Pergamon

Tetrahedron, Vol. 52, No. 13, pp. 4527-4554, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00216-5

TETRAHEDRON REPORT NUMBER 394

Solid-Phase Organic Reactions: A Review of the Recent Literature

Pedro H.H. Hermkens[♦*], *Harry C.J. Ottenheijm*[♦], *David Rees*[•]

[♦]*Scientific Development Group,NV Organon, PO Box 20, 5340 BH Oss, The Netherlands*

[•]*Scientific Development Group, Organon Labs.Ltd., Newhouse, Lanarkshire ML1 5SH, Scotland*

Abstract: Combinatorial chemistry has emerged as a powerful new technology for chemists to synthesise large numbers of compounds for biological evaluation. One of the techniques used in combinatorial chemistry is polymer supported or "solid-phase" organic synthesis. This article reviews the main chemical reactions reported between 1992-October 1995 using solid-phase support, focusing upon those suitable for synthesising small molecules. The reactions are presented in graphical format in a table according to reaction types. Examples presented include amide bond formation, aromatic substitutions, condensations, cycloadditions, diazotisation, enzymatic coupling, use of Grignard reagents, Michael additions, multiple component reactions, nucleophilic substitution, olefination, oxidations, protection/deprotection, reduction, immobilisation and cleavage. Finally, the information presented is evaluated briefly and some trends are discussed.

Combinatorial technologies allow large numbers of molecules to be prepared and tested rapidly. They comprise an integrated approach of combinatorial chemistry and high-throughput screening.

Combinatorial chemistry can be described as the preparation, most often but not exclusively on a solid supports of an ensemble of molecules referred to as "a library". These libraries are tested as single compounds or as mixtures. In its optimal form combinatorial technology involves robotics for the synthesis as well as for the screening stage, and computational medicinal chemistry for the library design.

Combinatorial chemistry is a collective term comprising several recent breakthroughs. These include solid-phase organic chemistry, combinatorial synthesis, new methods of structure elucidation based on deconvolution and tagging, and the growing awareness of structure-diversity and automation. These topics have been dealt with in several excellent reviews [1].

In addition to the use of solid-phase techniques for the synthesis of compound libraries several examples of libraries prepared using solution-phase have also been reported, for example by Panlabs[2], Glaxo[3], Pirrung[4a] and Rebek[4b-d]. The solution-phase work is not reviewed herein, rather in this contribution we wish to give a compilation of all reactions reported in the period 1992 - 1995 using solid-phase techniques. Reactions involving traditional oligomer synthesis and reactions involving resin bound reagents fall outside the scope of this review. Upon completion of this manuscript, we became aware of a compilation on solid-phase chemistry publications (Chiron), the format of which differs from ours[1g] and of another recent review[1f].

The period covered in this review is from 1992 until October 1995, since in 1992/1993 two key examples of solid-phase heterocyclic synthesis were published that have provided a tremendous impetus to further studies. The groups of Ellman[5] and Hobbs DeWitt[6] published general and facile routes to benzodiazepines. However, these were not the first publications in this domain. The techniques for solid-phase synthesis are based mainly on the pioneering work of Merrifield[7], and this was followed in the period 1970 - 1985 by some careful and elegant studies on solid-phase organic synthesis by Leznoff [8], Camps[9] and Frechet[10,11]. It was Camps who published, as early as 1974, a synthesis of benzodiazepines using solid-phase chemistry. Also the work of Rapoport[12] deserves to be mentioned.

One might wonder why the technique of solid-phase heterocyclic chemistry has been dormant for nearly three decades. One of the reasons might be that only recently have medicinal chemists been challenged by developments in biology and automation allowing the screening of a large number of compounds. The great advantage of combinatorial chemistry is that it has the potential to synthesise compounds faster than classical organic synthesis. Solid-phase chemistry is highly suited to combinatorial chemistry for reasons that include: easy work-up procedures; high yields by employing excess of reagents; and amenability to robotisation.

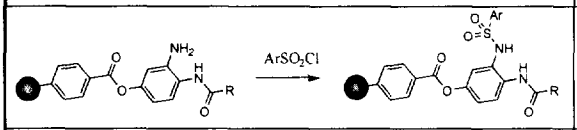
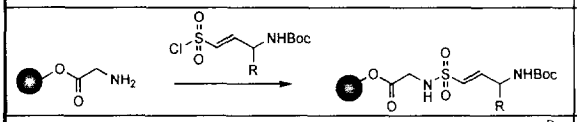
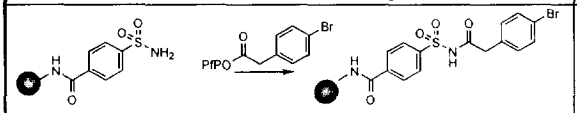
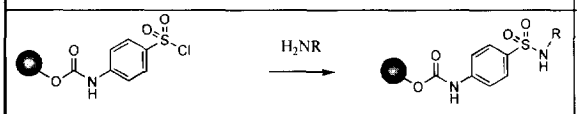
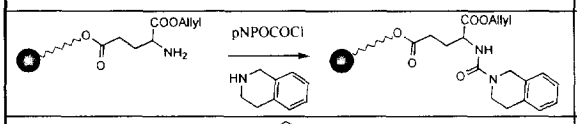
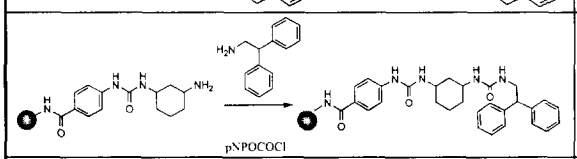
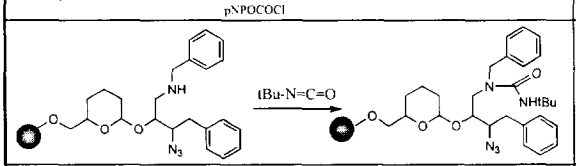
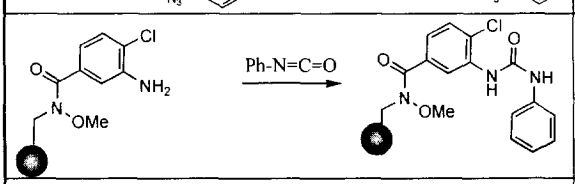
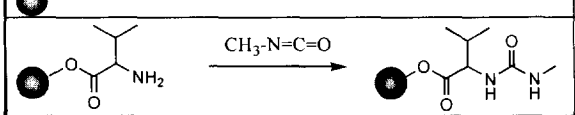
So far considerable effort has been put into the optimisation of solid-phase oligomer synthesis (peptides, DNA, RNA). However, it is obvious that no single class of compounds is able to cover the structural diversity required for all future drugs. The development of a broad array of organic reactions on solid support will increase the scope of combinatorial chemistry although we note that

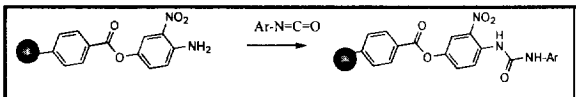
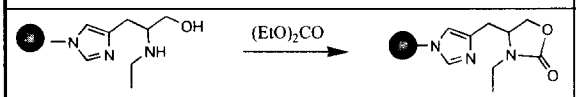
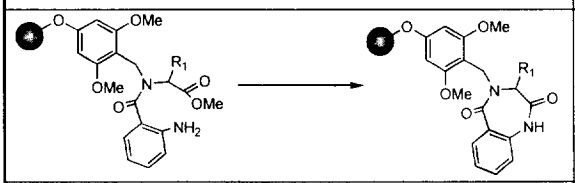
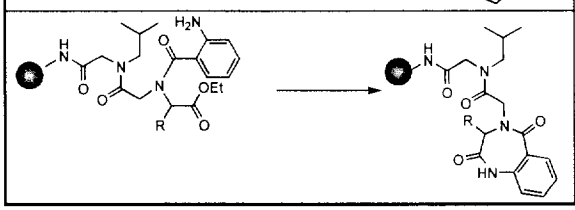
this is only one step in the synthesis of a compound library. We foresee a great challenge here for organic chemists. This review is meant to show that a start has been made, and that we probably have only glimpsed the tip of the iceberg.

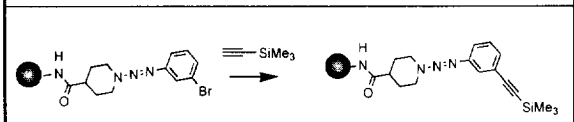
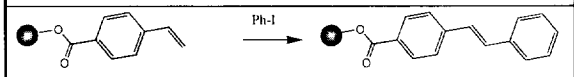
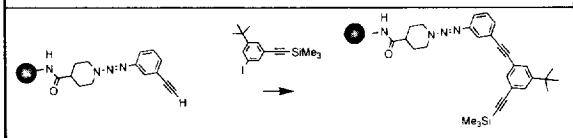
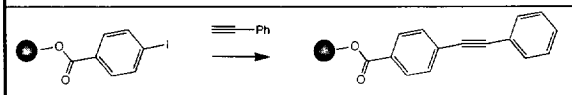
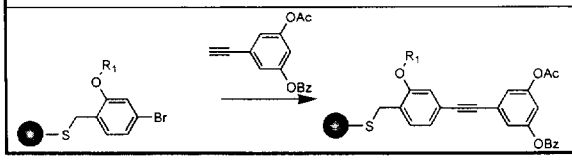
The reactions are presented in graphical format in the table according to the following categorisation, together with brief details of which resin was used, the number of examples reported and the yield.

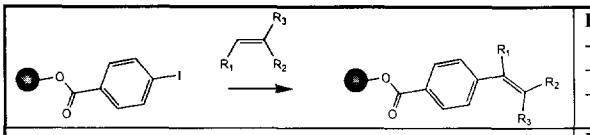
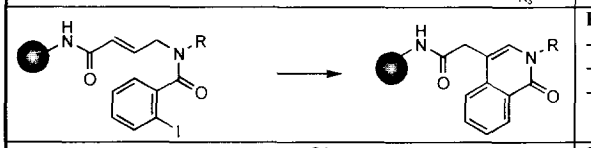
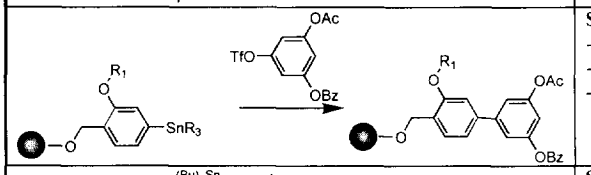
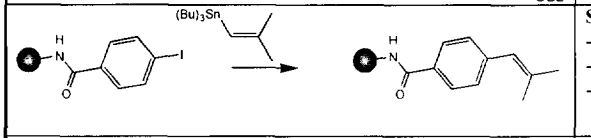
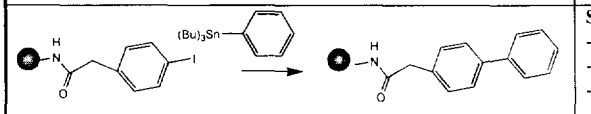
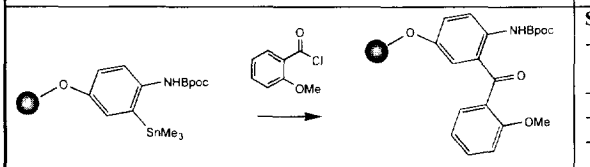
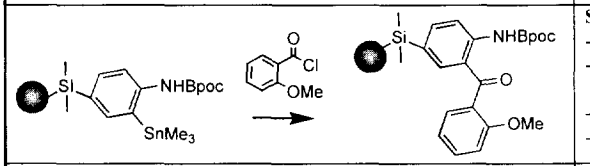
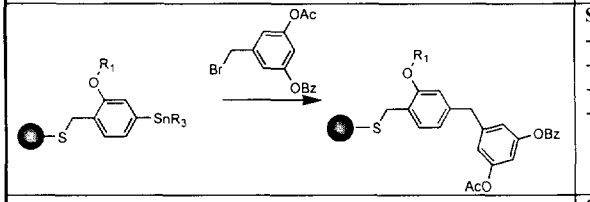
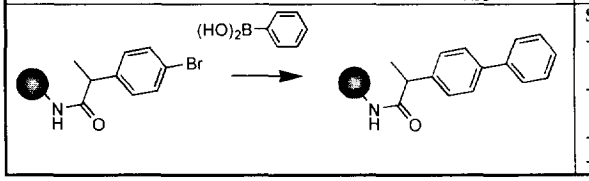
- **Amide bond formation**: sulfonamide, urea, urethane, lactam; only non-standard reactions are given; peptide-bond formation has not been covered.
- **Aromatic substitutions**: cross coupling (Heck, Stille, Suzuki), nucleophilic, electrophilic, Friedel-Craft
- **Condensations**: ketalisation, Claisen, Aldol, Knoevenagel, Pictet-Spengler, Bischler-Napieralski, imines
- **Cyclo-additions**: Diels-Alder, 1,3-dipolar
- **Diazotisation**
- **Enzymatic couplings**
- **Grignard reagents**
- **Michael additions**
- **Multiple component reactions**
- **Nucleophilic substitutions**: N-, O-, C-, S-alkylations, Mitsunobu, glycosidation
- **Olefination**: Horner-Emmons, Wittig
- **Oxidation**
- **Protection/deprotection**: only non-standard reactions
- **Reduction**
- **Immobilisation**: only non-standard reactions
- **Cleavage**: only non-standard reactions

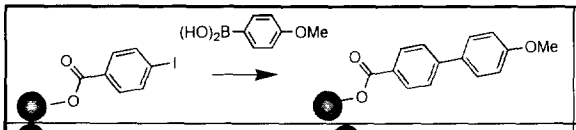
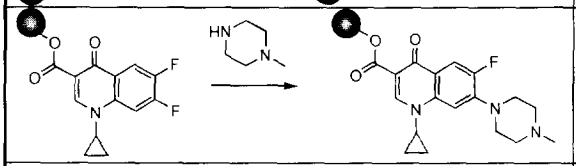
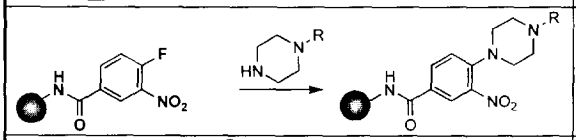
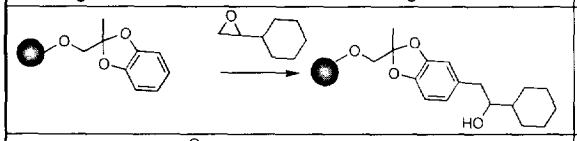
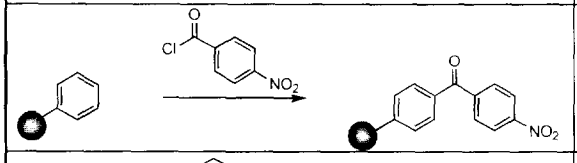
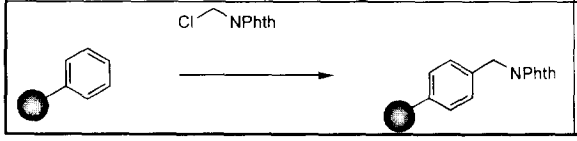
Table: Solid Phase Organic Reactions

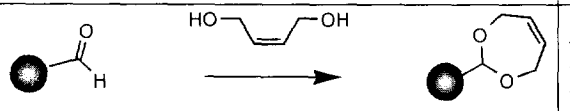
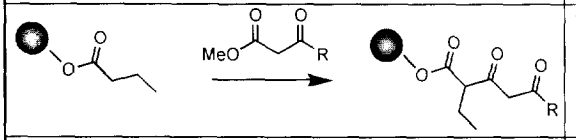
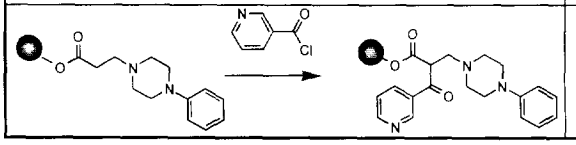
Type of Reaction:Amide bond formation	Comment	reference
	**Sulfonamide** - benzoic acid resin - several examples - yield: NR	13
	**Sulfonamide** - TentaGel S OH - 6 examples - yield: 60-70%	14
	**Sulfonamide** - aminomethylene resin - few examples - yield: NR	15a
	**Sulfonamide** - MeO-PEG soluble polymer - 6 examples - yield: NR	15b
	**Urea** - TentaGel S NH_2 - 8 examples - yield: NR	16
	**Urea** - TentaGel S RAM - 5 examples - yield: NR	17
	**Urea** - Merrifield resin - several examples - yield: >95%	18
	**Urea** - Merrifield resin - 8 examples - yield: NR	19
	**Urea** - Wang resin - 40 examples - yield: NR	6,19
	**Urea** - benzoic acid resin - several examples - yield: NR	13

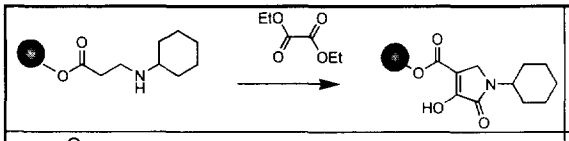
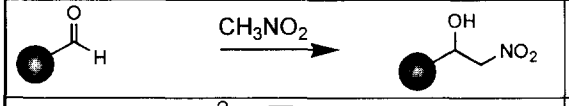
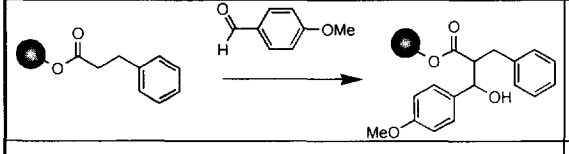
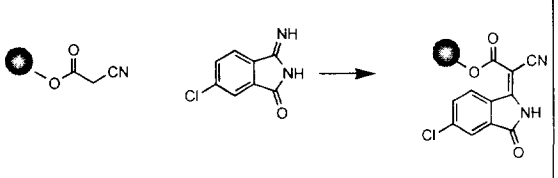
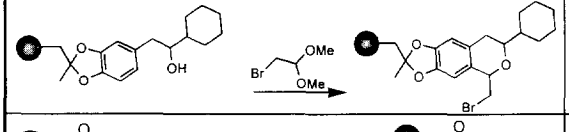
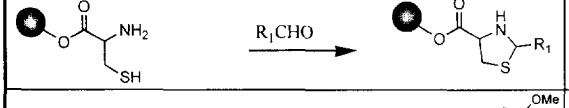
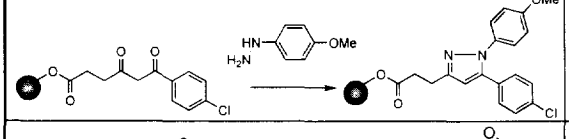
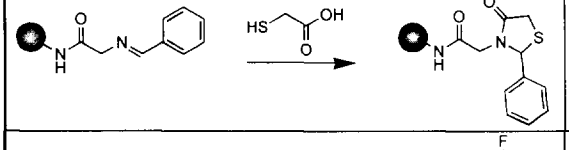
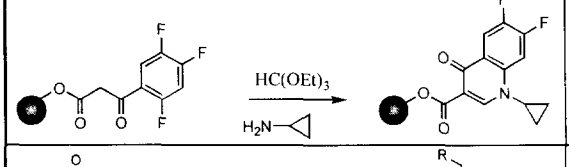
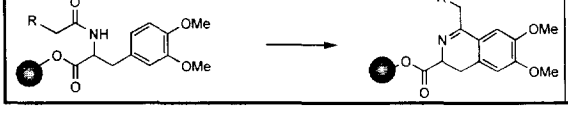
	**Urea** - benzoic acid resin - several examples - yield: NR	13
	**Urethane** - 2-chlorotriphenyl methyl resin - 4 examples - yield: NR	19
	**Lactam** - Merrifield resin - 11 examples - yield: 62-92%	21
	**Lactam** - Rink amide resin - 21 examples - yield: 34-90%	20

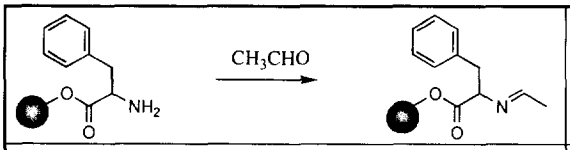
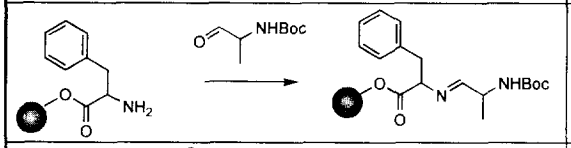
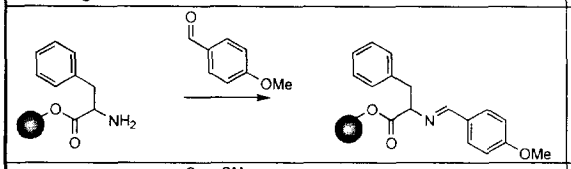
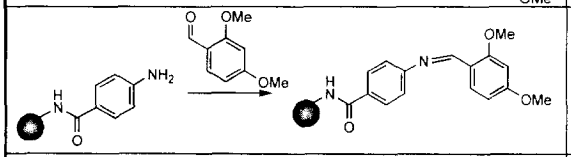
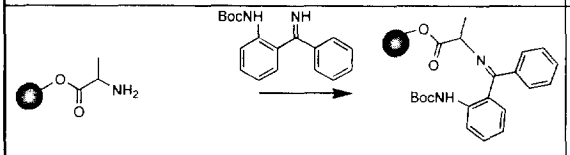
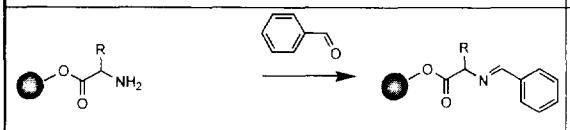
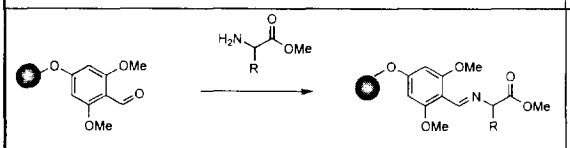
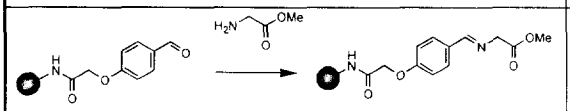
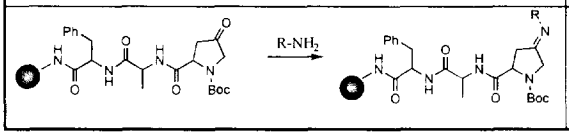
Type of Reaction: Aromatic Substitution	Comment	reference
	**Heck reaction** - aminomethylene resin - 1 example - hexamer phenyl acetylene oligomer (overall yield 50%)	22
	**Heck reaction** - Wang resin - 10 examples - yield: 64-91%	23
	**Heck reaction** - aminomethylene resin - 1 example - hexamer (overall yield: 50%)	22
	**Heck reaction** - Wang resin - 10 examples - yield: 64-91%	23
	**Heck reaction** - TentaGel - NpSSM linker - few examples - yield: NR	24

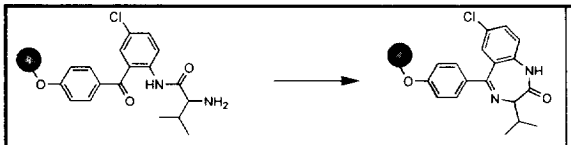
	**Heck reaction** - TentaGel - R_3 are EWG's - yield: 54->95%	25
	**Heck reaction** - Rink amide resin - 8 examples - yield: 65-92%	26
	**Stille reaction** - Merrifield resin - few examples - yield: NR	24
	**Stille reaction** - Rink amide resin - 8 examples - yield: >88%	27
	**Stille reaction** - Rink amide resin - few examples - yield: 21-33%	28
	**Stille reaction** - aminomethylene resin - HMPA linker - 16 examples - yield: >95%	5, 29
	**Stille reaction** - silicon linker - aminomethylene resin - 4 examples - yield: NR	30
	**Stille reaction** - TentaGel - NpSSM linker - few examples - yield: NR	24
	**Suzuki reaction** - aminomethylene resin - Safety-Catch Linker - 13 examples - yield: >90%	15a

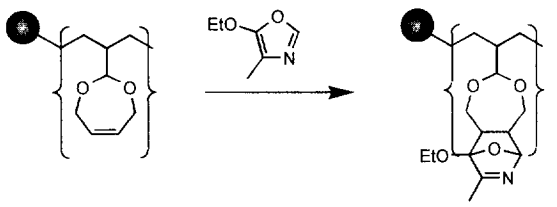
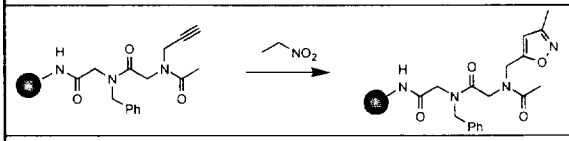
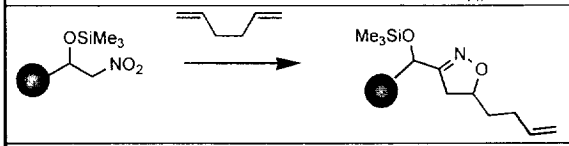
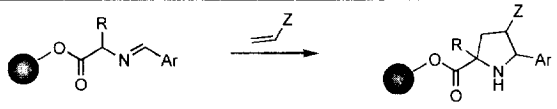
	**Suzuki reaction** - Merrifield resin - 15 examples - yield: >90%	31
	**Nucleophilic** - hydroxymethylene resin - 36 examples - yield: NR	19
	**Nucleophilic** - Rink amide resin - 76 examples - yield: >80%	32
	**Electrophilic** - Merrifield resin - 2 example - yield: NR	19
	**Friedel Craft** - polystyrene resin - 3 examples - yield: NR	33, 34
	**Friedel Craft** - polystyrene resin - 1 example - yield: NR	33

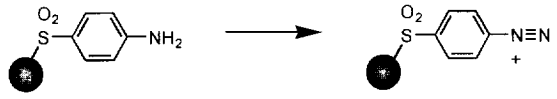
Type of Reaction: Condensation	Comment	reference
	**Ketalisation** - poly(vinylformal) - 1 example - yield: 46%	35
	**Claisen** - hydroxymethylene resin - 3 examples - yield:NR	19
	**Claisen** - hydroxymethylene resin - 24 examples - yield:NR	19

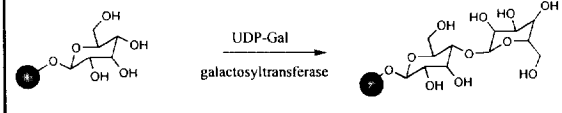
	**Claisen** -cyclization - Merrifield resin -2 examples -yield: NR	19
	**Aldol** - Merrifield resin - 1 example - yield: NR	36
	**Aldol** - Merrifield resin - 27 examples - yield: NR	37
	**Knoevenagel** - hydroxymethylene resin - 9 examples given - yield: NR	19
	**Pictet-Spengler** - Merrifield resin - 2 examples - yield: NR	19
	**Thiazolidine** -TentaGel S OH - 13 examples - yield: 0-94%	38
	**Pyrazole** -hydroxymethylene resin - 8 examples - yield: NR	19
	**4-Thiazolidinone** - TentaGel S NH_2 - 1 example - ^{13}C gel NMR - yield: 95%	39
	**Quinolones** - hydroxymethylene resin - 36 examples - yield: NR	19
	**Bischler-Napieralski** - Merrifield resin - 8 examples - yield: >40%	40

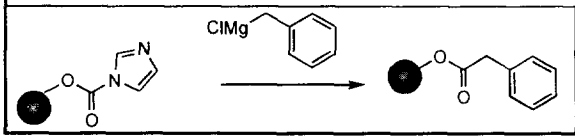
	**Imine formation** - Wang resin - 8 examples - yield: NR	19
	**Imine formation** - Wang resin - 6 examples - yield: NR	41
	**Imine formation** - imine not isolated - Wang resin - 90 examples - yield: 85-95%	42
	**Imine formation** - imine not isolated - Rink amide or Wang resin - 5 examples - yield: >90%	43
	**Imine formation** - Merrifield - 40 examples - yield: 5-100%	6,19
	**Imine formation** - TentaGel or SASRIN - 6 examples - ^{13}C gel NMR - yield: NR	44
	**Imine formation** - Merrifield resin - 4 examples - yield: NR	21
	**Imine formation** - TentaGel - 2 examples - ^{13}C gel NMR - slow reaction - yield: NR	44b
	**Imine formation** - Multipins - Rink amide resin - 11 examples - yield: >88%	45

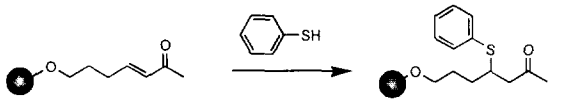
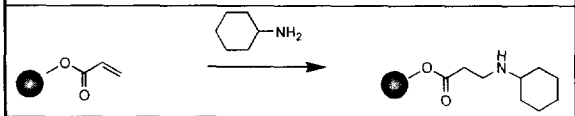
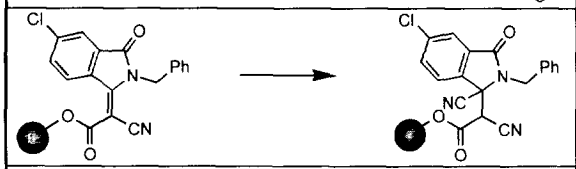
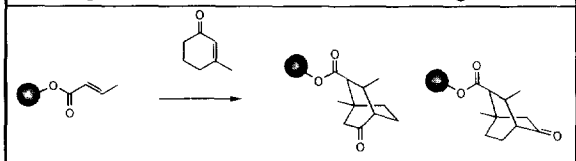
	**Imine formation** - Multipins - aminomethylene resin - 8 examples - yield: >95%	5, 29, 30

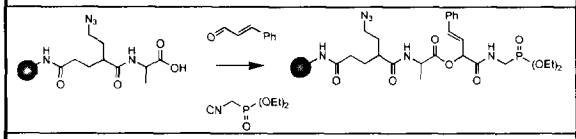
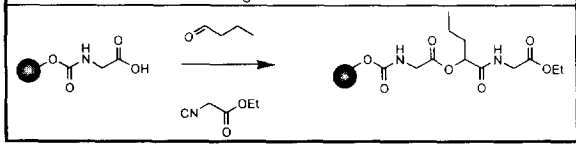
Type of Reaction: Cycloaddition	Comment	reference
	**Diels-Alder** - poly(vinylformal) - one example - yield: NR	35
	**1,3-Dipolar** - Rink amide resin - 11 examples - NSG's - yield: >80%	46
	**1,3-Dipolar** - Merrifield - 1 example - yield: NR	36
	**1,3-Dipolar** - TentaGel S AC or SASRIN - split/pool > 480 compounds - yield: 50-80%	44a

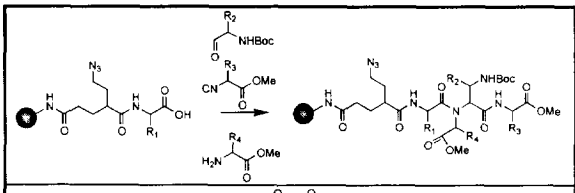
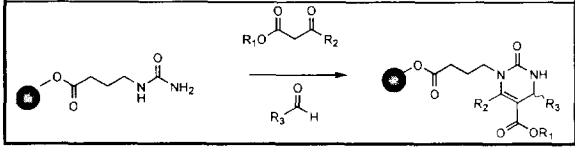
Type of Reaction: Diazotisation	Comment	reference
	- Spheron Ara 1000 - 1 example - yield: NR	47

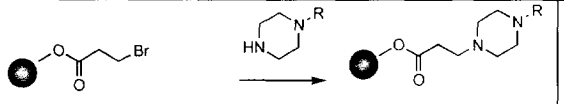
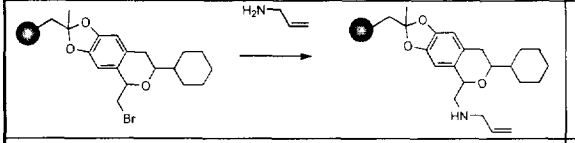
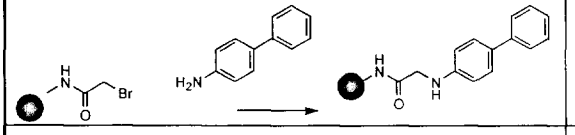
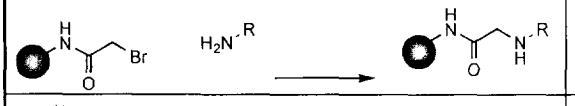
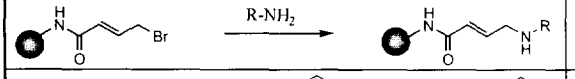
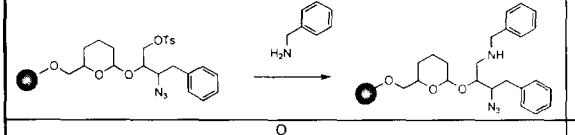
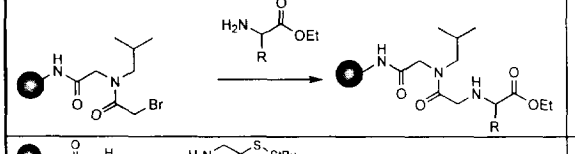
Type of Reaction:Enzymatic	Comment	reference
	- polyacrylamide resin or pore glass or amino propyl silica or PEGA resin - Glycopeptides - tetraoligomers	48-51

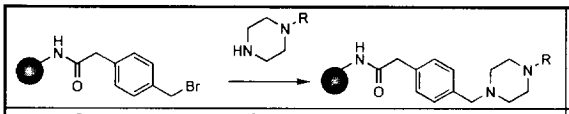
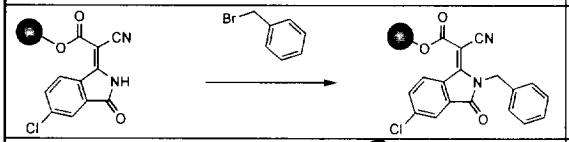
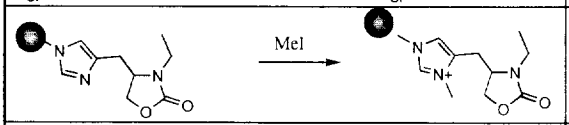
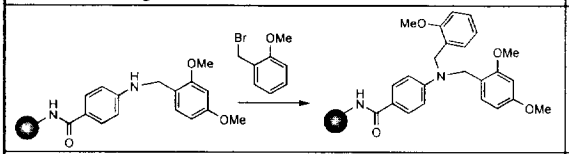
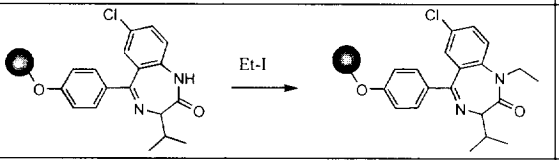
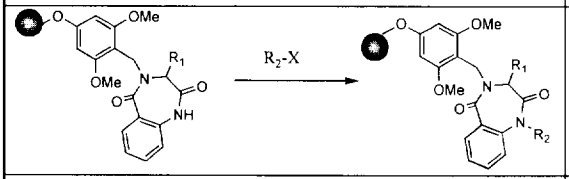
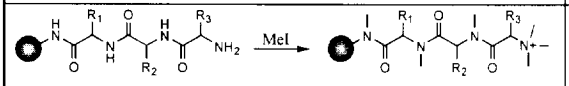
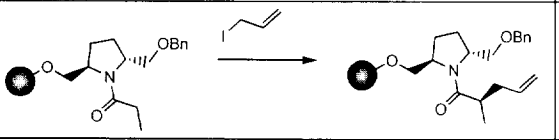
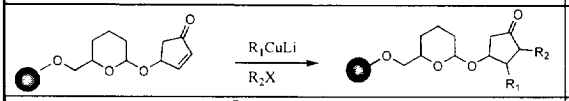
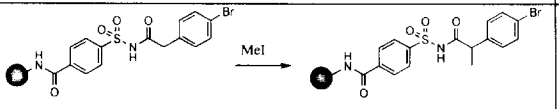
Type of Reaction:Grignard Reagent	Comment	reference
	- Wang resin - 1 example - no experimental data - yield: 70%	52

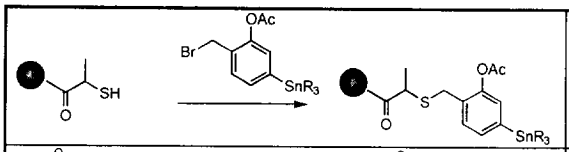
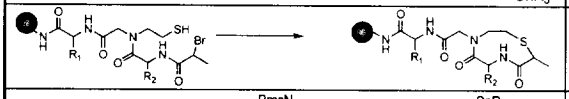
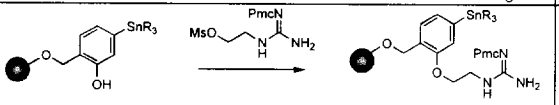
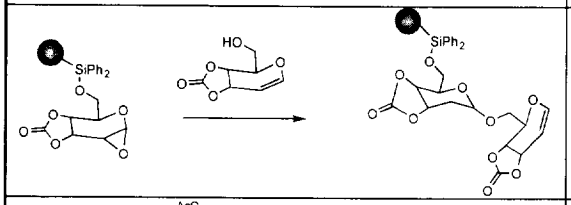
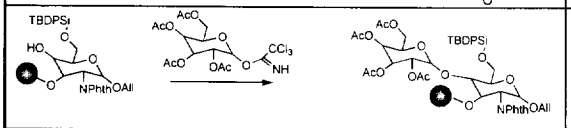
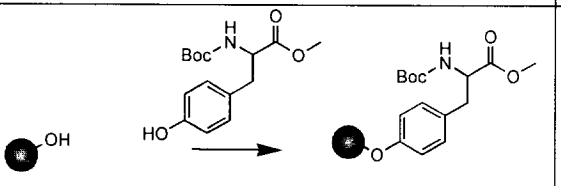
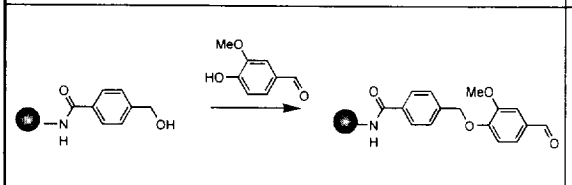
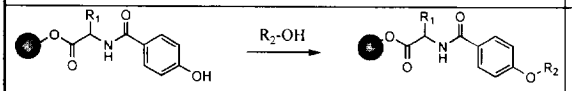
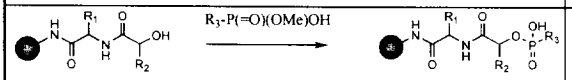
Type of Reaction: Michael Addition	Comment	reference
	- tritylchloride resin - 3 examples - yield: NR	53
	- Merrifield - 2 examples - yield: NR	19
	- hydroxymethylene resin - 9 examples - yield: NR	19
	tandem Micheal addition - Wang resin - 10 examples -yield:36-86% - endo/exo ratio= 6/1 to 18/1	74

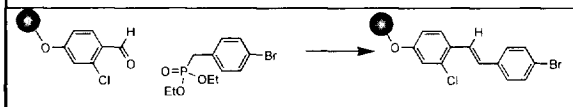
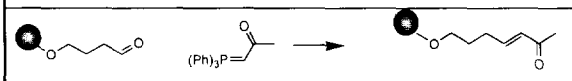
Type of Reaction: Multiple Component Reactions	Comment	reference
	**Passerini reaction** - 3 components - aminomethylene resin - yield: NR	54
	**Passerini reaction** - 3 components - MBHA resin - yield: NR	54

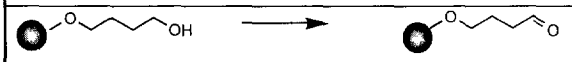
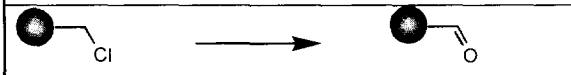
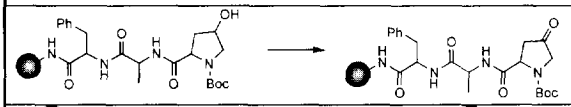
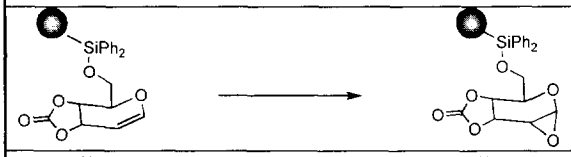
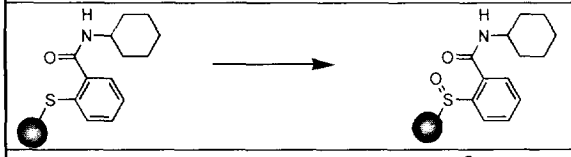
	**Ugi reaction** - 4 components - aminomethylene resin - yield: NR	54
	- Wang resin - 10 examples - yield: 67-98%	55

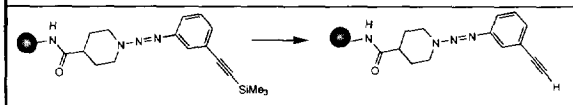
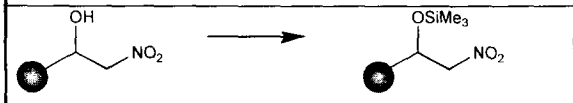
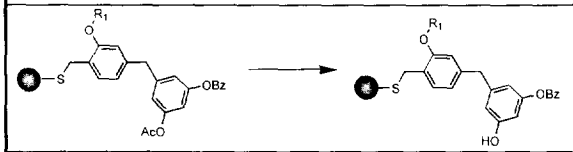
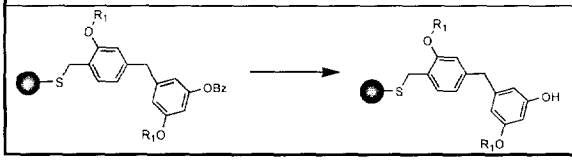
Type of Reaction: Nucleophilic Substitution	Comment	reference
	**N-alkylation** - hydroxymethylene resin - 24 examples - yield: NR	19
	**N-alkylation** - Merrifield resin - 6 examples - yield: NR	19
	**N-alkylation** - Rink amide resin - NSG's library >5000 compounds	56
	**N-alkylation** - Rink amide resin - several examples - yield: >90%	20,57
	**N-alkylation** - Rink amide resin - several examples	26
	**N-alkylation** - Merrifield resin - 4 examples - yield: >95%	18
	**N-alkylation** - Rink amide resin - several examples - yield: >90%	20
	**N-alkylation** - Rink amide resin - 2 examples - yield: 99%	58

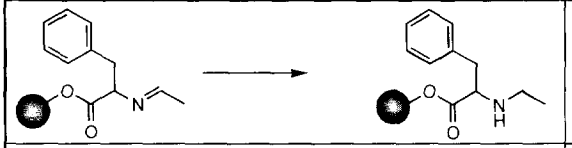
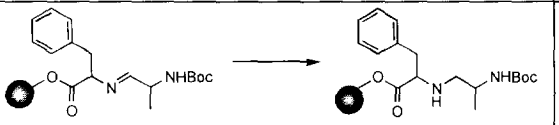
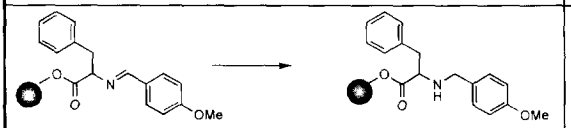
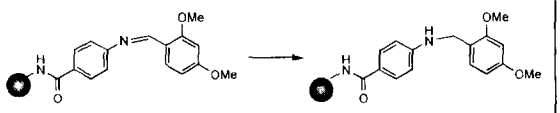
	**N-alkylation** - Rink amide resin - 114 examples - yield: >85%	32
	**N-alkylation** - hydroxymethylene resin - 9 examples - yield: NR	19
	**N-alkylation** - 2-Cl-trityl resin - 4 examples - yield: NR	19
	**N-alkylation** - Rink amide or Wang resin - 60 examples - yield: >98%	43
	**N-alkylation** - aminomethylene resin - several examples - yield: NR	5, 29
	**N-alkylation** - Merrifield resin - 5 examples - yield: NR	21
	**N-alkylation** - MBHA resin - libraries from libraries	59
	**C-alkylation** - Merrifield resin - 1 example - stereoseletivity 93.5:6.5	60
	**C-alkylation** - Merrifield resin - no details given	29b
	**C-alkylation** - aminomethylene resin - 13 examples - yield: 88-100%	15a

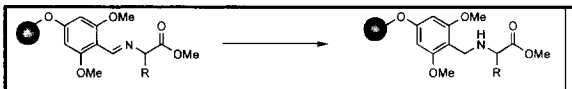
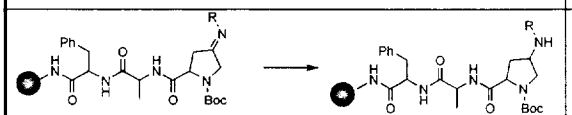
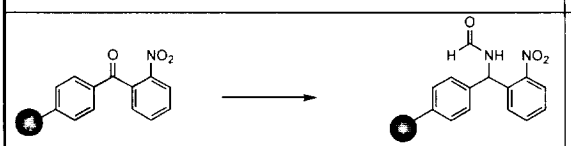
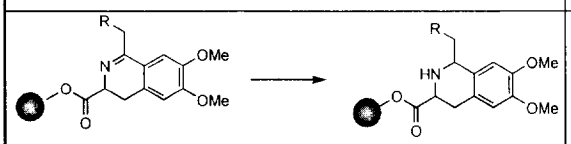
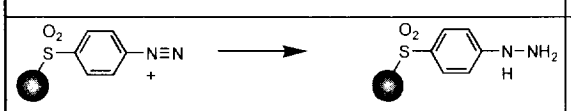
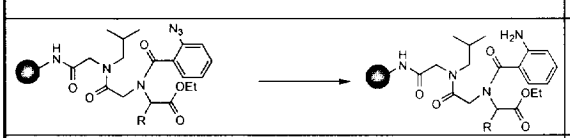
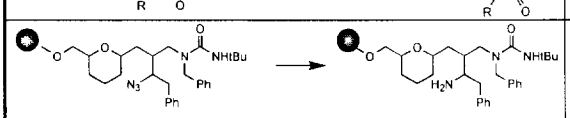
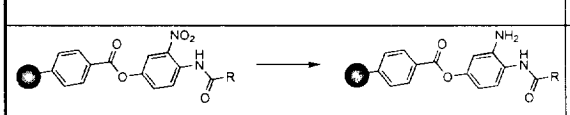
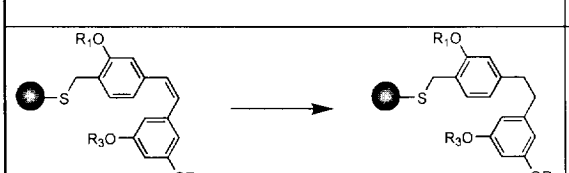
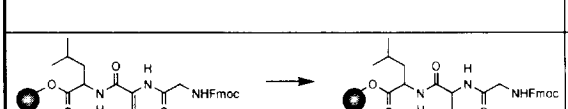
	**S-alkylation** - TentaGel - NpSSM linker - yield: NR	24, 61
	**S-alkylation** - TentaGel resin - several examples	58
	**O-alkylation** - Merrifield resin - several examples - yield: NR	24
	**O-alkylation** **Glycosidation** -polystyrene resin - tetrasaccharide -yield: >70%	62
	**O-alkylation** **Glycosidation** -MPEG-DOX resin - pentasaccharide -yield: NR	63
	**O-alkylation** **Mitsunobu** -hydroxymethylene resin - different solvents studied - yield: 85%	64
	**O-alkylation** **Mitsunobu** - TentaGel S RAM - 15 examples - yield: 72-99% - resin bound phenols gave also good results	65
	**O-alkylation** **Mitsunobu** - TentaGel S OH - 50 examples - library of 4200 compounds - yield: 39-99%	66
	**O-phosphorylation** **Mitsunobu** - TentaGel S NH_2 - several examples - library of 540 compounds - yield: NR	67

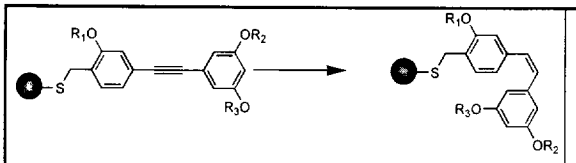
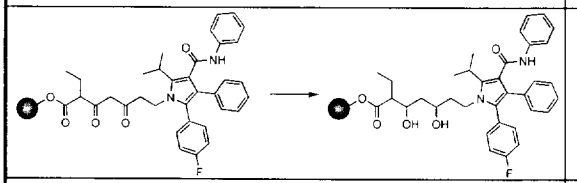
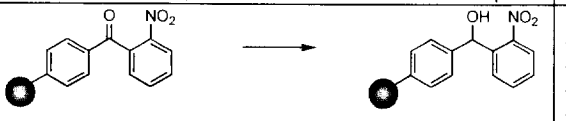
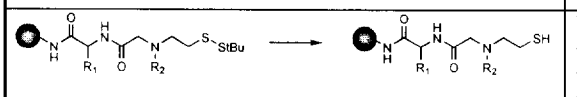
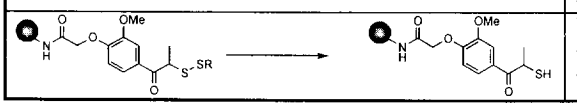
Type of Reaction: Olefination	Comment	reference
	**Horner-Emmons** -PAM resin -23 examples given -yield: 7-85% -hydroxystilbene library	68
	**Wittig** - trityl chloride resin - 3 examples given -yield: NR	53

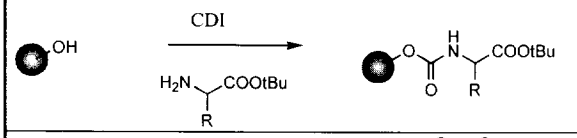
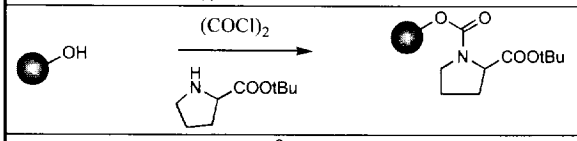
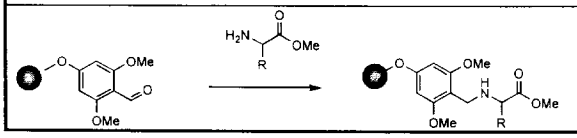
Type of Reaction: Oxidation	Comment	reference
	**Alcohol to aldehyde** - tritylchloride resin - 1 example - yield: NR	53
	**Chloromethyl to aldehyde** - Merrifield - 1 example - yield: NR	36
	**Alcohol to ketone** - Rink amide resin - 1 example - yield: >90%	45
	**Alkene to epoxide** - polystyrene resin - tetrasaccharide - yield: >70%	62
	**Sulfide to sulfoxide** Merrifield - 9 examples - yield: NR	19
	**Sulfide to sulfoxide or sulfone** -TentaGel S OH - 2 examples - yield: NR	38

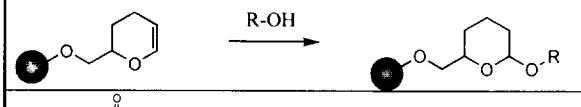
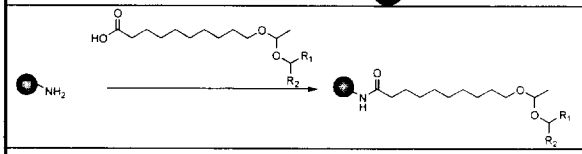
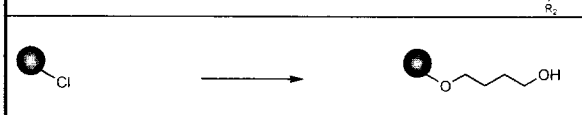
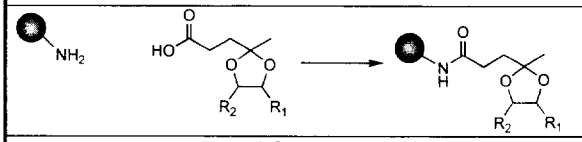
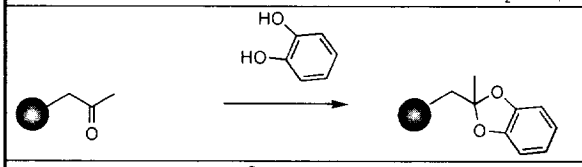
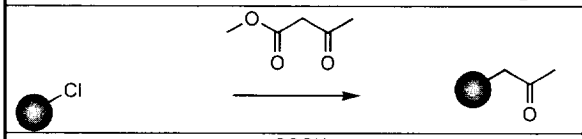
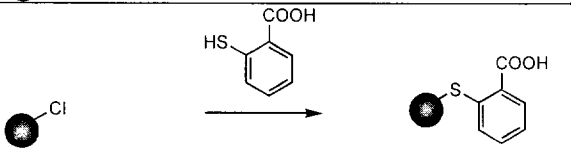
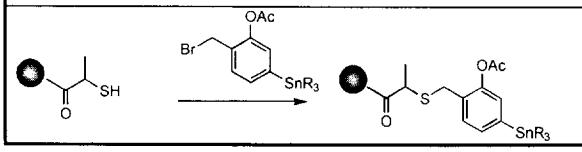
Type of Reaction: Protection / deprotection	Comment	reference
	- aminomethylene resin -1 example given - yield: NR - phenylacetylene oligomer synthesis	22
	- Merrifield resin - 1 example given - yield: NR	36
	- TentaGel - NpSSM linker - selective removal of acetate group - several examples - yield: NR	24
	- TentaGel - NpSSM linker - several examples - yield: NR	24

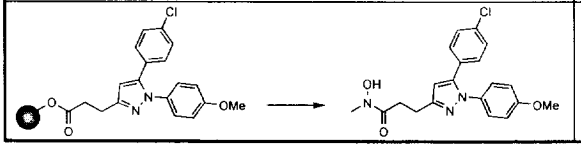
Type of Reaction: Reduction	Comment	reference
	**Imine to amine** - Wang resin - $NaCNBH_3$ - 8 examples - yield: NR	19
	**Imine to amine** - Wang resin - $NaCNBH_3$ - 6 examples - yield: NR	41
	**Imine to amine** - imine not isolated - Wang - $NaBH(OAc)_3$ - 90 examples - yield: 85-95%	42
	**Imine to amine** - imine not isolated - Rink amide or Wang resin - $NaCNBH_3$ - 5 examples - yield: >90%	43

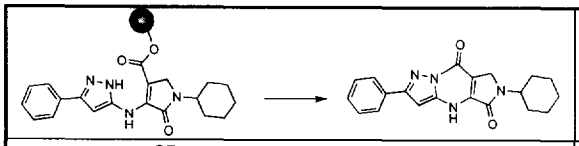
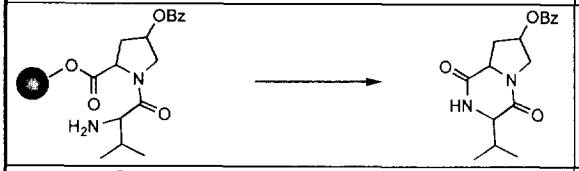
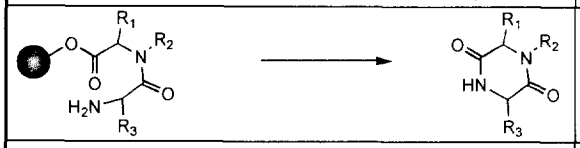
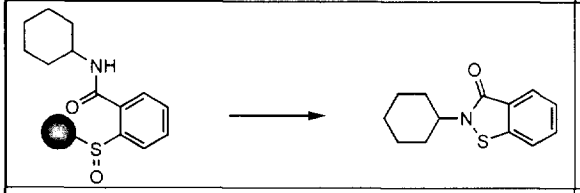
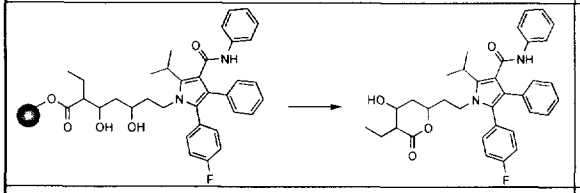
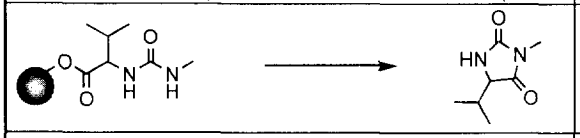
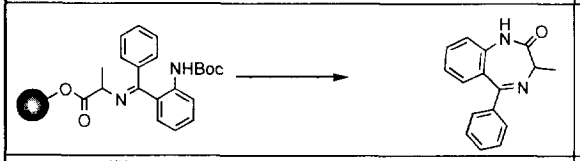
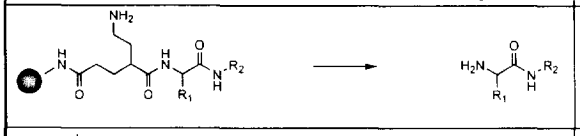
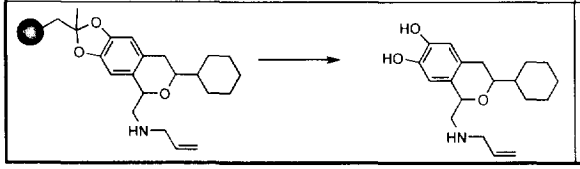
	**Imine to amine** - Merrifield resin - 4 examples - yield: NR	21
	**Imine to amine** - Multipins - Rink amide resin - 11 examples - yield: >88%	45
	**Ketone to amine** - Leukart reductive amination - NBHA resin - no experimental - yield: NR	34
	**Imine to amine** - Merrifield resin - $NaCNBH_3$ - 8 examples - yield: 25-30% - cis/trans ratio: 6/1	40
	**Diazo to hydrazine** - Spheron Ara 1000 - 1 example - yield: NR	47
	**Azide to amine** - Rink amide resin - 21 examples - yield: 34-90%	20
	**Azide to amine** - Merrifield - 9 examples - yield: > 95%	18
	**Nitro to amine** - benzoic acid resin - several examples - yield: NR	13
	**Alkene to alkane** - TentaGel - few examples - NpSSM linker - yield : NR - catalytic reduction	24
	**Alkene to alkane** - Wang resin - few examples - yield: 100% - stereoselective - catalytic reduction	69

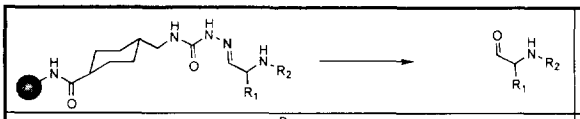
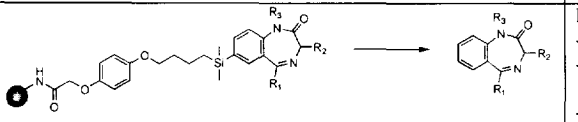
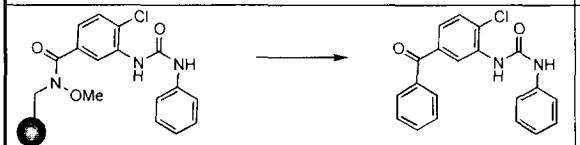
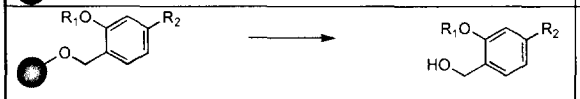
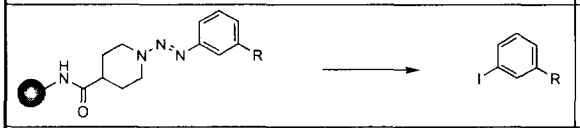
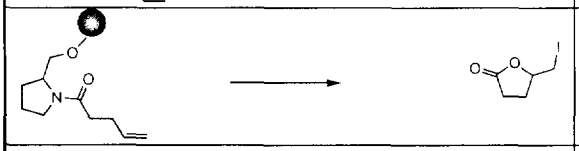
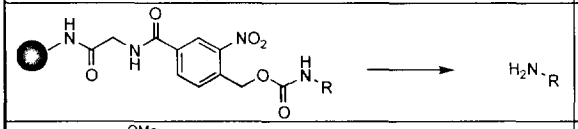
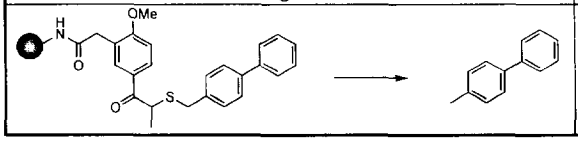
	**Alkyne to alkene** - TentaGel - few examples - NpSSM linker - yield : NR - catalytic reduction	24
	**Ester to alcohol** **Amide to amine** - 2-chloro-triphenylmethyl - 4 examples - yield: NR	19
	**Ketone to alcohol** - hydroxymethylene resin - 3 examples - yield: NR	19
	**Ketone to alcohol** - polystyrene resin - 1 example - $NaBH_4$ -yield: NR	34
	**Disulfide to thiol** -PS-PEG resin - few examples -yield: NR	58
	**Disulfide to thiol** -TentaGel S NH_2 - NpSSM linker	61

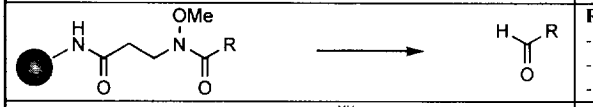
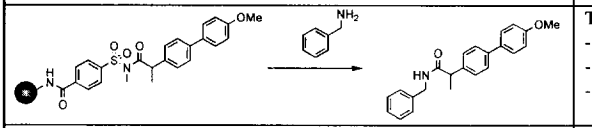
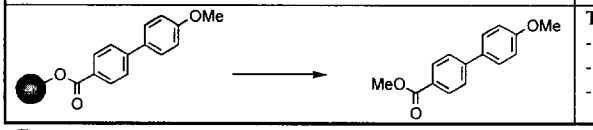
Type of Reaction: Non-standard immobilisation reactions	Comment	reference
	**Amine connection** - Wang or TentaGel S PHB resin - few examples - yield: 80%	52
	**Amine connection** - Tentagel S - 1 example - yield: 75%	52
	**Amine connection** - Merrifield resin - 4 examples - yield: NR	21

	**Alcohol connection** - Merrifield resin - several examples - yield: 66-95%	18, 29b, 70
	**Alcohol connection** - MBHA resin - few examples - yield: NR	71
	**Alcohol connection** - 2-chloro-triphenyl methyl resin - 1 example - yield: NR	53
	**Diol connection** - MBHA resin - several examples - yield: NR	71
	**Diol connection** - Modified Merrifield resin - 1 example - yield: NR	19
	**Carbon connection** - Merrifield resin - 1 example - yield: NR	19
	**Sulfur connection** - Merrifield resin - 9 examples - yield: NR	19
	**Sulfur connection** - TentaGel - NpSSM linker - yield: NR	24, 61

Type of Reaction: Non-standard cleavage from resin	Comment	reference
	**Amidation** - hydroxymethylene resin - 8 examples - yield: NR	19

	**Cyclization** - Merrifield resin - 8 examples - yield: NR	19
	**Cyclization** - Merrifield resin - 40 examples - yield: NR	19
	**Cyclization** - Wang resin - 1000 examples - yield: NR	42
	**Cyclization** - Merrifield resin - 9 examples - yield: NR	19
	**Cyclization** - hydroxymethylene resin - 3 examples - yield: NR	19
	**Cyclization** - Wang resin - 40 examples - yield: 4-81%	6, 19
	**Cyclization** - Merrifield resin - 40 examples - yield: 5-100%	6, 19
	**Cyclization** - aminomethylene resin - several examples - yield: NR	54
	**Deprotection** - Merrifield resin - 6 examples - yield: NR	19

	**Deprotection** - MBHA resin - 4 examples - yield: >90%	72
	**Deprotection** - silicon linker - aminomethylene resin - 4 examples - yield: 50-68%	30
	**Decarboxylation** - hydroxymethylene resin - 24 examples - yield: NR	19
	**Grignard** - Merrifield resin - 8 examples - yield: NR	19
	**Hydrogenation** - Merrifield resin - several examples - yield: NR	24
	**Iodination** - aminomethylene resin - 1 example - yield: NR	22
	**Iodolactonization** - Merrifield resin - 1 example - yield: NR	36
	**Iodolactonization** - Merrifield resin - 1 example - yield: 40%	73
	**Oxidation** - Spheron Ara 1000 - 1 example - yield: 83%	47
	**Photochemical** - MBHA resin - several examples - yield: NR	54
	**Photochemical** - NpSSM linker - TentaGel - several examples - yield: 58%	24, 61

	**Reduction** - Merrifield resin - 27 examples - yield: NR	37
	**Reduction** - Wang resin - 10 examples - yield: 36-86%	74
	**Reduction** - MBHA resin - few examples - yield: 25-40%	75
	**Transamidation** - Safety-Catch linker - 13 examples - yield: 88-98%	15a
	**Transesterification** - Merrifield resin - 15 examples - yield: 95%	31

Footnote:
●: resin
EWG: electron withdrawing group
NR: not reported
NSG: N-substituted glycine
pNP: para-nitrophenyl
HMPA: [4-(hydroxymethyl)phenoxy]acetic acid (linker)
NpSSM: 2-methoxy-5-[2[(2-nitrophenyl)dithio]-1-oxopropyl]phenyl acetic acid (linker)

From the information presented the following general trends can be identified and, based on these trends some potential areas for future developments within organic chemistry are tentatively identified.

Resins: The most-used polymer backbone is polystyrene, crosslinked with 1 or 2% divinylbenzene. The latter polymer is the preferred one for reactions at higher temperatures or for reactions with organometallic reagents. Some of the phenyl rings are functionalised (*e.g.* with CH_2OH) to allow attachment of small molecules. These resins withstand a wide range of reaction conditions, but some limitations can be observed:

- They are compatible with a wide range of polar and apolar solvents: *e.g.* DMF, NMP, alcohols, THF, acetonitrile, dichloromethane.
- Prolonged use of mechanical stirring can cause mechanical damage of the resin. Mixing is achieved by: vortexing by employing orbital shakers, ultrasonic or magnetic stirrers or by bubbling gas through the suspension. So far, the method of choice has not become evident.
- The temperature range for reactions described to date is about -78°C to 155°C, although the most commonly used is room temperature.
- A broad range of reagents is compatible with the conventionial resins employed, including acids (*e.g.* TFA, $POCl_3$), bases (*e.g.* DBU, RLi), Lewis acids (*e.g.* $BF_3.OEt_2$), reducing agents (*e.g.* $LiAlH_4$, DIBAH, $NaCNBH_3$), oxidising agents, homogenous transition metal complexes (*e.g.* $Pd(OAc)_2$, $Pd_2dba_3.CHCl_3$) and soluble salts (*e.g.* KtOBu). Solid-support based reagents are not usually used due to the solid-solid interactions. Sometimes a severely limiting factor in the choice of reagents is the nature of the linker attaching the molecule to the polymer.
- The large interior surface area of the resins is easily accessible for solvents and reagents. Extensive washing procedures are required in order to remove excess reagents and high boiling solvents from these interior spaces.

Expectation: Although the polystyrene based resins have been used successfully there is a need for new resins , possibly based on other polymeric backbones which will address some of the limitations of polystyrenes (mechanical strength, large interior surface). Recent developments include grafting polyoxyethylene onto the resin (TentaGels) and using "soluble" resins such as PEG[15b] . The TentaGels have a lower loading capacity than the polystyrene-based resins, but they swell better in polar solvents like methanol and water. Lately, PEGA resins have been used. These supports swell

extensively in a wide range of solvents and are freely permeable for very large molecules (*e.g.* enzymes)[51]. In the future non-porous materials might be used on which the linker is grafted.

Linkers: Most of the linkers used in the period 1992-1995 were originally developed for oligomer chemistry and afford carboxylic acids and amides after cleavage. This can be viewed as a severe limitation. However, several attempts to circumvent this problem have led to alternative immobilisation methods using the existing linkers to yield, after cleavage, alcohols[64] or amines[52] instead of carboxylic acids or amides. Also strategies have been developed in which the small molecules are released from the linker by a cyclization reaction[6,19, 42, 54]. Recently linkers that are cleaved to other functionalities[21, 18, 70, 71] (hetero atoms) and linkers that are cleaved under very selective and mild conditions (*e.g.* photochemical cleavage) have been reported (see Table; Type of Reaction: Non-Standard Immobilisation Reaction or Non-Standard Cleavage). There remains a major need to design linkers that yield after cleavage molecules without a trace of that linker (traceless linkers)[24,30,61].

Expectation: To extend the synthetic utility of linkers by multifunctional cleavage options, which enable the release of different functional groups depending on the reagent used for cleavage. An issue of economic importance is the regeneration of the linker after the cleavage reaction.

Reaction portfolio: The synthetic repertoire of solid phase organic chemistry is growing rapidly. However, so far only a small percentage of solution chemistry has been translated into solid-phase chemistry. At the moment the following classification can be made:

- *Robust, reliable SPOC reactions (many examples)*

  Acylations: amide-bond formations; related to peptide chemistry, urea formation.

  Alkylations: mainly N- and O-alkylations and less C- and S-alkylations

  Imine formation/reductive amination: Although many examples are given it seems that different amine/carbonyl combinations require different reaction conditions. No universal experimental procedure can be given at the moment

  Mitsunobu-type ether formation

  Cross Coupling reactions (Stille, Suzuki and Heck)

- *Emerging SPOC reactions*

  Of the following reaction types only a limited number of examples has been published. *Oxidations, reductions, heterocycle formation, cycloadditions, asymmetric reactions, multiple component reactions, organometallic reactions, carbanion reactions* (Aldol,

Claisen and Knoevenagel condensations), *olefination reactions, addition to carbon-carbon multiple bonds* (*e.g.* hydrogenation, Michael addition), *addition to carbon-heteroatom multiple bonds* (*e.g.* Grignard)

- *Undeveloped SPOC reactions*

  Of the following reaction types no examples or only a rare example have been reported. *Electrophilic and nucleophilic aromatic substitutions* (except Cross-Coupling), *reactions with highly reactive species* (radicals, carbenes, nitrenes, acyliminium etc.), *eliminations, rearrangments*.

Reaction monitoring: Compared to solution-phase organic synthesis, solid phase reactions are generally more difficult to monitor principally because the technique of "following a reaction by TLC" is not appropriate. Currently, the methods used for monitoring non-peptide solid-phase reactions include *i)* analysing the small molecule whilst it is still bound to the resin, *e.g.* FT-IR[52], ^{13}C gel NMR[39,44], MAS NMR[76], colour detection reagents for reactive functionalities[58,77] (*i.e.* NH_2, SH, COOH) or *ii)* removing a small portion of the resin and cleaving the small molecule fragment *e.g.* MALDI-TOF MS[78].

Expectations: There is a need for fast, robust methods to follow new solid phase reactions that can be performed non-destructively (*e.g.* NMR) or with a minimum amount of material (*e.g.* MALDI-TOF).

Standard experimental procedure for new SPOC reactions: During the period covered by this review several "solution-phase organic chemists" have made the switch to solid phase. Whilst the detailed experimental strategies that have been utilised in different laboratories are not known, it is possible to draw some general conclusions.

1. The starting point is the solution chemistry (reagents, solvents, temperature) of the same reaction and apply similar conditions on solid phase, provided they are amenable to the overall requirements of the resins and linkers described above.
2. The different combinations of resins and linkers are studied.
3. Subsequently, optimisation is sought towards high yielding, reliable and clean reactions by varying solvents, reagents, reagent concentrations and temperature. A synthesis robot may expedite this study. Monitoring of the reactions (*vide supra*) is important for a rapid feed-back in this optimisation procedure.
4. Finally, fast and easy purification steps are developed using *e.g.* the Solid Phase Extraction[79] procedure.

In conclusion, the rapidly emerging field of SPOC offers great opportunities and challenges for organic chemists. Some of these challenges include: extending the portfolio SPOC reactions, developing new, versatile methods for reaction monitoring, developing new linkers (traceless and multifunctional ones, *i.e.* one linker for different functionalities), new resins and fast purification methods. We foresee that more and more chemist will use SPOC and that the potential applications will not be limited to pharmaceuticals. Combinatorial chemistry based on SPOC has already been applied to the generation of new artificial receptors/host-guest complexes[80] (libraries of host molecules) and artificial catalysts/enzymes[81].

It was Merrifield who stated[82] in 1969 with regard to solid-phase organic chemistry: "A gold mine awaits discovery by organic chemists". This prompted Leznoff to add[8a] in 1978 "Many gold nuggets have now been mined ... and some iron pyrites". Nearly twenty years later one is inclined to conclude that we have only hit upon the first ore-layer.

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(*Received* 22 *February* 1996)