GREEN CHEMISTRY

Laurea Magistrale in Scienze Chimiche

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6 CFU – AA 2017-2018

Green Chemistry 09

GREEN TECHNIQUES FOR ORGANIC SYNTHESIS

SOLID-SUPPORTED SYNTHESIS

INTRODUCTION

Introduction

Solid-supported synthesis is a technology for the synthesis, separation, and purification of compounds useful in various major disciplines of chemistry including medicinal chemistry. Supported synthesis relies on the fact that the molecule under construction is attached to a solid bead. A key green aspect of supported synthesis is the separation of immobilized product by simple precipitation or phase separation

Introduction

The use of a polymer support offers the advantage of performing reactions in a minimum of solvents, and if possible without solvent, with decreasing by-products.

It allows separation of products by phase separation that can bypass the chromatographic purification stage where a large amount of organic solvents is required.

The recovered polymer support can be used again in the reaction sequence.

Introduction

Other greener benefits are:
the recycling of the solid support, the ease of automation and the pseudo dilution effect.
Solid-phase routes often allow the use of little excess reagent to force reactions to completion and excess reagents can be removed by scavenging or washing away at the end.

The main disadvantages of solid-phase chemistry are:
the limitations of the current range of commercially available supports and linkers
the limited means of monitoring reactions in real time.
Solid-phase routes also necessitate additional steps to link and cleave the support and are generally used to prepare laboratory-scale final product

Introduction

Solid-supported synthesis is a green synthesis as it eliminates complicated workup and purification procedures leading to a reduction in waste solvents and also the reagents in excess can be recovered by scavenging.
The supported reagents (and the associated by-products) are less volatile and less toxic than unsupported ones.

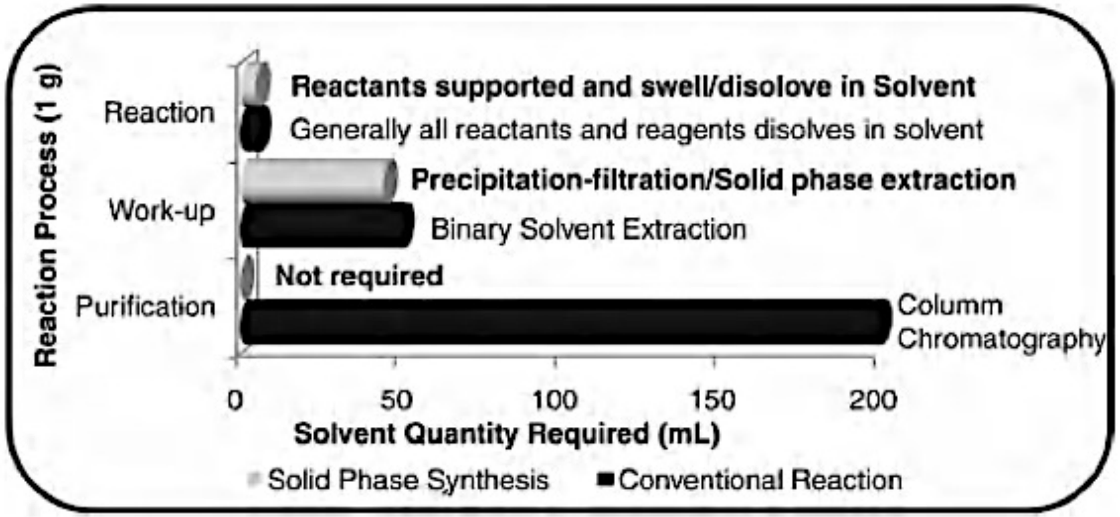


Figure 15.1 *Comparative solvent consumption in total reaction process.*

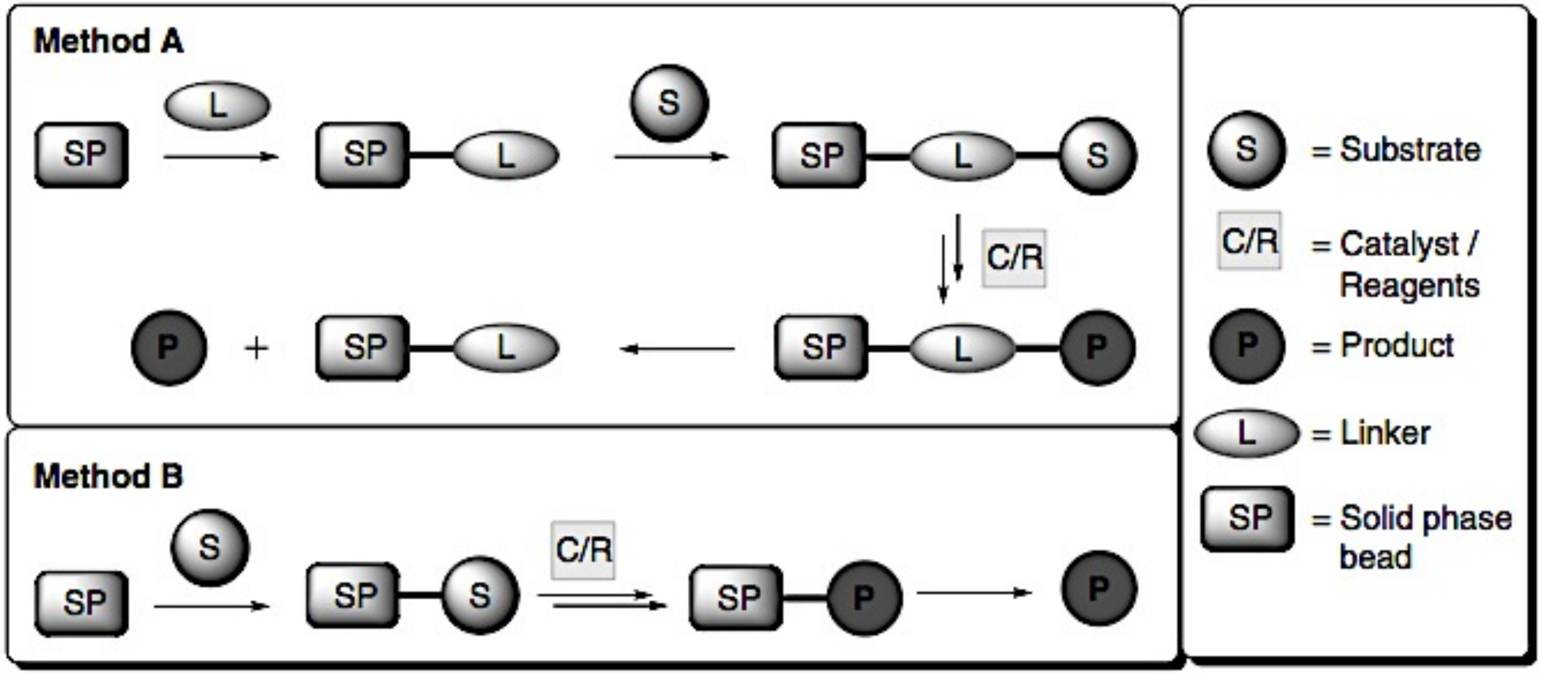
Introduction

New synthetic methodologies for solid-supported synthesis are routinely developed in all areas of organic chemistry including:

- **combinatorial synthesis,**
- **asymmetric synthesis**
- **parallel synthesis.**

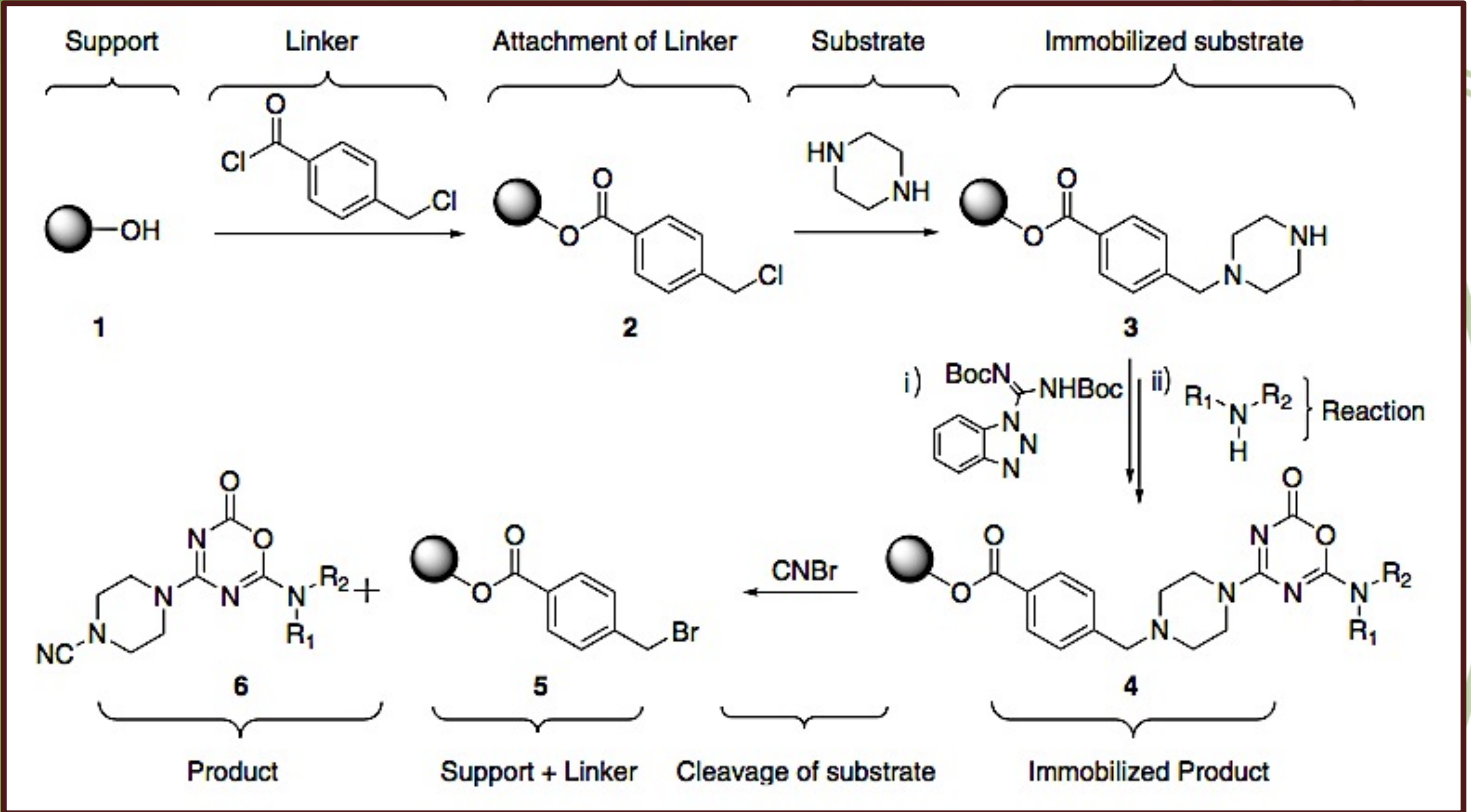
Polymer-supported synthesis has a great impact on the pharmaceutical industry to facilitate the early drug discovery process.

Techniques of Solid-Supported Synthesis



Scheme 15.1 *General technique of solid-supported synthesis.*

Techniques of Solid-Supported Synthesis



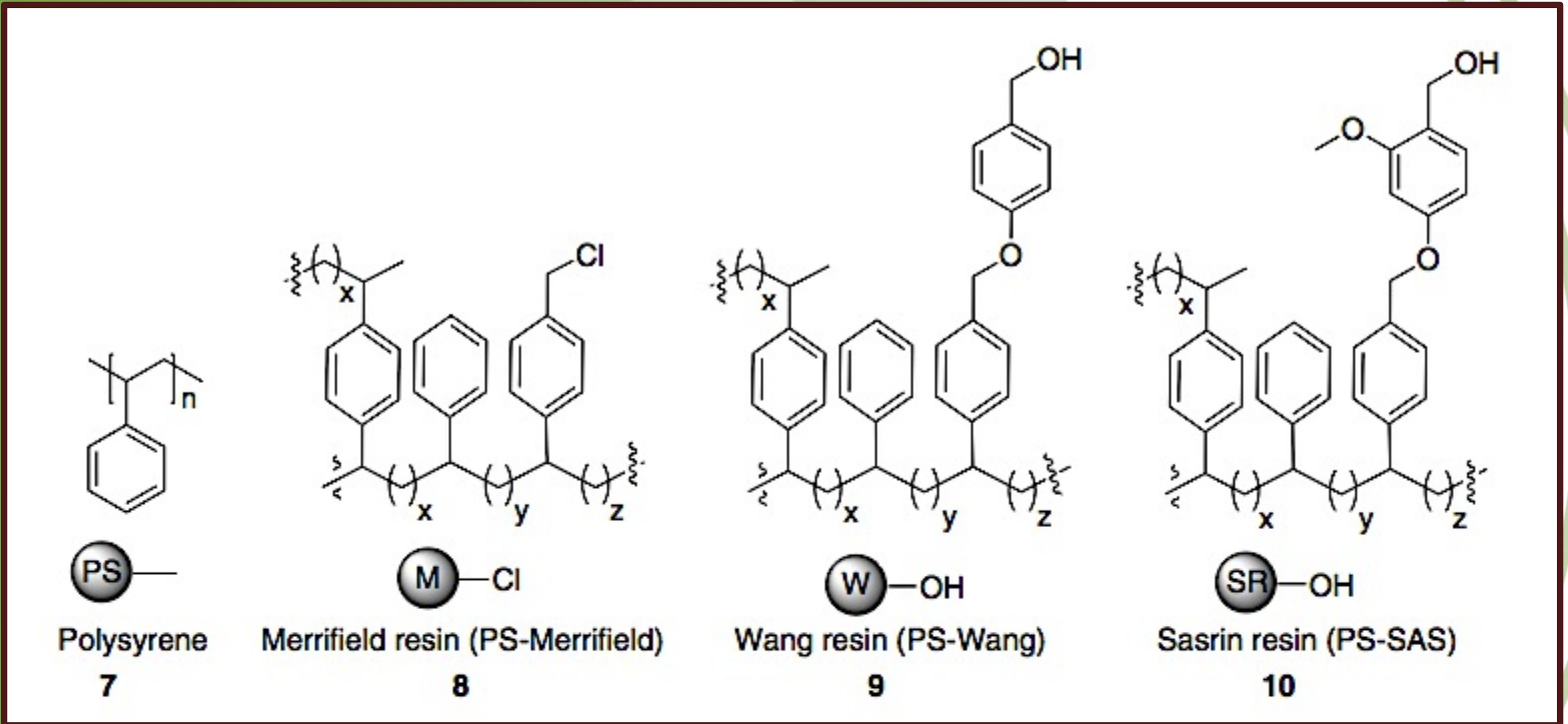
Supports for Supported Synthesis

The uses of macromolecular supports as a green media in organic synthesis relies on specific properties:

(i) stable and inert to the reaction conditions;
(ii) facilitate monitoring of reaction;
(iii) selectively cleavable at the end of synthesis;
(iv) recoverable;
(v) environmentally degradable.

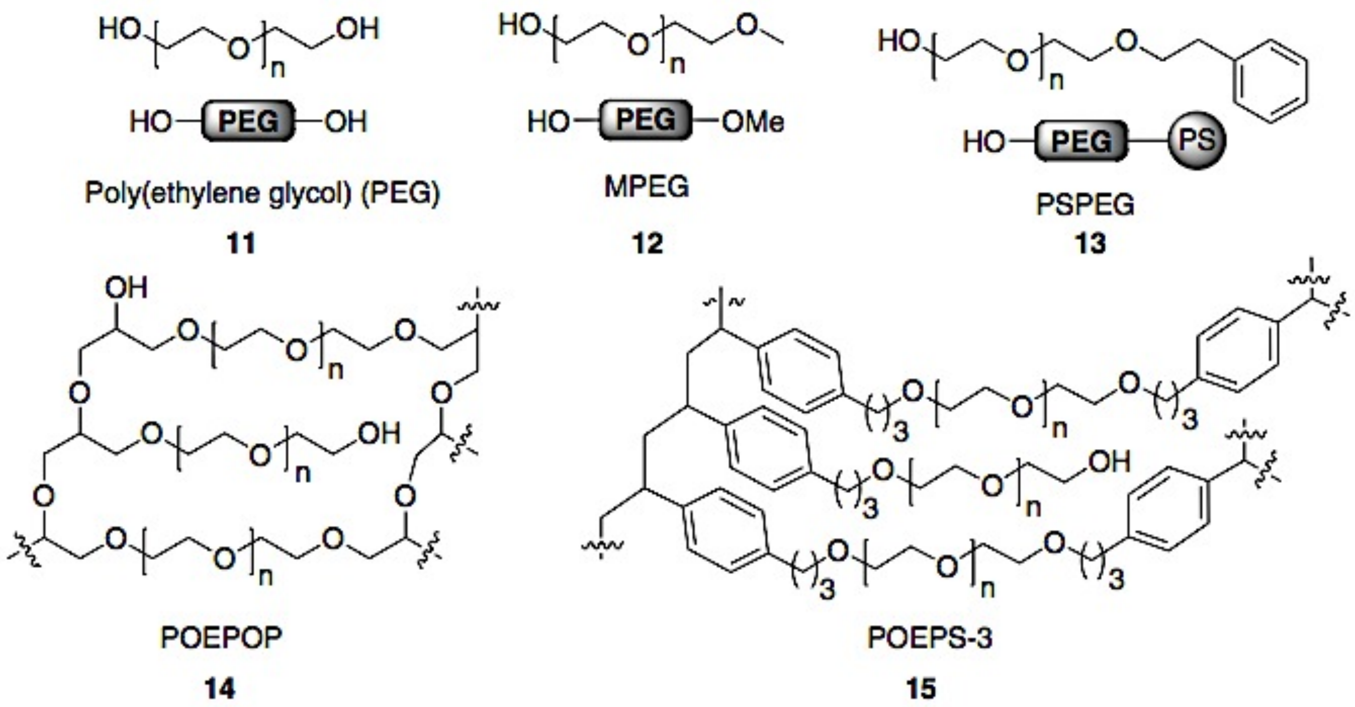
Supports for Supported Synthesis

There are two major classes of polymeric support: solid (insoluble but swell) polymer supports; and soluble polymer supports.



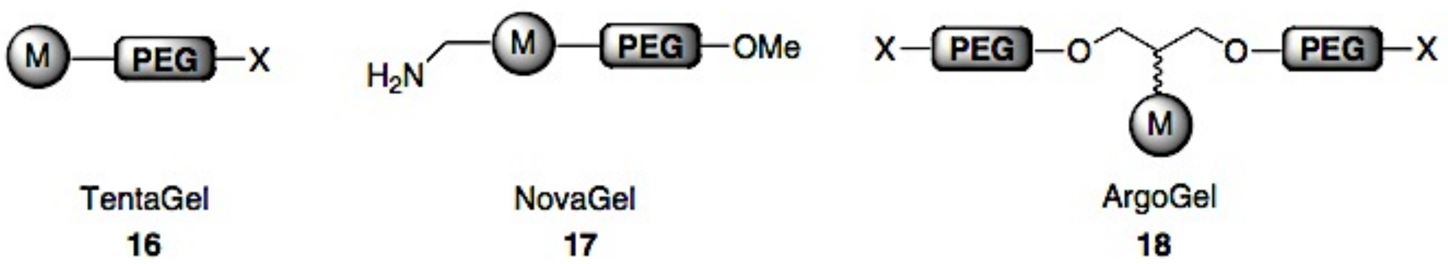
Supports for Supported Synthesis

There are two major classes of polymeric support: solid (insoluble but swell) polymer supports; and soluble polymer supports.



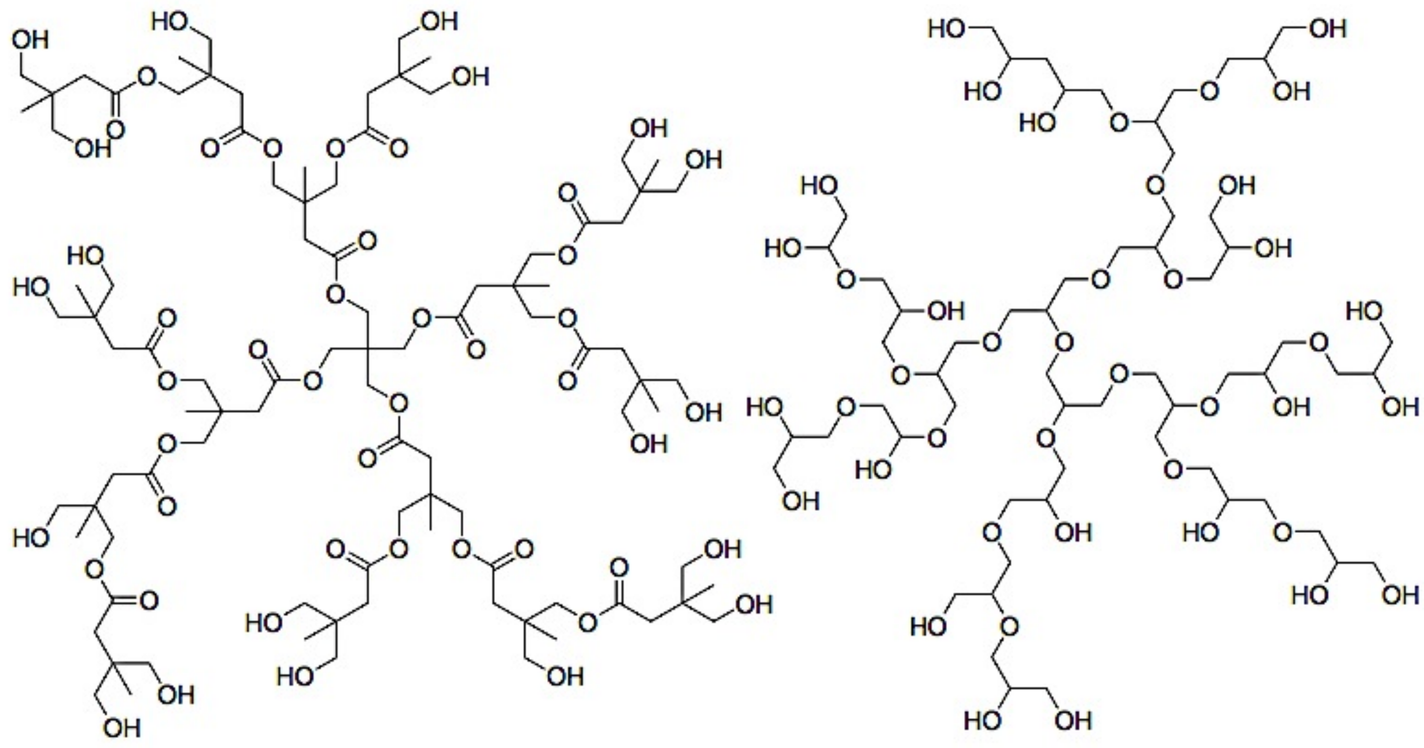
Scheme 15.4 *Soluble polymer supports.*

Supports for Supported Synthesis



Scheme 15.5 *Hybrid polymer supports.*

Supports for Supported Synthesis



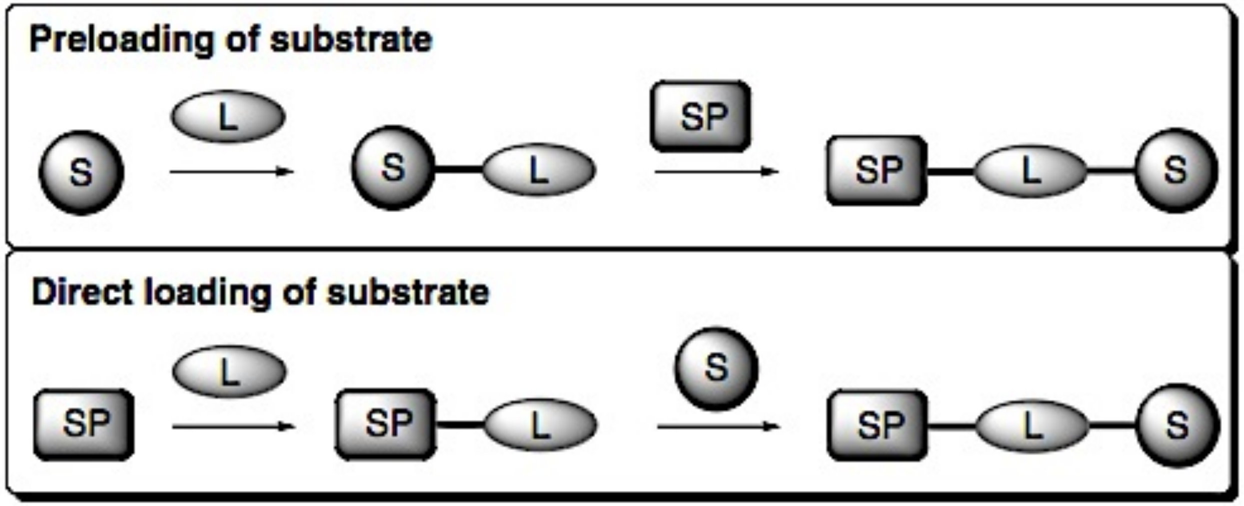
Polyester **19** Polyether **20**

Scheme 15.6 *Dendrimer supports for organic synthesis.*

Linkers for Solid-Supported Synthesis

Linker

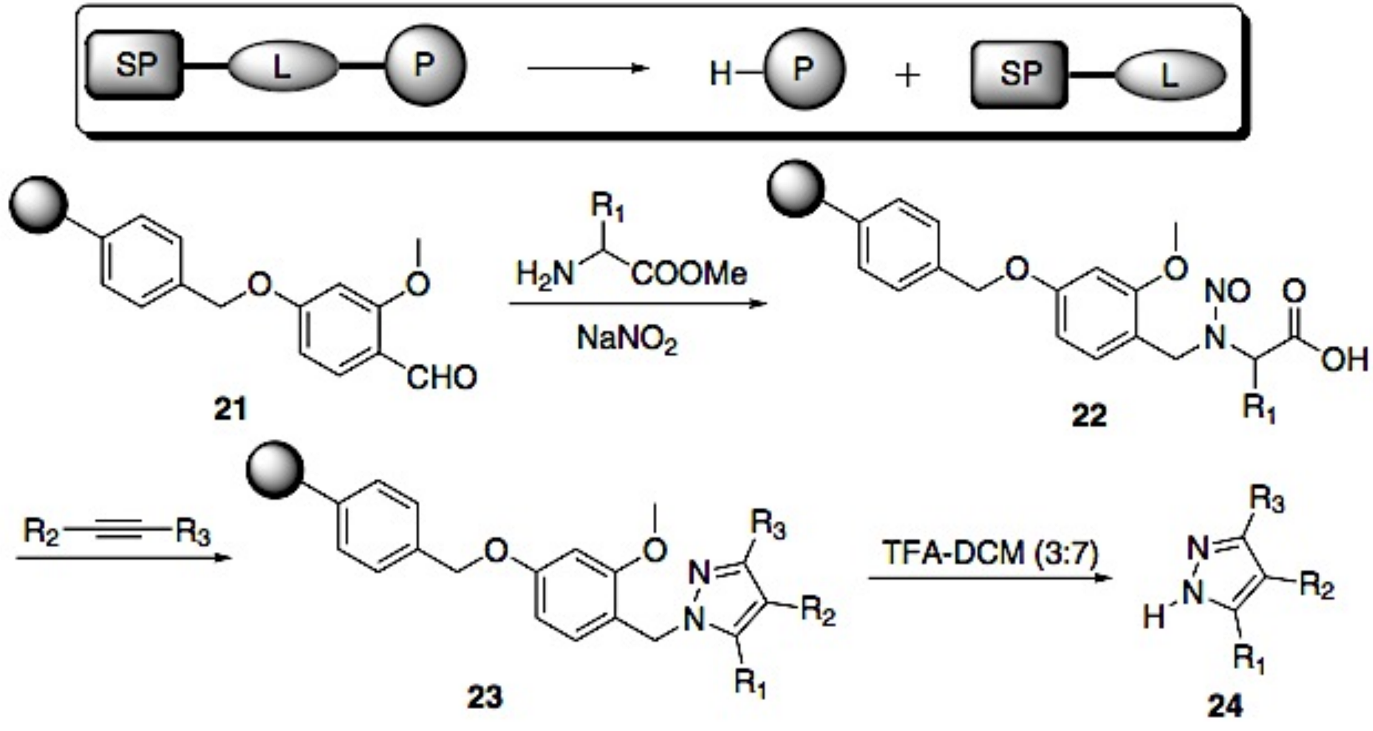
Bifunctional chemical moiety attaching a compound to a solid support or soluble support which can be cleaved to release compounds from the support



Scheme 15.7 *Linkage strategies for solid-supported synthesis.*

Linkers for Solid-Supported Synthesis

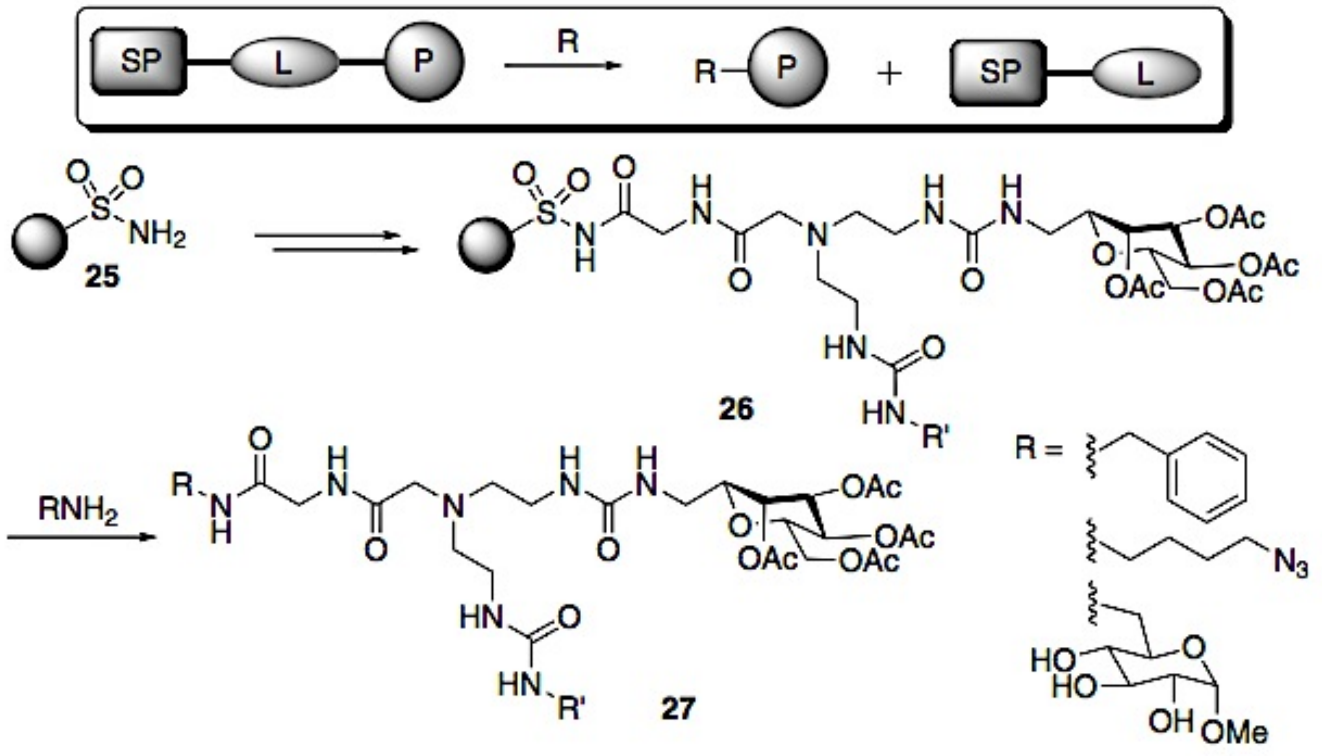
Traceless cleavage of linkers.



Scheme 15.8 *Traceless cleavage of linkers.*

Linkers for Solid-Supported Synthesis

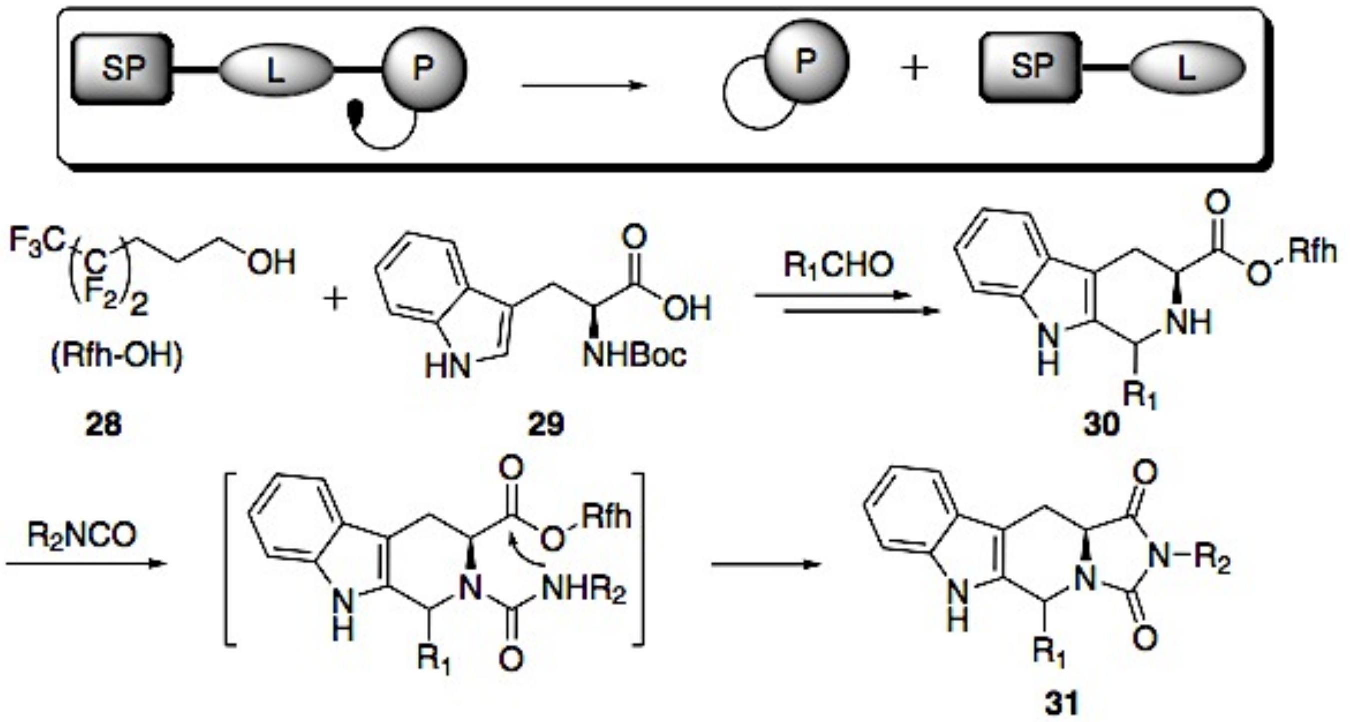
Functional cleavage of linkers.



Scheme 15.9 Functional cleavage of linkers.

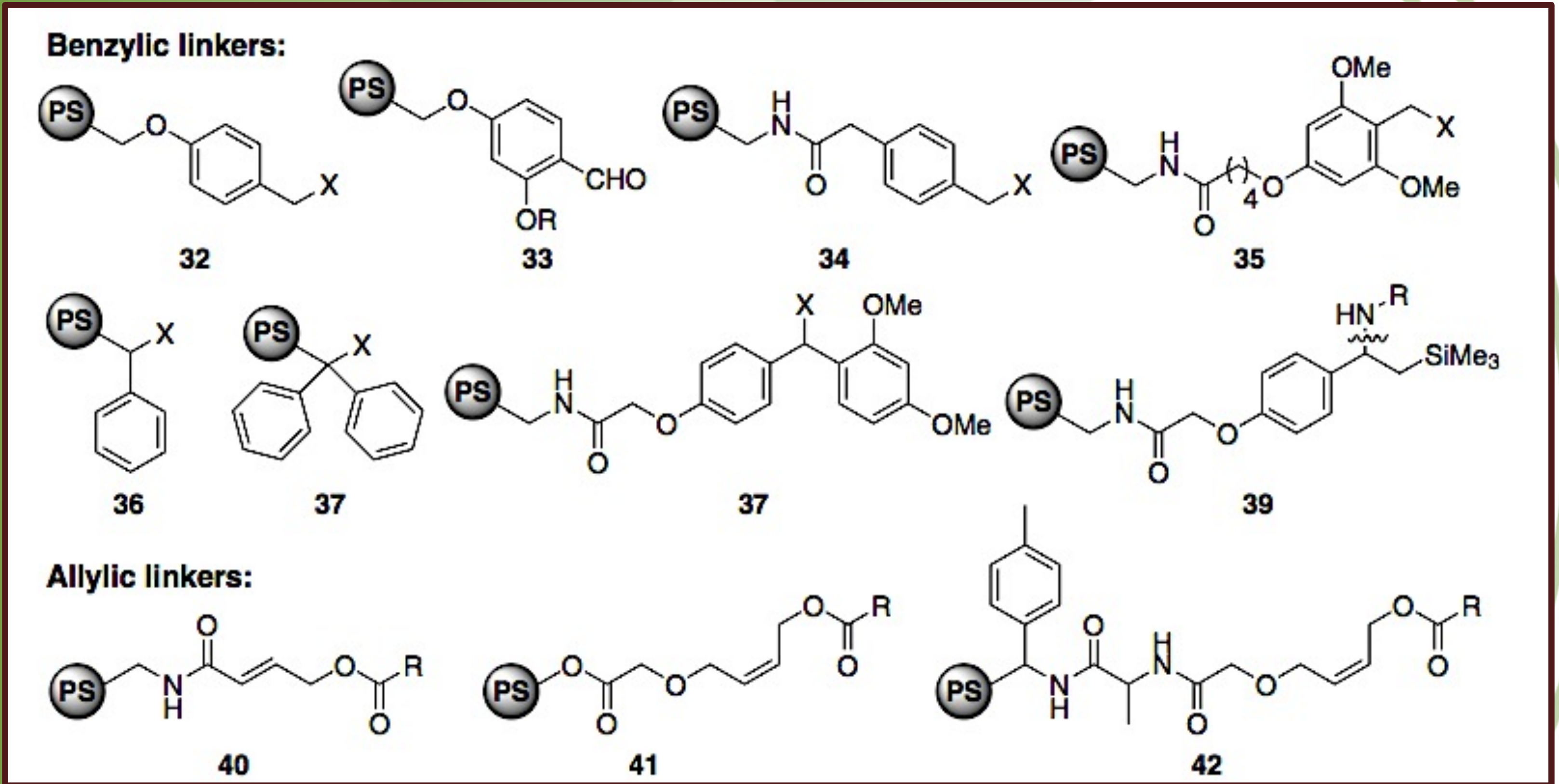
Linkers for Solid-Supported Synthesis

Cyclization cleavage of linkers

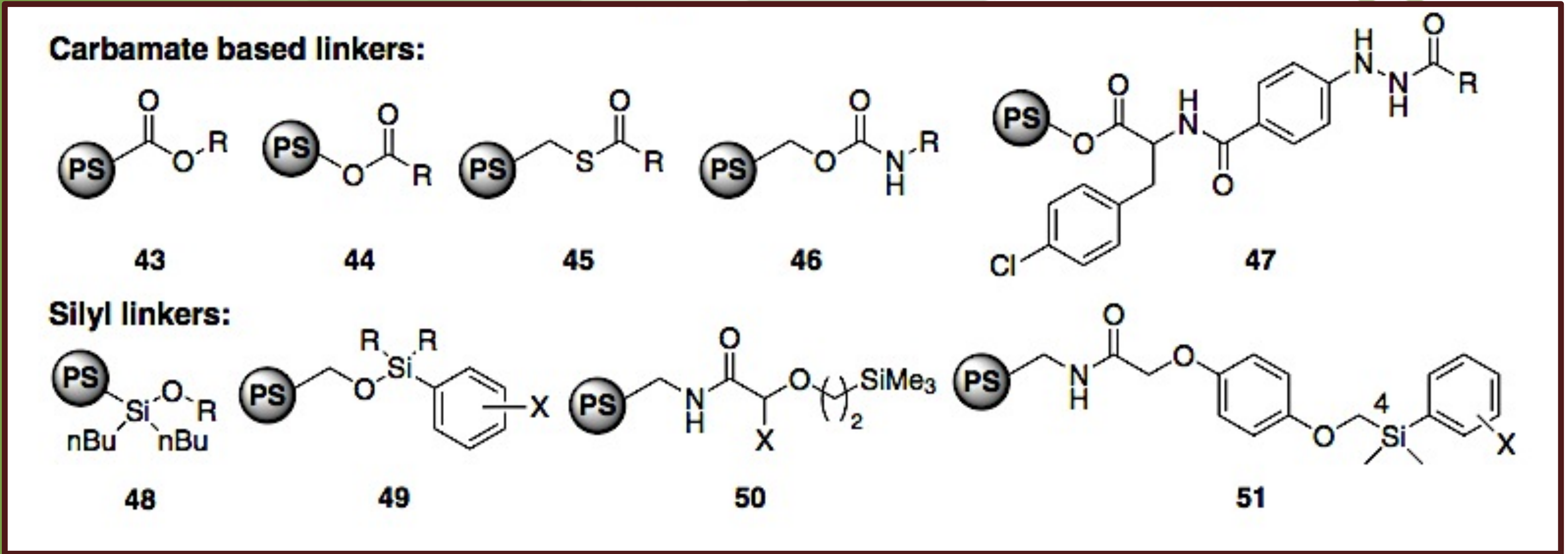


Scheme 15.10 Cyclization cleavage of linkers.

Linkers for Solid-Supported Synthesis



Linkers for Solid-Supported Synthesis



Reaction Monitoring

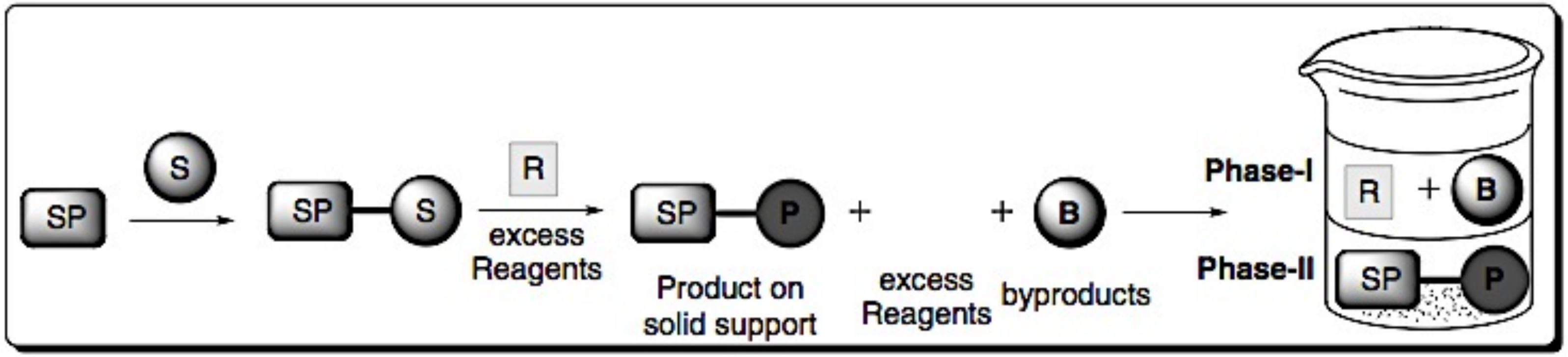
On-support monitoring and off-support monitoring are two methods used for the detection of reaction progress in solid-supported synthesis.

- **On-support monitoring is generally referred to as the nondestructive or on-bead method and represents compounds directly analyzed with the support.**
- **Off-support monitoring which is known as the off-bead or destructive method necessitates the cleavage of analytical samples from the support each time**

Separation Techniques

Phase separation

Phase separation is the separation of two different phases, such as "solid phase" and "liquid phase" or "two immiscible liquid phases," by trafficking the supported product in one phase and other excess reagents and by-products in another phase.

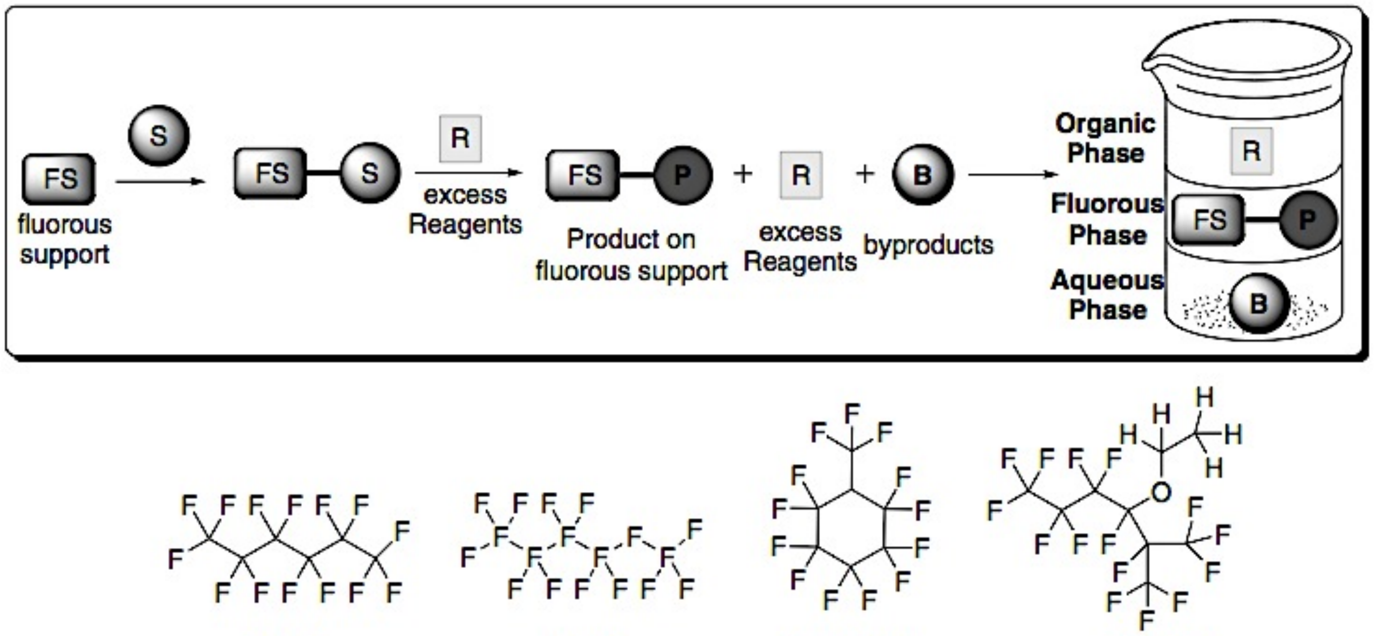


Scheme 15.12 *Solid-phase separation.*

Separation Techniques

Tag Strategy

The key to the technique is fluorous solid-phase extraction (FSPE) and fluorous solvent extraction which provides an easy and speedy method by which all intermediates and library members can be purified.



Scheme 15.13 *Fluorous phase separation by tag strategy and common fluorinated solvents.*

Separation Techniques

Tag Strategy

In fluorous liquid-phase extraction (FLPE), an organic–aqueous–fluorous triphasic extraction system can be used for product purification, since the fluorous phase is orthogonal to the organic and aqueous phases.

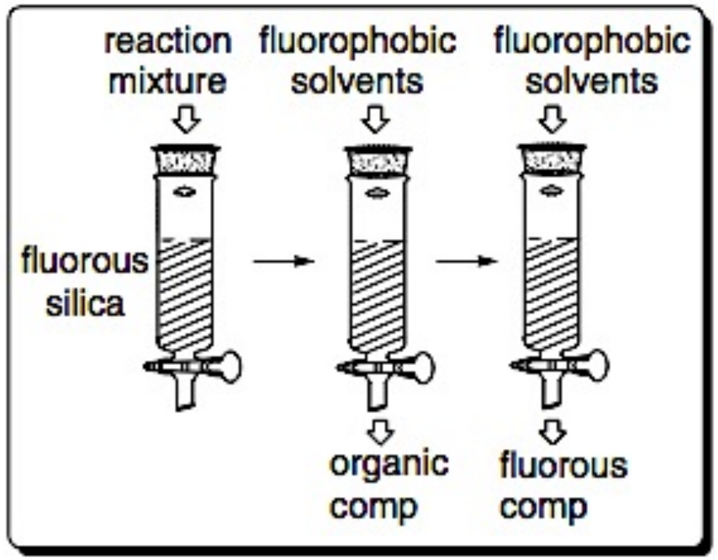
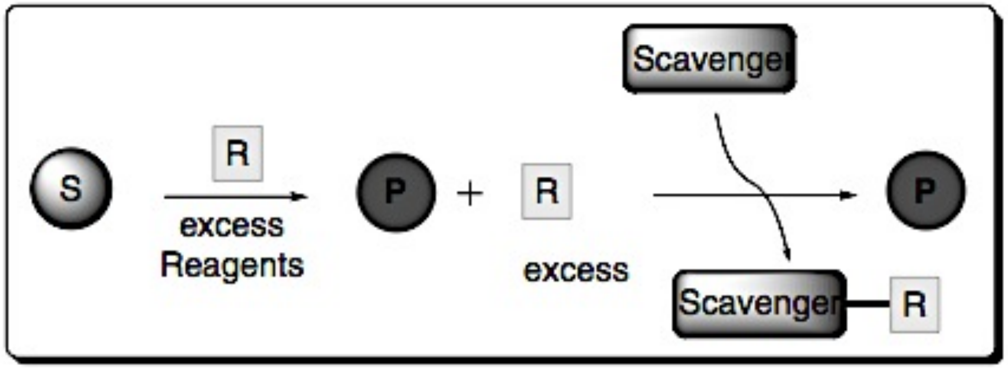


Figure 15.2 *Fluorous solid-phase extraction.*

Separation Techniques

Scavenger

Supported scavengers are reactive species that selectively sequester by-products and excess reagents from the reaction mixture and separated by filtration

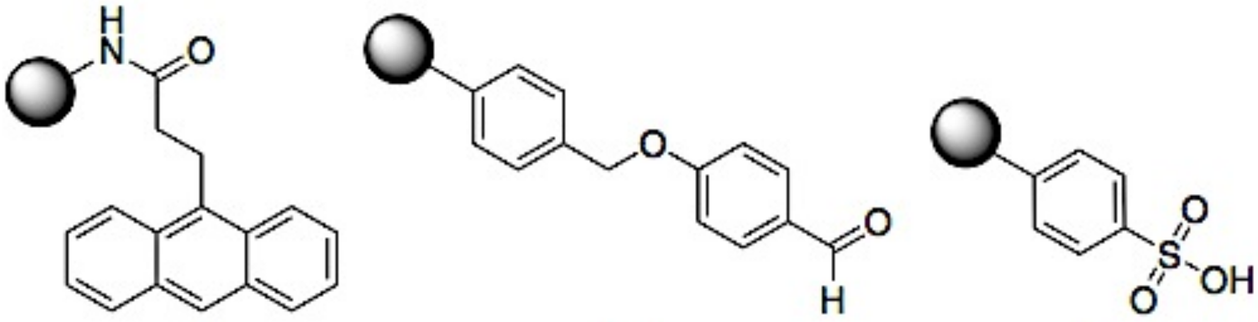


Scheme 15.14 *Separation by scavengers.*

Separation Techniques

Scavenger

Supported scavengers are reactive species that selectively sequester by-products and excess reagents from the reaction mixture and separated by filtration



52 **53** **54**

Scheme 15.15 *Examples of scavengers.*

Automation Techniques

Schematic presentation of automation where S1–S4 are the injection of different starting compounds, SR1–SR5 are a series of supported reagents, SS is supported scavengers for purification by scavenging by-product and excess starting material and finally P1–P4 are product outlets.

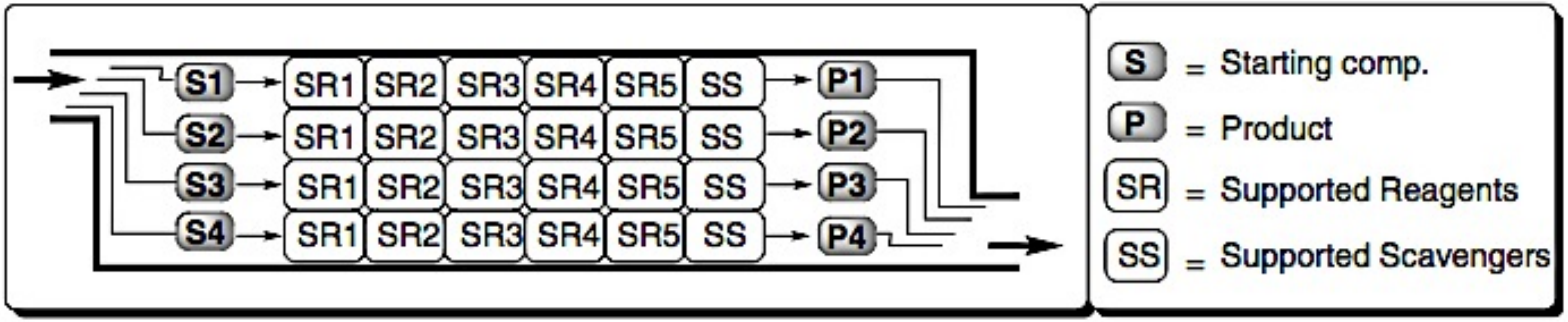
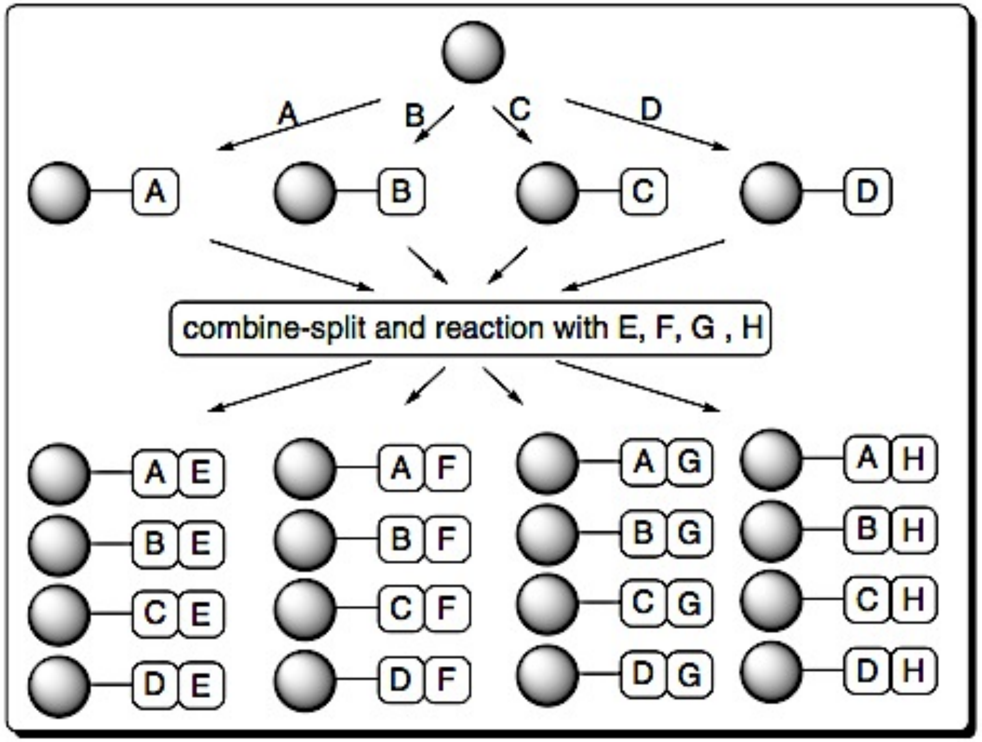


Figure 15.3 *Automated parallel synthesis in solid-supported synthesis.*

Automation Techniques

Split and combine (split and mix) technique

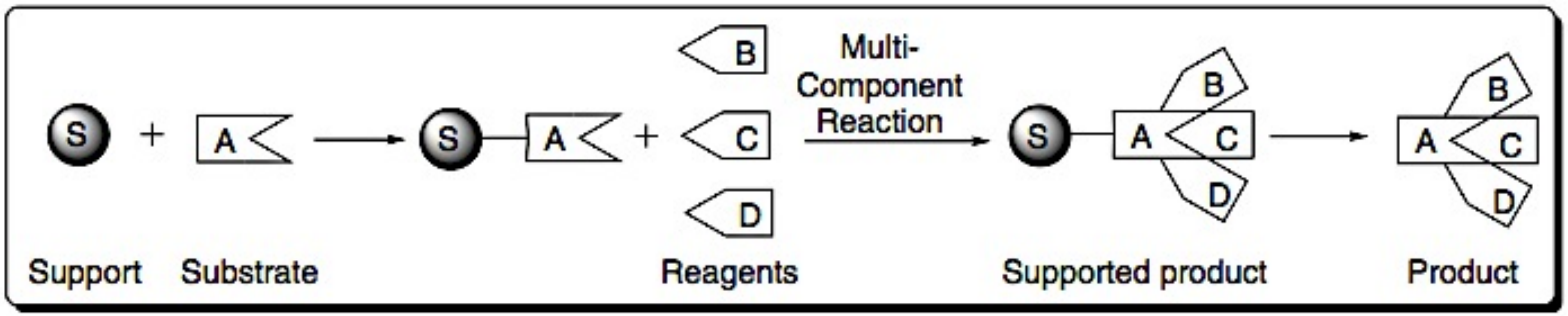


Scheme 15.16 *Split and combine protocol.*

Solid-Supported Heterocyclic Chemistry

Multicomponent reaction

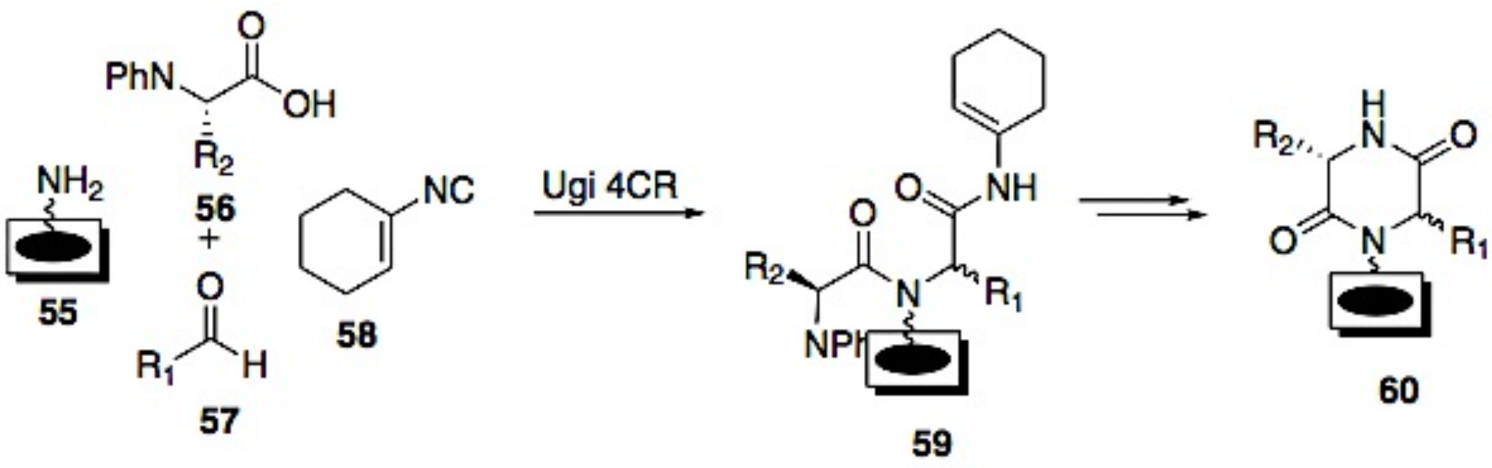
An MCR is an evolutionary approach for introducing structural diversity in a single-step synthetic operation.



Scheme 15.17 Supported multicomponent reaction.

Solid-Supported Heterocyclic Chemistry

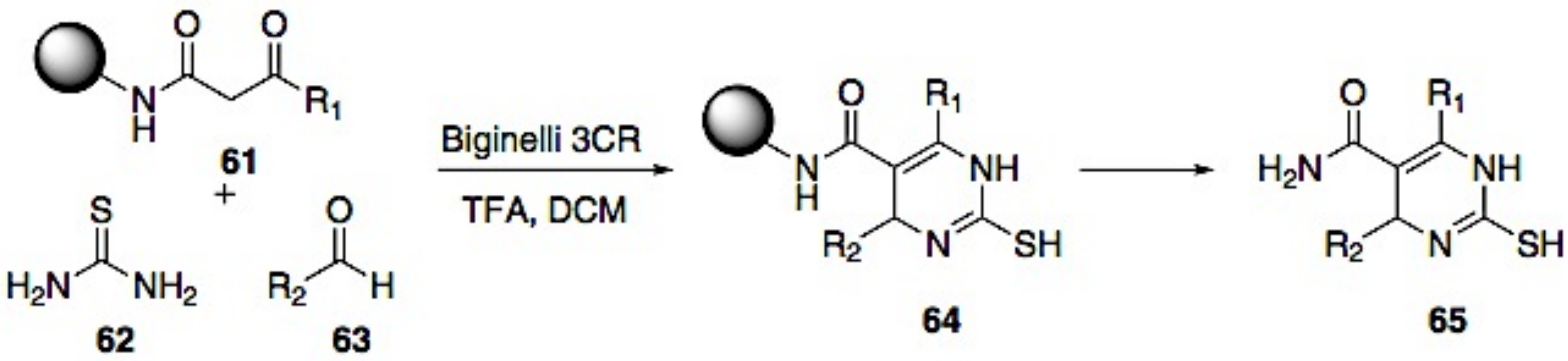
Ugi Reaction



Scheme 15.18 *Four-component Ugi reaction.*

Solid-Supported Heterocyclic Chemistry

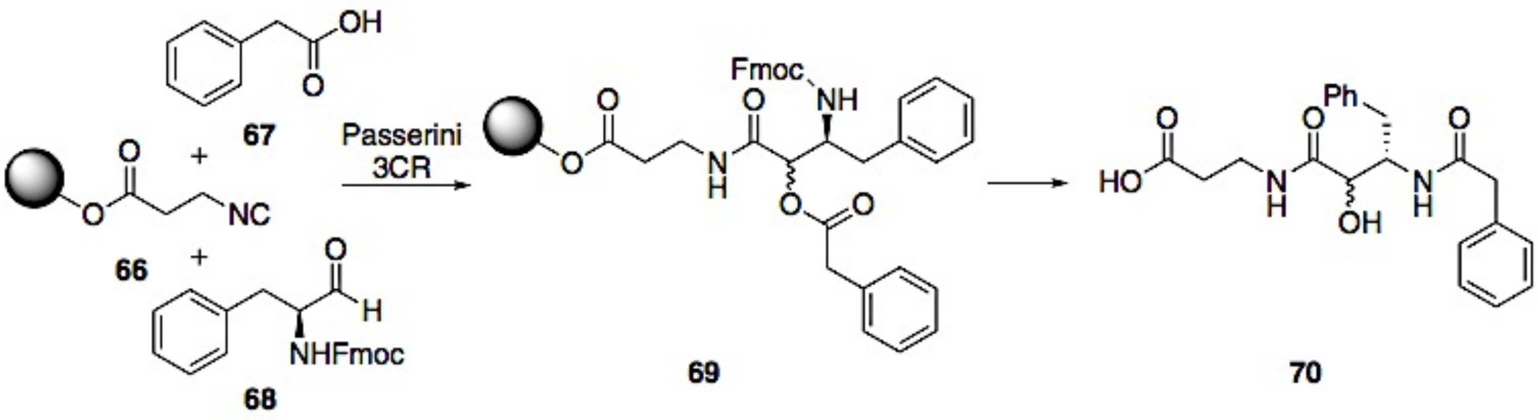
Biginelli Reaction



Scheme 15.19 Three-component Biginelli reaction.

Solid-Supported Heterocyclic Chemistry

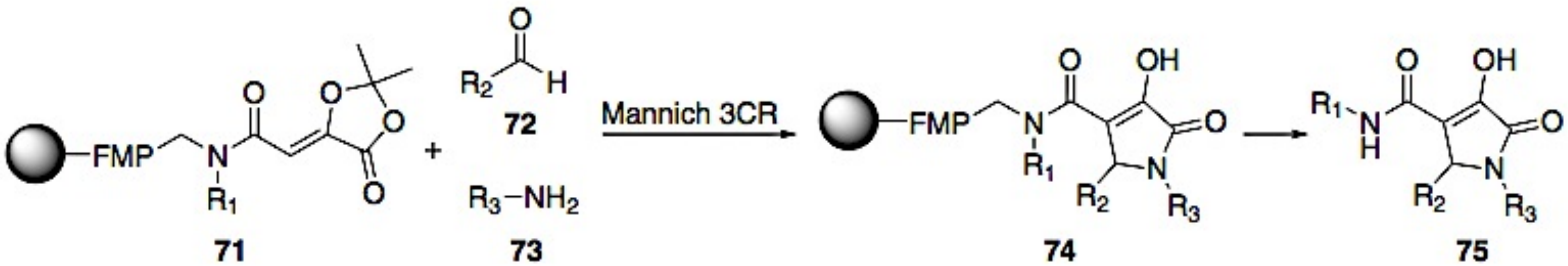
Passerini Reaction



Scheme 15.20 *Three-component Passerini reaction.*

Solid-Supported Heterocyclic Chemistry

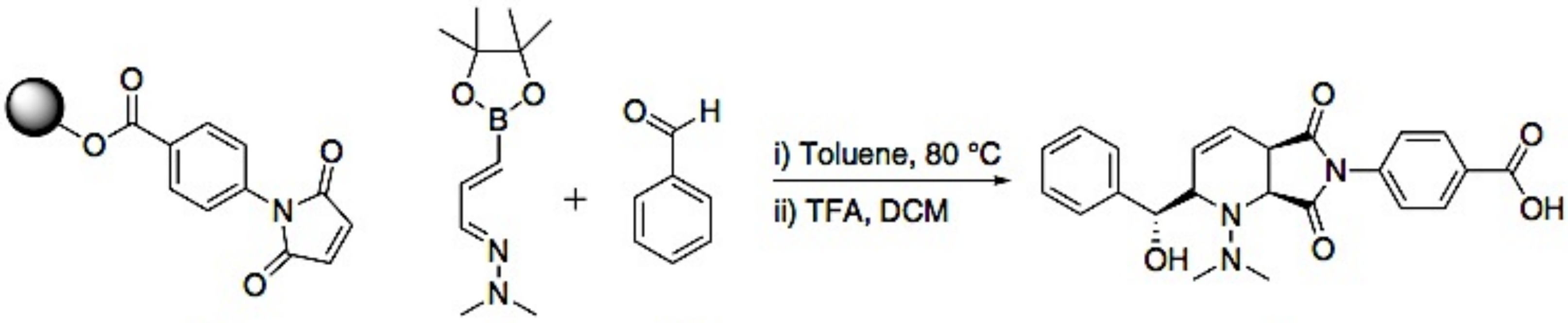
Mannich Reaction



Scheme 15.21 *Three-component Mannich reaction.*

Solid-Supported Heterocyclic Chemistry

Diels-Alder Reaction

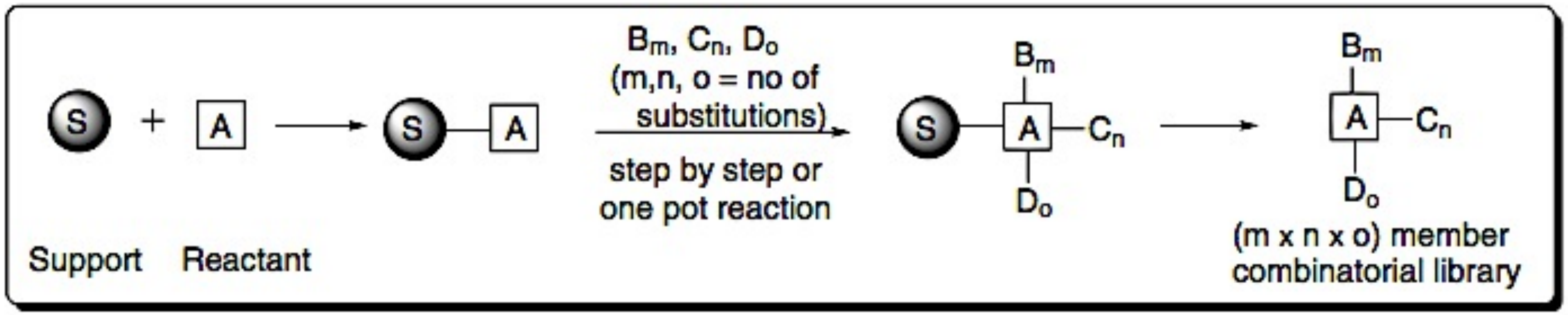


76 77 78 79

Scheme 15.22 *Three-component Diels–Alder reaction.*

Solid-Supported Heterocyclic Chemistry

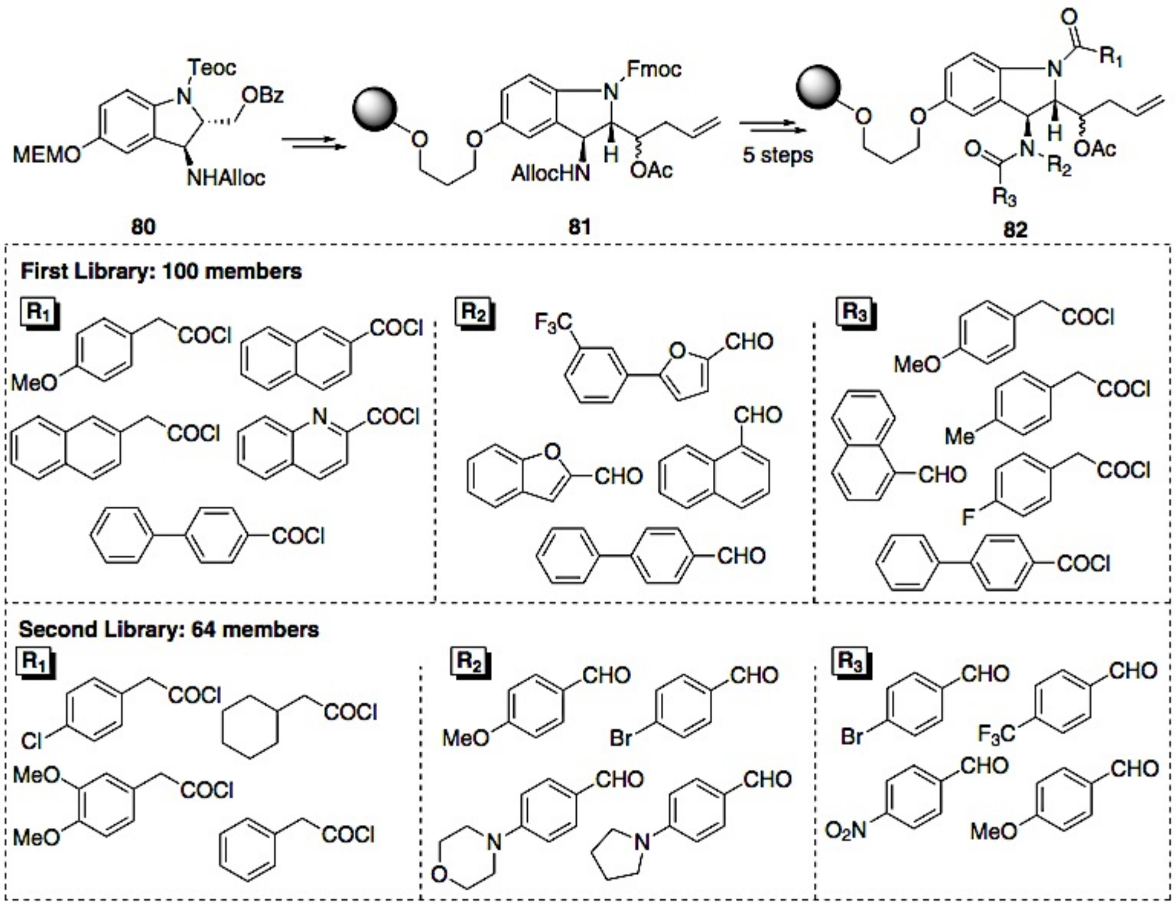
Combinatorial library synthesis



Scheme 15.23 *Combinatorial library synthesis on solid support.*

Solid-Supported Heterocyclic Chemistry

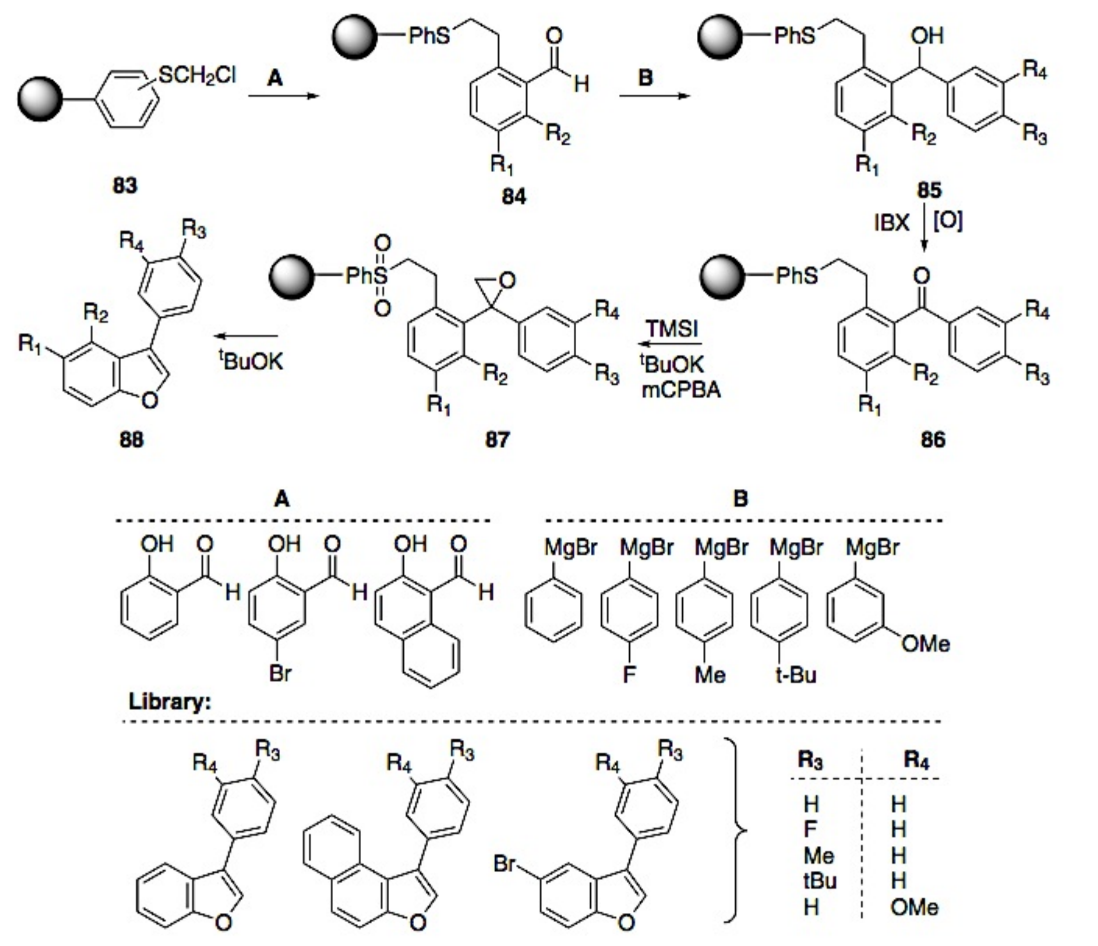
Combinatorial library synthesis



Scheme 15.24 *Solid-supported synthesis for the indoline based library generation.*

Solid-Supported Heterocyclic Chemistry

Combinatorial library synthesis



Scheme 15.25 Solid-supported bezofuran library synthesis.

Solid-Supported Heterocyclic Chemistry

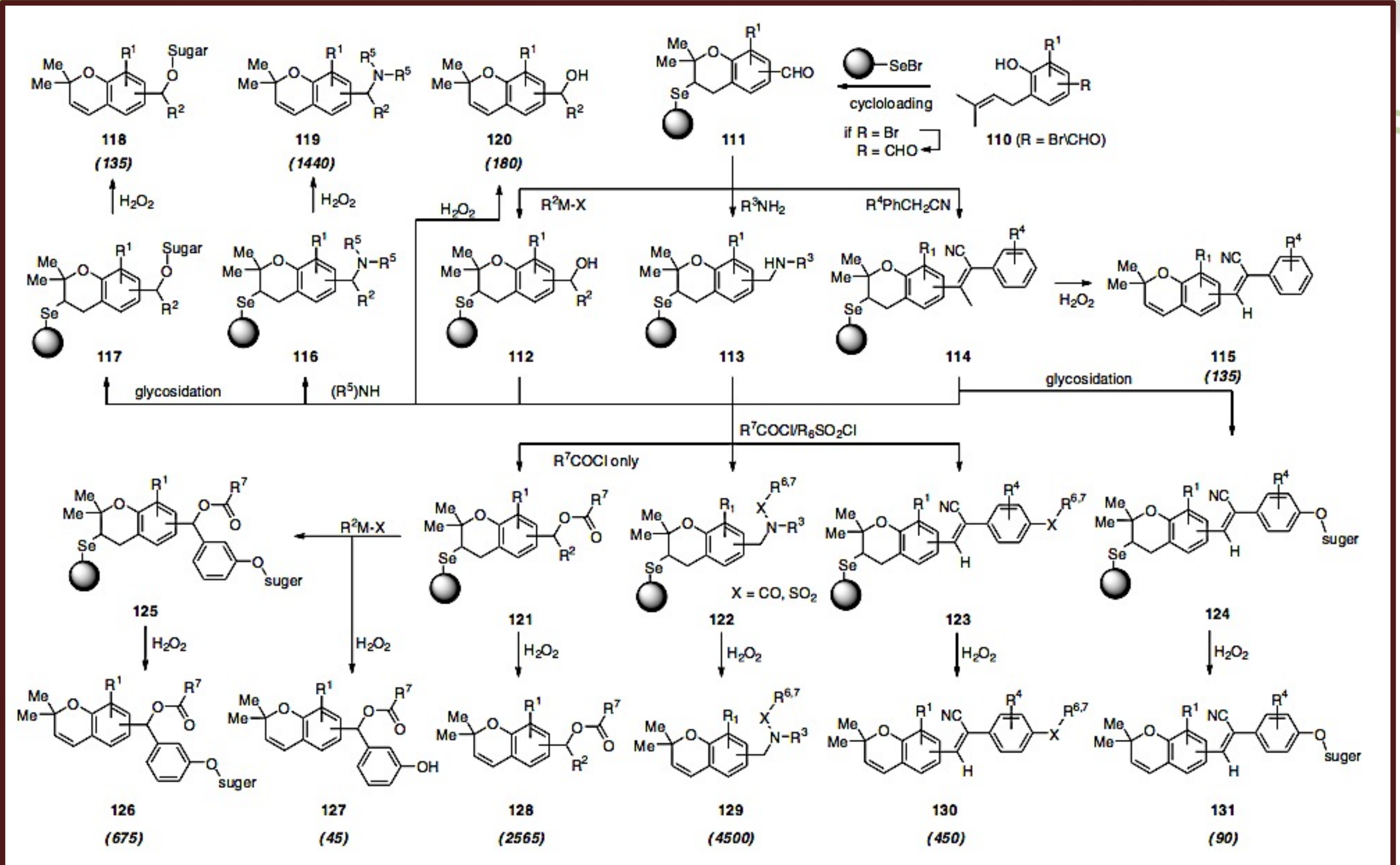
Diversity-oriented synthesis (DOS)

Diversity-oriented synthesis (DOS) is a strategy for quick access to molecule libraries with an emphasis on skeletal diversity.

Diversity-oriented organic synthesis has a tremendous impact in effectively utilizing the chemical space for drug discovery. A large number of compounds needed for structure–activity relationship studies have been generated by adopting a macromolecular carrier in DOS.

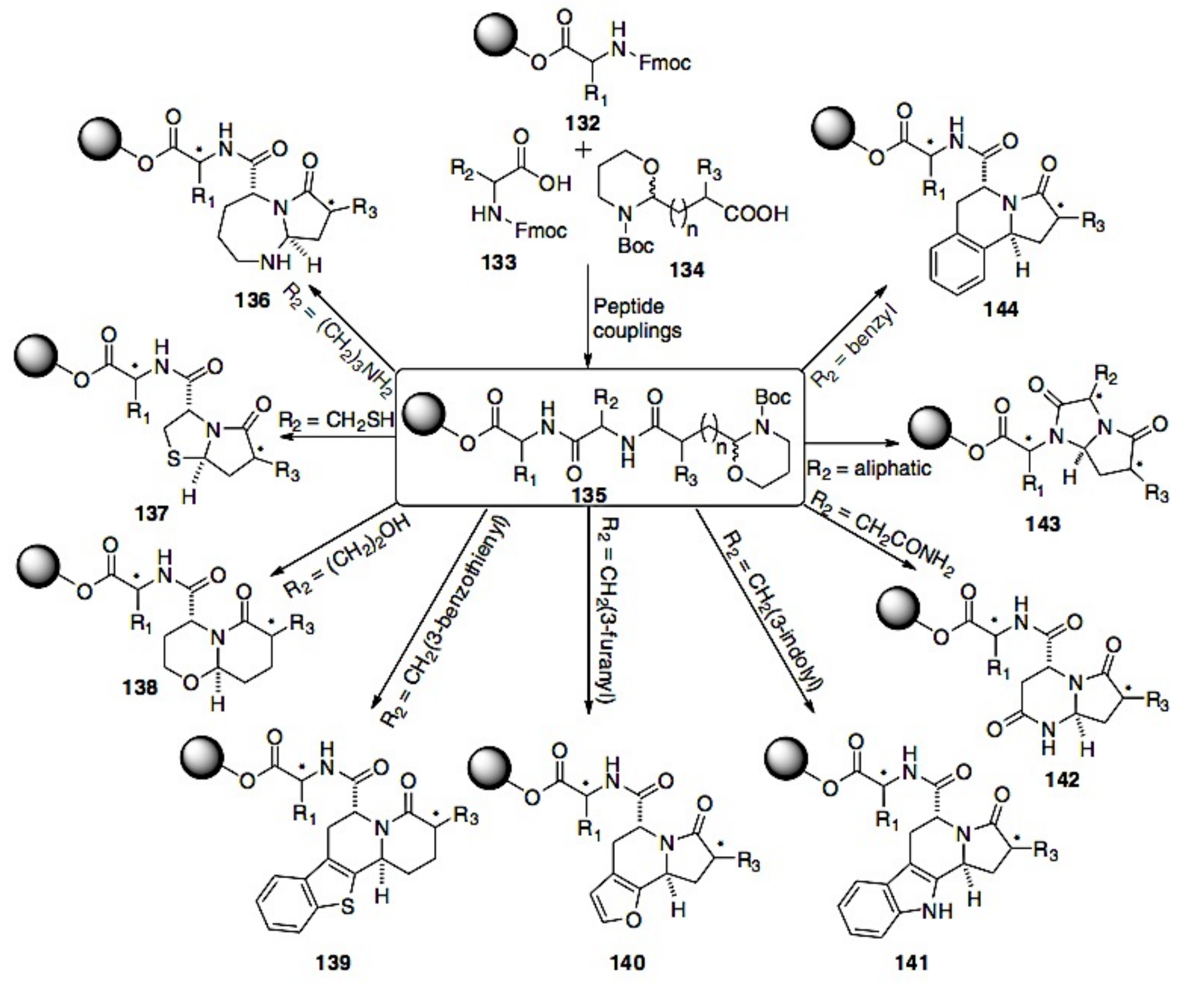
Solid-Supported Heterocyclic Chemistry

Diversity-oriented synthesis (DOS)



Solid-Supported Heterocyclic Chemistry

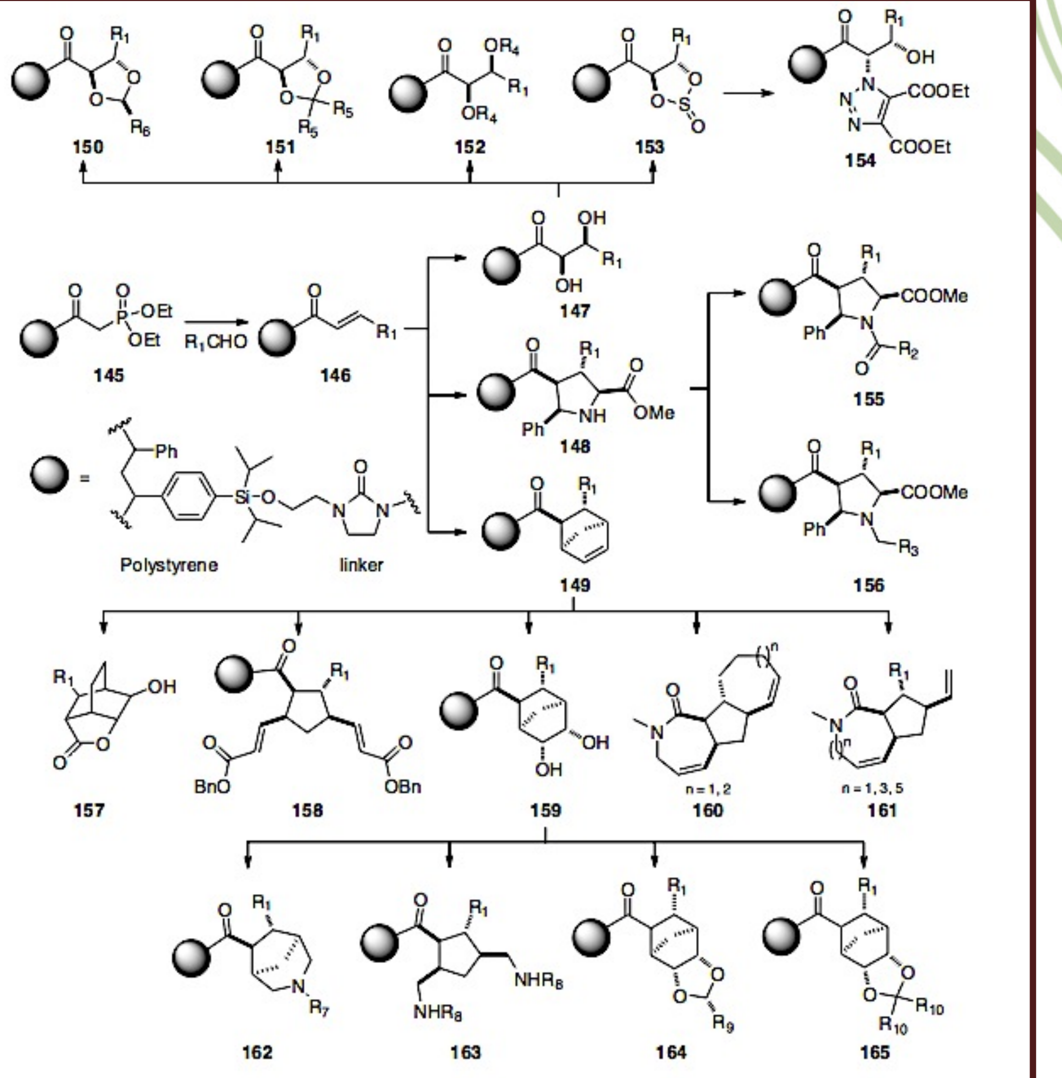
Diversity-oriented synthesis (DOS)



Scheme 15.28 Meldal's diversity-oriented synthesis.

Solid-Supported Heterocyclic Chemistry

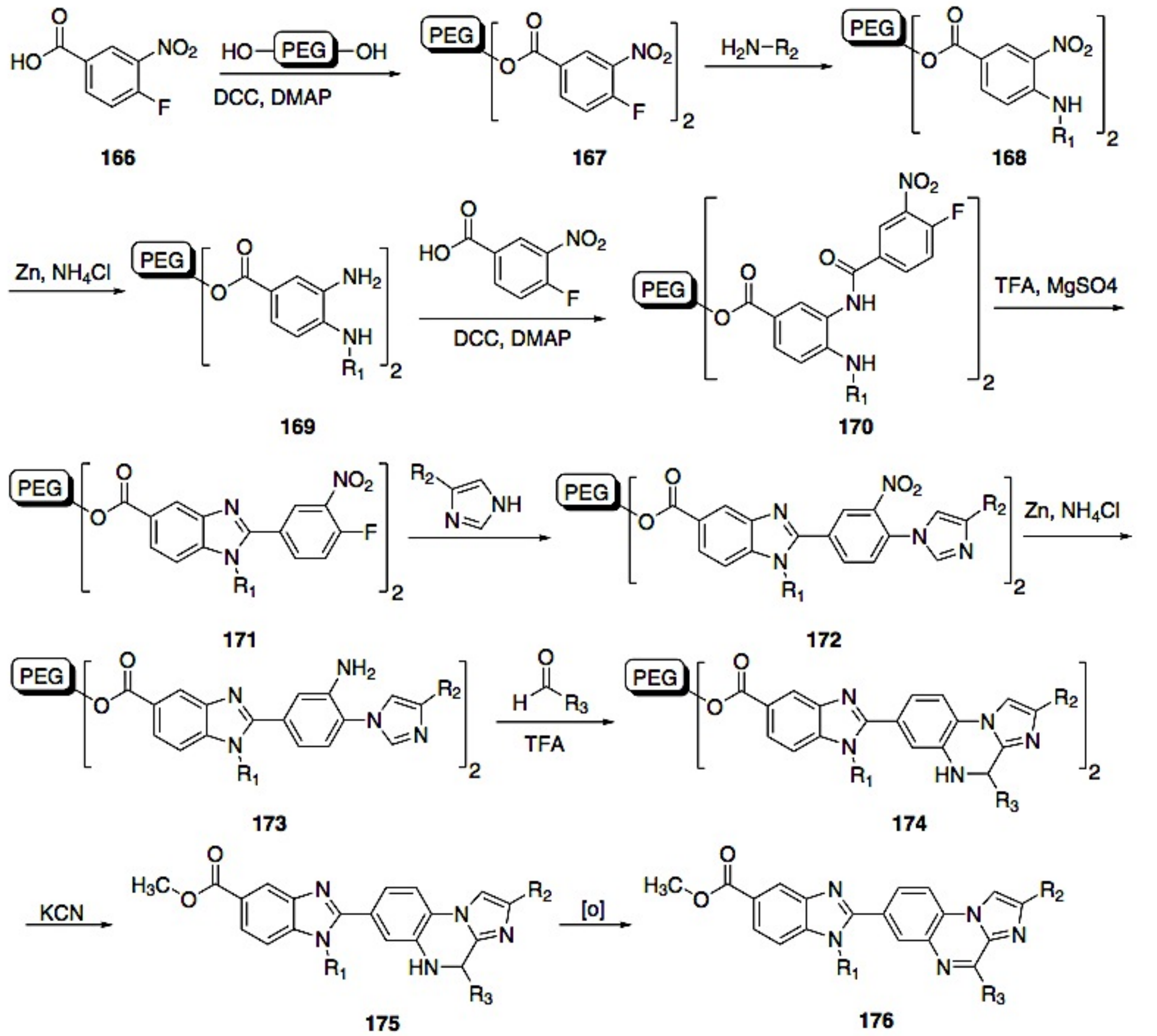
Diversity-oriented synthesis (DOS)



Scheme 15.29 Diversity-oriented synthesis of 242 compounds.

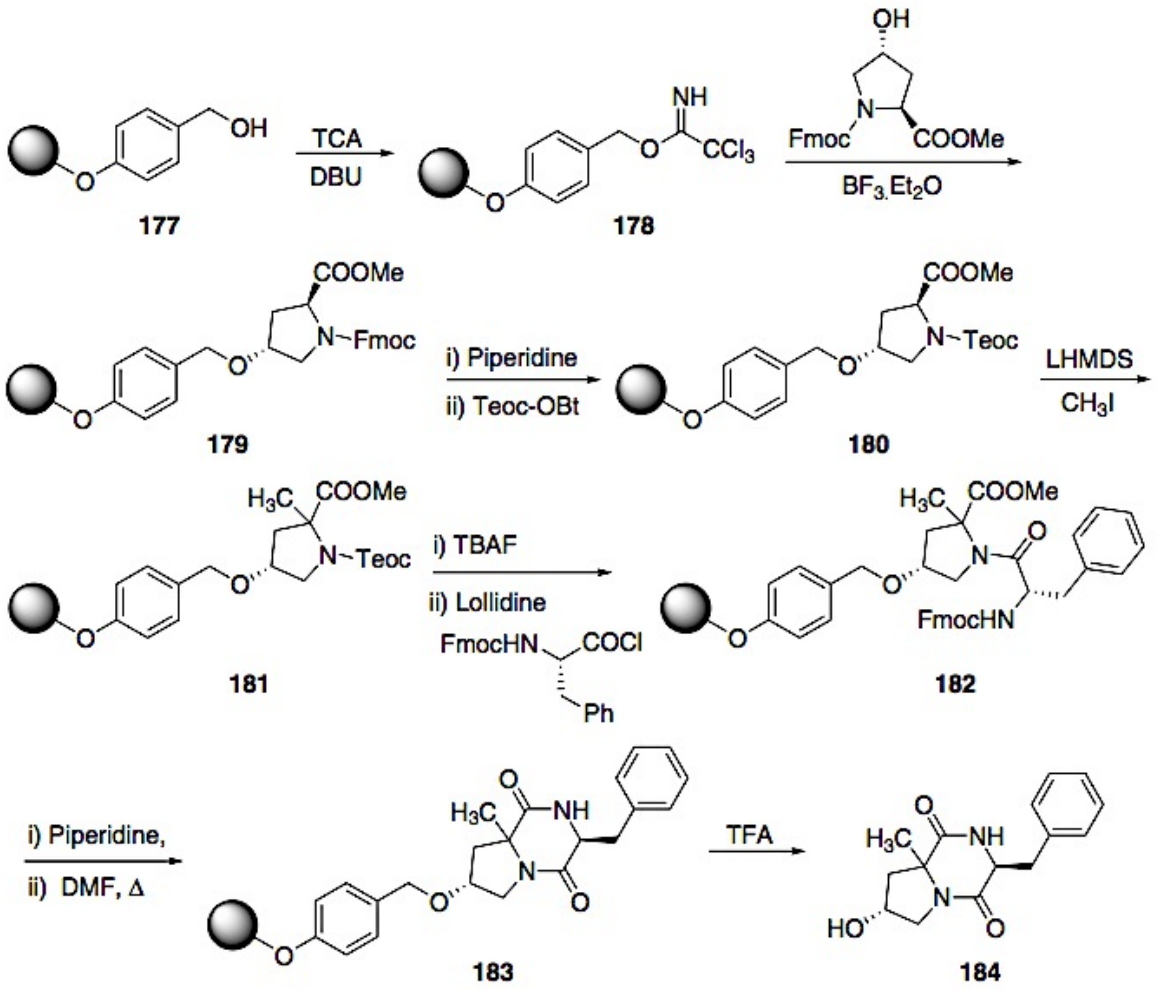
Solid-Supported Heterocyclic Chemistry

Multistep Parallel Synthesis



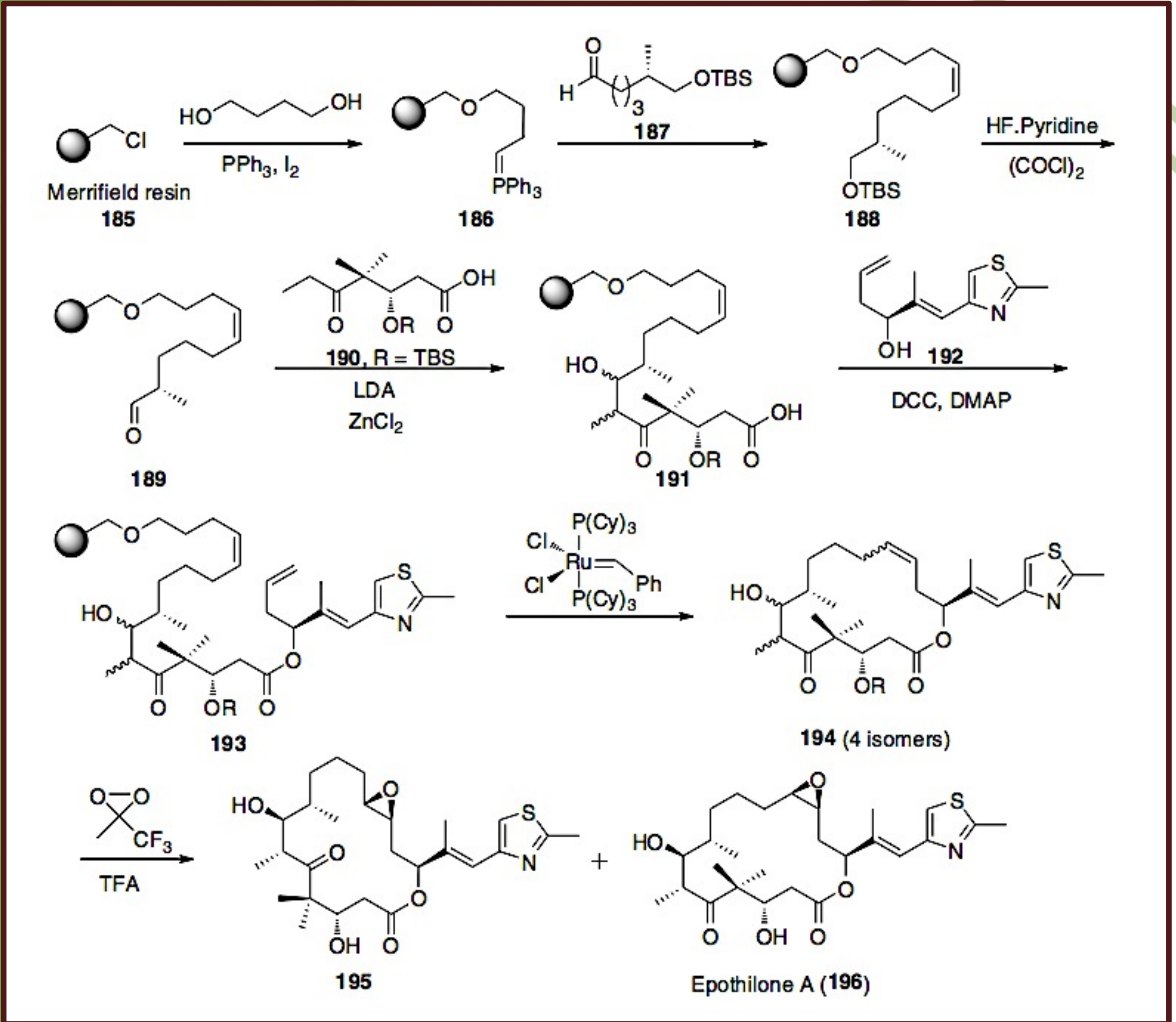
Solid-Supported Heterocyclic Chemistry

Multistep Parallel Synthesis

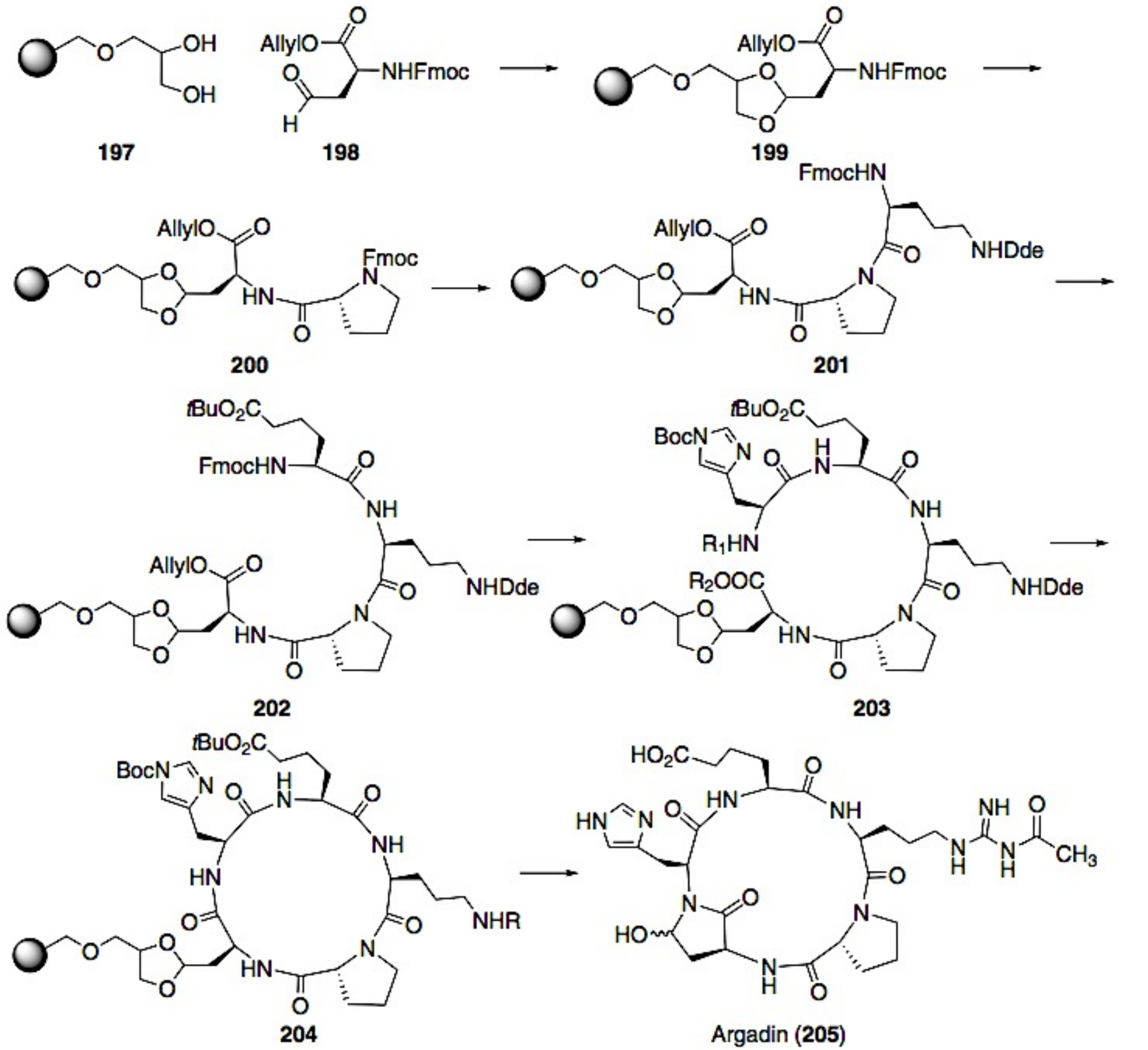


Scheme 15.31 *Multistep synthesis of 2,5-diketopiperazines on solid support.*

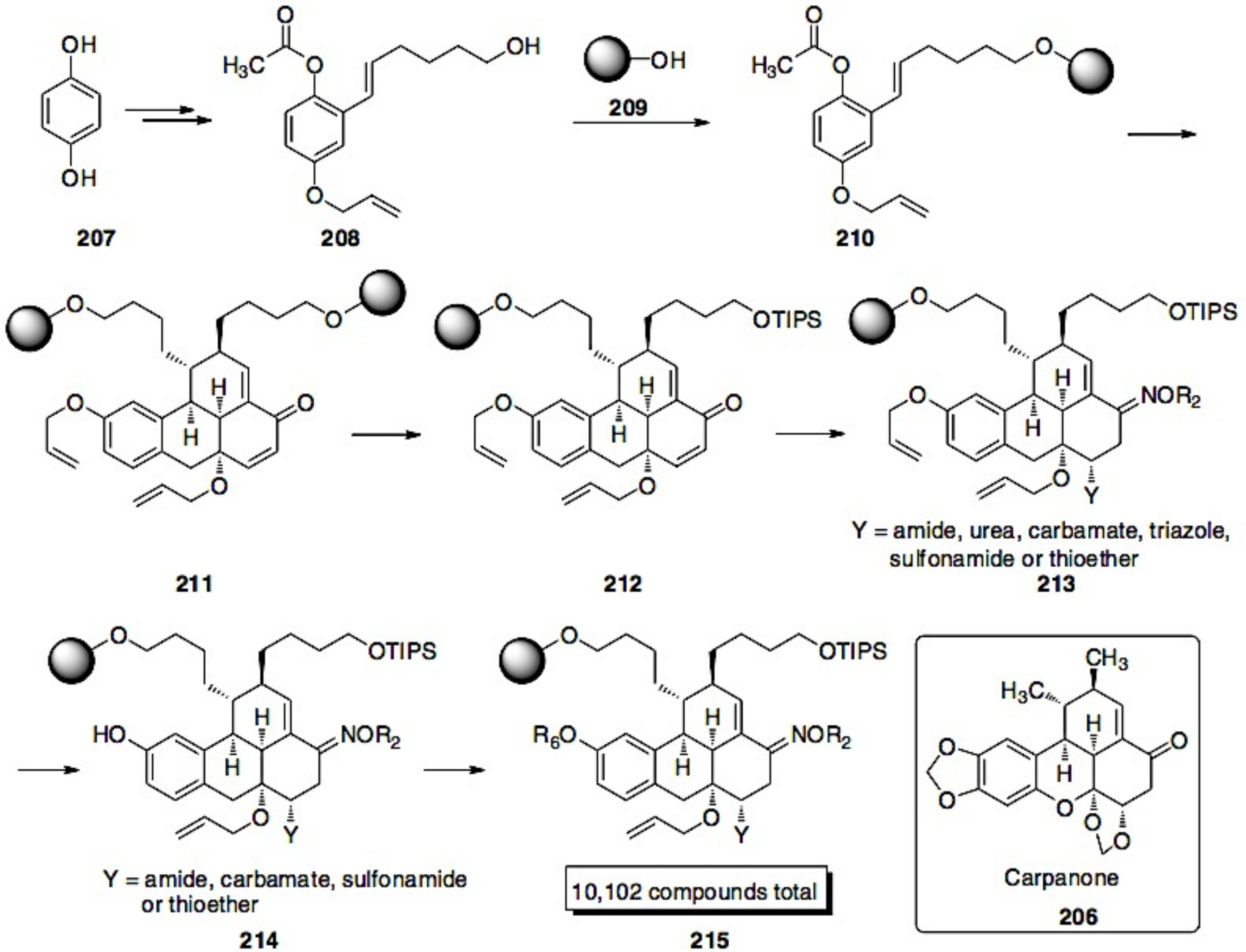
Solid-Supported Natural Products Chemistry



Solid-Supported Natural Products Chemistry

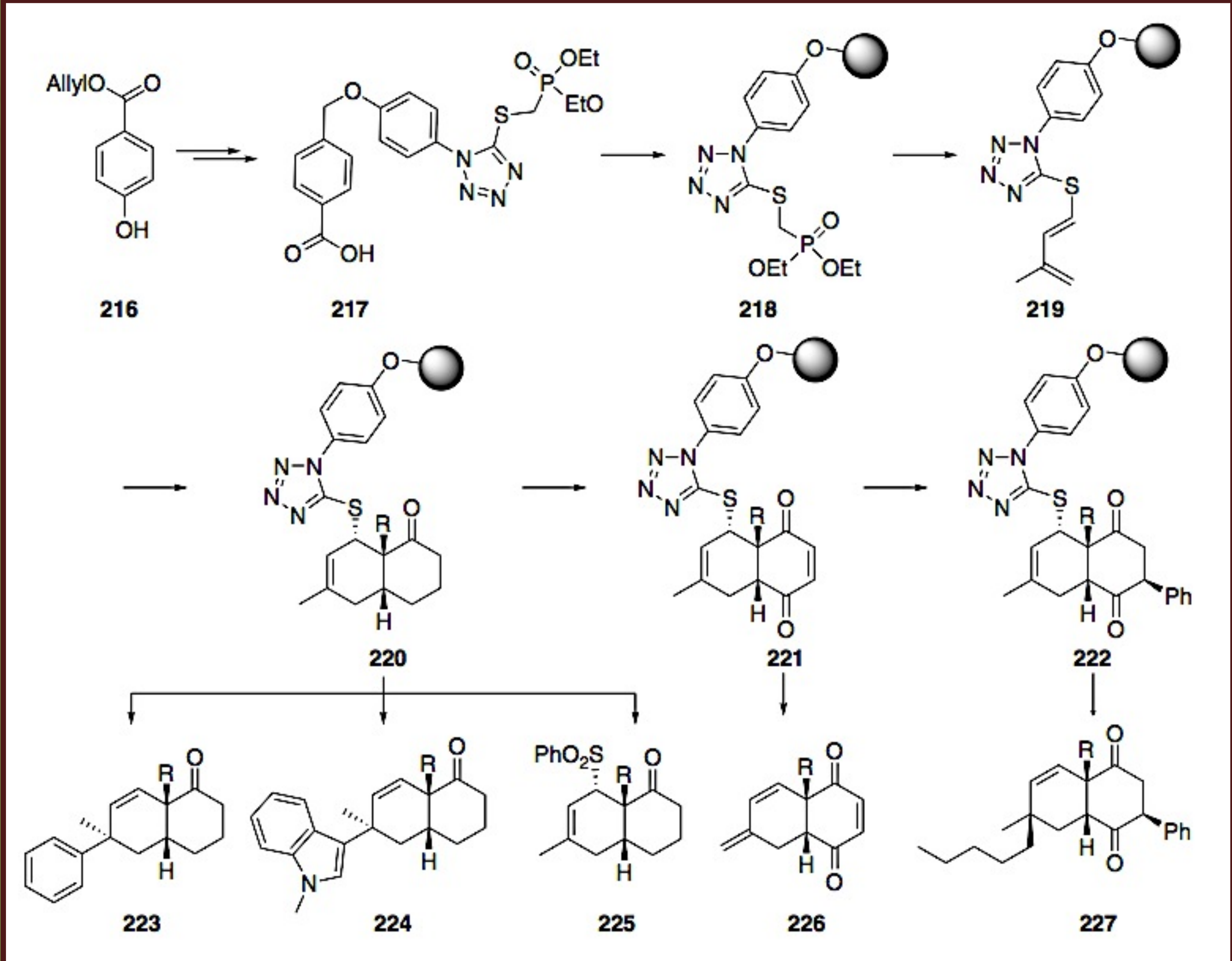


Solid-Supported Natural Products Chemistry

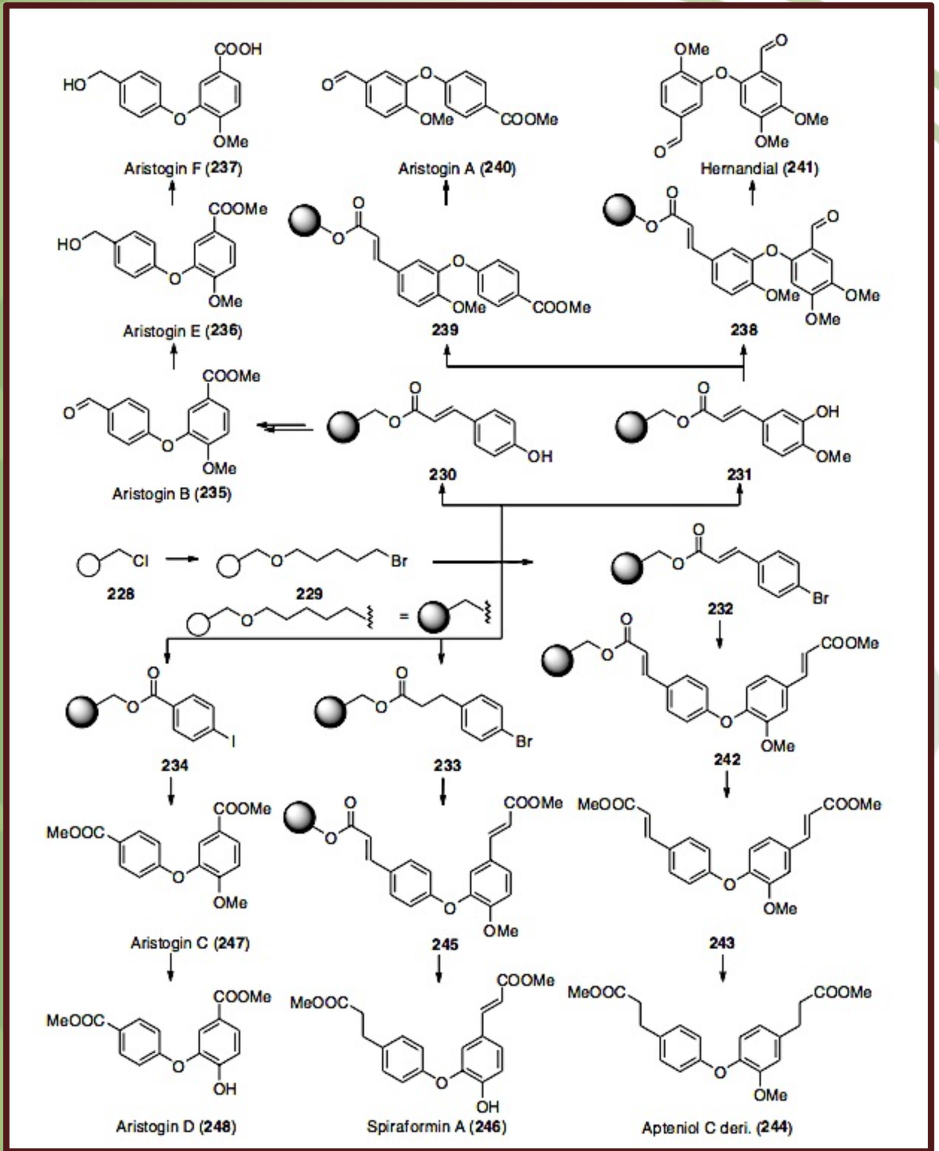


Scheme 15.34 *Shair and co-workers' 10 000-membered library of carpanone-like molecules.*

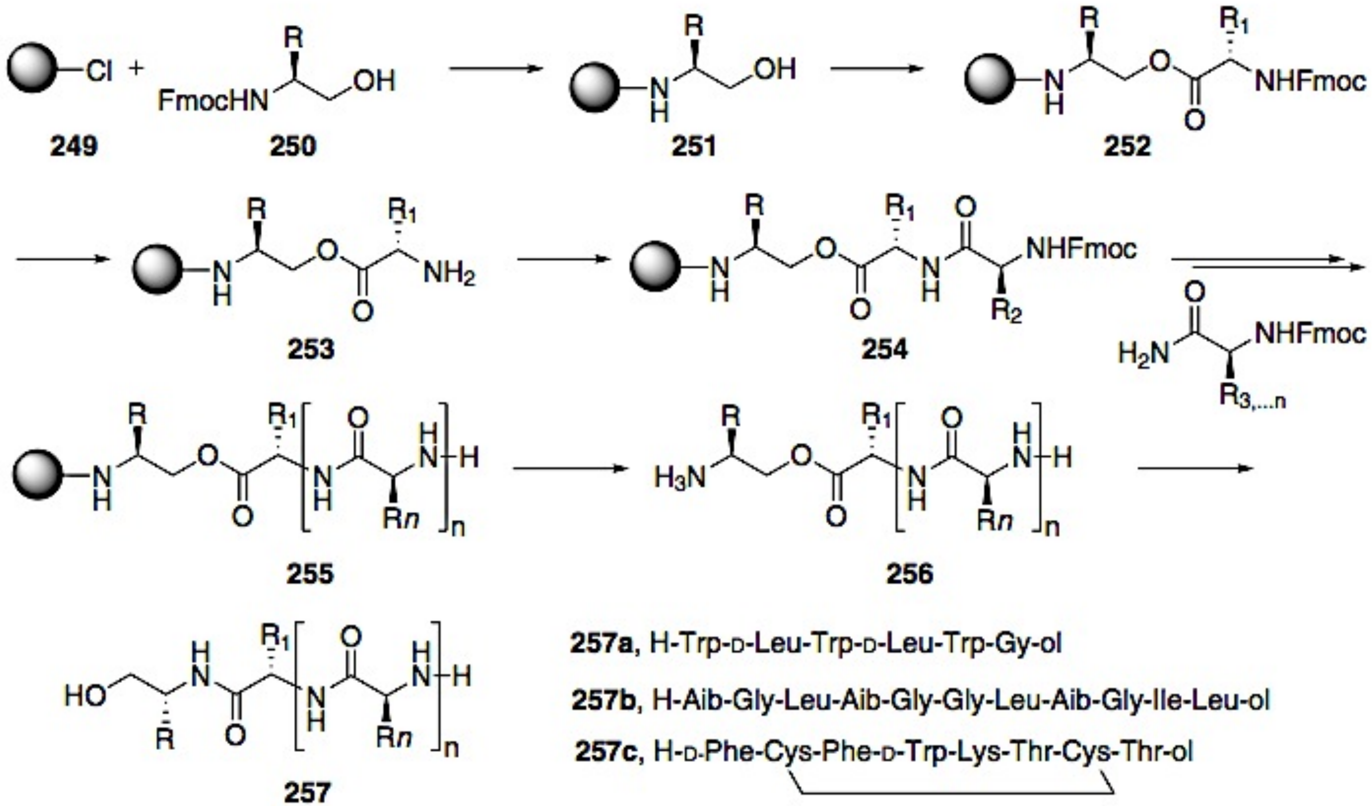
Solid-Supported Natural Products Chemistry



Solid-Supported Natural Products Chemistry

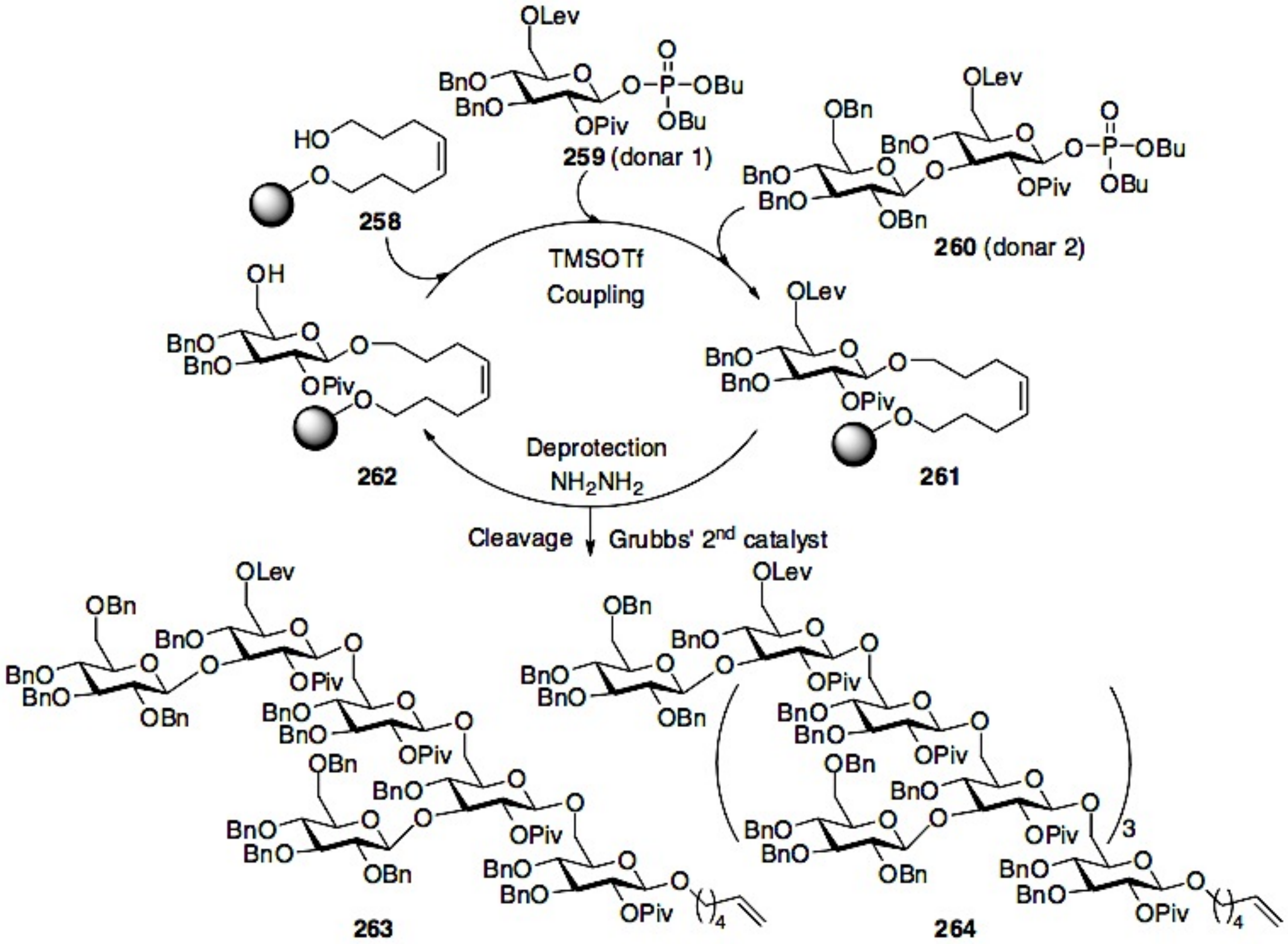


Solid-Supported Peptide Synthesis



Scheme 15.37 *Solid-supported peptide synthesis.*

Solid-Supported Carbohydrates Synthesis

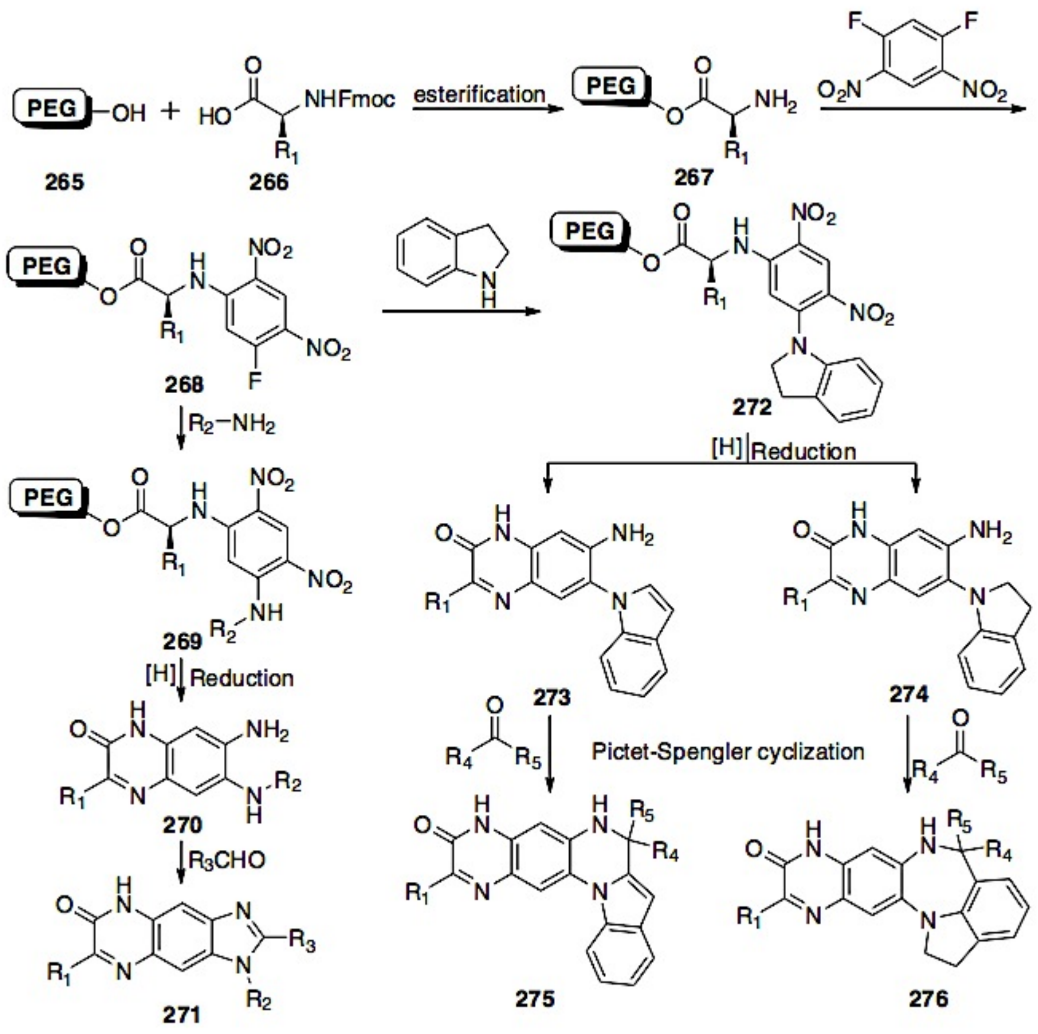


Scheme 15.38 *Seeberger's automated solid-phase synthesis of β-phytoalexin elicitor glucans.*

Soluble-Supported Synthesis

- The heterogeneous reaction conditions that insoluble polymers dictate often complicate the transfer of traditional solution-phase chemical methodologies to solid-phase synthesis.
- Soluble polymers has the potential to combine the best aspects of both solid-phase chemistry and solution-phase chemistry.
- The fundamentals of this process involve chemistry being performed on the soluble polymer attached derivatives with reagents and solvents in homogeneous solution.
- The main green feature of the soluble support is the isolation and purification of all the supported intermediates, compounds and the supports itself, in a cleavage step, through the simple precipitation and filtration method.

Soluble-Supported Synthesis

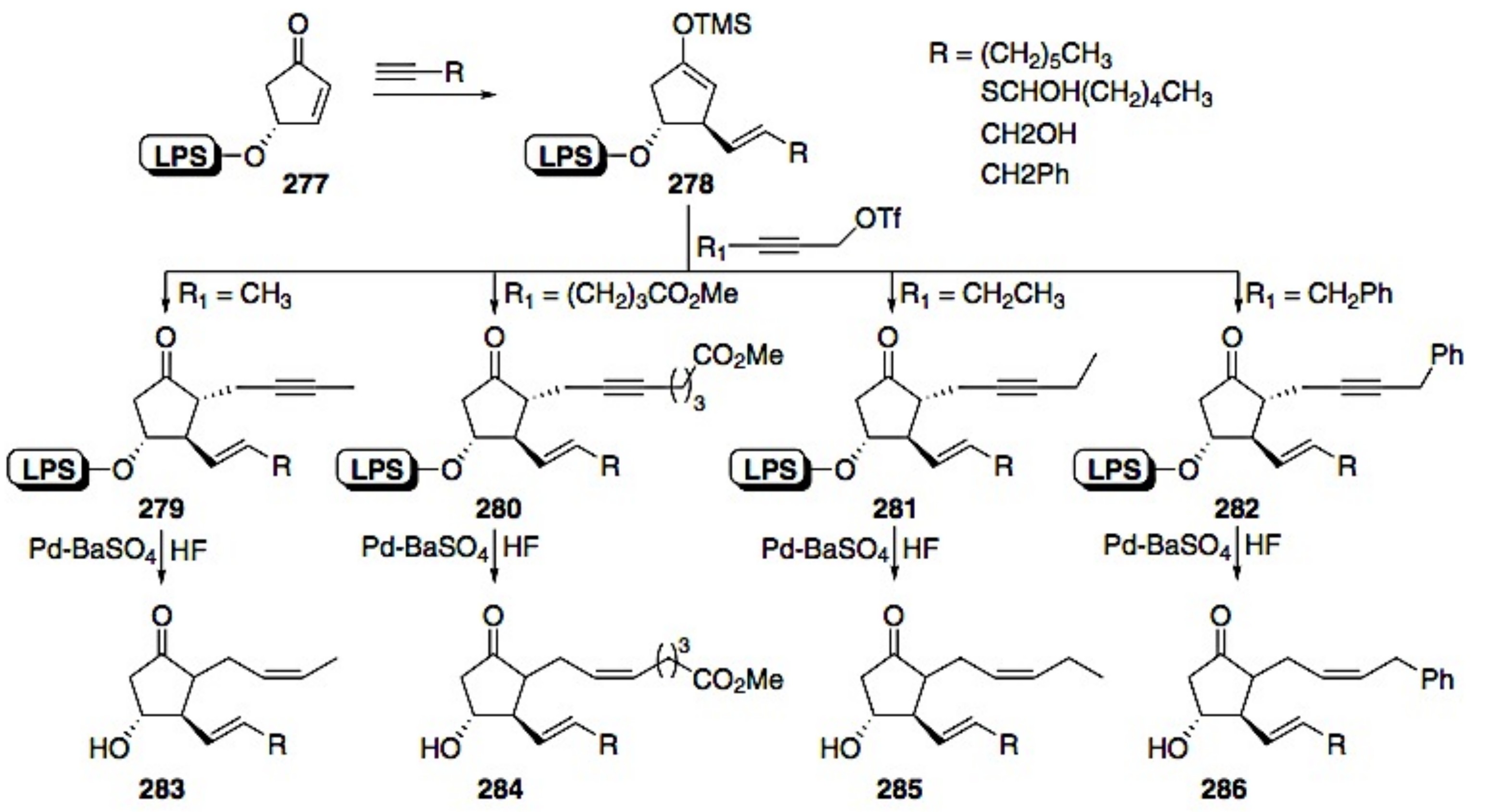


Scheme 15.39 PEG-supported multistep synthesis of quinoxalinone derivatives.

Poly(ethylene glycol)

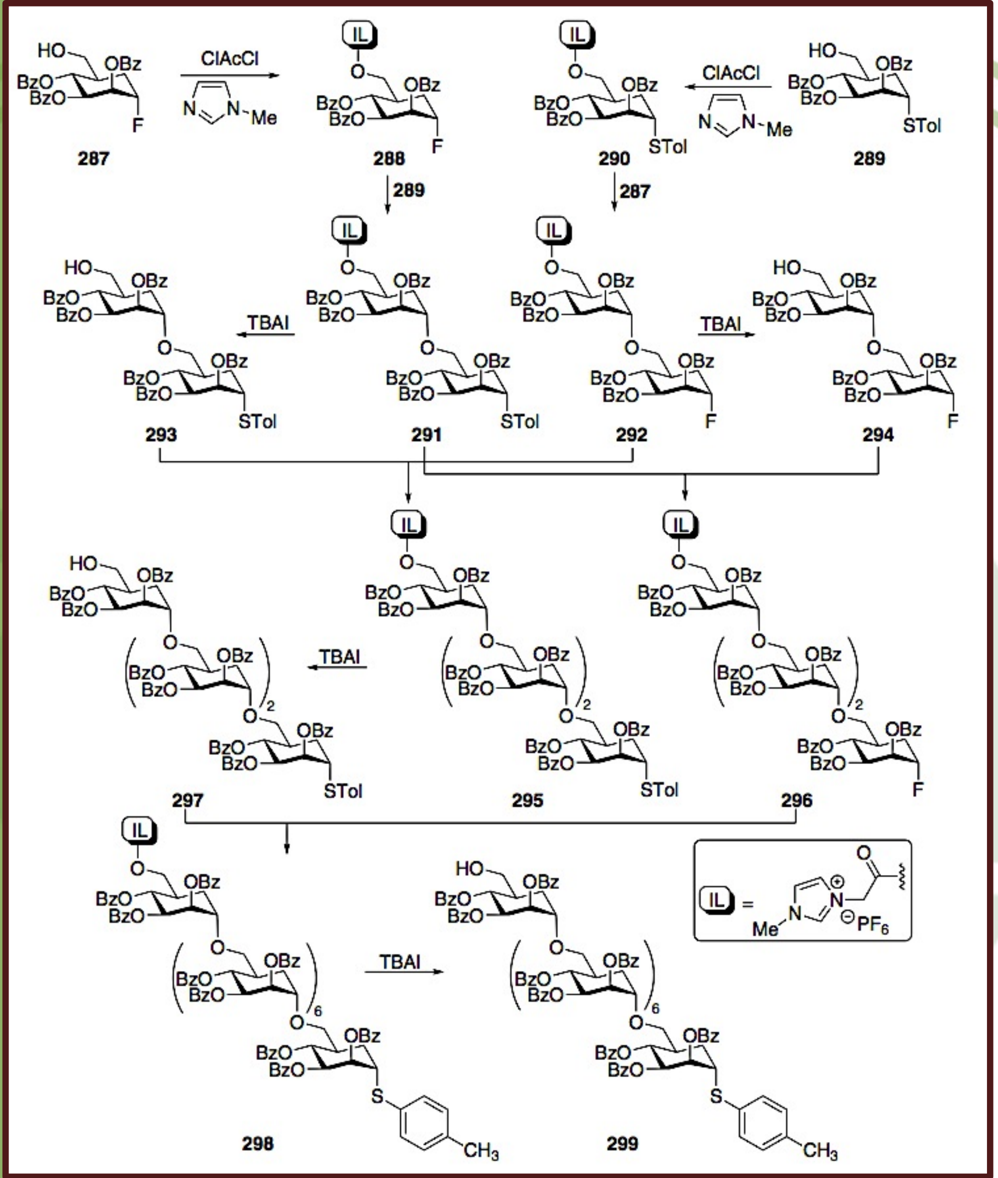
Soluble-Supported Synthesis

Linear Polystyrene (LPS)



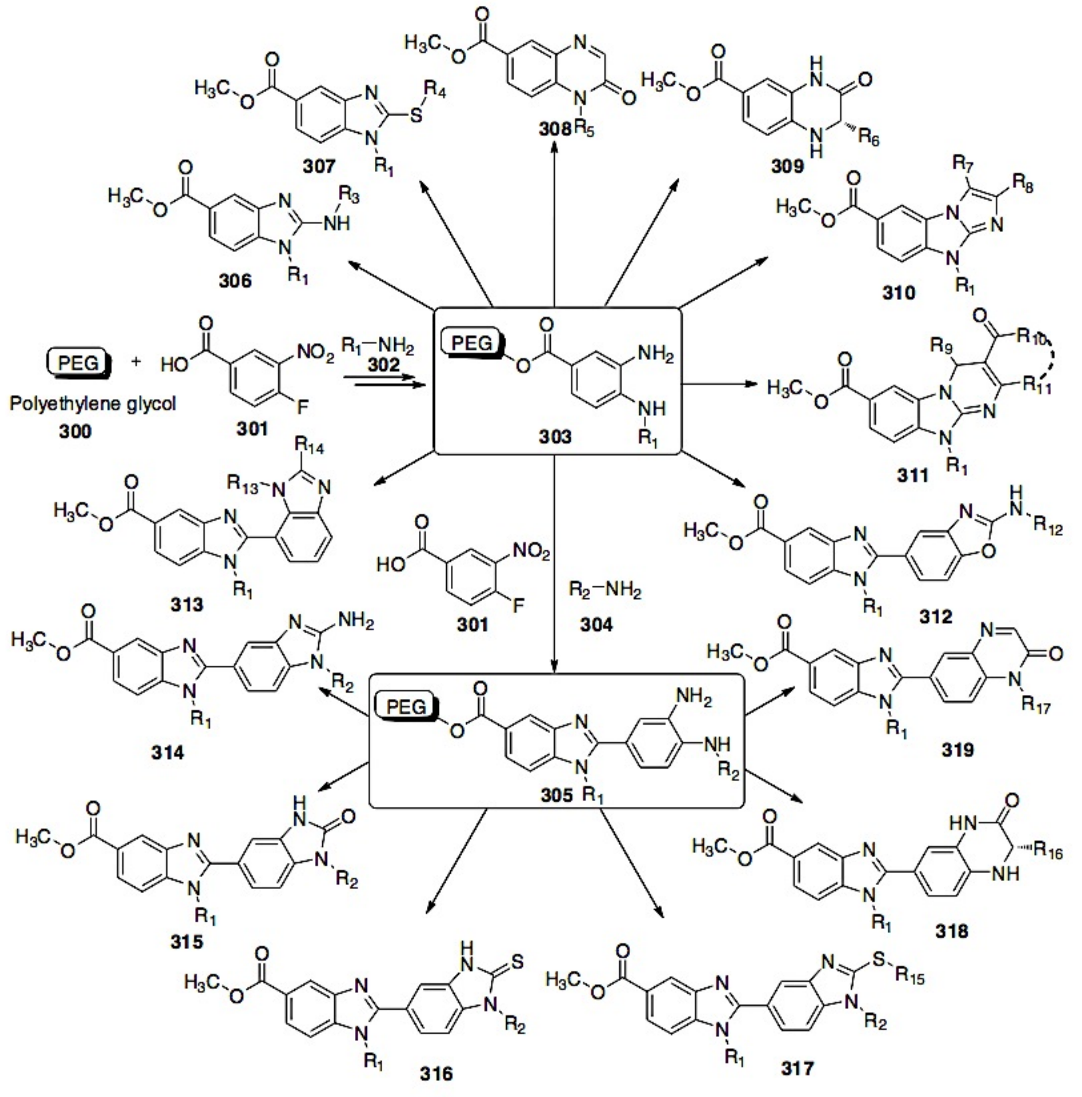
***Scheme 15.40** LPS-supported combinatorial synthesis of a prostanoid library.*

Soluble-Supported Synthesis



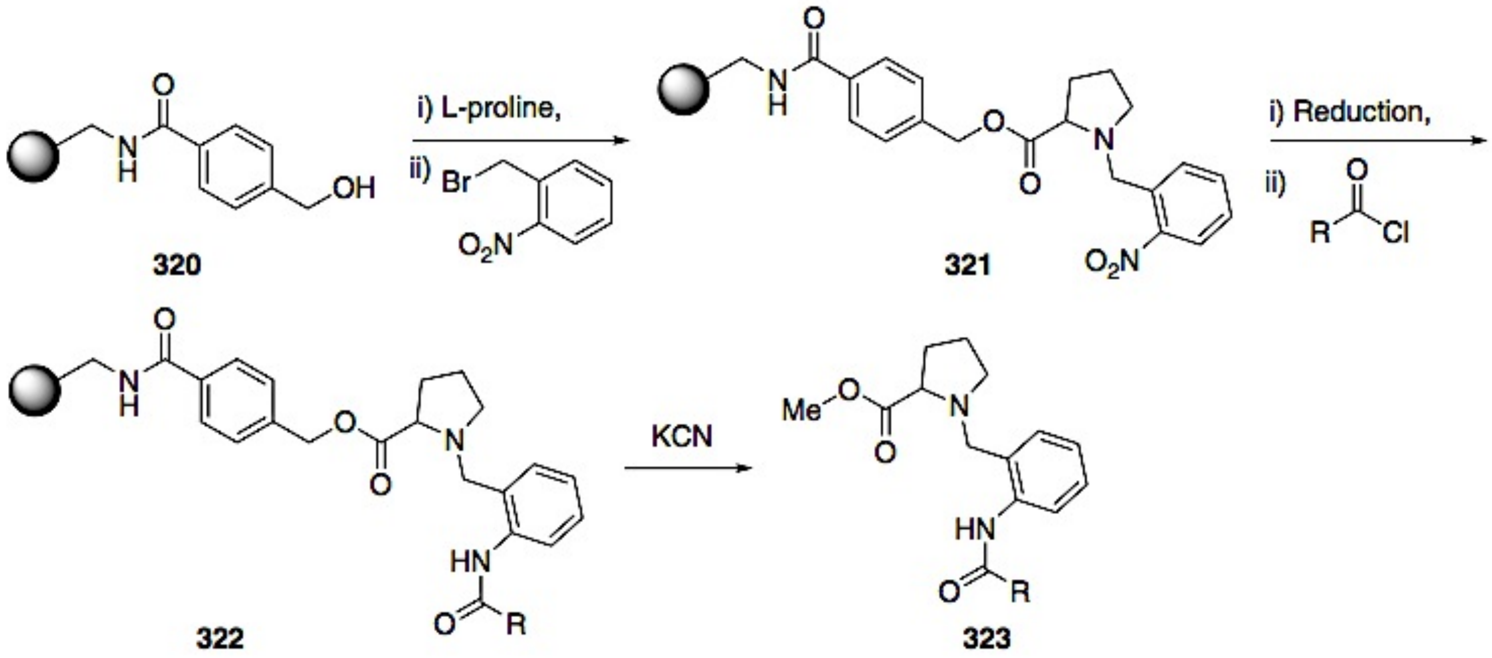
Ionic Liquids (IL)

Solid-Supported Synthesis and microwave synthesis



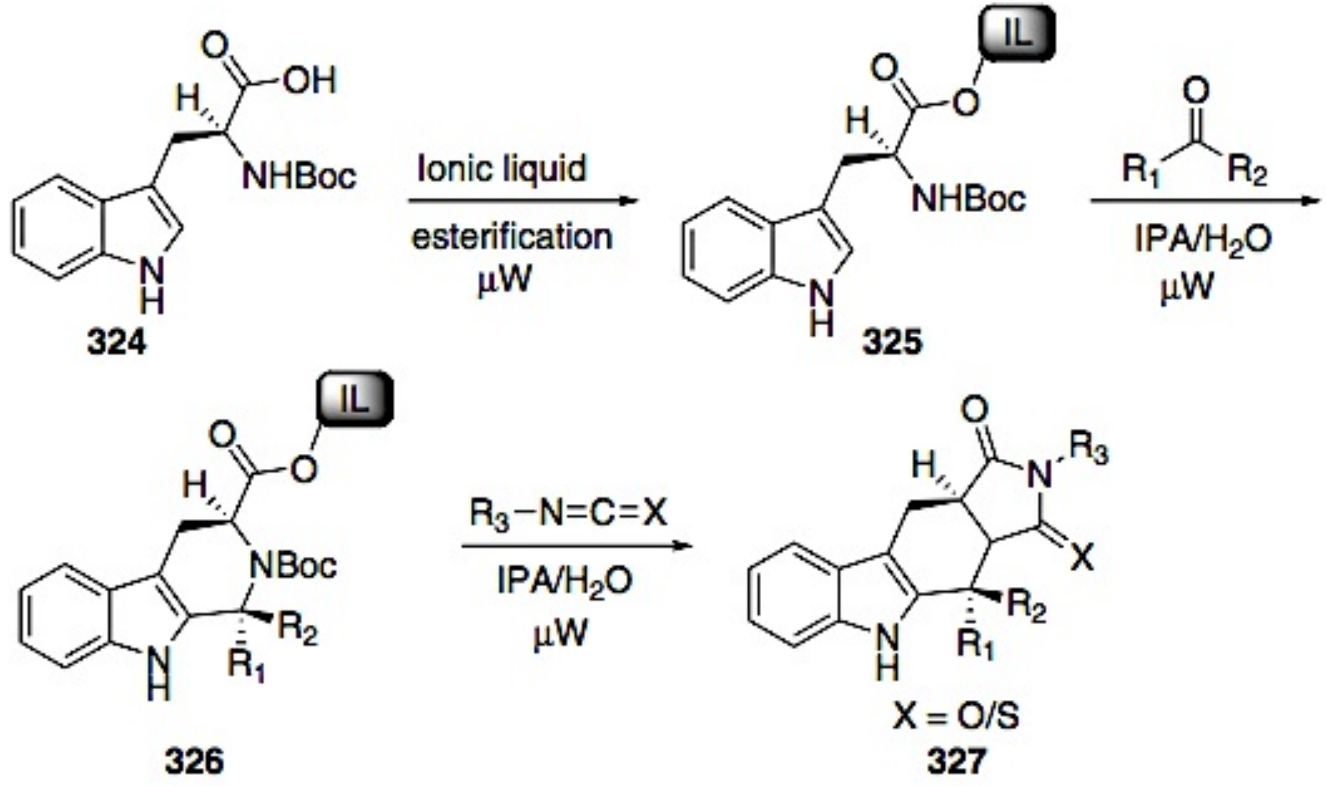
Scheme 15.42 *Hsiao et al.'s diversity-oriented synthesis using microwave synthesis and soluble- supported synthesis.*

Solid-Supported Synthesis Under Sonications



Scheme 15.43 *Solid-supported synthesis under sonication.*

Solid-Supported Synthesis in Green Media



Solid-Supported Synthesis and Photochemical Reactions