Recent developments in solid-phase organic synthesis

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Reviewing the literature published between October 1995 and October 1996

1 Introduction

This review covers literature published during the period between October 1995 and October 1996 with an emphasis placed upon small molecule synthesis. The material has been arranged arbitrarily by the author according to three broad categories; carbon–carbon bond forming reactions, carbon–heteroatom bond forming reactions and linkers and cleavage strategies. In cases where a reaction sequence involves transformations which fall into more than one category, an effort has been made to provide cross references where appropriate. The synthesis of biopolymers and biopolymer analogues has been largely excluded.

The huge current interest in solid-phase organic synthesis can largely be attributed to the development of combinatorial chemistry. Although it is not immediately apparent how some of the strategies presented would be applied to library preparation, they provide important contributions that help define scope and limitations within the rapidly developing area of solid-phase organic synthesis. The level of sophistication seen in solid-phase synthesis sequences is set to increase further as the impact of improvements in linker design, rapid on- and off-bead analytical technology and automated synthesis equipment is felt. Finally, the advantages offered by synthesising small molecules whilst attached to a solid support should not be restricted to combinatorial applications. In many cases a solid-phase synthesis may prove superior to the analogous solution chemistry. It is hoped that as further advances are made in the area of solid-phase small molecule synthesis, this long neglected area will become more widely accepted as an alternative to more traditional solution-phase approaches.

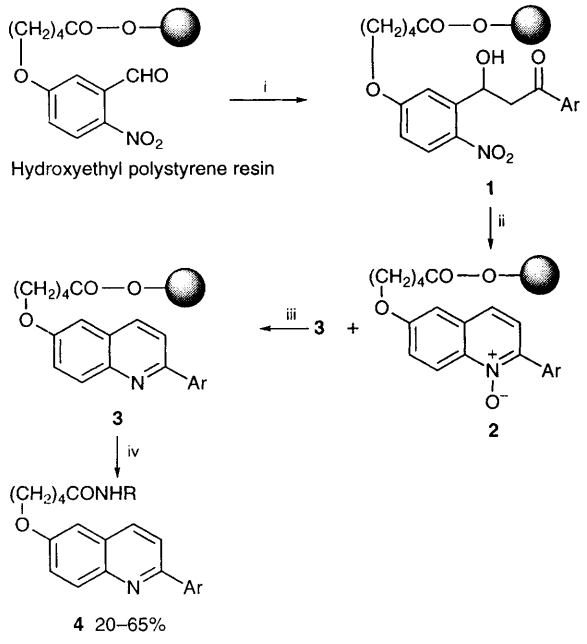
A number of reviews dealing with the areas of combinatorial chemistry and solid-phase synthesis have appeared in the literature over the last year.[1–12] A series of articles detailing more specific achievements of individual research groups working in the general area of combinatorial chemistry appeared in a dedicated issue of *Accounts of Chemical Research* are also included.[13–18]

2 Carbon–carbon bond formation

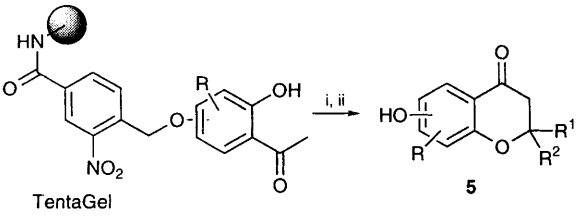
2.1 Reactions of enols, enolates and enolate equivalents

The reactions of enols and enolates with carbon electrophiles are amongst the most fundamental of processes for the construction of carbon frameworks in solution. Applications in the area of solid-phase synthesis have allowed access to a rich variety of acyclic, carbocyclic and heterocyclic structures. Crossed aldol condensations were used to construct the carbon framework of 2,6-disubstituted quinoline derivatives **4** (**Scheme 1**).[19] Reductive cyclisation of aldol adducts **1** furnished a mixture of the desired quinolines **3** along with the major *N*-oxide products **2**, which were further reduced to **3** using a titanium(III) reagent. Lewis acid assisted nucleophilic cleavage from the resin allowed an additional element of diversity to be introduced, providing twelve discrete quinolines **4**.

A method to prepare an encoded library of dihydrobenzopyrans **5** has been reported by chemists at Pharmacopeia (**Scheme 2**).[20] An aldol



Scheme 1 *Reagents and conditions*: i, ArCOMe, K_2CO_3, THF, reflux; ii, $SnCl_2{\cdot}2H_2O$, CH_2Cl_2–EtOH, reflux; iii, $TiCl_3$, CH_2Cl_2–toluene; iv, $AlMe_3$, RNH_2, CH_2Cl_2

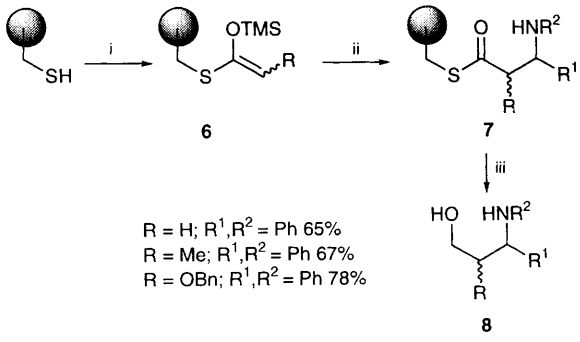


Scheme 2 *Reagents and conditions*: i, pyrrolidine, R^1COR^2; ii, *hν* 360 nm

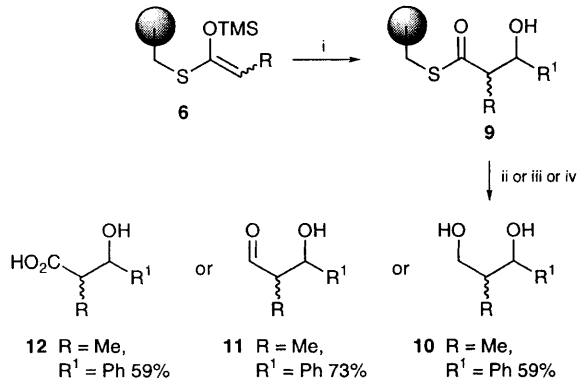
condensation–cyclisation sequence provided the heterocyclic framework in a single synthetic operation.

Resin-bound silyl enol ethers **6** have been shown to react efficiently with imines or aldehydes in the presence of catalytic $Sc(OTf)_3$ to afford *β*-amino thioesters **7** or *β*-hydroxy thioesters **9** (**Schemes 3** and **4**).[21,22] Reductive cleavage of the support-bound thioesters **7** or **9** with $LiBH_4$ gave the corresponding amino alcohols **8** or diols **10** respectively. Alternatively, *β*-hydroxy aldehydes **11** or *β*-hydroxy acids **12** could be obtained in good yield by hydrolysis or DIBAL-H reduction of **9**.

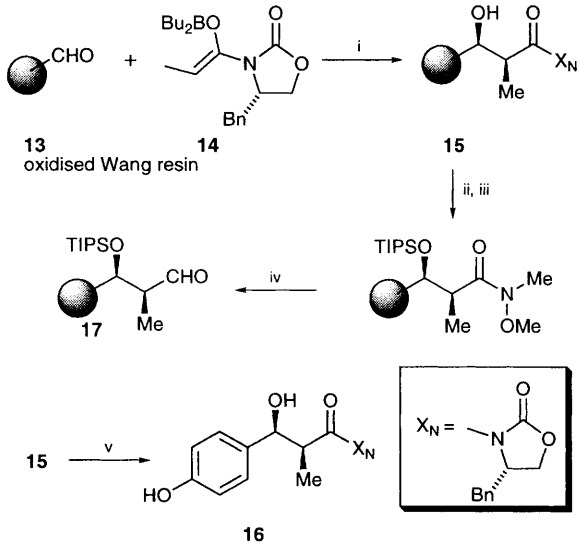
An iterative strategy for the stereocontrolled solid-phase synthesis of polyketide fragments by means of an asymmetric aldol reaction has been described (**Scheme 5**).[23] Resin-bound aldehyde **13** was prepared by oxidation of Wang resin using the sulfur trioxide–pyridine complex. Efficient aldol reaction with boron enolate **14** was demonstrated by on-bead IR spectroscopy of the resin-bound product **15**. Lewis-acid promoted cleavage from the resin



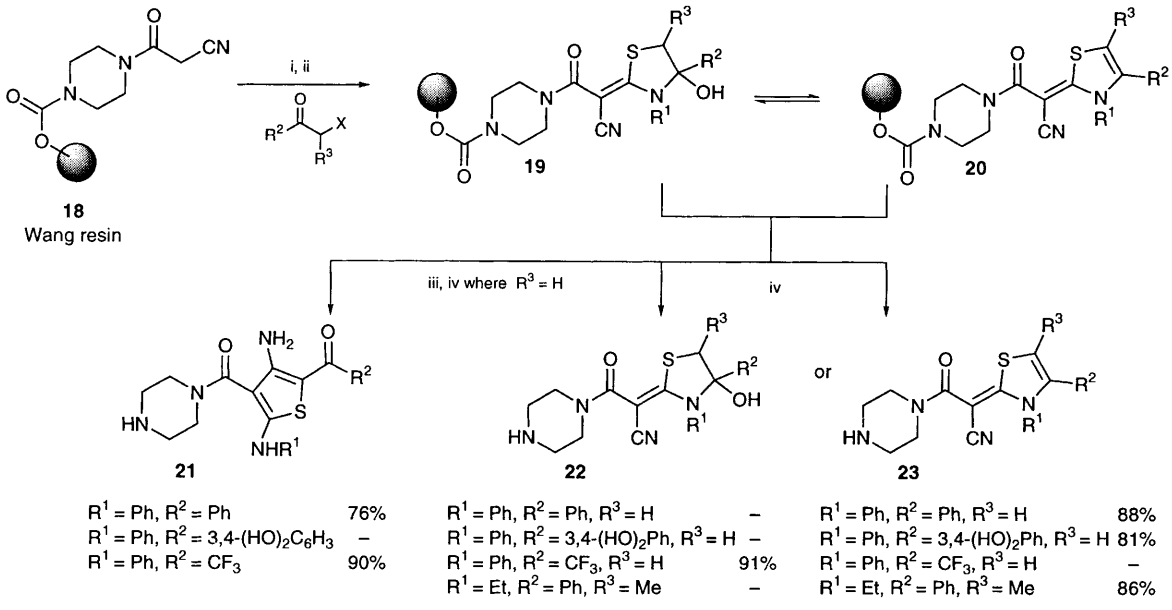
Scheme 3 *Reagents and conditions*: i, (a) RCH_2COCl, Et_3N, CH_2Cl_2; (b) TMSOTf, Et_3N, CH_2Cl_2; ii, 10 mol% $Sc(OTf)_3$, imine, CH_2Cl_2; iii) $LiBH_4$, Et_2O, rt



Scheme 4 *Reagents and conditions*: i, 20 mol% $Sc(OTf)_3$, aldehyde, CH_2Cl_2; ii, $LiBH_4$, Et_2O; iii, DIBAL-H, CH_2Cl_2; iv, 1 M NaOH–dioxane (1:4)



Scheme 5 *Reagents and conditions*: i, CH_2Cl_2; ii, TIPS-OTf, 2,6-lutidine; iii, MeNH(OMe)•HCl, $AlMe_3$; iv, DIBAL-H; v, BCl_3, CH_2Cl_2



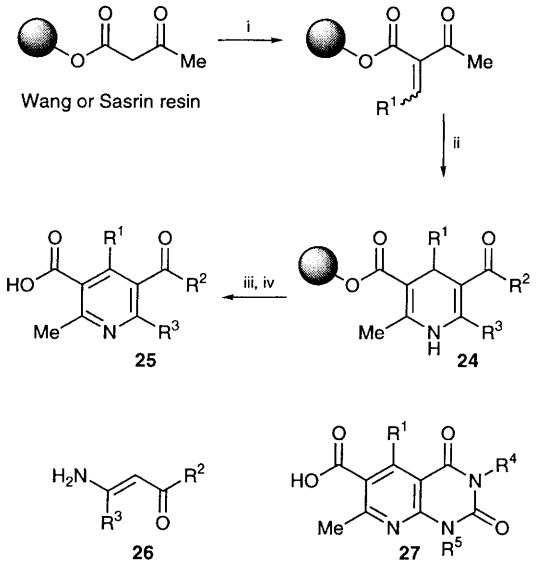
Scheme 6 *Reagents and conditions*: i, R^1NCS, DBU, DMF; ii, α-halo ketone, AcOH, DMF; iii, DBU, DMF; iv, TFA, CH_2Cl_2

provided the major *syn*-aldol **16** along with some *anti*-adduct which resulted from epimerisation of **16** under the cleavage conditions. Alternatively, the resin-bound aldol product **15** could be transformed to aldehyde **17** which would be able to take part in further solid-phase aldol reactions. The problem of elimination to provide some α,β-unsaturated aldehyde and the loss of some silicon protection may complicate the synthesis of larger fragments. However the work does illustrate the feasibility of preparing synthetic polyketide derived structures on solid support.

Knoevenagel-type condensations were employed as the key carbon–carbon bond forming reactions in recent solid-phase syntheses of a variety of heterocyclic structures (**Scheme 6**).[24] Reaction of cyanoacetyl compounds **18** with isothiocyanates was followed by condensation with α-haloketones to provide resin-bound heterocycles **19** or **20**. Treatment with DBU and subsequent cleavage from the resin returned substituted thiophenes **21** in some cases, depending upon the nature of R^1 and R^2 (in several examples complex mixtures resulted *e.g.* R^1 = phenyl; R^2 = 3,4-dihydroxyphenyl; R^3 = H). Alternatively, direct cleavage of the heterocycles under acidic conditions led to either **22** or **23**, again depending on the nature of R^1, R^2 and R^3.*

Sequential Knoevenagel and Hantzsch condensations provided the basis for two solid-phase dihydropyridine syntheses (**Schemes 7** and **59**).[25,26] In the example shown in **Scheme 7**, pyridines **25** were also accessed by oxidation of the corresponding dihydropyridines **24** using ceric ammonium nitrate. Appropriate choice of enamino carbonyl component **26** also allowed entry into bicyclic azine heterocycles such as pyrido[2,3-*d*]pyrimidines **27**.

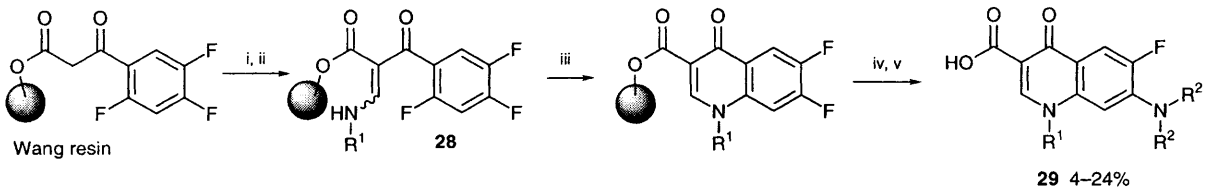
*The structure of compound **21** where R^1 = Ph, R^2 = CF_3 now been found to be incorrect. See *Tetrahedron Lett.*, 1996, **37**, 7865.



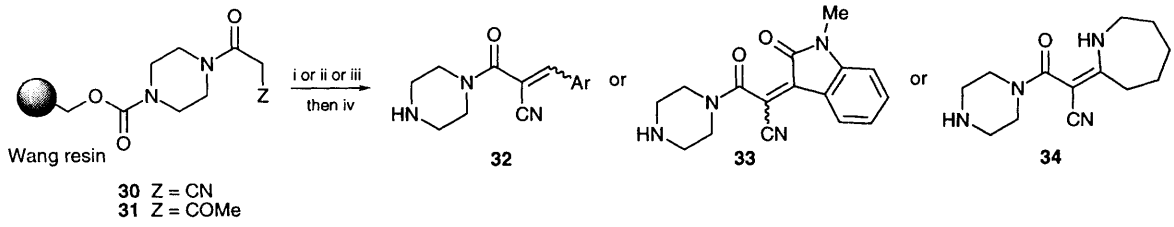
Scheme 7 *Reagents and conditions*: i, R^1CHO, piperidine, Pr^iOH–C_6H_6, heat; ii, **26**, DMF, heat; iii, CAN, DMA; iv, TFA, CH_2Cl_2

Knoevenagel-type condensation of a resin-bound β-keto ester with dimethylformamide dimethyl acetal followed by a conjugate addition–elimination sequence provided the oxo enamine **28**, a key intermediate in a solid-phase quinolone synthesis (**Scheme 8**).[27] Sequential intramolecular and intermolecular nucleophilic aromatic substitution reactions followed by cleavage from the solid support provided a number of quinolones **29** in fairly modest yields, but with good levels of purity.

Knoevenagel-type reactions have been investigated as a means of generating a variety of monoacyl piperazine containing structures **32–34** (**Scheme 9**).[28] Cyanoacetic acid derivative **30** underwent condensation with carbonyl containing



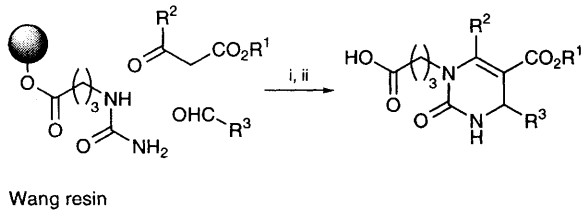
Scheme 8 *Reagents and conditions*: i, $(MeO)_2CHN(Me)_2$, THF; ii, NH_2R^1, THF; iii, tetramethylguandine, CH_2Cl_2, 55 °C; iv, $(R^2)_2NH$, NMP, 110 °C; v, TFA, CH_2Cl_2



Scheme 9 *Reagents and conditions*: i, ArCHO, piperidine–DMF; ii, 1-methylisatin, piperidine–DMF; iii, *O*-methylcaprolactim, piperidine–DMF; iv, TFA–CH_2Cl_2

coupling partners to provide adducts **32–34**. In contrast, β-keto-amide derivative **31** failed to provide any of the expected condensation products.

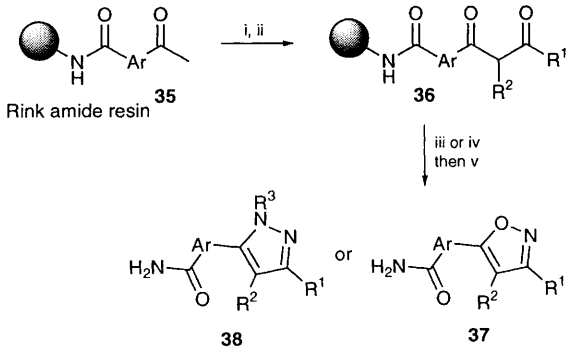
The combination of multiple-component coupling strategies with solid-phase synthesis has provided an area of considerable interest. Wipf and Cunningham have disclosed the results from their work on the solid-phase Biginelli dihydropyrimidine synthesis (**Scheme 10**).[29] Generally superior yields and purities were obtained to those for the analogous solution chemistry.



Scheme 10 *Reagents and conditions*: i, HCl, THF, 55 °C; ii, TFA, CH_2Cl_2

Claisen condensation of resin-bound keto amide derivatives **35** with non-enolisable ester derivatives provided β-dicarbonyl intermediates **36** (**Scheme 11**).[30] Subsequent tetrabutylammonium fluoride promoted alkylation, followed by treatment with hydroxylamine or a substituted hydrazine, afforded resin-bound isoxazoles or pyrazoles respectively. Cleavage from the resin provided a high yield of the desired heterocycles **37** or **38** in the majority of the cases examined.

Additional examples of the use of a solid-phase aldol and Knoevenagel-type reactions are shown in **Schemes 71** and **23**. Alkylation of enolate anions has also proved to be rewarding as a solid-phase

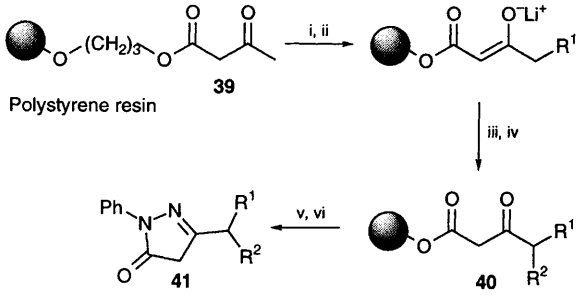


Scheme 11 *Reagents and conditions*: i, R^1CO_2Me, NaH; ii, TBAF then R^2X; iii, NH_2OH; iv, NH_2NHR^3; v, TFA, CH_2Cl_2

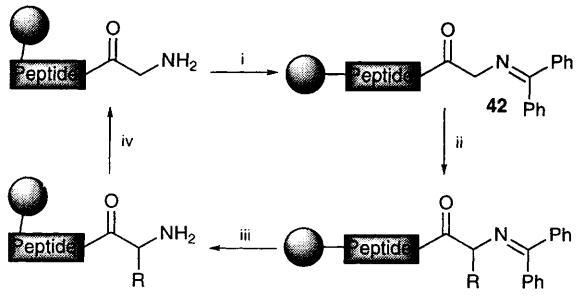
synthetic method, both in terms of efficiency and as a means of introducing diversity.

Tietze *et al.* have described an approach to the solid-phase synthesis of 1-phenylpyrazolone derivatives **41** involving sequential dialkylation of the dianion of resin-bound β-keto ester **39** with a number of alkyl and allylic halides (**Scheme 12**).[31] Efficient pyrazolone formation and cleavage from the resin was then achieved by treatment of β-keto ester derivative **40** with phenylhydrazine at 100 °C.

Unusual side-chain substitutions can be introduced during solid-phase peptide synthesis by alkylation of the Schiff's base of a resin-bound terminal glycine unit **42** (**Scheme 13**).[32] Schwesinger's hindered phosphazene bases were used to deprotonate intermediates **42** in the presence of alkylating agents. The sequence can be repeated, or combined with conventional solid-phase peptide synthesis to provide a powerful method for the introduction of unnatural amino acids. In its present form the sequence is not stereocontrolled, however the authors are currently



Scheme 12 *Reagents and conditions*: i, 6 equiv. LDA, THF; ii, R^1X, THF; iii, BuLi , THF; iv, R^2X, THF; v, PhNH-NH_2, THF; vi, toluene, 100 °C

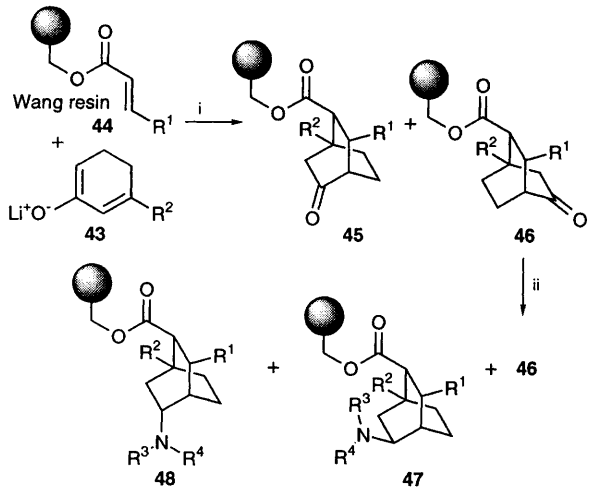


Scheme 13 *Reagents and conditions*: i, Ph_2CO, AcOH, NMP; ii, P_1–Bu^t or 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine(BEMP), RX, NMP; iii, 1 M HCl–THF (3:7); iv, further coupling

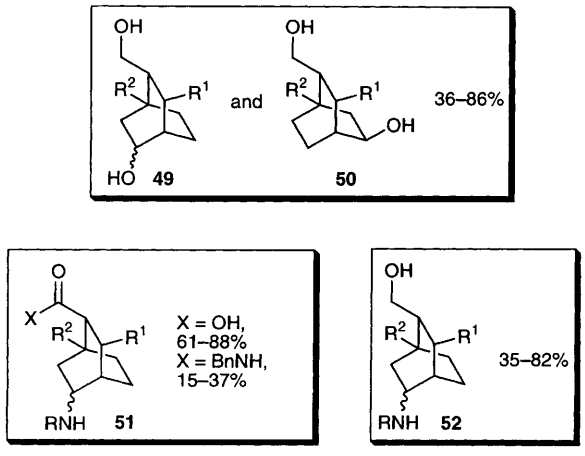
exploring this aspect as well the possibility of effecting geminal dialkylation.

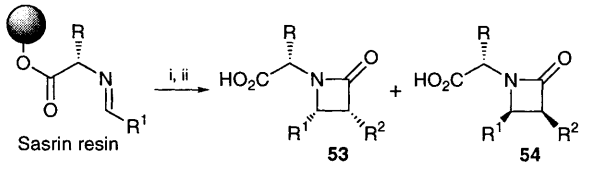
Bicyclo[2.2.2]octane derivatives **49–52** have been prepared by tandem Michael addition reaction between cyclohex-2-en-1-one lithium enolates **43** and resin-bound acrylates **44** (**Scheme 14**).[33] Reductive amination of the resulting mixture of bicyclic ketones **45** and **46** provided epimeric amines **47** and **48**, with the *exo*-ketone **46** remaining unchanged under the reaction conditions. A number of cleavage protocols including reduction with DIBAL-H, aminolysis or acid-catalysed hydrolysis provided an array of structures **49–52** containing the bicyclo-[2.2.2]octane core.

Additional examples of solid-phase enolate alkylation are shown in **Schemes 11** and **30**.



Scheme 14 *Reagents and conditions*: i, THF, –78 °C to rt; ii, amine, $NaBH(OAc)_3$, Na_2SO_4, CH_2Cl_2–AcOH (99:1), ultrasound





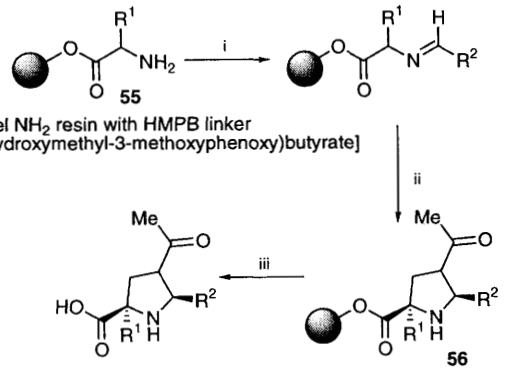
Scheme 15 *Reagents and conditions*: i, R^2CH_2COCl, Et_3N, CH_2Cl_2; ii, TFA–CH_2Cl_2

2.2 Pericyclic reactions

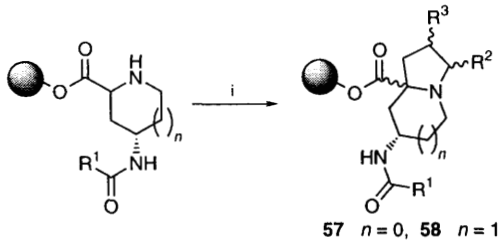
Staudinger cycloaddition of polymer-supported imines with ketenes provided a diversely substituted library of β-lactams **53–54** (**Scheme 15**).[34–36] In most cases mixtures of diastereoisomers were observed. Reported yields were good to excellent and a range of functionality (*e.g.* R = alkyl, heteroalkyl, R^1 = aryl, heteroaryl and R^2 = OR, NR_2 and alkyl) could be incorporated into the products.

In a series of papers and patents, Affymax chemists described the application of a [3+2] cycloaddition approach to the synthesis of pyrrolidine containing compounds. Condensation of resin-bound amino acids **55** with a series of aldehydes, followed by Lewis acid induced cycloaddition with electron-deficient olefins afforded the desired cyclic amines **56** (**Scheme 16**).[36–39] A similar thermally induced process provided the bicyclic pyrrolidine derivatives **57** and **58** (**Scheme 17**).

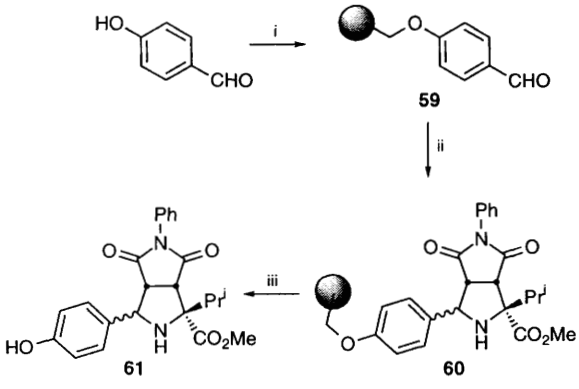
Chemists at Ceregen have also disclosed the results of their efforts to synthesise pyrrolidines **61** using a three-component [3+2] cycloaddition strategy (**Scheme 18**).[40] Reaction of resin-bound aldehyde **59** with an amino ester and *N*-phenylmaleimide under thermal conditions afforded cycloadducts such as **60**.



Scheme 16 *Reagents and conditions*: i, R^2CHO, $CH(OMe)_3$; ii, but-3-en-2-one, Ag_2NO_3, Et_3N, MeCN; iii, TFA, CH_2Cl_2



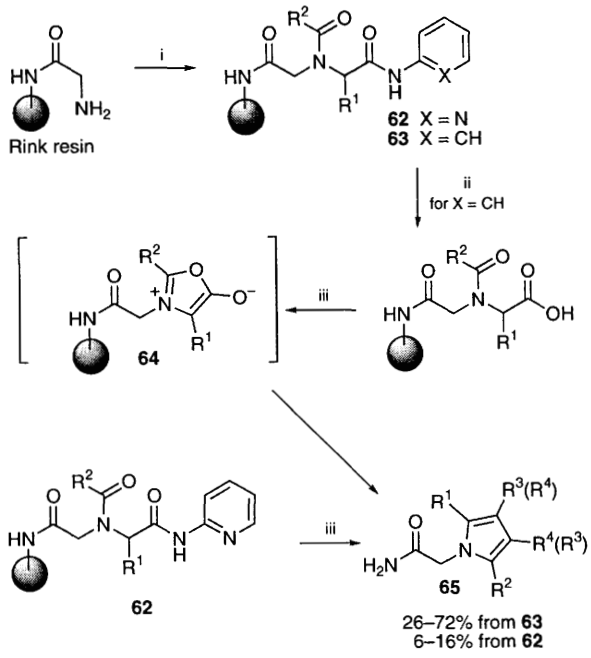
Scheme 17 *Reagents and conditions*: i, R^2CHO; ii, $R^3CH{=}CH_2$, base, heat



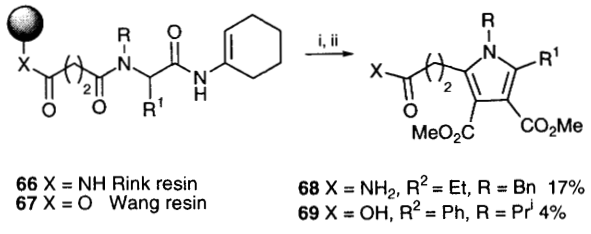
Scheme 18 *Reagents and conditions*: i, Wang resin, PPh_3, DEAD, THF; ii, leucine methyl ester•HCl, *N*-phenylmaleimide, Et_3N, AcOH, DMF, 100 °C; iii, TFA, CH_2Cl_2

1,3-Dipolar cycloaddition of alkynes with polymer-bound münchnones **64** has been used effectively to prepare a variety of tetra- and penta-substituted pyrroles **65** (**Scheme 19**).[41] The intermediate münchnones **64** were conveniently prepared from the Ugi reaction products **62** or **63** by either one- or three-step activation respectively.

Armstrong *et al.* have previously reported the synthesis of pyrroles **68**–**69** by cycloaddition of dimethyl acetylenedicarboxylate (DMAD) with resin-bound münchnones (**Scheme 20**), which had also been prepared from the products **66**–**67** of Ugi



Scheme 19 *Reagents and conditions*: i, R^1CHO, PhNC or 2-PyrNC, R^2CO_2H, $CHCl_3$–pyridine–MeOH, 65 °C; ii, (a) TEA, DMAP, Boc_2O, CH_2Cl_2; (b) LiOH, H_2O_2, THF–H_2O; iii, (a) R^3CCR^4, Ac_2O, 65–100 °C; (b) 20% TFA, CH_2Cl_2

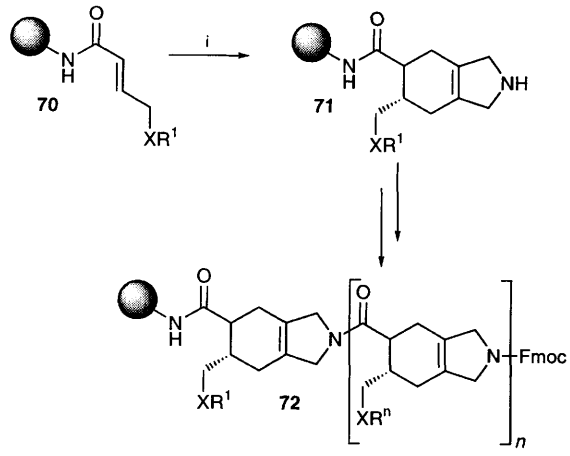


Scheme 20 *Reagents and conditions*: i, HCl, DMAD, toluene, heat; ii, TFA, CH_2Cl_2

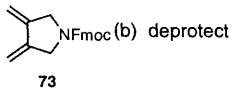
four-component condensations.[42] Introduction of a universal isocyanide component, 1-isocyanocyclohexene, allows one-step post-condensation activation. Unfortunately, the reported yields for the cycloaddition were rather low as was seen for the direct cyclisation of **62** above.

Boger has described the synthesis of non-hydrolysable peptidomimetics **72** by means of an iterative strategy in which a Diels–Alder reaction is employed as a key step (**Scheme 21**).[43] The resin-bound dienophile **70** is treated with a suitable diene **73** under thermal conditions to afford a cycloadduct **71**. Deprotection followed by coupling with another acrylic acid unit allowed the cycle to be repeated.

Still *et al.* reported methods for the preparation of a variety of encoded libraries, including a hetero-Diels–Alder library (**Scheme 22**).[44] Lewis acid promoted reaction of resin-bound imines **74** with dihydrofurans **75** provided the cycloadducts **76**, after release from the resin under photochemical condi-



Scheme 21 *Reagents and conditions*: i, (a) **73**, toluene, reflux; (b) deprotect



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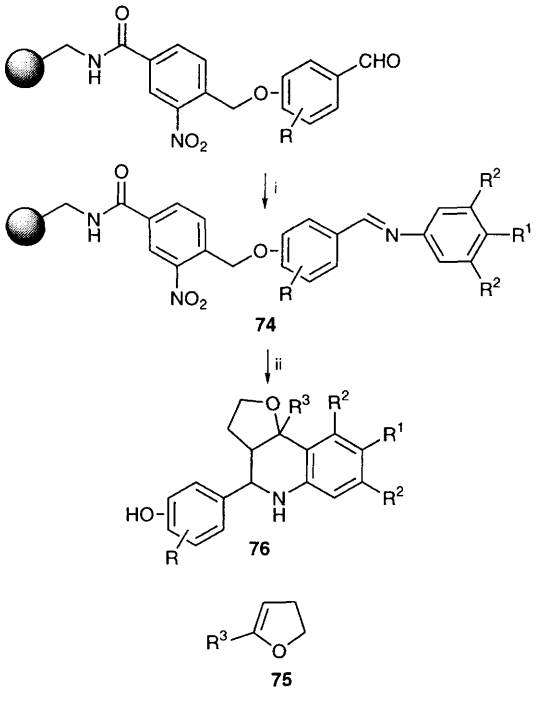
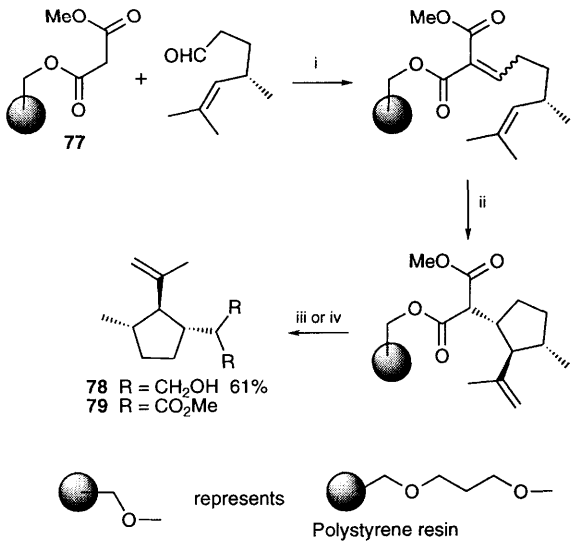


Scheme 22 *Reagents and conditions*: i, amine, toluene, 70 °C; ii, (a) **75**, $BF_3{\bullet}OEt_2$, CH_2Cl_2; (b) *hν* 350 nm, DMF

tions. The encoding tags, which are not shown, could later be released oxidatively allowing the identity of the azatricyclic product **76** to be deciphered.

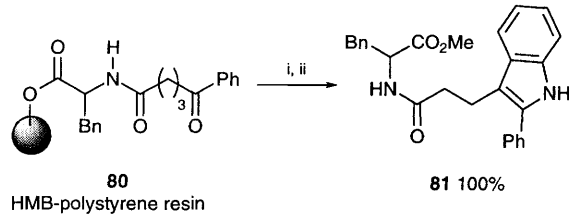
A selection of resin-bound five-membered carbocyclic structures have been prepared by a domino sequence involving Knoevenagel reaction of **77** with a series of unsaturated aldehydes followed by an intramolecular ene reaction.[45] Reductive cleavage from the resin provided diol **78** in 61% yield and 97% de. Alternatively, transesterification using $Ti(OEt)_4$ and methyl propionate provided diester **79**



Scheme 23 *Reagents and conditions*: i, piperidinium acetate, CH_2Cl_2, 20–40 °C; ii, $ZnBr_2$, CH_2Cl_2; iii, DIBAL-H, toluene; iv, $Ti(OEt)_4$, $EtCO_2Me$

(**Scheme 23**). Several substituted cyclohexanes were prepared in a similar way.

The Fischer synthesis has been used to generate fifteen indoles including **81** by reaction of ketone **80** with a series of hydrazines in the presence of protic or Lewis acids (**Scheme 24**).[46]

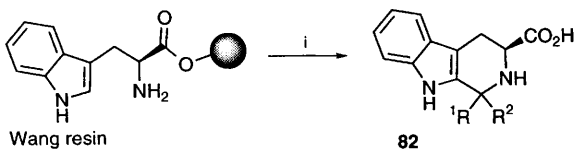


Scheme 24 *Reagents and conditions*: i, $C_6H_5NH\text{-}NH_2{\bullet}HCl$, $ZnCl_2$, AcOH, 70 °C; ii, MeOH–Et_3N (9:1)

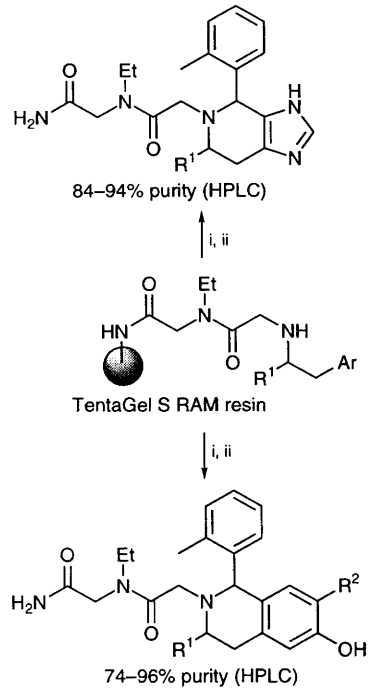
2.3 Electrophilic aromatic substitution

The general utility of electrophilic aromatic substitution is likely to be complicated by the reactivity of polystyrene synthesis supports and some linkers towards strongly electrophilic reagents. However, suitably electron-rich substrates or intramolecular situations have proved rewarding.

Several groups have described the synthesis of 1,2,3,4-tetrahydro-β-carbolines **82** using the Pictet–Spengler reaction of support-bound tryptophan derivatives with suitable carbonyl containing compounds (a representative example is shown in **Scheme 25**).[47–50] Either thermal or acidic cyclisation conditions were employed to secure the desired tricyclic products **82** in good yield, and in most cases good purity. A similar approach has been applied during recent tetrahydroisoquinoline and tetrahydroimidazopyridine syntheses (**Scheme 26**).[51]



Scheme 25 *Reagents and conditions*: i, (a) 4 equiv. aldehyde or ketone, TFA–CH_2Cl_2 (1:99); (b) TFA–H_2O (19:1)

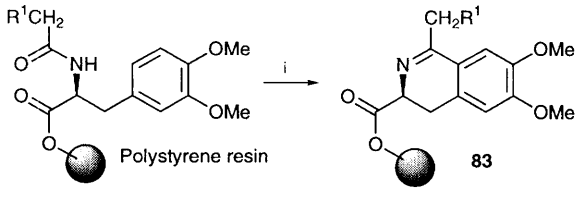


Scheme 26 *Reagents and conditions*: i, *o*-tolualdehyde, pyridine, 100 °C; ii, TFA, H_2O

The related Bischler–Napieralski reaction proved to be equally effective for the synthesis of dihydroisoquinolines **83** (**Scheme 27**).[52] Sodium cyanoborohydride reduction of the polymer-bound products **83** to tetrahydroisoquinolines was also reported.

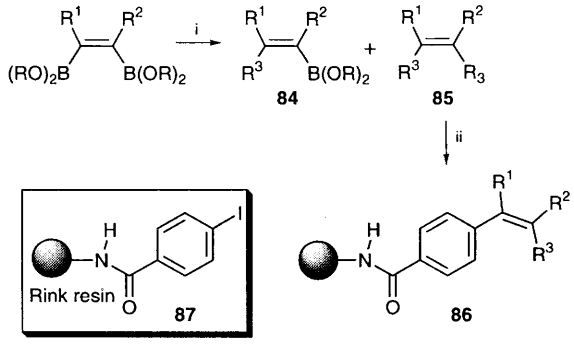
2.4 Organometallic chemistry

Due to mild reaction conditions and compatibility with a wide range of functional groups, palladium promoted reactions have become well established procedures for assembling carbon frameworks on solid support. Further examples of Suzuki,[53–58] Stille,[59–61] Heck,[59,62] and Sonogashira reactions have been reported.[53,63] The Heck reaction has also been used to effect macrocyclisation of a number of polyamide containing precursors on TentaGel resin, providing 20- to 24-membered rings in high yield.[64] Organozinc reagents have been found to be effective as the solution partner in the palladium catalysed synthesis of biaryls from resin-bound aryl bromides.[65]



Scheme 27 *Reagents and conditions*: i, $POCl_3$, toluene, 80 °C

An interesting approach to tetrasubstituted olefin synthesis on solid support adopted a technique termed resin capture, which allows a crude product from a solution-phase synthesis sequence to be selectively transferred onto a polymeric support.[57] Platinum catalysed diboration of an alkyne in solution, followed by Suzuki coupling of the crude reaction mixture with a 1.5-fold excess of an organohalide provided mono- and di-addition products **84** and **85** (**Scheme 28**). Only the mono-addition product **84** reacted with Rink resin-bound aryl iodide **87** to provide the desired resin-bound tetrasubstituted olefin **86**.

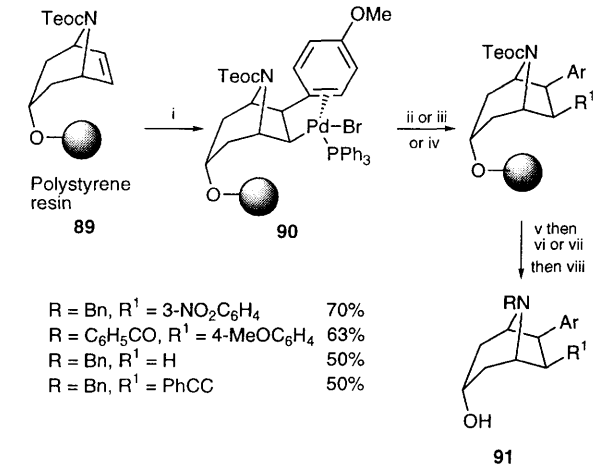


Scheme 28 *Reagents and conditions*: i,1.5 equiv. R^3X, $Pd(PPh_3)_2Cl_2$, 3 M KOH–DME, 80 °C; ii, **87**, 80 °C

Ellman has applied a palladium-mediated sequential three-component coupling reaction to the synthesis of tropane derivatives **91** (**Scheme 29**).[53] The *N*-protected tropane scaffold was attached to the polystyrene support through the THP linker. Subsequent reaction of the resin-bound alkene **89** with an aryl bromide and stoichiometric palladium reagent provided the palladium complex **90**. The stability of **90** towards β-hydride elimination allowed it to be separated from excess aryl bromide reagents and used in split synthesis sequences. Treatment of palladium complexes **90** with various coupling partners enabled further elements of diversity to be introduced.

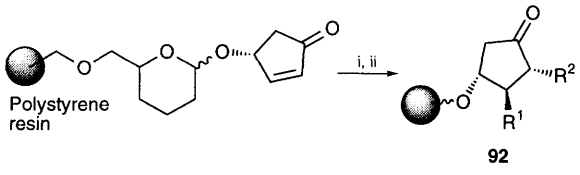
Ellman has described an approach to solid-phase synthesis of prostaglandin-type frameworks **92** by means of a conjugate addition–enolate alkylation sequence (**Scheme 30**).[60]

Syntheses of the azabicyclo[4.3.0]nonen-8-one ring systems **93** and **94** have been achieved through the use of solid-phase Pauson–Khand cyclisations (**Schemes 31** and **32**).[63] Two strategies were

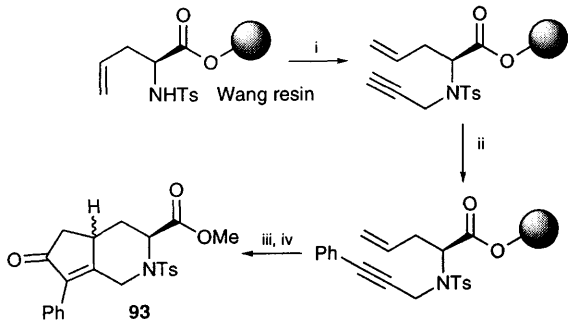


R = Bn, R^1 = 3-$NO_2C_6H_4$ 70%
R = C_6H_5CO, R^1 = 4-$MeOC_6H_4$ 63%
R = Bn, R^1 = H 50%
R = Bn, R^1 = PhCC 50%

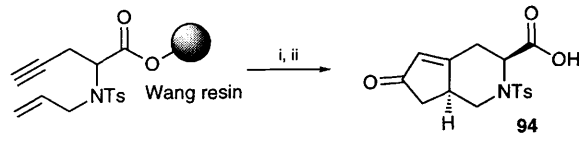
Scheme 29 *Reagents and conditions*: i, 4-$MeOC_6H_4$-Br, $Pd(PPh_3)_4$, THF, heat; ii, arylboronic acid, PPh_3, 2 M Na_2CO_3–THF, 66 °C; iii, formic acid, Et_3N, DMF, heat; iv, PhCCH, CuI, Bu_4NCl, DMF, 66 °C; v, TBAF, THF; vi, RCHO, $NaBH(OAc)_3$, DMF; vii, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate(HATU), Et_3N, $PhCO_2H$, DMF; viii, TFA–H_2O (20:1)



Scheme 30 *Reagents and conditions*: i, $R^1{}_2CuLi$; ii, R^2X



Scheme 31 *Reagents and yields*: i, prop-2-ynyl bromide, $CsCO_3$, DMF; ii, $(PPh_3)_2PdCl_2$, CuI, PhI, Et_3N, CH_2Cl_2; iii, $Co_2(CO)_8$, NMO, CH_2Cl_2; iv, TFA, CH_2Cl_2 (1:1)

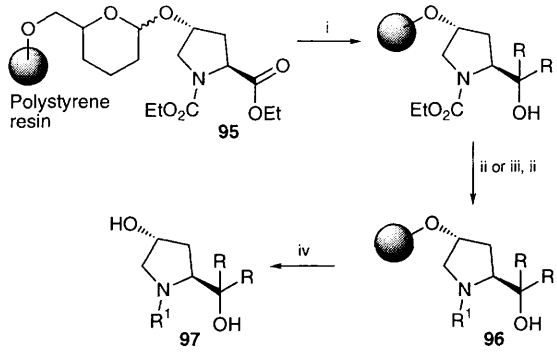


Scheme 32 *Reagents and conditions*: i, $Co_2(CO)_8$, NMO, CH_2Cl_2; ii, TFA, CH_2Cl_2

presented, both of which proceeded in good overall yields.

Still has reported further examples of the use of an encoding system, which effects attachment of the tags to synthesis supports using the rhodium catalysed reaction of diazo compounds with the support/substrate.[44,66–68] Intermolecular reaction of the rhodium carbenoid is thought to be fairly indiscriminate, which is not a serious problem for the coding application as only small quantities of the reagent are employed. From a synthetic point of view, intramolecular reactions of resin-bound rhodium carbenoids may prove rewarding. For an example of carbon–oxygen bond formation by means of an intermolecular reaction of a resin-bound carbenoid see **Scheme 43**.

The substituents R^1 and R present in pyrrolidine-2-methanol derivatives **97** are known to play an important part in determining the efficiency of the ligands as asymmetric catalysts. Ellman and Liu developed a solid-phase approach to the synthesis of ligands **97** which allowed variation of both R and R^1 (**Scheme 33**).[69] Addition of organomagnesium reagents to ester **95** followed by reductive alkylation of the pyrrolidine nitrogen provided resin-bound amino alcohols **96**. The products were evaluated for their efficiency as enantioselective catalysts for the addition of diethylzinc to aldehydes whilst attached to and after cleavage from the support.



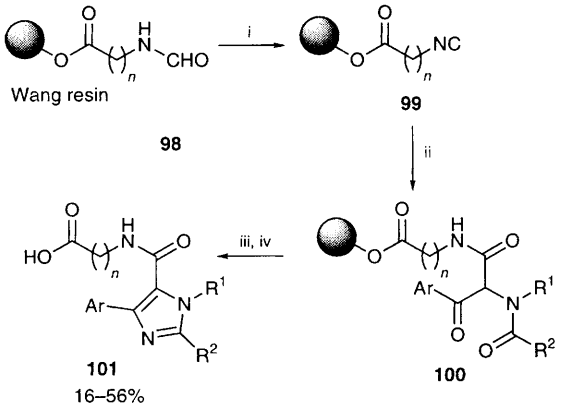
Scheme 33 *Reagents and conditions*: i, RMgBr; ii, Red-Al; iii, (a) KOH, BuOH–dioxane, reflux; (b) $(R^1CO)_2O$; iv, PPTS, $(ClCH_2)_2$–BuOH

Other examples of the use of organomagnesium and organolithium reagents during solid-phase organic synthesis can be seen in **Schemes 70** and **71**, including the generation of a resin-bound organolithium intermediate.

2.5 Ugi reaction

The Ugi reaction provides a powerful method for introducing several elements of diversity in a single synthetic step. As well as being targets of interest in their own right,[42,70] Ugi products have also been exploited as precursors to a variety of heterocyclic structures (see **Schemes 19** and **20**).

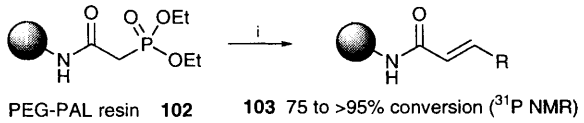
An approach to the solid-phase synthesis of imidazoles required the resin-bound intermediate **100**, which was readily prepared using an Ugi four component coupling reaction (**Scheme 34**).[71] The limited commercial availability of isocyanides led the researchers to prepare resin-bound isocyanides **99** by dehydration of the appropriate formamides **98**. Acid catalysed condensation of the Ugi products **100** with ammonium acetate, followed by cleavage from the resin provided the desired imidazoles **101**.



Scheme 34 *Reagents and conditions*: i, PPh_3, CCl_4, Et_3N, CH_2Cl_2; ii, ArC(=O)CHO, R^1NH_2, R^2CO_2H; iii, NH_4OAc, ACOH, 100 °C; iv, 10% TFA, CH_2Cl_2

2.6 Wittig and related reactions

Solid-phase Wittig chemistry has been known for some time; however the recent development of exceptionally mild methods for effecting the related Horner–Wadsworth–Emmons olefination make it particularly attractive for solid-phase synthesis. Resin-bound olefin **103** was prepared from phosphonate **102** as outlined in **Scheme 35**. The extent of reaction could be monitored using ^{31}P gel-phase NMR spectroscopy.[72] Other examples of Wittig-type olefination reactions are shown in **Schemes 63**, **74** and **75**.



Scheme 35 *Reagents and conditions*: i, LiBr, Et_3N, RCHO, MeCN

3 Carbon-heteroatom bond forming reactions

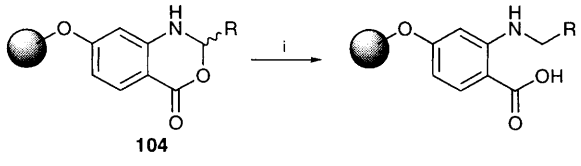
3.1 Carbon-nitrogen bond formation

Lithiated oxazolidinone bases have been found to be effective for the deprotonation of quinazoline-2,4-diones,[73] and benzodiazepines,[44,74] which can be alkylated efficiently with a variety of alkyl halides. Successive *N*-alkylation of amides has been exploited to prepare a library of peptidomimetics, based on a dipeptide scaffold.[75] Examples of the *N*-alkylation of sulfonamides can be seen in **Schemes 31** and **53**. Direct alkylation of resin-bound amines may be problematic in some cases due to over-alkylation, and reductive approaches are generally preferred.

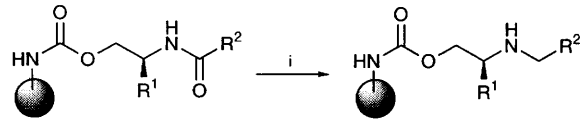
Reductive alkylation of amines with carbonyl compounds has proved to be an important solid-phase process, both due its efficiency and the commercial availability of a large number of amines, aldehydes and ketones. The borane–pyridine (BAP) complex was found to be an effective reducing agent for solid-phase reductive alkylation of a secondary amine with a number of aldehydes.[76] Reductive amination of ketones appeared to be somewhat less satisfactory with the BAP complex. Resin-bound amino acids were efficiently dialkylated using a two-fold excess of benzaldehyde and the BAP complex.

Modified procedures have been reported for the solid-phase reductive monoalkylation of primary amines with aldehydes using $NaCNBH_3$ in trimethyl orthoformate.[77] The influence of an added proton source on the problem of over alkylation was examined, and conditions developed for use with a variety of aldehydes.

Acid catalysed silane reduction of the intermediate aminals **104** has been described for the two-step *N*-alkylation of 2-carboxyanilines (**Scheme 36**).[78] The problem of over alkylation may also be avoided by reduction of the corresponding amide (**Scheme 37**).[79] In the example shown the BH_3•THF complex was found to be effective; furthermore the stability of carbamate functional groups to the reduction conditions allowed the sequence to be used in an iterative fashion to assemble oligocarbamates. For an example of amide reduction to provide a tertiary amine see **Scheme 33**.[69]



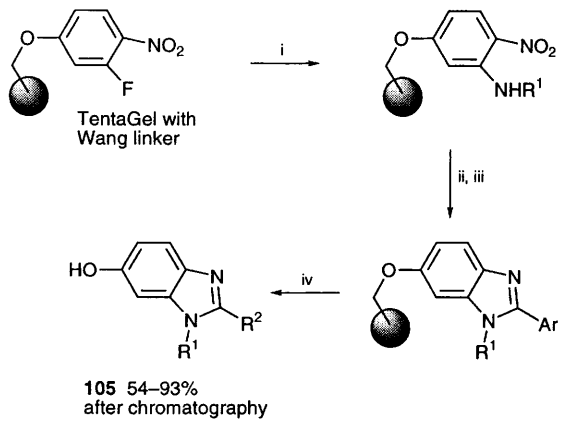
Scheme 36 *Reagents and conditions*: i, Et_3SiH, TFA



Scheme 37 *Reagents and conditions*: i, BH_3•THF, THF

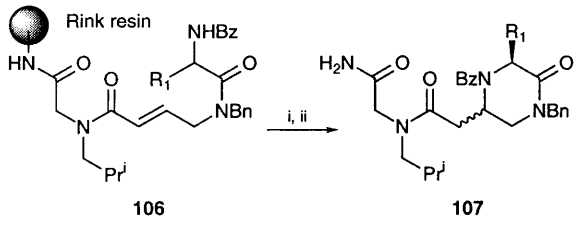
Functionalisation of electron deficient aromatic substrates by nucleophilic aromatic substitution with amines has been employed during the assembly of several heterocyclic frameworks (see **Scheme 8**). Shapiro *et al.* have shown that the progress of the S_NAr displacement of fluoride can be conveniently

monitored by ^{19}F gel-phase or MAS ^{19}F NMR.[80] A solid-phase synthesis of benzimidazoles **105** employing an S_NAr reaction has been reported by Berlex scientists (**Scheme 38**).[81] Other examples of S_NAr reactions on solid support have also appeared in the literature during the period covered by this review.[82]



Scheme 38 *Reagents and conditions*: i, R^1NH_2; ii, $NaBH_4$, $Cu(acac)_2$; iii, ArC(=NH)OEt•HCl, BuOH–DMF, 90 °C; iv, TFA, H_2O

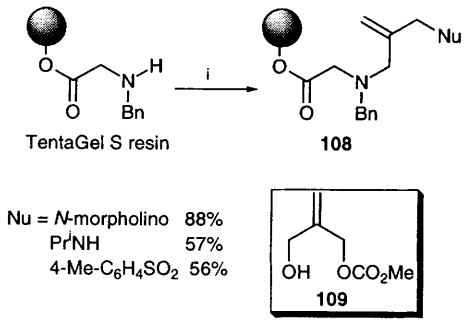
Inspiration for a solid-phase synthesis of constrained cyclic peptoids resulted from an attempt to cyclopropanate α,β-unsaturated amide **106**, which unexpectedly provided 2-oxopiperazine **107** (**Scheme 39**).[83] Further examples of *N*-alkylation by Michael addition can be seen in **Schemes 51** and **58**.



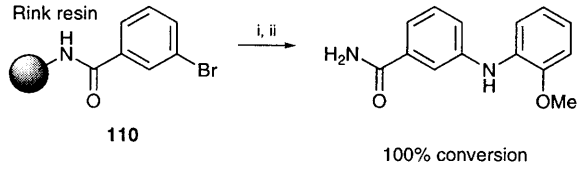
Scheme 39 *Reagents and conditions*: i, $Me_3SO^+ I^-$, NaH, DMSO; ii, TFA, H_2O.

A variety of efficient transition metal catalysed methods for solid-phase carbon–nitrogen bond formation have emerged. π-Allyl palladium chemistry has been used to prepare *N*-benzylglycine derivatives **108** by sequential addition of nucleophiles to a bis-allylic template **109** (**Scheme 40**).[84] The reactions of a variety of sulfur and nitrogen containing nucleophiles were examined.

The palladium catalysed substitution of resin-bound aryl bromides **110** with amines has been investigated (**Scheme 41**).[85] A number of substrates and palladium catalysts were examined, and in the majority of cases the coupling proceeded efficiently providing a useful method for the solid-phase synthesis of anilines.



Scheme 40 *Reagents and conditions*: i, (a) **109**, $Pd(PPh_3)_4$, THF, rt; (b) Ac_2O, py, DMF; (c) NuH, Pd(0), THF

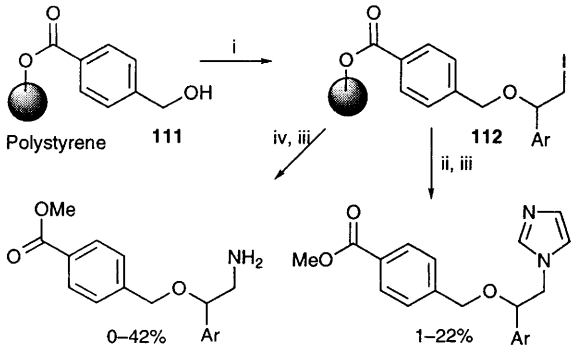


Scheme 41 *Reagents and conditions*: i, $Pd_2(dba)_3$, P(*o*-Tol)$_3$, 2-methoxyaniline, Bu^{t}ONa, toluene, heat; ii, TFA, CH_2Cl_2

3.2 Carbon–oxygen bond formation

The Mitsunobu reaction has continued to find applications in the solid-phase synthesis of aryl ethers.[20,40,58,86–88] Recently chemists at Chiron Mimitopes have disclosed a modified procedure for performing Multipin ether synthesis.[89] The reaction conditions were optimised by simultaneously varying the coupling conditions to which a series of pins were submitted.

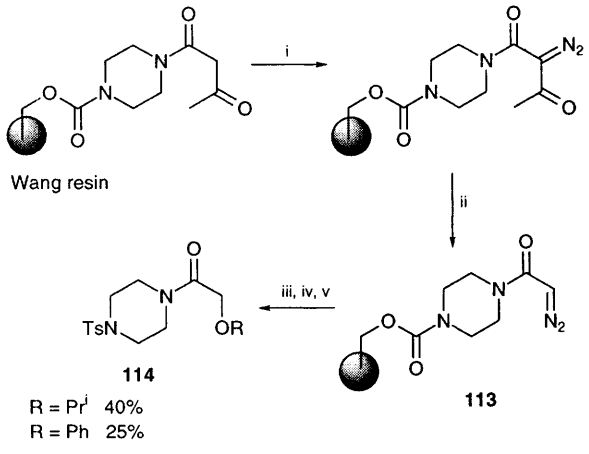
Resin-bound ethers have also been prepared by intermolecular iodoetherification of alkenes (**Scheme 42**).[90] Treatment of alcohols **111** with substituted styrenes in the presence of *N*-iodosuccinimide provided iodo ethers **112** which were



Scheme 42 *Reagents and conditions*: i, $ArCH=CH_2$, NIS, TfOH, DME; ii, (trimethylsilyl)imidazole, AgOTf, DMF, 85 °C; iii, NaOMe; iv, (a) $Bu_4N^+N_3^-$, DMF, 50 °C; (b) Et_3N, PhSH, $SnCl_2$, THF

reacted with (trimethylsilyl)imidazole or tetrabutylammonium azide. The purity of the crude products after cleavage from the resin was typically good; however the yields were somewhat disappointing. Repetitive oxymercuration has been described by Janda as an entry into soluble combinatorial libraries of polyether containing molecules on polyethylene glycol, but details are somewhat scant.[91]

Zaragoza *et al.* have prepared rhodium carbenoids from diazo compounds **113** on a polystyrene support, which underwent reaction with a series of alcohols to provide ethers **114** (**Scheme 43**).[92] The dispersion of the rhodium carbenoid on the support was expected to suppress dimerisation. Some degree of side-reaction with the polystyrene support might be expected on the basis of work employing rhodium carbenoids to attach encoding tags to synthesis resins.[44,66–68] However, by-products would be permanently immobilised on the support.



Scheme 43 *Reagents and conditions*: i, TsN_3, Pr^i_2EtN, DMF; ii, pyrrolidine, DMF; iii, ROH, Rh^{II} acetate, CH_2Cl_2; iv, TFA–CH_2Cl_2 (1:1); v, TsCl, Et_3N, py, CH_2Cl_2

For an example of direct *O*-alkylation of a phenol see **Scheme 76**.

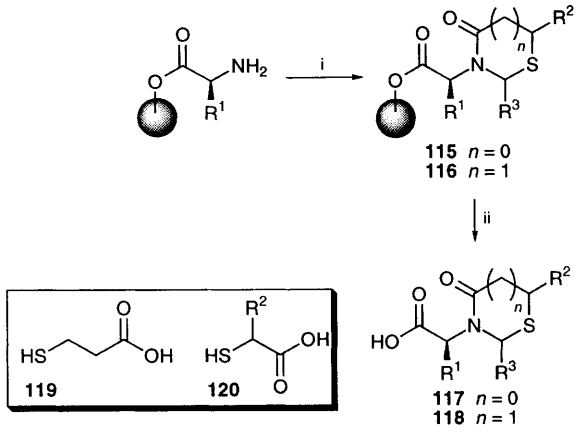
3.3 Carbon–phosphorus bond formation

The formation of phosphorus–carbon bonds on a solid support has attracted some attention and methods for the solid-phase preparation of α-aminophosphinic acids,[93] α-aminophosphonates,[94] and α-hydroxyphosphonates have been described.[95] For an example of the synthesis of a resin-bound phosphonium salt see **Scheme 63**.

3.4 Miscellaneous heterocyclic syntheses

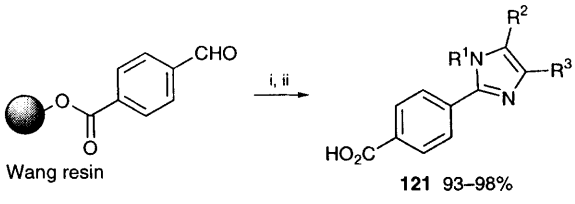
Due to the medicinal importance of heterocyclic compounds, the solid-phase synthesis of this class of structures has received a huge amount of attention. A number of solid-phase heterocyclic syntheses which are not included in other sections of this review will be outlined here.

Researchers at Affymax have reported the synthesis of resin-bound thiazolidin-4-ones **115** and thiazinan-4-ones **116** by condensation of a resin-bound amine with an aldehyde and either mercaptoacetic acids **120** or mercaptopropionic acids **119** (**Scheme 44**).[36,96–98] Thiazolidin-4-ones **117** were generally obtained in high yield after liberation from the resin, however, the yields of thiazinan-4-anones **118** were disappointing.



Scheme 44 *Reagents and conditions*: i, R^3CHO, **119** or **120**, C_6H_6, 80 °C; ii, TFA, CH_2Cl_2

Good yields of highly substituted imidazoles **121** were obtained by implementation of a multiple-component condensation approach (**Scheme 45**).[99] No restrictions on the types of aldehyde or primary amine were found for the cases examined, and either component could be employed as the polymer-bound input.

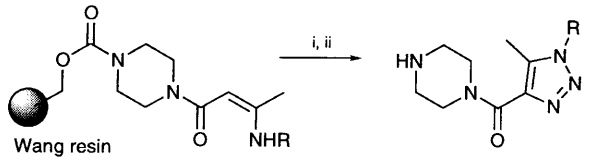


Scheme 45 *Reagents and conditions*: i, R^1NH_2, NH_4OAc, R^2COCOR^3, AcOH; ii, TFA, CH_2Cl_2

Other heterocyclic solid-phase syntheses recently reported include the synthesis of; 1,2,3-triazoles (**Scheme 46**),[100] 2-oxopiperazines,[83] benzodiazepines,[44,74] and quinazolinediones.[73]

4 Linkers and cleavage strategies

The well defined conditions routinely applied during solid-phase oligomer synthesis are often quite different from those required for the synthesis of small molecule targets, and consequently much



Scheme 46 *Reagents and conditions*: i, TsN_3, Pr^i_2NEt, DMF; ii, TFA, CH_2Cl_2

greater demands may be placed on linkers during the synthesis of non-oligomeric structures. Not surprisingly comparisons are often drawn between protecting groups and linkers. Indeed the great wealth of knowledge regarding functional group protection has been employed in designing linkers which allow product release under mild conditions (*e.g.* photochemical, Pd catalysis, fluoride) yet are also able to survive a sequence of challenging reaction conditions.

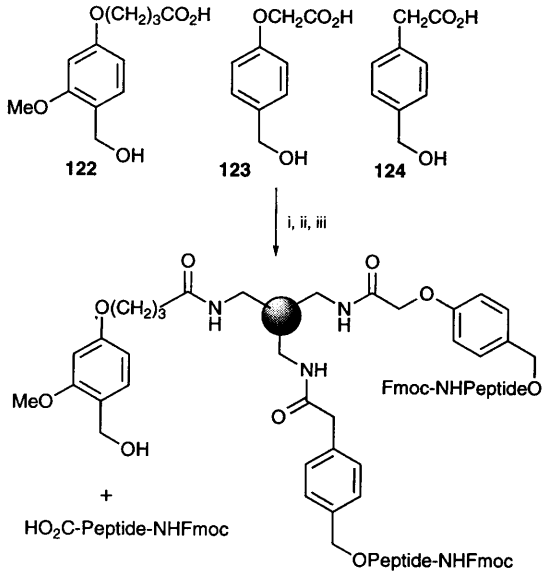
Cleavage of linkers designed for peptide synthesis necessitate the presence of a polar functionality on the molecule under construction, which is often undesirable. A number of linkers and cleavage strategies have been presented to overcome this problem; however further progress in this area is still required. Another area of interest is the development of sequential release systems, to allow portions of the material on the resin to be submitted to different tests. Such systems might also be used to introduce a series of chemical coding tags.

Most of the linkers seen in the previous sections are of the acid-cleavable Wang and Rink type. The following section will provide an overview of the use of alternative linkers and cleavage strategies. Examples of applications in the area of peptide and oligonucleotide chemistry have also been included, as the linkers employed may have general application or may lead to adaptations to allow small molecule synthesis. As in previous sections categorisation has been made according to reaction type, except in the case of silicon containing linkers which have been considered separately.

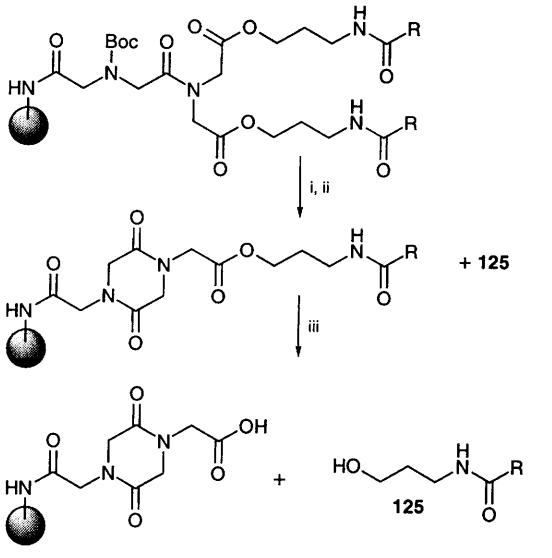
4.1 Acid induced cleavage

A simple multiple release system using a combination of benzyl alcohol derivatives has been described by Cardno and Bradley (**Scheme 47**).[101] The solid support is readily prepared by treatment of aminomethyl resin with a mixture of three hydroxy acids **122**–**124** in the presence of DIC. Solid-phase peptide synthesis was then used to prepare a resin-bound tripeptide, attached through linkers with different reactivities. Linker **122** could be cleaved using 1% TFA, linker **123** with 95% TFA with the third portion of the tripeptide retained on the support for sequencing, on-bead experiments or cleavage under more forcing conditions. A group from Ciba have employed an analogous approach in conjunction with an amine-based tagging system.[102]

The iminodiacetic acid based double cleavable linker (IDA-DC) provides a dual release system



Scheme 47 *Reagents and conditions*: i, aminomethyl polystyrene, DIC; ii, solid-phase peptide synthesis; iii, 1% TFA, CH_2Cl_2



Scheme 48 *Reagents and conditions*: i, TFA, CH_2Cl_2; ii, pH 7.5; iii, 2% NaOH

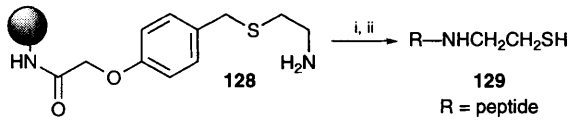
which has been used during the preparation of synthetic combinatorial libraries,[86] and the modification of teicoplanin aglycone (**Scheme 48**).[103] The IDA-DC linker strategy allows selective release of half of the material through diketopiperazine formation. The remaining material can be released separately by basic hydrolysis. Acid catalysed removal of the Boc protecting group from the secondary amine is required prior to diketopiperazine formation at pH 7.5. As well as providing a means of multiple release, the IDA-DC linker theoretically doubles the original loading level of the resin.

The utility of Ellman's THP linker for attaching hydroxy groups to a polymeric support has been further demonstrated during a number of studies (see **Schemes 29, 30** and **33**).[53,60,69] The THP protecting group has been used extensively in solution-phase synthesis, providing information regarding the likely properties of the corresponding linker. It is therefore not surprising that the THP linker has proved compatible with a variety of organotransition metal and carbanion chemistries.

The preparation of new polystyrene resins **126–127** based on acetal and thioacetal protecting groups has been reported, along with examples of the attachment and acid induced cleavage of phenol and carboxy functionalities.[104] Caesium thiolates were also reacted with resins **126** and **127**; the resulting thioacetals cleaved readily using 25% TFA but the analogous dithioacetals required more forcing conditions. It was suggested that the reactivity difference may be exploited by attaching a chemical coding system through the more robust dithioacetal linker, while compounds of interest would be linked through the corresponding thioacetal.

126 **127**

Peptides containing terminal thiol substitution are attractive targets for use in ligation approaches to peptide constructs (**Scheme 49**).[105] The thioether linker **128** allowed preparation of a modified peptide **129** which was used in the synthesis of an HIV-1 protease analogue. The linker may also find use in the synthesis of small molecules containing thiol substitution, although cleavage conditions are relatively harsh.

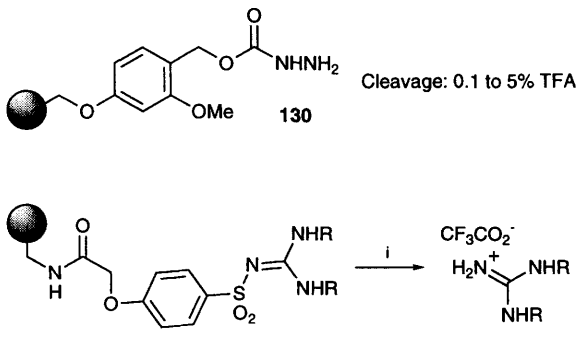


128 **129**
R = peptide

Scheme 49 *Reagents and conditions*: i, Boc solid-phase peptide synthesis; ii, HF, *p*-cresol

Peptide hydrazides have proved valuable intermediates in fragment condensation approaches to peptide synthesis, as well as for the preparation of conjugates. Coughlin has described a resin **130** suitable for the Fmoc solid phase synthesis of side-chain protected peptide hydrazides, the modified linker **130** allows cleavage under conditions which are less vigorous than those required by existing linkers.[106]

A sulfonyl linker has allowed the solid-phase synthesis of a guanidinium-based tweezer receptor (**Scheme 50**).[107] The linker was compatible with



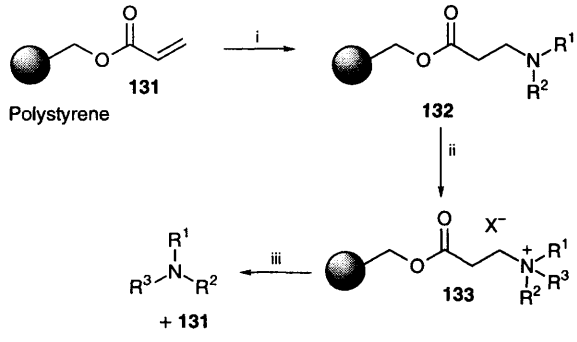
130

Scheme 50 *Reagents and conditions*: i, 10 equiv. CF_3SO_3H, thioanisole, CF_3CO_2H

standard Fmoc solid-phase peptide synthesis conditions, and could be cleaved under acidic conditions.

4.2 Base induced cleavage

Organon chemists have introduced the REM linker **131** which was used to prepare a small array of tertiary amines (**Scheme 51**).[108] Alkylation of amines **132** provided the corresponding quaternary ammonium salts **133**, which upon submission to basic conditions underwent Hofmann elimination to release the corresponding tertiary amines. The REM linker is regenerated at the end of the synthesis sequence.



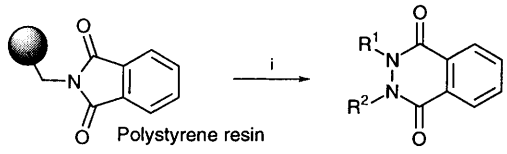
131 **132** **133** + **131**

Scheme 51 *Reagents and conditions*: i, R^1R^2NH; ii, R^3X, DMF; iii, Pr^i_2NEt, DMF or CH_2Cl_2

4.3 Nucleophilic cleavage

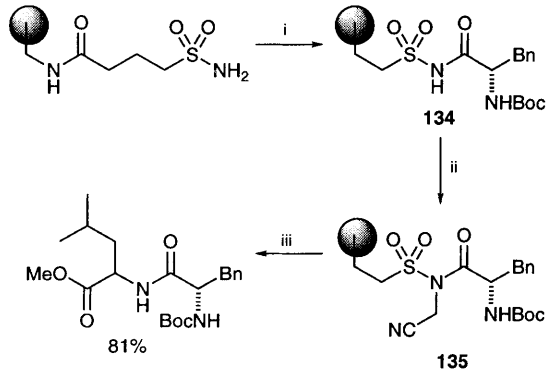
Intermolecular nucleophilic cleavage of a substrate from the solid support in such a way that the nucleophile is incorporated into the product provides an opportunity to introduce an additional element of diversity. Nielsen and Rasmussen have suggested the term combinatorial cleavage to describe the nucleophilic cleavage of a phthalimide linkage using a range of substituted hydrazines (**Scheme 52**).[109]

Ellman and co-workers have described a method which can be used to prepare a highly activated



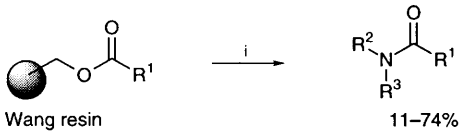
Scheme 52 *Reagents and conditions*: i, R^1NHNHR^2, CH_2Cl_2

acylsulfonamide 'safety-catch' linker **134** (**Scheme 53**).[110] Activation by cyanomethylation rather than methylation, as originally employed by Kenner, produces a more reactive intermediate **135** which can even be cleaved by poorly nucleophilic amines. The method allows limiting amounts of amines to be used in the cleavage step, avoiding removal of excess amine from the cleaved amide product.



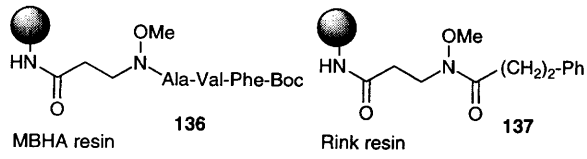
Scheme 53 *Reagents and conditions*: i, Boc-(L)-Phe-OH, PyBOP, Pr^i_2NEt; ii, ICH_2CN, Pr^i_2NEt; iii, Leu-OMe

Lewis acid assisted nucleophilic cleavage of resin bound esters has been shown to be an effective method for the preparation of secondary and tertiary amides (**Scheme 54**).[111] A variety of Lewis acids were examined, with $AlCl_3$ being preferred. Separation of the metal salts from the amide products was easily accomplished by solid phase extraction, providing crude products with a high level of purity. For a similar approach see **Schemes 1** and **14**.



Scheme 54 *Reagents and conditions*: i, R^2R^3NH, $AlCl_3$, CH_2Cl_2

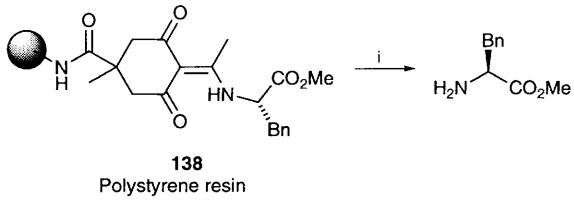
Two independent examples of the use of a linker based on the Weinreb amide for the synthesis of aldehydes and ketones have been reported . Reductive cleavage of resin-bound peptide **136** using $LiAlH_4$ provided a 40% yield of the peptide



aldehyde Boc-Phe-Val-Ala-H after purification.[112] Similarly, treatment of **137** with MeMgCl, BnMgCl, PhMgCl or $LiAlH_4$ provided the corresponding ketones or aldehyde in 77, 23, 33 and 10% yields respectively.[113] A thioester linker has also been employed for the reductive release of aldehydes from a polystyrene synthesis support (**Scheme 4**).

The preparation of a new linker for primary amines, which is based on the acetyldimedone protecting group, has been described by Hoffman-La Roche chemists (**Scheme 55**).[114] The linker **138** is stable to a range of basic and acidic conditions, yet is susceptible to nucleophilic cleavage using 2% hydrazine in DMF at room temperature.

Other examples of hydrolysis, transesterification and reduction of ester containing linkers have appeared elsewhere in this review.

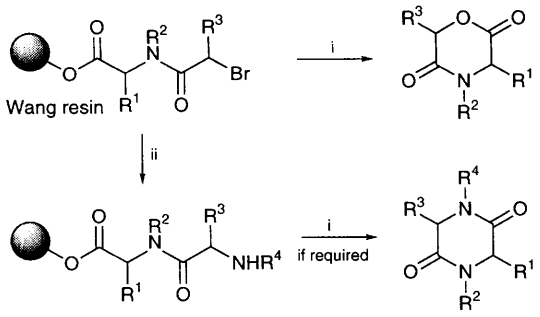


Scheme 55 *Reagents and conditions*: i, 2% NH_2NH_2, DMF

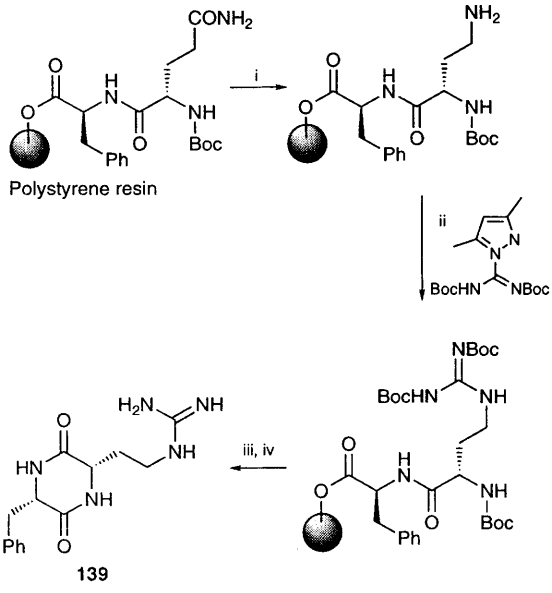
Methods which allow release of the target structure from the solid support to be combined with a key step such as a ring-forming reaction are attractive in terms of synthetic efficiency. Such cyclisative cleavage strategies might be described as 'traceless' as no additional functionality is required on the core structure in order to allow attachment to the resin. Although the mechanism of release is not strictly by nucleophilic cleavage in all of the following examples, they will be considered together as the net result is the same.

Cyclisative cleavage strategies have been successfully applied during the syntheses of diketomorpholines (**Scheme 56**),[115] and diketopiperazines (**Schemes 56** and **57**).[78,115,116] In most examples the acyclic precursor is released into solution where it undergoes cyclisation. Diketopiperazine **139** catalyses an enantioselective Strecker synthesis of (*S*)-phenylglycine derivatives. The unusual amino acid side-chain present in **139** was introduced by way of a Hofmann rearrangement–guanylation sequence (**Scheme 57**). The solid-phase approach to the catalyst **139** proved to be greatly superior to the solution-phase synthesis previously employed.

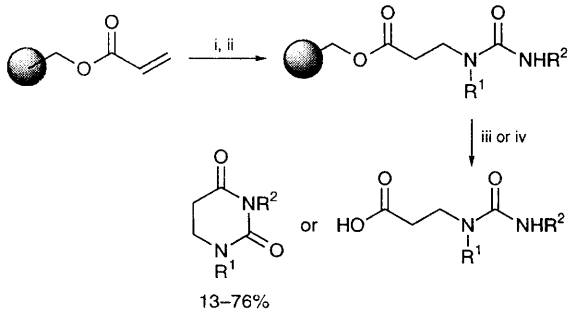
Dihydropyrimidine-2,4-diones (**Scheme 58**),[117] and dihydropyridines (**Scheme 59**) were synthesised



Scheme 56 *Reagents and conditions*: i, 95% TFA, H_2O; ii, R^4NH_2

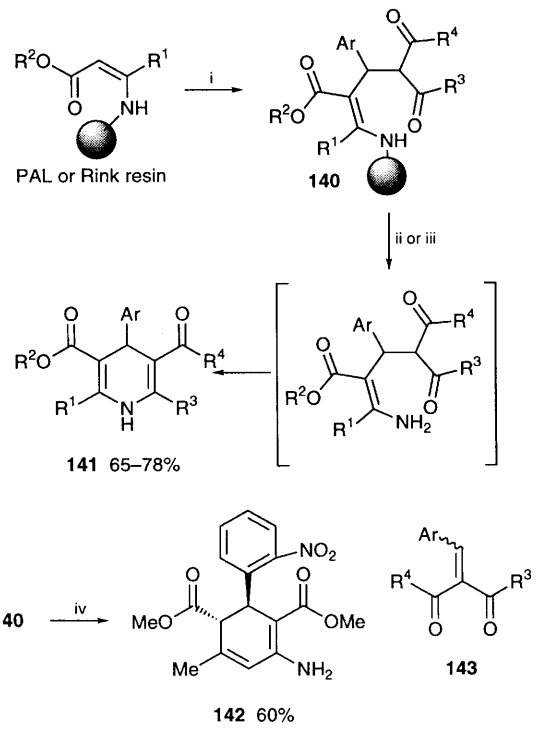


Scheme 57 *Reagents and conditions*: i, $PhI(O_2CCF_3)_2$, THF–H_2O–MeCN; ii, Pr^i_2NEt, DMF; iii, TFA, CH_2Cl_2; iv, HOAc, PhMe, 90 °C



Scheme 58 *Reagents and conditions*: i, R^1NH_2, DMSO; ii, R^2NCO, CH_2Cl_2; iii, 19:1 TFA–H_2O; iv, HCl, toluene, 95 °C

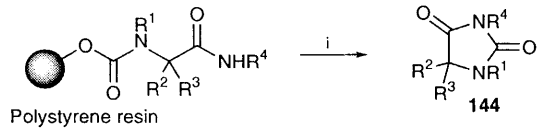
along similar lines.[26] Unexpectedly, an attempt to form dihydropyridine **141** from **140** (R^1, R^3 = Me) under thermal conditions in the presence of molecular sieves, returned carbocycle **142** as the principal product.



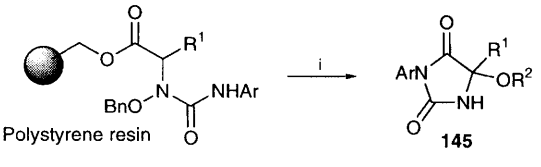
Scheme 59 *Reagents and conditions*: i, 4 Å sieves, **143**, pyridine 45 °C; ii, 95% TFA, THF; iii, 3% TFA, CH_2Cl_2; iv, 4 Å sieves, EtOH, 80 °C

Examples of the application of direct cyclisative cleavage to the syntheses of hydantoins **144**,[118] alkoxyhydantoins **145**,[119] quinazoline-2,4-diones **146**,[120,121] and pyrazolones **41** are shown in **Schemes 63**, **64**, **65** and **12**. In these examples it appears that the resin is directly displaced by intramolecular nucleophilic attack.

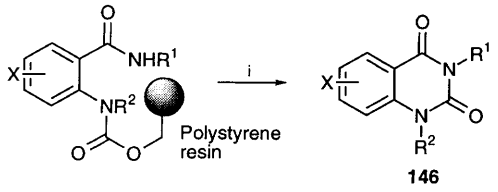
The Wittig reaction has also been used to effect cyclisative release of target structures from a polystyrene support (**Scheme 66**).[122] Commercially available polystyrene-bound diphenylphosphine **147** was used to prepare phosphonium salt **148**, which was further elaborated to amide **149**. Cleavage was



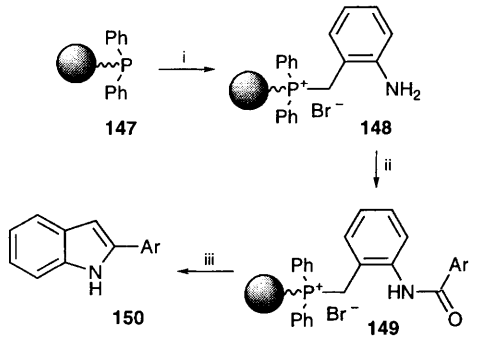
Scheme 60 *Reagents and conditions*: i, Et_3N, MeOH, 55–90 °C



Scheme 61 *Reagents and conditions*: i, Bu^tOK, R^2OH, rt



Scheme 62 *Reagents and conditions*: i, DMF, 125 °C

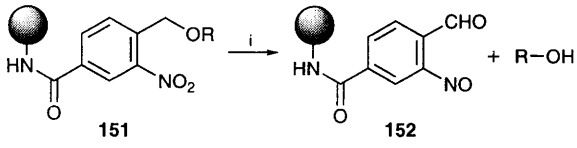


Scheme 63 *Reagents and conditions*: i, (a) 2-$NO_2C_6H_4CH_2Br$, citric acid, DMF; (b) sodium dithionite, H_2O–EtOH; ii, ArCOCl, py, CH_2Cl_2; iii, $KOBu^t$, toluene–DMF

achieved by intramolecular Wittig reaction to provide indole **150**.

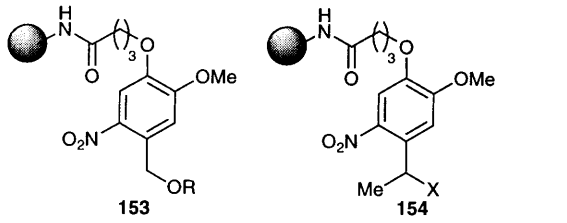
4.4 Photochemical cleavage

Photochemically cleavable linkers have proved extremely valuable for the solid-phase synthesis of oligomers and small molecules. The most popular class of photolabile linker relies on the *o*-nitrobenzyl photoredox process to effect release of the molecule of interest from the polymeric support under relatively mild conditions (**Scheme 64**). Although the *o*-nitrobenzyl linker **151** previously described by Rich has found continued use,[20,44,123] cleavage kinetics may be slow requiring prolonged irradiation which can result in side reactions. Additionally, the generation of a reactive nitrosoaldehyde **152** may trap liberated compounds, as well as providing a potential light filter.



Scheme 64 *Reagents and conditions*: i, *hv* 350 nm, DMF

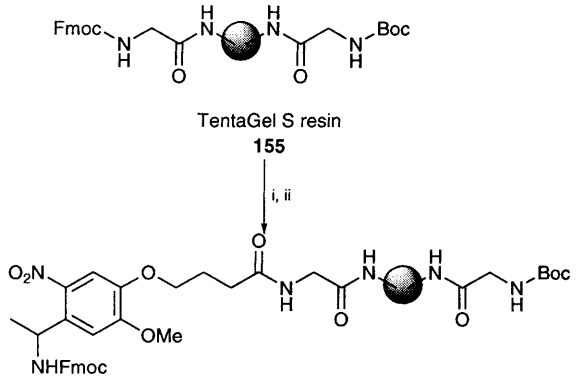
The synthesis and use of modified *o*-nitrobenzyl linkers such as **153** has been described.[124,125] Incorporation of alkoxy groups into the nitrophenyl ring has been found to lead to increased efficiency of photochemical cleavage. Affymax researchers also



X = O-alkyl, O-Ar, NR_2, SR
X = $NHCO_2R$, NHCONHR, $NHSO_2R$
X = OCO_2R, OCONHR, OCOSR
X = OCH_2OR, OCH_2SR

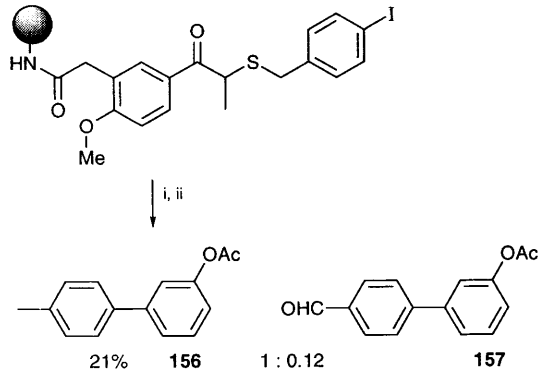
introduced a methyl substituent at the benzylic position of their photolabile linker **154**, which upon irradiation leaves a ketone rather than the more reactive aldehyde.[34,36,126] Teague has reported a facile synthesis of the Affymax linker **154** (X = NH_2) after encountering some experimental difficulties when following the reported synthesis of the aza analogue of **154**.[127] Photolabile linkers of the type described above will undoubtedly find continued use for tethering structures through polar functionality to solid-phase synthesis supports.

The Affymax photolabile linker has been incorporated into a dual release system as outlined in **Scheme 65**. Treatment of TentaGel S-NH_2 resin with a mixture of Boc- and Fmoc-protected glycine in the presence of a coupling reagent provides a differentially functionalised resin **155**.[36] Fmoc deprotection allows attachment of the Affymax aminobenzyl photolabile linker on which the target molecule can be assembled. The orthogonally (Boc) protected strand was used in this case to attach a secondary amine coding strand. Further examples of the implementation of photochemical cleavage strategies are shown in **Schemes 2** and **22**.



Scheme 65 *Reagents and conditions*: i, piperidine, DMF; ii, 4-{4-[1-(Fmoc-amino)ethyl]-2-methoxy-5-nitrophenoxy}butanoic acid, HATU, Pr^i_2NEt

Sucholeiki introduced the photolabile NpSSMpact linker for the solid-phase synthesis of biaryl compounds (**Scheme 66**).[61,128] The linker is compatible with Stille coupling conditions and is readily cleaved by irradiation at 350 nm under an inert atmosphere to provide biaryl compounds **156**,

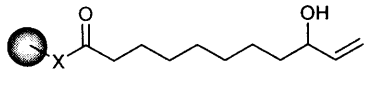


Scheme 66 *Reagents and conditions*: i, 3-acetoxyphenyltrimethyltin, $Pd_2(dba)_3$, LiCl, trifurylphosphine, NMP; ii, *hv* 350 nm, MeCN

along with a small quantity of the corresponding aldehyde **157**. The NpSSMpact linker is noteworthy as it provides a means of traceless release of biaryl compounds under mild conditions, but unfortunately, only a few examples have been provided by the author.

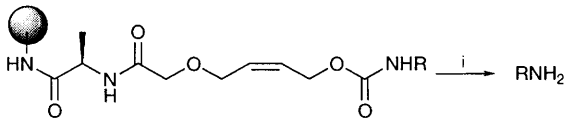
4.5 Transition metal mediated cleavage

The allyl and allyloxycarbonyl protecting groups have proved to be extremely valuable for masking a number of functional groups during solid- and solution-phase synthesis. It is perhaps not surprising that allyl based systems have also attracted some attention as linkers for use in solid-phase synthesis as cleavage can be achieved under mild conditions which are tolerant to a wide range of functionalities. A universal allyl linker **158** with a more reactive terminal olefin has been used for automated DNA and RNA synthesis and may also find applications in small molecule synthesis.[129] The allyl linker **159** previously described by Guibé was used to prepare a spider venom containing a terminal amine (**Scheme 67**).[130] Efficient release from the resin was carried out by treatment with a palladium catalyst and Bu_3SnH. Alanine placed in between the support and the linker was used as an internal standard against which the efficiency of release could be gauged.



Polystyrene/polyethylene glycol

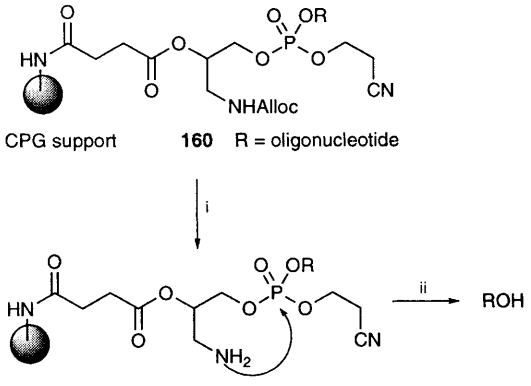
158



4-methylbenzhydrylamine polystyrene resin **159**

Scheme 67 *Reagents and conditions*: i, $(Ph_3P)_2PdCl_2$, Bu_3SnH, CH_2Cl_2–AcOH

Neighbouring group assisted hydrolysis has been presented as a mild means of detaching oligonucleotides from CPG resin **160** (**Scheme 68**).[131] Unmasking the amine functionality present in the linker side-chain was achieved by palladium catalysed removal of the allyloxycarbonyl protecting group. Subsequent release of the oligonucleotide was effected by hydrolysis at pH 10.

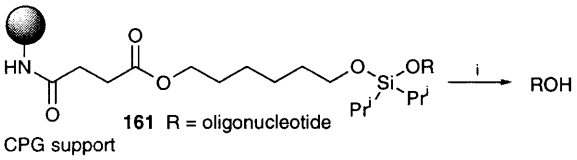


CPG support **160** R = oligonucleotide

Scheme 68 *Reagents and conditions*: i, $Pd(PPh_3)_4$, NH_4OAc, PPh_3, THF; ii, pH 10

4.6 Silicon containing linkers

A novel silyl derivatised CPG silica **161** has been described for use in solid-phase oligonucleotide synthesis. The 3′-hydroxy group was used as the point of attachment to the support (**Scheme 69**).[132] The linker is readily cleaved by fluoride treatment and allows base sensitive functionality to be retained in the cleaved product.

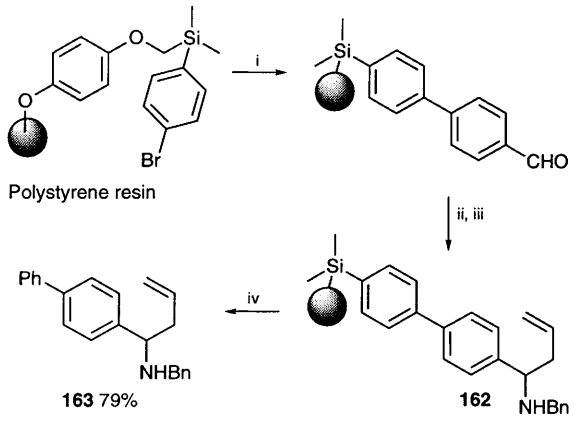


161 R = oligonucleotide

CPG support

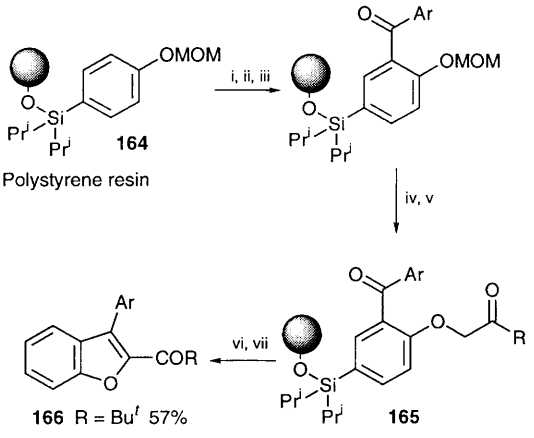
Scheme 69 *Reagents and conditions*: i, TBAF, THF

A number of examples of silicon-based systems for the traceless cleavage of small organic molecules have been disclosed. Traceless release of substituted phenyl derivatives **163** from **162** has been achieved using either neat TFA at 25 °C or CsF in a mixture of DMF and water at 110 °C (**Scheme 70**).[58] The linker is tolerant of a variety of conditions including halogen–metal exchange to generate resin-bound organolithium species and organomagnesium reagents. Liquid HF could also effect cleavage but was not compatible with some of the functionality present in the target structures.



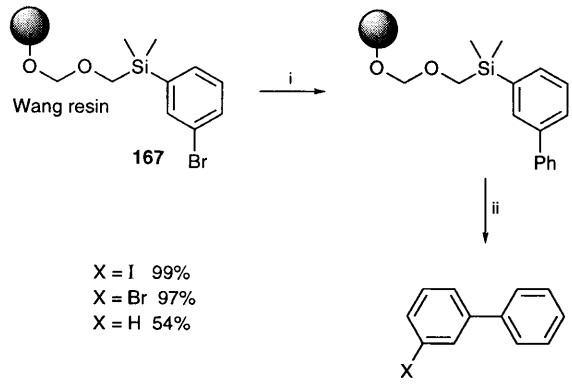
Scheme 70 *Reagents and conditions*: i, Pd^0, *p*-formylphenylboronic acid; ii, $BnNH_2$; iii, allylmagnesium bromide; iv, neat TFA

A diisopropylsilyloxy linker provided a means of traceless attachment during the synthesis of benzofurans **166** (**Scheme 71**).[133] The corresponding resin-bound derivatives **165** could be cleaved from the resin using TBAF in DMF at 60 °C. Alternatively, aryl silanols could be released by treatment of **165** with TFA. The linker proved stable to strongly basic conditions, and allowed *ortho*-metallation of resin-bound intermediates **164** using BuLi–TMEDA. Electrophilic substitution of silicon with bromine was also examined in one case.



Scheme 71 *Reagents and conditions*: i, (a) BuLi, TMEDA, Et_2O; (b) DMF; ii, 4-bromoanisole, BuLi, THF; iii, 1-hydroxy-1,2-benziodoxol-3(*1H*)-one, DMSO, THF; iv, 5% TFA, CH_2Cl_2; v, $BrCH_2COR$, Pr^i_2NEt, NMP; vi, DBU, NMP; vii, TBAF, DMF

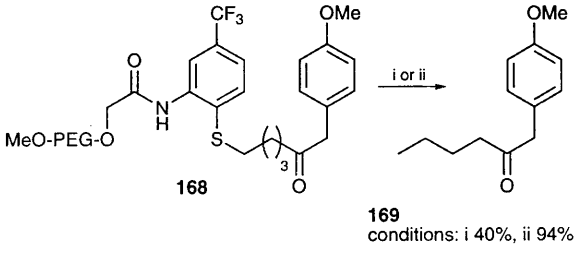
A silyl derivatised polystyrene resin **167** was used to prepare biaryls using the Suzuki cross-coupling reaction (**Scheme 72**).[54] Cleavage from the solid support was achieved by electrophilic *ipso*-substitution of the silicon linker with ICl, Br_2 or in somewhat lower yield by CF_3CO_2H. In two of the examples containing electron-rich substrates, additional electrophilic aromatic substitution occurred when bromine was used as the electrophile.



Scheme 72 *Reagents and conditions*: i, $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME; ii, ICl, CH_2Cl_2; or Br_2, pyridine, CH_2Cl_2; or CF_3CO_2H, Me_2S, CH_2Cl_2

4.7 Miscellaneous

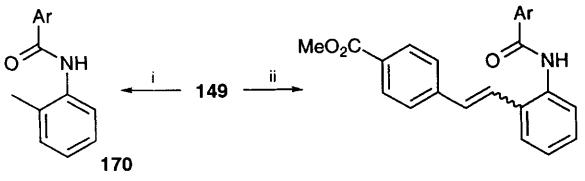
Thioether linker **168** provides a means of traceless attachment of derivative **169** to a soluble polymer MeOPEG (**Scheme 73**).[134] Cleavage was most efficient using hydrogenation over a heterogeneous Raney nickel catalyst. The investigators also examined radical generating conditions; however release was incomplete even after prolonged



Scheme 73 *Reagents and conditions*: i, Bu_3SnH, AIBN, C_6H_6; ii, H_2, Raney Ni

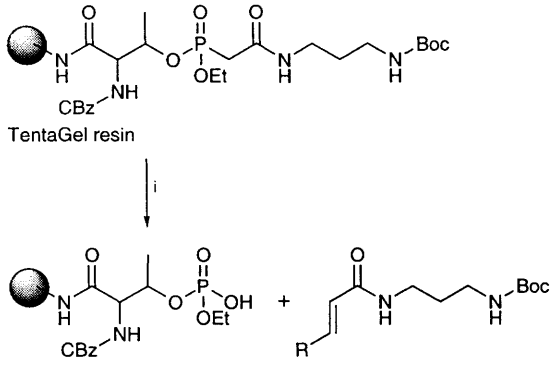
periods. Although the linker described above may prove useful in conjunction with soluble polymeric supports, it is unclear whether the use of a heterogeneous catalyst will prove to be as efficient for insoluble polymeric supports.

Two phosphorus containing linkers suitable for the solid-phase synthesis of alkenes by means of a react and release approach have been reported. Resin-bound diphenylphosphine was used to generate phosphonium salt **149** (see **Scheme 63**). Intermolecular Wittig reaction effected olefination and release from the support in a single step (**Scheme 74**).[122] Alternatively, methanolysis of **149** afforded **170** providing a traceless linker strategy for use in the synthesis of substituted toluenes. In contrast to the bulk of linker strategies, no polar functionality remains at the point at which the structures of interest were attached to the resin.



Scheme 74 *Reagents and conditions*: i, NaOMe, MeOH, reflux; ii, (a) 4-$CO_2MeC_6H_4CHO$, NaOMe, MeOH; (b) work up to remove excess aldehyde

A related react and release strategy employing the Horner–Wadsworth–Emmons reaction was used to prepare several (*E*)-alkenes (**Scheme 75**).[72] This approach benefits from milder reaction conditions, and a range of aliphatic, aromatic and unsaturated aldehydes have been incorporated. Excess aldehyde and lithium salts were removed by extraction of the products from aqueous bisulphite solution.



Scheme 75 *Reagents and conditions*: i, LiBr, Et_3N, RCHO, MeCN.

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