UNIVERSITY OF SOUTHAMPTON

Palladium-Cleavable Linkers: Solid-Phase Synthesis of 4-Methylene Pyrrolidines and Allylic Amines

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A thesis submitted for the degree of Doctor of Philosophy

Department of Chemistry

March 2002

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

PALLADIUM-CLEAVABLE LINKERS: SOLID-PHASE SYNTHESIS OF 4-METHYLENE PYRROLIDINES AND ALLYLIC AMINES

by Martyn Lewis Fisher

The solid-phase synthesis of several 4-methylene pyrrolidines has been used to demonstrate the viability of a cyclisation-cleavage reaction. The treatment of a reversed allylic linker with catalytic palladium(0) generated a π-allyl palladium species, which was released into solution and subsequently trapped by an intramolecular nucleophile. An imino-Sakurai reaction was the key step in the construction of the cyclisation-cleavage substrates and a carboxyethylated polystyrene resin, prepared from Merrifield resin, was used as the solid support in this study.

A reversed allylic linker, based on a phenyl ether template, was used in the preparation of allylic amines on the solid-phase. In this case the π-allyl palladium species released into solution was trapped by primary and secondary amines. The substrates were prepared by coupling secondary allylic alcohols to hydroxypolystyrene resin under Mitsunobu conditions.

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Acknowledgements

The author would like to thank Joan Street and Neil Wells for the NMR spectroscopy as well as John Langley and Julie Herniman for the Mass Spectrometry.

Professor Mark Bradley is thanked for the kind donation of AAEM resin.

In addition, the author would like to acknowledge the EPSRC for providing a QUOTA studentship and the use of the Chemical Database at Daresbury.[1]

It is better to be hated for what one is than loved for what one is not.

-André Gide

The last three years or so have certainly not been easy. However, with the help and support of many people I have over come numerous obstacles, which have threatened to thwart my progress. I firmly believe that all our experiences are important, no matter how negative they initially appear to be. Mistakes are there to learn from and I have learnt a lot on this journey.

My thanks go to Jean-Dominique Moriggi, Jim Hart, John Keily, Rob Hughes, Nigel Swain, Geoff Head, Alex Cecil, Marco Meloni, Sara Chunn and Jeremy Hinks. It has been a pleasure to work with you and I only hope that I have instilled some sense of tidiness into you! Thanks also go to Dr Richard Brown who has been more understanding than I could ever have hoped for. Then of course there is the extended 'Brown Group' family. In particular I would like to thank Ruth Mcquire, Matt Lucas, Mell Tyte, Jon Wilden and Simon Orchard for being great friends. A special mention must go to Mike Nunn who was always there for me, especially on 13th June 2000. I owe you one mate and will be in your debt forever!

Paul Dunford has shown me that together two men can defy the world. I look forward to spending the rest of my life with you.

Finally I would like to thank Jane and Phil Fisher for being the best parents anyone could ask for. This one's for you with all my love!

Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
AAEM	Acetoacetoxyethyl methacrylate
Ac	Acetyl
Acac	Acetylacetonate
AIBN	2,2'-Azoisobutyronitrile
Ala	Alanine
Alloc	Allyloxycarbonyl
aq.	Aqueous
Ar	Aryl
BHT	2,6-Di-*tert*-butyl-4-methylphenol (Butylated hydroxytoluene)
binap	2,2'-Bis(diphenylphosphino)-1,1'binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
b.p.	Boiling point
br	Broad (NMR and IR)
BSA	Bis(trimethylsilyl)acetamide
Bu	Butyl
CAS	Chemical Abstracts
cat.	Catalytic
Cy	Cyclohexyl
d	Doublet (NMR)
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DEAD	Diethylazodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIC	1,3-Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Ethylene glycol dimethyl ether (1,2-Dimethoxyethane)
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DMT	3,3'-Dimethoxytriphenylmethyl
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DVB	Divinylbenzene
e.e.	Enantiomeric excess
equiv.	Equivalents
Et	Ethyl
Fmoc	9-Fluorenylmethoxycarbonyl
GC	Gas Chromatography
HBD	Hormone binding domain
Gly	Glycine
Hep	Heptyl
HMDS	Hexamethyl disilazane

HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
hr	Hour
HRMS	High resolution mass spectrometry
i	*iso*
IR	Infra red
J	Coupling constant (NMR)
L	Ligand (general)
LCAA-CPG	Long-chain alkylamine controlled pore glass
LDA	Lithium diisopropylamide
Leu	Leucine
Lys	Lysine
m	Multiplet (NMR) or medium (IR)
m	*meta*
M	Molar
MAS	Magic angle spinning
m-CPBA	3-Chloroperbenzoic acid
Me	Methyl
Meq.	Milliequivalent
min	Minute
MOP	2-(Diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
m.p.	Melting point
MS	Mass spectrometry
Mtr	4-Methoxy-2,3,6-trimethylbenzene-sulfonyl
m.w.	Molecular weight
m/z	Mass / charge ratio
N	Normal
NBS	*N*-Bromosuccinimide
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
Nu	Nucleophile
o	*ortho*
Oct	Octyl
p	*para*
PDE	Phosphodiesterase
PEG	Poly(ethyleneglycol)
Ph	Phenyl
PNIPAM	Poly(*N*-isopropylacrylamide)
Pr	Propyl
PS	Polystyrene
psi	Pounds per square inch
ROMP	Ring-opening metathesis polymerisation
rt	Room temperature
s	Singlet (NMR) or strong (IR)
t	Triplet (NMR)
t	*tert*
TBAF	Tetrabutylammonium fluoride
Teoc	2-(Trimethylsilyl)ethoxycarbonyl
THP	Tetrahyropyran
THF	Tetrahydrofuran

Tf	Trifluoroacetate (Triflate)
TFA	Trifluoroacetic acid
t.l.c.	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMG	Tetramethylguanidine
TMS	Trimethylsilyl
TMSOK	Potassium trimethylsilanolate
Tol	Tolyl
Ts	Toluenesulfonyl (Tosyl)
UV	Ultraviolet
Val	Valine
v/v	Volume/volume ratio
w	Weak (IR)
W	Watt

1. The use of palladium in solid-phase organic synthesis

1.1 Solid-Phase Organic Synthesis

In 1963 Merrifield reported the synthesis of a tetrapeptide.[2] However, instead of using traditional methodology the synthesis involved the stepwise addition of protected amino acids to a growing peptide chain, which was bound to a solid resin particle *via* a covalent bond. In this instance the resin used was a nitro chloromethylated copolymer of styrene and divinylbenzene. Merrifield postulated that the porous gel structure of the beads allowed penetration of the reagents and yet diffusion and steric hindrance did not appear to greatly affect the efficiency of the reactions. Once the desired sequence of amino acids had been prepared the peptide was cleaved from the solid support.

Advantages of this methodology included the easy purification of the resin-bound intermediates after each coupling reaction. Purification was achieved by simply washing the resin with appropriate solvents. The ease of purification also allows the use of excess reagents, which can be used to drive a reaction to completion and are washed out upon work-up.

Since Merrifield's pioneering work the solid-phase synthesis of peptides has been finely tuned and a linker is now used to attach the substrate to the solid support. Various linkers have been designed so that a variety of conditions can be employed to cleave the product from the resin.[3-7]

More recently solid-phase synthesis has evolved and now the preparation of small organic molecules,[8-11] as opposed to bio-oligomers, has become the focus of many research groups' attention. As no single class of compounds can be expected to cover the structural diversity required for all therapeutic targets in the future small molecules are becoming increasingly important. There has been a significant effort to extend the repertoire of solid-phase synthetic methodology currently available.

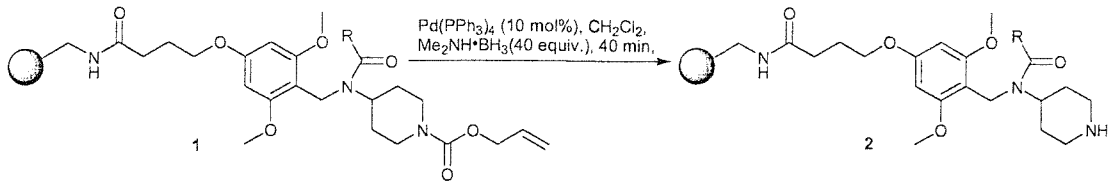
It is now possible to use a wide variety of reactions in solid-phase synthesis. Examples of these include the Heck, Stille and Suzuki couplings, Claisen condensation, Aldol condensation, Friedel-Craft aromatic substitution, Diels-Alder cycloaddition, alkylation, oxidation, reduction, olefination and enzymatic reactions.[12-20] Despite recent advances in solid-phase synthetic methodology and linker design, both of these areas require further development. Unfortunately, many of the linkers currently available were designed with peptide synthesis in mind and reveal polar functionality upon cleavage, which is often not desired in a target structure.[3-6] As a result much effort has been focussed towards linker development.

Palladium is of considerable importance in solid-phase organic synthesis. Not only does it catalyse numerous reactions, which are used regularly on the solid-phase but it is also employed in many strategies for cleaving molecules from the solid-support i.e. palladium-labile linkers. The following report gives a general overview of the types of transformations, on the solid-support, that palladium has been used to achieve. For more extensive reports the reader is directed to several excellent reviews that have been published over the last few years.[21,22]

1.2 π-Allyl Palladium Chemistry In Solid-Phase Organic Synthesis

Perhaps one of the best known applications of π-allyl palladium chemistry in solid-phase organic synthesis is the removal of allyl protecting groups from allylic esters, ethers and amines.[23] In the case of amines both the allyl and allyloxycarbonyl (Alloc) groups have been used successfully. [24] A recent study showed that the use of $Me_2NH{\bullet}BH_3$ (40 equiv., 40 min), as an allyl group scavenger, leads to quantitative removal of the Alloc group.[25] No allyl back alkylation was observed and other scavengers such as morpholine or phenylsilane ($PhSiH_3$) gave clearly inferior results in the model study (scheme 1.1). In addition, the authors also demonstrated the efficiency of this procedure in solid-phase peptide synthesis.

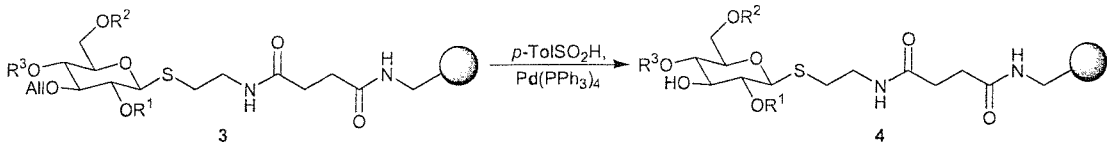
Scheme 1.1 Removal of an Alloc-protecting group by catalytic palladium.



In some instances neutral cleavage conditions are required, for example base-labile groups like Fmoc would be cleaved if morpholine were used as the allyl scavenger and sulfinic acids would potentially cleave acid-labile Boc groups. It has been demonstrated, using tripeptides attached to the solid-phase, that Alloc groups can be cleaved quantitatively using 10 mol% $Pd(PPh_3)_4$ and $PhSiH_3$ (24 equiv.) in dichloromethane.[26] The compatibility of these conditions with both acid- and base-labile groups was also observed.

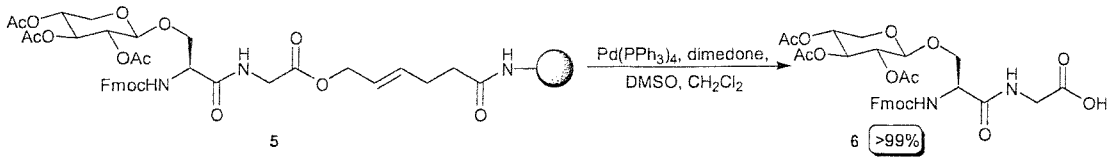
The cleavage of allyl ethers on the solid-phase, using a palladium(0)-catalysed allyl transfer reaction, has been illustrated using polyfunctionalised monosaccharide substrates **3** (scheme 1.2).[27] The protocol uses *p*-toluenesulfinic acid (4 equiv.), as both the allyl scavenger and proton source, and 25 mol% $Pd(PPh_3)_4$ over 18 hours at room temperature with 1,2-dimethoxyethane as the solvent.

Scheme 1.2 Deprotection of an allyl ether on the solid-phase.



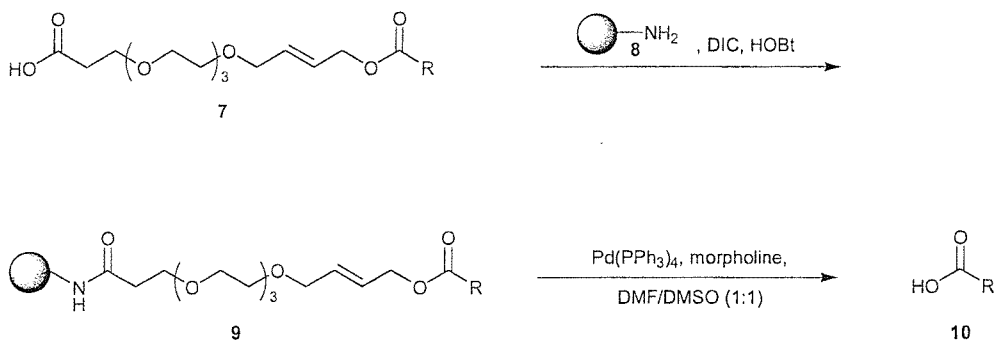
Allylic linkers, primarily based on allylic esters, have been investigated by many groups. A series of glycopeptides were prepared using a 4-hexene based linker attached to Sieber amide resin in isolated yields of greater than 79% (scheme 1.3).[28]

Scheme 1.3 The use of an allylic linker in the synthesis of glycopeptides.



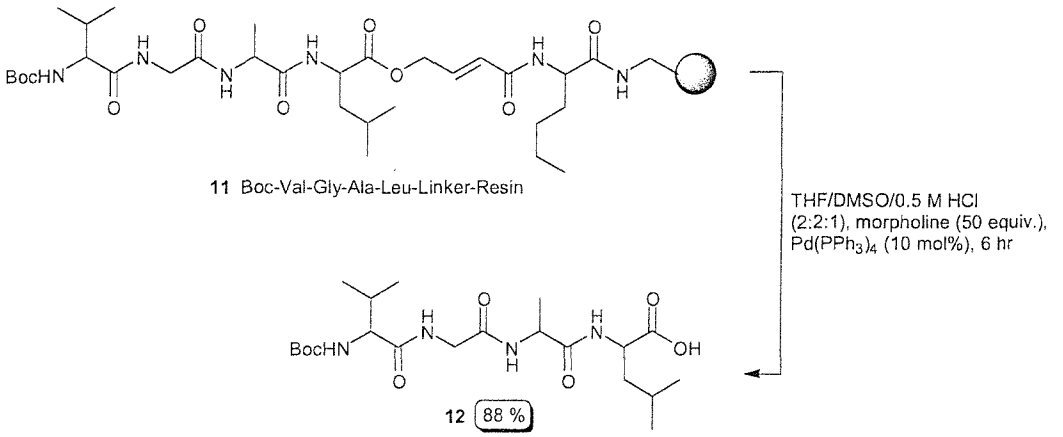
The same principle has been employed in the solid-phase synthesis of carboxylic acids **10** (scheme 1.4).[29-31] However, the authors introduced a flexible ethylene glycol spacer as they believed it would facilitate efficient access of the palladium(0) complex during the detachment reaction..

Scheme 1.4 The preparation of carboxylic acids **10** using an allylic linker.



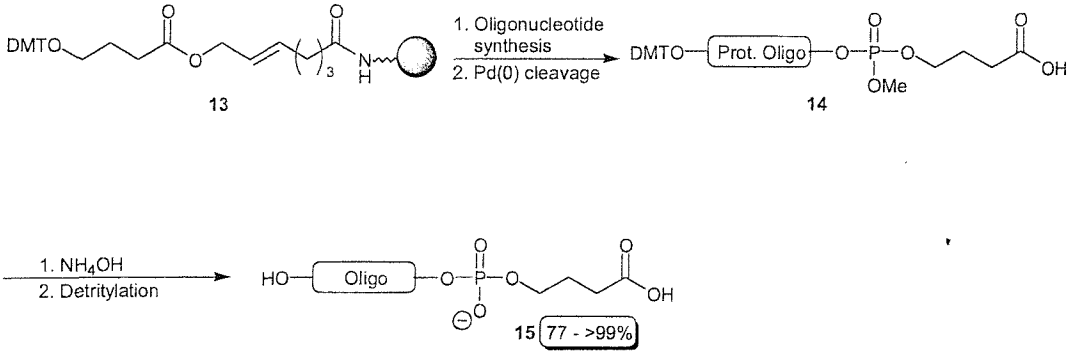
Protected peptides prepared on the solid-phase using allylic anchoring groups were cleaved from the resin, in very high yield (88%), under mild conditions (scheme 1.5).[32] These conditions, THF/DMSO/0.5 M HCl (2:2:1) with morpholine and $Pd(PPh_3)_4$, preserved the side-chain protecting groups. Other solvent systems were investigated, as was the use of various allyl scavengers such as HOBt and Bu_3SnH. Interestingly, efficient cleavage of the peptide was observed when the scavenger was omitted and 1.0 equivalent of catalyst was used. The authors suggested that in this case the PPh_3 may act as the scavenger.

Scheme 1.5 Cleavage of a protected peptide from the resin under mild conditions.



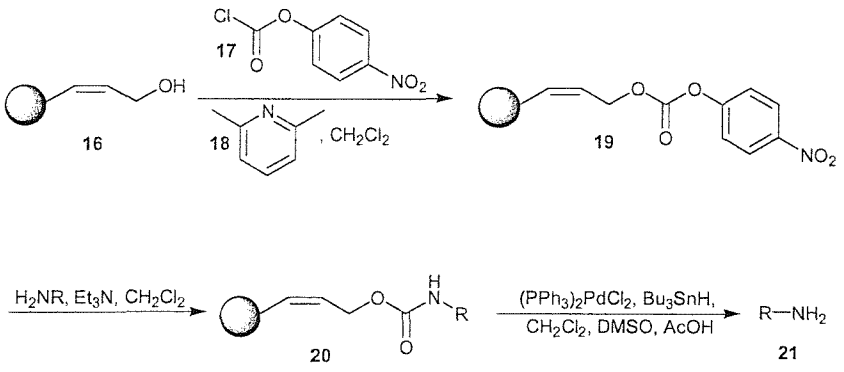
Allylic linkers have also been used successfully in the solid-phase synthesis of oligonucleotides **15** (scheme 1.6).[33,34] In this case the solid support was long-chain alkylamine controlled pore glass (LCAA-CPG). Cleavage conditions were $Pd_2(dba)_3$•$CHCl_3$, dppe, *n*-$BuNH_2$/HCO_2H (1.2 M) heated in THF at 55°C for up to 7 hours. High yields (77-99%) were obtained using this methodology and the authors noted that the cleavage reaction should be useful for the preparation of elaborate oligonucleotide conjugates as it is orthogonal to the commercially available *O*-methyl phosphoramidite protecting groups.

Scheme 1.6 Solid-phase oligonucleotide synthesis using an allylic linker.



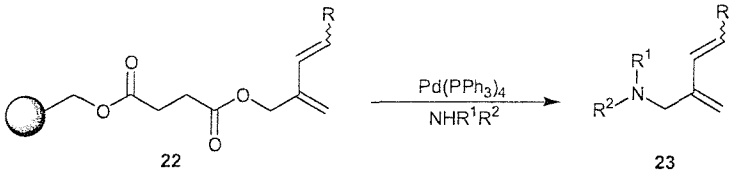
Carbamate methodology has been used to attach amines to an allyl linker (scheme 1.7).[35] The carbamate **20** is formed using the *p*-nitrophenylcarbonate method, and cleavage is achieved using palladium-catalysed allyl transfer to afford primary amines **21**.

Scheme 1.7 Solid-phase synthesis of amines **21** utilising an allylic linker.



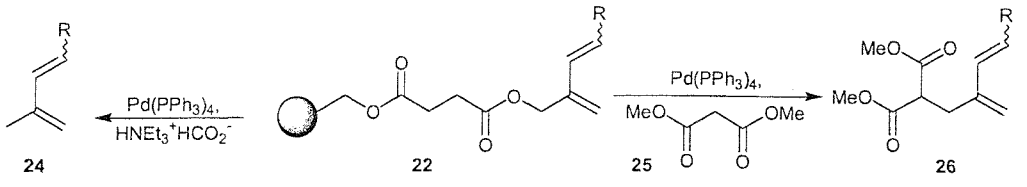
However, if the linker is constructed so that the π-allyl palladium species is released into solution then allylic products, such as allylic amine **23**, can be obtained (scheme 1.8).[36]

Scheme 1.8 The cleavage of a reversed allylic ester linkage.



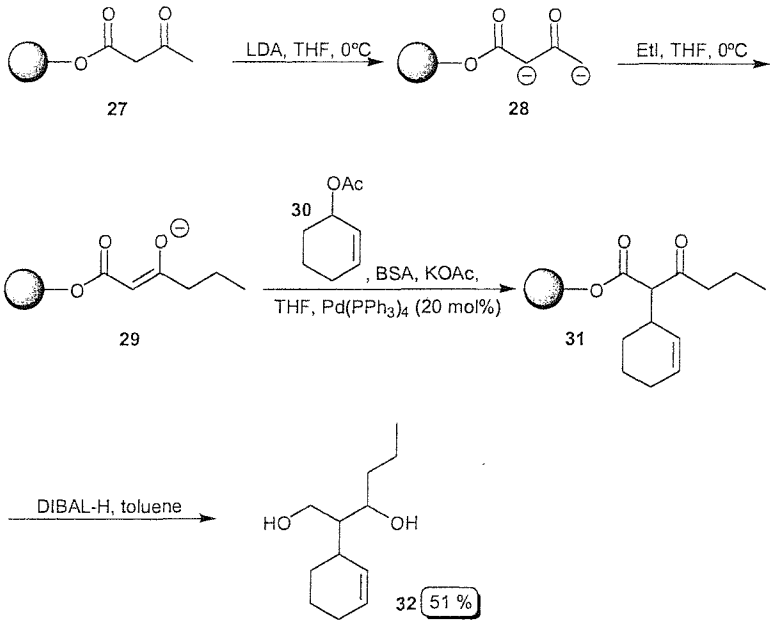
If a carbon nucleophile, such as dimethyl malonate **(25)**, is used then this acts as a traceless linker (scheme 1.9).[36] Ammonium formate was used as a hydride source for reductive cleavage of the product (scheme 1.9).[36]

Scheme 1.9 Traceless cleavage of a reversed allylic linkage.



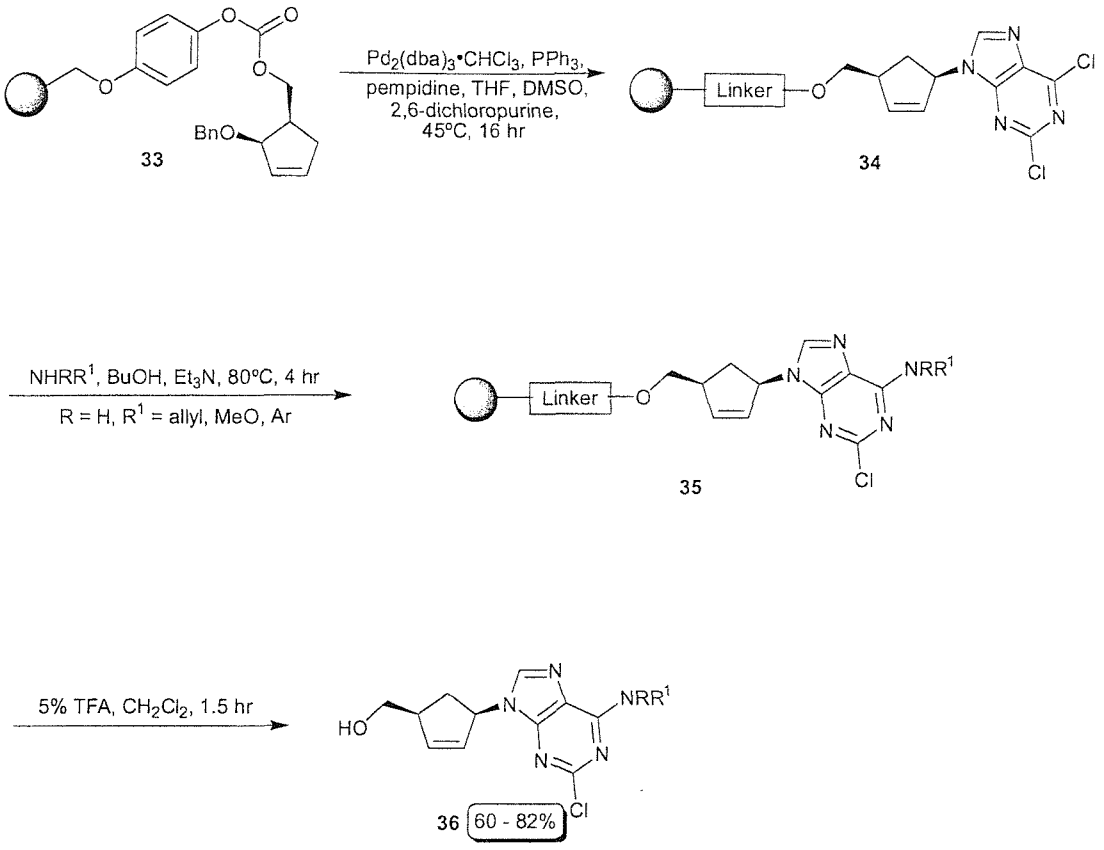
Under basic conditions different polymer-bound 1,3-dicarbonyl compounds **27** reacted as nucleophiles in palladium-catalysed allylic substitutions with a variety of allylic acetates (such as **30**), chlorides and carbonates (scheme 1.10). [37] The authors note that the availability of allylic substrates should make this methodology amenable for combinatorial synthesis.

Scheme 1.10 Palladium-catalysed allylic substitution on a solid support.



A solid-phase synthesis of carbocyclic nucleosides **36** has been developed in which the key step is a palladium-catalysed coupling of a purine derivative to a resin-bound allylic benzoate **33** (scheme 1.11).[38] Further functionalisation of the purine ring at the 6-position may be accomplished by thermal amination. The efficiency of the coupling is marked by the fact that no product containing an isomeric N7 purine linkage was observed in the final products cleaved from the resin. The isolated yields of the chromatographically purified desired products **36** were in the range 60 to 82%.

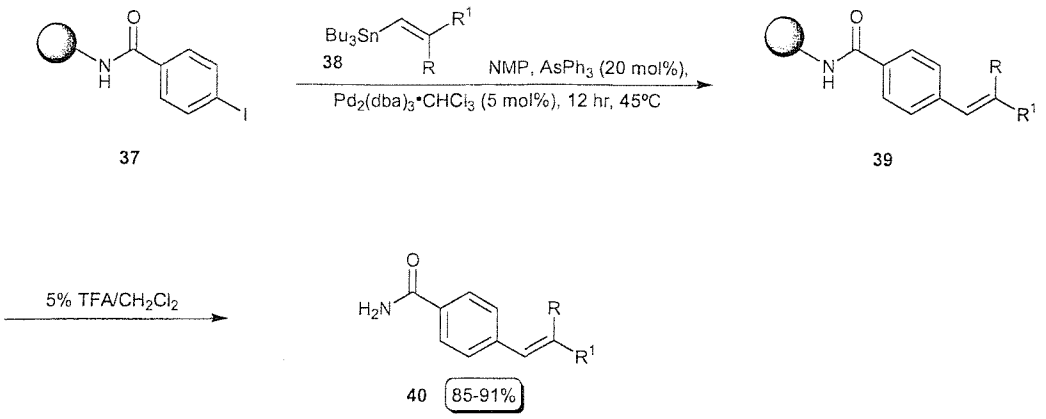
Scheme 1.11 Solid-phase synthesis of carbocyclic nucleosides.



1.3 The Stille Reaction In Solid-Phase Organic Synthesis

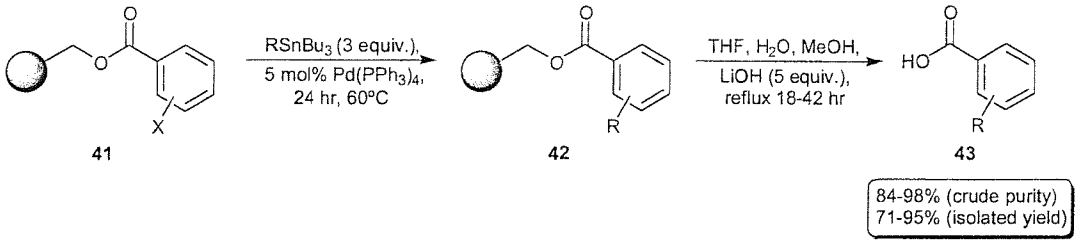
The Stille reaction is the palladium-catalysed coupling of organotin compounds with carbon electrophiles.[39-41] When using the Stille reaction in solid-phase synthesis either the organotin or carbon electrophile moiety can be attached to the solid support. Deshpande demonstrated that vinyl stannanes **38** couple smoothly with polymer-bound aryl iodides **37** (scheme 1.12).[42] Subsequent cleavage of the product from the Rink amide resin afforded the primary amides **40** in excellent yield (85-91%). The use of aryl stannanes was also studied.

Scheme 1.12 Coupling of a resin-bound aryl iodide **37** to a vinyl stannane **38**.



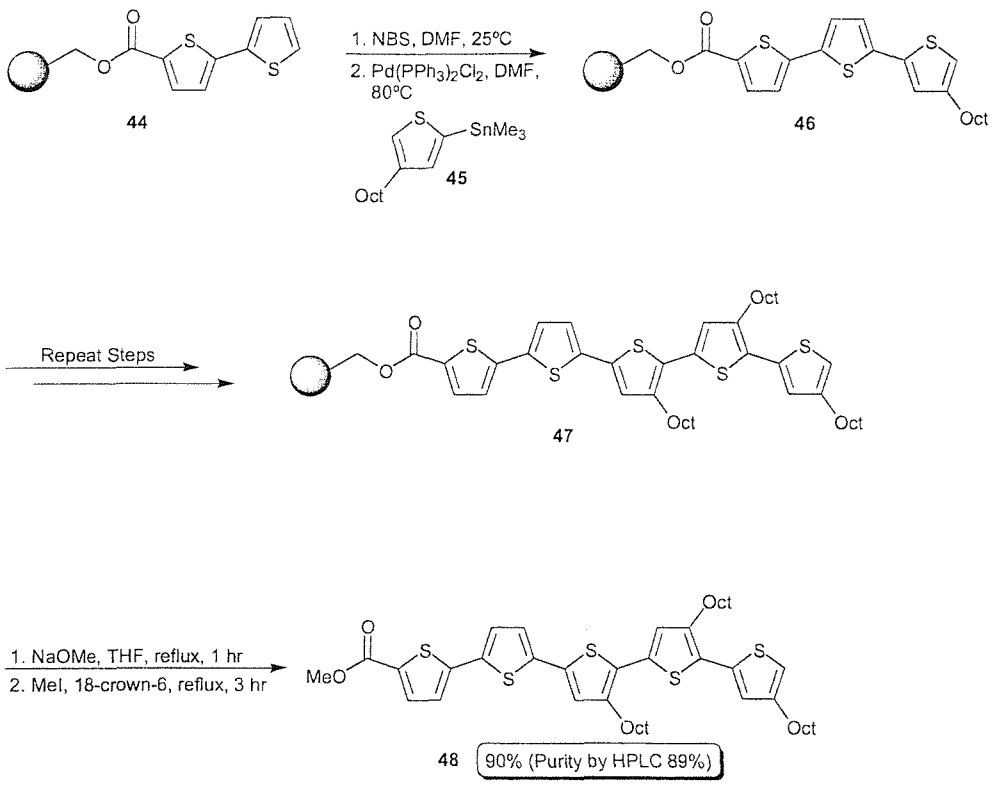
Stille cross coupling reactions on the solid-support have also been achieved using an ester linker leading to biaryl, heterobiaryl and styryl carboxylic acids **43** in high yield (71-95%) and purity (84-98%) (scheme 1.13).[43] Commercial Merrifield resin was esterified with various bromo and iodo benzoic acids using standard conditions (3 equiv. Cs_2CO_3, 0.5 equiv. KI, 1.5 equiv. benzoic acid, DMF, 80°C, 16 hr) to provide the desired substrates **41**.

Scheme 1.13 Palladium-catalysed biaryl synthesis on the solid-phase.



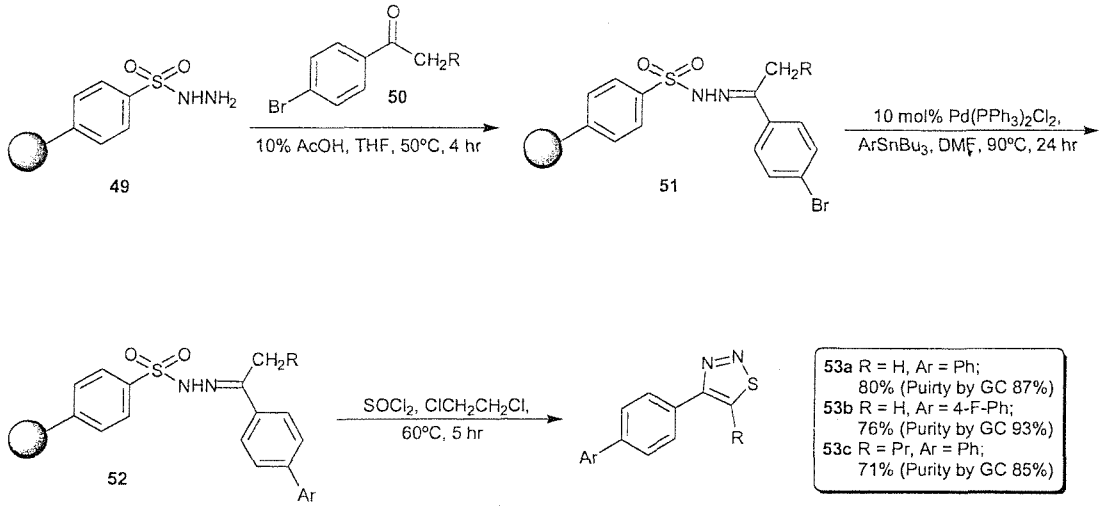
The solid-phase synthesis of asymmetric oligothiophenes on a chloromethylated macroporous resin, using an alternating sequence of bromination and Stille coupling reactions, has been used to prepare oligomers up to the pentamer **48** in excellent yield (90%) and purity (89-98%) (scheme 1.14).[44]

Scheme 1.14 The solid-phase synthesis of oligothiophenes.



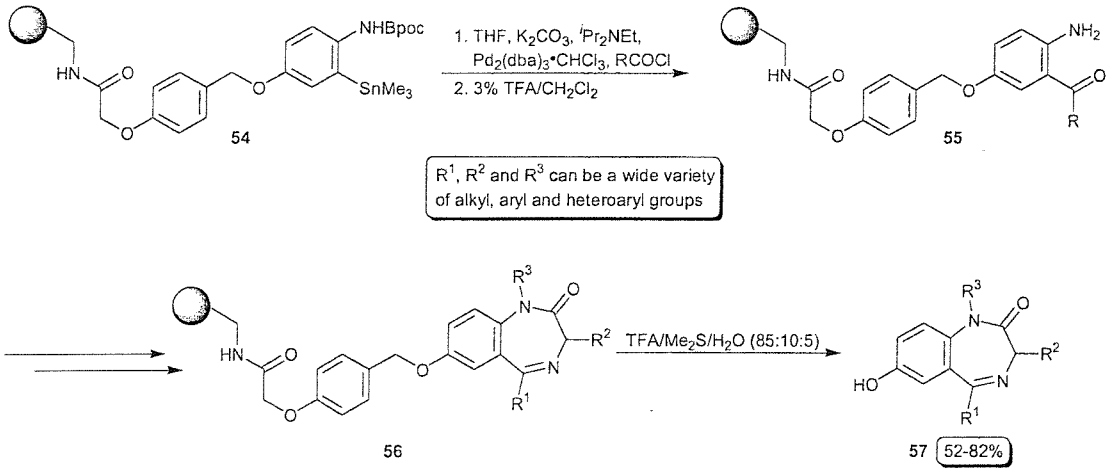
The Stille coupling reaction was used to introduce substituents in the solid-phase synthesis of 1,2,3-thiadiazoles **53a-c** (scheme 1.15).[45] Key steps included the 'resin capture' of ketones **50** by a polystyrene-sulfonylhydrazide resin **49**, modification of the substrate **51** by the Stille reaction and the cyclisative-cleavage of the desired products **53a-c**.

Scheme 1.15 Synthesis of 1,2,3-thiadiazoles **53a-c** using a 'catch and release' strategy.



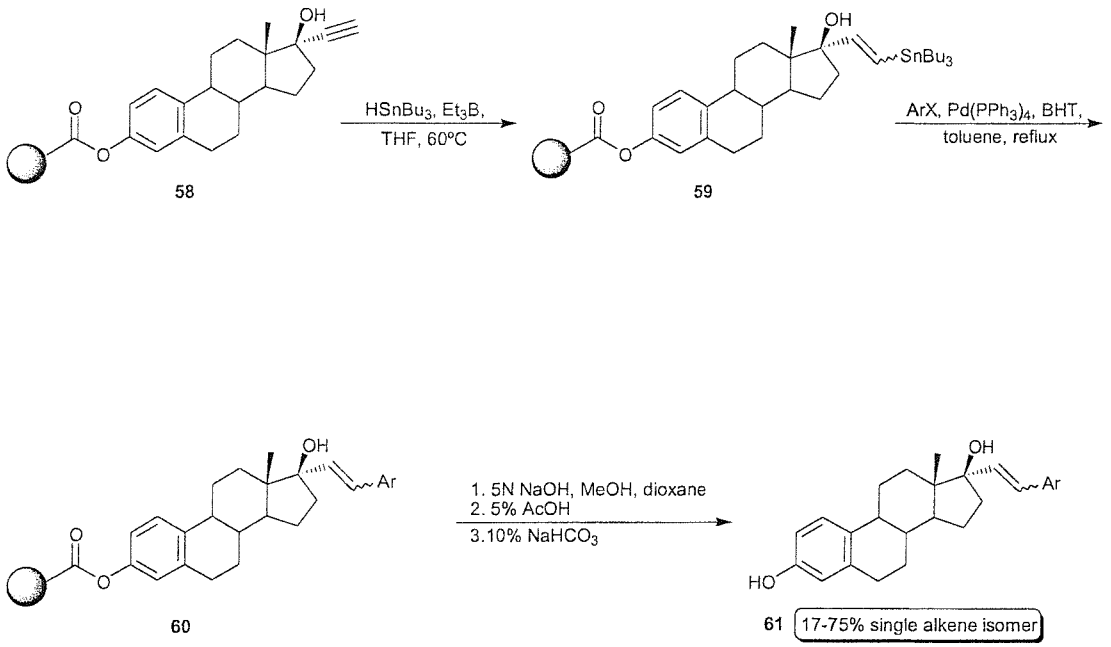
The coupling of the supported stannane **54** and aromatic or aliphatic acid chlorides was used in the synthesis of 1,4-benzodiazepine derivatives **57** (scheme 1.16).[46] Interestingly, the palladium catalyst of choice was $Pd_2(dba)_3$•$CHCl_3$ rather than $Pd(PPh_3)_4$ as use of latter required elevated temperatures, which caused some premature carbamate deprotection. Once the substrates had been constructed on the solid support they were cleaved by 10% TFA in moderate to good yield (52-82%).

Scheme 1.16 Structurally diverse 1,4-benzodiazepines **57** and the Stille reaction.



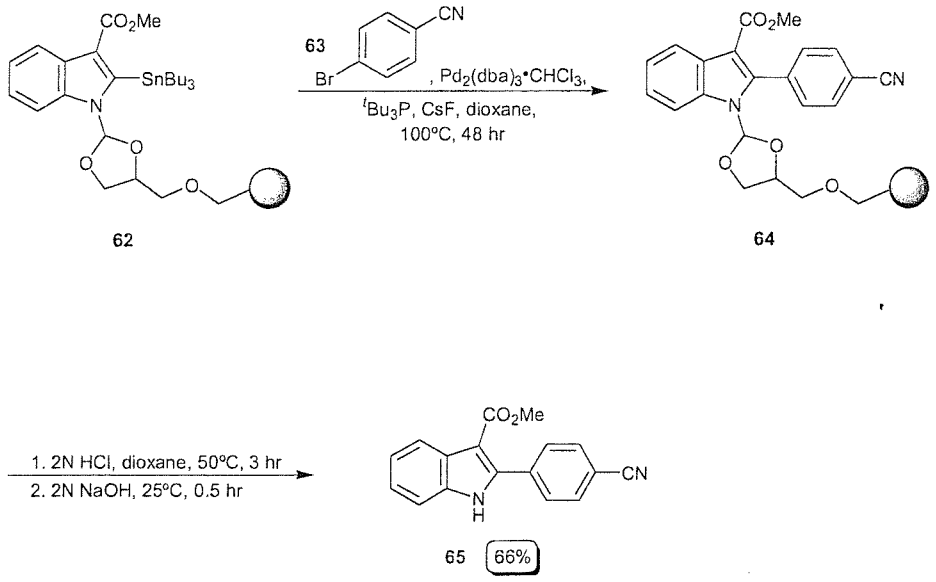
In order to develop probes for the hormone binding domain (HBD) of the estrogen receptor Stille couplings were used in order to access a variety of 17α-(aryl)-vinyl estradiols **61** (scheme 1.17).[47] Hydrostannylation of the resin-bound 17α-ethynyl estradiol **58** afforded the resin-bound stannanes **59**. A selection of substituted aryl halides were coupled to these, using unoptimised conditions, and subsequent hydrolysis from the solid-support afforded the desired products **61** as isomeric mixtures. The *E* and *Z* isomers were separated and the pure products isolated with varying success (17-75%). A linker derived from the 2-(trimethylsilylethoxy) methyl protecting group was used to immobilise steroidal vinyl triflates, which were shown to undergo palladium-catalysed coupling reaction to acetylenes and stannanes.[48]

Scheme 1.17 Preparation of estradiols **61** on the solid-phase.



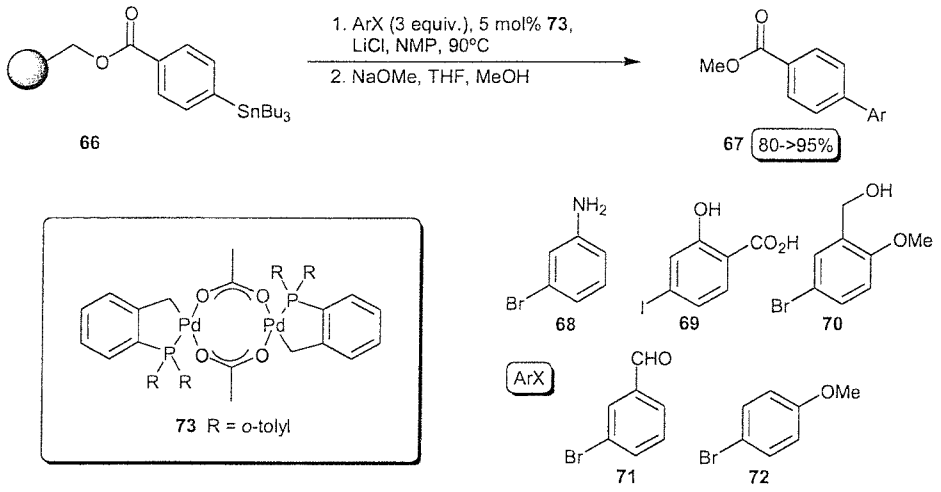
Indoles functionalised at the 2-position have been successfully generated using the Stille reaction (scheme 1.18).[49] This methodology has been incorporated into the authors search for selective dopamine D4 receptor antagonists.

Scheme 1.18 Functionalisation of resin-bound indoles *via* the Stille reaction.



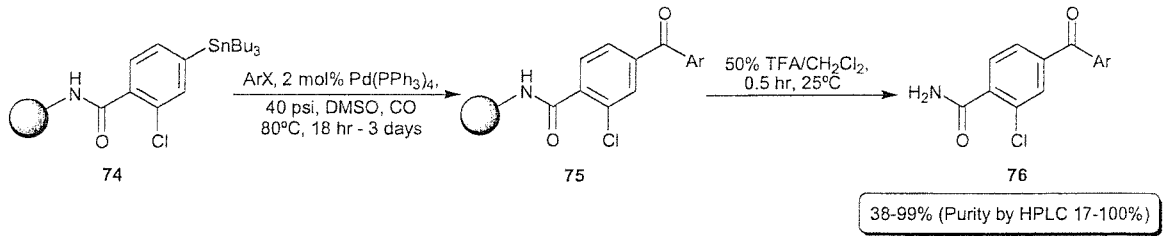
Polystyrene-bound stannyl species **66** undergoes a Stille coupling, catalysed by the palladacycle complex **73**, to provide a convenient and clean method for the synthesis of biaryls on the resin (scheme 1.19).[50] The authors reported that the use of traditional catalytic systems such as $Pd(PPh_3)_4$, $Pd(AsPh_3)_4$ and $Pd_2(dba)_3 \cdot CHCl_3$ gave inconsistent or unsatisfactory results for the coupling of the stannane **66** and aryl halides **68-72**. Sucholeiki also reported poor yields in the solid-phase synthesis of biaryls *via* the Stille reaction using traditional catalytic systems.[51] As a result the more unusual palladacycle **73** was used to give the desired products **67** in excellent yield (80->95%) after cleavage from the solid support.

Scheme 1.19 Synthesis of substituted biaryls **67** using the Stille coupling reaction.



Diaryl ketones **76**, bearing a wide variety of functional groups, were prepared with polymer-bound organostannanes **74** and aryl halides in the presence of carbon monoxide (scheme 1.20).[52] This synthesis constitutes a complementary approach to the synthesis of biaryl ketones *via* acid chlorides and is amenable to high throughput automated synthesis. Purity and yield of the cleaved products **76** varied greatly.

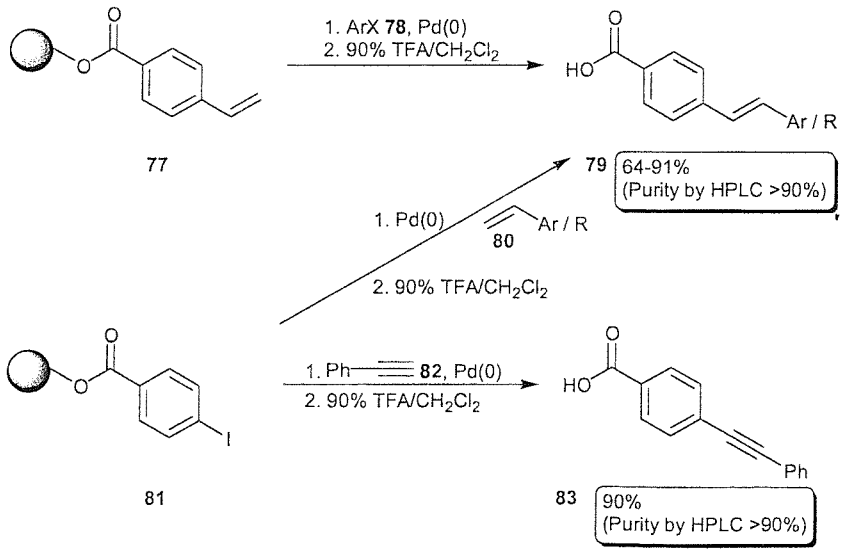
Scheme 1.20 Solid-phase synthesis of biaryl ketones **76** using the Stille reaction.



1.4 The Heck Reaction In Solid-Phase Organic Synthesis

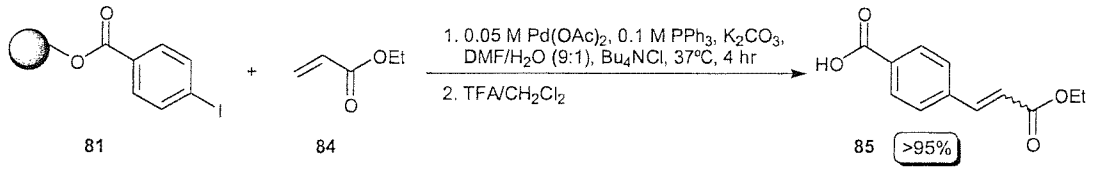
The Heck reaction involves the palladium-catalysed coupling between an aryl halide or triflate and a vinyl or terminal acetylene (Sonogashira reaction) functionality.[53-55] When used in solid-phase synthesis either the aryl electrophile or vinyl moiety can be attached to the support. Early studies showed that both resin-bound 4-vinylbenzoic acid **77** and 4-iodobenzoic acid **81** underwent couplings with aryl halides **78**, olefins **80** or phenylacetylene **(82)** respectively (scheme 1.21).[56] The choice of catalytic system depended on the substrates used but the most effective systems were $Pd(OAc)_2$, nBu$_4$NCl, Et_3N, DMF at 80°C for 16 hours or $Pd_2(dba)_3$•$CHCl_3$, P(2-Tol)$_3$, Et_3N, DMF at 100°C for 20 hours. The resulting 1,2-disubstituted alkenes **79** or acetylenes **83** were cleaved from the resin by 90% TFA/CH_2Cl_2 to give the desired products in high yield (64-91%) and purity (>90%).

Scheme 1.21 Heck reactions of polymer-bound aryl halides **81** or styrenes **77**.



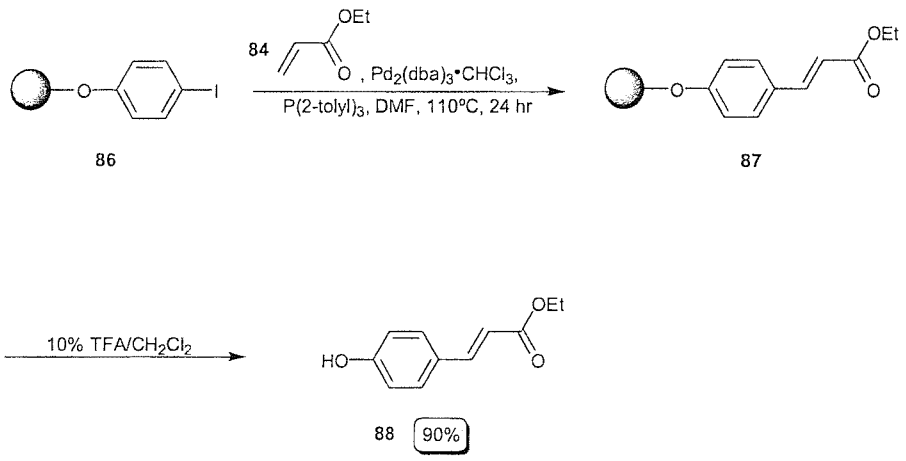
Further studies showed that high reaction temperatures are not required when a phase-transfer catalyst, such as Bu_4NCl, is used in an aqueous DMF solvent system.[57] Under the conditions described ethyl acrylate (**84**) was coupled to resin-bound 4-iodobenzoic acid **81** and cleaved in an overall yield of >95% (scheme 1.22).

Scheme 1.22 Heck reactions on a solid support using a phase-transfer catalyst.



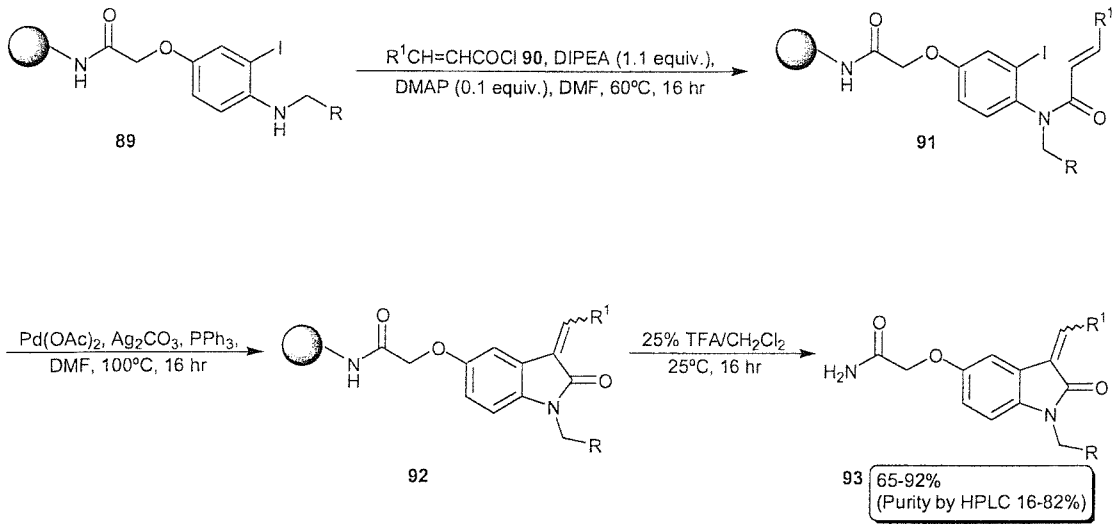
The Heck reaction was also shown to proceed efficiently when the iodide moiety was attached to Wang resin as a phenolic ether **86** (scheme 1.23).[58] In this case acid-catalysed hydrolysis provided phenols **88**.

Scheme 1.23 Intermolecular Heck reactions on a solid support.



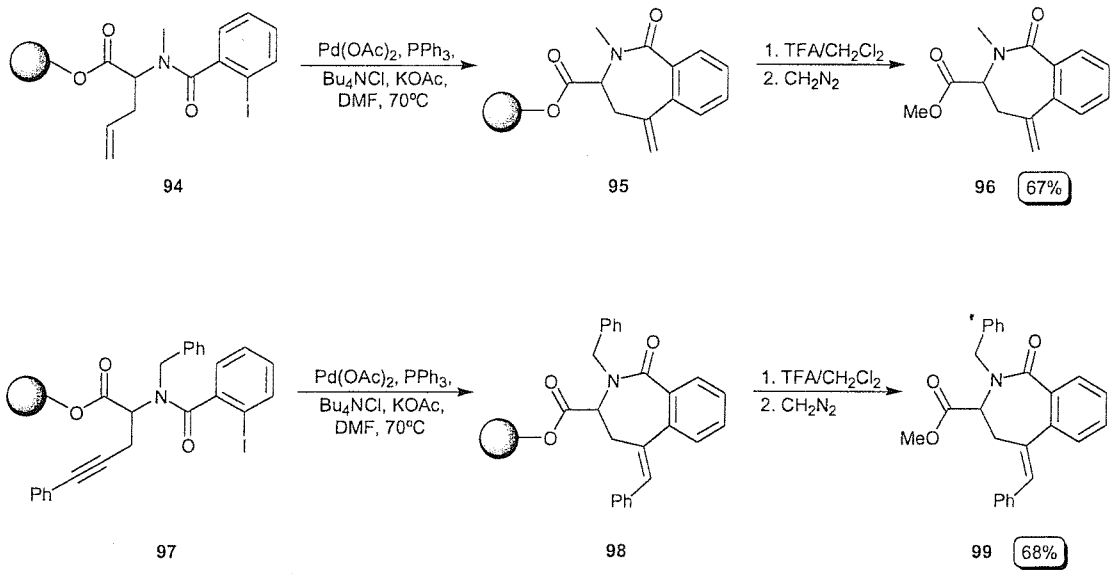
2-Oxindole derivatives **93** were prepared on Rink amide resin using an intramolecular Heck coupling (scheme 1.24).[59] Acylation of aniline **89** with a crotonyl chloride **90** provided the tertiary amide **91**. To affect cyclisation the resin **91** was treated with $Pd(OAc)_2$ (30 mol%), Ag_2CO_3 (2 equiv.), PPh_3 (0.6 equiv.) in DMF at 100°C for 16 hours.

Scheme 1.24 Intramolecular Heck reaction to give 2-oxindole **93** derivatives.



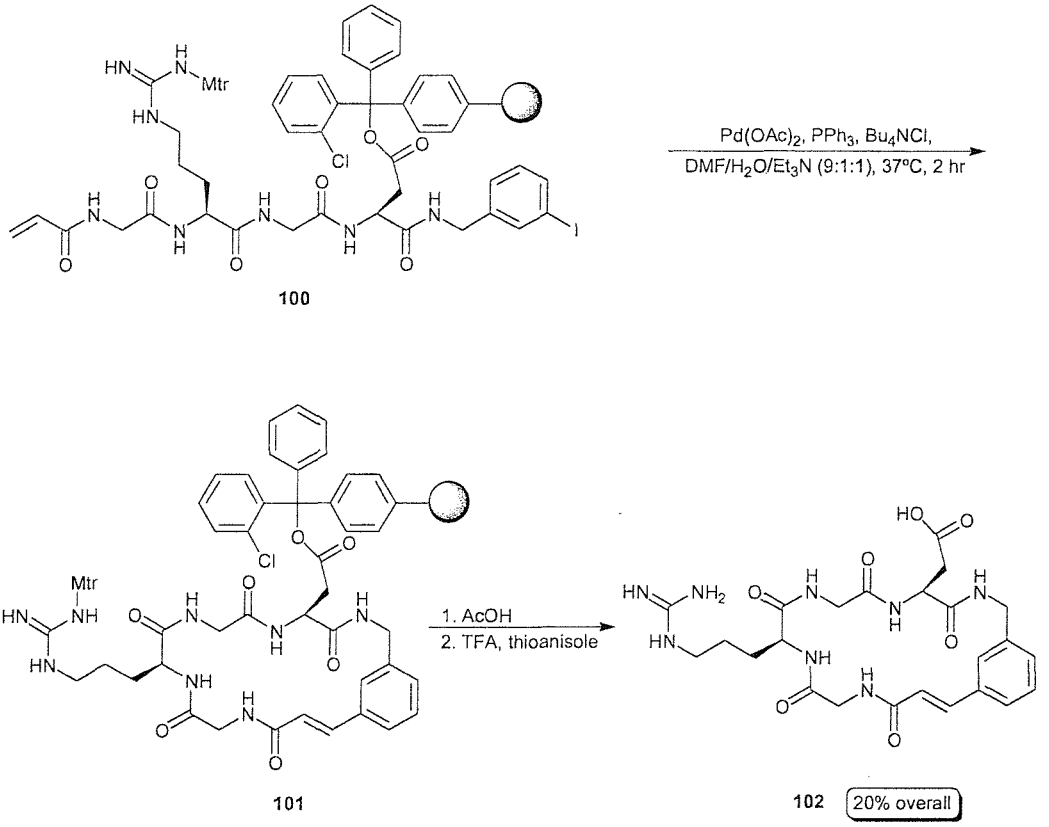
An intramolecular Heck coupling was also used to prepare substituted benzazepines **96** and **99** on the solid-phase (scheme 1.25).[60] Cyclisations of both alkene **94** and alkyne **97** substrates were successfully catalysed by 20 mol% $Pd(OAc)_2$ in the presence of a phase-transfer catalyst. A similar intramolecular Heck coupling, between a vinyl group and an aryl halide, has been used by several groups to prepare indole analogues on the solid-phase.[61,62]

Scheme 1.25 Intramolecular Heck reactions to give benzazepines **96** and **99**.



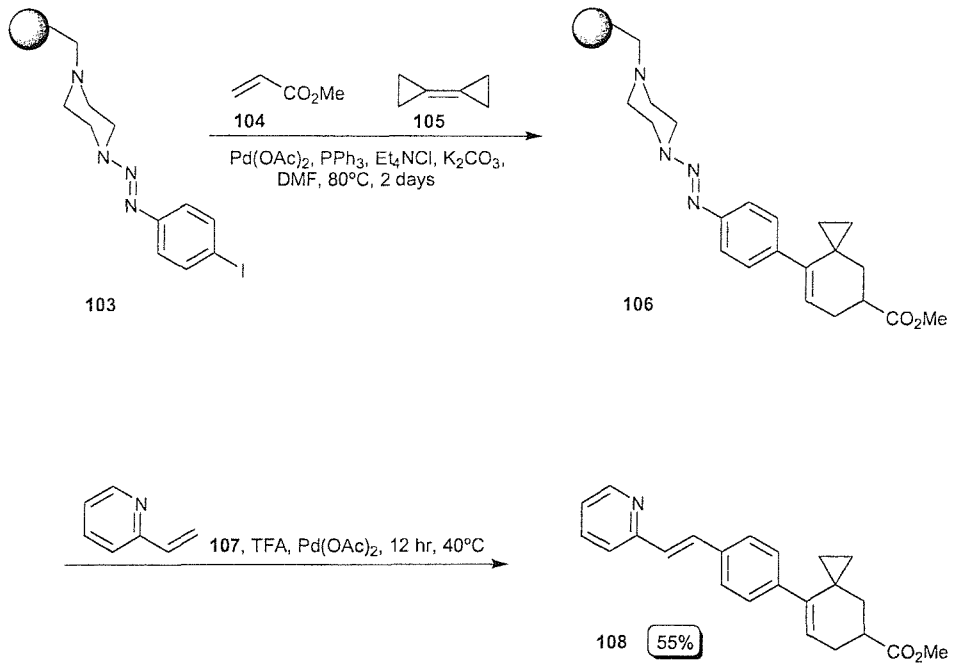
RGD-derivatives, such as macrocycle **102**, were prepared using a Heck reaction to effect cyclisation (scheme 1.26).[63] To allow 'head-to-tail' cyclisation the linear precursor **100** was anchored to a chlorotrityl resin through the β-carbonyl group of the aspartate residue.

Scheme 1.26 Solid-phase macrocyclisation using the Heck reaction.



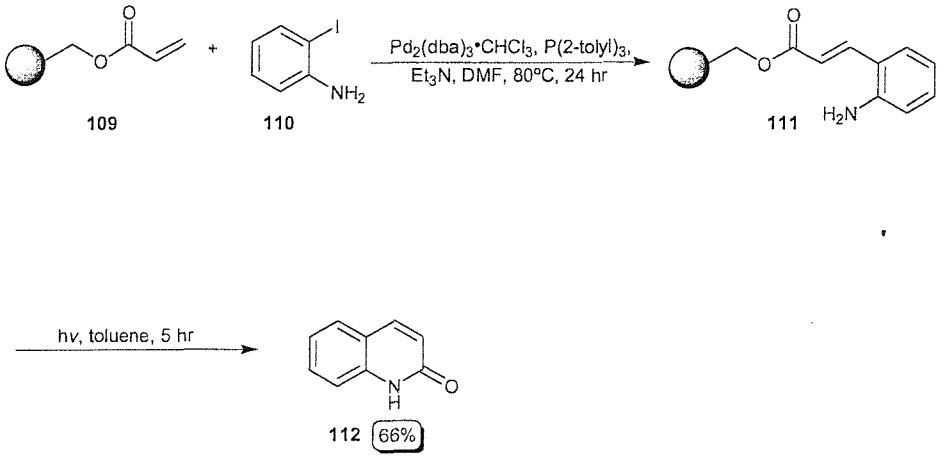
A reactive alkene **104**, an aryl halide **103** and a dienophile **105** react with one another in a domino Heck-Diels-Alder reaction to give spiro[2.5]octene derivatives **106**, in the course of which 3 carbon-carbon bonds are formed with high regioselectivity (scheme 1.27).[64] A further element of structural diversity can then be added by virtue of the use of the triazene linkage, which when cleaved by TFA provides the corresponding aryl diazonium salt.[64,65] The salt immediately reacts with the 2-ethenylpyridine **(107)** *via* a Heck reaction in the presence of $Pd(OAc)_2$ to afford the spirocycle **108** in a yield of 55% (>95%).

Scheme 1.27 The use of a domino Heck-Diels-Alder reaction to prepare spirocycles.



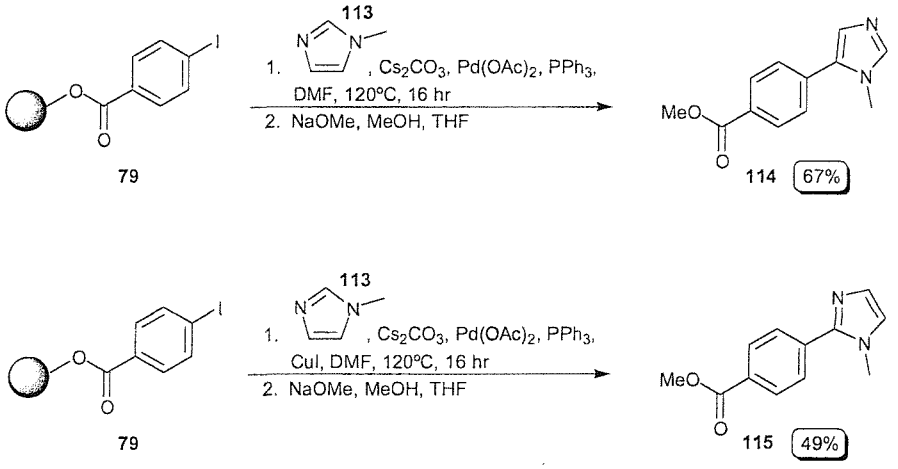
The immobilised 2-substituted cinnamate **111** was constructed by coupling 2-iodoaniline **(110)** to the REM resin **109** (scheme 1.28).[66] 2-Quinolone **(112)** was subsequently obtained, *via* a photoinduced cyclorelease, in a yield of 66%. The authors also investigated the construction of coumarins using this methodology.

Scheme 1.28 Preparation of 2-quinolone **(112)** *via* a photoinduced cyclorelease strategy.



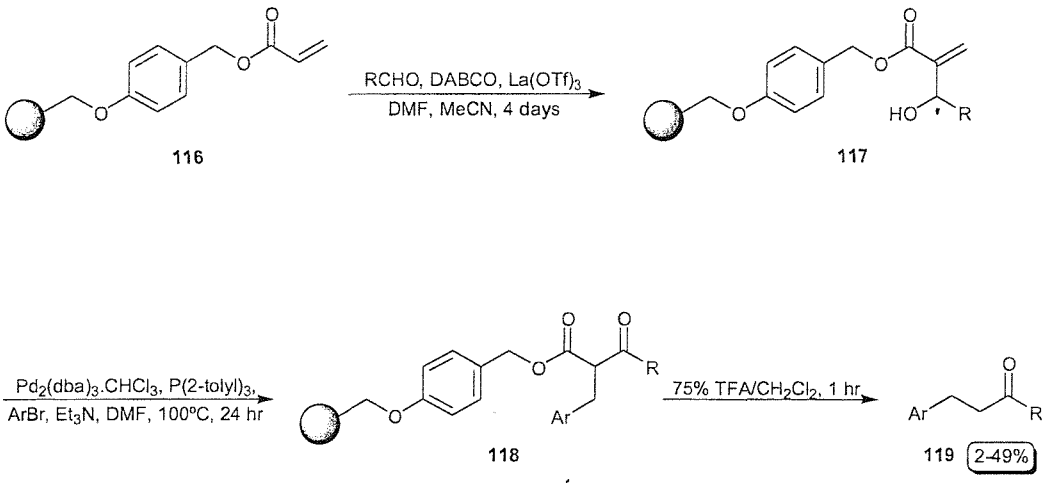
Regioselective palladium-catalysed monoarylation of azoles was achieved using iodobenzoate immobilised on a polymer support **79** (scheme 1.29).[67] The positional selectivity for the coupling reaction was dramatically influenced by the presence of CuI and no diarylation was observed in either case. No mechanism was offered by the authros to explain the role that the CuI plays in the regioselectivity.

Scheme 1.29 Selective arylation of *N*-methylimidazole **(113)**.



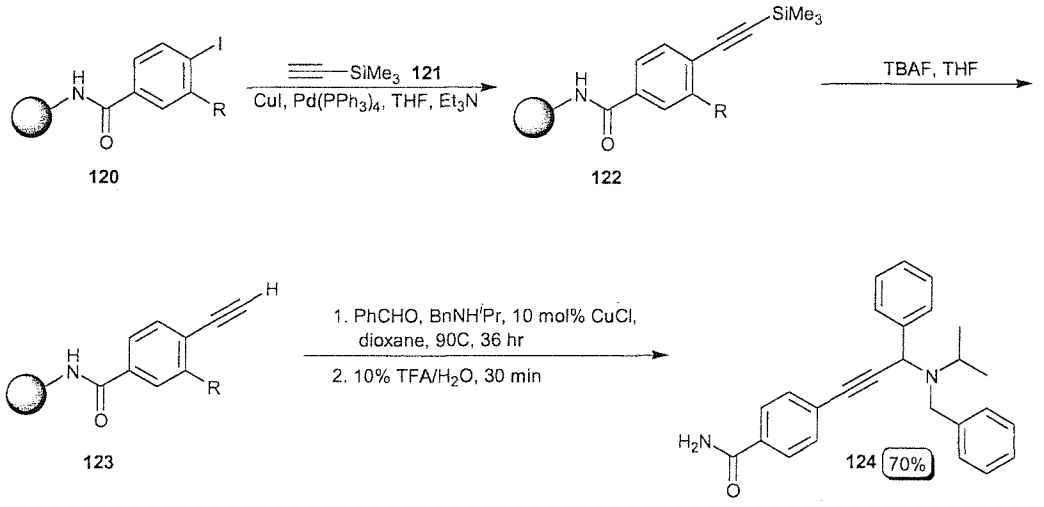
Sequential Baylis-Hillman and Heck reactions were employed on the solid-phase to generate a series of α-substituted β-keto esters **118** (scheme 1.30).[68] When cleaved from the resin by acid-catalysed hydrolysis with concomitant decarboxylation aryl ketones **119** were obtained in modest yields (2-49%).

Scheme 1.30 The use of sequential Baylis-Hillman and Heck reactions.



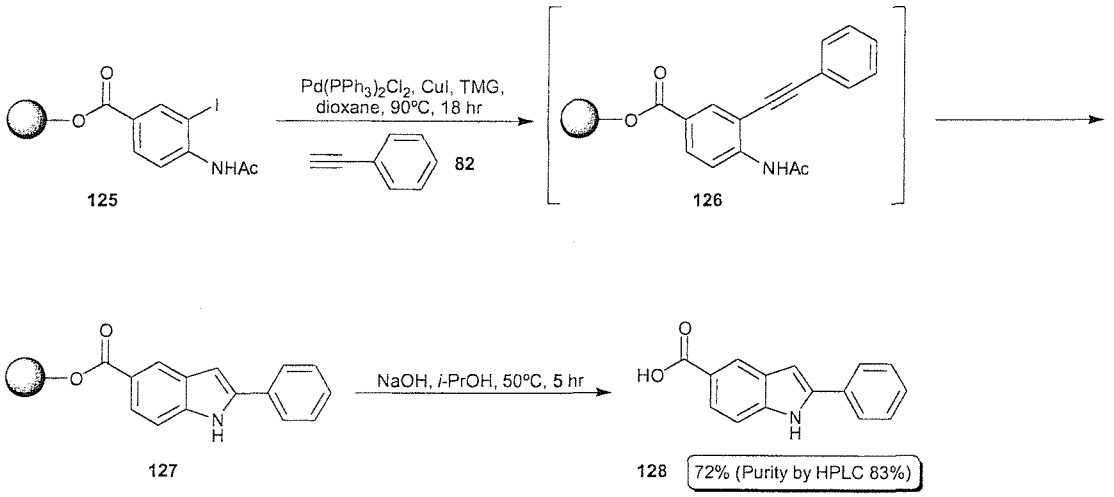
The Sonogashira reaction was used to introduce diversity into the alkyne component of amine **124** (scheme 1.31).[69] 4-Iodobenzoic acid was attached to a Rink resin using a carbodiimide coupling protocol. Reaction of the resin-bound aryl iodide **120** with trimethylsilylacetylene **(121)** in the presence of copper(I) and palladium(0) catalysts, afforded the corresponding silyl arylacetylene **122**. Desilylation gave the terminal alkyne **123**, which was then subjected to Mannich conditions to produce tertiary amines such as **124**. A limitations study of the Sonogashira reaction on the solid-phase was carried out by Mesmaeker *et al.*[70]

Scheme 1.31 Preparation of tertiary amines incorporating the Sonogashira reaction.



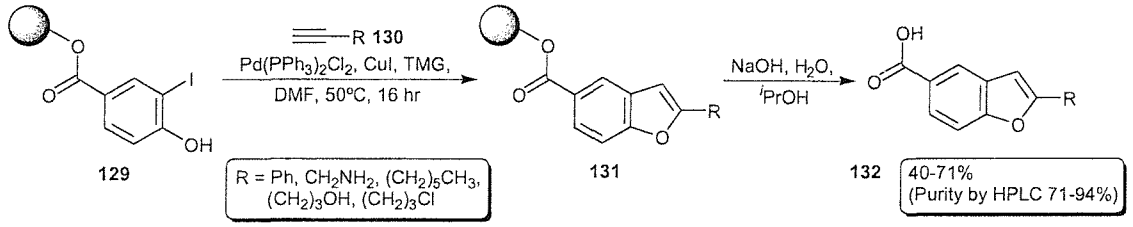
The Sonogashira reaction was also a key step in the synthesis of substituted indoles in the hands of several groups and all follow the same basic route.[71-73] Coupling of the alkyne **82** to the resin-bound aniline **125** provides intermediate **126**, which then cyclises *in situ* presumably with the assistance of palladium and/or copper species (scheme 1.32).[71] The resulting indoles **128** are cleaved from the resin in high yields and purity. In addition, a traceless *N*-sulfonyl linker was also developed for use in the solid-phase synthesis of indoles.[74]

Scheme 1.32 Preparation of indole **128** *via* heteroannulation of internal alkynes.



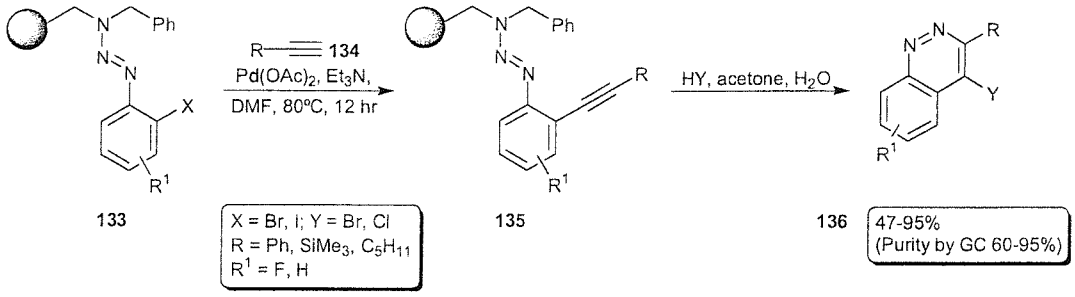
The same methodology has been used to construct benzofurans (scheme 1.33). In this case resin-bound phenols **129** are used instead of anilines **125**.[75]

Scheme 1.33 Preparation of benzofuran **133** *via* heteroannulation of internal alkynes.



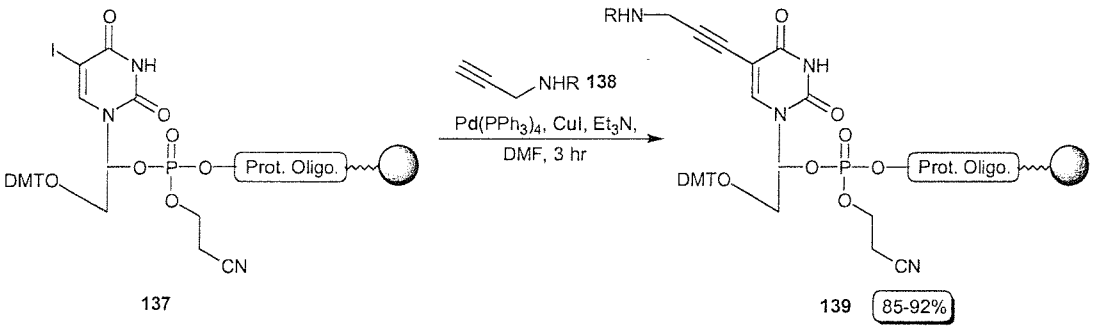
Palladium-catalysed alkynylations of triazene-bound 2-halo arenes **133** were used to provide the substrates **135** for a Richter-type cleavage protocol (scheme 1.34).[76] Copper was omitted from the reaction as it coordinated to the triazene moiety and this led to contamination of the final cinnoline products **136**.

Scheme 1.34 Preparation of cinnolines **136** from resin-bound alkynes **135**.



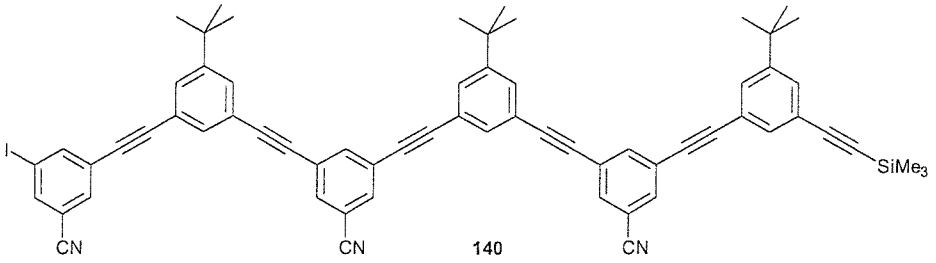
Modified oligonucleotides **139** have been prepared on the solid-phase using the mild Sonogashira coupling conditions to which the oligonucleotides were stable (scheme 1.35).[77]

Scheme 1.35 Modification of oligonucleotides on a solid-support.



Finally, phenylacetylene oligomers, such as hexamer **140**, were prepared *via* an iterative approach involving the Sonogashira coupling of resin-bound terminal alkynes with aryl iodides. The synthesis made use of a triazene linker that cleaves, upon treatment with iodomethane, to give an oligomer terminated at one end with an aryliodide and a TMS protected acetylene at the other.[78]

Figure 1.1 Phenylacetylene hexamer **140** prepared on a solid support.

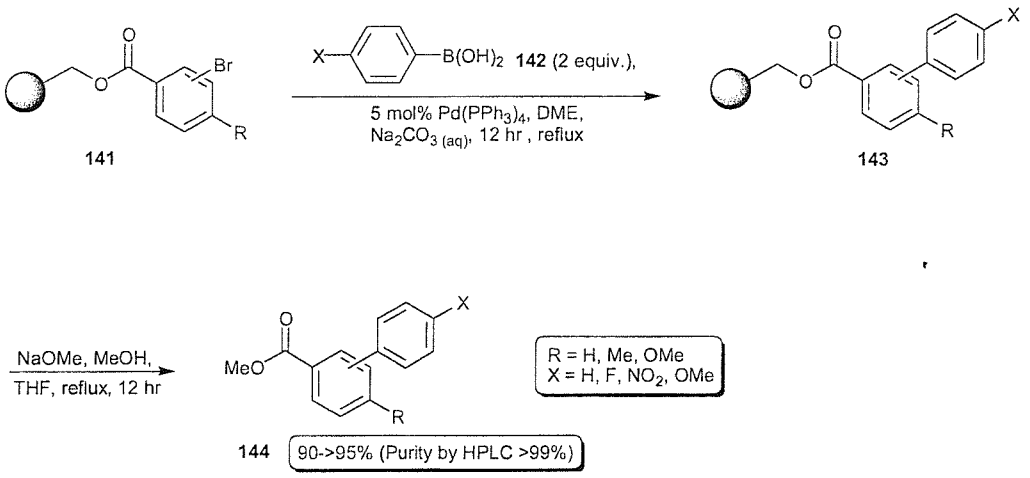


140

1.5 The Suzuki Reaction In Solid-Phase Organic Synthesis

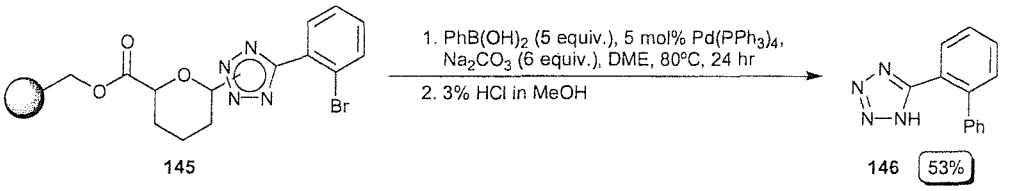
The Suzuki reaction involves the palladium-catalysed coupling of organoboron compounds, usually boronic acids, with carbon electrophiles such as aryl, alkenyl or alkynyl halides.[79-82] As with other palladium-catalysed coupling reactions on the solid-phase either one of the reactants can be attached to the solid support. Aryl halides **141**, attached to Merrifield resin *via* an ester linkage, underwent a cross-coupling reaction with aryl boronic acids **142** (scheme 1.36).[83] The biaryl products **144** were released from the solid-support by simple transesterification in excellent purity (>99%) and yield (90->95%). Similar reactions were investigated by Guiles *et al.*[84]

Scheme 1.36 Biaryl synthesis *via* Suzuki coupling on a solid support.



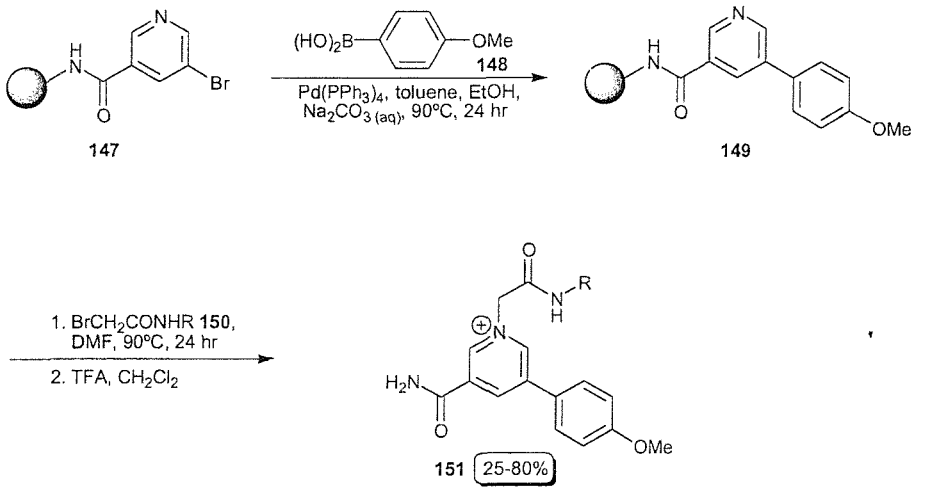
Biphenyltetrazole derivatives **146** have also been prepared, as possible angiotensin II receptor antagonists, using a solid-phase Suzuki coupling reaction (scheme 1.37).[85] In order to allow traceless cleavage from the support a dihydropyran carboxylic acid type linker was employed.

Scheme 1.37 Solid-phase synthesis of biphenyltetrazole derivatives **146**.



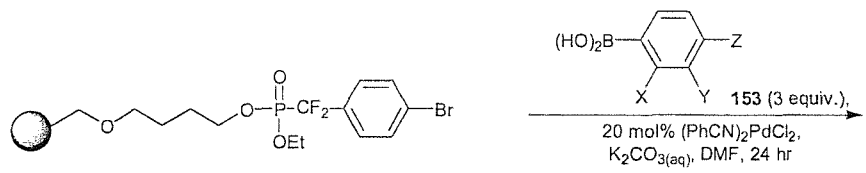
Other heteroaromatics, which have been prepared using a Suzuki coupling include biaryl benzimidazoles,[86] imdiazopyridines,[86] isoxazolinoisoquinolines,[87] and 1,3,5-trisubstituted pyridinium salts **151** (scheme 1.38).[88] A forty-membered library was prepared using the mix and split approach after an initial array of eleven compounds was synthesised. Although the products were obtained in moderate to good yields (25-80%) it should be noted that the reaction conditions were unoptimised.

Scheme 1.38 Introduction of aryl groups into a library of 1,3,5-trisubstituted pyridinium salts **151** using the Suzuki coupling.

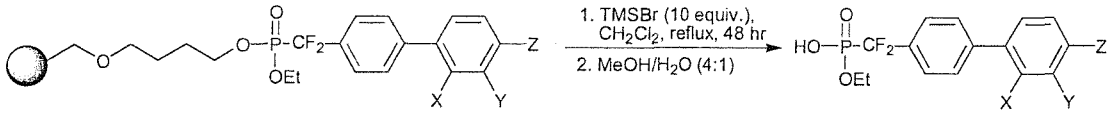


In an effort to obtain non-peptidyl inhibitors of protein tyrosine phosphatases non-peptidyl biaryl α,α-difluoromethylenephosphonic acids **155a-e** were prepared using non-cross-linked polystyrene as the support (scheme 1.39).[89] This allowed the reactions to be carried out under homogeneous conditions and the reactions to be followed using conventional ^{19}F NMR. Using the conditions described the Suzuki coupling reaction went to completion at room temperature in 24 hours. Cleavage from the resin afforded the products, including **155a-e**, in moderate to good yields (43-89%) and purity (80-99%).

Scheme 1.39 Non-peptidyl biaryl α,α-difluoromethylenephosphonic acids **155a-e**.



152



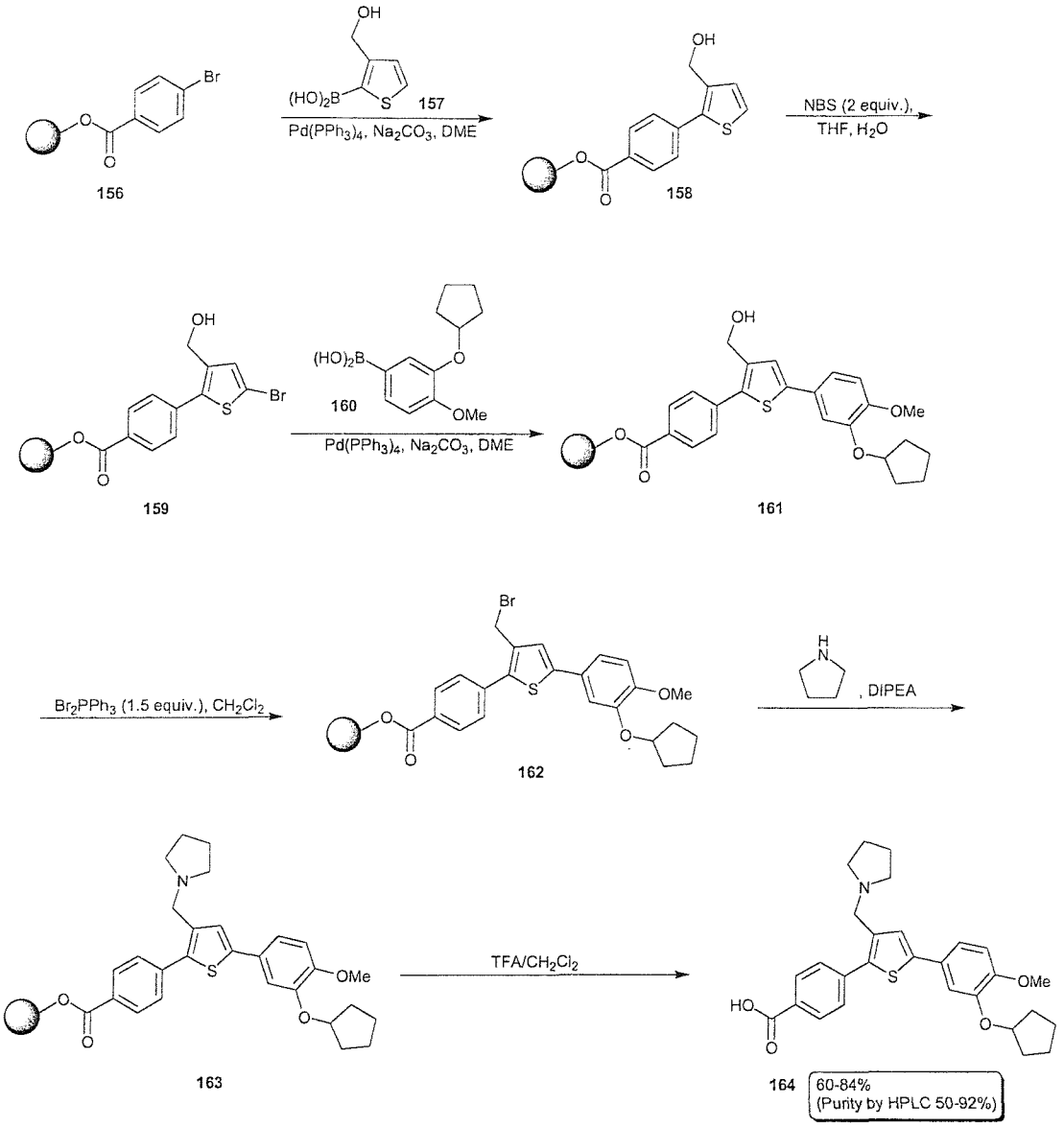
154

155a	X=Y=Z=H	89%	(98%)
155b	X=Y=H, Z=Ph	61%	(96%)
155c	X=Me, Y=Z=H	67%	(98%)
155d	X=Y=H, Z=Me	66%	(99%)
155e	X=Y=H, Z=F	75%	(99%)

Figures in parentheses indicates purity by HPLC

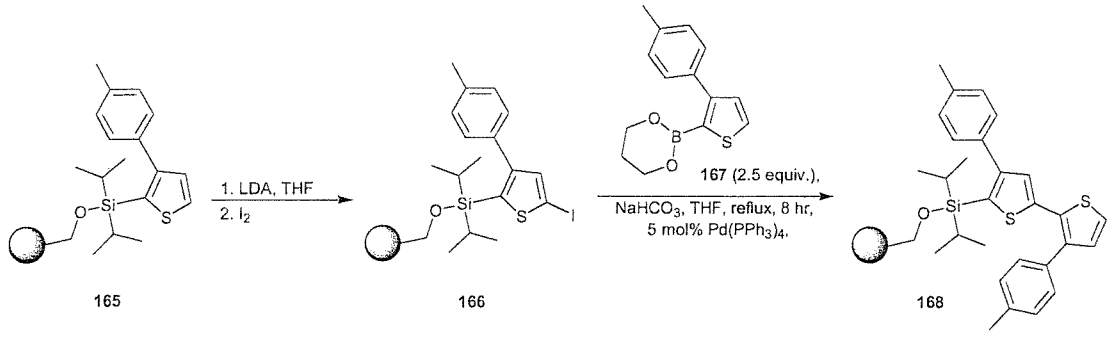
Substituted thiophene derivatives were prepared in order to investigate their activity against the PDE-4 enzyme.[90] Resin-bound 3-hydroxymethylthiophene **158** was employed as the scaffold to which various groups were added using palladium-catalysed reactions to form carbon-carbon bonds (scheme 1.40). The methodology developed allows convenient modification of the thiophene core from three directions to give highly substituted products **164**.

Scheme 1.40 Synthesis of novel PDE-4 inhibitors.



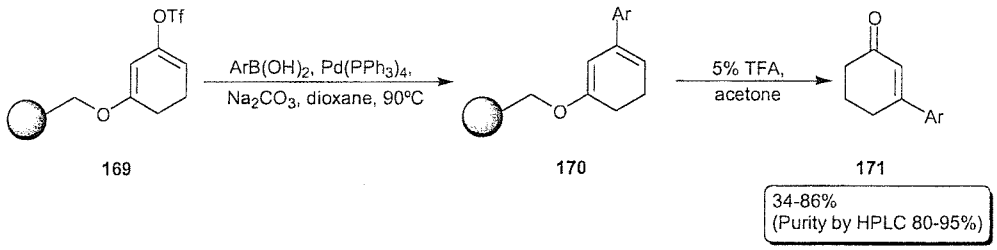
Novel sequences of iodination and Suzuki cross-coupling were employed in the preparation of regioregular head-to-tail coupled oligo(3-arylthiophene)s **168**. The authors investigated the construction of these thiophene polymers, which were attached to the solid support *via* an ester linker[91] and a silyl linker (scheme 1.41).[92]

Scheme 1.41 Synthesis of oligo(3-arylthiophene)s **168** using the Suzuki coupling.



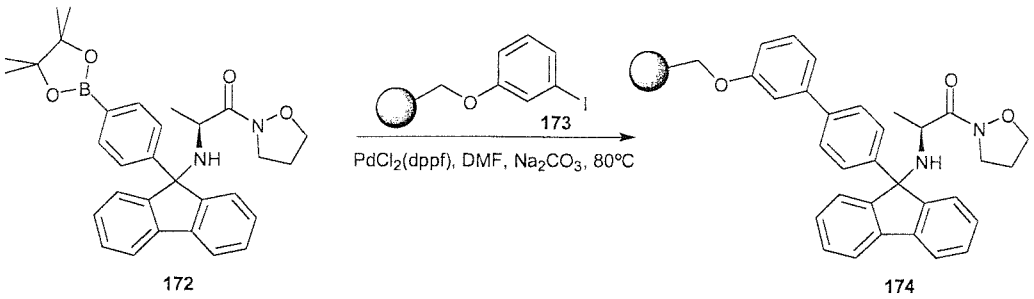
Carbon electrophiles other than organohalides have also been used in Suzuki cross coupling reactions on the solid-phase. The first reported use of a supported vinyl triflate **169** undergoing such a coupling used the reaction in the preparation of 2-cyclohexenones **171** (scheme 1.42).[93] The authors noted that only the desired enone product **171** was liberated from the resin upon exposure to the cleavage conditions in good yield (34-86%) and purity (80-95%).

Scheme 1.42 Use of resin-bound vinyl triflates **169** in the Suzuki coupling reaction.



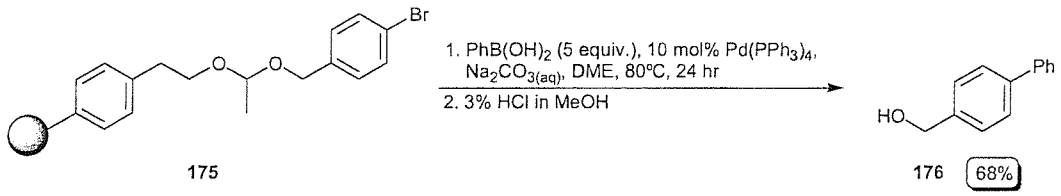
A novel linking strategy has been developed for synthesising configurationally stable α-amino aldehydes on the solid support (scheme 1.43).[94] In order to prepare the linker **174** a Suzuki coupling reaction was used whereby the fluorene species **172** was attached to the resin-bound aryl halide **173**.

Scheme 1.43 Fluorene based linker used in the preparation of α-amino aldehydes.



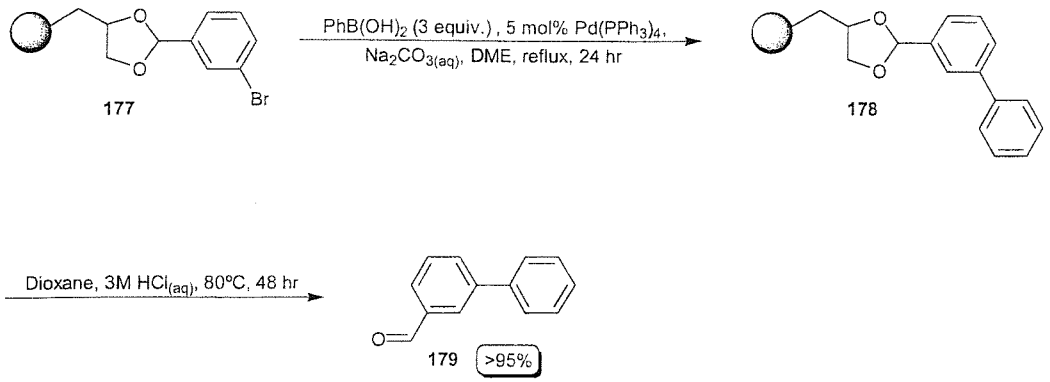
The use of Suzuki coupling reactions with other linkage strategies has also been studied. Both the Suzuki and Stille coupling reactions have been shown to be compatible with a photocleavable linker based on a pivaloylglycol group.[95] Whilst the Suzuki coupling was also shown to be compatible with an enzyme-labile linker.[96] Attachment of an aryl halide substrate to the resin *via* an acetal linkage **175** was compatible to the subsequent Suzuki coupling reaction (scheme 1.44).[97] Hydrolytic cleavage from the resin afforded biphenyl derivatives bearing a hydroxymethyl group, such as **176**, in good yield (60-70%).

Scheme 1.44 Compatibility of the Suzuki coupling reaction to an acetal linkage **175**.



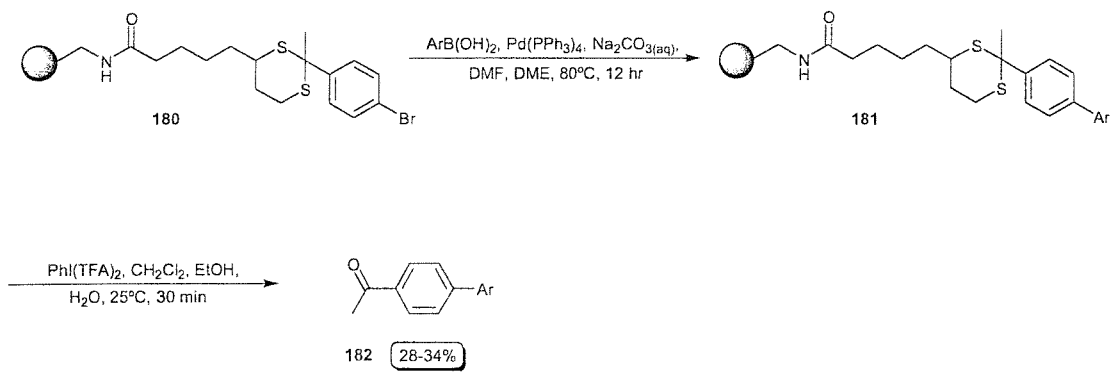
An acetal linkage **177** was used to attach an aryl halide substrate to the solid-support, thus allowing a mild hydrolytic cleavage, after performing a Suzuki coupling reaction, to afford biaryl aldehydes such as **179** (scheme 1.45).[98]

Scheme 1.45 Preparation of biaryl aldehydes **179**.



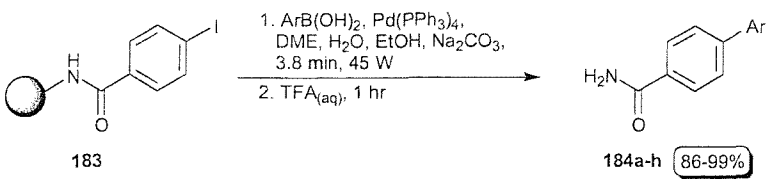
Aryl ketones were immobilised on a solid-support using a thioacetal based linker **180** (scheme 1.46).[99] The potential use of this linker was demonstrated in part by performing Suzuki couplings on the immobilised ketones **180**. Subsequent cleavage under mild conditions afforded several 4-acetylbiphenyls **182** in reasonable yield (28-34%).

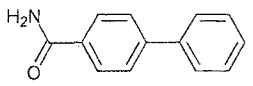
Scheme 1.46 Use of a thioacetal linker in the synthesis of biaryl ketones **182**.

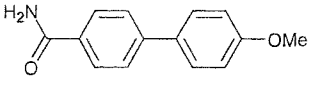


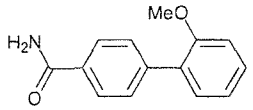
The microwave-assisted palladium-catalysed coupling of aryl and heteroaryl boronic acids with an iodo-substituted benzoic acid **183**, anchored to Rink amide TentaGel™, provided coupled products after a reaction time of only 3.8 minutes (scheme 1.47). [100] Reactions were carried out in a sealed Pyrex™ tube and only minimal decomposition of the polymeric support was observed. Cleavage of the coupled products under acidic conditions afforded a series of biaryl primary amides **184a-h** in good yield (86-99%).

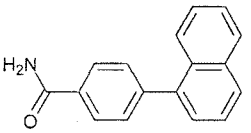
Scheme 1.47 Microwave-assisted Suzuki couplings.

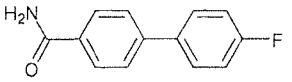


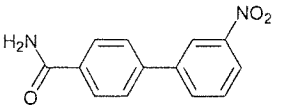

184a 98%

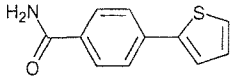

184b 96%

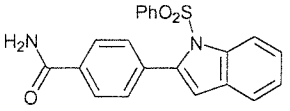

184c 88%


184d 99%


184e 99%

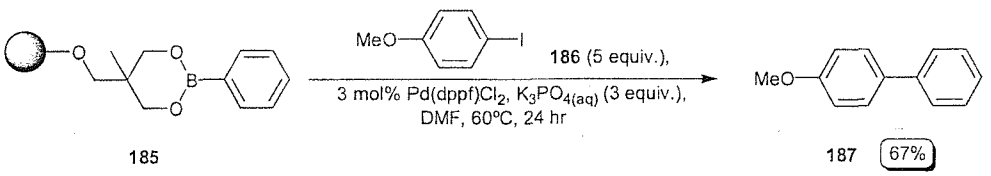

184f 89%


184g 86%


184h 89%

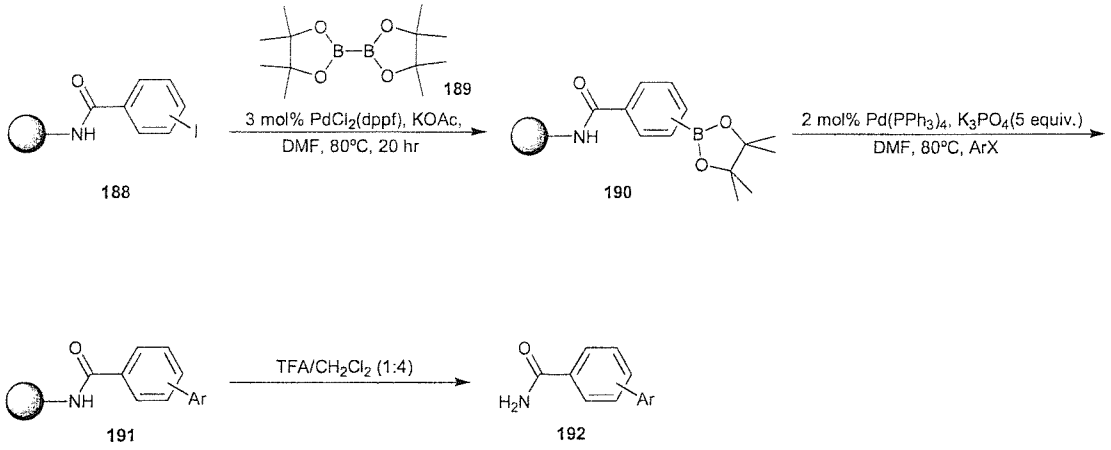
In contrast the viability of solid-supported boronic acids as reagents for Suzuki couplings has been successfully demonstrated (scheme 1.48). [101] Using the immobilised boronic acid **185** several functionalised biphenyl products, including **187**, were prepared in reasonable yield (45-75%). The authors are currently looking to expand this approach to other types of reactions involving boronic acids.

Scheme 1.48 The use of supported boronic acids **185** in Suzuki couplings.



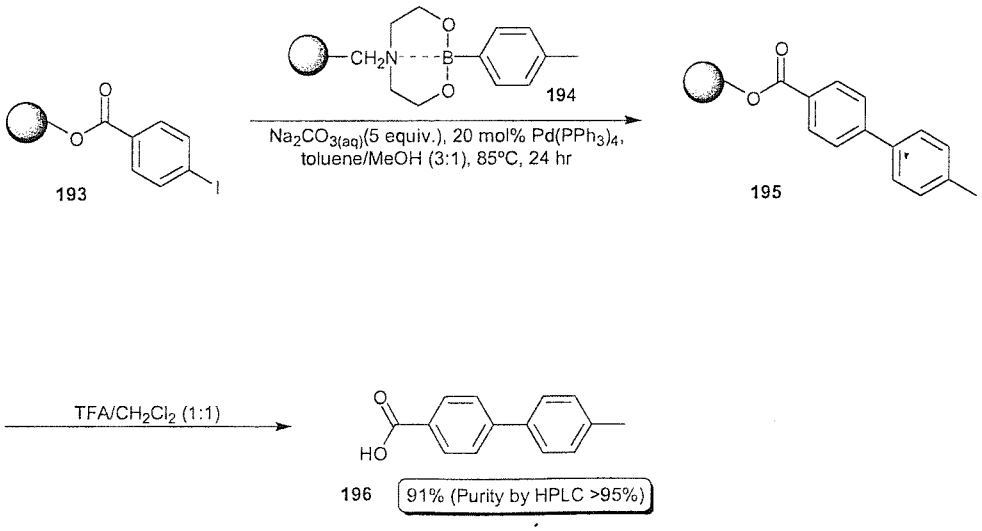
Treatment of polymer-bound iodides **188** with the pinacol ester of diboron **189** under palladium(0) catalysis gave the corresponding resin-bound boronates **190** (scheme 1.49). [102] Suzuki coupling reactions were then successfully carried out with a variety of aryl halides and the boronate **190**. Cleavage from the resin afforded the expected products **192** in good yield (26-95%).

Scheme 1.49 Preparation of biaryl species **192** using resin-bound boronates **190**.



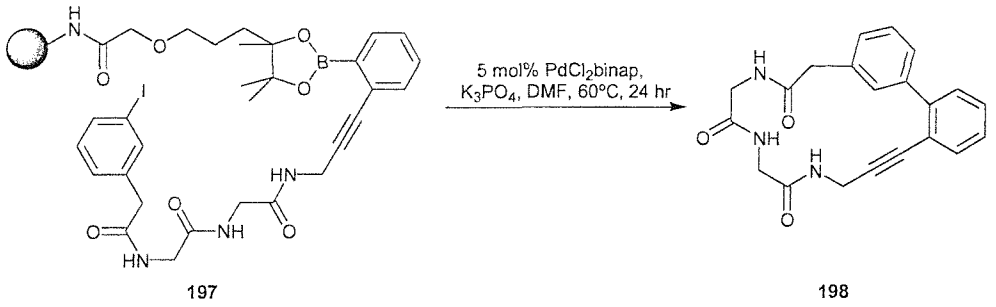
A Suzuki resin-to-resin transfer system has been described and successful results obtained (scheme 1.50). [103] Resin-bound boronic acid **194** is hydrolysed in an aqueous system and the free boronic acid generated *in situ* is able to react with the resin-bound aryl iodide **193** providing 100% conversion to the biaryl species **195**. Anhydrous systems were also investigated in which alcohols act to release the free boronic acid species by transesterification.

Scheme 1.50 A Suzuki resin-to-resin transfer system in the synthesis of biaryls **195**.



The use of a Suzuki coupling reaction to effect a supported macrocyclisation was successful and provided a route to β-turn mimics such as **198** (scheme 1.51).[104]

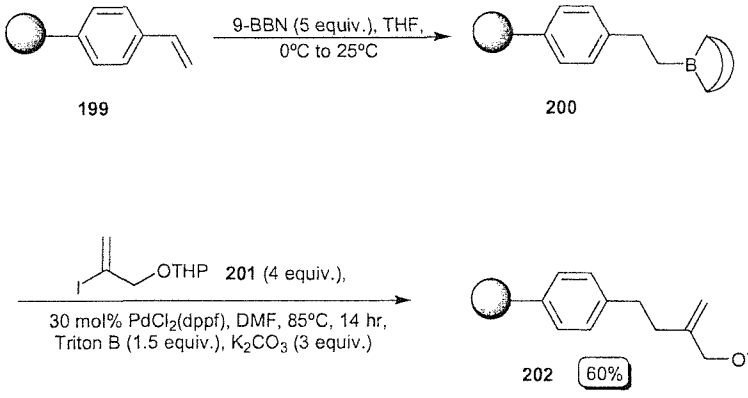
Scheme 1.51 Macrocyclisations *via* the Suzuki reaction.



197 198

Treatment of the vinyl resin **199** with 9-BBN afforded polymer-bound alkylborane **200** (scheme 1.52). [105] The latter underwent palladium-catalysed Suzuki cross coupling reactions with a variety of aromatic, vinylic and aliphatic halides, including vinyl iodide **201**, in moderate to excellent yield (55-85%). Not only is the polymer-bound alkylborane **200** a versatile precursor for the preparation of various functionalised resins but the procedure could be extended to introduce diversity on polymer-bound scaffolds bearing a double bond.

Scheme 1.52 The use of resin-bound alkylboranes **200** in the Suzuki coupling.

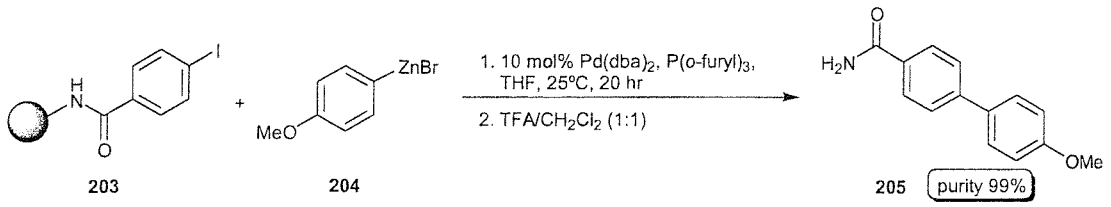


199 200 202 60%

1.6 Miscellaneous Palladium-Catalysed Reactions on the Solid-Phase

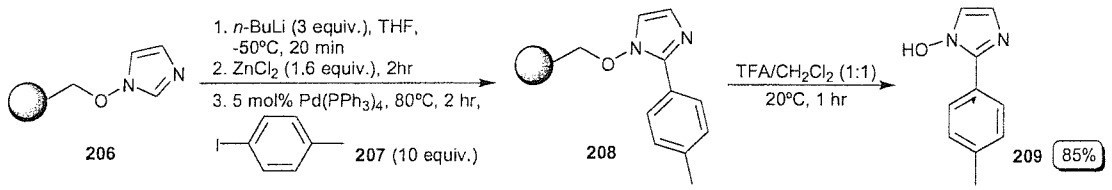
The palladium-catalysed coupling of aryl halides **203** or triflates with aryl zinc bromides **204** (Negishi coupling) is a useful alternative to the Suzuki coupling when the desired boronic acids are not easily prepared, or contain functionality not compatible with Suzuki reaction conditions (scheme 1.53).[106]

Scheme 1.53 Negishi coupling as an alternative to the Suzuki coupling.



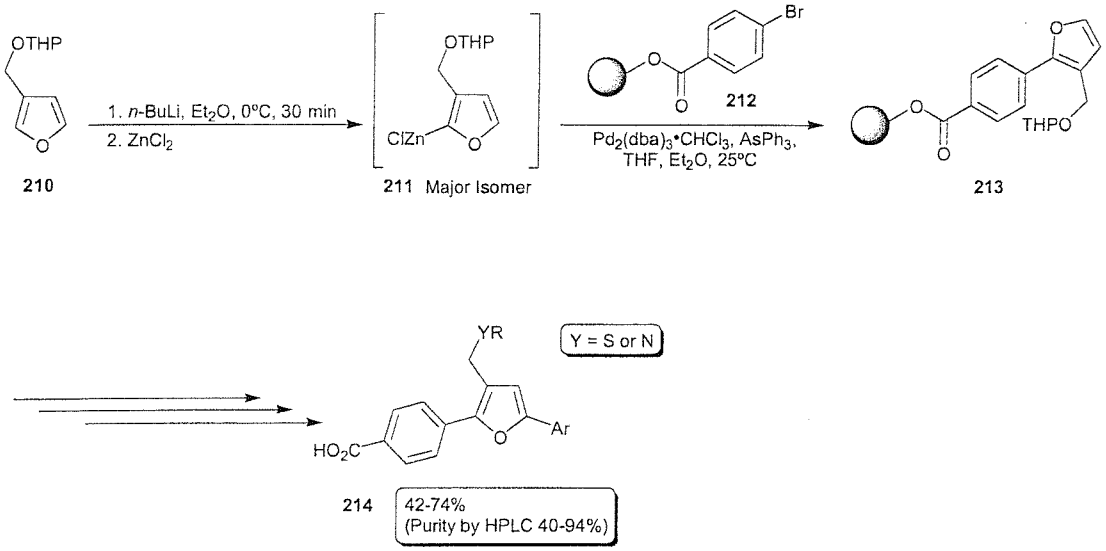
This strategy was used to prepare substituted 1-hydroxyimidazoles **209** (scheme 1.54).[107] Resin-bound 1-hydroxyimidazole **206** was selectively deprotonated at C-2 with BuLi and the resulting anion transmetallated with zinc chloride to give the resin-bound imidazol-2-ylzinc chloride. This was cross-coupled with aryl and heteroaryl iodides, such as 4-iodotoluene **(207)**, under palladium(0) catalysis. Cleavage from the solid support afforded 2-aryl/heteroaryl substituted 1-hydroxyimidazoles such as **209**.

Scheme 1.54 Resin-bound imidazol-2-ylzinc chloride and the preparation of 2-aryl/heteroaryl substituted 1-hydroxyimidazoles **209**.



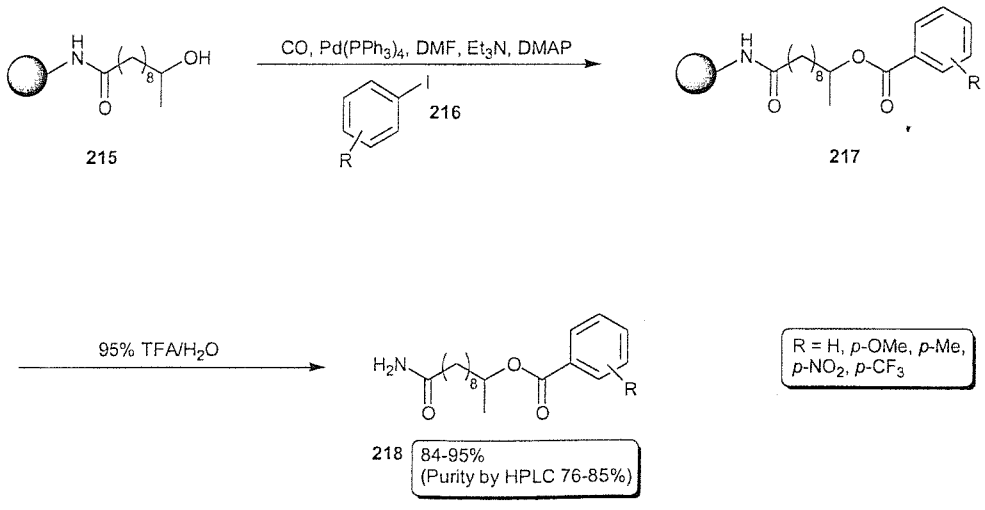
A series of highly substituted bi-aryl furan derivatives **214** were also prepared using the Negishi reaction (scheme 1.55).[108]

Scheme 1.55 The use of Negishi reagents in the synthesis of furan derivatives **214**.



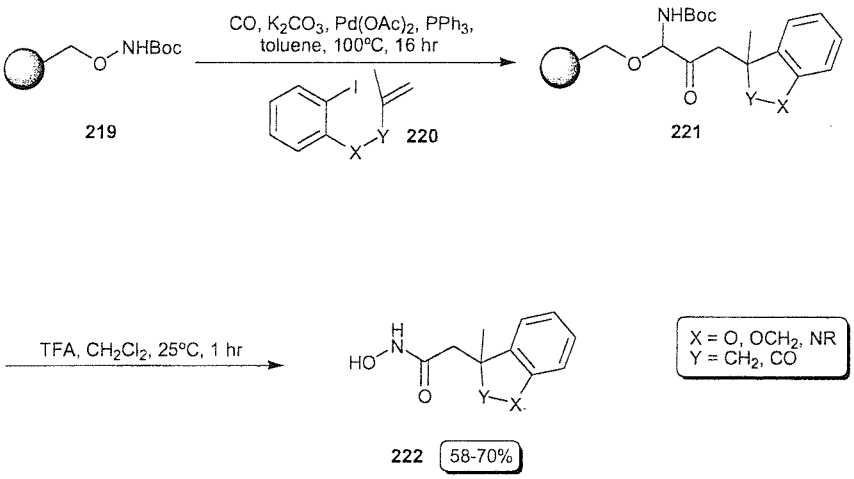
Palladium-catalysed carbonylation, using carbon monoxide and aryl iodides **216**, was accomplished in high yields (84-95%) by Takahashi *et al* (scheme 1.56).[109] A series of esters **218** and amides were prepared using the reaction with resin-bound alcohols **215** and amines and the Multipin^{TM} system.

Scheme 1.56 Preparation of esters using carbon monoxide, supported alcohols **215** and aryl iodides **216**.



Carbonylation was also used in the elaboration of a series of aryl iodides **220** into heterocyclic hydroxamates **222** (scheme 1.57).[110] Protected hydroxylamine **219** undergoes a termolecular reaction with the aryl iodide **220** and carbon monoxide in the presence of catalytic palladium(0) to afford the desired resin-bound products **221**. Deprotection and cleavage from the solid-support provided a series of hydroxamic acids **222** in reasonable yield (58-70%).

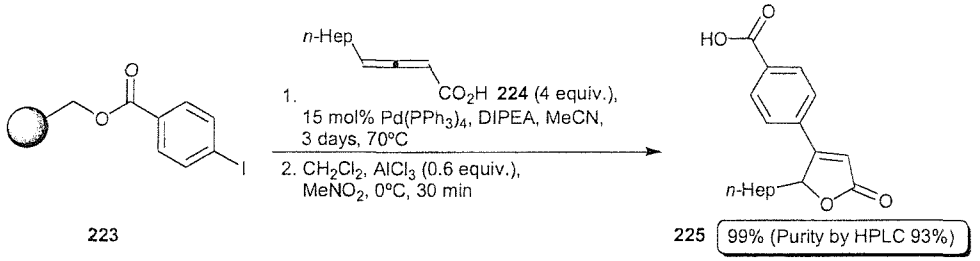
Scheme 1.57 Synthesis of hydroxamic acids **222** using a carbonylation reaction.



Benzyl protecting groups were successfully removed from carbohydrate substrates attached to the solid-support upon treatment with palladium nanoparticles (10-40 Å diameter) under an atmosphere of hydrogen at 40°C. The deprotection was shown to proceed in a yield of 95% after 36 hours.[111]

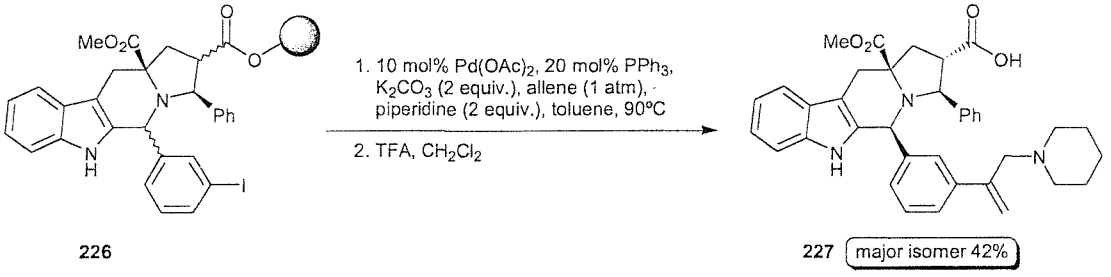
Supported aryl iodide **223** reacted efficiently with the 1,2-allenic carboxylic acid **224** under palladium(0) catalysis (scheme 1.58).[112] The resulting butenolide **225** was readily cleaved from the resin in a Lewis acid-catalysed process in good yield (99%) and purity (93%). The authors noted that yields were reduced when either the amount of catalyst or allenoic acid were increased. Likewise, the reaction was base dependant and bases such as K_2CO_3 or triethylamine gave poor results.

Scheme 1.58 Solid-phase reaction of 1,2-allenic carboxylic acid **224** and resin-bound aryl iodide **223**.



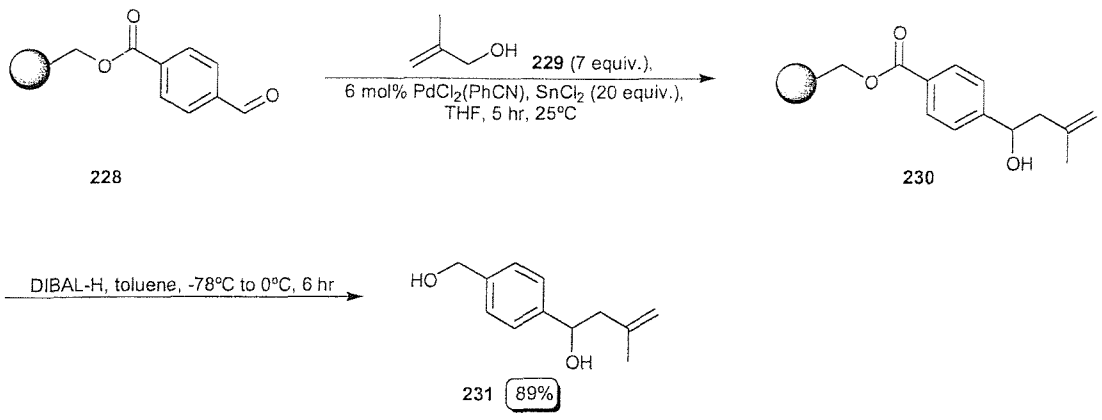
The resin-bound aryl iodide **226** undergoes a one-pot reaction with allene and piperidine to afford the allylic amine **227** after cleavage from the resin (scheme 1.59).[113]

Scheme 1.59 One-pot synthesis of allylic amines on the solid-support.



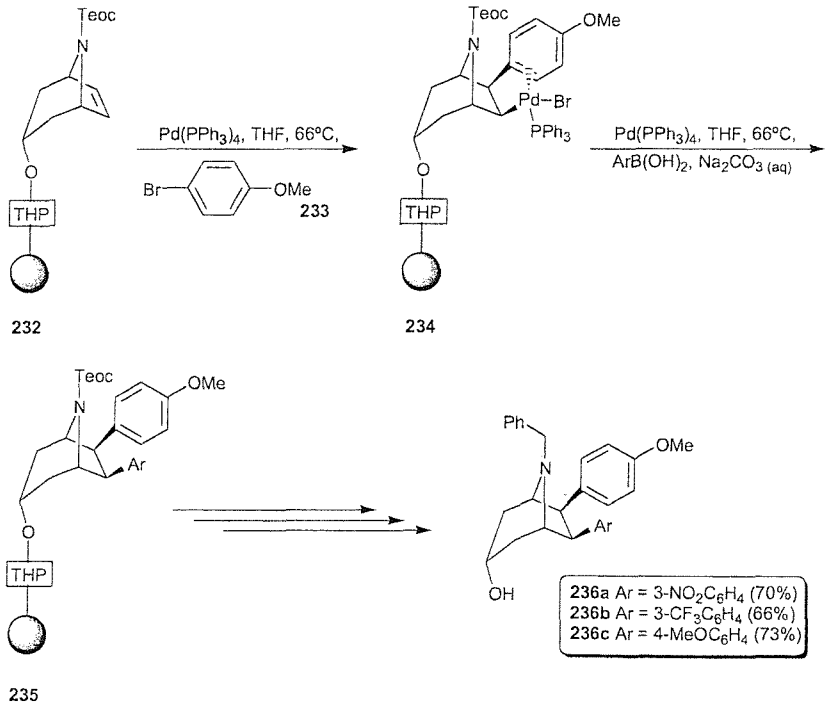
The palladium-catalysed carbonyl allylation of aldehydes by allylic alcohols was carried out on the solid-phase (scheme 1.60).[114] Preliminary studies used the resin-bound benzaldehyde **228** and 2-methyl-2-propen-1-ol **(229)**. The reaction was monitored by IR and the disappearance of the aldehyde C-H stretching band at 2385 cm^{-1}. Reductive cleavage from the resin afforded benzyl alcohol **231** in excellent yield (89%). The authors noted that the availability of allylic alcohols and aldehydes makes this methodology very attractive for solid-phase synthesis and the generation of compound libraries.

Scheme 1.60 Palladium-catalysed carbonyl allylation by allylic alcohols with $SnCl_2$.



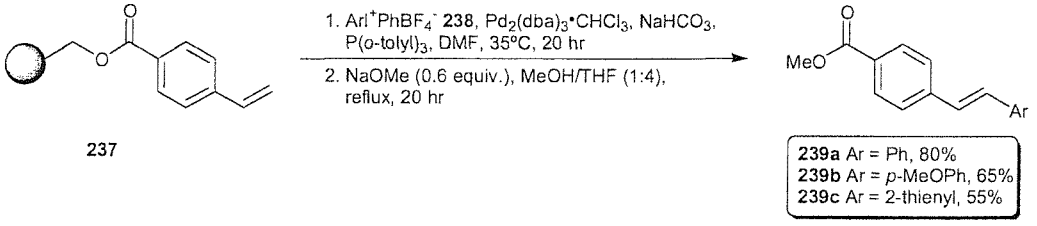
Tropane derivatives were prepared by modifying the resin-bound 'scaffold' structure **232** (scheme 1.61).[115] The first step in the sequence was a palladium-mediated three-component coupling process. Oxidative addition of Pd(0) into the aryl halide bond is followed by insertion into the alkene of the 'scaffold' **232**. The resulting support-bound intermediate **234** underwent a variety of reactions including the Suzuki coupling reaction using aryl boronic acids to give the tropane derivatives **236a-c** in good yield (66-73%) after cleavage from the resin.

Scheme 1.61 Preparation of tropane derivatives **236a-c** using a three-component coupling process.



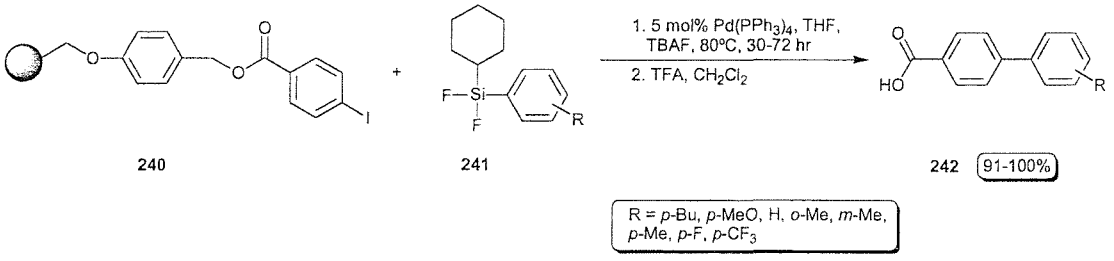
Non-toxic iodonium salts **238** were used in palladium-catalysed Heck-type cross coupling reactions with the resin-bound styrene **237** (scheme 1.62).[116] The use of this reagent was also investigated in Sonogashira and Suzuki-type couplings successfully.

Scheme 1.62 Use of iodonium salts in a Heck-type reaction.



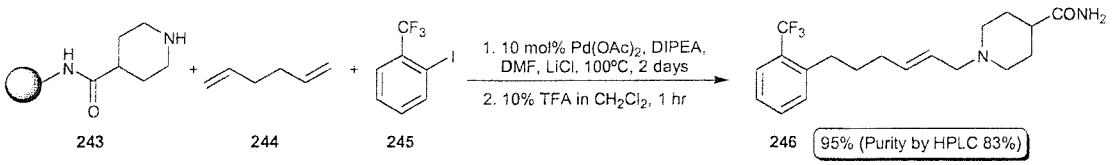
Arylhalosilanes have been successfully used as an alternative to using organo stannanes and boranes in palladium-catalysed carbon-carbon bond forming reactions (scheme 1.63).[117,118] A collection of unsymmetrical biaryls **242** were prepared from a resin-bound aryl iodide **240** and an aryl(alkyl)(difluoro)silane such as **241** in the presence of palladium and fluoride. Cleavage from the resin afforded the desired products **242** in high yield (91-100%).

Scheme 1.63 Arylhalosilanes in palladium-catalysed couplings.



The palladium-catalysed three component coupling of aryl iodides, dienes and amines is an efficient method for preparing aryl substituted allylic amines (scheme 1.64).[119] The reaction was successfully transferred to the solid-phase whereby a resin-bound amine **243** was reacted with 1,5-hexadiene **(244)** and aryl iodide **245**. Cleavage from the resin provided the primary amide **246** in good yield (95%) and purity (83%).

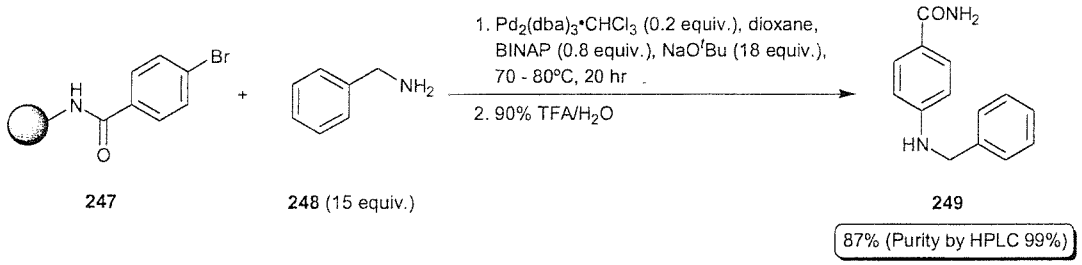
Scheme 1.64 Palladium-catalysed three-component coupling reaction.



243 244 245 246

Various groups have looked at the palladium-catalysed amination of aryl bromides.[120,121] Here the aryl bromide **247** is attached to the solid-support and reacted with the amine **248** in the presence of palladium(0) (scheme 1.65). It was noted by the authors that chelating ligands such as BINAP provided the products in significantly better yields, for example amine **249** in 87%.[120]

Scheme 1.65 Palladium-catalysed aryl amination.



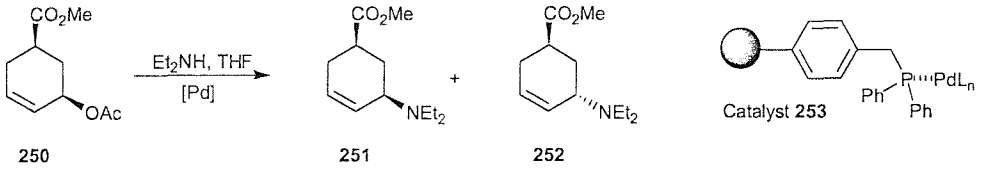
247 248 (15 equiv.) 249

1.7 The use of supported palladium catalysts in organic synthesis

The scope of solid-phase organic synthesis continues to expand. However, more recently there has been a move away from the preparation of libraries on solid-phase, mainly due to the problems associated with monitoring reactions. Instead multiple parallel solution-phase synthesis employing polymer-supported reagents, catalysts or scavengers is becoming more favoured.[122-127] One clear advantage which this approach offers is that the catalysts and certain reagents may be re-generated.

The use of polymer-supported palladium catalysts has proved to be a valuable tool in organic synthesis. Trost *et al* reported one of the first uses of a solid-supported analogue of tetrakis(triphenylphosphine)palladium(0) in 1978.[128] Chloromethyl polystyrene was treated with lithium diphenylphosphide followed by a palladium source to give catalyst **253** (scheme 1.66). Interestingly, the reaction of allylic acetate **250** with diethylamine in the presence of catalytic **253**, afforded the substitution product **251** with net retention of stereochemistry. In contrast, the use of non-supported tetrakis(triphenylphosphine)palladium(0) afforded a 2:1 mixture of diastereomers **251** and **252**. The authors attributed this 'steric steering' effect to the inability of the amine nucleophile to coordinate the supported palladium intermediate.

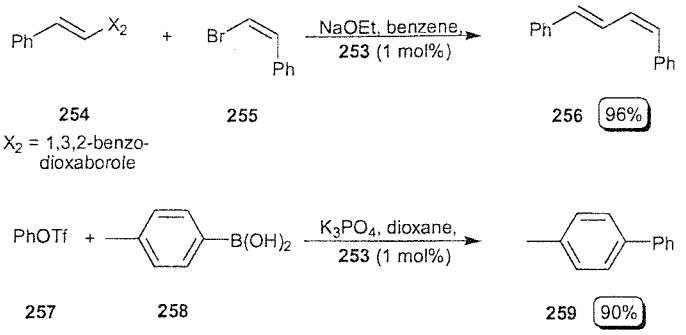
Scheme 1.66 Trost's early work with polystyrene-supported palladium.



Catalyst	251	252	yield (%)
$Pd(PPh_3)_4$	67	33	85
253	100	0	83

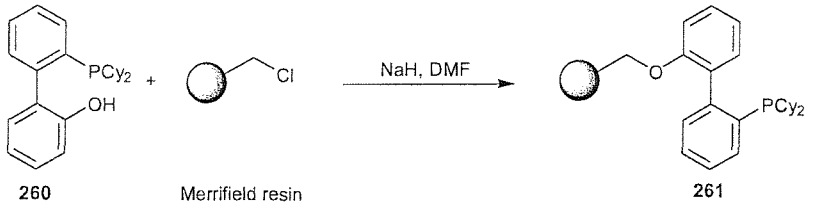
The use of palladium/phosphinated polystyrene **253** as a catalyst in the Heck reaction was investigated and encouraging results were obtained.[129] The same catalyst has been used,[130] to effect the Suzuki coupling of organoboranes, such as **254** and **258**, with alkenyl halides **255** and aryl triflates **257** (scheme 1.67). In most cases the chemical yields were superior to those obtained using an analogous solution-phase catalyst. After ten cycles the catalyst showed no loss of activity. Fenger and Le Drian obtained similar results with the same catalyst.[131]

Scheme 1.67 Suzuki couplings catalysed by a supported palladium catalyst.



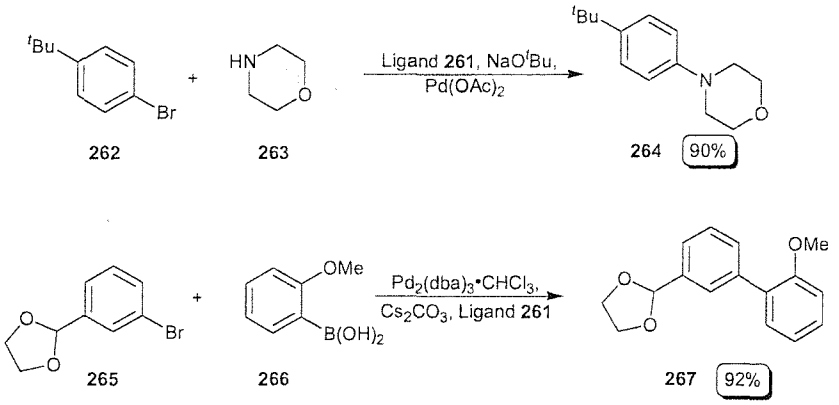
The polymer-supported dialkylphosphinobiphenyl ligand **261** was shown to be active for amination and Suzuki reactions using unactivated aryl halides.[132] The ligand was prepared in solution and then attached to the solid-support by reacting it with Merrifield resin (scheme 1.68).

Scheme 1.68 Preparation of polymer-supported ligand **261**.



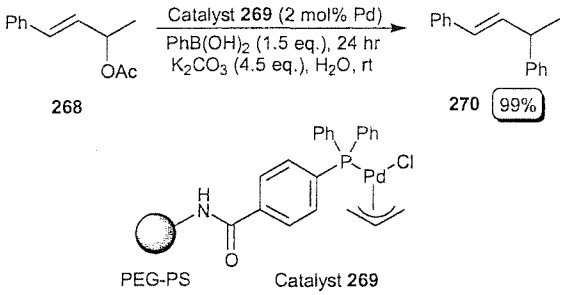
A selection of aryl halides, including 1-bromo-4-*tert*-butylbenzene **(262)**, were reacted with amines, such as morpholine **(263)**, dibutylamine and benzylamine, in the presence of the polymer-supported ligand **261**, palladium(II) acetate and NaO^{t}Bu to afford the corresponding amination products in excellent yield (scheme 1.69).[132] The ligand **261** was also used effectively in the Suzuki coupling of arylboronic acids and aryl halides as shown below (scheme 1.69).

Scheme 1.69 Amination and Suzuki coupling reactions involving polymer-supported ligand **261**.



The use of aqueous solvents is desirable as organic solvents can prove costly and are often harmful to the environment. Uozumi *et al* have developed palladium complexes supported on amphiphilic polystyrene-based resins containing PEG grafts (**269**, scheme 1.70).[133] These catalysts facilitated the Suzuki coupling of aryl halides to arylboronic acids and exhibited high activities. In addition, these catalysts have been shown to be effective in the arylation of allyl acetates such as **268** (scheme 1.70).

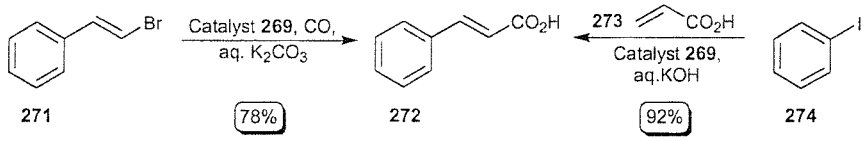
Scheme 1.70 Catalytic arylation of allylic acetate **268** in water.



Further work by Uozumi *et al* showed that the amphiphilic resin-supported palladium complex **269** was effective in catalysing the hydroxycarbonylation of aryl halides in water.[134] This methodology further allowed the hydroxycarbonylation of alkenyl halides and hence the preparation of cinnamic acid (**272**) from bromostyrene (**271**) in a yield of 78% (scheme 1.71).[134] Cinnamic acid (**272**) was also obtained, using the same catalyst

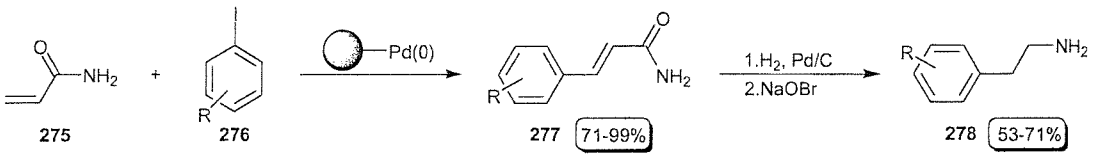
269, from the Heck reaction of iodobenzene (**274**) with acrylic acid (**273**) in a yield of 92% (scheme 1.71).

Scheme 1.71 Cinnamic acid (**272**) from bromostyrene (**271**) or iodobenzene (**274**).



2-Arylethylamines, an important moiety in many pharmacologically active molecules, have been synthesised *via* the Heck couplings of acrylamide (**275**) and aryl iodides **276** using a polymer-bound palladium catalyst (scheme 1.72).[135] In this case the desired catalyst was obtained from poly(styryl)phenanthroline and $Pd(OAc)_2$. Reduction of the cinnamide **277** followed by Hoffman reaction afforded the desired 2-arylethylamines **278** in acceptable yield. The authors also treated the cinnamide **277** with NaOCl, followed by acid, to obtain arylacetaldehydes.[136]

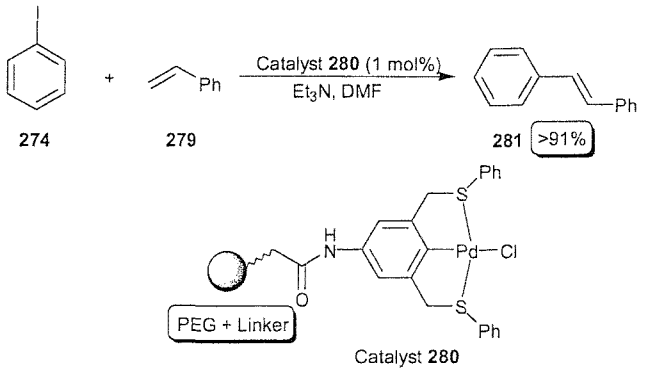
Scheme 1.72 Synthesis of 2-arylethylamines **278** *via* a Heck coupling.



R = H, 4-Me, 4-OMe, 2-Cl, 3-NO_2, 4-Br

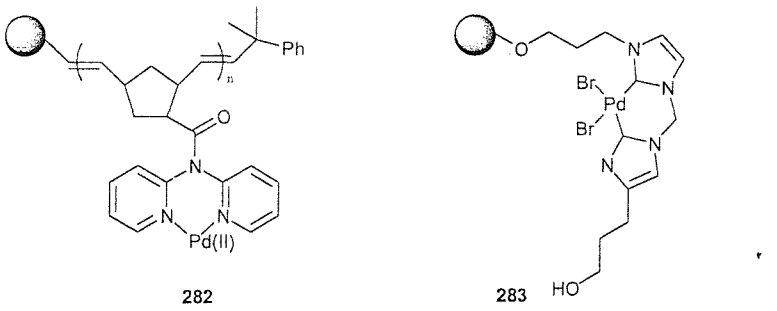
A particularly robust catalyst **280** (both thermally and oxidatively stable) was prepared by immobilising palladium onto a soluble PEG polymer with a tridentate ligand (scheme 1.73).[137] It was an effective catalyst for the Heck coupling between aryl iodides and alkenes and was successfully reused three times without loss of activity.

Scheme 1.73 Use of a tridentate SCS Palladium(II) complex in the Heck reaction.



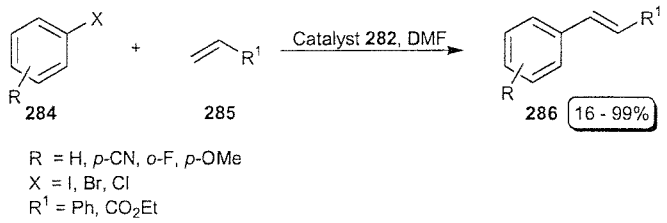
Other supported catalysts, which have been shown to effect Heck couplings, include **282** and **283** (figure 1.2). The bipyridyl-palladium(II) complex **282** was very effective in promoting the coupling of aryl halides with styrene or *n*-butyl acrylate.[138] No loss of catalytic activity was observed after three cycles and all yields were superior to those obtained using an analogous solution-phase catalyst. The supported palladium carbene complex **283** was attached to polystyrene through a Wang linkage (figure 1.2). In the reaction of bromobenzene with butyl acrylate or styrene, the Heck products were obtained in 82% and 72% yield respectively, after two days. A loss of activity was only observed after the catalyst had been used for four cycles.

Figure 1.2 Solid-supported palladium complexes used in Heck coupling reactions.



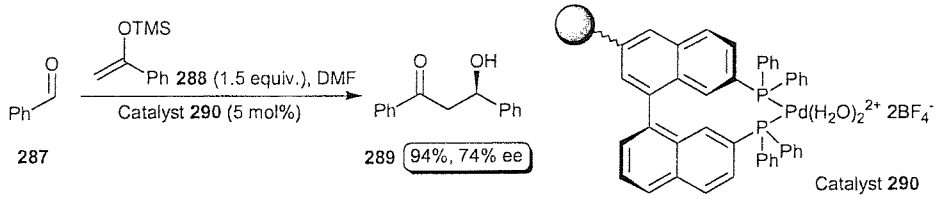
Catalyst **282** (figure 1.2) was prepared *via* a ring-opening metathesis polymerisation (ROMP).[139] It successfully promoted the Heck coupling of aryl halides **284** and alkenes **285** (scheme 1.74) and, to a lesser extent, the amination of aryl bromides. The authors noted that the system used is characterised by a straightforward synthesis as well as by a high temperature, pH and chemical stability.

Scheme 1.74 Heck coupling of aryl halides **284** and alkenes **285**.



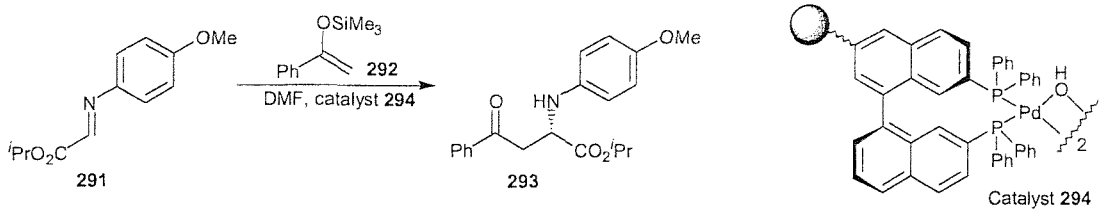
Enantioselective C-C bond formation has been achieved using polymer-supported BINAP catalysts. The palladium complex **290** has been shown to catalyse the asymmetric aldol reaction (scheme 1.75).[140] Addition of water (0.2 equiv.) leads to an improved chemical yield.

Scheme 1.75 Asymmetric aldol reaction catalysed by a supported BINAP complex **290**.



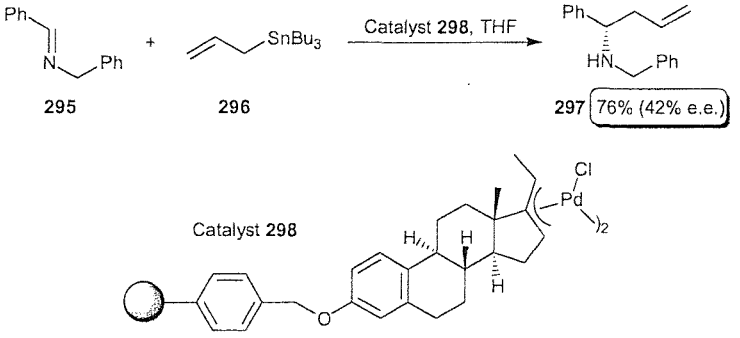
The related μ-hydroxo palladium catalyst **294** was shown to catalyse asymmetric Mannich-type reactions (scheme 1.76).[140] This new catalyst was obtained by treating the aqua-complex **290** with dilute aqueous sodium hydroxide. The reaction of silyl enol ether **292** with imine **291** proceeded in 95% chemical yield and the benzoylalanine derivative **293** was obtained in 81% e.e.

Scheme 1.76 Asymmetric Mannich-type reaction.



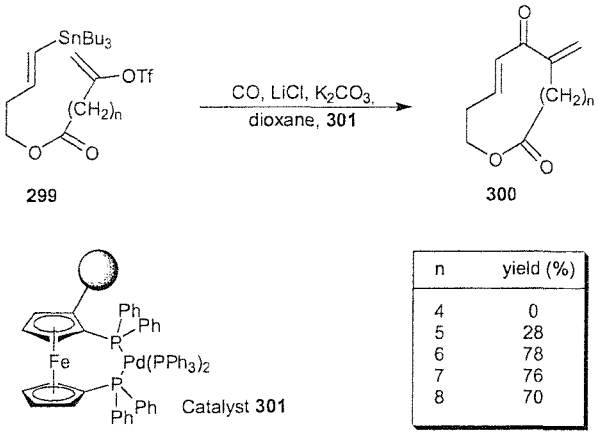
Asymmetric allylation of imines **295** with allyltributyltin (**296**) was facilitated successfully by the supported π-allyl palladium catalyst **298** (scheme 1.77).[141] However, whilst the catalyst **298** gave reasonable yields and enantioselectivity, reactions took six days to reach completion. Consistent results were obtained when the catalyst was reused.

Scheme 1.77 The enantioselective allylation of imines.



The supported bis[(diphenylphosphino)ferrocene]-derived catalyst **301** was successfully used in the synthesis of large-ring keto lactones *via* intramolecular carbonylative coupling of vinyl triflates with vinyl stannanes (scheme 1.78).[142] Traditional solution-phase palladium catalysts failed to effect the desired reaction in acceptable purity and yield. Catalyst **301** was prepared on a highly cross-linked polymeric support with a low functional group loading in order to achieve active site isolation. Trost *et al* used a different approach in order to prepare a 27-membered ring macrolide whereby a bis(benzenesulphonyl)alkane was coupled to a vinyl epoxide in the presence of a polymer-bound palladium complex.[143]

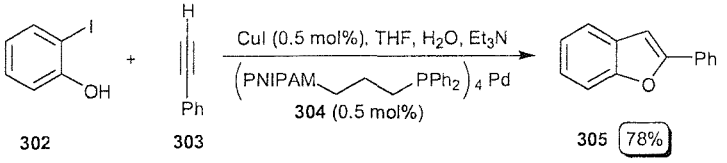
Scheme 1.78 Synthesis of large-ring keto lactones **300** *via* a carbonylative coupling reaction.



n	yield (%)
4	0
5	28
6	78
7	76
8	70

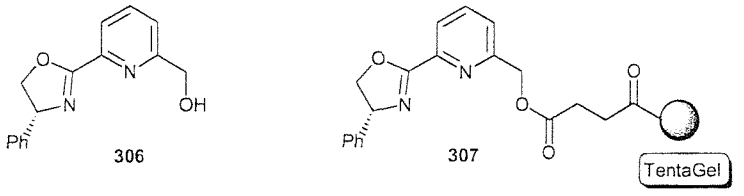
The use of linear poly(*N*-isopropylacrylamide) polymers, which are soluble in cold water but insoluble in hot water was investigated.[144] Polymer precipitation is therefore effected by heating an aqueous solution of the polymer or by addition of a solvent such as hexane. The PNIPAM supported phosphine is converted to polymer-bound catalyst **304** when treated with $Pd_2(dba)_3 \cdot CHCl_3$ in aqueous ethanol. Such catalysts were effective in promoting allylic substitution reactions and the coupling of aryl iodides to terminal alkynes.[145] This methodology was developed further to allow the synthesis of 2-phenylbenzofuran **(305)** (scheme 1.79).[144]

Scheme 1.79 The synthesis of 2-phenylbenzofuran **(305)** using PNIPAM-bound Pd(0).



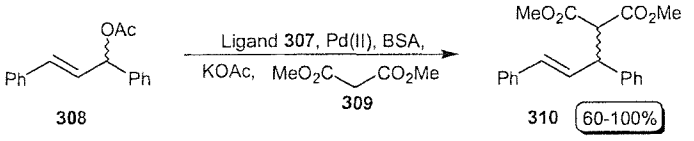
Chiral palladium complexes, which were bound to both polystyrene and polyethyleneglycol-containing resins have been developed.[146] This was achieved by synthesising the chiral ligand **306** and grafting it to the resins *via* an ester linkage to give supported ligands such as **307** (figure 1.3).

Figure 1.3 Chiral ligands used in enantioselective palladium-catalysed alkylation.



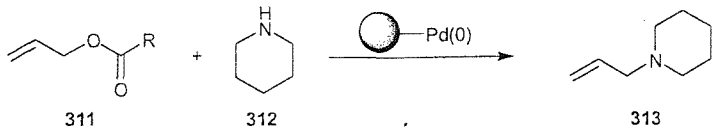
Allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate **(308)** with dimethyl malonate **(309)** was the model reaction used to evaluate the methodology (scheme 1.80). The desired product **310** was obtained in high yield (60-100%) with good enantioselectivity (80% e.e.).

Scheme 1.80 Alkylation of *rac*-1,3-diphenyl-2-propenyl acetate **(308)** with dimethyl malonate **(309)**.



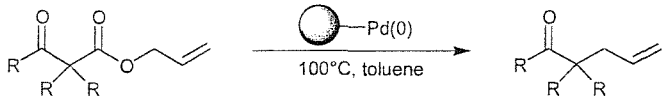
The use of diphenylphosphine-terminated ethylene oligomers as ligands for palladium was investigated by Bergbreiter *et al.*[147] Anionic oligomerisation of ethylene with *n*-butyllithium and subsequent quenching with $ClPPh_2$ afforded the desired ligand. Finally, treatment with $Pd(PPh_3)_4$ at 100 C gave the desired catalyst. An important property of such a catalyst is its temperature dependant solubility, which allows its removal by precipitation upon cooling. The catalyst was shown to be effective in various reactions including the substitution of allylic esters **311** by secondary amines, such as piperidine **(312)** (scheme 1.81). This reaction was based on earlier work completed by the authors using polystyrene-supported palladium catalysts.[148,149]

Scheme 1.81 The substitution of allylic esters **311** by piperidine **(312)**.



The decarboxylative rearrangement of allyl esters of β-keto carboxylates **314** occurs thermally at high temperatures (170-200 C) and can be catalysed at lower temperatures by $Pd(PPh_3)_4$. Similar rearrangements were observed using the polyethylene-bound palladium catalyst (scheme 1.82).[147]

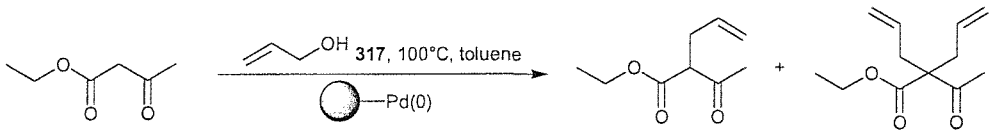
Scheme 1.82 Decarboxylative rearrangement of allyl esters of β-keto carboxylates **314**.



314 **315**

The authors also determined that, under these conditions, mixtures of allyl alcohol **(317)** and a simple ester of a β-keto carboxylate **316** afforded mixtures of mono- **318** and disubstituted **319** products (scheme 1.83).

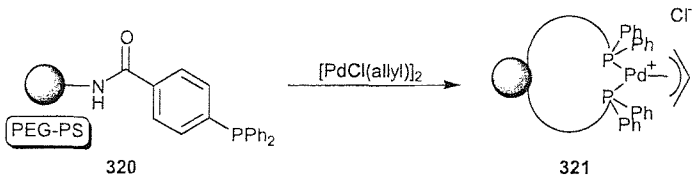
Scheme 1.83 Alkylation of a β-keto carboxylate **316** with allyl alcohol **(317)**.



316 **318** 70:30 **319**

Amphiphilic palladium-phosphine complex **321** has been prepared on a polyethylene glycol-polystyrene graft copolymer resin (scheme 1.84).[150,151] It was obtained by treatment of the supported ligand **320** with $[PdCl(\pi\text{-}C_3H_5)]_2$ at ambient temperature for 10 min.

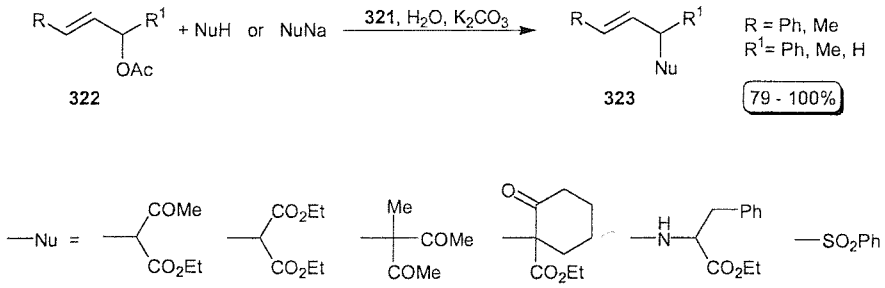
Scheme 1.84 Preparation of amphiphilic palladium-phosphine complex **321**.



320 **321**

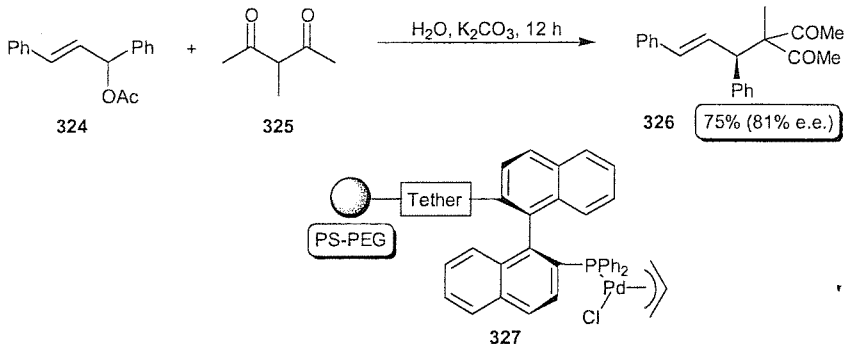
The activity of complex **321**, in water, was demonstrated in the allylic substitution of allyl acetates **322** (scheme 1.85).[150,151] The use of water as the solvent allows the use of nucleophiles which are insoluble in usual organic solvents, for example the hydrochloride salt of leucine ethyl ester.

Scheme 1.85 Allylic substitution of allyl acetates **322** in aqueous media.



The authors subsequently developed a system, based on the MOP ligand, which catalysed the asymmetric allylic substitution of allyl acetates. Thus, asymmetric substitution of 1,3-diphenyl-2-propenyl acetate **(324)** with 3-methyl-2,4-pentanedione **(325)** was carried out in the presence of 2 mol% palladium of the catalyst resin **327** to give the optically active product **326** (scheme 1.86).[152]

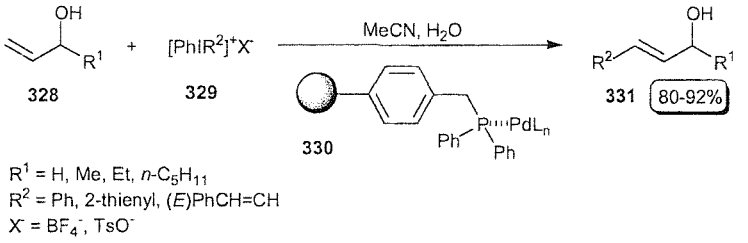
Scheme 1.86 Asymmetric allylic substitution of allyl acetates **324** in aqueous media.



The cross-coupling reaction of allylic alcohols **328** with hypervalent iodonium salts **329**, to form carbon-carbon bonds, was investigated (scheme 1.87).[153] The couplings were performed at room temperature under extremely mild conditions, even in the absence of

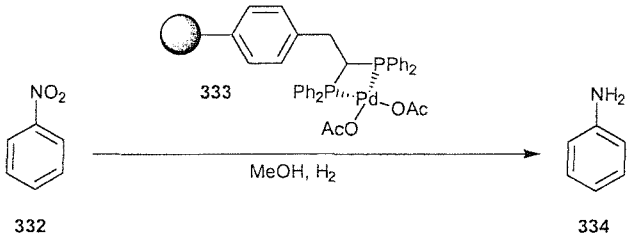
base. As with many examples of polymer-bound catalysts the polymeric-palladium complex **330** was reused more than ten times with no decrease in activity.

Scheme 1.87 Palladium-catalysed coupling of allylic alcohols **328** and hypervalent iodonium salts **329**.



Benvenuti *et al* prepared a palladium(II) complex on polystyrene beads modified with a bidentate bis(diphenylphosphine) ligand **333** (scheme 1.88).[154] Detailed hydrogenation studies, using the reduction of nitrobenzene **(332)** as a model reaction, demonstrated the reusability of the catalyst **333**. Furthermore, the chemoselective reduction of α,β-unsaturated aldehydes was also achieved under mild conditions.

Scheme 1.88 Reduction of nitrobenzene using a supported-palladium catalyst **333**.



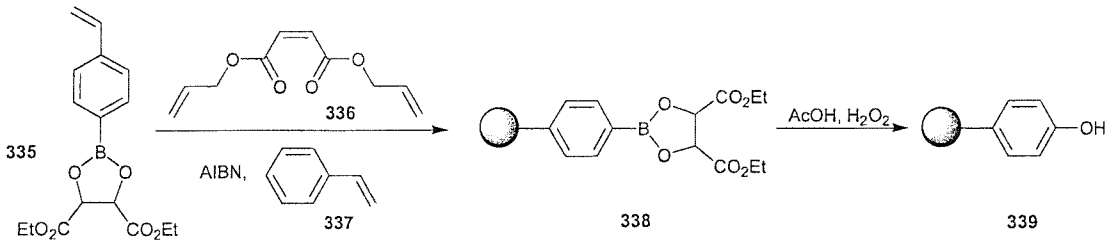
Other types of materials which have successfully been used to support palladium complexes include polysiloxane,[155] controlled-pore glass beads,[156] polyimide beads,[157] copolymer micelles,[158] clay,[159] silica [160] and charcoal.[161-163]

2. Resin preparation and loading

2.1 The synthesis of hydroxypolystyrene (343) and other polymers containing phenolic groups

In general, resins containing functional groups are prepared by either of two procedures: preparation of reactive functional monomers and their copolymerisation with a suitable cross-linking reagent, or chemical modification of a preformed cross-linked polymer. The first preparation of a cross-linked polystyrene resin containing hydroxystyrene units was reported by Letsinger and Hamilton in 1959 (scheme 2.1).[164] Their product **339** was obtained by the copolymerisation of the ethyl tartrate ester of *p*-vinyl-benzeneboronic acid **335** with styrene **(337)** and diallyl maleate **(336)** followed by oxidation of the copolymer with hydrogen peroxide. The infrared spectrum of the copolymer **339** obtained showed the presence of hydroxyl groups along with other undesired functionalities.

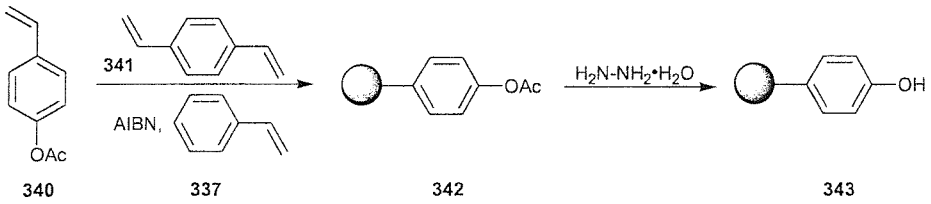
Scheme 2.1 A route to hydroxystyrene copolymer **339** *via* a boronic acid ester.



The polymerisation of hydroxystyrene was investigated by various groups. [165,166] However, spontaneous self-polymerisation at temperatures as low as 0°C, in the absence of an initiator, meant that the procedure was difficult to control. Arshady, Kenner and Ledwith reported the copolymerisation of *p*-acetoxystyrene **(340)** with styrene **(337)** and divinylbenzene **(341)** in 1974 (scheme 2.2).[167] The copolymer obtained was subsequently treated with hydrazine hydrate to obtain hydroxypolystyrene resin **(343)**. However, problems associated with the synthesis of *p*-acetoxystyrene **(340)** and subsequent removal of the acetyl groups made this route undesirable. Despite these limitations this resin was used to prepare methionine enkephalin and various isosteric

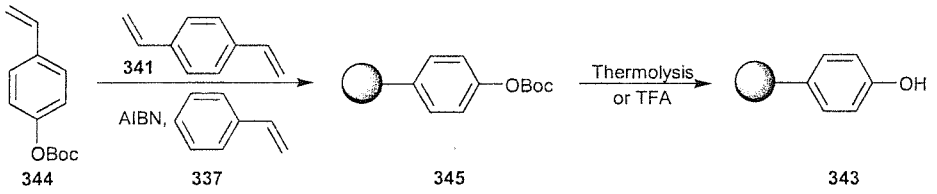
analogues,[168] as well as a Bombesin-like peptide fragment.[169] The commercial availability of the monomer now makes the exploitation and synthesis of phenolic-based supports a more attractive proposition.[170]

Scheme 2.2 A route to hydroxypolystyrene **(343)** *via p*-acetoxystyrene **(340)** copolymerisation.



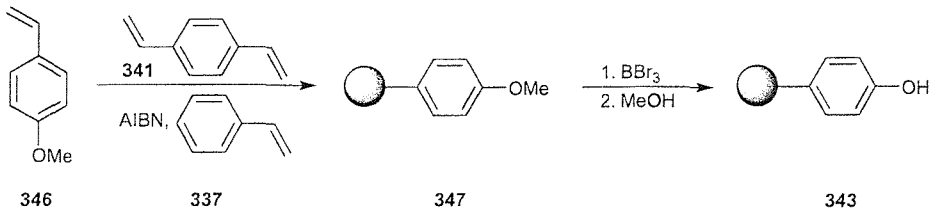
Fréchet *et al* used *p*-tert-butoxycarbonyloxystyrene **(344)** in 1983 in order to overcome the problems associated with the synthesis of *p*-acetoxystyrene **(340)** and subsequent removal of the acetyl groups (scheme 2.3). [171] This monomer was observed to be stable at room temperature and copolymerisation, with styrene **(337)** and divinylbenzene **(341)**, proceeded cleanly. Removal of the tert-butoxycarbonyl groups from the copolymer was effected by TFA or thermolysis.

Scheme 2.3 Synthesis and deprotection of poly(*p*-tert-butoxycarbonyloxystyrene) **(345)**.



Beaded copolymers of styrene **(337)**, *p*-methoxystyrene **(346)** and divinylbenzene **(341)** were obtained by suspension copolymerisation of various mixtures of the monomers (scheme 2.4).[172] Reaction of the polymer **347** with boron tribromide in dichloromethane, followed by methanolysis in carbon tetrachloride, provided a simple and general route to hydroxypolystyrene **(343)**.

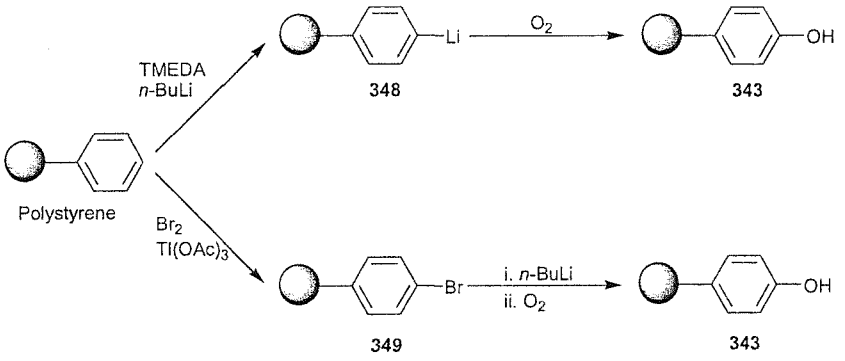
Scheme 2.4 Hydroxypolystyrene (**343**) polymers *via* *p*-methoxypolystyrene (**347**).



346 **337** **347** **343**

The first route to hydroxypolystyrene (**343**), which involved the chemical modification of a preformed cross-linked polymer, was reported in 1979 (scheme 2.5).[173] Polystyryllithium (**348**) was generated directly from polystyrene by lithiation with *n*-butyllithium and tetramethylethylenediamine,[174] or *via* a bromination-lithiation route.[175] Interestingly, the latter proved to offer better control of the degree of functionalisation of the resin. Quenching of the polystyryllithium (**348**) with oxygen afforded the desired hydroxypolystyrene (**343**). Resin prepared using this method has been successfully employed in the solid-phase synthesis of oligosaccharides.[176]

Scheme 2.5 Chemical modification of polystyrene to afford hydroxypolystyrene (**343**).



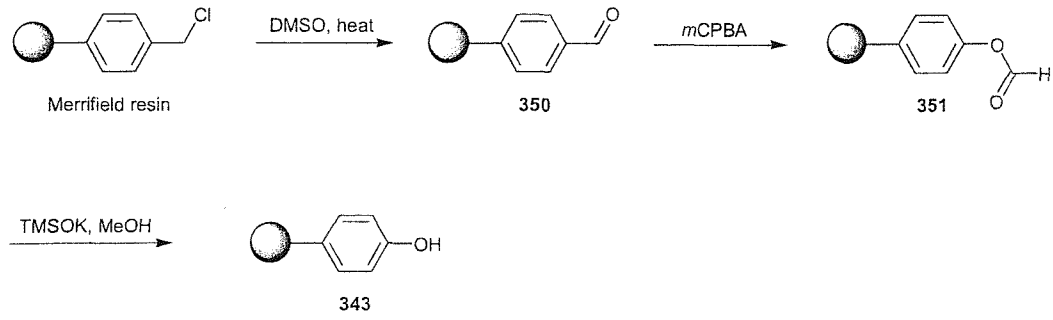
348 **343** **349** **343**

2.2 Hydroxypolystyrene (343) *via* the acylation and subsequent Baeyer-Villiger oxidation of polystyrene

A simple, efficient and cheap synthesis of hydroxypolystyrene (**343**) was desired, which involved the chemical modification of a preformed cross-linked polymer. Initially, the conversion of Merrifield resin, *via* a Swern oxidation, to the resin-bound benzaldehyde **350** was investigated (scheme 2.6).[177-179] This was expected to give the corresponding

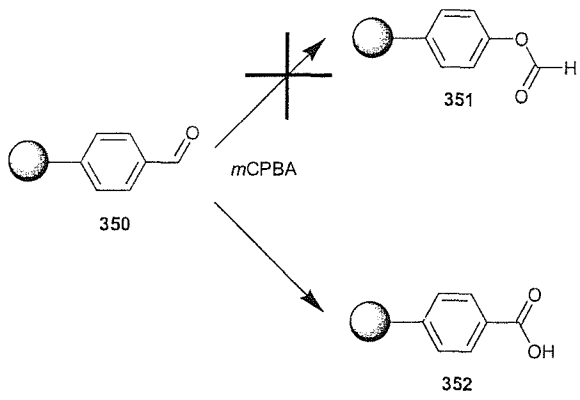
formate **351**, upon treatment with *m*CPBA, which could be hydrolysed to afford hydroxypolystyrene **(343)**.

Scheme 2.6 Proposed synthesis of hydroxypolystyrene **(343)**.



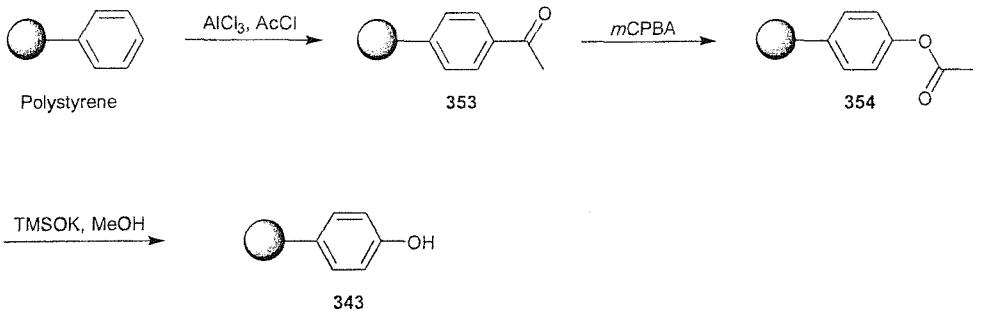
Unfortunately, the Baeyer-Villiger oxidation gave the corresponding acid **352** rather than the desired formate **351** (scheme 2.7).[180-183] This result is perhaps not unexpected as hydrogen atoms have a relatively high migratory aptitude.[178,182] Indeed, when subjected to the same conditions benzaldehyde gives a mixture of both products in roughly equal quantities. [184]

Scheme 2.7 Possible products from the Baeyer-Villiger oxidation of resin **350**.



It was thought that by replacing the hydrogen with a substituent that has a lower migratory aptitude with respect to the aryl group, for example a primary alkyl group, the appropriate intermediate could be prepared. A new route, which utilised polystyrene as the starting material, was therefore proposed (scheme 2.8).

Scheme 2.8 Synthesis of hydroxypolystyrene **(343)** from polystyrene.



Polystyrene was acylated under standard Friedel-Craft conditions to give the resin-bound acetophenone **353**. [185,186] The infrared spectrum of resin **353** included a strong carbonyl absorption at 1679 cm^{-1} (figure 2.2), whilst the infrared spectrum of polystyrene exhibited no absorption in this region as expected (figure 2.1). Treatment of the resin-bound acetophenone **353** with *m*CPBA afforded the resin-bound acetate **354**. [187] The progress of the reaction was monitored by the loss of the infrared absorption, due to the ketone carbonyl, at 1679 cm^{-1} and the appearance of a new absorption, at 1759 cm^{-1}, due to the acetate carbonyl (figure 2.3). The use of other peracid systems, including $AcOH/H_2O_2$ and TFA/H_2O_2, was investigated but *m*CPBA remained the reagent of choice.[182,183]

Subsequent hydrolysis, using potassium trimethylsilanolate and methanol, afforded the desired hydroxypolystyrene **(343)**.[62,188] The infrared spectrum of the hydroxypolystyrene **(343)** showed that all the carbonyl groups had been removed, however, the hydroxyl group could not be visualised despite washing the resin with aqueous acid (figure 2.4). When treated with bromocresol green (a test for acids), hydroxypolystyrene **(343)** gave a positive result. That is to say that the solution went from blue to yellow upon the addition of the resin.

Figure 2.1 Infrared spectrum of polystyrene.

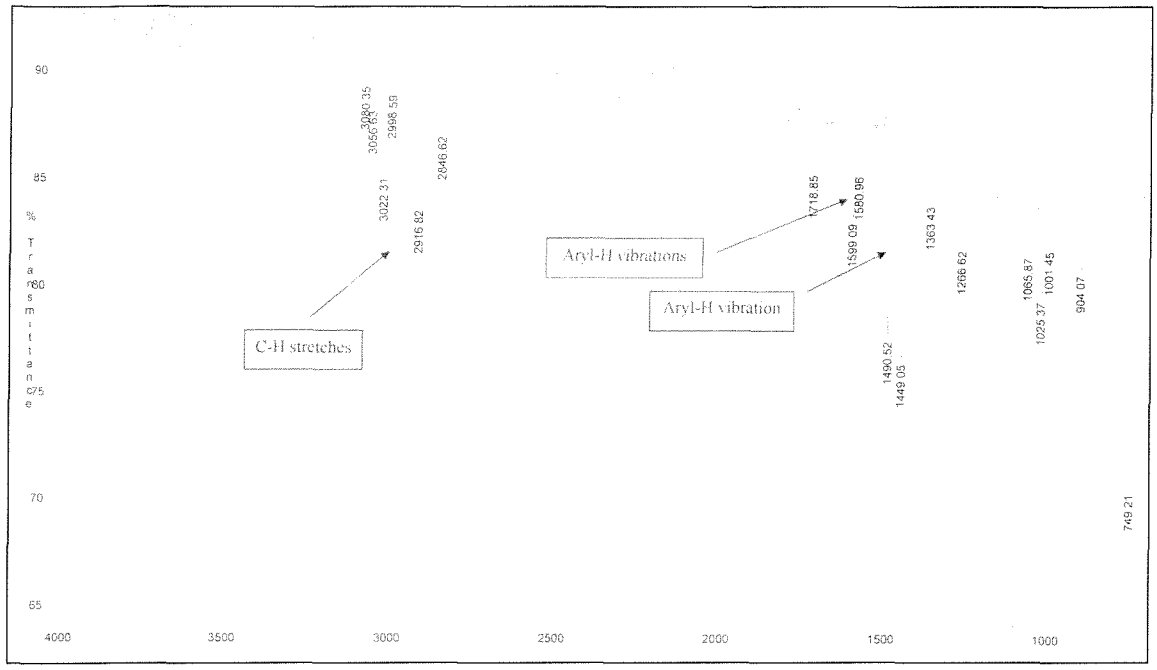


Figure 2.2 Infrared spectrum of resin-bound acetophenone **(353)**.

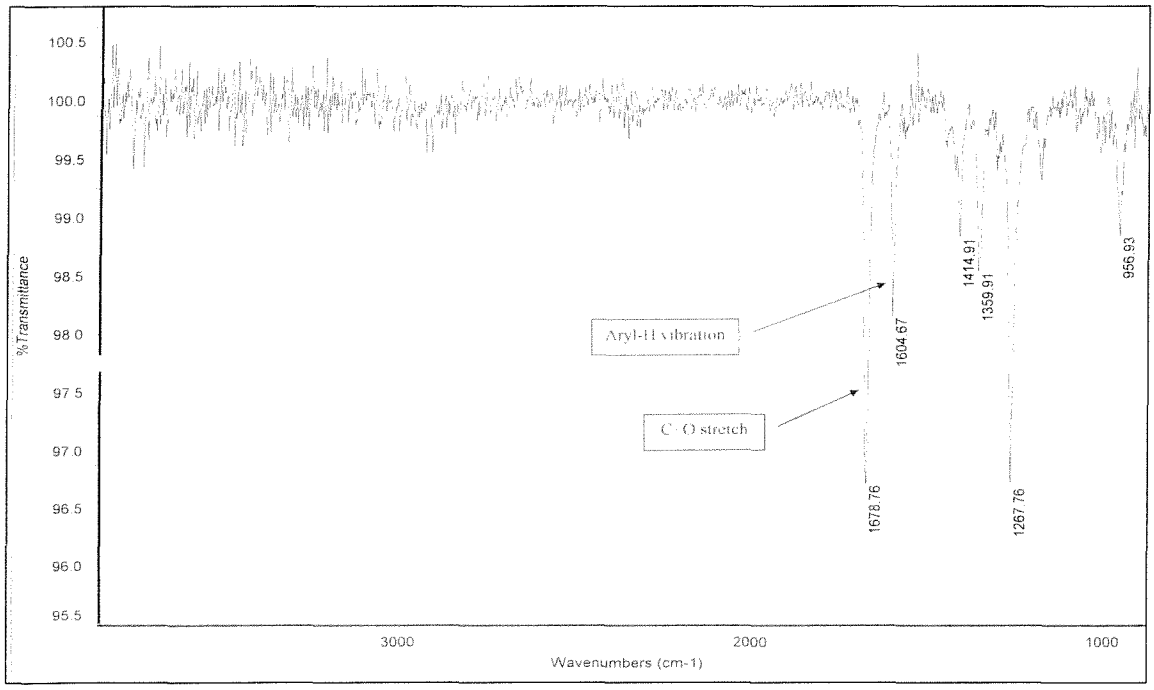


Figure 2.3 Infrared spectrum of resin-bound acetate **(354)**.

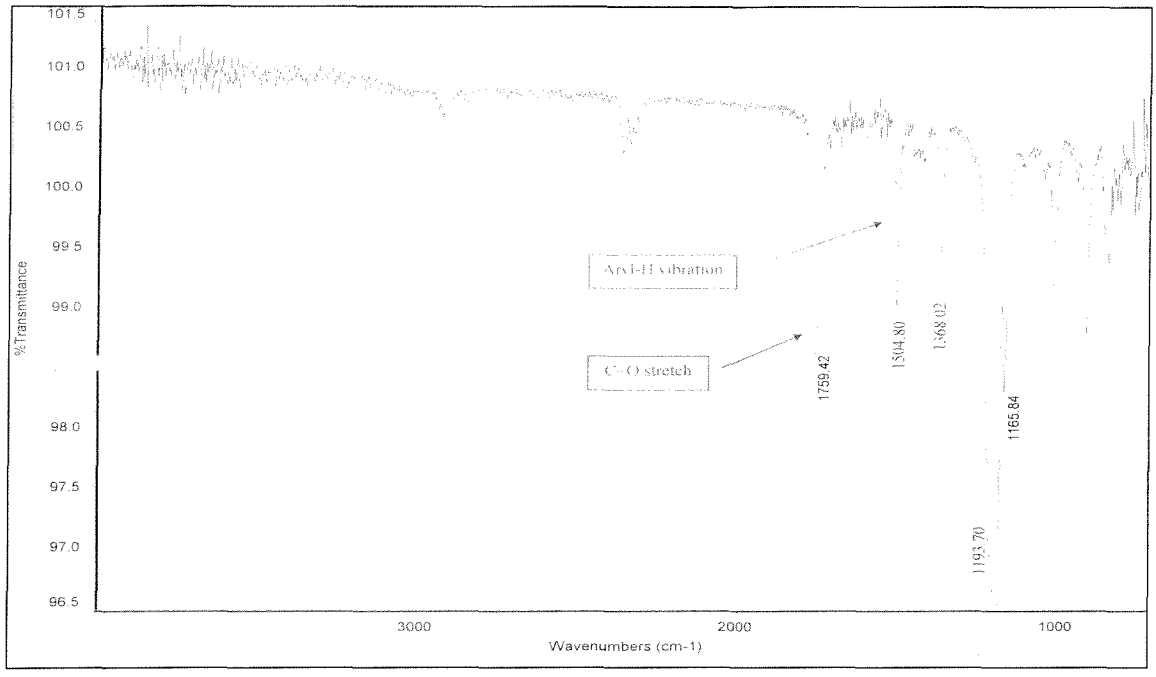
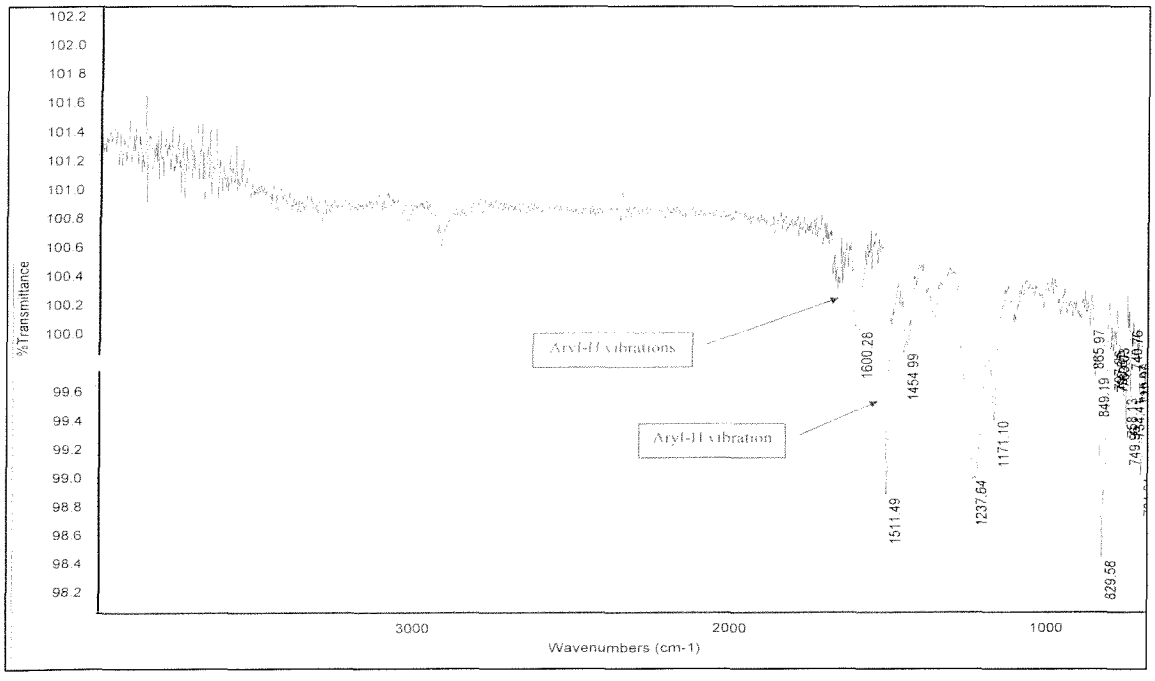


Figure 2.4 Infrared spectrum of hydroxypolystyrene **(343)**.

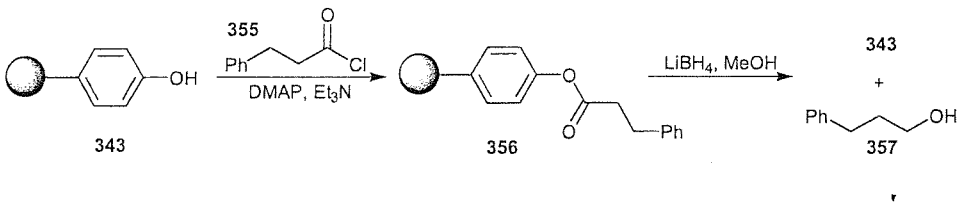


Subsequent to completing this work it was found that a similar method for preparing hydroxypolystyrene (**343**) had been reported in the literature.[189] In this synthesis resin-bound acetophenone **353** was prepared using the same method. However, in this case the Baeyer-Villager oxidation of the resin-bound acetophenone **353** was accomplished by subjecting the starting material **353** to peracetic acid in refluxing chloroform over 6 days. Other oxidising reagents were investigated, including *m*CPBA, by the authors but they reported either no reaction, cross-linking of the resin or poor conversion. The resin-bound acetate **354** was easily hydrolysed in THF by the addition of a 0.1 N NaOH solution at 50°C as well as by hydrazine hydrate in dioxane at 25°C over 40 hours.

2.3 Calculation of the loading of hydroxypolystyrene (343)

In order to calculate the loading of the hydroxypolystyrene (**343**) obtained a simple two-step process was adopted (scheme 2.9). Initially the resin was coupled to dihydrocinnamoyl chloride (**355**), using catalytic DMAP, to give the resin-bound dihydrocinnamate **356**. Double couplings were performed to ensure that complete esterification had been achieved. Quantification, by GC[†], of the dihydrocinnamyl alcohol (**357**) obtained upon treating resin **356** with $LiBH_4$ allowed the loading of the hydroxypolystyrene (**343**) to be calculated. Several batches of hydroxypolystyrene (**343**) were prepared with loadings varying from 1.5 mmol/g to 2.2 mmol/g.

Scheme 2.9 Two-step process to calculate the loading of hydroxypolystyrene (**343**).

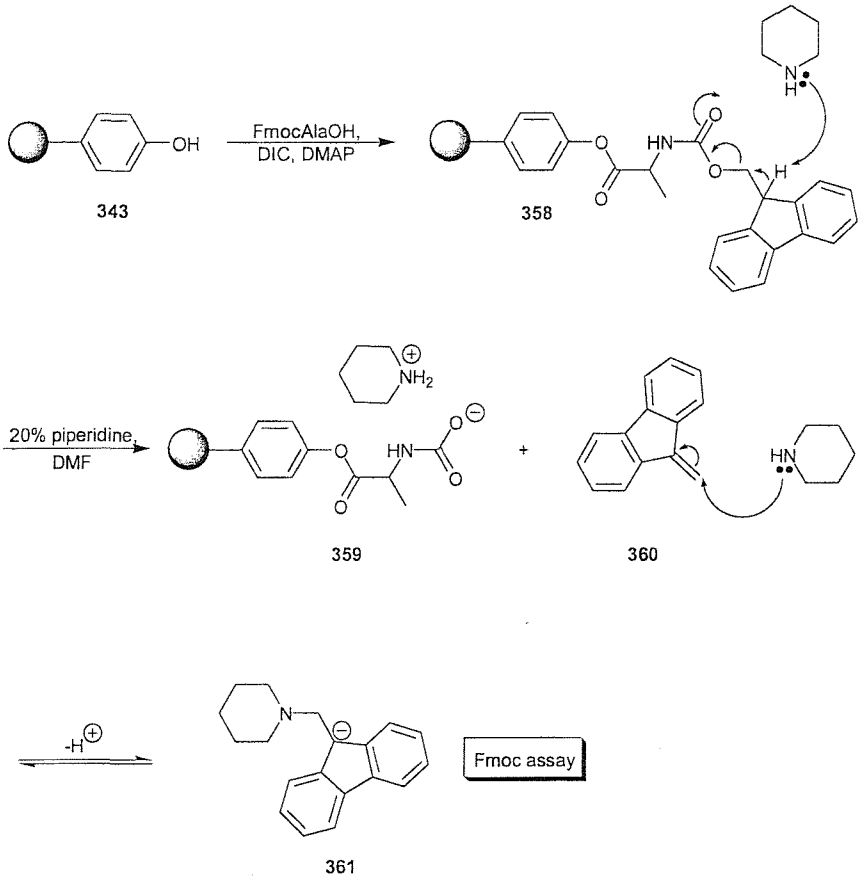


The loading of hydroxypolystyrene (**343**) was also calculated using an Fmoc assay.[190-193] [194] Initially, FmocAlaOH was coupled to the resin using carbodiimide chemistry (scheme 2.10). The subsequent cleavage of Fmoc, in the presence of piperidine, and its

[†] A calibration curve was constructed using authentic samples of known concentration, which thus allowed the concentration of the unknown sample to be calculated.

quantification by a UV assay at 300 nm allows the loading of the hydroxypolystyrene **(343)** to be calculated.

Scheme 2.10 Calculation of hydroxypolystyrene **(343)** loading *via* an Fmoc assay.



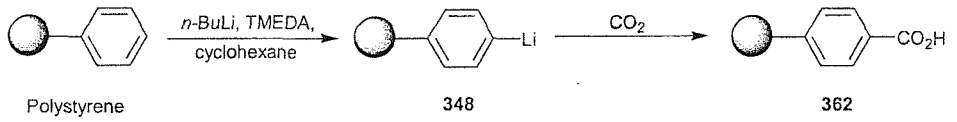
Loading calculations obtained *via* an Fmoc assay were found to be in reasonable agreement with those obtained *via* the dihydrocinnamyl alcohol **(357)** method. For a typical batch of resin the former gave a loading of 1.89 mmol/g and the latter 2.10 mmol/g.

2.4 Polymers containing carboxylic acid functionality and their use in solid-phase synthesis

Literature searches reveal that resins containing carboxylic acid functional groups have been used much more infrequently that other types of resins. Indeed, those resins bearing either an alcohol or amine group have tended to be favoured for attaching linkers to a solid support.

It appears that the most commonly used resin of this type is carboxylated polystyrene **(362)**, which was prepared in 1976 by lithiation of polystyrene and subsequent quenching with carbon dioxide.[174,175] However, carboxylated polystyrene **(362)** has also been prepared by treating the resin-bound aldehyde **350** (scheme 2.7) with an oxidising agent such as chromic acid.[179]

Scheme 2.11 Quenching of polystyryllithium **(348)** with carbon dioxide.



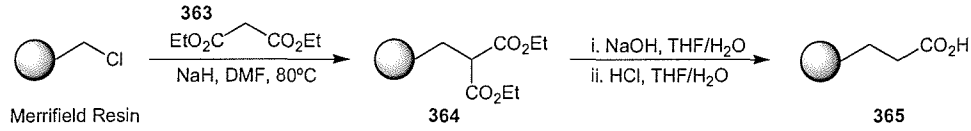
Various uses of carboxylated polystyrene **(362)** as a solid support for organic synthesis are reported in the literature and these include the preparation of homopropargylic alcohols,[195] isoxazolinoisoquinoline heterocycles,[87] aromatic 1,2-diazines,[196] isoxazoles and isoxazolines,[197] polyisoxazolines,[198] symmetrical dihydroxy aromatic compounds,[199] asymmetric crotylation reactions,[200] and the synthesis of norbornene-derived substrates using a Pauson-Khand reaction.[201]

In recent studies on the synthesis of furans *via* an intramolecular radical cyclisation, a TentaGel™ carboxy resin was found to give superior results to carboxylated polystyrene **(362)**.[202] The former is composed of a cross-linked polystyrene core to which 3000-4000 m.w. polyethylene glycol chains are attached. The ends of the PEG chains have been functionalised with carboxyl groups. The authors attributed the variance in results to the notion that, in the PEG-based support, the radical intermediates would be prevented from approaching, and thus being quenched by the benzylic protons of the polystyrene backbone.

2.5 The synthesis of carboxyethylated polystyrene (365)

The resin-bound malonate **364** was obtained by alkylation of Merrifield resin with the sodium salt of diethylmalonate **(363)** (scheme 2.12).[203] Hydrolysis of the diester **364** and subsequent decarboxylation afforded carboxyethylated polystyrene **(365)**. As with hydroxypolystyrene **(343)**, carboxyethylated polystyrene **(365)** gave a positive result when treated with bromocresol green. However, the change in colouration was observed to be more rapid with the latter.

Scheme 2.12 Synthesis of carboxyethylated polystyrene **(365)**.



The synthesis was monitored closely by infrared spectroscopy. Merrifield resin exhibited no significant absorption in the carbonyl region as expected (figure 2.5). A strong absorption at 1726 cm^{-1} was observed in the infrared spectrum of the malonate **364** (figure 2.6), whereas the desired product **365** exhibited a characteristic absorption at 1708 cm^{-1} (figure 2.7).

Figure 2.5 Infrared spectrum of Merrifield resin.

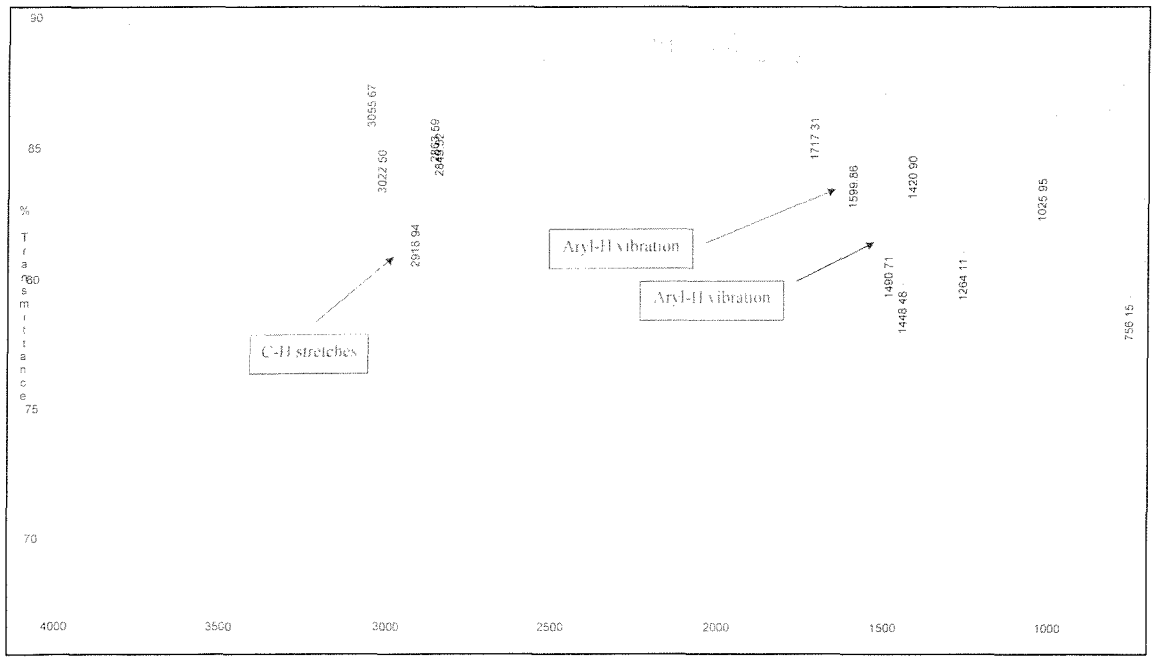


Figure 2.6 Infrared spectrum of resin-bound malonate **364**.

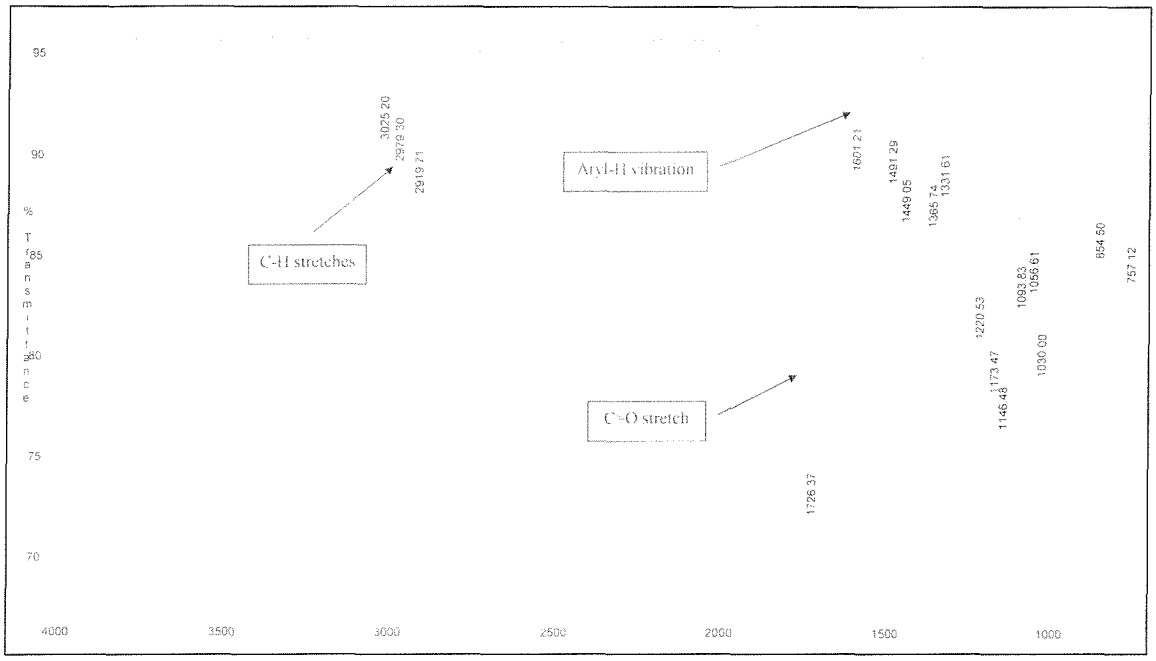
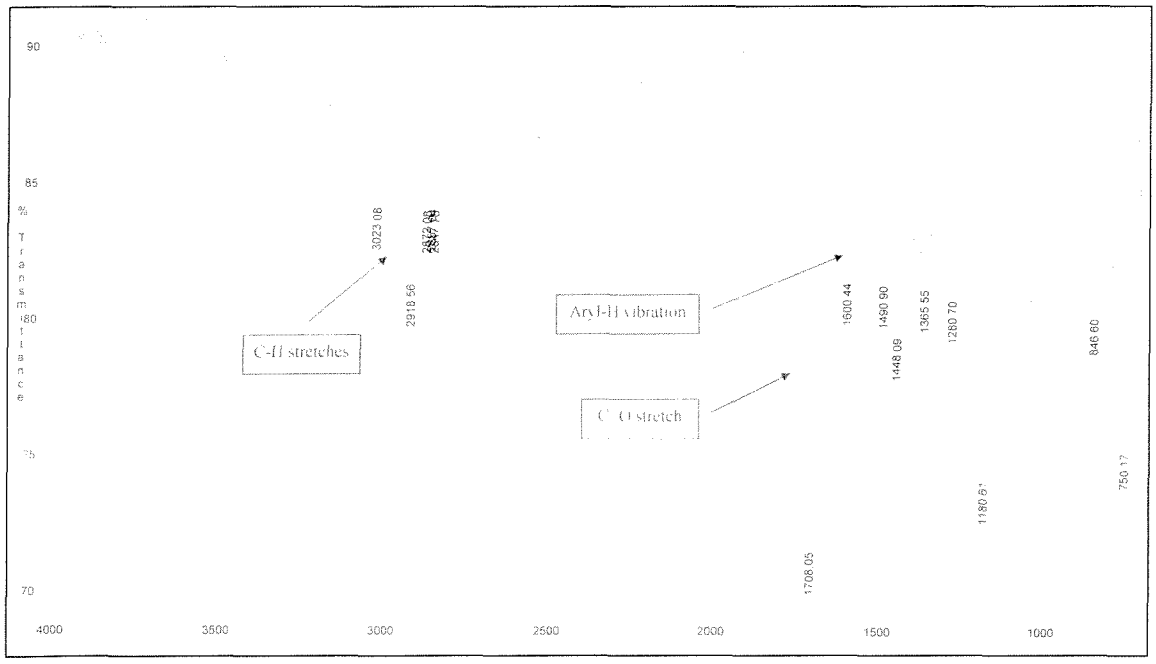
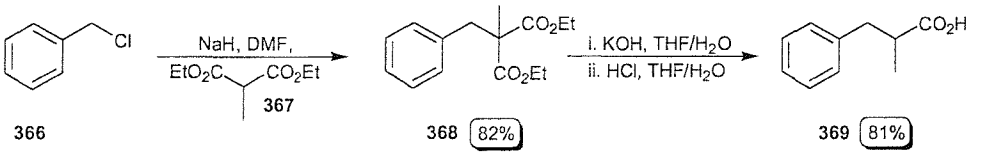


Figure 2.7 Infrared spectrum of carboxyethylated polystyrene **(365)**.



2-Methyl-3-phenylpropanoic acid (**369**) was used to model the use of carboxyethylated polystyrene (**365**) in solution-phase studies. This was synthesised in an analogous synthesis involving the alkylation of benzyl chloride (**366**) with diethyl methylmalonate (**367**),[204-206] and then hydrolysis and decarboxylation (scheme 2.13).[206-209]

Scheme 2.13 Synthesis of 2-methyl-3-phenylpropanoic acid (**369**).



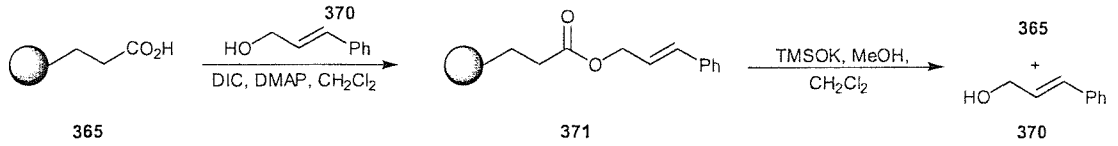
The solution-phase studies were carried out first and it was thought that the methyl group adjacent to the carbonyl group would reduce the lability of the linkage. However, when the synthesis was transferred onto the solid-phase the steric hindrance surrounding the ester appeared to strongly disfavour decarboxylation, hence the methyl group was not used.

2.6 Calculation of the loading of carboxyethylated polystyrene (365)

Several methods were used to determine the loading of carboxyethylated polystyrene (**365**). Initially, cinnamyl alcohol (**370**) was coupled to the acid resin **365** using carbodiimide chemistry (scheme 2.14). Cleavage of the cinnamate **371** released the cinnamyl alcohol (**370**), which had been captured by the carboxyethylated polystyrene (**365**), into solution and allowed its quantification by GC[‡]. This in turn allowed the loading of the carboxyethylated polystyrene (**365**) to be calculated. A typical loading was found to be between 0.84 and 1.02 mmol/g.

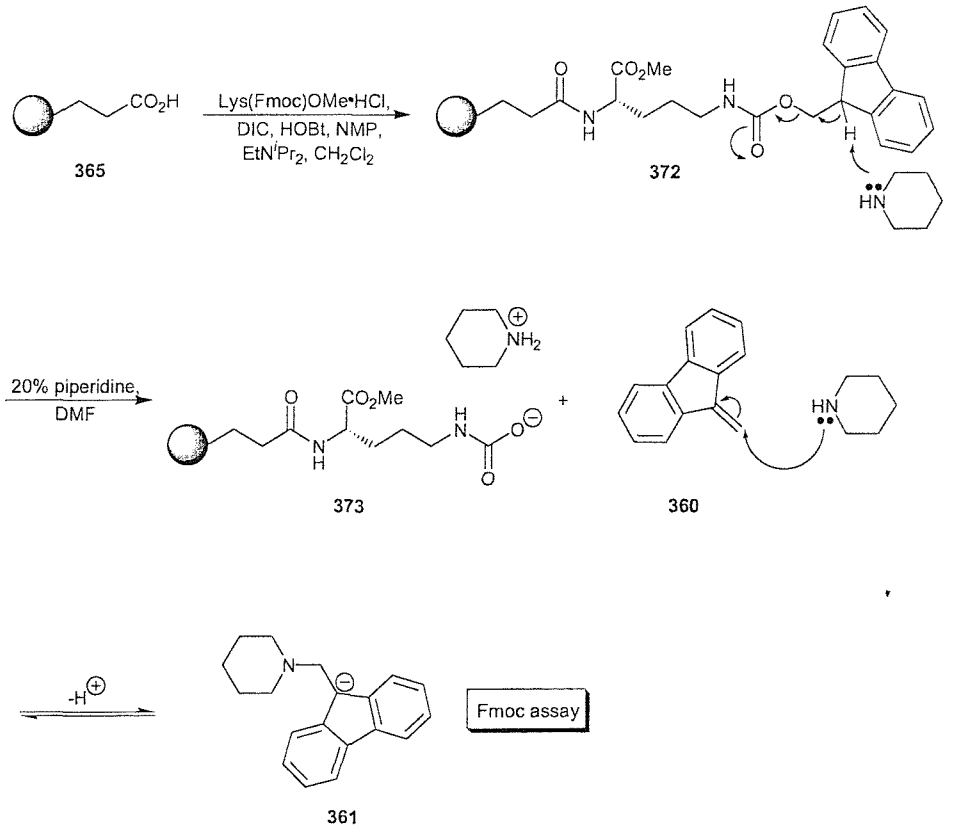
[‡] In order to quantify the cleaved cinnamyl alcohol (**370**), naphthalene was used as an internal standard in conjunction with a standard solution of authentic cinnamyl alcohol.

Scheme 2.14 Carboxyethylated polystyrene **(365)** loading determination.



The loading of carboxyethylated polystyrene **(365)** was also calculated, in a similar manner to the method for the hydroxypolystyrene **(343)**, using an Fmoc assay.[190-193 194] However, in this case, Lys(Fmoc)OMe was coupled to the resin using carbodiimide chemistry (scheme 2.15). The subsequent cleavage of Fmoc, in the presence of piperidine, and its quantification by a UV assay at 300 nm allowed the loading of the carboxyethylated polystyrene **(365)** to be calculated.

Scheme 2.15 The calculation of carboxyethylated polystyrene **(365)** loading *via* an Fmoc assay.



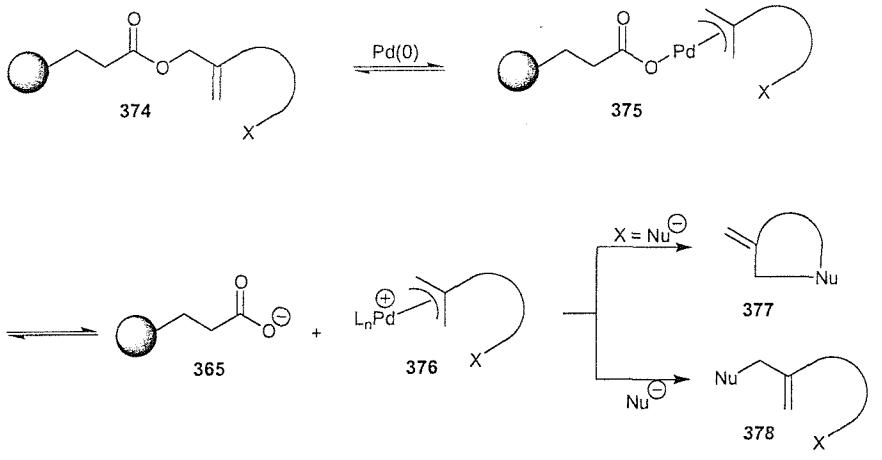
Loading calculations obtained *via* an Fmoc assay were found to be in reasonable agreement with those obtained *via* the cinnamyl alcohol method. For a typical batch of carboxyethylated polystyrene **(365)** the former gave a loading of 0.70 mmol/g and the latter 0.84 mmol/g.

3. The solid-phase synthesis of 4-methylene pyrrolidines using a cyclisation-cleavage strategy

3.1 The design of a reversed allylic linker

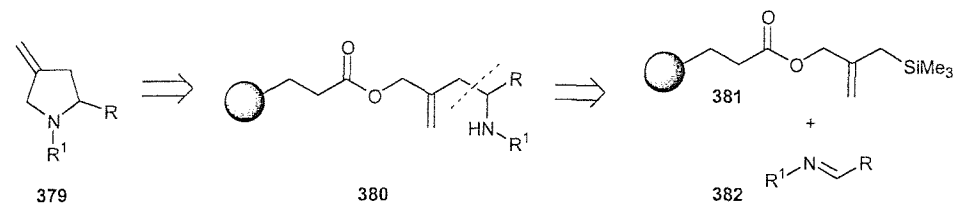
Several linkers, which rely upon the palladium-catalysed cleavage of allylic systems, have been reported releasing carboxylic acids, amines (through an intermediate carbamic acid) or molecules through 'traceless' cleavage from the resin.[29-31,35,36,210-212] It was imagined that a reversed allylic linker **374** would provide a mild means of generating electrophilic π-allyl palladium species, which could be trapped with heteroatom- or carbon-centred nucleophiles to release cyclic **377** or acyclic **378** products from the solid-phase (scheme 3.1). Indeed, cyclorelease strategies have been successfully employed in the synthesis of many heterocycles to date.[213,214]

Scheme 3.1 The palladium-catalysed cleavage of a reversed allylic linker **374**.



In order to demonstrate the viability of a palladium-catalysed cyclisation-cleavage the solid-phase synthesis of 4-methylenepyrrolidines **379** was chosen to be investigated (scheme 3.2).[215-220] A key intermediate was the homoallylic amine **380**, which could be derived from the reaction of a resin-bound allylic nucleophile **381** with an imine **382**.[221-225]

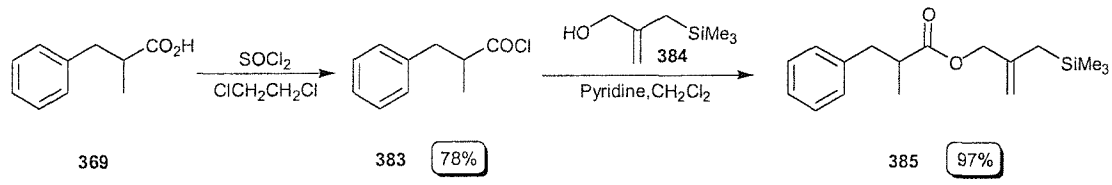
Scheme 3.2 A retrosynthetic analysis of pyrrolidine **379**.



3.2 The synthesis of 4-methylene pyrrolidines – A solution model

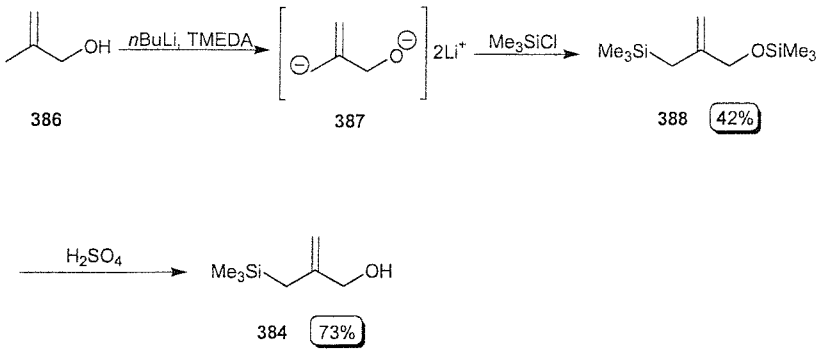
Before attempting any solid-phase work the analogous solution chemistry was investigated. As described earlier 2-methyl-3-phenylpropanoic acid **(369)** was used to model the use of the carboxyethylated polystyrene **(365)** in solution-phase studies. Conversion of acid **369** to the acid chloride **383**,[209] followed by esterification with the known alcohol **384**,[226] provided the allylsilane **385** in an overall yield of 76% (scheme 3.3).

Scheme 3.3 The preparation of allylsilane **385**.



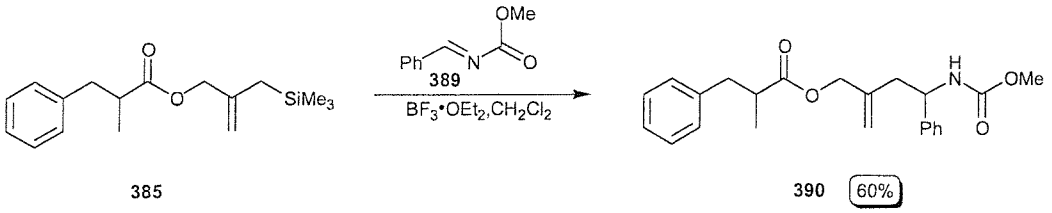
Alcohol **384** was readily prepared from 2-methyl-2-propen-1-ol **(386)** (scheme 3.4).[226,227] The allylic alcohol **386** was treated with *n*-butyllithium to give the corresponding dianion **387**, which afforded 2-(trimethylsiloxymethyl) allyltrimethylsilane **(388)** when quenched with trimethylsilyl chloride. Interestingly, the purity of the product depended on the polarity of the reaction solvent and it is desirable to remove as much hexane from the *n*-butyllithium as possible before proceeding with the addition of the allylic alcohol **386**. Hydrolysis of the silyl ether **388** in dilute aqueous acid readily provided alcohol **384**.

Scheme 3.4 The synthesis of 2-(hydroxymethyl)allyltrimethylsilane **(384)**.



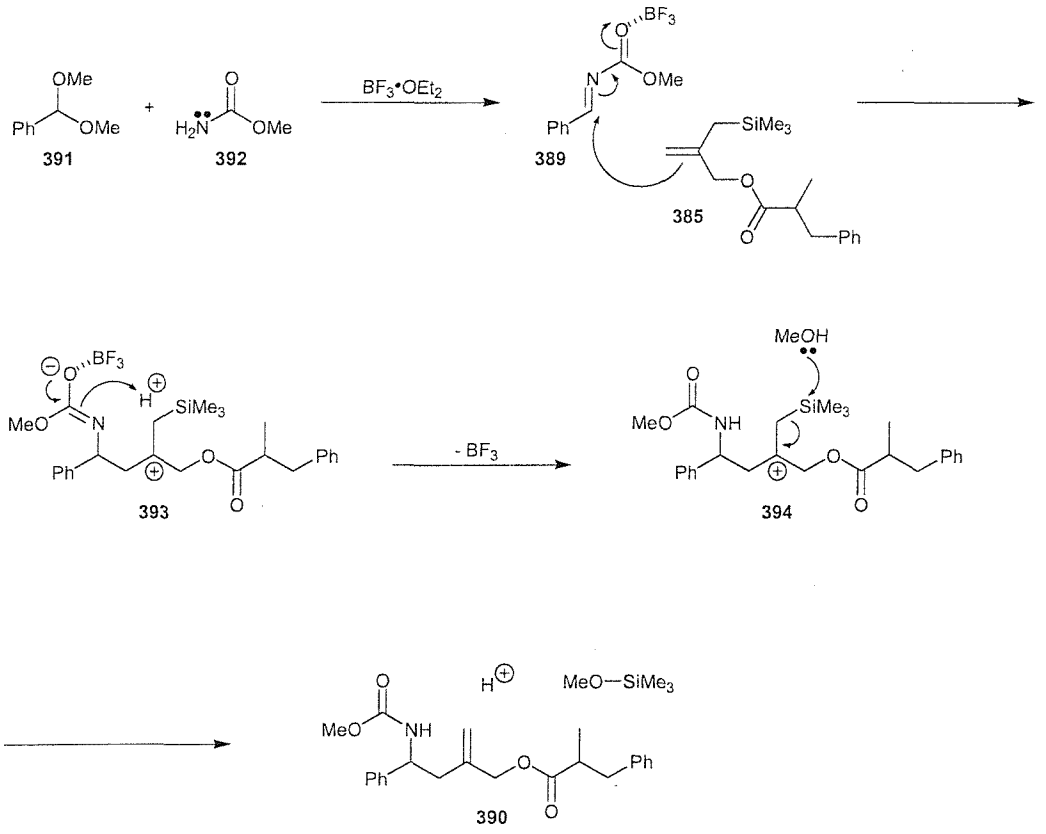
Initially, the desired homoallylic amine **380** (scheme 3.2) was generated containing an *N*-acyl group. It was thought that this group would generate a more electrophilic iminium species **382** and therefore readily facilitate attack by the allyl trimethylsilane **381**.[222,225,228-232] A one-pot synthesis of *N*-acyl homoallylic amines, utilising $BF_3{\bullet}OEt_2$ as a Lewis acid, was used to prepare the *N*-methoxycarbonyl species **390** (scheme 3.5).[225]

Scheme 3.5 The use of a Sakurai-type reaction to generate homoallylic amine **390**.



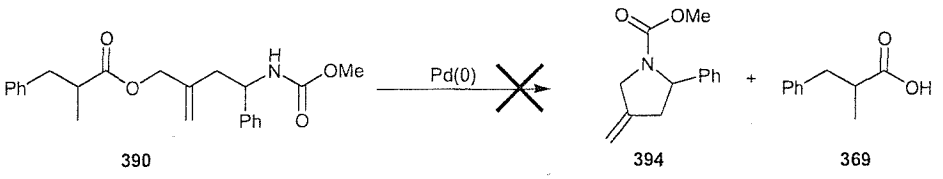
Treatment of benzaldehyde dimethyl acetal **(391)** with $BF_3{\bullet}OEt_2$ gives the oxonium cation, which undergoes nucleophilic attack by methylcarbamate **(392)** to generate the *N*-acyl iminium species **389** after loss of methanol (scheme 3.6). This in turn is attacked by the allyl trimethylsilane **385** to give the desired product **390**.

Scheme 3.6 Proposed mechanism for the formation of homoallylic amine **390**.



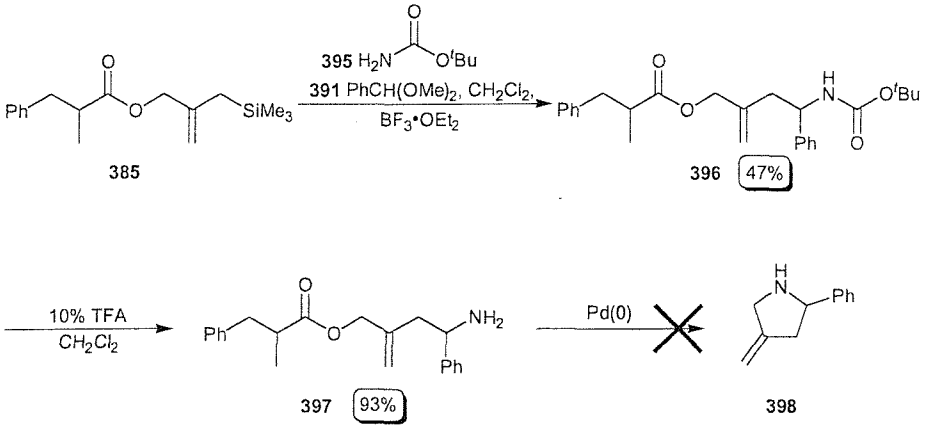
At this point, the palladium-catalysed cyclisation of **390** was examined (scheme 3.7). Various conditions were investigated but no cyclisative-cleavage of homoallylic amine **390** could be affected. Potassium carbonate and triethylamine were used as bases with $Pd(acac)_2$ and dppe or $Pd(PPh_3)_4$ as the catalyst system.[216,217,233-235] The lack of success was probably due to the poor nucleophilicity of the carbamate nitrogen. Therefore NaHMDS was used to generate the carbamate anion but again no cyclisation was observed.[236] In all cases ^1H NMR spectra of the crude reaction mixtures showed the presence of the acyclic starting material **390** and gave no indication that any by-products were present.

Scheme 3.7 The attempted cyclisative-cleavage of homoallylic amine **390**.



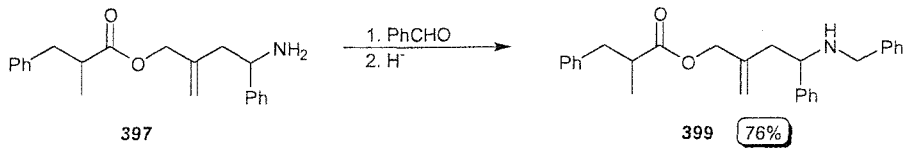
In order to increase the nucleophilic character of the nitrogen a new synthetic strategy was adopted. The *N*-methoxycarbonyl group was replaced with the *N*-tert-butoxycarbonyl moiety. Deprotection of the *N*-Boc protected amine **396**, with TFA, would provide access to the primary amine **397**.[237,238] Unfortunately, all attempted palladium-catalysed cyclisations on the new substrate **397** produced a complex mixture, which contained some starting material **397** according to the ^{1}H NMR spectra (scheme 3.8). The apparent absence of the desired cyclisation product **398** in the reactions of **397** was thought to be due to possible polymerisation reactions or dialkylation of the primary amino group. However, no other products could be isolated to provide evidence for this proposal.

Scheme 3.8 Synthesis and attempted cyclisative-cleavage of homoallylic amine **397**.



To avoid the potential dialkylation reactions the primary amine **397** was replaced with secondary amine **399**, which could be obtained *via* the reductive alkylation of the former (scheme 3.9). The strategy employed to obtain the secondary amine **399** can be considered as two steps. Initially, the imine is formed by the condensation of benzaldehyde and amine **397**. Subsequent reduction affords the desired secondary amine **399**. This method is desirable, when compared to the standard alkylation of an amine with an alkyl halide, as it produces few side products such as tertiary and quaternary amines.

Scheme 3.9 The reductive alkylation of amine **397**.



397 399 76%

The Borch reduction,[239] using sodium cyanoborohydride, has been the most popular method to date for effecting reductive alkylation reactions.[240,241] Early solution reaction protocols used 5N HCl in absolute methanol as the solvent at room temperature over 3 days.[239] Numerous primary and secondary amines were used effectively, however, it was noted that the rate determining step appeared to be formation of the intermediate iminium species. When used on the solid-phase a similar protocol was employed.[240,242] The resin-bound amine was reacted with the aldehyde of choice (20 equiv.) and sodium cyanoborohydride (30 equiv.). In this case a mixture of trimethylorthoformate and dichloromethane (1:1) containing 1% acetic acid was used as the solvent. Other groups found that the reductive alkylation needed to be carried out in two distinct steps with the imine formation being carried out in trimethylorthoformate over 18 hours at room temperature and the reduction in 1% acetic acid in DMF over 3 days.[241]

An alternative hydride source was desired in order to avoid residual cyanide in the product or workup waste stream. Sodium triacetoxyborohydride has been shown to be effective in reductive alkylation reactions. In solution, reactions were carried out in 1,2-dichloroethane or THF using a mixture of the carbonyl compound, the amine (1.5 equivalents), sodium triacetoxyborohydride (1.5 equiv.) and acetic acid (1 equiv.).[243] In the solid-phase sodium triacetoxyborohydride has been used with 1% acetic acid in DMF as the solvent.[244] Use of dichloroethane as a solvent has also been investigated.[245]

The conditions investigated were based on these observations reported in the literature for the reductive alkylation of primary amines with aldehydes (table 3.1). Campbell had demonstrated that benzylimine intermediates are too stable to be reduced without the addition of an external proton source.[242] With this in mind 1% acetic acid was used in all reactions investigated.

Table 3.1 Reductive alkylation conditions investigated.

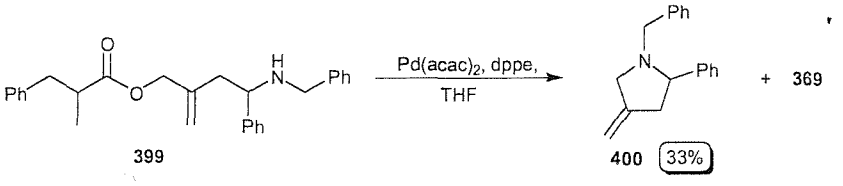
Entry	$[(OAc)_3BH]^-$ salt	Solvent†	"H^-" equiv.	PhCHO equiv.	Time	Imine	Product
1	NMe_4^+	$(EtO)_3CH$	5	10	1.5 h	59%	-
2	Na^+	DMF	5	1.6	2.5 h	-	21%‡
3	Na^+	DMF	8	1.6	24 h	-	50%
4	Na^+	DCE	4	1.0	4 days	-	69%*
5	NMe_4^+	DCE	4	1.0	4 days	-	76%

† This contained AcOH (1%). DCE indicates 1,2-dichloroethane.
* The corresponding tertiary amine was also isolated (20%).
‡ Starting material **397** was also isolated (45%).

The most efficient conditions found were therefore 1% acetic acid in 1,2-dichloroethane using 1.0 equivalent of benzaldehyde and 4.0 equivalents of tetramethylammonium triacetoxyborohydride (entry 5, table 3.1). No dialkylation was observed with the secondary amine **399** being obtained in a 76% yield. Tetramethylammonium triacetoxyborohydride is more soluble than the sodium salt in organic solvents, which is an important consideration when transferring the conditions to the solid-phase.

The palladium-catalysed cyclisation of amine **399** was attempted several times (scheme 3.10). Initially, at room temperature with 10 mol% $Pd(acac)_2$ and 15 mol% dppe in THF no pyrrolidine **400** was observed in the crude reaction mixture. However, subjecting amine **399** to the same conditions at reflux afforded the pyrrolidine **400** in 33% yield along with some unreacted starting material **399** (40%).

Scheme 3.10 Cyclisative-cleavage of secondary amine **399**.



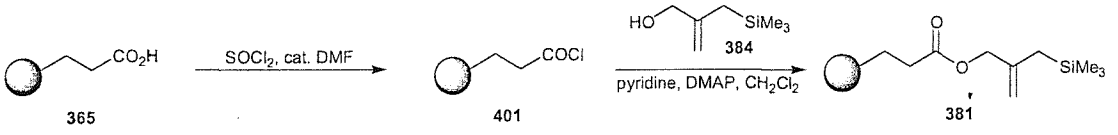
In order to attempt to drive the cleavage to completion, the reaction was heated at reflux for 25 hours with a further quantity of catalyst and ligand being added after 13 hours. However, under these conditions no further material was obtained.

Although the reaction was incomplete, for the corresponding solid-phase process the desired product was expected to be released from the resin, with any unreacted starting material remaining attached. It was concluded that the solution model had justified the viability of the solid-phase synthesis of pyrrolidine **400** and further optimisation could be carried out on the solid-phase.

3.3 Transfer of the solution model to the solid-phase

In accordance with the solution model, acid resin **365** was treated with thionyl chloride so as to allow attachment of the allylic alcohol **384** to the support (scheme 3.11).[198,199] However, microanalysis of the acid chloride resin **401** indicated that approximately 4 μmol/g of sulfur had been incorporated into the resin and this could potentially interfere with the catalysts used later in the synthesis. In addition, it appeared that the immobilisation of alcohol **384** onto the resin **401** was both inefficient and unclean. The IR spectrum of the product **381** contained numerous absorptions, which could be attributed to both ester and amide carbonyl groups. The latter may have potentially arisen from the use of catalytic DMF in the preparation of the acid chloride resin **401**. This method of attaching the allylsilane **384** to the solid-support was abandoned.

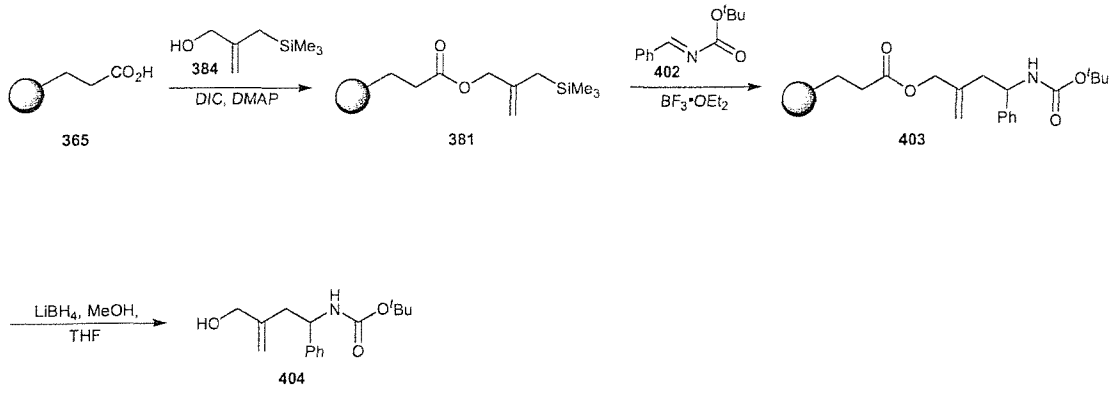
Scheme 3.11 Preparation and coupling of the resin-bound acid chloride **401**.



Ultimately, a standard carbodiimide coupling reaction of the acid resin **365** and allylic alcohol **384** was employed (scheme 3.12).[246,247] The only point of note being that 4.0 equivalents of DMAP were required to avoid the rearrangement of the DIC-acid adduct.[248-250] The formation of the acylisourea by-product, in the absence of a large excess of DMAP, was clearly seen in the 'on-bead' IR spectrum at 1681 cm^{-1}. A successful

coupling was characterised by a frequency shift of the carbonyl stretch, in the 'on-bead' IR spectrum, from 1715 cm^{-1} to 1735 cm^{-1}.

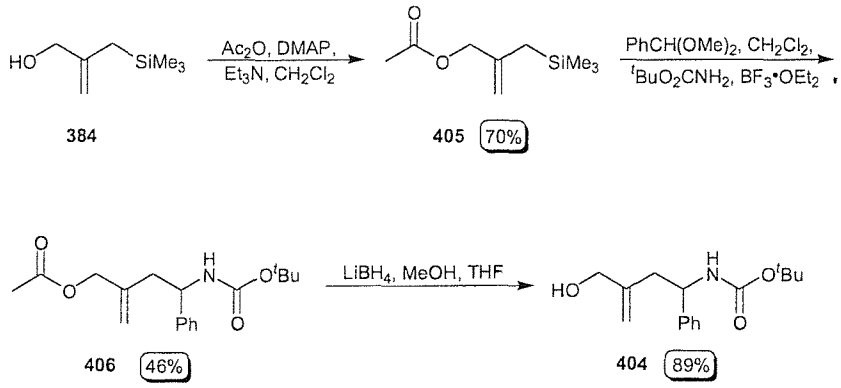
Scheme 3.12 Synthesis of homoallylic amine **403**.



8.0 equivalents of imine **402** were generated *in situ* and reacted with the resin-bound silane **381** to give the *N*-Boc protected amine **403** (scheme 3.12). In order to show that *N*-Boc protected amine **403** had been formed a sample was cleaved by treatment with $LiBH_4$ (scheme 3.12).[251,252] The cleaved material obtained was compared to an authentic sample of alcohol **404** however, a large amount of silyl material was obtained, and the results were inconclusive suggesting that this step was very inefficient.

An authentic sample of **404** was prepared from the alcohol **384**, which was acetylated to give the acetate **405** (scheme 3.13). This was converted to the *N*-Boc protected amine **406**, which was then reduced to afford alcohol **404**.

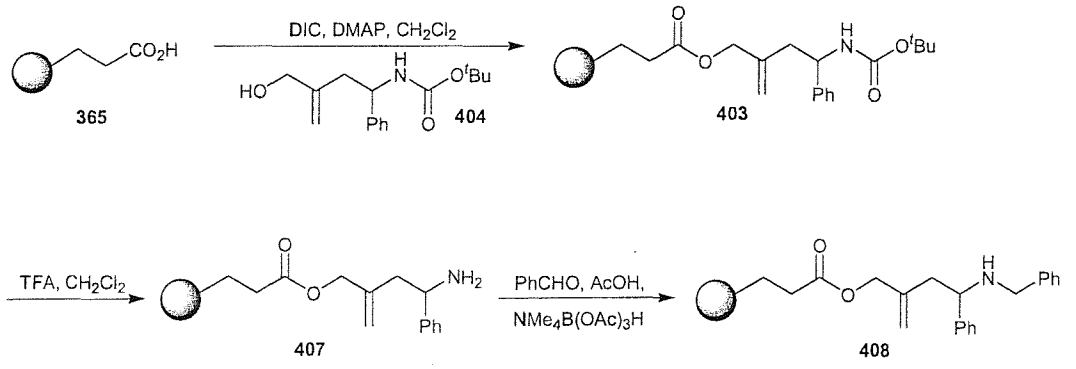
Scheme 3.13 Preparation of alcohol **404** in solution.



3.4 Verification of the final steps in the synthesis *via* the coupling of an advanced alcohol intermediate to the resin

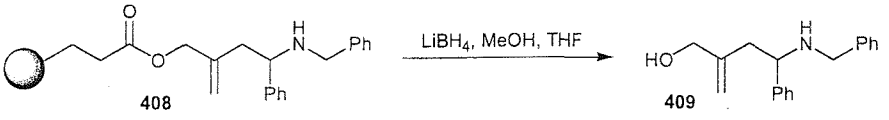
Having shown that the synthesis of resin **403** was inefficient, it was decided that further optimisation of the reductive alkylation and cyclisation-cleavage steps should use material generated by coupling an advanced intermediate **404** to the acid resin **365**. Removal of the *N*-Boc protecting group from **403** by TFA followed by reductive alkylation, using 10.0 equivalents of benzaldehyde and 8.0 equivalents of tetramethyl ammonium triacetoxyborohydride, gave the secondary amine **408** (scheme 3.14).

Scheme 3.14 Synthesis of secondary amine **408** on the resin.



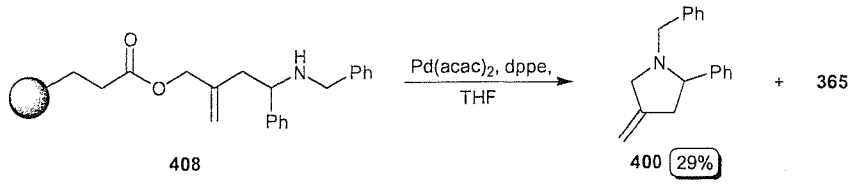
As before some of the resin **408** was treated with $LiBH_4$ to cleave a sample of alcohol **409** for analysis (scheme 3.15).[251,252] Analysis of the crude sample obtained suggested that the reductive alkylation had been successful. Indeed the ^1H NMR spectrum suggested than the desired product was the only allylic species present in the cleaved material. All attempts to isolate alcohol **409** were unsuccessful and samples continually contained unidentified impurities. However, the yield was estimated at 60% from inspection of the ^1H NMR spectrum.

Scheme 3.15 Reductive cleavage of alcohol **409** from the solid-support.



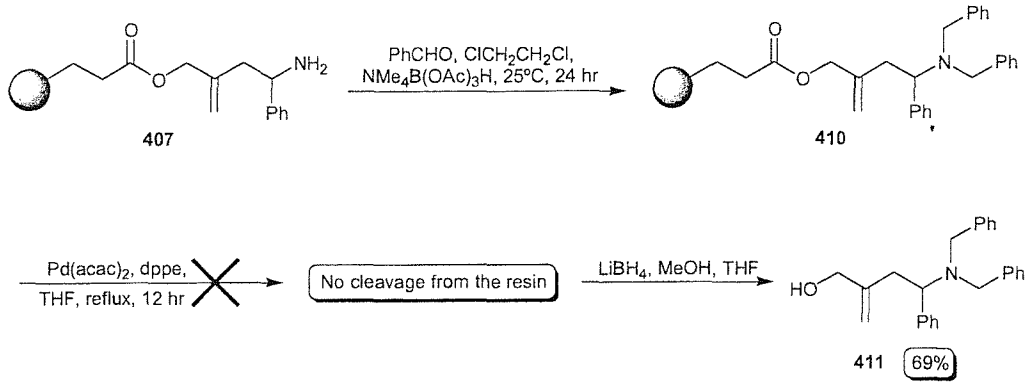
Despite the suspected presence of a number of different species on the resin **408**, a cyclisation-cleavage reaction was attempted. Gratifyingly, treatment of secondary amine **408** with 30 mol% $Pd(acac)_2$ and 20 mol% dppe in THF at reflux afforded the desired pyrrolidine **400**. Although the crude reaction filtrate contained essentially pure product it was filtered through a pad of silica, to remove traces of ligand and catalyst, and gave the isolated product **400** in a yield of 29%. Whilst the reaction conditions remained unoptimised, and some substrate remained on the resin, according to the IR spectrum of the residual resin, the feasibility of a palladium-catalysed cyclisation-cleavage from the solid-phase had been successfully demonstrated (scheme 3.16).

Scheme 3.16 Palladium-catalysed cyclisative-cleavage of pyrrolidine **400**.



In addition, the dialkylated resin **410** was prepared from the resin-bound primary amine **408** by reductive alkylation (scheme 3.17). No material of any significance was cleaved from the resin **410** under the palladium cyclisative-cleavage conditions. However, when the residual resin **410** was treated with $LiBH_4$ tertiary amine **411** was obtained (69%). This therefore demonstrated that the dialkylated resin **410** had been prepared and also that it was not cleaved when exposed to the palladium cyclisative-cleavage conditions.

Scheme 3.17 Preparation and cleavage of dialkylated amine **410**.



3.5 Optimisation of the solid-phase Sakurai-type reaction

Optimisation of the Sakurai-type reaction was carried out by changing the quantity of imine **402** or BF_3•OEt_2 and varying the reaction time.[225] The results are shown below (table 3.2). In order to determine the relative efficiencies of the Sakurai-type reactions alcohol **404** was reductively cleaved from the resin **403** as before (scheme 3.13) and it is the isolated yield of **404**, with respect to the loading of resin **365**, which is reported. This comparison is possible as the same batch of allylsilane **381** was used in all experiments and so the loading of this material was constant, although unknown. Also the reductive cleavage step was shown to have gone to completion by 'on bead' IR analysis of the resin at the end of the cleavage i.e. there was no observable ester peak.

Table 3.2 Optimisation of the Sakurai-type reaction (scheme 3.12).

Entry	Imine **402** equiv.*	BF_3•OEt_2 equiv.*	Time (hr)	Yield (%)†
1	15	5	28	60
2	15	9	28	49
3	8	5	12	25
4	8	12	12	16
5	8	4	12	25
6	15	8	12	61
7	23	8	12	70
8	23	8	6	70
9	23	8	3	70
10	23	4	3	70

† Isolated yields after purification by column chromatography. These are based on the calculated loading of resin **365** assuming quantitative conversion for all solid-phase reactions. An estimated error of ± 5% is associated with these results.

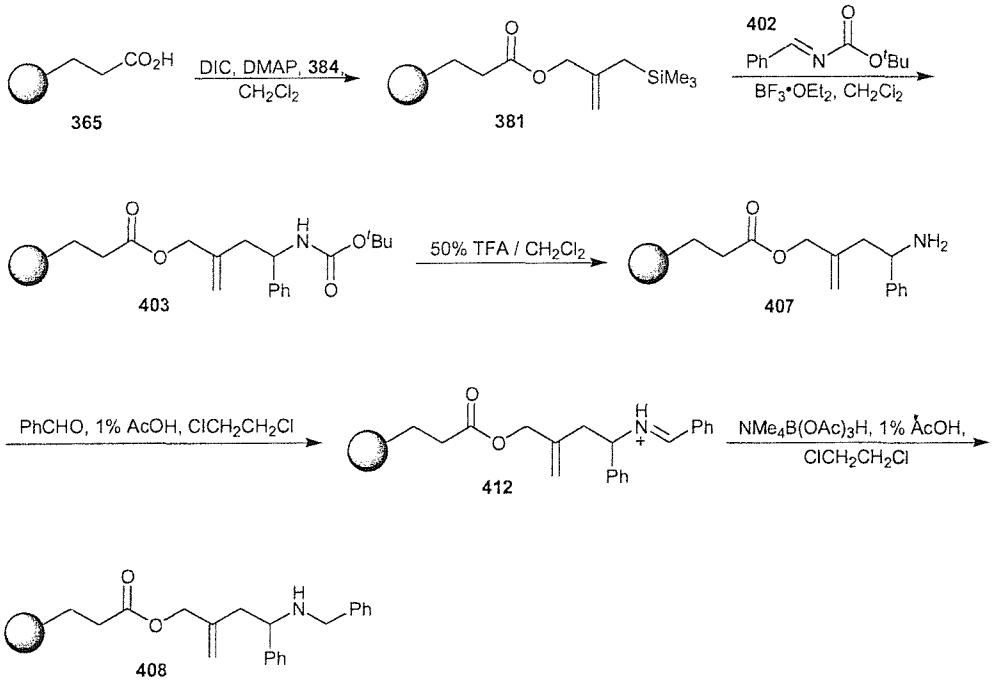
* Quantities of reagents are based on the calculated loading of resin **365** assuming quantitative conversions for all solid-phase reactions.

These results clearly show that the yield generally increases with the amount of preformed imine **402** used in the Sakurai-type reaction. A major concern with this reaction was that the Lewis acid would deprotect the product **403** as it was formed. Indeed, entries 2 and 6 (table 3.2) suggest that leaving the reaction for an extended

period of time lowers the yield. However, there is no other evidence to support this theory. The most efficient conditions found (entry 10, table 2) were therefore adopted and a large batch of resin **403** (4.4 g) was prepared. Similar chemistry has been used to prepare a carbamate linker for *N*-acyliminium ion reactions on the solid-support.[253] In this case it is the *N*-acyliminium ion which is attached to the support rather than the nucleophile.

Deprotection of the *N*-Boc protected amine **403**, using a 50% TFA solution in dichloromethane, gave the primary amine **407** after 30 minutes. Reductive alkylation, to give the secondary amine **408**, was then achieved in two steps rather than using the 'one-pot' method.[241] The imine **412** was formed, collected by filtration and briefly washed with dichloromethane before its subsequent reduction to afford the resin-bound secondary amine **408** following an optimised synthesis (scheme 3.18). Formation of the iminium species **412** was characterised by an absorption in the 'on-bead' IR spectrum at 1643 cm^{-1}. For completeness the *N*-Boc protected amine **403** was also investigated as a cyclisation substrate but all attempted cyclisations provided no significant material, other than dppe residues, upon inspection of the ^{1}HMR spectrum of the cleaved material.

Scheme 3.18 The optimised synthesis of amine **408** on the solid-phase.



3.6 Optimisation of the palladium-catalysed cyclisative-cleavage reaction

With a reasonable quantity of the secondary amine **408** available optimisation of the palladium-catalysed cyclisative-cleavage step could be investigated (table 3.3). Initially, 1.5 equivalents of the ligand (dppe), with respect to the catalyst, were used as this was the quantity used in the solution model. The resin was simply heated at reflux, in THF, for 12 hours with the ligand and catalyst.

Table 3.3 Optimisation of the cyclisative-cleavage of amine **408** (scheme 3.16).

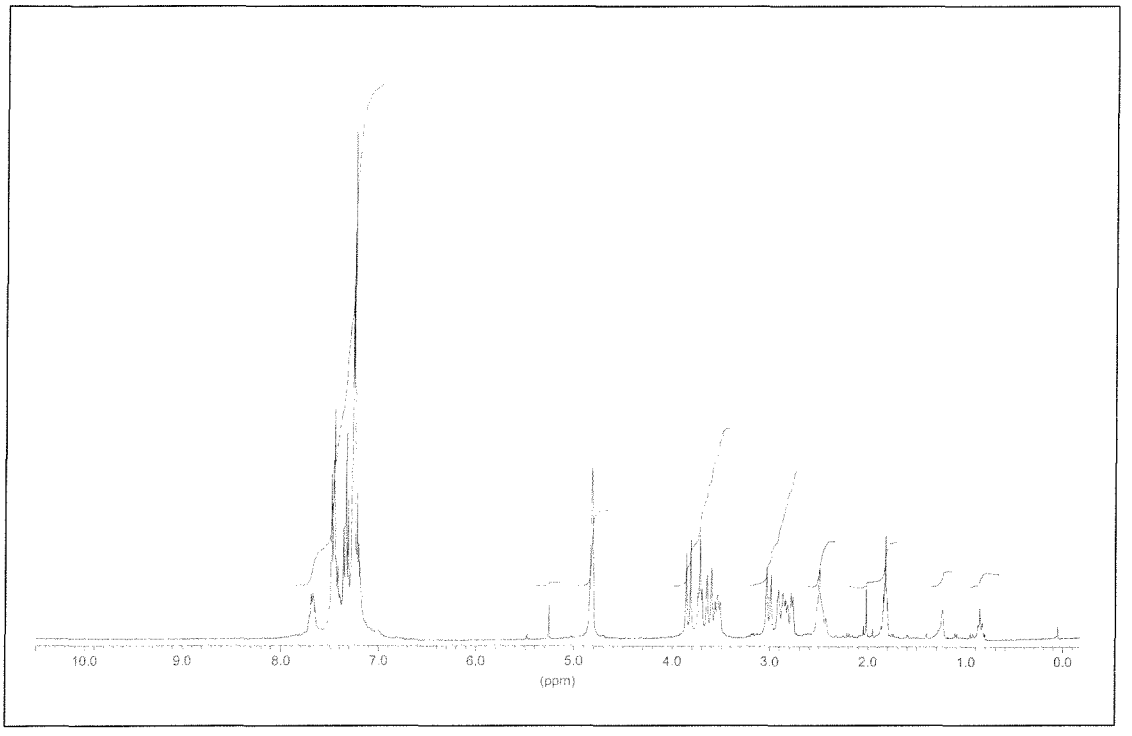
Entry[‡]	Catalyst	Pd (mol%)[*]	dppe (mol%)[*] (equiv. w.r.t. Pd)	Yield (%)[†]
1	$Pd(acac)_2$	50	75 (1.5)	9
2	$Pd(acac)_2$	25	38 (1.5)	18
3	$Pd(acac)_2$	10	15 (1.5)	5
4	$Pd(acac)_2$	5	8 (1.5)	Trace
5	$Pd(acac)_2$	2	3 (1.5)	0
6	$Pd(acac)_2$	10	30 (3.0)	95
7	$Pd(acac)_2$	5	15 (3.0)	40
8	$Pd(acac)_2$	5	30 (6.0)	18
9	$Pd(PPh_3)_4$	10	-	23
10	$Pd_2(dba)_3 \cdot CHCl_3$	10	15 (1.5)	14

[†] Isolated yields after purification by column chromatography. These are based on the calculated loading of resin **365** assuming quantitative conversion for all solid-phase reactions. An estimated error of ± 5% is associated with these results.
[‡] All reactions were carried out using 200 mg (~ 0.1 mmol) of starting resin **408** in THF (4 mL).
[*] Quantities of reagents are based on the calculated loading of resin **365** assuming quantitative conversions for all solid-phase reactions.

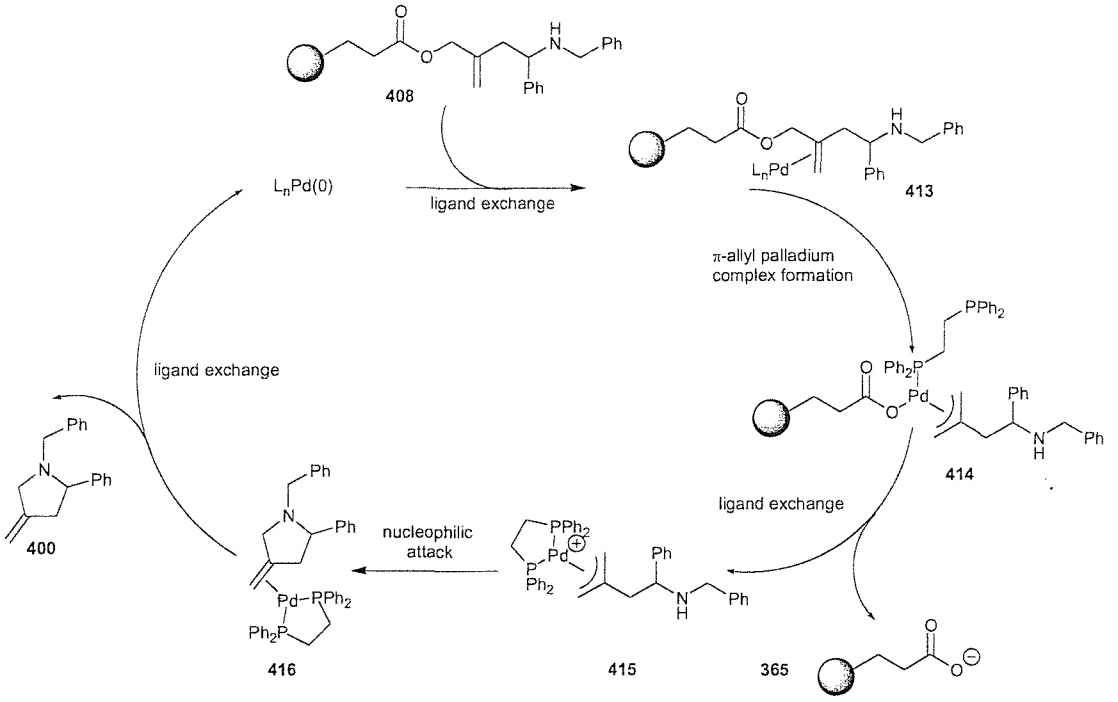
The results show that with 1.5 equivalents of dppe, with respect to palladium, the palladium catalyst did not act stoichiometrically, let alone catalytically (entries 1-5, table 3.3). However, when the amount of ligand was increased to 3.0 equivalents the palladium/dppe system worked very efficiently affording the pyrrolidine **400** in an isolated yield of 95% (entry 6, table 3.3). It should be noted that, in this case, the crude

material obtained from the resin contained only a small amount of catalyst residues and little evidence of other impurities was observed in the ^{1}H NMR spectrum (figure 3.1). It is suggested that the excess dppe is important as it drives the equilibrium between the π-allyl-palladium complexes **413** and **414** (scheme 3.19). This would be important as the latter is likely to be the more reactive species and therefore intramolecular nucleophilic attack would be more favourable.

Figure 3.1 ^{1}H NMR spectrum of the crude material cleaved from resin **408**.



Scheme 3.19 Proposed mechanism for the palladium-catalysed cleavage of amine **408**.

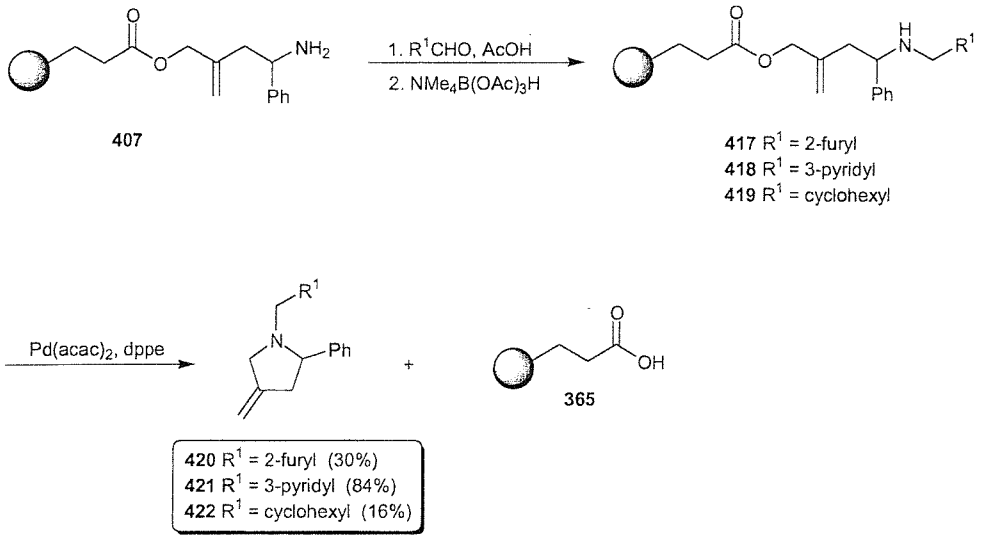


3.7 Solid-phase synthesis of 4-methylene pyrrolidine analogues

Examination of the synthesis of pyrrolidine **400**, using the method described, revealed two opportunities for the introduction of different substituents, in the Sakurai-type reaction or in the reductive alkylation. The latter approach was investigated first as a route into new pyrrolidines. Reductive alkylation of amine **407**, using either 2-furaldehyde or 3-pyridinecarboxaldehyde, demonstrated that R^1 (scheme 3.20) could be successfully varied, affording pyrrolidines **420** and **421** after submission to the cyclisative-cleavage conditions. In each case the reductive alkylation was carried out in two steps with the imine being prepared, isolated and then reduced. The cyclised products were subsequently obtained in yields of 30% and 84% respectively. The low yield for the former may be due to dialkylation and other side reactions. However, the crude cleaved material was reasonably pure implying that these impurities remained attached to the resin.

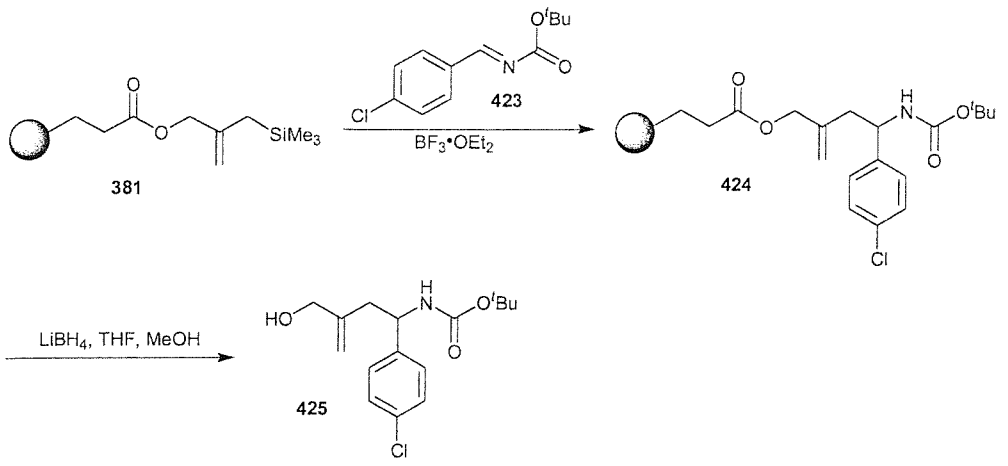
A further example **422** was prepared with cyclohexane carboxaldehyde. In this a 'one-pot' reductive alkylation was used as the imine formed would not be as stable as the conjugated imines formed in the synthesis of secondary amines **417** and **418**. In order to reduce the amount of dialkylation the reaction was only left to run for 1.5 hours. Palladium-catalysed cyclisative-cleavage of the resulting secondary amine **419** gave the pyrrolidine **422** in a yield of 16%. As with the furyl example it is thought that the low yield arises from an inefficient reductive alkylation rather than the cyclisative-cleavage step.

Scheme 3.20 Variation of substituents introduced during the reductive alkylation step.



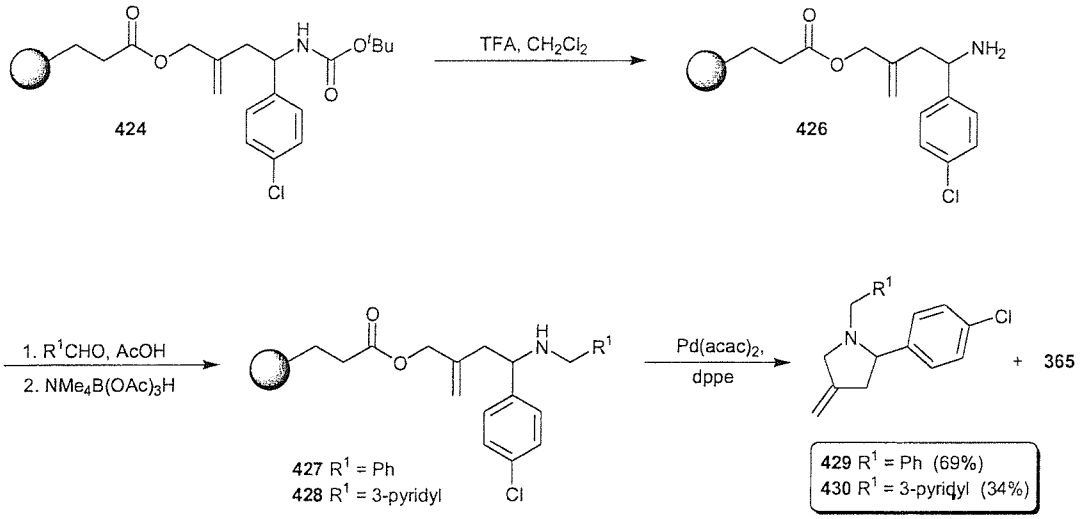
The second substituent, which could be introduced during the Sakurai-type reaction, was successfully replaced with the 4-chlorophenyl group (scheme 3.21). In this case the imine **423** is formed by the condensation of *t*-butyl carbamate and 4-chlorobenzaldehyde. The success of the Sakurai-type reaction was confirmed by examination of the 'on bead' IR spectrum and by the quantitative reductive cleavage of alcohol **425** from resin **424**.

Scheme 3.21 Introduction of the 4-chlorophenyl substituent.



Deprotection of **424**, reductive alkylation with either benzaldehyde or 3-pyridine carboxaldehyde and the subsequent palladium-catalysed cyclisative-cleavage afforded pyrrolidines **429** and **430** in yields of 69% and 34% respectively (scheme 3.22).

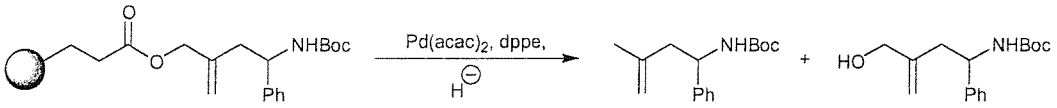
Scheme 3.22 Preparation of pyrrolidines containing a 4-chlorophenyl group.



3.8 Traceless cleavage from the resin

Interestingly, treatment of the resin **403** recovered from an attempted palladium-catalysed cyclisation-cleavage reaction with $LiBH_4$ in THF afforded a reduced product **431** in 80% yield rather than the expected allylic alcohol **404** (scheme 3.23). In this case it appeared that the palladium-catalyst had remained associated with the recovered resin **403** and in its presence the hydride is able to attack the resulting π-allyl palladium species to afford the substituted propene derivative **431** in a traceless cleavage from the solid-support.[6,254] Other sources of hydride equivalents that have been used to cleave allylic systems include tributyltin hydride and triethylammonium formate. [30,36,210]

Scheme 3.23 Traceless cleavage of the reversed allylic linker **403**.



403 **431** **404**

3.9 Conclusion

In summary, the viability of a palladium-catalysed cyclisation-cleavage reaction has been demonstrated by the solid-phase synthesis of pyrrolidines **400**, **420** to **422**, **429** and **430**.[257] A solution model has been used to demonstrate the principles of a reversed allylic linker. However, little optimisation of reaction conditions was carried out in the construction of the solution model. Once the synthesis of pyrrolidine **400** had been achieved in a modest yield (33%) an investigation into the solid-phase synthesis of pyrrolidine **400** followed.

A key intermediate in the reaction sequence is the homoallylic amine **403** which was derived from the reaction of a resin-bound nucleophile **381** and an imine **402** (scheme 3.18). Optimisation of this imino-Sakurai reaction showed that, in the presence of $BF_3 \cdot OEt_2$ (4 equiv.), the resin-bound allylsilane **381** reacted with a large excess of the preformed imine **402** (23 equiv.) over 3 hours to give the homoallylic amine **403** in excellent yield.

The reductive alkylation of resin-bound primary amine **407** appeared to be best carried out using a two-step protocol (scheme 3.18). Initially, the resin-bound iminium species **412** was generated, isolated by filtration and briefly washed. Subsequent reduction with tetramethylammonium triacetoxyborohydride, in the presence of 1% acetic acid over several days, afforded the desired secondary amine **408**. Although dialkylation was a potential problem it has been demonstrated that any tertiary amine **410** present would not be cleaved from the resin under the palladium cyclisative-cleavage conditions. Furthermore, the homoallylic amine **403** was not cleaved under these conditions.

The final palladium-catalysed cyclisative cleavage step provided the essentially pure pyrrolidine **400** in a yield of 95% once the reaction conditions were optimised. It appeared that 10 mol% of $Pd(acac)_2$ along with 30 mol% of dppe was required to obtain the product efficiently. The use of less phosphine ligand with respect to the palladium catalyst resulted in a significant reduction in the yield.

In order to demonstrate the scope of the palladium-catalysed cyclisation-cleavage further pyrrolidine analogues **420** to **422**, **429** and **430** were prepared. New groups were introduced in both the imino-Sakurai and the reductive alkylation reactions. It is worth noting that in each case aldehydes are used to introduce the new groups. Therefore, the large number of commercially available aldehydes would certainly allow the generation of a library of pyrrolidine analogues using this strategy. In addition, this strategy should be amenable to the solid-phase synthesis of other heterocyclic and carbocyclic compounds and this is what further work should focus on.

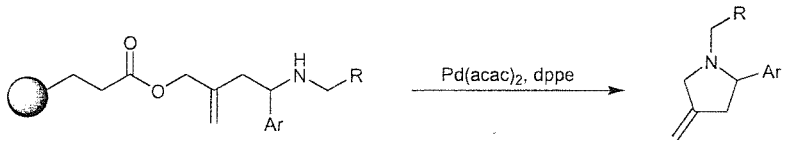
Finally, the intermolecular palladium-catalysed nucleophilic cleavage of the reversed allylic linker, using $LiBH_4$ as a source of hydride, has been shown to release substituted propene derivatives **431** in a traceless manner (scheme 3.23). Further investigation into the use of other nucleophiles, including carbon- and sulfur-centred nucleophiles, in an intermolecular cleavage of this reversed allylic linker **374** (scheme 3.1) is also warranted.

4. The palladium-catalysed nucleophilic release of allylic amines from hydroxypolystyrene (343)

4.1 The design of an allylic phenyl ether linker

The cyclisation cleavage of allylic carboxylates **432**, under mild conditions, affords pyrrolidines **433** as described in the previous chapter (scheme 4.1).[257] Although the ester linkage contained in **432** proved compatible with acidic conditions (Boc-deprotection with TFA), it was readily cleaved under nucleophilic conditions such as hydride reduction.

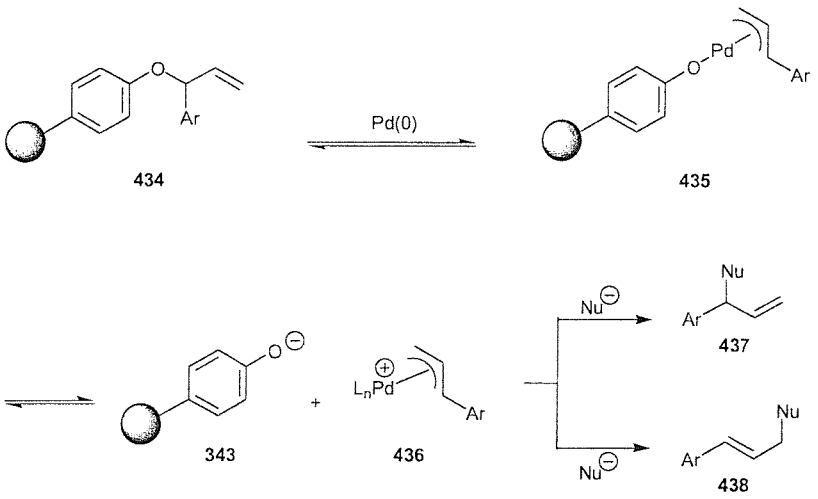
Scheme 4.1 Cyclisation cleavage of allylic carboxylates **432**.



432 **433**

A complementary strategy was desired in which the linkage would be compatible with nucleophilic conditions and an allylic phenyl ether linkage appeared to have this characteristic (scheme 4.2). According to the literature allylic phenyl ethers are stable to nucleophiles in the absence of palladium, but readily cleaved by amines in the presence of catalytic Pd(0).[148,256,258,259] Therefore, it was imagined that the allylic phenyl ether linker **434** would provide a mild means of generating electrophilic π-allyl palladium species **436**, which could be trapped with heteroatom- or carbon-centred nucleophiles to release products **437** and **438** from the solid-phase. However, it was also thought that the linker would be stable to nucleophilic conditions, such as hydride reductions, in the absence of palladium. In order to demonstrate this, the palladium-catalysed release of allylic amines from hydroxypolystyrene resin (**343**) was investigated (scheme 4.2).

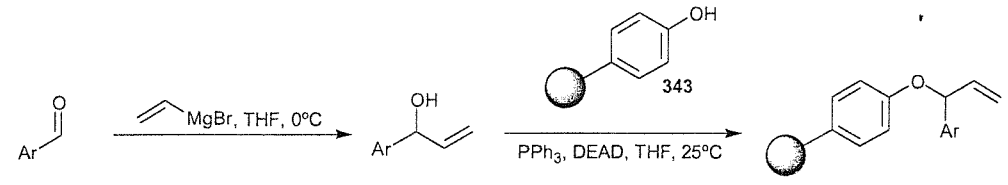
Scheme 4.2 The palladium-catalysed cleavage of a supported allylic phenyl ether linker **434**.



4.2 Preparation of the resin-bound allyl ether substrates

The approach chosen to obtain the allyl ethers **434a-d** employed a Mitsunobu coupling reaction to form the ether bond.[260-262] Allylic alcohols **440a-d** were prepared by treating the corresponding aldehydes **439a-d** with vinyl magnesium bromide in acceptable to good yield (41-82%) and subsequently coupled to the hydroxypolystyrene resin **(343)** under Mitsunobu conditions. The presence of the secondary allylic ether **434d** (scheme 4.3) was supported by signals at 138.4 (CH), 116.4 (CH_2) and 81.1 (CH) ppm in the gel-phase ^{13}C NMR spectrum.[260]

Scheme 4.3 Synthesis of immobilised allyl ethers **434a-d**.



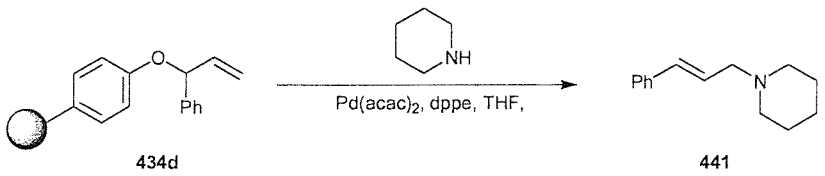
439a Ar = 3-pyridyl
439b Ar = *p*-Cl(C_6H_4)
439c Ar = 2-furyl
439d Ar = Ph

440a (41%)
440b (73%)
440c (78%)
440d (82%)

4.3 Optimisation of the palladium-catalysed cleavage reaction

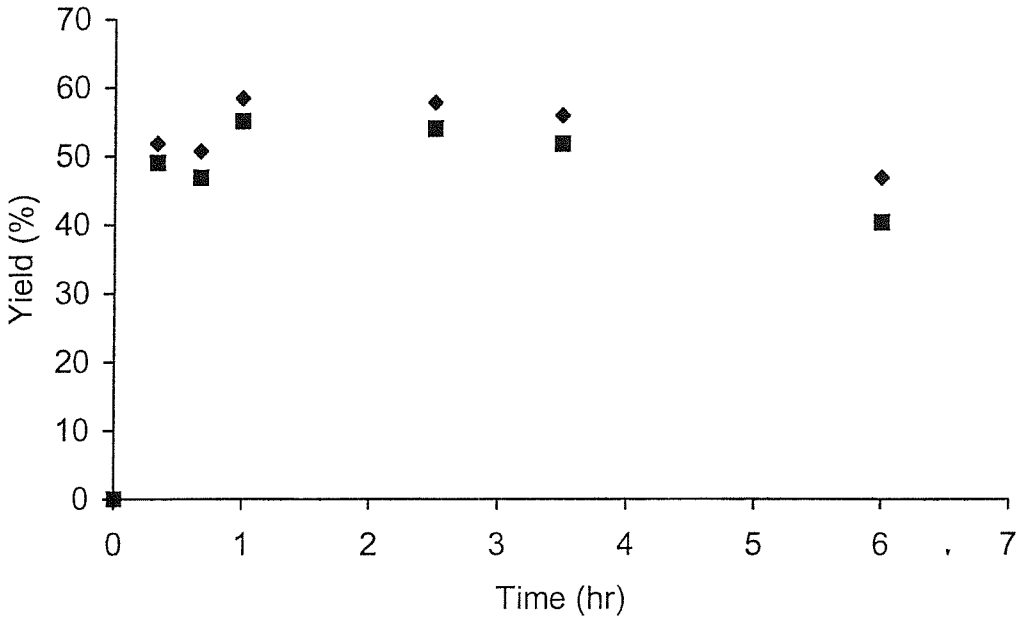
Nucleophilic cleavage of allyl ether **434d** was first investigated with piperidine in the presence of $Pd(acac)_2$ and dppe (scheme 4.4). In order to optimise the cleavage conditions the effect of changing various reaction parameters, including amount of catalyst (entries 1 to 5, table 4.1), reaction time (figure 4.1), amount of ligand (entries 6 to 9, table 4.1) and amount of piperidine (entries 10 to 15, table 4.1) was investigated.

Scheme 4.4 Nucleophilic cleavage of resin **434d** with piperidine.



434d 441

Figure 4.1 Effect of reaction time on the yield of the cleaved amine **441**.†



† Two experiments were run in parallel with the corresponding to the first experiment and the corresponding to the second. Both reactions were performed using 150 mg (~0.29 mmol) of starting resin **434d**, 5 mol% $Pd(acac)_2$, 10 mol% dppe and piperidine (5 equiv.) with respect to the loading of the initial resin **343**, assuming quantitative conversions for solid-phase reactions. Both reactions were carried out in THF (3 mL) and the reactions were monitored by GC using phenanthrene as an internal standard.

Monitoring of the release of product **441** over time by GC showed that prolonged reaction times (3 to 8 hours) at reflux led to slow degradation or subsequent reaction of the product (figure 4.1). In addition, all attempted reactions at room temperature failed to afford any cleaved material **441**. Key experiments included briefly heating the $Pd(acac)_2$ and dppe in an attempt to form the active catalytic species before addition of the remaining reagents at room temperature or simply mixing all the reagents together at room temperature.

Table 4.1 Effect of changing various reaction parameters on the yield of amine **441**.[a]

Entry	$Pd(acac)_2$ (mol%)[b]	Time (hr)	dppe (mol%)[b]	Piperidine (equiv.)[b]	Yield[c] (%)
1	**0**	12	0	5	0
2	**2**	12	6	5	45
3	**5**	12	15	5	48
4	**10**	12	30	5	51
5	**20**	12	60	5	53
6	5	1.5	**5**	5	65
7	5	1.5	**10**	5	70
8	5	1.5	**15**	5	71
9	5	1.5	**25**	5	0[d]
10	5	1.5	10	**1**	70[e]
11	5	1.5	10	**2**	69
12	5	1.5	10	**3**	66
13	5	1.5	10	**5**	65
14	5	1.5	10	**10**	66

[a] All reactions were carried out using 150 mg (~ 0.20 mmol) of starting resin **434d** in THF (3 mL).
[b] Yields and amounts of reagents are all based on the initial loading of the resin **343**, assuming quantitative conversions for solid-phase reactions.
[c] Reported yields were calculated by GC using phenanthrene as an internal standard. An error of ± 5% is associated with these results.
[d] This experiment was performed in duplicate to confirm the result.
[e] This corresponds to a yield of 52% after purification by column chromatography.

As expected the reaction did not proceed in the absence of $Pd(acac)_2$ and dppe (entry 1, table 4.1). This result is consistent with the initial observation that the allyl ether linkage should be stable under nucleophilic conditions. Interestingly, when 5 equivalents of dppe are used with respect to the palladium no catalytic activity is observed (entry 9, table 4.1). This result would suggest that such an excess of ligand causes all the palladium present to be coordinated by the dppe as an inactive species.

The most efficient conditions found (entry 10, table 2) were therefore adopted and a maximum yield (70% by GC, 52% isolated after flash chromatography) was achieved after 1 to 2 hours at reflux with 5 mol% $Pd(acac)_2$ and 10 mol% dppe. The amount of catalyst could be reduced further (2 mol%) with a modest decrease in the yield of **441**, (entry 2, table 4.1) although 5 mol% catalyst was routinely used. Efficient cleavage required only 1 equivalent of piperidine (entry 10, table 4.1) and resubmitting the recovered resin to the cleavage conditions failed to afford any additional amine **441**. Only a trace amount of the regioisomeric secondary amine **437** (figure 4.2) was present in the crude product (determined from the ^1H NMR spectrum).

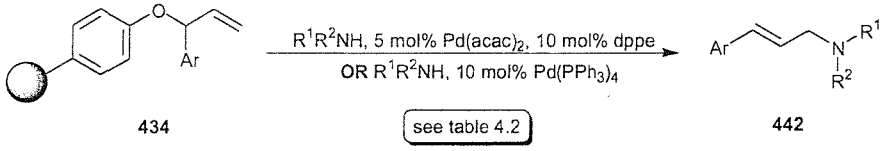
In addition no material appeared to be cleaved from resin **434d** when it was treated with a mixture of TFA and dichloromethane (1:1) for 30 minutes at room temperature (standard Boc-deprotection conditions). However, when the resin **434d** was exposed to acid (TFA) and then the palladium-catalysed cleavage conditions, in the presence of piperidine, no allylic amine **441** was produced (scheme 4.4). This suggested that the allylic phenyl ether linkage **434** may be incompatible with acidic conditions. Indeed, when protonated the phenolic resin **343** becomes a good leaving group and so perhaps this result is not unexpected.

4.4 Synthesis of further allylic amines using the palladium-catalysed release strategy

To investigate the scope of the palladium-catalysed nucleophilic cleavage process, the reactions of four different amines with four resin-bound allylic ethers were investigated. Allylic alcohols **440a-d** were immobilised on hydroxypolystyrene resin **(343)** as

described earlier, and the resulting resins **434a-d** were subjected to the cleavage conditions in the presence of different amines (scheme 4.5).

Scheme 4.5 Palladium-catalysed nucleophilic cleavage to give allylic amines **442** (table 4.2).



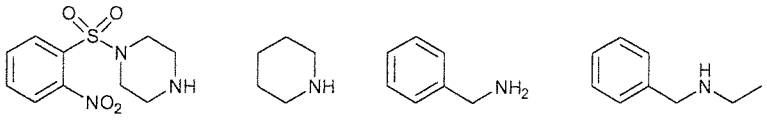
434 442

Table 4.2 Palladium-catalysed nucleophilic cleavage of allylic amines (scheme 4.5).[c]

Entry	Ar	Amine (figure 4.2)	Catalyst	Product	Yield (%)[a]
1	Ph	Piperidine	$Pd(acac)_2$/dppe	**441**	52
2	Ph	$BnNH_2$[b]	$Pd(PPh_3)_4$	**443**	76
3	Ph	EtNHBn	$Pd(acac)_2$/dppe	**444**	49
4	*p*-Cl(C_6H_4)	$BnNH_2$[b]	$Pd(acac)_2$/dppe	**445**	55
5	*p*-Cl(C_6H_4)	$BnNH_2$	$Pd(PPh_3)_4$	**445**	69
6	*p*-Cl(C_6H_4)	$BnNH_2$[b]	$Pd(PPh_3)_4$	**445**	76
7	*p*-Cl(C_6H_4)	Piperidine	$Pd(acac)_2$/dppe	**446**	72 (62)[e]
8	*p*-Cl(C_6H_4)	Piperidine	$Pd(PPh_3)_4$	**446**	77
9	*p*-Cl(C_6H_4)	EtNHBn	$Pd(acac)_2$/dppe	**447**	67
10	*p*-Cl(C_6H_4)	**454**	$Pd(acac)_2$/dppe	**448**	49
11	3-pyridyl	$BnNH_2$[b]	$Pd(PPh_3)_4$	**449**	30
12	3-pyridyl	Piperidine	$Pd(acac)_2$/dppe	**450**	53
13	3-pyridyl	EtNHBn	$Pd(acac)_2$/dppe	**451**	51
14	3-pyridyl	**454**[d]	$Pd(acac)_2$/dppe	**452**	61
15	2-furyl	**454**	$Pd(acac)_2$/dppe	**453**	Trace

[a] Isolated yield (see chapter **4.5**) of purified product based on the loading of the hydroxypolystyrene resin (**343**), assuming quantitative conversion for solid-phase reactions. An error of ± 5% is associated with these results.
[b] 4 Equivalents of benzylamine were used.
[c] All reactions were carried out using 150 mg (~ 0.20 mmol) of starting resin **434a-d** in THF (3 mL). 1 Equivalent of amine was used, unless otherwise stated, along with 5 mol% $Pd(acac)_2$, 10 mol% dppe or 10 mol% $Pd(PPh_3)_4$ based on the loading of the hydroxypolystyrene resin (**343**).
[d] 2 Equivalents of **454** were used.
[e] Duplicate reaction.

Figure 4.2 Amines used in the cleavage reaction (scheme 4.5 and table 4.2).



454

All reactions afforded the desired products in acceptable yield (30-77%) with the exception of that using the 2-furyl-substituted allylic ether as the substrate. For this unsuccessful reaction it is unclear whether the failure of the overall process originated in the initial immobilisation of **440c** or at the cleavage step as no conclusive analytical data could be obtained on resin **434c**.

A by-product **455**, arising from the attack by the acetylacetonate ligand, was observed in varying quantities (0-10%) in all reactions using $Pd(acac)_2$ (figure 4.3). This problem was avoided in later experiments by simply swapping the catalyst to $Pd(PPh_3)_4$ (entries 2, 5, 6, 8 and 11, table 4.2). In addition, if any regioisomeric secondary amine **437** (figure 4.2) was present in the crude cleaved material it was estimated to be present in trace amounts (<5%) by examination of the ^1H NMR spectra.

Figure 4.3 By-products obtained in palladium-catalysed cleavage reactions.

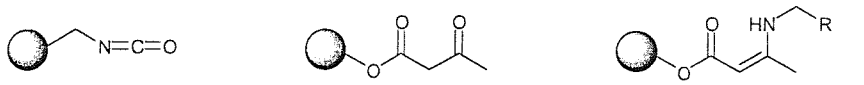
455 456

The intermolecular substitution reactions of allylic acetates with primary amines has been reported not to be a useful process due to the formation of by-products arising from diallylation and direct nucleophilic attack on the ester. In this case the latter side reaction was not an issue, although unsurprisingly, reactions using 1 equivalent of benzylamine in the solid-phase led to a certain amount (approx. 50% by inspection of the ^1H NMR spectrum) of diallylated material **456** (entry 5, figure 4.3). Formation of **456** was significantly reduced (<5% by inspection of the ^1H NMR spectrum), but not eliminated, by using 4 equivalents of the primary amine.

4.5 The use of scavenger resins to purify allylic amine products

Purification of the cleaved products **443** to **453** was required due to the presence of some unreacted primary and secondary amines in the crude products. Excess unreacted starting amines were therefore removed using scavenger resins (figure 4.4).[263-270] Once the excess starting amines had been removed column chromatography was used in order to remove the catalyst and ligand residues.

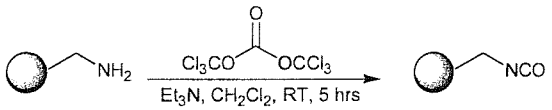
Figure 4.4 Isocyanate **457** and acetoacetoxy **458** scavenger resins.



Isocyanate resin **457** AAEM resin **458** Immobilised primary amine **459**

Secondary amines were conveniently scavenged from the reaction mixtures containing tertiary amine products using the isocyanate resin **457**.[265,266,269] The latter was easily prepared by reacting triphosgene and triethylamine with aminomethyl polystyrene **(460)** (1.3 mmol/g) at room temperature (scheme 4.6).[266] The infrared spectrum of the resin-bound isocyanate **457** included a strong carbonyl absorption at 2263 cm^{-1}.

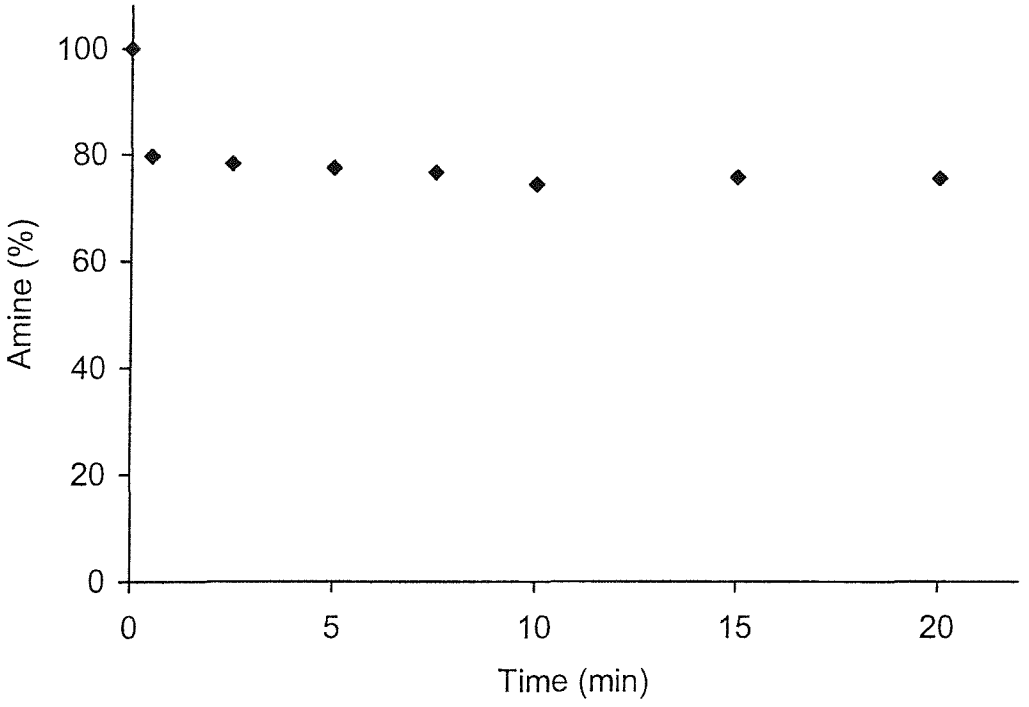
Scheme 4.6 Synthesis of isocyanate resin **457**.



460 **457**

In order to gain an insight into the rate at which the isocyanate resin **457** is capable of scavenging secondary amines a sample of the resin **457** was exposed to an excess of EtNHBn and the loss of amine monitored by GC over time (figure 4.5). The results indicated that after 5 minutes all the potential scavenger sites had been used. Furthermore, since the amount of scavenged EtNHBn was known, the loading of the isocyanate resin **457** was calculated as being 1.08 mmol/g.

Figure 4.5 Removal of EtNHBn by isocyanate resin **457**.[†]

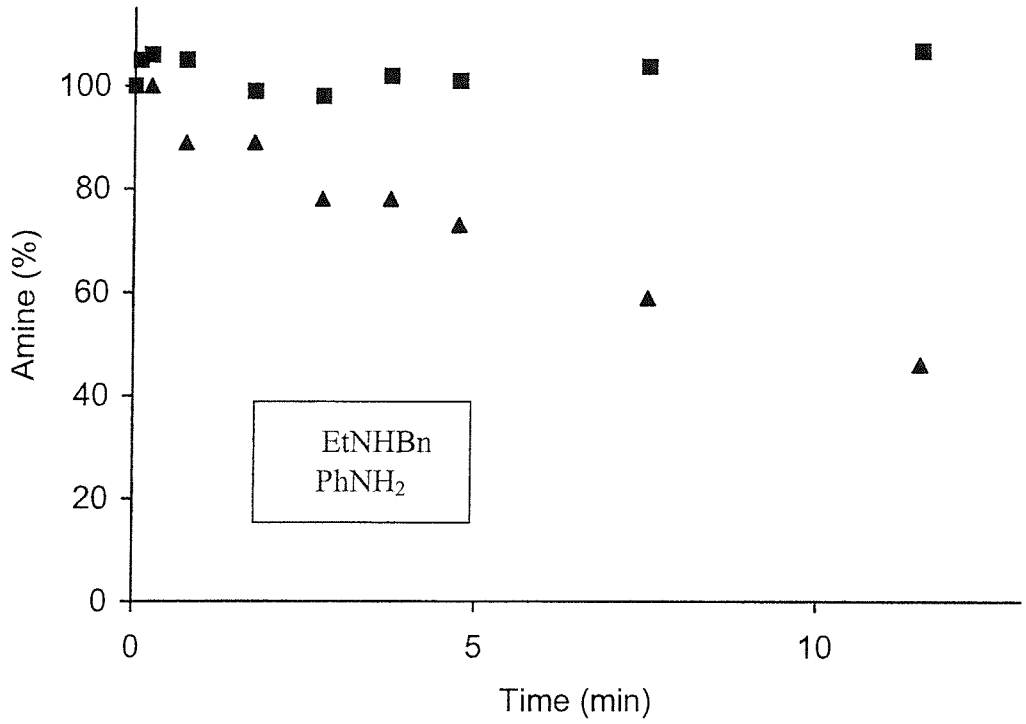


[†] 150 mg of scavenger resin **457** (~0.16 mmol) was added to a solution of EtNHBn (0.65 mmol) in CH_2Cl_2 (3 mL) and the loss of EtNHBn monitored over time by GC using naphthalene as an internal standard (see figure 4.1).

Primary amines were conveniently scavenged from those reaction mixtures containing secondary amine products using acetoacetoxy ethyl methacrylate (AAEM) resin **458** (figure 4.4).[263,264] In this case the primary amine is immobilised onto the solid-support as the corresponding enamine **459** (figure 4.4).

Commercially available AAEM resin **458**, with a loading of 3.0 mmol/g (available from Avecia Ltd.), was subjected to an equimolar mixture of EtNHBn and benzylamine and the loss of each amine monitored by GC over time (figure 4.6). The results indicated that after 10 minutes, at room temperature in THF, approximately 60% of the benzylamine had been removed by the AAEM resin **458** from the mixture, whilst no loss of EtNHBn could be detected. These results were consistent with the observations made by Bradley *et al.*[263,264]

Figure 4.6 Selective removal of benzylamine by AAEM resin **458** in the presence of EtNHBn.[†]



[†] 330 mg of scavenger resin **458** (~1.0 mmol) was added to a solution of EtNHBn (0.5 mmol) and $BnNH_2$ (0.5 mmol) in THF (3 mL) at room temperature and the loss of each amine monitored over time by GC using naphthalene as an internal standard (see figure 4.1).

4.6 Conclusion

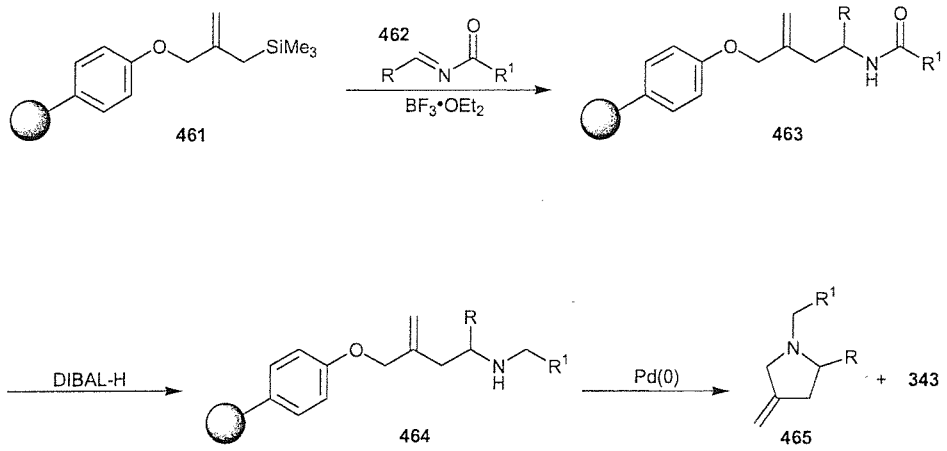
In summary, a facile synthesis of immobilised allylic phenyl ethers **434a-d** has been described (scheme 4.3). This involves the reaction of aldehydes **439a-d** with vinyl magnesium bromide and the attachment of the resulting allylic alcohols **440a-d** to the solid-support *via* a Mitsunobu reaction. In addition, the viability of a palladium-catalysed nucleophilic release reaction has been demonstrated by the solid-phase synthesis of various allylic amines **441** and **443** to **453** in moderate to excellent yields (table 4.2).[271]

During this process extensive optimisation of the cleavage reaction conditions was carried out, which included changing the catalyst from $Pd(acac)_2$ to $Pd(PPh_3)_4$ in order to avoid the acetylacetonate ligand by-product **455** (figure 4.3). The allylic phenyl ethers **434a-d** are resistant to a variety of basic and nucleophilic conditions until activated with

catalytic palladium. However, it would appear that the allylic ether linkage is not stable to acidic conditions.

A synthesis of 4-methylenepyrrolidines **465** (chapter 3), using the allylic ether linker, is proposed so as to investigate the stability of the linkage further (scheme 4.7). In this proposed synthesis the key amide intermediate **463** requires reduction, which it was thought could be effected by DIBAL-H.

Scheme 4.7 Proposed route to 4-methylenepyrrolidines involving the reduction of amide **463**.



The allylic amine structural motif is present in a large number of biologically active molecules, and the methodology described may present a means of preparing arrays of allylic amines for screening.[272-276] Future studies would focus on the elaboration of the resin-bound allylic ethers **434** and cleavage in the presence of other nucleophiles.[212]

Furthermore, it has been demonstrated how the use of selective scavenger resins can be used to remove excess starting amines in order to assist in the purification of the crude material cleaved from the resin.

5. Experimental

General methods

All reactions requiring anhydrous conditions were performed in dry glassware under an atmosphere of nitrogen or argon. Dichloromethane, 1,2-dichloroethane, DMF, triethylamine were distilled over calcium hydride. Tetrahydrofuran was distilled over sodium wire and benzophenone. All reagents were purchased from Sigma Aldrich, Fisher, Novabiochem or Lancaster and used as such.

Column flash chromatography was carried out using Merck 60 Mesh silica. Column dimensions are reported as width by height of silica.

IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument, a Bio-Rad FTS 135 instrument using a Golden Gate adaptor or a Nicolet Impact 400 instrument using a Thunderdome adaptor. Absorptions are described as strong (s), medium (m), weak (w) or broad (br).

UV studies were carried out on a Perkin-Elmer Lambda 2 UV/VIS spectrophotometer or a Hewlett-Packard 8452A diode array spectrophotometer.

^{1}H- and ^{13}C-NMR spectra were recorded as $CDCl_3$ solutions on a JEOL GX270, a Bruker AC300, a Bruker AM300 or a Bruker DPX400 spectrometer. Chemical shifts are reported in δ units using $CHCl_3$ as an internal standard. Coupling constants (*J*) are reported in Hertz. HR-MAS ^{1}H-NMR spectra were recorded using the Bruker DPX400 spectrometer (CPMG pulse sequence) fitted with a 4mm MAS probehead and TMS was used as an internal standard.[277]

Low resolution mass spectra were obtained on a Fisons VG platform single quadrupole mass spectrometer in electron spray ionisation mode. The relative intensity of peaks is reported in parentheses.

Microanalyses were obtained from University College, London or MEDAC Ltd., Egham.

Melting points were measured on a Gallenkamp electrothermal melting point apparatus.

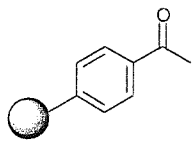
GC analysis was carried out using a Varian 3800 fitted with a 30 m x 0.25 mm DB120 fused silica column and connected to a Hewlett Packard 3396 Series II integrator. Both the injector and detector temperatures were set at 220°C.

Naming of compounds according to the IUPAC rules was assisted by the ACD/Name software version 2.52 (January 1997) designed by Advanced Chemistry Development Inc., Canada. In the naming of solid-supported materials 'polystyryl' and 'polystyrene' refers to a copolymer of styrene and 2% divinylbenzene.

All loadings of resins and equivalents of reagents in solid-phase reactions are calculated from the measured loading of the hydroxypolystyrene resin **(343)** or carboxyethylated polystyrene resin **(365)** as appropriate.

5.1 Resin preparation and loading

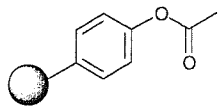
Acetyl polystyrene (353)



Acetyl chloride (11.5 mL, 12.6 g, 160 mmol) was added dropwise to a suspension of polystyrene resin (1% DVB cross-linked, 20.6 g) and finely ground $AlCl_3$ (21.5 g, 160 mmol) in carbon disulfide (200 mL) at 0°C under a nitrogen atmosphere. The suspension was heated at reflux for 5.5 hours. The resin was allowed to cool to room temperature, collected by filtration and washed with dichloromethane, water (CAUTION! Vigourous reaction with the residual $AlCl_3$), aqueous HCl (2N), water, DMF, MeOH and dichloromethane (500 mL of each). Drying the resin under vacuum (50°C) for 2 hours afforded the desired product **353** as a yellow solid (21.78 g).

IR (on-bead) υ_{max} : 1679s (C=O), 1605m, 1415w, 1360m, 1268s, 957w cm^{-1}.
^{1}H-MAS NMR δ : 2.55 (br s, -$COCH_3$).

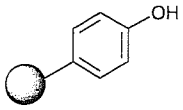
Polystyryl acetate (354)



*m*CPBA (70.0 g, ~ 0.22 mol) was added to a suspension of resin **353** (21.18 g) in dichloromethane (200 mL) at room temperature and stirred for 1 day. The resin was collected by filtration, washed with dichloromethane, MeOH, water, MeOH, dichloromethane (200 mL of each) and dried under vacuum (50°C) for 2 hours to give the desired product **354** as a pale yellow solid (21.77 g).

IR (on-bead) υ_{max} : 1759s (C=O), 1505m, 1368m, 1194s, 1166s cm^{-1}.
^{1}H-MAS NMR δ : 2.28 (br s, -O_2CCH_3).

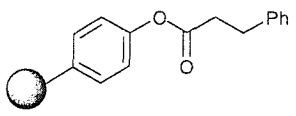
Hydroxypolystyrene resin (343)



Dichloromethane (160 mL) and MeOH (60 mL) were added to a mixture of the resin-bound acetate **354** (18.0 g) and TMSOK (13.2 g, 0.10 mol) at room temperature under a nitrogen atmosphere. The suspension turned brown and was stirred overnight. The resin was collected by filtration, washed with dichloromethane, MeOH, water, aqueous HCl (2N), water, MeOH, dichloromethane (200 mL of each) and dried under vacuum (50°C) for 2 hours. This afforded the desired product **343** as a beige solid (15.48 g, 1.89 - 2.06 mmol/g).

IR (on-bead) υ_{max} : 1600m, 1511s, 1455m, 1238s, 1171m, 830s cm^{-1}.

Polystyryl 3-phenylpropionate (356)



Hydroxypolystyrene resin **(343)** (500 mg) was suspended in dichloromethane (6 mL) under a nitrogen atmosphere. DMAP (12 mg, 0.1 mmol) and triethylamine (730 μL, 5.1 mmol) were added and the reaction cooled to 0°C (ice-bath). The acid chloride (843 mg, 5.0 mmol) was added dropwise. After 10 minutes the ice-bath was removed and the reaction stirred at room temperature overnight. The resin was collected by filtration, washed with dichloromethane, MeOH, water, DMF, MeOH, dichloromethane (100 mL of each) and dried under vacuum (50°C) for 2 hours. The isolated resin was subjected to the same conditions a second time. This afforded the title product **356** as a beige solid (704 mg).

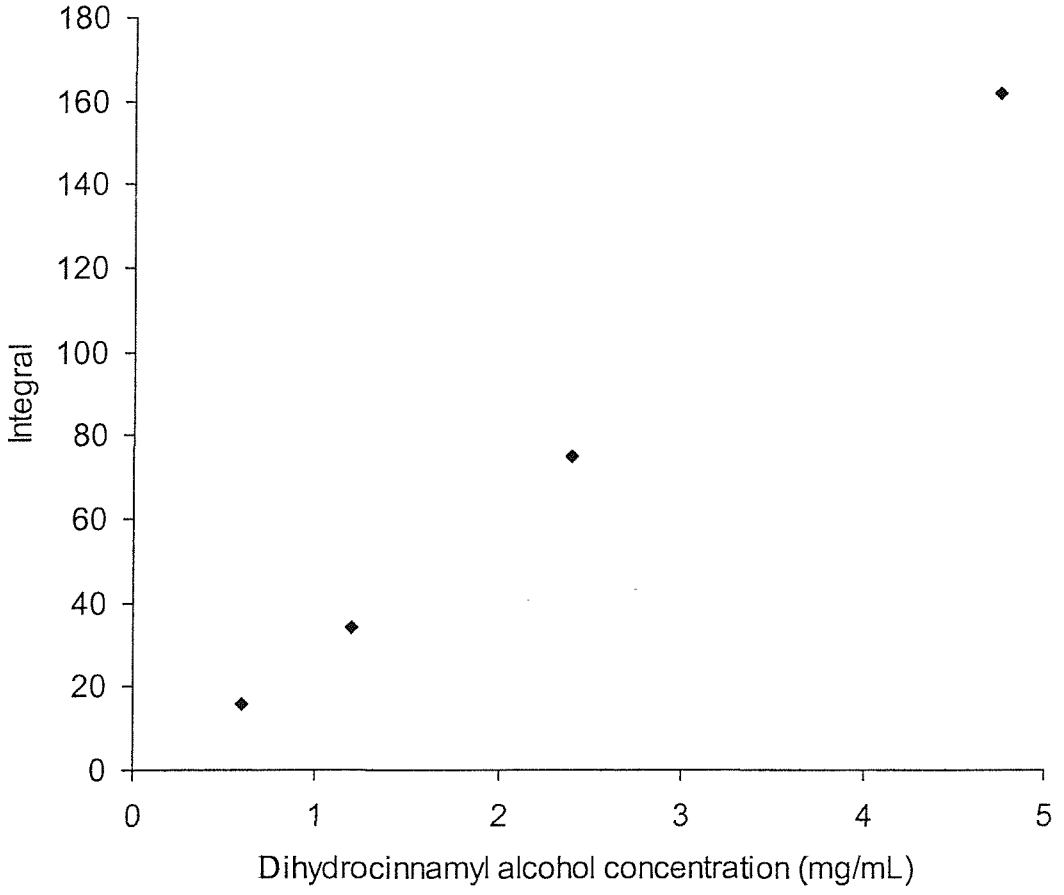
IR (on-bead) υ_{max} : 1755s (C=O), 1504m, 1454w, 1201s, 1166s, 1130s, 1077w, 1017w, 841m, 744s cm^{-1}.
^{1}H-MAS NMR δ : 3.05 (br s, $-O_2CCH_2CH_2Ph$), 2.88 (br s, $-O_2CCH_2CH_2Ph$).

Loading determination of hydroxypolystyrene (343) *via* cleavage and quantification of dihydrocinnamyl alcohol

The resin **356** (201.0 mg) was suspended in THF (3 mL), under a nitrogen atmosphere, at 0°C (ice-bath). A solution of $LiBH_4$ (2M in THF, 1.0 mL, 2.0 mmol) was added dropwise, followed by methanol (80 μL, 2.0 mmol). The ice-bath was removed and the reaction allowed to warm to room temperature and stirred overnight. The resin was collected by filtration, washed with MeOH (30 mL) and dichloromethane (30 mL) and dried under vacuum (50°C) for 2 hours. The filtrate solvent was removed under vacuum and the residue dissolved in dichloromethane (12 mL). This was washed with saturated aqueous $NaHCO_3$ solution (2 x 8 mL), brine (10 mL) and dried ($MgSO_4$). The sample was diluted to 50 mL with MeOH and analysed by GC. This was compared to the calibration curve obtained using authentic samples of known concentration (Figure 5.1).

Dihydrocinnamyl alcohol has a retention time of 2.74 min at a column temperature of 150°C.

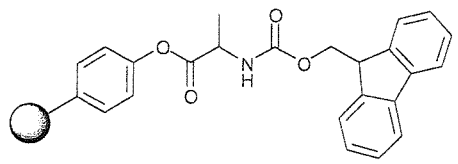
Figure 5.1 Calibration curve used to quantify dihydrocinnamyl alcohol.



For the cleaved sample an integral of 27.2 was obtained, which corresponds to a dihydrocinnamyl alcohol concentration of 0.87 mg/mL.

- ⇨ 43.5 mg of dihydrocinnamyl alcohol was cleaved from the sample of resin **356**.
- ⇨ (201.0 – 43.5)mg of resin **353** contains 0.32 mmol of functional sites,
- ⇨ Loading of resin **353** is 2.06 mmol/g.

Polystyryl 2-{[(9*H*-9-fluorenylmethoxy)carbonyl]amino}propanoate (358)



Dichloromethane (3 mL) was added to a mixture of the resin **343** (100 mg), DIC (76 mg, 0.6 mmol), DMAP (73 mg, 0.6 mmol) and FmocAlaOH (202 mg, 0.65 mmol), under a nitrogen atmosphere, at room temperature. The reaction was stirred overnight, the resin collected by filtration and washed with dichloromethane, methanol, DMF, methanol and dichloromethane (30 mL of each). The resin was subjected to the same coupling conditions a second time and then dried under vacuum (50°C) for 2 hours to give the desired product **358** as an orange solid (108 mg).

IR (on-bead) υ_{max} : 1731s br (C=O), 1651m, 1603m, 1506s, 1450m, 1170s, 1074m, 836s, 820s, 744s cm^{-1}.

Loading of hydroxypolystyrene (343) *via* an Fmoc-assay[190-193 194]

A sample of resin **358** of known mass (5.9 mg) was shaken in a 20 % solution of piperidine in DMF (10 mL) for 30 minutes. The suspension was diluted to a volume of 20 mL with the latter and the absorbance recorded at 300 nm according to the literature method.

Recorded absorbance = 2.74

⇨ Amount of Fmoc present on 1.0 g resin = $\frac{2.74 \times \text{volume (mL)} \times 1000}{\text{Resin mass (mg)} \times 7800 \text{ (mL/mmol)}}$

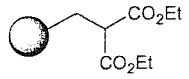
⇨ $= \frac{2.74 \times 20 \times 1000}{5.9 \times 7800}$ mmol

⇨ = 1.19 mmol

⇨ Loading of resin **358** = 1.19 mmol/g

⇨ Loading of resin **353** = 1.89 mmol/g

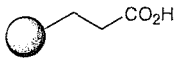
Diethyl-2-polystyrylmethylmalonate (364)



Diethylmalonate (5.29 g, 5.0 mL, 33.0 mmol) was added dropwise, over 20 minutes, to a suspension of sodium hydride (60 % dispersion in mineral oil, 33.0 mmol, 1.33 g) in DMF (35 mL). After hydrogen evolution ceased Merrifield resin (~1 meq Cl/g, 2% cross-linked with DVB, 5.0 g) was added and the reaction heated at 60°C for 14 hours. The reaction was cooled to room temperature and the resin collected by filtration, washed with dichloromethane, methanol, water, methanol and dichloromethane (2 x 20 mL each) and dried under vacuum for 2 hours (50°C). This afforded the title product **364** as a white solid (5.04 g).

IR (on-bead) υ_{max} : 3025w, 2979w, 2920m, 1726s (C=O), 1601w, 1491w, 1449m, 1366m, 1332m, 1146s, 1030s, 854m, 757m cm^{-1}.
^{1}H-MAS NMR δ : 4.10 (br s, -$CO_2CH_2CH_3$), 3.60 (br s, -CH), 1.17 (br s, -$CO_2CH_2CH_3$).

Carboxyethylated polystyrene resin (365)

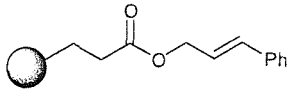


A suspension of the functionalised polystyrene **364** (1.0 g, ~1.0 mmol) in THF (20 mL) and aqueous potassium hydroxide (2M, 2.0 mL) was heated at reflux for 15 hours. The reaction was allowed to cool to room temperature and the resin was collected by filtration and washed with water, methanol, ether and dichloromethane (2 x 20 mL each). The resin was suspended in THF (20 mL) and aqueous hydrochloric acid (2M, 2.0 mL) was added. The reaction was heated at reflux for 2.5 hours. After cooling to room temperature the resin was collected by filtration, washed with water, methanol, ether and

dichloromethane (2 x 20 mL each) and dried under vacuum for 2 hours (50°C). This afforded the title product **365** as a white solid (0.95 g, 0.71 - 0.84 mmol/g).

IR (on-bead) υ_{max} : 3023w, 2919m, 1708s (C=O), 1600m, 1491m, 1448m, 1366m, 1281m, 1181s, 847m, 750s cm^{-1}.

1-Phenyl-1-propenyl 3-polystyrylpropanoate (371)



The carboxyethylated resin **365** (6.00 g) was suspended in dichloromethane (85 mL). DMAP (2.62 g, 21.4 mmol), DIC (3.87 mL, 3.12 g, 24.2 mmol) and cinnamyl alcohol (3.24 g, 24.2 mmol) were added and the reaction stirred at room temperature for 12 hours. The resin was collected by filtration, washed with dichloromethane, methanol, dichloromethane (250 mL of each) and dried under vacuum (50°C) for 2 hours. The resin was subjected to the same coupling conditions a second time to give the desired product **371** as a white solid (6.48 g)

IR (on-bead) υ_{max} : 3026m, 2921m, 1729s (C=O), 1604m, 1489m, 1444m, 1163s, 978s cm^{-1}.

Loading determination of carboxyethylated polystyrene (365) *via* cleavage and quantification of cinnamyl alcohol

The resin **371** (225.2 mg) was suspended in dichloromethane (2 mL). Methanol (0.5 mL) and TMSOK (60 mg, 0.5 mmol) were added and the reaction stirred overnight. The resin was collected by filtration, washed with dichloromethane (200 mL) and MeOH (80 mL) and dried under vacuum (50°C) for 2 hours. The filtrate was concentrated to a volume of approximately 30 mL under vacuum, naphthalene (15.4 mg) was added and the sample analysed by GC in order to quantify the cleaved cinnamyl alcohol. Cinnamyl alcohol has a retention time of 3.94 min and naphthalene of 2.11 min at a column temperature of 150°C.

A sample containing a known mass of naphthalene (30.7 mg) and cinnamyl alcohol (41.5 mg) was analysed and integrals of 25.8 and 23.4 obtained respectively. The constant (X) reflects the detector's response where,

$$\frac{\text{Integral (Cinnamyl alcohol)}}{\text{Integral (Naphthalene)}} = \frac{\text{X Mass (Cinnamyl alcohol)}}{\text{Mass (Naphthalene)}}$$

Therefore X = 1.49

Considering the unknown sample,

$$\text{Mass (Cinnamyl alcohol)} = \frac{\text{X Mass (Naphthalene) x Integral (Naphthalene)}}{\text{Integral (Cinnamyl alcohol)}}$$

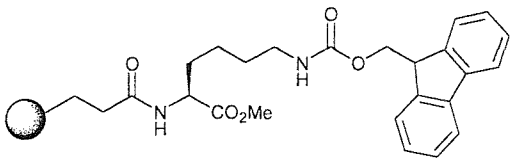
GC analysis of this sample gave integrals of 18.2 for both naphthalene and cinnamyl alcohol,

$$\text{Mass (Cinnamyl alcohol)} = \frac{1.49 \times 15.4 \text{ mg} \times 18.2}{18.2}$$

Mass (Cinnamyl alcohol) = 22.9 mg

This was cleaved from resin **371** (225.2 mg), which corresponds to a loading of 0.84 mmol/g for the carboxyethylated polystyrene resin **(365)**.

Methyl 6-{[(9*H*-9-fluorenylmethoxy)carbonyl]amino}-2-[(3-polystyrylpropanoyl) amino]hexanoate (372)



The carboxy resin **365** (100 mg) was added to a solution of DIC (38 mg, 0.3 mmol) and HOBt (41 mg, 0.3 mmol) in dichloromethane (1.0 mL) and stirred for 30 minutes. A solution of H-Lys(Fmoc)-OMe.HCl (130 mg, 0.34 mmol) in NMP (1.0 mL) and *N*,*N*-diisopropylethylamine (52 μL, 0.3 mmol) was added and the reaction stirred overnight. The resin was collected by filtration and washed with dichloromethane, DMF, dichloromethane, methanol and dichloromethane (15 mL each) and dried under vacuum for 2 hours (50°C). This afforded the title product **372** as a yellow solid (117 mg).

IR (on-bead) υ_{max} : 3027w, 2927m, 1725s (C=O), 1680s (C=O), 1605m, 1515s, 1495s, 1450s cm^{-1}.

Loading of carboxyethylated polystyrene resin (365) *via* an Fmoc-assay [190-193 194]

A sample of resin **372** of known mass (7.9 mg) was shaken in a 20 % solution of piperidine in DMF (10 mL) for 30 minutes. The suspension was diluted to a volume of 25 mL with the latter and the absorbance recorded at 300 nm according to the literature method.

Recorded absorbance = 1.34

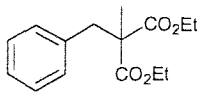
⇨ Amount of Fmoc present on 1.0 g resin = $\frac{1.34 \times \text{volume (mL)} \times 1000}{\text{Resin mass (mg)} \times 7800 \text{ (mL/mmol)}}$

⇨ $= \frac{1.34 \times 25 \times 1000}{7.9 \times 7800}$ mmol

⇨ = 0.54 mmol

⇨ Loading of resin **365** = 0.71 mmol/g

Diethyl-2-benzyl-2-methylmalonate (368)[204,206]

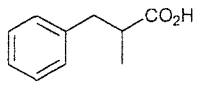


$C_{15}H_{20}O_4$ (mw: 264.32 g/mol)

Diethylmethylmalonate (6.80 mL, 6.88 g, 39.5 mmol) was added dropwise, over 20 minutes, to a suspension of sodium hydride (1.74 g, 43.5 mmol, 60 % dispersion in mineral oil) in dry DMF (40 mL). When the addition was completed, and hydrogen evolution ceased, benzyl chloride (4.55 mL, 5.00 g, 39.5 mmol) was added and the solution stirred at 55°C overnight. Upon cooling to room temperature the reaction was quenched with water (20 mL) and extracted with ether (3 x 30 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum gave the known title compound **368** as a colourless oil (8.52 g, 32.4 mmol, 82 %). No further purification was required and the spectroscopic details were consistent with those in the literature.[204,206]

CAS Number: [55114-30-2].
IR (film) υ_{max} : 2982s, 1731s, 1605s, 1584w, 1496w cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$) δ : 7.30-7.11 (5H, m, C**H** aromatic), 4.20 (4H, q, J = 7.2 Hz, -$CH_2$$CH_3$), 3.23 (2H, s, Ph$CH_2$-), 1.34 (3H, s, -$CH_3$), 1.27 (6H, t, J = 7.2 Hz, -$CH_2$$CH_3$).
^{13}C NMR (68 MHz, $CDCl_3$) δ : 172.09 (-CO_2-), 136.39 (**C** aromatic), 130.36, 128.30 & 127.02 (**C**H aromatic), 61.43 (-$CO_2$$CH_2$$CH_3$), 54.97 (Ph$CH_2$**C**-), 41.26 (Ph$CH_2$-), 19.87 (-$CH_3$), 14.16 (-$CH_2$$CH_3$).
MS (CI) *m/z* (rel. intensity): 265 (44[M+H]$^+$), 218 (27), 190 (100), 173 (26), 145 (45), 117 (31), 91 (83).

2-Methyl-3-phenylpropionic acid (369)[206]



$C_{10}H_{12}O_2$ (mw: 164.20 g/mol)

Diethyl-2-benzyl-2-methylmalonate **(368)** (9.15 g, 34.8 mmol) was added dropwise to a refluxing solution of potassium hydroxide (16.65 g, 0.30 mol) in water (100 mL). The mixture was heated a reflux for 3 hours, diluted with water (75 mL) and the reaction volume reduced by half under vacuum. This was heated at reflux for a further 2 hours, diluted with water (50 mL) and the reaction volume reduced, under vacuum, to approximately 35 mL. The resulting solution was acidified with conc. H_2SO_4 (20 mL) and heated at reflux for 55 hours. After cooling to room temperature the aqueous solution was extracted with ether (5 x 50 mL) and the combined organic layers washed with brine (25 mL), dried ($MgSO_4$) and concentrated under vacuum to afford the known title compound **369** as a straw coloured liquid (4.64 g, 28.3 mmol, 81 %). No further purification was required and the spectroscopic details were consistent with those in the literature.[205,206,209]

CAS Number: [1009-67-2].

IR (film) υ_{max} : 3028s, 2937s, 2658m, 1703s, 1603w, 1495m, 1453m, 745w, 700s cm^{-1}.

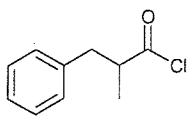
^{1}H NMR (270 MHz, $CDCl_3$) δ : 7.33-7.16 (5H, m, C**H** aromatic), 3.08 (1H, dd, *J* = 12.6 Hz, 7.2 Hz, PhCH**H**-), 2.84-2.63 (2H, m, -C**H**CH_3 & PhC**H**H-), 1.18 (3H, d, *J* = 6.3 Hz, -CH_3).

^{13}C NMR (68 MHz, $CDCl_3$) δ : 182.58 (-**C**O_2H), 139.00 (**C** aromatic), 128.98, 128.39 & 126.40 (**C**H aromatic), 41.22 (PhCH_2**C**H-), 39.26 (Ph**C**H_2-), 16.43 (-**C**H_3).

MS (CI) *m/z* (rel. intensity): 163 (22$[M-H]^+$), 145 (13), 107 (23), 91 (100).

4.2 The solid-phase synthesis of 4-methylene pyrrolidines using a cyclisation-cleavage strategy

2-Methyl-3-phenylpropanoyl chloride (383)[209]

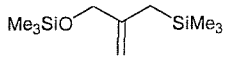


$C_{10}H_{11}OCl$ (mw: 182.65 g/mol)

Thionyl chloride (3.10 mL, 5.06 g, 42.5 mmol) was added to a solution of 2-methyl-3-phenylpropionic acid **(369)** (4.65 g, 28.3 mmol) in dichloroethane (30 mL). The resulting solution was heated at reflux for 17 hours and the solvent removed under vacuum to give a yellow residue. This was distilled at reduced pressure (1 mmHg, b.p. 39-43°C) to afford the known title compound **383** as a colourless liquid (4.01 g, 21.9 mmol, 78 %). The spectroscopic details were consistent with those in the literature.[209]

CAS Number: [38385-67-0].
IR (film) υ_{max} : 3062m, 3027s, 2978s, 2934s, 1783s, 1602m, 1495s, 1452s, 1377m, 937s, 882s, 853s cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$) δ : 7.36-7.17 (5H, m, C**H** aromatic), 3.24-3.09 (2H, m, PhC**HH**-), 2.82-2.71 (1H, m, $PhCH_2C\mathbf{H}$-), 1.29 (3H, d, J = 6.2 Hz, -$C\mathbf{H}_3$).
^{13}C NMR (68 MHz, $CDCl_3$) δ : 177.15 (-**C**OCl), 137.72 (**C** aromatic), 129.18, 128.80 & 127.06 (**C**H aromatic), 53.40 ($PhCH_2\mathbf{C}H$-), 39.38 ($Ph\mathbf{C}H_2$-), 16.77 (-$C\mathbf{H}_3$).
b.p.: 39-43 °C (1 mmHg).

1,1,1-Trimethylsilyl{2-[(1,1,1-trimethylsilyl)methyl]}allyl ether (388)[226]



$C_{10}H_{24}OSi_2$ (mw: 216.47 g/mol)

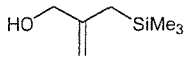
The reaction vessel was charged with *n*-butyllithium (2.18 M in hexane, 84.0 mL, 183.0 mmol), which was concentrated under vacuum to give a thick oil. The system was charged with nitrogen and the *n*-butyllithium cooled to 4°C (ice-bath). Anhydrous ether (85 mL) and tetramethylethylenediamine (27 mL) were added and the reaction stirred for 5 minutes. Dropwise addition of 2-methyl-2-propen-1-ol **(386)** (5.80 mL, 4.98 g, 69.0 mmol) resulted in a vigorous reaction and the lithium alkoxide was produced as a white precipitate. Anhydrous THF (60 mL) was added to give a slightly cloudy yellow solution, which was allowed to warm to room temperature over 3 hours. The reaction was stirred at room temperature for a further 37 hours to afford the dianion as a red gum. This was cooled to –55°C (dry-ice/ethanol bath) and stirred for 15 minutes. Trimethylsilyl chloride (39.0 mL, 33.6 g, 309.0 mmol) was added in one portion causing

the solution to turn milky white. After 5 minutes the reaction was allowed to warm to room temperature and stirred for a further 15 minutes.

The mixture was added to ether (500 mL) and saturated aqueous $NaHCO_3$ solution (300 mL) was cautiously added. The two layers were separated and the aqueous layer was washed with ether (2 x 200 mL). The combined organic layers were washed with water (250 mL), saturated aqueous $CuSO_4$ solution (2 x 200 mL), water (150 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was removed under vacuum to give the crude product as an orange oil (13.10 g). Purification by distillation (6 mmHg, b.p. 66-71°C) afforded the known title compound **388** as a colourless liquid (6.35 g, 29.3 mmol, 42 %). The spectroscopic details were consistent with those in the literature.[226]

CAS Number: [83378-96-5].
IR (film) υ_{max} : 2955s, 1646m, 1640m, 1249s, 1052m, 880-839s cm^{-1}.
^{1}H NMR (100 MHz, $CDCl_3$) δ : 4.92-4.90 (1H, m, >C=CH**H**), 4.68-4.67 (1H, m, >C=C**H**H), 3.98 (2H, s, -C**H$_2$**OTMS), 1.53 (2H, br s, -C**H$_2$**TMS), 0.15 (9H, s, -CH$_2$O**TMS**), 0.03 (9H, s, -CH$_2$**TMS**).
^{13}C NMR (75 MHz, $CDCl_3$) δ : 147.01 (>**C**=CH$_2$), 106.76 (>C=**C**H$_2$), 67.14 (-**C**H$_2$OTMS), 23.40 (-**C**H$_2$TMS), 1.49 (-O**TMS**), -1.21 (-CH$_2$**TMS**).
b.p.: 66-71°C (6 mmHg).

2-[(1,1,1-Trimethylsilyl)methyl]-2-propen-1-ol (384)[226]



$C_7H_{16}OSi$ (mw: 144.29 g/mol)

Aqueous sulphuric acid (1M, 15.0 mL) was added to a solution of 1,1,1-trimethylsilyl{2-[(1,1,1-trimethylsilyl)methyl]}allyl ether **(388)** (6.33 g, 29.0 mmol) in THF (50 mL). The mixture was stirred vigorously for 1.5 hours at room temperature after which K_2CO_3 was added until effervescence ceased. The two layers were separated and the aqueous layer was extracted with ether (2 x 30 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum gave the crude product (4.63 g) as a colourless liquid. Purification by

distillation (10 mmHg, b.p. 73-78°C) afforded the known title compound **384** as a colourless liquid (3.06 g, 21.2 mmol, 73 %). The spectroscopic details were consistent with those in the literature.[226,227]

CAS Number: [81302-80-9].

IR (film) υ_{max} : 3600-3100s, 2954s, 1645s, 1249s, 1051s, 890-830s cm^{-1}.

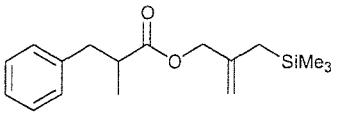
^{1}H NMR (100 MHz, $CDCl_3$) δ : 4.91-4.89 (1H, m, >C=C**H**H), 4.67-4.66 (1H, m, >C=CH**H**), 3.98 (2H, s, -C**H$_2$**OH), 1.86 (1H, br s, CH$_2$O**H**), 1.53 (2H, s, -C**H$_2$**TMS), 0.03 (9H, s, CH$_2$**TMS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ : 147.01 (>**C**=CH$_2$), 106.75 (>C=**C**H$_2$), 67.14 (-**C**H$_2$OH), 23.39 (-**C**H$_2$TMS), -1.21 (-CH$_2$**TMS**).

MS (CI) *m/z* (rel. intensity): 144 (6[M]$^+$), 129 (49), 73(100[TMS]$^+$).

b.p.: 73-78°C (10 mmHg).

2-[(1,1,1-Trimethylsilyl)methyl]allyl 2-methyl-3-phenylpropanoate (385)



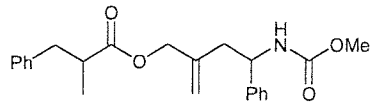
$C_{17}H_{26}O_2Si$ (mw: 290.48 g/mol)

2-[(1,1,1-Trimethylsilyl)methyl]-2-propen-1-ol **(384)** (1.44 g, 10.0 mmol) was dissolved in dichloromethane (25 mL) and cooled to 4°C (ice-bath). Pyridine (890 μL, 11.0 mmol) was added followed by 2-methyl-3-phenylpropanoyl chloride **(383)** (1.83 g, 10.0 mmol) in dichloromethane (10 mL). The reaction was stirred at room temperature for 35 minutes during which time a fine white precipitate formed. The suspension was washed with aqueous $KHSO_4$ (0.1 M, 2 x 15 mL), saturated aqueous $NaHCO_3$ (15 mL), brine (15 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum gave the crude product as a milky liquid (3.60 g). Purification by flash chromatography (4.0 x 10.0 cm silica), eluting with an ether/hexane mixture (3:97), afforded the title compound **385** as a colourless liquid (2.84 g, 9.8 mmol, 97 %).

IR (film) υ_{max} : 3063m, 2952s, 1734s, 1639m, 1604w, 1496m, 1248s, 1163s, 852s, 699s cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.32-7.16 (5H, m, C**H** aromatic), 4.81 (1H, d, J = 1.5 Hz, >C=CH**H**), 4.69 (1H, s, >C=C**H**H), 4.42 (2H, s, -$CO_2C\mathbf{H}_2$-), 3.08 (1H, dd, J = 6.6 Hz, 13.2 Hz, PhC**H**HCH-), 2.88-2.65 (2H, m, $PhCH_2C\mathbf{H}$- & PhCH**H**CH-), 1.47 (2H, s, -$C\mathbf{H}_2$TMS), 1.20 (3H, d, J = 6.6 Hz, -$C\mathbf{H}_3$), 0.05 (9H, s, -**TMS**).
^{13}C NMR (75 MHz, $CDCl_3$) δ : 175.91 (>**C**=O), 141.81 (>**C**=CH_2), 139.47 (**C** aromatic), 129.15, 128.53 & 126.48 (**C**H aromatic), 109.61 (>C=**C**H_2), 67.82 (-$CO_2C\mathbf{H}_2$-), 41.70 ($PhCH_2C\mathbf{H}$-), 39.88 ($PhC\mathbf{H}_2$-), 23.56 (-$C\mathbf{H}_2$TMS), 17.03 (-$C\mathbf{H}_3$), -1.30 (-**TMS**).
MS (CI) *m/z* (rel. intensity): 290 (4[M]$^+$), 221 (9), 143 (19), 119 (21), 91 (63), 73 (100).

2-{2-[(Methoxycarbonyl)amino]-2-phenylethyl}allyl 2-methyl-3-phenylpropanoate (390)[225]



$C_{23}H_{27}NO_4$ (mw: 381.47 g/mol)

A solution of methylcarbamate (87 mg, 1.15 mmol) and benzaldehyde dimethyl acetal (170 μL, 1.15 mmol) in dichloromethane (5 mL) was cooled to –78°C (dry-ice/acetone bath). Boron trifluoride etherate (285 μL, 329 mg, 2.32 mmol) was added and the solution allowed to warm to room temperature. Stirring for 20 minutes afforded a yellow solution, which was cooled to –78°C (dry-ice/acetone bath). 2-[(1,1,1-trimethylsilyl)methyl]allyl 2-methyl-3-pheylpropanoate **(385)** (300 mg, 1.03 mmol) in dichloromethane (1.0 mL) was added dropwise over 10 minutes. The reaction was stirred at –20°C (dry-ice/aqueous $CaCl_2$ bath) for 1 hour and then allowed to warm to room temperature over 2 hours. Saturated aqueous $NaHCO_3$ solution (10 mL) was added and the mixture extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum gave the crude product (600 mg) as a colourless oil. Purification by flash chromatography (4.0 x 7.0 cm silica), eluting with an ethyl acetate/petroleum ether [30-40°C] (20:80) mixture, afforded the title compound **390** as a colourless gum (230 mg, 0.6 mmol, 60 %).

IR (film) υ_{max} : 3331br, 2931s, 1731s (-CO_2-), 1698s (-$NHCO_2$-), 1656w, 1603w, 1532s, 1454s, 1248s, 1164s, 1043m, 912w, 746m, 700s cm^{-1}.

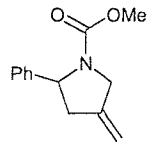
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.42-7.15 (10H, m, C**H** aromatic), 5.08 (2H, br s, -CO_2C**H**H- & PhC**H**-), 4.96 (1H, s, -CO_2CH**H**-), 4.84 (1H, s, -N**H**), 4.46 (2H, s, >C=C$\mathbf{H_2}$), 3.62 (3H, s, -$CO_2\mathbf{CH_3}$), 3.05 (1H, dd, J = 6.6 Hz, 13.2 Hz, PhC**H**HCH-), 2.87-2.66 (2H, m, PhCH_2C**H**- & PhCH**H**CH-), 2.51-2.33 (2H, m, PhCHC$\mathbf{H_2}$-), 1.20 (3H, d, J = 6.6 Hz, -$\mathbf{CH_3}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ : 175.87 (PhCH_2CHMe**C**O_2-), 156.44 (-NH**C**O_2Me), 142.36 (>**C**=CH_2), 140.11 & 139.39 (**C** aromatic), 129.13, 128.80, 128.55, 127. 63, 126.53 & 126.30 (**C**H aromatic), 116.61 (>C=**C**H_2), 66.73 (-CHCO_2CH_2-), 53.75 (Ph**C**H-), 52.34 (-NHCO_2CH_3), 41.68 (CH_3**C**H-), 40.63 (PhCH**C**H_2-), 39.87 (Ph**C**H_2-), 17.09 (**C**H_3CH-).

MS (EI) *m/z* (rel. intensity): 405.6 (18), 404.5 (74[M+Na]$^+$), 383.5 (23), 382.5 (100[M+H]$^+$), 308.5 (5), 307.4 (27).

HRMS (EI) *m/z* : 404.1836; $C_{23}H_{27}NO_4Na$ ([M+Na]$^+$) requires 404.1832.

Attempted cyclisation of carbamate 390 to afford methyl 4-methylene-2-phenyl-1-pyrrolidine carboxylate (394)



$C_{13}H_{15}NO_2$ (mw: 218.26 g/mol)

2-{2-[(Methoxycarbonyl)amino]-2-phenylethyl}allyl 2-methyl-3-phenylpropanoate **(390)** (155 mg, 0.40 mmol) was dissolved in THF (6 mL). Palladium(II) acetylacetonate (12.0 mg, 39.4 μmol, 10 mol%) and 1,2-bis(diphenylphosphino) ethane (24.0 mg, 60.3 μmol, 15 mol%) in THF (2 mL) were added and the resulting yellow solution stirred at room temperature, under an atmosphere of nitrogen, for 24 hours. Inspection of the crude ^{1}H NMR indicated that no reaction had occurred.

This procedure was repeated with the following modifications,

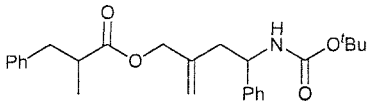
1. As above but with anhydrous K_2CO_3 (60 mg, 0.44 mmol) added at the start and $Pd(acac)_2$/dppe being substituted for $Pd(PPh_3)_4$ (46 mg, 40 μmol, 10 mol%).

2. As 1 but triethylamine (85 μL, 0.60 mmol) replaced the K_2CO_3. After 19 hours at room temperature the reaction was heated at reflux overnight.

3. The substrate **390** (90 mg, 0.24 mmol) was dissolved in THF (4 mL) and cooled to –78°C (acetone/dry-ice bath). Sodium bis(trimethylsilyl)amide (0.7 M in THF, 345 μL, 0.26 mmol) was added and the reaction allowed to stir whilst the catalyst was prepared. THF (4 mL) was added to a mixture of dppe (9.0 mg, 22.6 μmol, 10 mol%) and $Pd_2(dba)_3$•$CHCl_3$ (15.0 mg, 14.5 μmol, 6 mol%) and the solution heated at reflux for 5 minutes. The substrate solution was added *via* a cannula and stirred at room temperature for 30 minutes.

In each case no desired product **394** was observed and in many cases a complex mixture was obtained.

2- { 2- [(*tert*-Butoxycarbonyl) amino] -2- phenylethyl} allyl 2-methyl-3-phenylpropanoate (396)[225]



$C_{26}H_{33}NO_4$ (mw: 423.55 g/mol)

A solution of *tert*-butylcarbamate (260 mg, 2.22 mmol) and benzaldehyde dimethyl acetal (333 μL, 338 mg, 2.22 mmol) in dichloromethane (6 mL) was cooled to –78°C (dry-ice/acetone bath). Boron trifluoride etherate (550 μL, 636 mg, 4.48 mmol) was added and the solution allowed to warm to room temperature. Stirring for 20 minutes afforded a yellow solution, which was cooled to –78°C (dry-ice/acetone bath). 2-[(1,1,1-trimethylsilyl)methyl]allyl 2-methyl-3-pheylpropanoate **(385)** (560 mg, 1.93 mmol) in dichloromethane (3 mL) was added dropwise over 10 minutes. The reaction was stirred

at –20°C (dry-ice/aqueous $CaCl_2$ bath) for 1 hour and then allowed to warm to room temperature over 2 hours. Saturated aqueous $NaHCO_3$ solution (7 mL) was added and the mixture extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum gave the crude product (900 mg) as a yellow oil. Purification by flash chromatography (4.5 x 6.0cm silica), eluting with an ethyl acetate/petroleum ether [30-40°C] (10:90) mixture, afforded the title compound **396** as a cream solid (380 mg, 0.90 mmol, 47 %).

IR (CH_2Cl_2 solution) υ_{max} : 3059m, 2976m, 1727s, 1701s, 1496m, 1454m, 1365m, 1249m, 1166s, 700s cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.37-7.16 (10H, m, C**H** aromatic), 5.06 (1H, s, -CO_2CH**H**-), 4.97 (1H, s, -CO_2C**H**H-), 4.92-4.73 (2H, m, -N**H** & PhC**H**-), 4.50-4.39 (2H, m, >C=C**H$_2$**), 3.05 (1H, dd, *J* = 6.6 Hz, 12.9 Hz, PhC**H**HCH-), 2.86-2.66 (2H, m, PhC**H$_2$**C**H**- & PhCH**H**CH-), 2.49-2.32 (2H, m, PhCHC**H$_2$**-), 1.41 (9H, s, -C**Me$_3$**), 1.20 (3H, d, *J* = 6.6 Hz, -C**H$_3$**).

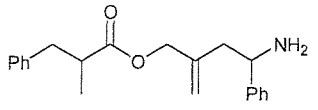
^{13}C NMR (75 MHz, $CDCl_3$) δ : 175.79 (-**C**O_2-), 155.29 (-NH**C**O-), 142.87 (>**C**=CH_2), 140.24 & 139.41 (**C** aromatic), 129.13, 128.73, 128.54, 127.45, 126.51 & 126.30 (**C**H aromatic), 116.28 (>C=**C**H_2), 79.84 (-**C**Me_3), 66.73 (-CO_2**C**H_2-), 53.34 (-**C**HPh), 41.68 (-**C**HCH_3), 40.89 (PhCH**C**H_2-), 39.88 (-**C**H_2Ph), 28.48 (-C**Me$_3$**), 17.07 (-**C**H_3).

MS (EI) *m/z* (rel. intensity): 462.2 (21$[M+K]^+$), 446.3 (89$[M+Na]^+$), 425.3 (26), 424.3 (100$[M+H]^+$), 369.3 (19), 368.2 (94), 324.1 (17).

Anal. Calcd. for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found C, 73.62; H, 7.85; N, 3.32.

m.p.: 101-103°C.

2-(2-Amino-2-phenylethyl)allyl 2-methyl-3-phenylpropanoate (397)



$C_{21}H_{25}NO_2$ (mw: 323.43 g/mol)

TFA (700 μL) was added to a colourless solution of 2-{2-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}allyl 2-methyl-3-phenylpropanoate **(396)** (308 mg, 0.73 mmol) in

dichloromethane (7 mL). The resulting orange solution was stirred at room temperature for 2.5 hours. Saturated aqueous $NaHCO_3$ solution (20 mL) was added and the mixture extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed under vacuum to afford the title compound **397** as a yellow oil (220 mg, mmol, 93 %).

IR (film) υ_{max} : 3370m, 3212w, 3027s, 2934s, 1730s (C=O), 1653m, 1603m, 1493s, 909s, 731s, 700s cm^{-1}.

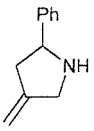
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.38-7.17 (10H, m, **CH** aromatic), 5.06 (1H, s, -CO_2**CH**H-), 5.01 (1H, s, -CO_2CH**H**-), 4.51 (2H, s, >C=C**H_2**), 4.07 (1H, dd, *J* = 9.6 Hz, 5.0 Hz, PhC**H**-), 3.06 (1H, dd, *J* = 12.5 Hz, 6.6 Hz, PhC**H**HCH-), 2.87-2.67 (2H, m, PhCH_2C**H**- & PhCH**H**CH-), 2.25-2.23 (2H, m, PhCHC**H_2**-), 1.20 (3H, d, *J* = 7.4 Hz, -**CH_3**).

^{13}C NMR (75 MHz, $CDCl_3$) δ : 175.89 (-**C**O_2-), 145.81 (>**C**=CH_2), 141.20 & 139.41 (**C** aromatic), 129.14, 128.66, 128.56, 127.32, 126.54 & 126.45 (**C**H aromatic), 115.63 (>C=**C**H_2), 66.56 (-CO_2**C**H_2-), 53.98 (-**C**HPh), 44.11 (PhCH**C**H_2-), 41.74 (-**C**HCH_3), 39.90 (-**C**H_2Ph), 17.13 (-**C**H_3).

MS (EI) *m/z* (rel. intensity): 326.3 (5), 325.3 (23), 324.2 (100$[M+H]^+$).

HRMS (EI) *m/z* : 346.1777; $C_{21}H_{25}NO_2Na$ ($[M+Na]^+$) requires 346.1778.

Attempted cyclisation of amine 397 to afford 4-methylene-2-phenylpyrrolidine (398)



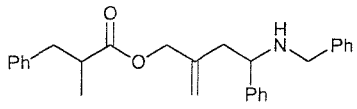
$C_{11}H_{13}N$ (mw: 159.22 g/mol)

Palladium(II) acetylacetonate (6.0 mg, 19.7 μmol, 10 mol%) and 1,2-bis(diphenylphosphino) ethane (12.0 mg, 30.2 μmol, 15 mol%) were added to a solution of the starting material **397** (80 mg, 0.20 mmol) in THF (2 mL). The yellow solution was stirred, under an atmosphere of nitrogen, at room temperature for 12 hours. No reaction was observed by t.l.c.

OR

A solution of $Pd_2(dba)_3 \cdot CHCl_3$ (8 mg, 7.7 μmol), triphenylphosphine (22.0 mg, 83.9 μmol) and triethylamine (59 μL, 0.42 mmol) in THF (2.5 mL) was stirred at 30°C, under a nitrogen atmosphere, for 10 minutes. The substrate **397** (90mg, 0.28 mmol), in THF (3 mL), was added to the yellow catalyst solution and the reaction heated at reflux for 5 hours. After cooling to room temperature the reaction was quenched with saturated aqueous $NaHCO_3$ solution (7 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed under vacuum to give a yellow oil. ^1H NMR showed this to be a complex mixture containing no product **398**.

2-{Phenyl-2-[(phenylmethyl)amino]ethyl}-2-propenyl 2-methyl-3-phenylpropanoate (399)



$C_{28}H_{31}NO_2$ (mw: 413.56 g/mol)

Acetic acid (30 μL) in dichloroethane (1 mL), followed by tetramethylammonium triacetoxyborohydride (79 mg, 0.3 mmol), was added to a solution of 2-(2-amino-2-phenylethyl)allyl 2-methyl-3-phenylpropanoate **(397)** (50 mg, 0.15 mmol) and benzaldehyde (15 μL, 15.9 mg, 0.15 mmol) in dichloroethane (2 mL). The solution was stirred at room temperature for 17 hours after which time t.l.c. indicated that no product had formed. A further quantity of tetramethylammonium triacetoxyborohydride (79 mg, 0.3 mmol) and acetic acid (30 μL) were added and the reaction stirred for a further 3 days. Saturated aqueous $NaHCO_3$ solution (7 mL) was added and the mixture extracted with dichloromethane (4 x 10 mL). The combined organic layers were washed with brine (7 mL), dried ($MgSO_4$) and the solvent removed under vacuum to give the crude product as a colourless oil. Purification by flash chromatography (3.2 x 4.5 cm silica), eluting with an ether/hexane (1:4) mixture, afforded the title compound **399** as a colourless oil (47 mg, 0.11 mmol, 76 %).

IR (film) υ_{max} : 3438br w, 3060m, 3025m, 2931m, 1731s (C=O), 1650m, 1602m, 1493s, 1453s, 1377m, 1162s, 1116m, 1028m, 912m cm^{-1}.

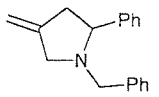
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.38-7.16 (15H, m, **CH** aromatic), 5.02 (1H, d, J = 5.1 Hz, >C=C**H**H), 4.94 (1H, s, >C=CH**H**), 4.93 (2H, s, -CO_2CH_2-), 3.78 (1H, dd, J = 8.1 Hz, 5.9 Hz, PhC**H**-), 3.68 (1H, d, J = 13.2 Hz, PhC**H**HN-), 3.50 (1H, d, J = 13.2 Hz, PhCH**H**N-), 3.05 (1H, dd, J = 12.5 Hz, 6.6 Hz, PhC**H**HCH-), 2.84-2.65 (2H, m, $PhCH_2$C**H**- & PhCH**H**CH-), 2.42-2.35 (2H, m, PhCHCH_2-), 1.19 (3H, d, J = 6.6 Hz, -CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ : 175.82 (-**C**O_2-), 145.85 (>**C**=CH_2), 141.03, 140.60 & 139.40 (**C** aromatic), 129.13, 128.64, 128.54, 128.29, 127.39, 127.07 & 126.53 (**C**H aromatic), 115.52 (>C=**C**H_2), 66.46 (-CO_2**C**H_2-), 60.11 (-**C**HPh), 51.68 ($PhCH_2$N-) 43.00 (PhCH**C**H_2-), 41.69 (-**C**HCH_3), 39.85 (-**C**H_2Ph), 17.09 (-**C**H_3).

MS (EI) *m/z* (rel. intensity): 416.7 (4), 415.6 (29), 414.6 (100$[M+H]^+$).

HRMS (EI) *m/z* : 414.2420; $C_{28}H_{32}NO_2$ ($[M+H]^+$) requires 414.2428.

4-Methylidene-2-phenyl-1-(phenylmethyl)tetrahydro-1*H*-pyrrole (400)



$C_{18}H_{19}N$ (mw: 249.34 g/mol)

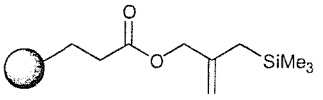
Palladium(II) acetylacetonate (5.9 mg, 19.4 μmol, 10 mol%) and 1,2-bis(diphenylphosphino) ethane (11.6 mg, 29.1 μmol, 15 mol%) were added to a solution of the starting material **399** (80 mg, 0.19 mmol) in THF (4 mL). The yellow solution was stirred, under an atmosphere of nitrogen, at reflux for 13 hours. T.l.c. indicated that starting material **399** was still present. A further quantity of palladium(II) acetylacetonate (5.9 mg, 19.4 μmol, 10 mol%) and 1,2-bis(diphenylphosphino) ethane (11.6 mg, 29.1 μmol, 15 mol%) was added and the reaction heated at reflux for a further 12 hours.

After allowing the reaction to cool to room temperature saturated aqueous $NaHCO_3$ solution (4 mL) was added and the mixture extracted with dichloromethane (5 x 8 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and the solvent removed under vacuum to give the crude product as a yellow gum (88 mg).

Purification by flash chromatography (2.0 cm x 3.0 cm), eluting with an ether/hexane (2:98) mixture, afforded the title compound **400** as a colourless oil (15 mg, 60.2 μmol, 33 %) and recovered starting material (21 mg, 51.1 μmol, 64 %).

IR (film) υ_{max} : 3060m, 3026m, 2923m, 2787s, 1662m, 1601m, 1492s, 1452s, 1359m, 1142w, 1073w, 910s, 878s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.53-7.24 (10H, C**H** aromatic), 4.86 (2H, s, >C=C**H$_2$**), 3.88 (1H, d, *J* = 12.9 Hz, PhC**H**H-), 3.66 (1H, d, *J* = 13.9 Hz, PhCH$_2$NC**H**H-), 3.57 (1H, dd, *J* = 10.4 Hz, 6.9 Hz, PhC**H**-), 3.04 (1H, d, *J* = 12.9 Hz, PhCH**H**-), 2.92 (1H, d, *J* = 13.9 Hz, PhCH$_2$NCH**H**-), 2.89-2.80 (1H, m, PhCHC**H**H-), 2.57-2.45 (1H, m, PhCHCH**H**-).
^{13}C NMR (75 MHz, $CDCl_3$) δ : 147.13, 142.74 & 139.45 (**C** aromatic & >**C**=CH$_2$), 128.70, 128.32, 127.74, 127.54 & 126.98 (**C**H aromatic), 104.84 (>C=**C**H$_2$), 69.82 (Ph**C**H-), 58.86 (Ph**C**H$_2$-), 58.19 (PhCH$_2$N**C**H$_2$-), 42.98 (PhCH**C**H$_2$-).
MS (EI) *m/z* (rel. intensity): 251.3 (18), 250.3 (100[M+H]$^+$).
HRMS (EI) *m/z* : 250.1592; $C_{18}H_{20}N$ ([M+H]$^+$) requires 250.1596.

2-[(1,1,1-Trimethylsilyl)methyl]allyl 3-polystyrylpropanoate (381)

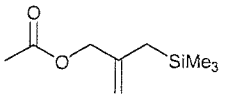


The acid resin **365** (1.0 g) was suspended in dichloromethane (12 mL) and stirred for 5 minutes. DMAP (488 mg, 4.0 mmol), DIC (628 μL, 504 mg, 4.0 mmol) and 2-[(1,1,1-trimethylsilyl)methyl]-2-propen-1-ol **(384)** (576 mg, 4.0 mmol) were added and the reaction stirred at room temperature for 17 hours. The resin was collected by filtration, washed with dichloromethane and methanol (100 mL each) and dried under vacuum for 2 hours (50°C). This afforded the title product **381** as a white solid (0.95 g).

IR (on-bead) υ_{max} : 3027m, 2922s, 1734s (C=O), 1601m, 1493s, 1451s, 1248s, 1153s cm^{-1}.
^{1}H-MAS NMR δ : 4.89 (br s, >C=CHH), 4.78-4.58 (br m, >C=CH**H**), 4.45 (br s, -CO$_2$C**H$_2$**-), 1.50 (br s, -C**H$_2$**TMS), 0.00 (br s, -**TMS**).

^{13}C NMR (Gel-phase, 75 MHz, $CDCl_3$) δ : 172.55 (>**C**=O), 141.78 (>**C**=CH_2), 109.63 (>C=**C**H_2), 67.77 (-CO_2**C**H_2-), 23.70 (-**C**H_2TMS), -1.28 (-**TMS**).

2-[(1,1,1-Trimethylsilyl)methyl]-2-propenyl ethanoate (405)



$C_9H_{18}O_2Si$ (mw: 186.33 g/mol)

DMAP (85 mg, 0.7 mmol) and triethylamine (2.02 mL, 1.47 g, 14.5 mmol) were added to a solution of 2-[(1,1,1-trimethylsilyl)methyl]-2-propen-1-ol **(384)** (2.0 g, 13.9 mmol) in dichloromethane (20 mL). The colourless solution was cooled to 4°C (ice bath) and acetic anhydride (1.43 mL, 1.48 g, 14.5 mmol) was added. The reaction was allowed to warm to room temperature and was stirred for 1.5 hours. Saturated aqueous $NaHCO_3$ solution (12 mL) was added and the mixture was extracted with ether (3 x 25 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum afforded the crude product as a colourless oil (2.5 g). Purification by flash chromatography (3.3 x 5.0 cm silica), eluting with an ether/hexane (2:98) mixture, afforded the known title compound **405** as a colourless oil (1.81 g, 9.7 mmol, 70 %). The spectroscopic details were consistent with those in the literature.[278]

CAS Number: [72047-94-0].

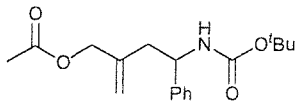
IR (film) υ_{max} : 3081w, 2954s, 1744s, 1643m, 1420m, 1373m, 1248s, 1225s, 1160w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ : 4.89 (1H, s, =CH**H**), 4.73 (1H, s, =C**H**H), 4.44 (2H, s, -CO_2**C**H_2-), 2.12 (3H, s, **C**H_3CO_2-), 1.54 (2H, s, -**C**H_2SiMe_3), 0.05 (9H, s, -Si(**C**H_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ : 170.63 (>**C**=O), 141.59 (>**C**=CH_2), 109.55,(>C=**C**H_2), 67.82 (-CO_2**C**H_2-), 23.5 (**C**H_3CO_2-), 20.88 (-**C**H_2Si-), -1.51 (-Si(**C**H_3)$_3$).

MS (CI) *m/z* (rel. intensity): 187 (4$[M+H]^+$), 186 (5$[M]^+$), 143 (21), 117 (35), 73 (100).

2-[2-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)-2-phenylethyl]-propenyl ethanoate (406)



$C_{18}H_{25}NO_4$ (mw: 319.40 g/mol)

A solution of *tert*-butylcarbamate (1.27 g, 10.8 mmol) and benzaldehyde dimethylacetal (1.62 mL, 1.64 g, 10.8 mmol) in dichloromethane (35 mL) was cooled to –78°C (dry-ice/acetone bath). Boron trifluoride etherate (2.65 mL, 21.6 mmol) was added and the reaction allowed to warm to room temperature. Stirring for 20 minutes afforded a yellow solution, which was cooled to –78°C (dry-ice/acetone bath). 2-[(1,1,1-Trimethylsilyl)methyl]-2-propenyl ethanoate **(405)** (1.71 g, 9.2 mmol) in dichloromethane (5 mL) was added dropwise over 10 minutes and the reaction was stirred at room temperature for 4 hours. Saturated aqueous $NaHCO_3$ solution (15 mL) was added and the mixture was extracted with dichloromethane (4 x 25 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and the solvent removed under vacuum to afford the crude product as a yellow solid. Purification by flash chromatography (3.3 x 4.0 cm silica), eluting with an ether/hexane mixture (3:7), followed by recrystallisation from hexane/ether afforded the title product **406** as a white solid (1.36 g, 4.26 mmol, 46 %).

IR (CH_2Cl_2 solution) υ_{max} : 3436m, 2980s, 1737s (-CO_2-), 1712s (-$NHCO_2$-), 1495s, 1367s, 1240s, 1167s, 1026m, 919w cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.41-7.26 (5H, m, C**H** aromatic), 5.18 (1H, s, >C=CH**H**), 5.04 (1H, s, >C=C**H**H), 4.95-4.80 (2H, br m, -N**H** & PhC**H**-), 4.55 (1H, d, *J* = 13.0 Hz, -CO_2CH**H**-), 4.50 (1H, d, *J* = 13.0 Hz, -CO_2C**H**H-), 2.62-2.53 (2H, m, PhCHC**H**$_2$-), 2.13 (3H, s, -CO_2C**H**$_3$), 1.43 (9H, s, C**Me**$_3$).

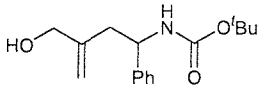
^{13}C NMR (100 MHz, $CDCl_3$) δ : 170.78 (-**C**O_2-), 155.31 (-HN**C**O_2-), 142.61 (>**C**=CH_2), 140.21 (**C** aromatic), 128.76, 127.49 & 126.32 (**C**H aromatic), 116.52 (>C=**C**H_2), 79.71 (-**C**Me_3), 66.86 (-CO_2**C**H_2-), 53.39 (>**C**HPh), 41.20 (PhCH**C**H_2-), 28.48 (-C**Me**$_3$), 21.09 (-**C**H_3).

MS (EI) *m/z* (rel. intensity): 321.3 (18), 320.3 (100[M+H]$^+$).

Anal. Calcd. for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.95; H, 7.94; N, 4.36.

m.p.: 86-88°C.

1,1-Dimethylethyl-*N*-[3-(hydroxymethyl)-1-phenyl-3-butenyl]carbamate (404)



$C_{16}H_{23}NO_3$ (mw: 277.36 g/mol)

2-[2-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)-2-phenylethyl]-propenyl ethanoate **(406)** (1.07 g, 3.35 mmol) was dissolved in THF (20 mL) and cooled to 0°C (ice bath). A solution of lithium borohydride (2M in THF, 2.42 mL, 4.83 mmol) was added followed by methanol (50 μL, 1.21 mmol). The reaction was stirred at room temperature for 16 hours. Saturated aqueous $NaHCO_3$ solution (10 mL) was added and the mixture extracted with ether (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and the solvent removed under vacuum to give the crude product as a white solid. Recrystallisation from dichloromethane/hexane afforded the title compound **404** as a white solid (789 mg, 2.98 mmol, 89 %).

IR (CH_2Cl_2 solution) υ_{max} : 3604w, 3435m, 2931m, 1709s (C=O), 1604w, 1495s, 1262s, 1167s, 1022m cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.32-7.18 (5H, m, C**H** aromatic), 5.06 (1H, s, -C=C**H**H), 4.99-4.90 (2H, br m, PhC**H**- & -N**H**), 4.88 (1H, s, -C=CH**H**), 4.03 (2H, s, -**CH$_2$**OH), 2.54 (1H, dd, *J* = 14.6 Hz, 5.9 Hz, PhCHCH**H**-), 2.43 (1H, dd, *J* = 14.6 Hz, 8.8 Hz, PhCHC**H**H-), 2.23 (1H, br s, -O**H**), 1.36 (9H, s, -C**Me$_3$**).

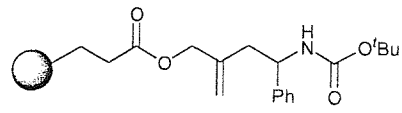
^{13}C NMR (100 MHz, $CDCl_3$) δ : 155.89 (-**C**O$_2$-), 145.34 (**C** aromatic), 142.51 (>**C**=CH$_2$), 128.78, 127.50 & 126.41 (**C**H aromatic), 114.38 (>C=**C**H$_2$), 79.90 (-**C**Me$_3$), 66.45 (-**C**H$_2$OH), 53.78 (-**C**HPh), 41.95 (PhCH**C**H$_2$-), 28.50 (-C**Me$_3$**).

MS (EI) *m/z* (rel. intensity): 279.3 (12), 278.3 (77[M+H]$^+$), 223.3 (13), 222.1 (100).

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.32; H, 8.40; N, 5.02.

m.p.: 132-134°C.

2- { 2- [(*tert*-Butoxycarbonyl) amino] -2- phenylethyl} allyl 3-polystyrylpropanoate (403)



A. DIC Coupling

Dichloromethane (4 mL) was added to a mixture of the resin **365** (240 mg), DMAP (101 mg, 0.84 mmol) and 1,1-dimethylethyl-*N*-[3-(hydroxymethyl)-1-phenyl-3-butenyl]carbamate **(404)** (230 mg, 0.84 mmol). DIC (130 μL, 105 mg, 0.84 mmol) was added and the reaction stirred for 14 hours. The resin was collected by filtration, washed with dichloromethane, methanol and dichloromethane (3 x 10 mL each) and dried under vacuum for 2 hours (50°C). This afforded the title compound **403** as a white solid (242 mg).

B. Imino-Sakurai type reaction

A solution of *t*-butylcarbamate (5.6 g, 48.0 mmol) and benzaldehyde dimethylacetal (7.2 mL, 48.0 mmol) in dichloromethane (50 mL) was cooled to –78°C (acetone/dry-ice bath). Boron trifluoride diethyl etherate (960 μL, 8.0 mmol) was added and the solution allowed to warm to room temperature. After 30 minutes the resulting yellow solution was transferred, *via* a cannula, to a suspension of the resin **381** (4.0 g) in dichloromethane (20 mL) at 0°C (ice bath). This was allowed to warm to room temperature and stirred for 4.5 hours. The resin was collected by filtration, washed with dichloromethane and methanol (200 mL each) and dried under vacuum for 2 hours (50°C) to afford the title product **403** as a white solid (4.35 g).

IR (on-bead) υ_{max} : 3061w, 3025m, 2919s, 2848w, 1731s (C=O), 1705s (C=O), 1651w, 1601m, 1492s, 1452s, 1164s cm^{-1}.

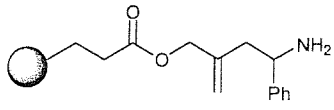
^{1}H-MAS NMR δ : 5.08 (-CO_2C**H**H-), 4.92 (-CO_2CH**H**-), 4.85 (-**NH** & PhC**H**-), 4.50 (br s, >C=C**H_2**), 2.45 (PhCHC**H_2**-), 1.35 (-C**Me_3**).

Cleavage of 1,1-dimethylethyl-*N*-[3-(hydroxymethyl)-1-phenyl-3-butenyl]carbamate (404) from resin 403

The resin **403** (200 mg) was suspended in THF (3.0 mL) and cooled to 0°C (ice bath). Lithium borohydride (2N in THF, 1.0 mL, 2.0 mmol) was added followed by methanol (80 μL, 2.0 mmol) and the reaction stirred at room temperature overnight. The resin was collected by filtration and washed with dichloromethane (30 mL) and methanol (30 mL). Removal of the filtrate solvent under vacuum afforded a white solid, which was dissolved in saturated aqueous $NaHCO_3$ solution (5 mL). This was extracted with dichloromethane (6 x 10 mL) and the combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed under vacuum and the crude product purified by flash chromatography (1.5 x 6.0 cm silica), eluting with an ether/hexane mixture (40:60), to afford the alcohol **404** as a white solid (26 mg, 94 μmol, 100 % based on loading of resin **365**).

The spectroscopic data were in agreement with those reported earlier.

2-(2-Amino-2-phenylethyl)allyl 3-polystyrylpropanoate (407)

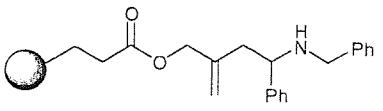


TFA (2 mL) was added to a suspension of resin **403** (200 mg) in dichloromethane (2 mL). After 20 minutes the resin was collected by filtration and then suspended in a solution of *N,N*-diisopropylamine (500 μL) in dichloromethane (5 mL). After 10 minutes the resin was collected by filtration, washed with dichloromethane (50 mL) and dried under vacuum for 2 hours (50°C). This afforded the title product **407** as a white solid (192 mg).

IR (on-bead) υ_{max} : 3027m, 2917m, 2847w, 1726s (C=O), 1651w, 1595m, 1485s, 1445s cm^{-1}.

^{1}H-MAS NMR δ : 5.10 (br s, $-CO_2CHH-$), 5.03 (br s, $-CO_2CHH-$), 4.55 (br s, $>C=CH_2$), 4.10 (br s, PhC**H**-), 2.50-2.28 (br m, $PhCHCH_2-$).

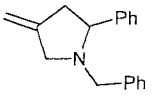
2-{Phenyl-2-[(phenylmethyl)amino]ethyl}-2-propenyl 3-polystyrylpropanoate (408)



Benzaldehyde (2.3 mL, 2.28 g, 21.5 mmol) and acetic acid (1.0 mL) were added to a suspension of the resin **407** (2.15 g) in dichloroethane (50 mL). After stirring at room temperature overnight the resin was collected by filtration. This was then suspended in a solution of tetramethylammonium triacetoxyborohydride (4.5 g, 17.2 mmol) in acetic acid (1.0 mL) and dichloroethane (50 mL). The suspension was stirred at room temperature for 24 hours and then the resin was collected by filtration. After washing with dichloromethane (250 mL) and methanol (100 mL) the resin was dried under vacuum for 2 hours (50°C). This afforded the title product **408** as a white solid (2.28 g).

IR (on-bead) υ_{max} : 3027m, 2917s, 1731s (C=O), 1595m, 1490s, 1445s cm^{-1}.
^{1}H-MAS NMR δ : 5.02 (br s, >C=C**H**H), 4.91 (br s, >C=CH**H**), 4.86 (br s, -$CO_2C\mathbf{H}_2$-), 3.80 (br s, PhC**H**-), 3.68 (br s, PhC**H**HN-), 3.50 (br s, PhCH**H**N-), 2.40 (br s, PhCHC$\mathbf{H}_2$-).

4-Methylidene-2-phenyl-1-(phenylmethyl)tetrahydro-1*H*-pyrrole (400) *via* the cyclisation-cleavage of resin 408

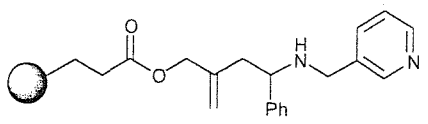


$C_{18}H_{19}N$ (mw: 249.34 g/mol)

Palladium(II) acetylacetonate (2.7 mg, 8.9 μmol, 10 mol%), 1,2-bis(diphenylphosphino) ethane (10.6 mg, 26.6 μmol, 30 mol%) and resin **408** (200 mg) in THF (4 mL) was heated at reflux, under a nitrogen atmosphere, for 12 hours. The resin was collected by filtration and washed with dichloromethane (30 mL). The filtrate solvent was removed under vacuum to afford an orange residue (23 mg). Purification by flash chromatography (1.5 x 5.0 cm silica), eluting with an ether/hexane mixture (2:98), afforded the title compound **400** as a colourless oil (21 mg, 84 μmol, 95 %).

The spectroscopic data were in agreement with those reported earlier.

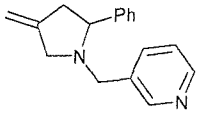
2-{Phenyl-2-[(3-pyridylmethyl)amino]ethyl}-2-propenyl 3-polystyrylpropanoate (418)



3-Pyridinecarboxaldehyde (410 µL, 460 mg , 4.3 mmol) and acetic acid (200 µL) were added to a suspension of the resin **407** (600 mg) in dichloroethane (10 mL). After stirring at room temperature overnight the resin was collected by filtration and washed with dichloroethane (20 mL). The resin was suspended in a solution of tetramethylammonium triacetoxyborohydride (1.63 g, 6.2 mmol) in acetic acid (200 µL) and dichloroethane (10 mL). The suspension was stirred at room temperature for 24 hours and then the resin was collected by filtration. After washing with dichloromethane (250 mL) and methanol (100 mL) the resin was dried under vacuum for 2 hours (50°C). This afforded the title compound **418** as a white solid (629 mg).

IR (on-bead) υ_{max} : 3027m, 2922m, 2852w, 1731s (C=O), 1595s, 1490s, 1450s, 749s cm^{-1}.

3-[(Methylene-2-phenyltetrahydro-1H-1-pyrrolyl)methyl]pyridine (421)



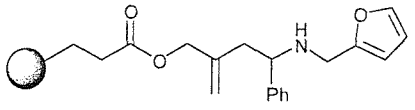
$C_{17}H_{18}N_2$ (mw: 250.34 g/mol)

Palladium(II) acetylacetonate (5.4 mg, 17.7 µmol, 10 mol%), 1,2-bis(diphenylphosphino) ethane (21.5 mg, 54.0 µmol, 30 mol%) and resin **418** (500 mg) in THF (10 mL) was heated at reflux for 12 hours. The resin was collected by filtration and washed with dichloromethane (50 mL). The filtrate solvent was removed under vacuum to afford an orange residue (61 mg). Purification by flash chromatography (1.5

x 5.0 cm silica), eluting with an ether/hexane mixture (60:40), afforded the title compound **421** as a colourless oil (25 mg, 100 μmol, 85 %).

IR (CH_2Cl_2 solution) υ_{max} : 3023m, 1652w, 1605m, 1506s, 1457s, 1077m, 754s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.51 (2H, br s, C(2)**H** & C(6)**H** pyridyl), 7.65 (1H, d, *J* = 7.9 Hz, C(4)**H** pyridyl), 7.51-7.22 (6H, m, C(5)**H** pyridyl & C**H** phenyl), 4.89 (2H, s, >C=C**H$_2$**), 3.84 (1H, d, *J* = 13.4 Hz, -NC**H**HAr), 3.66-3.58 (2H, m, PhCH- & -NCH**H**C=CH_2), 3.11 (1H, d, *J* = 13.4 Hz, -NCH**H**Ar), 2.95 (1H, dd, *J* = 13.9 Hz, 2.0 Hz, -NC**H**HC=CH_2), 2.86 (1H, dd, *J* = 15.9 Hz, 6.5 Hz, PhCHC**H**H-), 2.53 (1H, ddd, *J* = 12.9 Hz, 9.9 Hz, 2.5 Hz, PhCHCH**H**-).
^{13}C NMR (75 MHz, $CDCl_3$) δ : 150.03 & 148.57 (**C**H aromatic), 146.24 (>**C**=CH_2), 142.13 (**C** aromatic), 136.48 (**C**H aromatic), 134.76 (**C** aromatic), 128.81, 127.77 & 123.48 (**C**H aromatic), 105.32 (>C=**C**H_2), 69.93 (Ar**C**H-), 58.74 (Ar**C**H_2-), 55.41 (ArCH_2N**C**H_2-), 42.79 (ArCH**C**H_2-).
MS (EI) *m/z* (rel. intensity): 252.3 (20), 251.2 (100$[M+H]^+$).
HRMS (EI) *m/z* : 251.1543; $C_{17}H_{19}N_2$ ($[M+H]^+$) requires 251.1543.

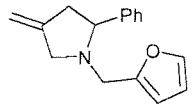
2-{Phenyl-2-[(2-furylmethyl)amino]ethyl}-2-propenyl 3-polystyrylpropanoate (417)



2-Furaldehyde (360 μL, 413 mg, 4.3 mmol) was added to a suspension of the resin **407** (600 mg) in dichloroethane (10 mL). After stirring at room temperature overnight the resin was collected by filtration and washed with dichloroethane (20 mL). The resin was then suspended in a solution of tetramethylammonium triacetoxyborohydride (1.63 g, 6.2 mmol) in acetic acid (200 μL) and dichloroethane (10 mL). The suspension was stirred at room temperature for 24 hours and then the resin was collected by filtration. After washing with dichloromethane (250 mL) and methanol (100 mL) the resin was dried under vacuum for 2 hours (50°C). This afforded the title compound **417** as a white solid (634 mg).

IR (on-bead) υ_{max} : 3026m, 2926m, 2851w, 1729s (C=O), 1599m, 1489s, 1444s cm^{-1}.

1-(2-Furylmethyl)-4-methylene-2-phenylpyrrolidine (420)

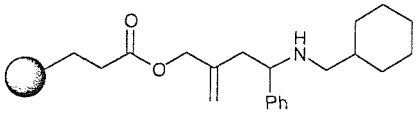


$C_{16}H_{17}NO$ (mw: 239.32 g/mol)

Palladium(II) acetylacetonate (5.5 mg, 18.0 μmol, 10 mol%), 1,2-bis(diphenylphosphino) ethane (21.3 mg, 53.5 μmol, 30 mol%) and resin **417** (500 mg) in THF (10 mL) was heated at reflux for 12 hours. The resin was collected by filtration and washed with dichloromethane (50 mL). The filtrate solvent was removed under vacuum to afford an orange residue (47 mg). Purification by flash chromatography (1.5 x 5.0 cm silica), eluting with dichloromethane, afforded the title compound **420** as a colourless oil (19 mg, 79 μmol, 29 %).

IR (CH_2Cl_2 solution) υ_{max} : 3054m, 1644m, 1597m, 1502s, 1451s, 1072m, 805s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.48-7.26 (6H, m, C(5)**H** furyl & C**H** phenyl), 6.31 (1H, s, C(4)**H** furyl), 6.13 (1H, s, C(3)**H** furyl), 4.91 (1H, s, >C=C**H**H), 4.88 (1H, s, >C=CH**H**), 3.79-3.74 (2H, m, -NC**H**HAr & -NCH**H**C=CH_2), 3.56 (1H, dd, *J* = 9.9 Hz, 6.8 Hz, PhCH-), 3.27 (1H, d, *J* = 14.4 Hz, -NCH**H**Ar), 3.13 (1H, dd, *J* = 13.4 Hz, 2.5 Hz, -NC**H**HC=CH_2), 2.81 (1H, dd, *J* = 16.4 Hz, 6.8 Hz, PhCHC**H**H-), 2.53 (1H, m, PhCHCH**H**-).
^{13}C NMR (100 MHz, $CDCl_3$) δ : 152.84 & 146.73 (**C** aromatic), 142.34, 128.98, 128.05, 127.90, 110.45 & 108.53 (**C**H aromatic), 105.37 (>C=**C**H_2), 69.08 (Ph**C**H-), 58.83 (Ar**C**H_2-), 49.37 (ArCH_2N**C**H_2-), 43.02 (PhCH**C**H_2-).
MS (EI) *m/z* (rel. intensity): 241.3 (19), 240.3 (100$[M+H]^+$).
HRMS (EI) *m/z* : 240.1389; $C_{16}H_{18}NO$ ($[M+H]^+$) requires 240.1388.

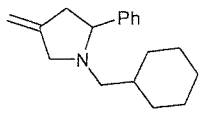
2-{Phenyl-2-[(cyclohexylmethyl)amino]ethyl}-2-propenyl 3-polystyrylpropanoate (419)



Cyclohexane carboxaldehyde (360 μL, 334 mg, 3.0 mmol), acetic acid (100 μL) and tetramethylammonium triacetoxyborohydride (800 mg, 3.0 mmol) were added to a suspension of the resin **407** (600 mg) in dichloroethane (10 mL). After stirring at room temperature for 1.5 hours the resin was collected by filtration, washed with dichloromethane and methanol (100 mL each) and dried under vacuum for 2 hours (50°C). This afforded the title compound **419** as a white solid (641 mg).

IR (on-bead) υ_{max} : 3031m, 2916s, 2846m, 1729s (C=O), 1604m, 1489s, 1444s cm^{-1}.

1-(Cyclohexylmethyl)-4-methylene-2-phenylpyrrolidine (422)



$C_{18}H_{25}N$ (mw: 255.40 g/mol)

Palladium(II) acetylacetonate (5.5 mg, 18.0 μmol, 10 mol%), 1,2-bis(diphenylphosphino) ethane (21.3 mg, 53.5 μmol, 30 mol%) and resin **419** (500 mg) in THF (10 mL) was heated at reflux for 12 hours. The resin was collected by filtration and washed with dichloromethane (50 mL). The filtrate solvent was removed under vacuum to afford an orange residue (54 mg). Purification by flash chromatography (1.5 x 5.0 cm silica), eluting with an ether/hexane mixture (3:97), afforded the title compound **422** as a colourless oil (8 mg, 31 μmol, 16 %).

IR (CH_2Cl_2 solution): 3012w, 2934m, 2840m, 1648w, 1602m, 1505s, 1064m, 767s, 713s cm^{-1}.

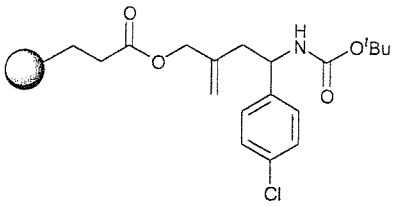
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.43-7.21 (5H, m, C**H** aromatic), 4.92 (1H, s, >C=C**H**H), 4.87 (1H, s, >C=CH**H**), 3.90 (1H, d, J = 13.9 Hz, C_6H_{11}C**H**HN-); 3.36 (1H, dd, J = 9.9 Hz, 6.5 Hz, PhC**H**-), 2.85 (1H, d, J = 13.9 Hz, C_6H_{11}CH**H**N-), 2.76 (1H, dd, J = 16.4 Hz, 6.5 Hz, PhCHC**H**H-), 2.43-2.33 (1H, m, PhCHCH**H**-), 2.27 (1H, t, J = 11.4 Hz, cyclohexyl), 2.07 (1H, d, J = 12.4 Hz, $C_6H_{11}CH_2$NC**H**H-), 1.88 (1H, dd, J = 11.4 Hz, 3.5 Hz, cyclohexyl), 1.69-1.59 (3H, m, cyclohexyl), 1.53 (1H, d, J = 12.4 Hz, $C_6H_{11}CH_2$NCH**H**-), 1.44-1.38 (1H, m, cyclohexyl), 1.28-1.02 (3H, m, cyclohexyl), 0.82-0.64 (2H, m, cyclohexyl).

^{13}C NMR (100 MHz, $CDCl_3$) δ : 147.99 & 143.72 (**C** aromatic & >**C**=CH_2), 128.70, 127.95 & 127.45 (**C**H aromatic), 104.68 (>C=**C**H_2), 70.82 (Ph**C**H-), 61.84 (-N**C**$H_2C_6H_{11}$), 59.58 ($C_6H_{11}CH_2NCH_2$-), 43.45 (PhCH**C**H_2-), 37.20 (**C**H cyclohexyl), 32.42, 31.64, 27.25, 26.66 & 26.45 (-**C**H_2- cyclohexyl).

MS (EI) *m/z* (rel. intensity): 257.3 (18), 256.2 (100$[M+H]^+$).

HRMS (EI) *m/z* : 256.2069; $C_{18}H_{26}N$ ($[M+H]^+$) requires 256.2065.

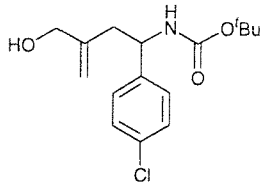
2- { 2- [(*tert*-Butoxycarbonyl) amino] -2- (4-chlorophenyl)ethyl} allyl 3-polystyrylpropanoate (424)



A solution of *t*-butylcarbamate (1.4 g, 12.0 mmol) and 4-chlorobenzaldehyde (1.69 g, 12.0 mmol) in dichloromethane (15 mL) was cooled to –78°C (acetone/dry-ice bath). Boron trifluoride diethyl etherate (240 μL, 284 mg, 2.0 mmol) was added and the solution allowed to warm to room temperature. After 30 minutes the resulting yellow solution was transferred, *via* a cannula, to a suspension of the resin **381** (1.0 g) in dichloromethane (5 mL) at 0°C (ice bath). This was allowed to warm to room temperature and stirred for 6 hours. The resin was collected by filtration, washed with dichloromethane and methanol (100 mL each) and dried under vacuum for 2 hours (50°C) to afford the title product **424** as a white solid (1.06 g).

IR (on-bead) υ_{max} : 3024m, 2921m, 1715br s (C=O), 1602m, 1492s, 1450s, 1365s, 1244m, 1159s, 1093m cm^{-1}.

Cleavage of 1,1-dimethylethyl-*N*-[3-(hydroxymethyl)-1-(4-chlorophenyl)-3-butenyl]carbamate (425) from resin 424



$C_{16}H_{22}ClNO_3$ (mw: 311.80 g/mol)

The resin **424** (200 mg) was suspended in THF (3.0 mL) and cooled to 0°C (ice bath). Lithium borohydride (2N in THF, 1.0 mL, 2.0 mmol) was added followed by methanol (80 μL, 2.0 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The resin was collected by filtration and washed with dichloromethane (30 mL) and methanol (30 mL). Removal of the filtrate solvent under vacuum afforded a white solid, which was dissolved in saturated aqueous $NaHCO_3$ solution (10 mL). This was extracted with dichloromethane (5 x 15 mL) and the combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed under vacuum and the crude product purified by flash chromatography (1.5 x 5.0 cm silica), eluting with an ether/hexane mixture (40:60), to afford the title compound **425** as a white solid (27 mg, 87 μmol, 100 % based on loading of resin **365**).

IR (CH_2Cl_2 solution) υ_{max} : 3612w, 3427m, 2924m, 1714s (C=O), 1602w, 1499s, 1256s, 1172s, 1024m, 854s, 767s cm^{-1}.

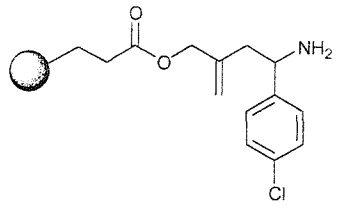
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.31 (2H, d, J = 8.4 Hz , C**H** aromatic), 7.23 (2H, d, J = 8.4 Hz , C**H** aromatic), 5.11 (1H, s, -C=C**H**H), 4.90 (1H, s, -C=CH**H**), 4.85 (1H, br s, ArC**H**-), 4.07 (2H, s, -C**H**$_2$OH), 2.55 (1H, dd, J = 13.9 Hz, 5.0 Hz, PhCHCH**H**-), 2.43 (1H, dd, J = 13.9 Hz, 9.4 Hz, PhCHC**H**H-), 2.37 (1H, br s, -O**H**), 1.39 (9H, s, -C**Me**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ : 155.79 (-**C**O$_2$-), 144.80 (**C** aromatic), 141.73 (>**C**=CH$_2$), 133.12 (**C** aromatic), 128.87 & 127.76 (**C**H aromatic), 114.78 (>C=**C**H$_2$), 80.13 (-**C**Me$_3$), 66.32 (-**C**H$_2$OH), 53.20 (-**C**HAr), 41.58 (ArCH**C**H$_2$-), 28.45 (-C**Me**$_3$).

MS (EI) *m/z* (rel. intensity): 315.3 (7), 314.3 (35), 313.2 (17), 312.3 (100[M+H]$^+$).

m.p.: 122-124°C.

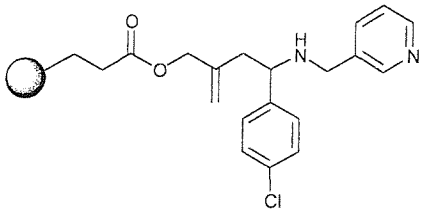
2-[2-Amino-2-(4-chlorophenyl)ethyl]allyl 3-polystyrylpropanoate (426)



TFA (8 mL) was added to a suspension of resin **424** (850 mg) in dichloromethane (8 mL). After 30 minutes the resin was collected by filtration and washed with a solution of *N,N*-diisopropylamine (10 mL) in dichloromethane (80 mL) followed by dichloromethane (200 mL). The resin was dried under vacuum for 2 hours (50°C). This afforded the title compound **426** as a white solid (807 mg).

IR (on-bead) υ_{max} : 3027m, 2922m, 2852w, 1730s (C=O), 1600m, 1495s, 1450s cm^{-1}.

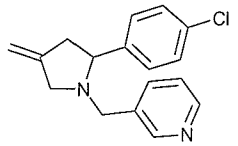
2-{(4-Chlorophenyl)-2-[(3-pyridylmethyl)amino]ethyl}-2-propenyl 3-polystyrylpropanoate (428)



3-Pyridinecarboxaldehyde (240 μL, 268 mg, 2.5 mmol) and acetic acid (160 μL) were added to a suspension of the resin **426** (350 mg) in dichloroethane (8 mL). After stirring at room temperature overnight the resin was collected by filtration and washed with dichloroethane (25 mL). The resin was suspended in a solution of tetramethylammonium triacetoxyborohydride (950 mg, 3.6 mmol) and acetic acid (160 μL) in dichloroethane (8 mL). The suspension was stirred at room temperature for 24 hours and then the resin was collected by filtration. After washing with dichloromethane (250 mL) and methanol (100 mL) the resin was dried under vacuum for 2 hours (50°C). This afforded the title compound **428** as a white solid (371 mg).

IR (on-bead) υ_{max} : 3027m, 2922s, 1725s (C=O), 1595m, 1490s, 1450s cm^{-1}.

3-{[2-(4-Chlorophenyl)-4-methylenetetrahydro-1*H*-1-pyrrolyl]methyl}pyridine (430)

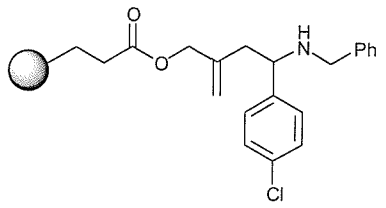


$C_{17}H_{17}ClN_2$ (mw: 284.78 g/mol)

Palladium(II) acetylacetonate (2.2 mg, 7.2 μmol, 10 mol%), 1,2-bis (diphenylphosphino) ethane (8.5 mg, 21.4 μmol, 30 mol%) and resin **428** (200 mg) in THF (4 mL) was heated at reflux for 12 hours. The resin was collected by filtration and washed with dichloromethane (50 mL). The filtrate solvent was removed under vacuum to afford an orange residue. Purification by flash chromatography (1.5 x 5.0 cm silica), eluting with an ether/hexane mixture (60:40), afforded the title compound **430** as a colourless oil (7 mg, 25 μmol, 34 %).

IR (CH_2Cl_2 solution): 3029m, 1621m, 1597m, 1502s, 1451s, 1045m, 842s, 776s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.53 (2H, br s, C(2)**H** & C(6)**H** pyridyl), 7.66 (1H, d, *J* = 7.4 Hz, C(4)**H** pyridyl), 7.46-7.25 (5H, m, C(5)**H** pyridyl & C**H** phenyl), 4.90 (2H, s, >C=C**H$_2$**), 3.81 (1H, d, *J* = 13.4 Hz, -NC**H**HAr), 3.66-3.58 (2H, m, ArC**H**- & -NCH**H**C=CH_2), 3.15 (1H, d, *J* = 13.4 Hz, -NCH**H**Ar), 2.97 (1H, d, *J* = 13.4 Hz, -NC**H**HC=CH_2), 2.86 (1H, dd, *J* = 16.4 Hz, 6.5 Hz, ArCHC**H**H-), 2.54-2.45 (1H, m, ArCHCH**H**-).
^{13}C NMR (75 MHz, $CDCl_3$) δ : 150.30 & 148.82 (**C**H aromatic), 146.58 (>**C**=CH_2), 142.50 (**C** aromatic), 136.73 (**C**H aromatic), 135.03 (**C** aromatic), 129.73, 128.01 & 123.73 (**C**H aromatic), 105.54 (>C=**C**H_2), 70.19 (Ar**C**H-), 59.04 (Ar**C**H_2-), 55.70 (ArCH_2N**C**H_2-), 43.10 (ArCH**C**H_2-).
MS (EI) *m/z* (rel. intensity): 288.2 (5), 287.1 (35), 286.1 (16), 285.1 (100[M+H]$^+$).
HRMS (EI) *m/z* : 285.1160; $C_{17}H_{18}ClN_2$ ([M+H]$^+$) requires 285.1159.

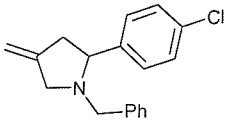
2-{(4-Chlorophenyl)-2-[(phenylmethyl)amino]ethyl}-2-propenyl 3-polystyrylpropanoate (427)



Benzaldehyde (380 μL, 371 mg, 3.5 mmol) and acetic acid (160 μL) were added to a suspension of the resin **426** (350 mg) in dichloroethane (8 mL). After stirring at room temperature overnight the resin was collected by filtration and washed with dichloroethane (25 mL). The resin was suspended in a solution of tetramethylammonium triacetoxyborohydride (730 mg, 2.8 mmol) and acetic acid (160 μL) in dichloroethane (8 mL). The suspension was stirred at room temperature for 24 hours and then the resin was collected by filtration. After washing with dichloromethane (250 mL) and methanol (100 mL) the resin was dried under vacuum for 2 hours (50°C). This afforded the title compound **427** as a white solid (359 mg).

IR (on-bead) υ_{max} : 3027m, 2917m, 1730s (C=O), 1600m, 1495s, 1450s cm^{-1}.

1-Benzyl-2-(4-chlorophenyl)-4-methylenepyrrolidine (429)



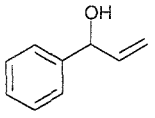
$C_{18}H_{18}ClN$ (mw: 283.79 g/mol)

Palladium(II) acetylacetonate (2.2 mg, 7.2 μmol, 10 mol%), 1,2-bis(diphenylphosphino) ethane (8.5 mg, 21.4 μmol, 30 mol%) and resin **427** (200 mg) in THF (4 mL) was heated at reflux for 12 hours. The resin was collected by filtration and washed with dichloromethane (50 mL). The filtrate solvent was removed under vacuum to afford an orange residue. Purification by flash chromatography (1.5 x 5.0 cm silica), eluting with an ether/hexane mixture (2:98), afforded the title compound **429** as a colourless oil (14 mg, 50 μmol, 69 %).

IR (CH_2Cl_2 solution): 2987m, 1638m, 1605m, 1512s, 1449s, 1062m, 858s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.47-7.30 (9H, m, C**H** aromatic), 4.87 (2H, s, >C=C**H$_2$**), 3.83 (1H, d, *J* = 13.4 Hz, PhC**H**H-), 3.66 (1H, d, *J* = 13.9 Hz, PhCH$_2$NC**H**H-), 3.56 (1H, dd, *J* = 9.9 Hz, 6.5 Hz, ArC**H**-), 3.06 (1H, d, *J* = 13.4 Hz, PhCH**H**-), 2.94 (1H, d, *J* = 13.9 Hz, PhCH$_2$NC**H**H-), 2.83 (1H, dd, *J* = 16.4 Hz, 6.5 Hz, ArCHC**H**H-), 2.55-2.40 (1H, m, ArCHCH**H**-).
^{13}C NMR (75 MHz, $CDCl_3$) δ : 146.54, 141.40, 139.15 & 133.08 (**C** aromatic & >**C**=CH$_2$), 129.07, 128.88, 128.68, 128.39 & 127.10 (**C** aromatic), 105.08 (>C=**C**H$_2$), 69.07 (Ar**C**H-), 58.76 (Ph**C**H$_2$-), 58.13 (PhCH$_2$N**C**H$_2$-), 42.95 (ArCH**C**H$_2$-).
MS (EI) *m/z* (rel. intensity): 287.2 (6), 286.2 (35), 285.2 (18), 284.2 (100[M+H]$^+$).
HRMS (EI) *m/z* : 284.1203; $C_{18}H_{19}ClN$ ([M+H]$^+$) requires 284.1206.

5.3 The solid-phase synthesis of allylic amines using a nucleophilic release strategy

1-Phenyl-prop-2-en-1-ol (440d) [279]



$C_9H_{10}O$ (mw: 134.18 g/mol)

A solution of vinylmagnesium bromide (1.0 M in THF, 125 mL, 125 mmol) was added dropwise to a solution of benzaldehye (11.5 mL, 12.0 g, 113 mmol) in THF (40 mL) at 0°C (ice-bath) under a nitrogen atmosphere. The bath was removed and the reaction allowed to warm to room temperature and stirred for a further 1 hour. Saturated aqueous NH_4Cl solution (150 mL) was added and the aqueous phase extracted with dichloromethane (2 x 80 mL), Et_2O (2 x 80 mL) and EtOAc (2 x 80 mL). The organic layers were combined, washed with brine (80 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum gave the crude product as a yellow oil. Purification by distillation (3 mmHg, 90-94°C) gave the known title compound **440d** as a colourless liquid (12.5 g, 93 mmol, 82 %). The spectroscopic details were consistent with those in the literature.[279]

CAS Number: [4393-06-0].

IR (film) υ_{max} : 3383br s (OH), 3033m, 2878w, 1499m, 1459m, 1201m, 1121m, 1030s, 995s, 932s cm^{-1}.

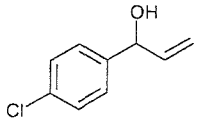
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.43-7.25 (5H, m, C**H** aromatic), 6.07 (1H, ddd, *J* = 17.4 Hz, 10.2 Hz, 5.6 Hz, -C**H**=CHH), 5.36 (1H, d, *J* = 17.4 Hz, PhC**H**-), 5.25-5.18 (2H, m, -CH=CH**H** & -CH=C**H**H), 2.22 (1H, br s, -O**H**).

^{13}C NMR (75 MHz, $CDCl_3$) δ : 142.8 (**C** aromatic), 140.4 (-**C**H=CHH), 128.7, 127.9 & 126.5 (**C**H aromatic), 115.3 (-CH=**C**HH), 75.5 (Ph**C**H-).

MS (CI) *m/z* (rel. intensity): 133 (100[M-H]$^+$), 117 (39), 105 (83), 92 (56), 77 (81), 51 (42).

b.p.: 90-94°C (3 mmHg).

1-(4-Chlorophenyl)-prop-2-en-1-ol (440b) [279]



C_9H_9OCl (mw: 168.62 g/mol)

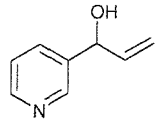
A solution of vinylmagnesium bromide (1.0 M in THF, 94 mL, 94 mmol) was added dropwise to a solution of 4-chlorobenzaldehye (12.0 g, 85 mmol) in THF (50 mL) at 0°C (ice-bath) under a nitrogen atmosphere. The bath was removed and the reaction allowed to warm to room temperature and stirred for a further 1 hour. Saturated aqueous NH_4Cl solution (100 mL) was added and the aqueous phase extracted with dichloromethane (4 x 100 mL). The organic layers were combined, washed with brine (50 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum gave the crude product as an orange oil. Purification by distillation (3 mmHg, 117-120°C) gave the known title compound **440b** as a colourless liquid (10.5 g, 62 mmol, 73 %). The spectroscopic details were consistent with those in the literature.[279]

CAS Number: [58824-54-7].

IR (film) υ_{max} : 3582s, 3398s br (OH), 3086m, 3019m, 2877s, 1640m, 1598m, 1490s, 1409s, 1293m, 1228s, 1185m, 1090s, 1030s, 1010s, 985s, 925s, 840s, 829s cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.39-7.26 (4H, m, C**H** aromatic), 6.01 (1H, ddd, *J* = 16.4 Hz, 9.9 Hz, 5.9 Hz , -C**H**OH), 5.35 (1H, d, *J* = 16.9 Hz, -C**H**=CHH), 5.24-5.18 (2H, m, -CH=C**H**H & -CH=CH**H**), 4.67 (1H, br s, -O**H**).
^{13}C NMR (75 MHz, $CDCl_3$) δ : 141.16 (**C** aromatic), 140.06 (-**C**H=CHH), 133.51 (**C** aromatic), 128.82 & 127.87 (**C**H aromatic), 115.78 (-CH=**C**H_2), 74.84 (-**C**H).
MS (CI) *m/z* (rel. intensity): 168 (40$[M]^+$), 133 (100), 115 (40), 77 (71), 55 (43).
b.p.: 117-120°C (3 mmHg).

1-Pyridin-3-yl-prop-2-en-1-ol (440a) [280]



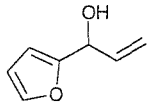
C_8H_9NO (mw: 135.17 g/mol)

A solution of vinylmagnesium bromide (1.0 M in THF, 130 mL, 130 mmol) was added dropwise to a solution of 3-pyridinecarboxaldehye (10.6 mL, 12.0 g, 112 mmol) in THF (100 mL) at 0°C (ice-bath) under a nitrogen atmosphere. The bath was removed and the reaction allowed to warm to room temperature and stirred for a further 1 hour. Saturated aqueous NH_4Cl solution (100 mL) was added and the aqueous phase extracted with dichloromethane (4 x 150 mL). The organic layers were combined, washed with brine (100 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum gave the crude product as a brown oil. Purification by distillation (3 mmHg, 128-134°C) gave the known title compound **440a** as a colourless liquid (6.2 g, 46 mmol, 41 %). The spectroscopic details were consistent with those in the literature.[280]

CAS Number: [144825-44-5].
IR (film) υ_{max} : 3407s br (OH), 3052m, 2884w, 1637m, 1602m, 1487s, 1152s, 1027s, 874w, 787s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.49 (1H, d, *J* = 2.2 Hz, C(2)**H** pyridyl), 8.41 (1H, dd, *J* = 4.4 Hz, 1.5 Hz, C(6)**H** pyridyl), 7.73 (1H, dt, *J* = 8.1 Hz, 2.2 Hz, C(4)**H** pyridyl), 7.26 (1H, dd, *J* = 8.1 Hz, 4.4 Hz, C(5)**H** pyridyl), 6.07-5.96 (1H, m, -C**H**OH), 5.35 (1H, d, J = 16.9 Hz, -C**H**=CHH), 5.24-5.20 (2H, m, -CH=C**H**H & -CH=CH**H**), 4.46 (1H, br s, -O**H**).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.52 & 148.01 (**C**(2)H & **C**(6)H pyridyl), 139.91 (-**C**H=CH_2), 138.76 (**C** aromatic), 134.59 (**C**(4)H pyridyl), 123.71 (**C**(5)H pyridyl), 116.01 (-CH=**C**H_2), 72.93 (-**C**H).
MS (ES) *m/z* (rel. intensity): 137.0 (9), 136.0 (100$[M+H]^+$).
b.p.: 128-134°C (3 mmHg).

1-(Furan-2-yl)-prop-2-en-1-ol (440c) [281]

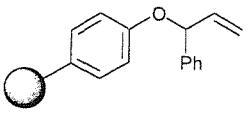


$C_7H_8O_2$ (mw: 124.14 g/mol)

A solution of vinylmagnesium bromide (1.0 M in THF, 140 mL, 140 mmol) was added dropwise to a solution of 2-furaldehye (10.2 mL, 11.8 g, 123 mmol) in THF (50 mL) at 0°C (ice-bath) under a nitrogen atmosphere. The bath was removed and the reaction allowed to warm to room temperature and stirred for a further 1 hour. Saturated aqueous NH_4Cl solution (80 mL) was added and the aqueous phase extracted with Et_2O (4 x 50 mL). The organic layers were combined, washed with brine (50 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum gave the crude product as a yellow oil. Purification by distillation (3 mmHg, 70-74°C) gave the known title **440c** compound as a colourless liquid (11.9 g, 96 mmol, 78 %). The spectroscopic details were consistent with those in the literature.[281]

CAS Number: [119619-38-4].
IR (film) ν_{max} : 3320s br (OH), 3043m, 2913w, 1589m, 1483s, 1164s, 1042s, 896w cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.41 (1H, dd, *J* = 2.0 Hz, 1.0 Hz, C(1)**H** furyl), 6.35 (1H, dd, *J* = 3.0 Hz, 2.0 Hz, C(4)**H** furyl), 6.27 (1H, d, *J* = 3.0 Hz, C(3)**H** furyl), 6.14 (1H, ddd, *J* = 15.9 Hz, 10.4 Hz, 5.5 Hz, -C**H**OH), 5.44 (1H, d, *J* = 17.3 Hz, -C**H**=CHH), 5.33-5.22 (2H, m, -CH=C**H**H & -CH=CH**H**), 4.55 (1H, -O**H**).
^{13}C NMR (75 MHz, $CDCl_3$) δ : 154.24 (**C**(2) furyl), 142.85 (**C**(5)H furyl), 137.50 (-**C**H=CH_2), 114.86 (-CH=**C**H_2), 110.73 (**C**(3)H furyl), 107.91 (**C**(4)H furyl), 79.82 (-**C**HOH).
MS (CI) *m/z* (rel. intensity): 124 (100$[M]^+$), 107 (27), 95 (42), 67 (74).
b.p.: 70-74°C (3 mmHg).

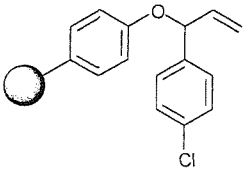
1-Phenylallyl polystyryl ether (434d)



1-Phenyl-prop-2-en-1-ol **(440d)** (3.83 g, 28.5 mmol) and triphenylphospine (7.46 g, 28.4 mmol) were added to a suspension of hydroxypolystyrene **(365)** (2.52 g) in THF (40 mL) under a nitrogen atmosphere. The suspension was cooled to 0°C (ice-bath) and after 10 minutes DEAD (4.50 mL, 4.98 g, 28.6 mmol) was added dropwise. The ice-bath was removed and the resulting orange suspension was stirred at room temperature overnight. The resin was collected by filtration, washed with dichloromethane, DMF, MeOH and DMF (100 mL of each) and dried under vacuum (50°C) for 2 hours. This afforded the title product **434d** (3.16 g) as a beige solid.

IR (on-bead) υ_{max} : 3373m, 3234w, 1667m, 1610m, 1511s, 1449m, 1237s, 1171m, 840s, 827s, 793m cm^{-1}.
^{13}C NMR (Gel-phase, 75 MHz, $CDCl_3$) δ : 138.4 (Ph**C**H-), 116.4 (**C**H_2), 81.1 (-**C**H=CH_2).

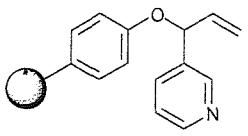
1-(4-Chlorophenyl)allyl polystyryl ether (434b)



1-(4-Chlorophenyl-prop-2-en-1-ol **(440b)** (4.21 g, 25.0 mmol) and triphenylphospine (7.52 g, 28.7 mmol) were added to a suspension of hydroxypolystyrene **(365)** (2.50 g) in THF (40 mL) under a nitrogen atmosphere. The suspension was cooled to 0°C (ice-bath) and after 10 minutes DEAD (4.5 mL, 4.98 g, 28.6 mmol) was added dropwise. The ice-bath was removed and the resulting orange suspension was stirred at room temperature overnight. The resin was collected by filtration , washed with dichloromethane, DMF, MeOH and dichloromethane (100 mL of each) and dried under vacuum (50°C) for 2 hours. This afforded the title product **434b** (3.55 g) as a beige solid.

IR (on-bead) υ_{max} : 3310m, 3193w, 1665m, 1610m, 1511s, 1490m, 1238s, 828s cm^{-1}.

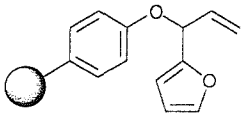
1-(3-Pyridyl)allyl polystyryl ether (434a)



1-(Pyridin-3-yl)-prop-2-en-1-ol **(440a)** (3.05 g, 22.6 mmol) and triphenylphospine (5.92 g, 22.6 mmol) were added to a suspension of hydroxypolystyrene **(365)** (2.04 g) in THF (30 mL) under a nitrogen atmosphere. The suspension was cooled to 0°C (ice-bath) and after 10 minutes DEAD (3.60 mL, 3.98 g, 22.9 mmol) was added dropwise. The ice-bath was removed and the resulting orange suspension was stirred at room temperature overnight. The resin was collected by filtration, washed with dichloromethane, DMF, MeOH and dichloromethane (150 mL of each) and dried under vacuum (50°C) for 2 hours. This afforded the title product **434a** (2.61 g) as a brown solid.

IR (on-bead) υ_{max} : 3295m, 3191m, 1662m, 1612m, 1511s, 1455m, 1356w, 1238s, 1174m, 841m, 827s cm^{-1}.

1-(2-Furyl)allyl polystyryl ether (434c)

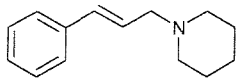


1-(Furan-2-yl)-prop-2-en-1-ol **(440c)** (2.78 g, 22.6 mmol) and triphenylphospine (5.92 g, 22.6 mmol) were added to a suspension of hydroxypolystyrene **(365)** (2.07 g) in THF (30 mL) under a nitrogen atmosphere. The suspension was cooled to 0°C (ice-bath) and after 10 minutes DEAD (3.60 mL, 3.98 g, 22.9 mmol) was added dropwise. The ice-bath was removed and the resulting orange suspension was stirred at room temperature overnight. The resin was collected by filtration, washed with dichloromethane, DMF,

MeOH and dichloromethane (150 mL of each) and dried under vacuum (50°C) for 2 hours. This afforded the title product **434c** (2.58 g) as a brown solid.

IR (on-bead) υ_{max} : 1665w, 1601m, 1511s, 1483w, 1446m, 1360m, 1233s, 1173m, 845s, 829s cm^{-1}.

1-(3-Phenyl-allyl)-piperidine (441)



$C_{14}H_{19}N$ (mw: 201.31 g/mol)

Palladium(II) acetylacetonate (3.1 mg, 10.2 μmol, 5 mol%), 1,2-bis(diphenylphosphino) ethane (8.1 mg, 20.3 μmol, 10 mol%) were added to a suspension of resin **434d** (148.2 mg) in THF (3 mL). Piperidine (17.3 mg, 0.20 mmol, 1.0 equiv.) was added and the reaction heated at reflux, under a nitrogen atmosphere, for 1.5 hours. The resin was collected by filtration, washed with dichloromethane (50 mL) and the filtrate solvent removed under vacuum to afford an orange oil. Purification by column chromatography (9.0 x 1.5 cm silica), using an ether/hexane (1:1) eluent system, afforded the known title product **441** as a yellow oil (20.9 mg, 10.4 mmol, 52 %). The spectroscopic details were consistent with those in the literature.[282]

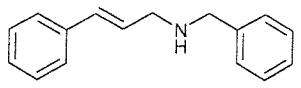
CAS Number: [5882-82-6].

^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.39-7.20 (5H, m, C**H** aromatic), 6.51 (1H, d, J = 15.9 Hz, ArC**H**=CH-), 6.32 (1H, dt, J = 15.9 Hz, 6.5 Hz, ArCH=C**H**-), 3.14 (2H, d, J = 6.5 Hz, ArCH=CHC**H$_2$**-), 2.46 (4H, br s, -NC**H$_2$**CH_2CH_2-), 1.66-1.59 (4H, m, -NCH_2C**H$_2$**CH_2-), 1.50-1.43 (2H, m, -NCH_2CH_2C**H$_2$**-).

^{13}C NMR (300 MHz, $CDCl_3$) δ : 136.83 (**C** aromatic), 132.58 (Ar**C**H=CH-), 128.23 (**C**H aromatic), 127.17 (ArCH=**C**H-), 126.96 & 126.21 (**C**H aromatic), 61.65 (-N**C**H_2CH=CH-), 54.38 (-N**C**$H_2CH_2CH_2$-), 25.76 (-NCH_2**C**H_2CH_2-), 24.33 (-NCH_2CH_2**C**H_2-).

MS (EI) *m/z* (rel. intensity): 203.2 (14), 202.1 (100[M]$^+$).

Benzyl-(3-phenyl-allyl)amine (443)

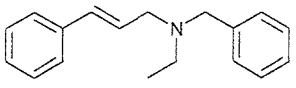


$C_{16}H_{17}N$ (mw: 223.31 g/mol)

Tetrakis(triphenylphosphine)palladium(0) (12.1 mg, 10.5 μmol, 5 mol%) and benzylamine (107.0 mg, 0.84 mmol, 4.0 equiv.) were added to a suspension of resin **434d** (149.8 mg, 0.21 mmol) in THF (3 mL). The reaction was heated at reflux, under a nitrogen atmosphere, for 2 hours. The resin was collected by filtration, washed with dichloromethane (60 mL) and the filtrate solvent removed under vacuum to afford an orange oil (170 mg). Purification by column chromatography (6.0 x 1.5 cm silica), using a methanol/dichloromethane (1:99) eluent system, afforded the title product **443** as a yellow oil (35.7 mg, 0.16 mmol, 76 %). The spectroscopic details were consistent with those in the literature.[283,284]

CAS Number: [40032-55-1].
IR (CH_2Cl_2 solution): 2925m, 1600m, 1508s, 1082s, 764s, 711s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.45-7.17 (10H, m, C**H** aromatic), 6.54 (1H, d, J = 15.9 Hz, PhC**H**=CH-), 6.36 (1H, dt, J = 15.9 Hz, 4.8 Hz, PhCH=C**H**-), 3.78 (2H, s, -NC**H**$_2$Ph), 3.32 (2H, d, J = 4.8 Hz, -NC**H**$_2$CH=CH-).
^{13}C NMR (75 MHz, $CDCl_3$) δ : 140.26 & 137.19 (**C** aromatic), 131.12, 128.59, 128.31, 127.98, 127.14, 126.78 & 126.22 (**C**H aromatic & **C**H alkene), 53.20 (-N**C**H$_2$Ph), 51.06 (-N**C**H$_2$CH=CH-).
MS (EI) *m/z* (rel. intensity): 225.1 (18), 224.1 (100[M+H]$^+$).

Benzyl-ethyl-(3-phenyl-allyl)amine (444)



$C_{18}H_{21}N$ (mw: 251.37 g/mol)

Palladium(II) acetylacetonate (3.1 mg, 10.2 μmol, 5 mol%), 1,2-bis(diphenylphosphino) ethane (8.1 mg, 20.3 μmol, 10 mol%) were added to a suspension of resin **434d** (150.0

mg) in THF (3 mL). Benzylethylamine (27.1 mg, 0.20 mmol, 1.0 equiv.) was added and the reaction heated at reflux, under a nitrogen atmosphere, for 1.5 hours. The resin was collected by filtration, washed with dichloromethane (50 mL) and the filtrate solvent removed under vacuum to afford an orange oil. Purification by column chromatography (9.0 x 1.5 cm silica), using an dichloromethane/hexane (3:1) eluent system, afforded the known title product **444** as a yellow oil (25.2 mg, 10.0 mmol, 49 %).[285]

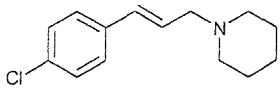
CAS Number: [40596-41-6].

^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.40-7.24 (10H, m, C**H** aromatic), 6.55 (1H, d, J = 15.4 Hz, PhC**H**=CH-), 6.32 (1H, dt, J = 15.9 Hz, 6.5 Hz, PhCH=C**H**-), 3.66 (2H, s, -NC**H**$_2$Ph), 3.27 (2H, d, J = 6.5 Hz, -NC**H**$_2$CH=CH-), 2.61 (2H, q, J = 7.4 Hz, -NC**H**$_2$CH$_3$), 1.12 (3H, t, J = 7.4 Hz, -NCH$_2$C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ : 139.87 & 137.64 (**C** aromatic), 132.77, 129.41, 128.94, 128.61, 128.13, 127.71 & 127.26 (**C**H aromatic), 126.68 (PhCH=**C**H-), 58.12 (PhCH=CH**C**H$_2$-), 56.11 (-N**C**H$_2$Ph), 47.64 (-N**C**H$_2$CH$_3$), 12.28 (-NCH$_2$**C**H$_3$).

MS (EI) *m/z* (rel. intensity): 253.1 (19), 252.1 (100[MH$^+$]).

1-[3-(4-Chlorophenyl)allyl)]piperidine (446)



$C_{14}H_{18}NCl$ (mw: 235.75 g/mol)

Tetrakis(triphenylphosphine)palladium(0) (11.0 mg, 9.5 μmol, 5 mol%) and piperidine (15.8 mg, 0.19 mmol, 1.0 equiv.) were added to a suspension of resin **434b** (148.7 mg, 0.19 mmol) in THF (3 mL). The reaction was heated at reflux, under a nitrogen atmosphere, for 1.5 hours. The resin was collected by filtration, washed with dichloromethane (50 mL) and the filtrate solvent removed under vacuum to afford an orange oil (49 mg). Purification by column chromatography (6.0 x 1.5 cm silica), using a methanol/dichloromethane (5:95) eluent system, afforded the known title product **447** as a yellow oil (34.4 mg, 146 μmol, 77 %).

OR

Using palladium(II) acetylacetonate (2.9 mg, 9.5 μmol, 5 mol%), 1,2-bis(diphenylphosphino)ethane (7.6 mg, 19.0 μmol, 10 mol%) as the catalyst system afforded the known title product **446** as a yellow oil (32.3 mg, 137 μmol, 72 %).

CAS Number: [92378-22-8].

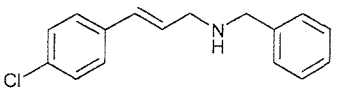
IR (CH_2Cl_2 solution): 2946m, 2890w, 1632w, 1604m, 1581m, 1498m, 1374m, 810s cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.29 (2H, d, J = 8.6 Hz, C**H** aromatic), 7.25 (2H, d, J = 8.6 Hz, C**H** aromatic), 6.44 (1H, d, J = 15.9 Hz, ArC**H**=CH-), 6.27 (1H, dt, J = 15.9 Hz, 7.0 Hz, ArCH=C**H**-), 3.10 (2H, dd, J = 7.0 Hz, 1.0 Hz, ArCH=CHC**H$_2$**-), 2.42 (4H, br s, -NC**H$_2$**CH$_2$CH$_2$-), 1.69-1.55 (4H, m, -NCH$_2$C**H$_2$**CH$_2$-), 1.50-1.41 (2H, m, -NCH$_2$CH$_2$C**H$_2$**-).

^{13}C NMR (100MHz, $CDCl_3$) δ : 135.72 & 133.20 (**C** aromatic), 131.78 (Ar**C**H=CH-), 128.90 (**C**H aromatic), 127.93 (ArCH=**C**H-), 127.71 (**C**H aromatic), 61.92 (-N**C**H$_2$CH=CH-), 54.82 (-N**C**H$_2$CH$_2$CH$_2$-), 26.09 (-NCH$_2$**C**H$_2$CH$_2$-), 24.45 (-NCH$_2$CH$_2$**C**H$_2$-).

MS (EI) *m/z* (rel. intensity): 277.0 (8), 239 (5), 238.0 (35), 235.9 (100[M+H]).

Benzyl-[3-(4-Chlorophenyl)allyl]amine (445)



$C_{16}H_{16}ClN$ (mw: 257.76 g/mol)

Tetrakis(triphenylphosphine)palladium(0) (11.0 mg, 9.5 μmol, 5 mol%) and benzylamine (81.4 mg, 0.76 mmol, 4.0 equiv.) were added to a suspension of resin **434b** (151.5 mg, 0.19 mmol) in THF (3 mL). The reaction was heated at reflux, under a nitrogen atmosphere, for 1.5 hours. The resin was collected by filtration, washed with dichloromethane (60 mL) and the filtrate solvent removed under vacuum to afford an orange oil (90 mg). Purification by column chromatography (6.0 x 1.5 cm silica), using an ether/hexane (40:60) eluent system, afforded the title product **445** as a yellow oil (37.2 mg, 144 μmol, 76 %).

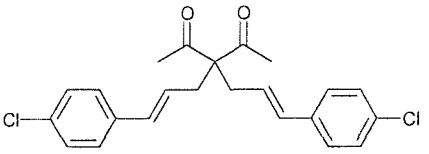
OR

Using benzylamine (20.4 mg, 0.19 mmol, 1.0 equiv.) afforded the title product **445** as a yellow oil (33.8 mg, 0.13 mmol, 69%).

IR (CH_2Cl_2 solution): 3429m, 2957m, 1623w, 1605m, 1583m, 1508s, 1089s, 852s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.42-7.35 (9H, m, C**H** aromatic), 6.52 (1H, d, J = 16.2 Hz, ArC**H**=CH-), 6.30 (1H, dt, J = 16.2 Hz, 4.8 Hz, ArCH=C**H**-), 3.77 (2H, s, -NC**H**$_2$Ph), 3.46 (2H, d, J = 4.8 Hz, -NC**H**$_2$CH=CH-).
^{13}C NMR (100 MHz, $CDCl_3$) δ : 140.09, 135.64 & 132.95 (**C** aromatic), 130.15, 129.13, 128.69, 128.47, 128.20, 127.46 & 127.06 (**C**H aromatic & **C**H alkene), 53.39 (-NC**H**$_2$Ph), 51.07 (-NC**H**$_2$CH=CH-).
MS (EI) *m/z* (rel. intensity): 302.1 (3), 301.1 (13), 300.1 (8), 299.1 (39$[M+K]^+$), 261.1 (6), 260.1 (35), 259.1 (17), 258.1 (100$[M+H]^+$).
HRMS (EI) *m/z* : 258.1047; $C_{16}H_{17}ClN$ ($[M+H]^+$) requires 258.1050.

The corresponding acetylacetonate adduct **455** (12.1 mg, 0.03 mmol, 10 %) was isolated from the reaction using palladium(II) acetylacetonate (2.9 mg, 9.5 μmol, 5 mol%), 1,2-bis(diphenylphosphino)ethane (7.6 mg, 19.0 μmol, 10 mol%) as the catalyst system.

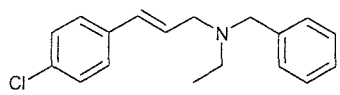
3,3-di[(*E*)-3-(4-chlorophenyl)-2-propenyl]-2,4-pentanedione (455)



$C_{23}H_{22}Cl_2O_2$ (mw: 407.42 g/mol)

IR (film) υ_{max} : 1698s (C=O), 1491s, 1359m, 1093s, 1012m, 969m cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.23-7.11 (8H, m, C**H** aromatic), 6.52 (2H, d, J = 16.0 Hz, ArC**H**=CH-), 6.27 (2H, dt, J = 16.0 Hz, 4.9 Hz, ArCH=C**H**-), 2.85 (4H, d, J = 4.9 Hz, -CC**H**$_2$CH=CH-), 2.08 (6H, s, -COC**H**$_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ : 205.76 (**C**=O), 135.34 & 133.45 (**C** aromatic), 133.28, 128.91, 127.51 & 124.12 (**C**H alkene & aromatic), 70.83 (-**C**-COMe), 34.72 (-**C**H$_2$-), 27.48 (-COCH$_3$).
MS (EI) *m/z* (rel. intensity): 411.3 (3), 410.2 (17), 409.2 (8), 408.2 (26$[M+H]^+$).

Benzyl-[3-(4-chlorophenyl)allyl]-ethyl amine (447)

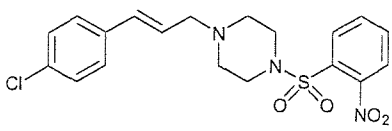


$C_{18}H_{20}ClN$ (mw: 285.81 g/mol)

Palladium(II) acetylacetonate (2.9 mg, 9.5 μmol, 5 mol%), 1,2-bis(diphenylphosphino) ethane (7.5 mg, 18.8 μmol, 10 mol%) were added to a suspension of resin **434b** (152.3 mg, 0.19 mmol) in THF (3 mL). Ethylbenzylamine (25.8 mg, 0.19 mmol, 1.0 equiv.) was added and the reaction heated at reflux, under a nitrogen atmosphere, for 1.5 hours. The resin was collected by filtration, washed with dichloromethane (60 mL) and the filtrate solvent removed under vacuum to afford an orange oil (57 mg). Purification by column chromatography (8.0 x 1.5 cm silica), using a methanol/dichloromethane (3:97) eluent system, afforded the title product **447** as a yellow oil (36.4 mg, 12.7 μmol, 67 %).

IR (film) υ_{max} : 2962m, 1629m, 1599m, 1579m, 1506s, 1056s, 847s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.38-7.24 (9H, m, C**H** aromatic), 6.49 (1H, d, *J* = 15.9 Hz, ArC**H**=CH-), 6.27 (1H, dt, *J* = 15.9 Hz, 6.5 Hz, ArCH=C**H**-), 3.64 (2H, s, -NC**H$_2$**Ph), 3.25 (2H, dd, *J* = 6.5 Hz, 1.0 Hz, ArCH=CHC**H$_2$**-), 2.59 (2H, q, *J* = 7.0 Hz, -NC**H$_2$**CH_3), 1.11 (3H, t, *J* = 7.0 Hz, -NCH_2C**H$_3$**).
^{13}C NMR (100 MHz, $CDCl_3$) δ : 139.65, 135.91 & 133.05 (**C** aromatic), 131.13 (Ar**C**H=CH-), 129.12, 128.84, 128.40 & 127.63 (**C**H aromatic), 127.05 (ArCH=**C**H-), 58.00 (ArCH=C**H**CH_2-), 55.86 (-N**C**H_2Ph), 47.55 (-N**C**H_2CH_3), 12.08 (-NCH_2**C**H_3).
MS (EI) *m/z* (rel. intensity): 289.1 (5), 287.9 (35), 287.0 (16), 286.0 (100[M+H]).
HRMS (EI) *m/z* : 286.1369; $C_{18}H_{21}ClN$ ($[M+H]^+$) requires 286.1363.

1-[3-(4-Chlorophenyl)allyl]-4-(2-nitrobenzenesulfonyl)piperazine (448)



$C_{19}H_{20}ClN_3O_4S$ (mw: 421.90 g/mol)

Palladium(II) acetylacetonate (2.8 mg, 9.3 μmol, 5 mol%), 1,2-bis(diphenylphosphino) ethane (7.4 mg, 18.6 μmol, 10 mol%) were added to a suspension of resin **434b** (155.3 mg, 0.19 mmol) in THF (3 mL). 1-(2-Nitrobenzenesulfonyl)piperazine **(454)** (52 mg, 0.19 mmol, 1.0 equiv.) was added and the reaction heated at reflux, under a nitrogen atmosphere, for 1.5 hours. The resin was collected by filtration, washed with dichloromethane (60 mL) and the filtrate solvent removed under vacuum to afford an orange oil (96 mg). Purification by column chromatography (9.0 x 1.5 cm silica), using a methanol/dichloromethane (4:96) eluent system, afforded the title product **448** as a yellow oil (39.2 mg, 9.3 μmol, 49 %).

IR (CH_2Cl_2 solution): 2956m, 1605m, 1589s, 1520s, 1362s, 1347s, 1165s, 861s, 769s cm^{-1}.

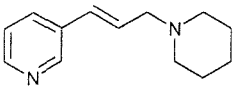
^{1}H NMR (300 MHz, $CDCl_3$): 7.96-7.93 (2H, m, C**H** aromatic), 7.72-7.67 (2H, m, C**H** aromatic), 7.28-7.25 (4H, m, C**H** aromatic), 6.47 (1H, d, J = 15.9 Hz, ArC**H**=CH-), 6.15 (1H, dt, J = 15.9 Hz, 6.5 Hz, ArCH=C**H**-), 3.27-3.24 (4H, m, -SO_2NCH_2-), 3.15 (2H, d, J = 6.5 Hz, ArCH=CHC**H$_2$**-), 2.58-2.55 (4H, m, , -$SO_2NCH_2CH_2$-).

^{13}C NMR (100 MHz, $CDCl_3$): 148.71 & 135.29 (**C** aromatic), 133.91 (**C**H aromatic), 133.50 (**C** aromatic), 132.61, 131.60, 131.09, 128.92, 127.72, 126.47 & 124.25 (**C**H aromatic & **C**H alkene), 60.62 (ArCH=CH**C**H_2-), 52.55 (-SO_2N**C**H_2-), 46.13 (-$SO_2NCH_2CH_2$-).

MS (EI) *m/z* (rel. intensity): 423.2 (42), 421.9 (100$[M+H]^+$).

HRMS (EI) *m/z* : 422.0936; $C_{19}H_{21}ClN_3O_4S$ ($[M+H]^+$) requires 422.0941.

3-(3-Piperidin-1-yl-propenyl)pyridine (450)



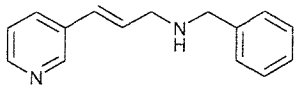
$C_{13}H_{18}N_2$ (mw: 202.30 g/mol)

Palladium(II) acetylacetonate (2.9 mg, 9.7 μmol, 5 mol%), 1,2-bis(diphenylphosphino) ethane (7.7 mg, 19.4 μmol, 10 mol%) were added to a suspension of resin **434a** (149.0 mg) in THF (3 mL). Piperidine (16.5 mg, 0.19 mmol, 1.0 equiv.) was added and the reaction heated at reflux, under a nitrogen atmosphere, for 1.5 hours. The resin was collected by filtration, washed with dichloromethane (50 mL) and the filtrate solvent

removed under vacuum to afford an orange oil (32 mg). Purification by column chromatography (7.0 x 1.5 cm silica), using a methanol/dichloromethane (5:95) eluent system, afforded the title product **450** as an orange oil (21.1 mg, 10.4 mmol, 53 %).

IR (CH_2Cl_2 solution): 2890w, 1625w, 1608m, 1585m, 1498m, 1374m, 817s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.56 (1H, br s, C(2)**H** pyridyl), 8.43 (1H, br s, C(6)**H** pyridyl), 7.68 (1H, dt, *J* = 8.0 Hz, 1.5 Hz, C(5)**H** pyridyl), 7.21 (1H, dd, *J* = 7.9 Hz, 5.0 Hz, C(4)**H** pyridyl), 6.48 (1H, d, *J* = 15.9 Hz, ArC**H**=CH-), 6.36 (1H, dt, *J* = 15.9 Hz, 6.5 Hz, ArCH=C**H**-), 3.13 (2H, dd, *J* = 6.5 Hz, 1.0 Hz, ArCH=CHC**H$_2$**-), 2.43 (4H, br s, -NC**H$_2$**CH_2CH_2-), 1.64-1.56 (4H, m, -NCH_2C**H$_2$**CH_2-), 1.47-1.42 (2H, m, -NCH_2CH_2C**H$_2$**-).
^{13}C NMR (100 MHz, $CDCl_3$) δ : 148.88 & 148.72 (**C**(2)H & **C**(6)H pyridyl), 133.04 (**C**(4)H pyridyl), 130.15 (Ar**C**H=CH-), 129.40 (ArCH=**C**H-), 123.83 (**C**(5)H pyridyl), 62.10 (-N**C**H_2CH=CH-), 55.07 (-N**C**$H_2CH_2CH_2$-), 26.33 (-NCH_2**C**H_2CH_2-), 24.65 (-NCH_2CH_2**C**H_2-).
MS (EI) *m/z* (rel. intensity): 204.0 (16), 203.0 (100[M+H]).
HRMS (EI) *m/z* : 203.1547; $C_{13}H_{18}N_2$ ($[M+H]^+$) requires 203.1548.

Benzyl-(3-pyridin-3-yl-allyl)amine (449)



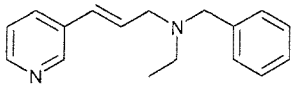
$C_{15}H_{16}N_2$ (mw: 224.30 g/mol)

Tetrakis(triphenylphosphine)palladium(0) (11.3 mg, 9.8 μmol, 5 mol%) and benzylamine (84.2 mg, 0.78 mmol, 4.0 equiv.) were added to a suspension of resin **434d** (151.6 mg, 0.19 mmol) in THF (3 mL). The reaction was heated at reflux, under a nitrogen atmosphere, for 2 hours. The resin was collected by filtration, washed with dichloromethane (60 mL) and the filtrate solvent removed under vacuum to afford an orange oil (119 mg). This was dissolved in dichloromethane (5 mL) and AAEM resin **458** (195 mg, 0.59 mmol) was added. The suspension was stirred at room temperature for 2 hours. The resin was collected by filtration, washed with dichloromethane (80 mL) and the filtrate solvent removed under vacuum to afford an orange oil (49 mg). Purification by column chromatography (6.0 x 1.5 cm silica), using a

methanol/dichloromethane (2:98) eluent system, afforded the title product **449** as a yellow oil (12.8 mg, 57.0 μmol, 30 %).

IR (film) υ_{max} : 3427w, 2964m, 1614w, 1586m, 1498s, 1052s, 864s, 774s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.59 (1H, br s, C(2)**H** pyridyl), 8.47 (1H, br s, C(6)**H** pyridyl), 7.69 (1H, dt, *J* = 7.9 Hz, 1.5 Hz, C(5)**H** pyridyl), 7.37-7.24 (6H, m, C(4)**H** pyridyl & C**H** phenyl), 6.55 (1H, d, *J* = 16.2 Hz, ArC**H**=CH-), 6.40 (1H, dt, *J* = 16.2 Hz, 5.8 Hz, ArCH=C**H**-), 3.84 (2H, s, -NC**H$_2$**Ph), 3.45 (2H, d, *J* = 5.8 Hz, -NC**H$_2$**CH=CH-).
^{13}C NMR (75 MHz, $CDCl_3$) δ : 149.80 & 148.67 (**C**(2)H & **C**(6)H pyridyl), 137.02 (**C** aromatic), 132.70 (**C**H aromatic), 131.95 (**C** aromatic), 129.15, 128.42, 128.14, 127.39, 126.77 & 122.98 (**C**H aromatic), 54.49 (-NH**C**H$_2$Ph), 52.32 (-NH**C**H$_2$CH=CH-).
MS (EI) *m/z* (rel. intensity): 226.1 (17), 225.1 (100$[M+H]^+$).
HRMS (EI) *m/z* : 225.1390; $C_{15}H_{16}N_2$ ($[M+H]^+$) requires 225.1392.

Benzyl-ethyl-(3-pyridin-3-yl-allyl)amine (451)



$C_{17}H_{20}N_2$ (mw: 252.35 g/mol)

Palladium(II) acetylacetonate (3.0 mg, 9.8 μmol, 5 mol%), 1,2-bis(diphenylphosphino) ethane (7.8 mg, 19.5 μmol, 10 mol%) were added to a suspension of resin **434a** (151.3 mg, 0.20 mmol) in THF (3 mL). Benzylethylamine (26.4 mg, 0.20 mmol, 1.0 equiv.) was added and the reaction heated at reflux, under a nitrogen atmosphere, for 1.5 hours. The resin was collected by filtration, washed with dichloromethane (80 mL) and the filtrate solvent removed under vacuum to afford an orange oil (107 mg). Purification by column chromatography (9.0 x 1.5 cm silica), using a methanol/dichloromethane (2:98) eluent system, afforded the title product **451** as a yellow oil (25.3 mg, 10.0 mmol, 51 %).

IR (film) υ_{max} : 2987m, 1612w, 1599m, 1584m, 1501s, 1038s, 873s, 765s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.58 (1H, d, *J* = 1.0 Hz, C(2)**H** pyridyl), 8.45 (1H, dd, *J* = 4.5 Hz, 1.0 Hz, C(6)**H** pyridyl), 7.68 (1H, dt, *J* = 7.9 Hz, 2.0 Hz, C(5)**H** pyridyl), 7.39-7.21 (6H, m, C(4)**H** pyridyl & C**H** phenyl), 6.52 (1H, d, *J* = 16.2 Hz, ArC**H**=CH-), 6.36 (1H, dt, *J* = 16.2 Hz, 6.2 Hz, ArCH=C**H**-), 3.64 (2H, s, -C**H$_2$**Ph), 3.97 (2H, dd, *J* = 6.2

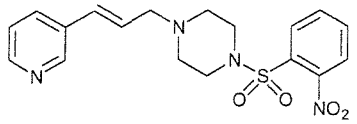
Hz, 1.0 Hz, ArCH=CHC**H**$_2$-), 2.59 (2H, q, J = 7.0 Hz, -NC**H**$_2$CH$_3$), 1.11 (3H, t, J = 7.0 Hz).

^{13}**C NMR** (100 MHz, $CDCl_3$) δ : 148.77 & 148.66 (**C**(2)H & **C**(6)H pyridyl) , 139.90 (**C**(3) pyridyl), 133.21 (**C** phenyl), 133.05 (**C**(4)H pyridyl), 131.08 (Ar**C**H=CH-), 129.30, 128.85 & 128.64 (**C**H phenyl), 127.30 (ArCH=**C**H-), 123.79 (**C**(5)H pyridyl), 58.31 (-N**C**H$_2$CH=CH-), 56.16 (-N**C**H$_2$Ph), 47.90 (-N**C**H$_2$CH$_3$), 12.34 (-NCH$_2$**C**H$_3$).

MS (EI) *m/z* (rel. intensity): 254.1 (19), 252.1 (100[M+H]).

HRMS (EI) *m/z* : 253.1706; $C_{17}H_{21}N_2$ ([M+H]$^+$) requires 253.1705.

1-(2-Nitrobenzenesulfonyl)-4-(3-pyridin-3-yl-allyl)piperazine (452)



$C_{18}H_{20}N_4O_4S$ (mw: 388.44 g/mol)

Palladium(II) acetylacetonate (3.0 mg, 9.8 μmol, 5 mol%), 1,2-bis(diphenylphosphino) ethane (7.7 mg, 19.3 μmol, 10 mol%) were added to a suspension of resin **434d** (152.5 mg, 0.19 mmol) in THF (3 mL). 1-(2-Nitrobenzenesulfonyl)piperazine **(454)** (103.0 mg, 0.38 mmol, 2.0 equiv.) was added and the reaction heated at reflux, under a nitrogen atmosphere, for 3 hours. The resin was collected by filtration, washed with dichloromethane (60 mL) and the filtrate solvent removed under vacuum to afford an orange oil (132 mg). This was dissolved in dichloromethane (7 mL) and isocyanate resin **457** (230 mg, 0.25 mmol) was added. The suspension was stirred at room temperature for 1 hour. T.l.c. indicated that some amine **454** remained and so a further quantity of isocyanate resin **457** (80 mg, 0.09 mmol) was added and stirring continued for another 2 hours. The resin was collected by filtration, washed with dichloromethane (80 mL) and the filtrate solvent removed under vacuum to afford an orange oil (57 mg). Purification by column chromatography (7.0 x 1.5 cm silica), using a methanol/dichloromethane (3:97) eluent system, afforded the title product **452** as a yellow oil (47.2 mg, 12.2 mmol, 61 %).

IR (CH_2Cl_2 solution): 2947m, 1602m, 1584s, 1525s, 1356s, 1347s, 1159s, 833s, 762s cm^{-1}.

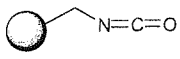
^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.56 (1H, br s, C(2)**H** pyridyl), 8.44 (1H, d, J = 3.5 Hz, C(6)**H** pyridyl), 7.94 (1H, dd, J = 7.0 Hz, 2.0 Hz, C**H** aromatic), 7.71-7.42 (4H, m, C**H** aromatic), 7.23 (1H, dd, J = 7.9 Hz, 4.4 Hz, C**H** aromatic), 6.50 (1H, d, J = 15.9 Hz, ArC**H**=CH-), 6.24 (1H, dt, J = 15.9 Hz, 6.5 Hz, ArCH=C**H**-), 3.34-3.31 (4H, m, -$SO_2NCH_2CH_2$-), 3.18 (2H, d, J = 6.5 Hz, ArCH=CHC**H$_2$**-), 2.58-2.55 (4H, m, -$SO_2NCH_2CH_2$-).

^{13}C NMR (100 MHz, $CDCl_3$) δ : 149.07, 148.55, 134.16 & 133.35 (**C**H aromatic), 132.64 (**C** aromatic), 131.86, 131.35, 130.57, 128.37, 124.53 & 123.93 (**C**H aromatic & **C**H alkene), 60.80 (ArCH=CH**C**H$_2$-), 52.80 (-SO_2N**C**H$_2$-), 46.27 (-$SO_2NCH_2CH_2$-).

MS (EI) *m/z* (rel. intensity): 390.1 (20), 389.1 (98.8[M+H]), 215.1 (41), 213.1 (100).

HRMS (EI) *m/z* : 389.1287; $C_{18}H_{21}N_4O_4S$ ($[M+H]^+$) requires 389.1284.

Polystyrylmethyl isocyanate resin (457)[266]



Aminomethyl resin (2.0 g, 2.6 mmol), triphosgene (1.04 g, 3.5 mmol), triethylamine (3.6 mL, 13.1 mmol) and dichloromethane (30 mL) were mixed together and stirred at room temperature, under a nitrogen atmosphere, for 5 hours. The resin was collected by filtration, washed with dichloromethane, chloroform, ether, THF, ether, THF and dichloromethane (25 mL of each) and dried under vacuum (50°C) for 2 hours. This afforded the known title product **457** as a yellow solid (1.98 g).

IR (on-bead): 2263s (NCO), 1493s, 1452s, 1266s, 1063m cm^{-1}.

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