 25-50% trifluoroacetic acid (TFA) in CH₂Cl.

(2) Add first amino acid:

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PS—⬡—CH_2ClH^+ $^{\ominus}OC(=O)$—RNH—boc $X^{\oplus}$

↓

PS—⬡—$\overset{H_2}{C^2}$—$OC(=O)RNH_2$—boc

| CF_3COOH
| 20^oC, 30 min
↓

PS—⬡—$\overset{H_2}{C^2}$—$OC(=O)R$—NH_3 }   +   :N(Et)$_3$

to remove
$H^{\oplus}$

↓ HOOC—R'—NHboc

PS—⬡—$\overset{H_2}{C^2}$—$OC(=O)R$—$\overset{H}{N}$—$C(=O)$—R'NHboc
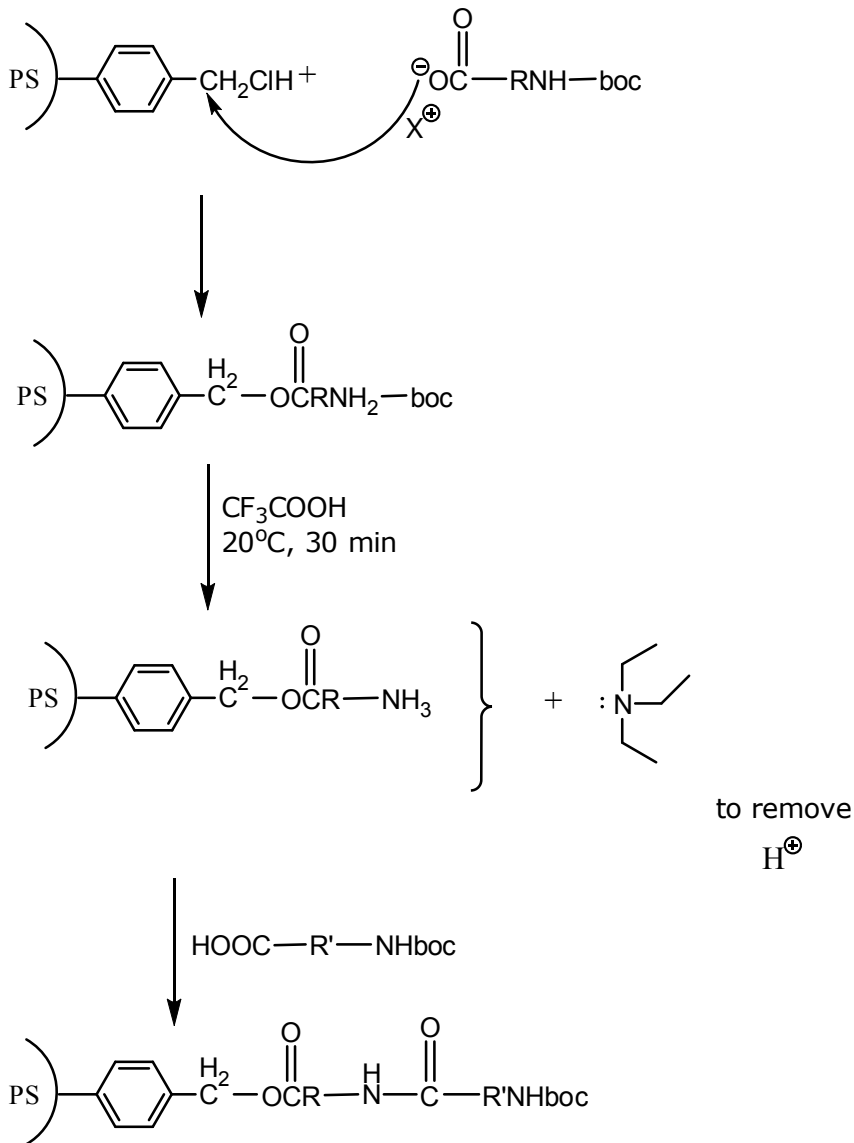
Needs coupling agent to speed process:
 - facilitate $-NH_2$ + $-COOH$ rxn by increasing reactivity of $-COOH$
 - dicyclohexylcarbodiimide (DCC)
   → activates COOH