Synthesis of unsaturated α-amino acid derivatives by palladium catalysed modification of the α-side chain

A thesis submitted for the degree of

Doctor of Philosophy

by

Peter Thomas Glink

The Department of Organic Chemistry

The University of Adelaide

September 1993

A little knowledge is a dangerous thing.

Table of Contents

Abstract

A number of routes to unsaturated α-amino acid derivatives by modification of the side chain of suitably protected amino acid precursors are discussed, particularly palladium catalysed processes.

Two *L*-vinylglycine derivatives were prepared from optically pure *L*-methionine. These compounds were investigated as the olefinic moiety in palladium catalysed Heck reactions with a variety of vinyl and aryl halides and trifluoromethanesulphonates. A number of β,γ-unsaturated α-amino acid derivatives were prepared without racemisation of the chiral α-centre.

A protected propargylglycine was prepared in racemic and chiral forms and was converted to γ and *E*-δ-tributylstannylallylglycine derivatives by palladium catalysed hydrostannantion. These two vinylstannanes were investigated as partners in Stille coupling with halides and triflates and a number of γ,δ-unsaturated α-amino acid derivatives were prepared. Some interesting phenomena were observed, including *cine*-substituted products formed from reaction of the γ-stannane, phenyl substituted products arising from migration of a phenyl group from a triphenylarsine ligand, and the propensity for aryl triflates to couple in the absence of lithium chloride. Symmetrical 1,3-dienes were prepared stereospecifically from the vinylstannanes by copper(II) mediated dimerisation. No racemisation of the α-centre was observed for these reactions.

The two vinylstannanes were converted to γ and *E*-δ-iodoallylglycine derivatives by electrophilic substitution with iodine. These vinyliodides were investigated in Heck coupling with olefins and Stille coupling with organostannanes, with moderate success. Coupling with terminal alkynes in the presence of palladium(0) and copper(I) cocatalysts yielded a number of enynes. Carboethoxylation of the iodides by a palladium catalysed reaction with ethanol under a carbon monoxide atmosphere was also undertaken. No racemisation occurred at the α-centre for any of these reactions.

Addition of hexamethylditin to the triple bond of the propargylglycine derivative yielded a *cis*-bis(trimethylstannyl)allylglycine derivative. This compound was investigated in a number of Stille and iododestannylation reactions.

Statement

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying.

Signed: . Date: 20/9/93

Acknowledgements

When looking back over the last three and a half years of study, there are a number of people who must be thanked for their contribution towards the completion of this work. Foremost amongst these people is my supervisor, Geoff Crisp, whose ideas, encouragement and enthusiasm never waned, his ability to find references in the twinkling of an eye never ceased to amaze and whose cheap sarcasm never raised a laugh!

I have been fortunate to share lab space with a group of people who have made coming in to uni enjoyable. To these people, the past and present members of 'Ye Olde Lab 5' and now lab seven, and particularly (chronologically) George 'Skurry' Skouroumounis, Mick Pitt, Bernard 'Bernie' Flynn, Adam 'The Big A' Meyer and Martin 'Skatole Max' Merrett, I send a heartfelt thankyou for friendship, advice, chemicals and occasionally clean glassware. I would particularly like to thank George and Bernie for their major contributions, practically and theoretically, towards turning this inept chemist into (I hope) a slightly less inept chemist. Thanks to Adam and Martin for proofraeding this thesis. Thanks for all the triflates, too, Adam.

I would like to acknowledge the past and present members of the Crisp group ("the packet of Crisp's") for their good humour, helpful advice and stimulating discussion.

To other members of the research school, academic and technical staff I would also like to extend my gratitude and best wishes for the future.

Thanks also to the tax payers of Australia for allowing me to ride the gravy train throughout my Ph.D. years with an Australian Postgraduate Research Award.

My family deserve a big thankyou for constant encouragement to pursue my academic career this far and for the comfortable and loving environment at home.

I salute you all!

List of abbreviations.

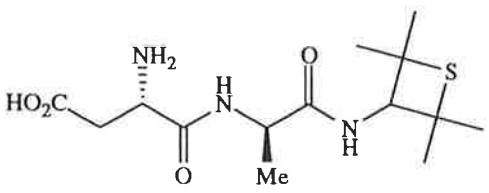
AIBN	Azobisisobutyronitrile
CBz	Carbobenzyloxy ($PhCH_2CO_2$-)
dba	Dibenzylidineacetone
d.e.	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DMAP	N,N-4-(dimethylamino)pyridine
DMF	Dimethylformamide
DMFDMA	Dimethylformamide dimethylacetal
DMSO	Dimethylsulphoxide
e.e.	Enantiomeric excess
HMPA	Hexamethylphosphoramide
IR	Infra red
L	Ligand
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilizide
LICA	Lithium cyclohexylisopropylamide
M	Transition metal
NBS	N-Bromosuccinimide
NMP	N-Methylpyrollidinone
NMR	Nuclear magnetic resonance
MS	Mass spectrometry
o-Tol	*o*-Tolyl (*o*-$CH_3C_6H_4$-)
PDC	Pyridinium dichromate
PTC	Phase transfer catalyst
TBDMS	*t*-Butyldimethylsilyl
Tf	(Trifluoromethyl)sulphonyl
THF	Tetrahydrofuran

Introduction

α-Amino acids in the form of peptides, proteins and enzymes are amongst the most important biological compounds because of their vital role in sustaining life.[1,2] To date, the number of known naturally occurring amino acids is approaching one thousand,[3] with unnatural amino acids becoming increasingly important in areas such as pharmaceuticals,[4] agrochemicals[5] and food products.[6] This is because unnatural amino acids can, in some cases, mimic the biological roles or enzymatic functions of their natural analogues. For instance, a number of drugs are derived from the non-natural *D*-amino acid series, such as the anticancer agent, buseralin (**1**).[4] This nonapeptide is believed to be active partly because of its resistance to proteases *in vivo*, that is, the inability of enzymes to hydrolyse the peptide bond of *D*-amino acids. *D*-Alanine is an unnatural amino acid which is produced annually in bulk quantities because of its utility in the synthesis of the artificial sweetener, alitame (**2**).[7] Unnatural amino acid derivatives are also used in the synthesis of novel peptides and proteins in an attempt to furnish information about the mode of action of particular enzymes.[8] In addition to their biological properties, amino acids are extremely important from a chemist's viewpoint as synthetic intermediates and chiral auxiliaries.[9,10] This is especially true for the proteinogenic amino acids because they are readily available, optically pure, multifunctional molecules.[10] This is sometimes referred to as the synthetic approach *via* the chiral pool. Another very common approach to α-amino acids has, in recent years, been the asymmetric construction of one of the four bonds which comprise the chiral α-centre.[9] Although this approach has produced excellent results, it is often plagued by problems associated with the separation of enantiomers and the removal and recovery of chiral auxiliaries. The use of enantiomeric separation techniques, such as enzymatic resolution, and chiral catalysts can overcome these problems to some extent.

PyroGlu-His-Trp-Ser-Tyr-*D*-Ser(Bu^t)-Leu-Arg-Pro-NHEt

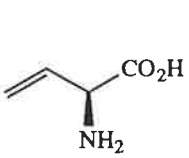
Buseralin, **1**



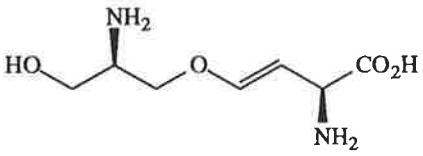
Alitame, **2**

An important class of non-proteinogenic α-amino acids are those which possess olefinic or acetylenic groups in the α-side chain. Many of these compounds, some of which are found

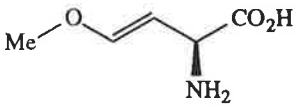
naturally, have been shown to act as irreversible mechanism based inhibitors of a number of pyridoxal phosphate dependent and, to a lesser extent, flavin dependent enzymes.[11] These unsaturated amino acids include olefinic compounds [*e.g.* vinylglycine (**3**),[12] rhizobitoxin (**4**),[13] 4-methoxyvinylglycine (**5**),[14] 3-methyleneaspartic acid (**6**),[15] 3,4-didehydroglutamic acid (**7**),[16] 3-halovinylglycines (**8**),[17] allylglycine (**9**),[11b,18] 4-haloallylglycines (**10**)[19]] and acetylenic compounds [*e.g.* propargylglycine (**11**),[20] ethynylglycine (**12**)[21]]. Mechanism based inhibitors (also known as k_{cat} inhibitors or suicide substrates) are a class of irreversible inactivators of specific target enzymes where the target enzyme participates in its own destruction by catalytic unmasking of a latent functional group at some stage of the catalytic cycle of the enzyme.[11]



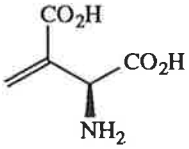
3



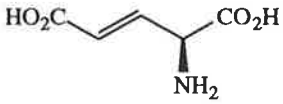
4



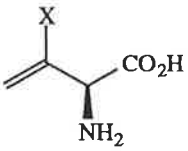
5



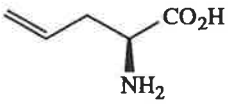
6



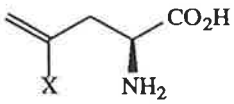
7



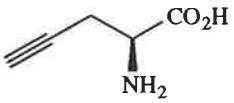
8



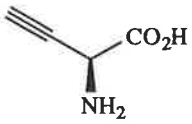
9



10



11

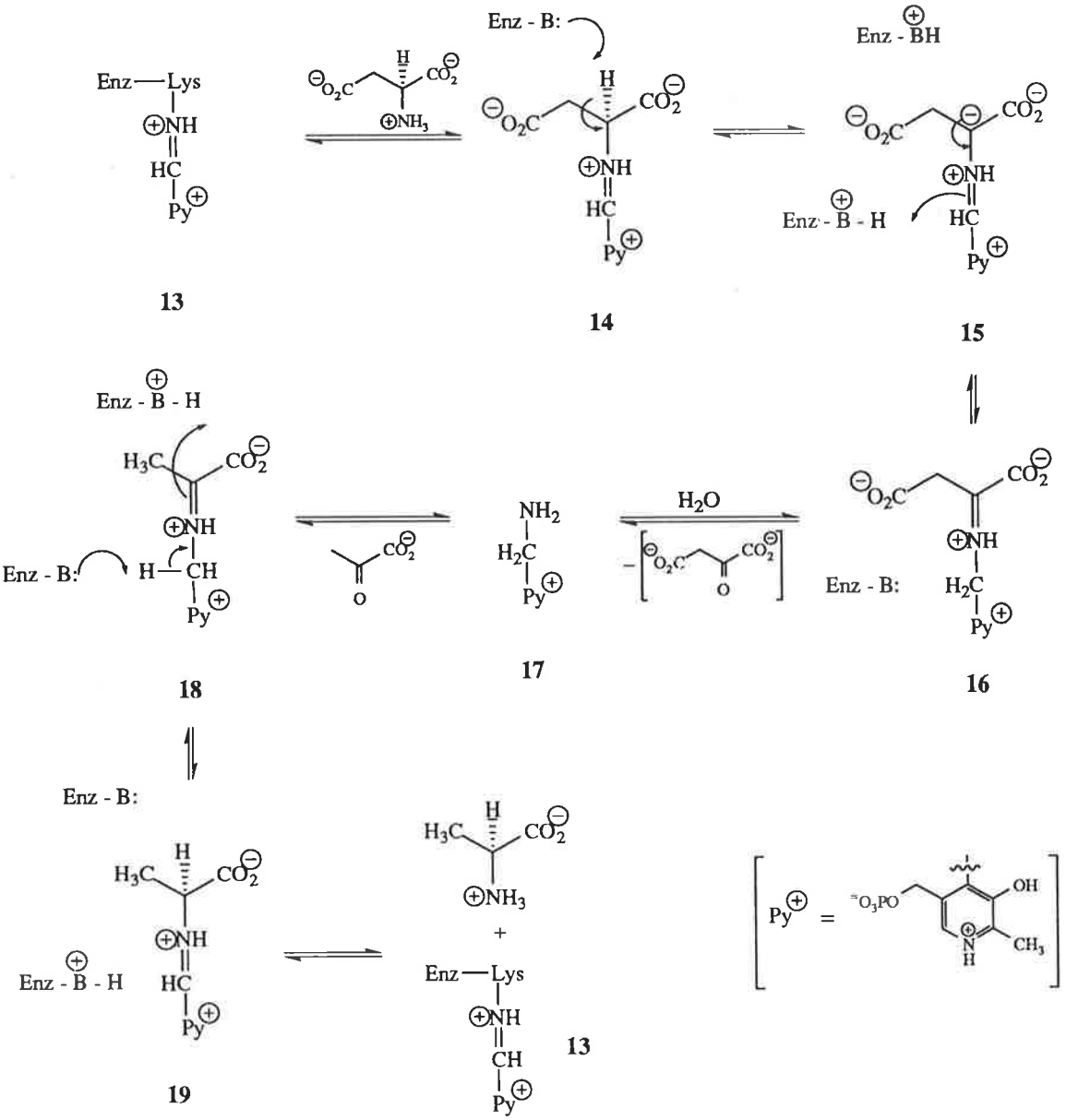


12

Pyridoxal phosphate dependant enzymes generally catalyse chemical changes at the α, β and γ-positions of proteinogenic amino acids.[11] The types of enzymes which react at the α-cabon include transaminases (*e.g. L*-aspartate and *L*-alanine transaminases) and decarboxylases (*e.g.* glutamate decarboxylase); those which react at the β-carbon include decarboxylases (aspartate decarboxylase) and β-eliminators (*e.g.* tryptophanase); and those which catalyse chemical changes at the γ-carbon include γ-cystathionase (elimination) and γ-cystathionine synthetase (replacement). These enzymes are vital to biosynthesis and metabolism of the relevant amino acids and inhibition can result in the disruption to the growth of cells, tissues and even whole organisms. As examples of the biological roles of pyridoxal phosphate dependant enzymes and the effects unsaturated α-amino acids can have on such enzymes,

aspartate transaminase and γ-cystathionase will be briefly discussed.

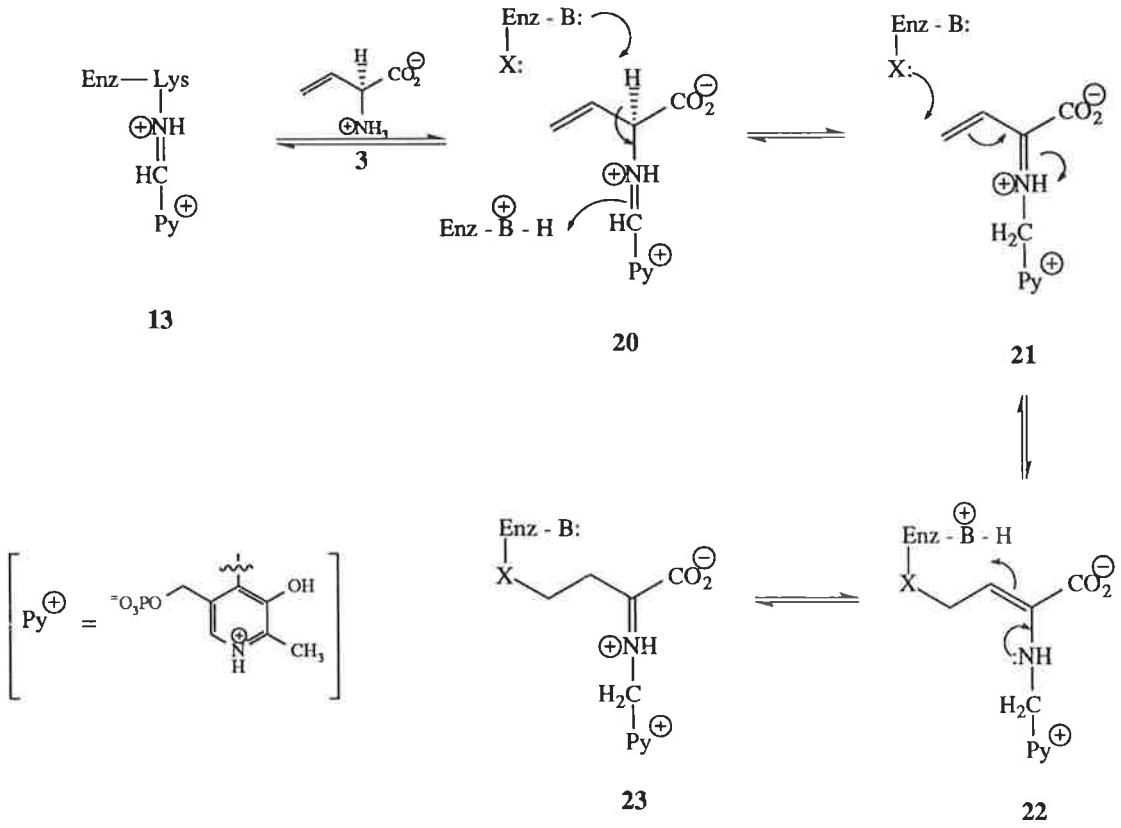
Aspartate transaminase has been one of the most studied enzymes in terms of its structure and catalytic mechanism.[11a] Its primary biological role is in the conversion of *L*-aspartic acid and pyruvic acid to oxaloacetate and *L*-alanine, although some other suitable amino acid substrates will also be converted to the corresponding α-ketoacids. The enzymatic process begins with the cofactor, pyridoxal phosphate, bound to the active site of the enzyme *via* an imine linkage to the ε-amino group of a lysine residue (**13**) (*Scheme 1.1*). Transaldimination occurs between **13** and aspartic acid, freeing the lysine amino group. Once the aldimine (**14**) has formed, the acidity of apartic acid's α-hydrogen is increased and the amino acid moiety is



Scheme 1.1

deprotonated by a basic group in the enzyme active site to form an extensively stabilised anion (**15**). Protonation of this intermediate occurs at what was the aldehyde carbon of the pyridoxal moiety, and results in the ketimine (**16**). Hydrolysis of **16** produces oxaloacetate and pyridoxamine phosphate (**17**). From this point, the mid-point of the transamination, the reverse sequence of reactions proceeds with pyruvate as substrate. Thus, **17** is transformed into the pyruvate ketimine (**18**) from which isomerisation occurs to produce the *L*-alanine aldimine (**19**) *via* a deprotonation-protonation sequence in a face specific manner. Hydrolysis of **19** to the product, *L*-alanine, is facilitated by transaldimination with the lysine ε-amino group in the active site.

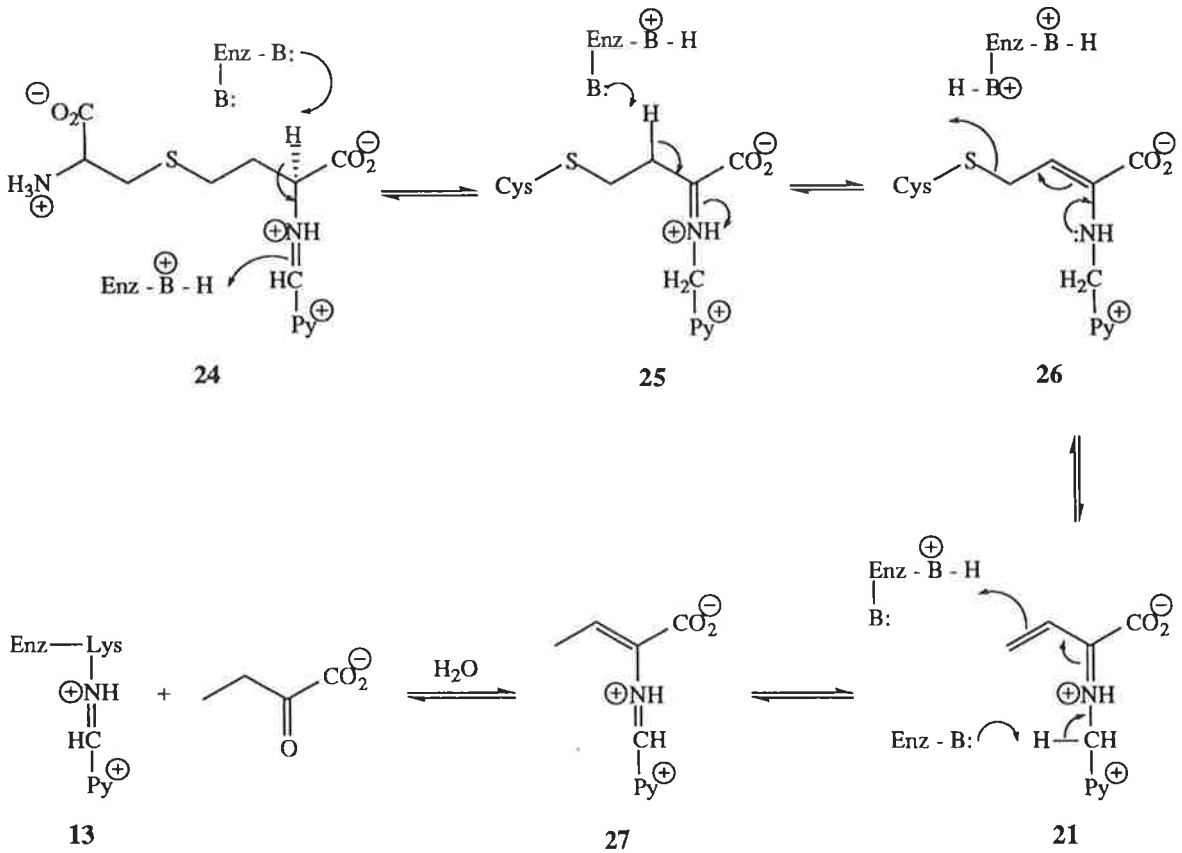
L-Vinylglycine has been shown to inactivate *L*-aspartate transaminase irreversibly.[12] This process has been studied intensely and a mechanism of inactivation has been proposed (*Scheme 1.2*). *L*-Vinylglycine (**3**) is a suiable substrate for the enzyme's active site and transaldimination occurs to yield aldimine **20**. Removal of the α-proton and protonation at what was the aldehyde carbon forms the ketimine (**21**). This step unmasks the latent electrophilic functional group, the conjugated protonated imine, which is prone to Michael addition by a suitable nucleophilic group in the enzyme's active site, possibly the ε-amino



Scheme 1.2

group of a lysine residue. This results in the formation of an enamine (**22**) which is protonated to form the ketimine, **23**. This adduct does not hydrolyse because the arrangement of the necessary basic and acidic groups in the enzyme's active site has been distorted from that of usual enzyme activity. Thus, the enzyme has become covalently linked to the coenzyme *via* the deactivator linker. In effect, the enzyme has catalysed a reaction which has led to its destruction so inactivation by this process has been termed 'suicide' inhibition.[11b]

γ-Cystathionase, found in mammalian liver, has the biological role of breaking down the sulphur containing amino acid, cystathionine, by γ-elimination to form α-ketobutyrate and *L*-cysteine. The mechanism by which this process occurs is shown in *Scheme 1.3*.[11a] The aldimine (**24**) formed between cystathionine and pyridoxal phosphate is isomerised to the ketimine, **25**. This intermediate is deprotonated at the β-carbon of the amino acid moiety to form the resonance stabilised anion (effectively an enamine, **26**). The enamine (**26**) assists in the elimination of the γ-substituent, the cysteine thiolate, to form a β,γ-unsaturated ketimine (**21**) which is tautomerised to the α,β-unsaturated aldimine (**27**). Hydrolysis yields α-ketobutyrate and **13**.

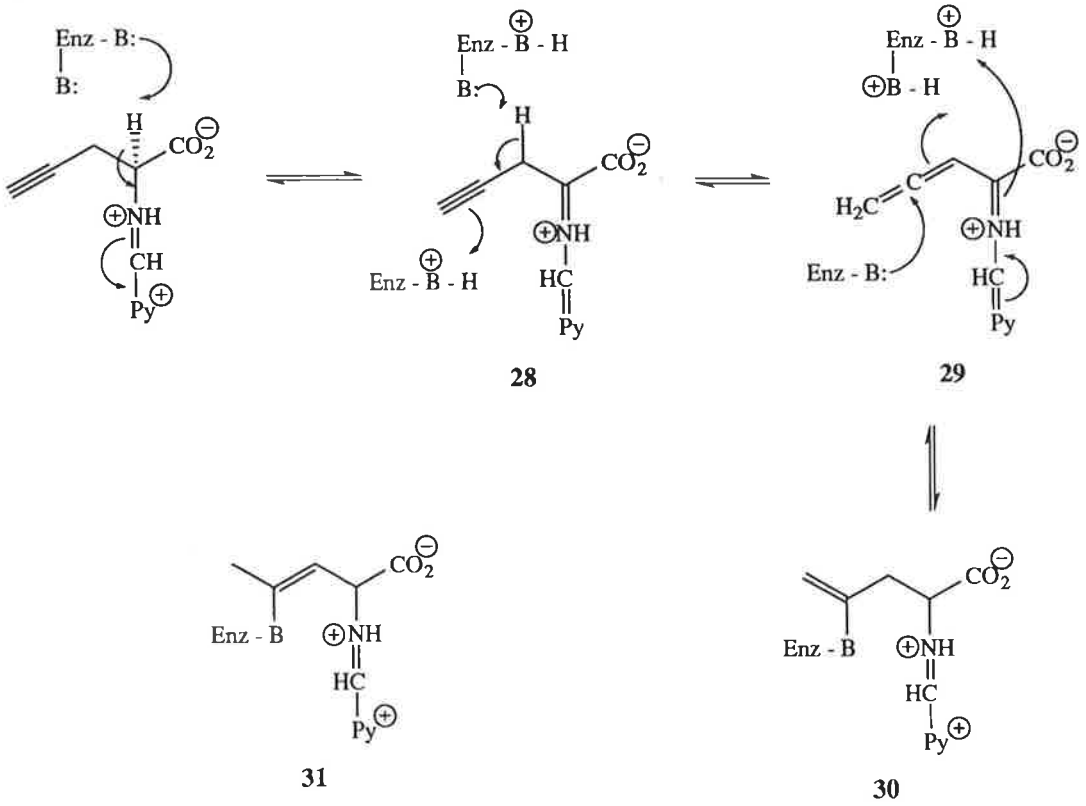


24 25 26

13 27 21

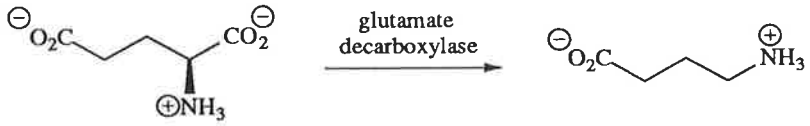
Scheme 1.3

Propargylglycine has been shown to deactivate a number of pyridoxal phosphate dependant enzymes, including γ-cystathionase.[20] A proposed mechanism is shown in *Scheme 1.4*. As in the inhibition of aspartate transaminase by vinylglycine the key step is the unmasking of the latent electrophilic functional group in the α-side chain. For propargylglycine (**11**), this intermediate arises by deprotonation at the β-centre of the ketimine (**28**) by a basic group in the active site. This β-carbanion assists in the rearrangement to the conjugated allene, **29**. The central carbon of the allene is susceptible to nucleophilic attack by a deprotonated basic group (most probably a cysteine or tyrosine residue)[20a] and a covalent bond is formed between the enzyme and the inactivator, which is linked to the coenzyme (*i.e.* structure **30**). The actual structure of this adduct has been proposed to be possibly the double bond isomer, **31** formed by a slightly different sequence of the proton exchanges, isomerisations and nucleophilic attack.[20c]



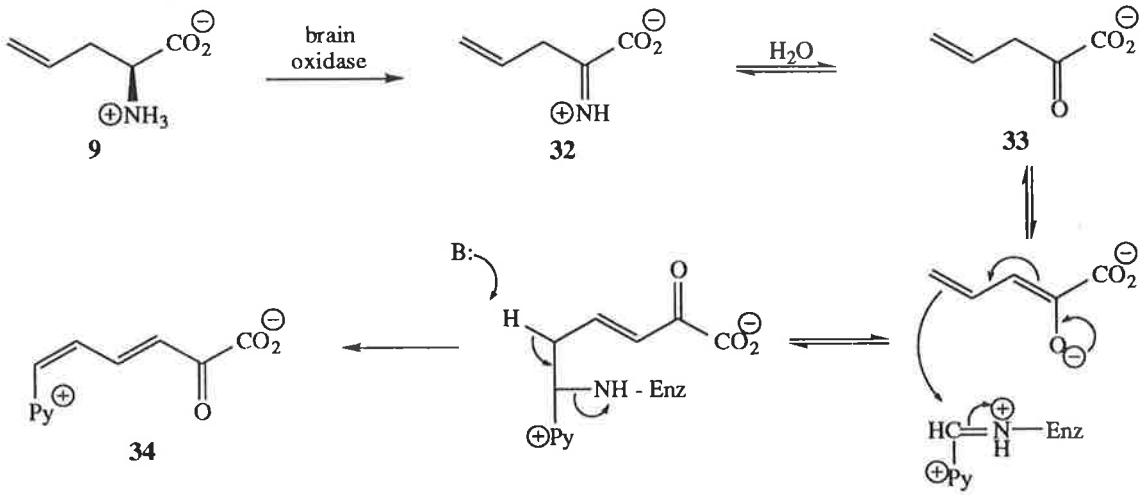
Scheme 1.4

Allylglycine (**9**) has been found to inhibit glutamate decarboxylase, the enzyme responsible for producing γ-aminobutyric acid (GABA) in the brain (*Scheme 1.5*).[11b] Inhibitors of this enzyme are, as a consequence, neuroconvulsants, and allylglycine has been shown to induce seizures in cats, rats and baboons.[22] The mechanism by which allylglycine inactivates glutamate decarboxylase in the brain has been proposed to occur by derivatisation of



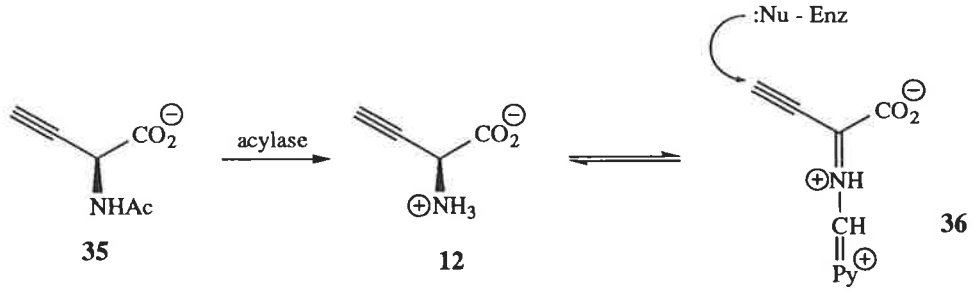
Scheme 1.5

the pyridoxal phosphate coenzyme and not by Michael addition of a suitable nucleophile in the enzyme active site toward a conjugated imine.[11b] Allylglycine has been shown to undergo oxidation in the brain to the imino acid (**32**) which is then hydrolysed to 2-keto-4-pentenoate (**33**) (*Scheme 1.6*).[23] This compound (**33**) has been shown to inhibit glutamate decarboxylase presumably by attack of its dienolate anion onto the electrophilic imine group of the enzyme bound cofactor. This reaction has been proposed to lead to the formation of a conjugated keto acid derivative (**34**).



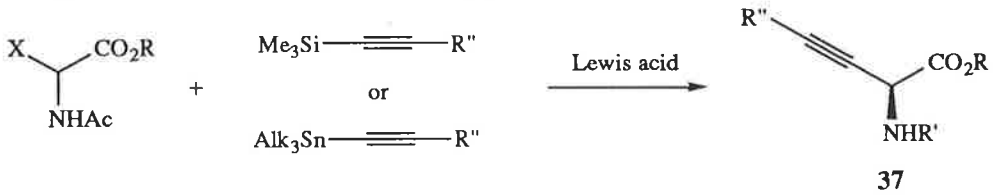
Scheme 1.6

Ethynylglycine derivatives, acetylenic analogues of vinylglycines, are biologically active[21] and synthetically challenging[24] molecules. The simplest α-ethynyl-α-amino acid, 2-amino-3-butynoic acid (ethynylglycine, **12**) is a naturally occurring compound which has not been synthesised or isolated in its free form owing to its sensitivity in aqueous media.[21] However, its N-acetyl derivative (**35**) has been obtained and shown to possess antimicrobial characteristics towards Gram-positive bacteria and inhibits alanine racemase.[21b] This enzymatic activity may arise through Michael addition of a suitable nucleophilic group in the enzyme to a conjugated acetylenic ketimine (**36**) (*Scheme 1.7*), similar to the mechanism of inactivation proposed for vinylglycine in *Scheme 1.2*.[11b] Because of the sensitivity of α-ethynyl amino acids, their synthesis has proven to be quite difficult. Derivatives of the parent compound (**12**) have been prepared by Williams[24a,b] and Metcalf.[24c,d] Both utilised Friedel-



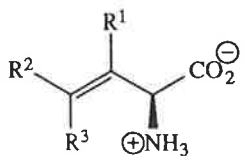
Scheme 1.7

Crafts alkynylation conditions in the reactions of α-haloglycinates with trimethylsilyl and trialkylstannyl alkynes (*Scheme 1.8*). A number of compounds of the general structure (**37**) were obtained, although the free amino acids were too unstable for isolation. α-Alkyl-α-ethynylglycine derivatives have been prepared by a number of procedures and the corresponding free amino acids are stable compounds.[25]



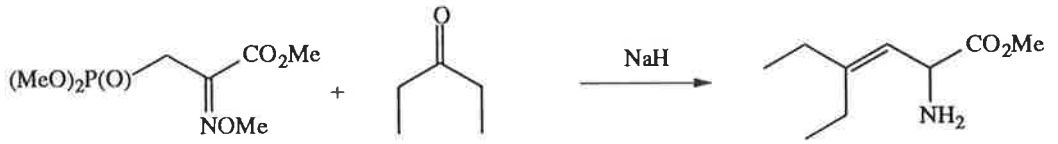
Scheme 1.8

With the recent advances in the understanding of molecular recognition and enzyme reaction mechanisms and the effects of mechanism based inhibitors, a number of research groups have become interested in the preparation of enzyme inhibitors with predetermined properties in mind. This has particularly occurred for unsaturated α-amino acids and their derivatives. These types of compound have become quite challenging synthetic targets because of the complications associated with double bond isomerisation and migration and racemisation of the α-centre. This is particularly true of the vinylglycines (**38**). In recent years a number of general routes to the parent compound, vinylglycine (R^1,R^2,R^3 = H), and more structurally complex vinylglycines have appeared as synthetically challenging routes to potential enzyme inhibitors. The synthesis of *L*-vinylglycine (**3**) has been undertaken most successfully by the oxidative degradation of a suitably modified, optically pure amino acid such as methionine,[26] glutamic acid[27] and homoserine.[28] For more complex substituted vinylglycines, a number of

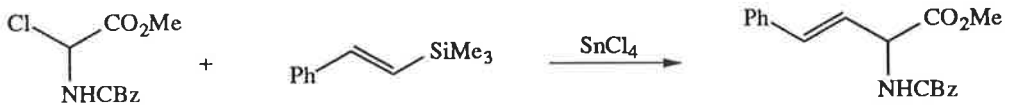


38

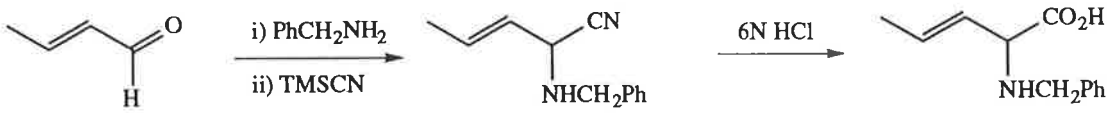
methods have been employed, but have been limited by the nature of the substituents present in the reagents, problems associated with double bond control and variable enantiomeric purities. Methods which provide 4-substituted vinylglycines (**38**, R^1 = H, R^2 and/or R^3 = alkyl, aryl) as *E* or *Z*-isomers stereospecifically include Elder's Wittig methodology of serine derived phosphoranes and phosphonates with aldehydes (*E*-products only) and ketones (*Scheme 1.9*);[29] Angst's amidoalkylation of alkenylsilanes with glycine cation intermediates (*E* or *Z* formed depending on the geometry of the vinylsilane, *Scheme 1.10*);[30] Greenlee's Strecker reactions (*E*-product from *E*-aldehyde, *Scheme 1.11*);[31] Castelhano's vinyl Grignard reagent attack on an α-chloroglycinate derivative (*E*-product from the *E*-Grignard reagent, *Scheme 1.12*);[32] and Hopkins' oxidative rearrangement of γ-phenylseleno-α,β-unsaturated esters (*E*-product only, *Scheme 1.13*).[33]



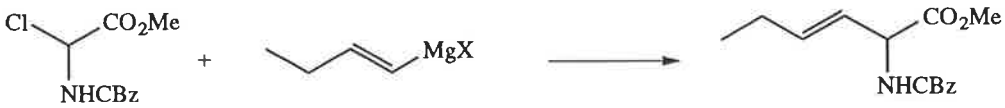
Scheme 1.9



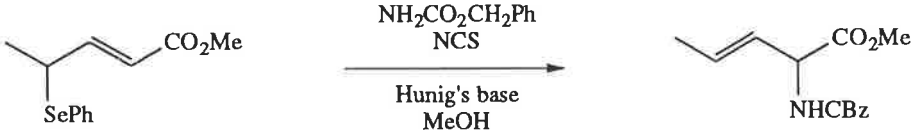
Scheme 1.10



Scheme 1.11

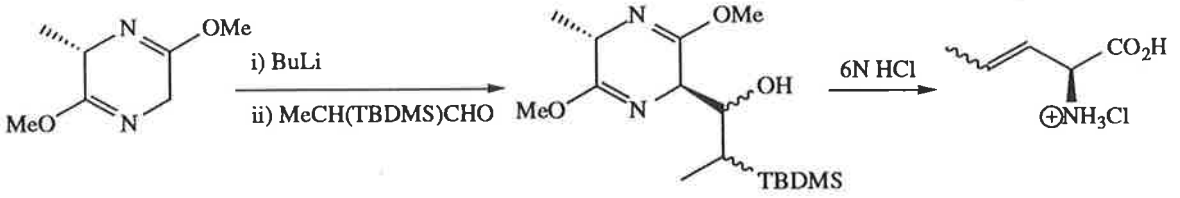


Scheme 1.12

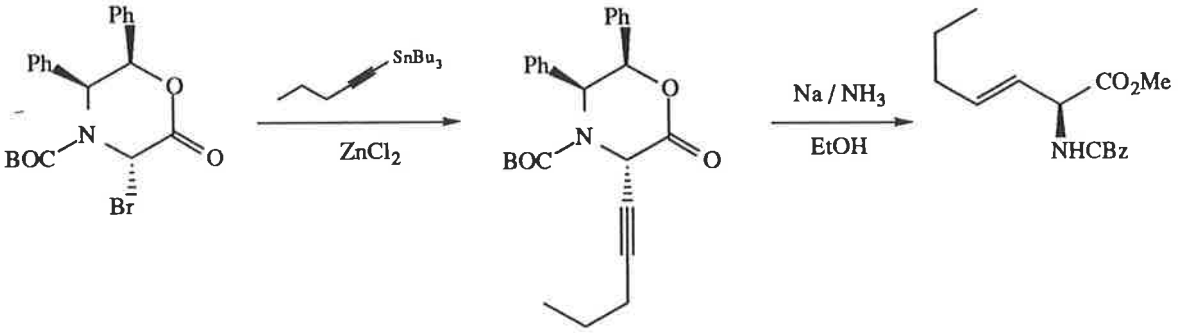


Scheme 1.13

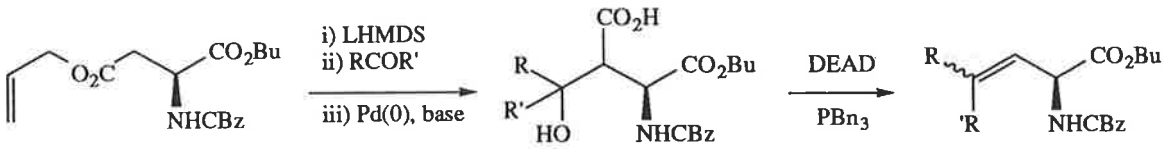
A number of general methods have appeared in the literature to date which provide vinylglycines in high enantiomeric excess. These include Schöllkopf's bis-lactim ether (derived from cyclo-[*L*-val-gly]) alkylation-elimination sequence (excellent d.e., but poor geometric



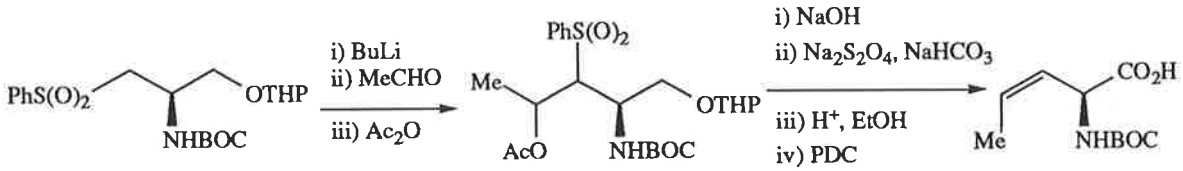
Scheme 1.14



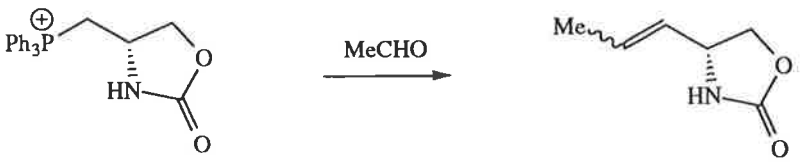
Scheme 1.15



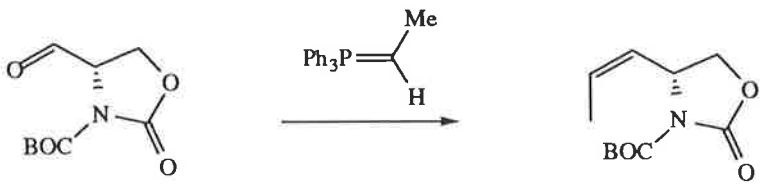
Scheme 1.16



Scheme 1.17

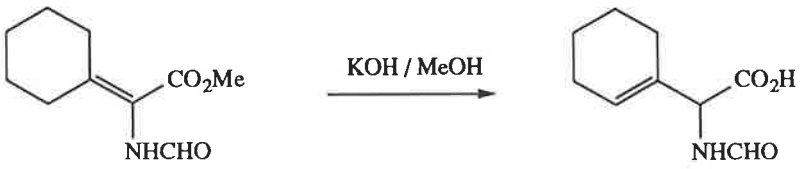


Scheme 1.18

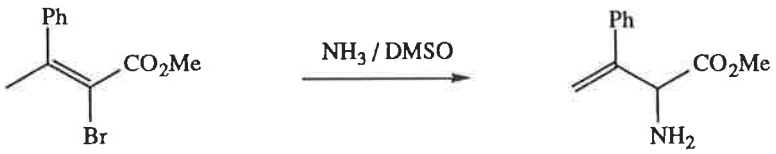


Scheme 1.19

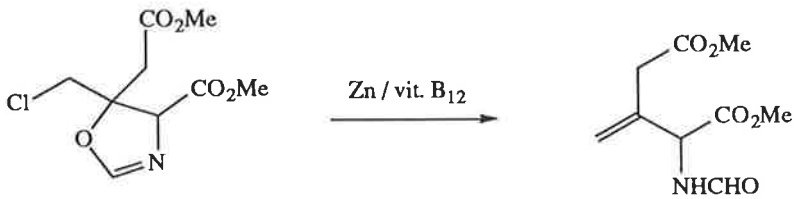
control when *E*,*Z*-mixtures are possible) (*Scheme 1.14*);[34] Williams' alkynylation-reduction of an electrophilic chiral glycine template (only *E*-formed, but e.e. is only about 70%) (*Scheme 1.15*);[35] Baldwin's alkylation-elimination of an *L*-apsartic acid derivative (high e.e., inconsistent geometrical control) (*Scheme 1.16*);[36] Sasaki's alkylation-elimination-desulphonylation of a *L*-serine derived sulphone (excellent e.e. and only *Z*-isomers formed) (*Scheme 1.17*);[37] and Sibi's[38] and Beaulieu's[39] Wittig reactions of *L*-serine derived synthons (high yielding, high e.e.'s, variable *E*:*Z* ratios) (*Schemes 1.18* and *1.19*). 3-Substituted vinylglycines (**41**, $R_1 \neq H$) have been prepared successfully by Suzuki's saponification-isomerisation method to yield cycloalkenylglycines (*Scheme 1.20*),[40] Wemple's isomerisation-amination of α-bromo-α,β-unsaturated esters (*Scheme 1.21*),[41] and by Angst's vitamin B_{12} catalysed reductive elimination of chloromethyl substituted oxazolines (*Scheme 1.22*).[30] A number of the reactions listed above yield racemic products, but could theoretically become enantioselective by the use of chiral auxiliaries. A number of procedures for the synthesis of α-vinyl-α-substituted glycines have also appeared.[42]



Scheme 1.20



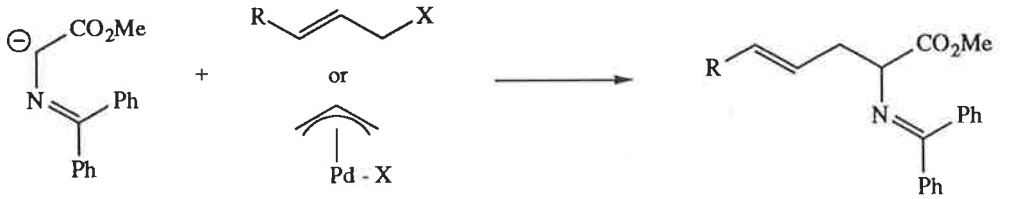
Scheme 1.21



Scheme 1.22

Although many of these reactions provide substituted vinylglycines with good stereospecificity, the types of functional groups which can be accommodated are limited since the intermediates in these reactions are possibly subjected to electrophilic or nucleophilic attacks, basic or acidic conditions, reductions, eliminations, *etc*. In many of the examples above, the double bond substituents are restricted to simple alkyl or aromatic groups.

Allylglycine derivatives have been more accessible to organic chemists because they are less prone to double bond migration than the vinylglycines. A general route which is commonly employed for their synthesis is the reaction of a suitable glycine anion equivalent with an allyl electrophile (commonly halides,[43] or allyl acetates and carbonates in the presence of palladium(0) catalysts[44]) (*e.g. Scheme 1.23*). Alternatively, nucleophilic attack by allylic organometallic species (*e.g.* allyl tin,[45] boron,[46] zinc,[46] titanium,[46] silicon[47] and magnesium[32] reagents) toward a glycine cation equivalent yields a number of allylglycine derivatives (*Scheme 1.24*).



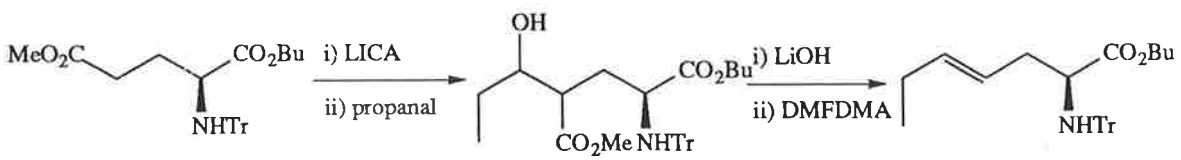
Scheme 1.23

X = halogen, OMe, OAc
M = metal.

Scheme 1.24

Formation of allylglycine derivatives by modification of the α-side chain has been less studied, but a number of routes have been investigated including Baldwin's Wittig reactions of an *L*-aspartic acid semialdehyde derivative (*Scheme 1.25*)[48] and alkylation-elimination sequences with glutamic acid derivatives (*Scheme 1.26*).[49]

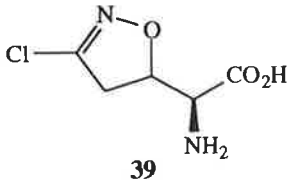
Scheme 1.25



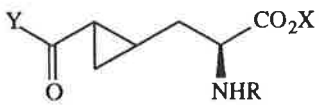
Scheme 1.26

In addition to their interesting biological properties, olefinic and acetylenic α-amino acids and their derivatives are versatile synthetic intermediates. The unsaturated functional group is able to participate in a number of reactions and this has been utilised in the synthesis of

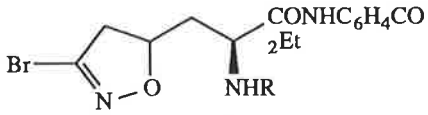
a number of physiologically active molecules. As examples of vinylglycines as synthetic intermediates, Rapoport has utilised epoxidation of *D*-vinylglycine as a starting point for the synthesis of aziridinomitosenes,[50] and Wade has examined dipolar cycloaddition reactions of chloronitrile oxide with vinylglycine derivatives in the synthesis of acivicin (**39**).[51] Allylglycines have been transformed to cyclopropanes (for the synthesis of glutamate antagonists useful for the treatment of central nervous system disorders, *e.g.* **40**)[52] and isoxazoles (to prepare compounds which have been shown to delay the onset of cataracts and also inhibit human T-lymphocyte transformations *in vivo*, *e.g.* **41**).[53]



39



40

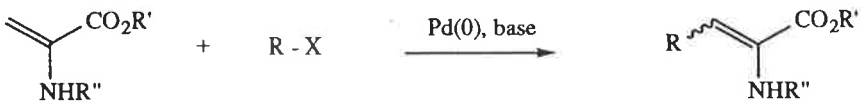


41

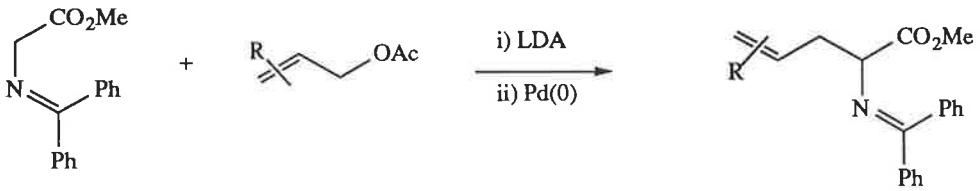
We wished to explore palladium catalysed coupling reactions in the synthesis of vinyl and allylglycine derivatives. This methodology appears to have great potential for the synthesis of unsaturated amino acids. There are a number of common coupling reactions which result in products containing various degrees of unsaturation and are extremely chemoselective meaning that almost all common functional groups are tolerated and the reactions often proceed under mild conditions.[54] This cannot be said for many non-transition metal carbon-carbon bond forming processes. The mechanisms for many of these types of reactions are well understood and lead to products with good stereocontrol. Reagents for the coupling reactions (*e.g.* aryl and vinyl halides and triflates,[55] olefins, alkynes, allyl halides/acetates/carbonates, organo stannanes[56]/boranes/silanes, *etc*) are easily prepared through a number of standard synthetic procedures. As well as these advantages, catalytic reactions are desirable for the large scale preparation of compounds because of the economical use of catalytic agents.[57]

A number of syntheses of unsaturated α-amino acids and their derivatives which have appeared in the literature have utilised palladium catalysis in key steps. These reactions include Heck reactions of α,β-unsaturated alanine derivatives with vinyl and aryl halides and triflates (*Scheme 1.27*) studied by a number of groups;[58-61] Genet's reaction of nucleophilic glycine anion equivalents with π-allyl palladium intermediates (*Scheme 1.28*), which have been extensively studied with chiral catalysts for the preparation of chiral allylglycine derivatives;[44] Jackson's coupling of the organozinc intermediate derived from β-iodoalanine with aryl iodides

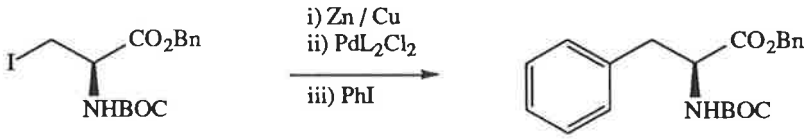
and a vinyl triflate (*Scheme 1.29*);[62] Gore's sequential Heck addition-allylation of allenes in the presence of vinyl and aryl halides and a glycine anion equivalent (*Scheme 1.30*);[63] Kellogg's rearrangement of imino acid allyl ester derivatives to α-allyl-α-amino acids (*Scheme 1.31*);[64] Itaya's Heck reaction between a vinylglycine derivative and an iodonucleoside in the synthesis of wybutosine (*Scheme 1.32*);[65] Yoo's kainic acid synthesis which proceeded *via* olefin insertion-carbonylation process of a vinylglycinol derivative (*Scheme 1.33*);[66] Ohfune's aminocarbonylation of a propargylglycine equivalent for the synthesis of 4-methyleneglutamic acid derivatives (*Scheme 1.34*);[67] Leanna's Stille and Suzuki coupling reactions of bromoallylglycine derivative (*Scheme 1.35*);[68] and Crisp and Robertsons's coupling of a propargylglycine derivative with a variety of aryl and vinyl halides and triflates (*Scheme 1.36*).[69]



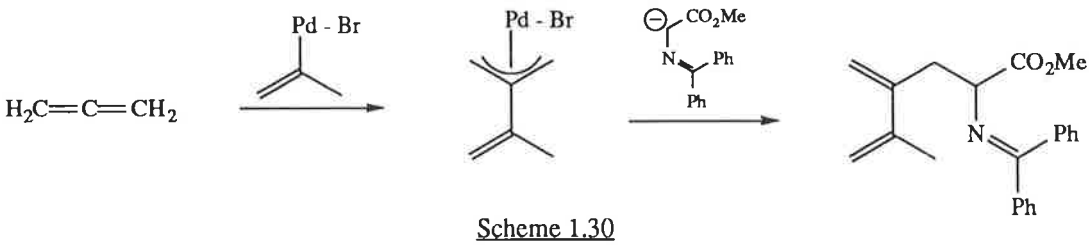
Scheme 1.27



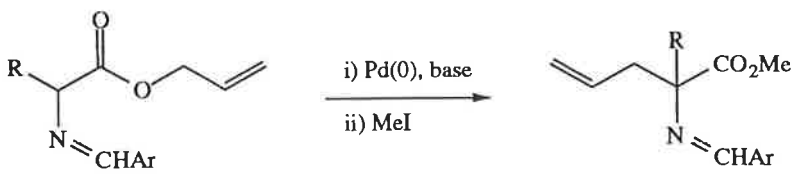
Scheme 1.28



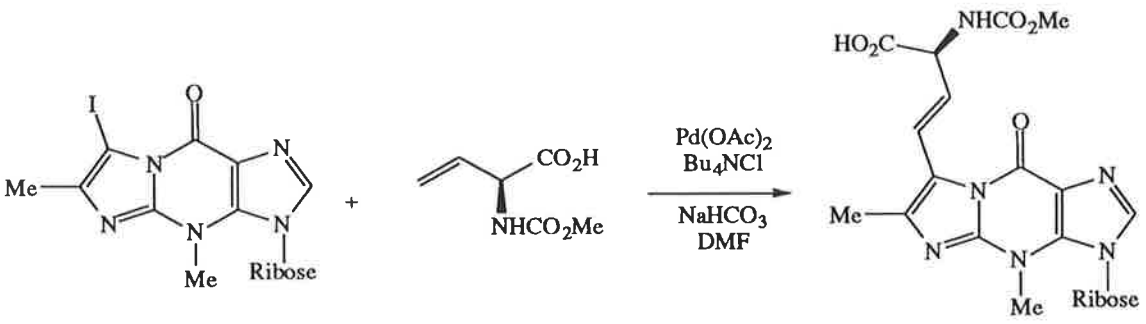
Scheme 1.29



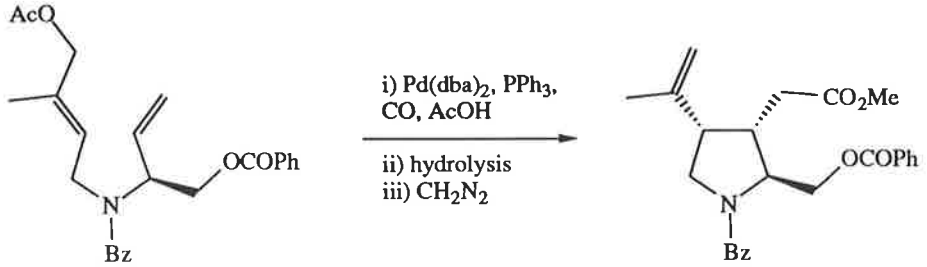
Scheme 1.30



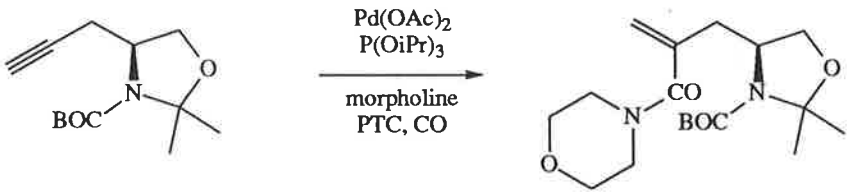
Scheme 1.31



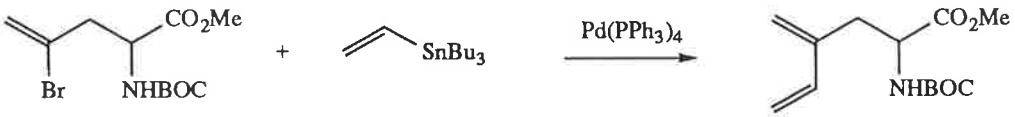
Scheme 1.32



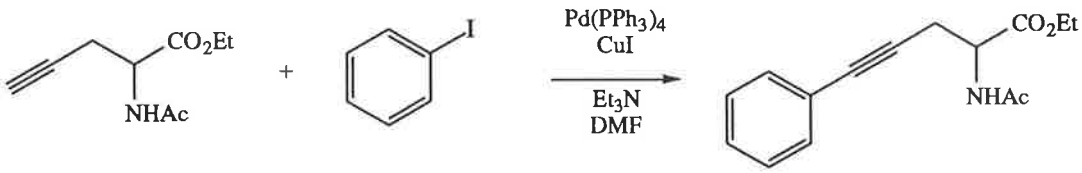
Scheme 1.33



Scheme 1.34



Scheme 1.35



Scheme 1.36

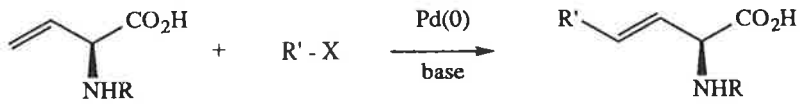
We believed that a number of common reactions catalysed by palladium(0) would be conceptually simple approaches to vinyl and allylglycine derivatives. For this end, we wished to investigate vinyl and allylglycine derivatives functionalised in the α-side chain by groups which would readily partake in palladium mediated carbon-carbon bond formation such as olefinic, nucleophilic (vinylstannanes), and electrophilic (vinyl halides and triflates) functional groups and investigate the scope of their reactivity in Heck, Stille and other common coupling processes for the synthesis of a variety of unsaturated α-amino acids. Since this procedure is

one of modification of the existing α-side chain of α-amino acids, rather than formation of the chiral α-centre, we required the ability to synthesise the precursors in optically active form and couple them under conditions which would not lead to racemisation. The particular compounds we prepared and the types of coupling reactions in which they were studied are outlined in the chapters to follow.

Heck reactions of vinylglycine derivatives.

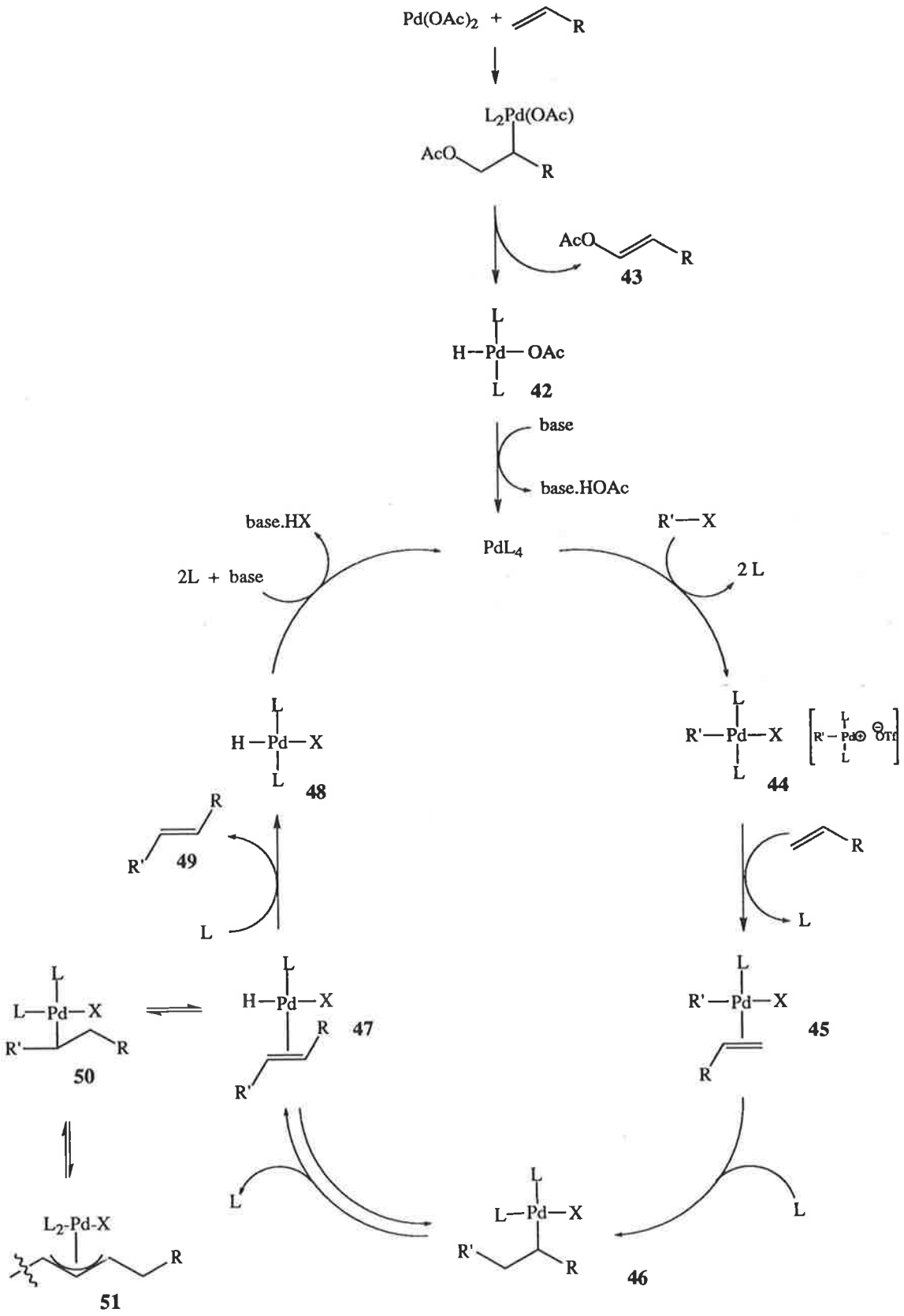
2.1 Introduction; Heck reactions.

Since a number of 4-substituted vinylglycine derivatives are biologically active as enzyme inhibitors, we wished to study some common palladium catalysed processes for the preparation of such compounds from readily obtainable starting materials. One conceptually simple approach is *via* the Heck reaction. This could be carried out between a vinylglycine derivative (as the olefinic moiety) and a variety of organic electrophiles, namely vinyl and aryl halides and triflates (*Scheme 2.1*).



Scheme 2.1

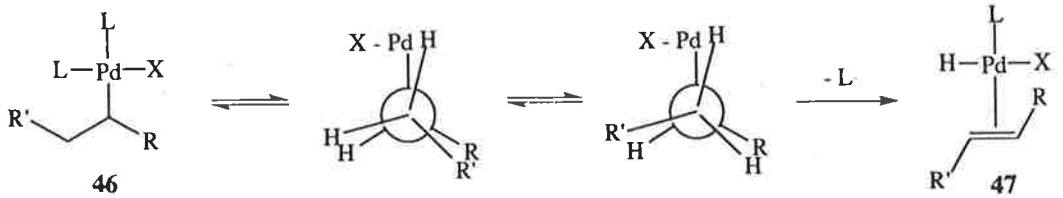
The Heck reaction (the vinylation of organic halides and triflates) has been known for about twenty years and is an extremely versatile, catalytic method for forming carbon-carbon bonds using palladium catalysts.[54,70] The coupling reaction proceeds through a series of common reactions of palladium compounds - oxidative addition,[71a] olefin insertion,[71b] β-hydride elimination[71c] and reductive elimination.[54,71a,72] The proposed catalytic cycle (*Scheme 2.2*) begins with either a palladium(0) catalyst directly, commonly tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$], or by reduction *in situ* of a palladium(II) precursor, usually palladium(II) acetate or bis(triphenylphosphine)palladium(II) chloride [$PdCl_2(PPh_3)_2$]. This reduction may proceed by addition of, for example, palladium acetate to the olefin followed by β-hydride elimination of hydridopalladium(II) acetate (**42**) to yield a vinyl acetate (**43**) followed by base induced reductive elimination to palladium(0),[70a] although recent evidence suggests that reduction of Pd(II) to Pd(0) can also occur merely by heating the catalyst precursor in the presence of solvent (DMF, DMSO or acetonitrile)[59a] or base.[73] The active palladium(0) catalyst undergoes oxidative addition of the organo halide or triflate to form an organopalladium(II) halide (triflate) (**44**). It is believed that the intermediate formed from reaction of an organohalide differs from that of a triflate in that the former exists effectively as a covalent species and the latter as an ion pair with a cationic palladium atom.[74,75] Alkylpalladium(II) species with sp^3-hybridised carbons β to palladium which bear at least one hydrogen atom are unstable and will readily eliminate a β-hydrogen in a *syn*-manner,[54] so the



Scheme 2.2

choice of organo halides (triflates) is limited to vinyl, aryl, allyl and benzyl groups. The electron deficient intermediate **44** then coordinates to the π-electrons of the olefin to form the

complex **45**. Double bond insertion occurs next in a *syn*-manner to form an alkylpalladium(II) halide (triflate) (**46**). This step could theoretically yield two regioisomers, but for the reaction of terminal alkenes, and particularly those which bear electron withdrawing groups, it occurs regiospecifically to yield an intermediate in which the vinyl/aryl group has added to the terminal end of the double bond presumably for steric and electronic factors.[54,70] The σ-alkylpalladium(II) intermediate (**46**) is unstable and undergoes β-hydride elimination. In terms of the regiochemistry, β-hydride elimination will usually occur to yield the conjugated product (diene or aryl alkene) rather than an isolated alkene.[70] If two β-hydrogens are available on the same carbon atom (*e.g.* for reactions of terminal alkenes) then elimination will proceed with the hydrogen atom for which the *syn*-coplanar eclipsed conformation of the transition state is lowest in energy, which generally leads to the *E*-isomer (*Scheme 2.3*). Thus, for the Heck coupling of a terminal alkene the expected product is the *E*-alkene, terminally substituted. The β-hydride elimination (*Scheme 2.2*) yields a π-complex (**47**) between the hydridopalladium halide (triflate) and the coupled product. This intermediate may undergo ligand assisted dissociation to the respective components (*i.e.* **48** and **49**). Once dissociated, the hydridopalladium(II) halide (triflate) (**48**) rapidly undergoes reductive elimination in the presence of a base to regenerate the active palladium(0) catalyst and complete the catalytic cycle.



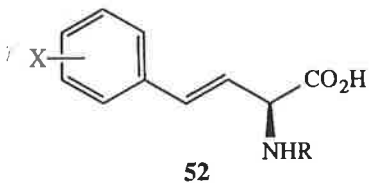
Scheme 2.3

As an alternative to dissociation, the intermediate **47** may undergo *syn*-addition of hydridopalladium(II) to reform **46** or produce the regioisomer (**50**) from addition in the 'reverse' manner.[70a] For reactions of a vinyl halide (triflate) (R' = alkene) this σ-allyl intermediate (**50**) can isomerise to a π-allylpalladium(II) halide (triflate) (**51**) which is susceptible to nucleophilic attack on the allyl group. For this reason, non-nucleophilic bases (*e.g.* tertiary amines, inorganic salts) are used in Heck reactions. In addition, stereochemistry about the double bond of what was the vinyl halide (triflate) moiety may be lost through an elimination-addition-elimination isomerisation (*e.g.* for a *Z*-vinyl halide, this sequence may lead to the formation of the thermodynamically more stable *E,E*-diene). However, Jeffery found

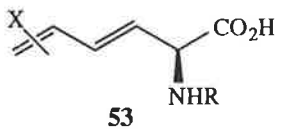
that under certain conditions the Heck coupling reaction proceeded with total retention of stereochemistry about what was the vinyl halide.[76] In these so-called 'Jeffery conditions' an olefin and vinyl halide (triflate) couple in DMF in the presence of a ligandless palladium(0) catalyst, formed from palladium(II) acetate, potassium carbonate and a solid-liquid phase transfer catalyst, tetrabutylammonium chloride.

Itaya has used Heck reactions of a vinylglycine derivative with an iodonucleoside and its corresponding base in the synthesis of wybutosine (*Introduction, Scheme 1.32*) and these have been the only examples of coupling reaction of its type.[65] Esterified vinylglycine derivatives are sensative to base and double bond migration occurs readily to form the corresponding α,β-unsaturated isomers.[26a] Since the Heck reaction is carried out under mildly basic conditions, Itaya reacted *L*-vinylglycine protected only on nitrogen and double bond migration was not observed.[65] Although the yields were low, the products from those Heck reactions were found not to have undergone racemisation at the chiral α-centre of the vinylglycine moiety.

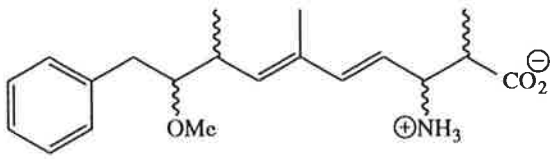
We wished to extend Itaya's results into a methodology study of the coupling reactions of N-protected vinylglycine with a variety of organo halides and triflates. These reactions would yield unsaturated α-amino acids of the types **52** and **53**. A number of compounds have been prepared with similar structures to these by some of the methods discussed in the introduction. Compounds **52** and **53** may have enzymatic inhibitory and antibiotic properties similar to those of other vinylglycines. A number of amino acids which occur naturally have conjugated diene functionality in the side chain, such as **54**, a component of the cyclic heptapeptide, cyanoginosin-LA.[77]



52



53

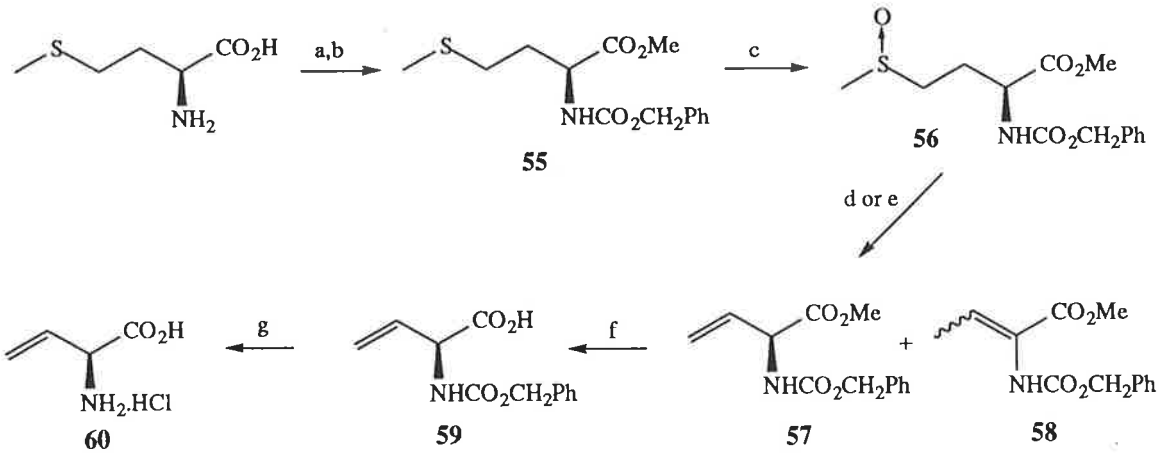


54

The synthesis of *L*-vinylglycine has been reported in the literature a number of times[26] and formation of an N-protected derivative was our initial target.

2.2 Synthesis of vinylglycine derivatives.

Methyl N-benzyloxycarbonyl-*L*-vinylglycinate (**57**) (benzyloxycarbonyl ≡ CBz) was prepared from 98% optically pure *L*-methionine following the procedure of Rapoport (*Scheme 2.4*).[26a] Thus, *L*-methionine was esterified with dimethoxypropane/hydrochloric acid and the amine protected using benzylchloroformate under Schotten-Baumann conditions in excellent yield for both steps. Oxidation of the sulphide (**55**) with sodium periodate in methanol and water resulted in a near quantitative yield of the sulphoxide (**56**) presumably as a mixture of diastereomers. Pyrolysis of the sulphoxide using the conditions outlined by Meffre (*i.e.* heating in *o*-dichlorobenzene at 170° in the presence of calcium carbonate)[26c] gave low yields of **57** and relatively large quantities of the α,β-unsaturated isomers (**58**) which were produced by base catalysed isomerisation of the initially formed β,γ-unsaturated product. Rapoport's modified method of pyrolysis (heating and oscillating the sulphoxide in a suitably sized flask under vacuum and collecting the pyrosylate) is reported to occur efficiently and is suitable for large scale preparation of **57**.[26b,50] Thus, placing up to 20g of sulphoxide (**56**) in a one litre flask in a preheated Aldrich kugelrohr at 180-190° and 0.2-0.3Torr with rapid oscillation (*ca* 100min^{-1}) for 1-2 hours and collecting the pyrosylate in an ice cooled bulb, followed by chromatography, consistently resulted in moderate to good yields of methyl N-CBz-*L*-vinylglycinate as a colourless oil. Meffre reported that this compound is a solid with low melting point,[26c] but we were unable to obtain it in crystalline form. Very little of the α,β-unsaturated isomers (**58**) was obtained by this method (between 5 and 10%). Our sample of



(a) dimethoxypropane, conc. HCl (cat.), 25°, 48h, 93%; (b) $PhCH_2OCOCl$, $NaHCO_3$, EtOAc, H_2O, 95%; (c) $NaIO_4$, MeOH, H_2O, 98%; (d) $CaCO_3$, *o*-dichlorobenzene, 160°, 19%; (e) Kugelrohr distillation, 180°, 0.2mm, 78%; (f) AcOH, 1N HCl, reflux, 68%; (g) 6N HCl, reflux, 53%.

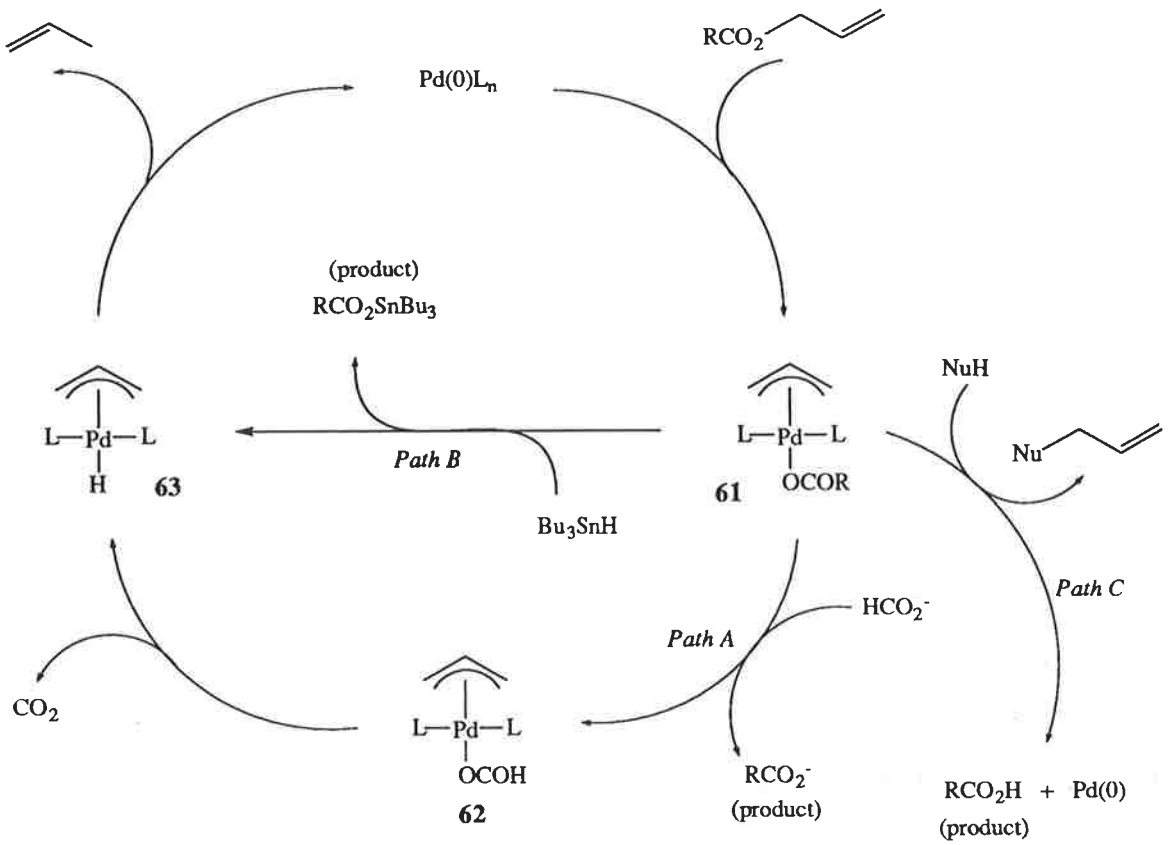
Scheme 2.4

57 had an optical rotation consistant with that reported in the literature (-11.8° [*c*3.0, MeOH], *c.f.* lit. -11.8° [*c*1.8, MeOH][26a]).

As esterified vinylglycines are not suitable for Heck reactions, because of their tendency to undergo base induced double bond migration, we sought a method for selectively hydrolysing the ester to the carboxylic acid without removing the CBz-group, migrating the double bond or racemising the α-centre. Rapoport found that for base catalysed hydrolysis of **57** with lithium hydroxide in acetone and water double bond migration accompanied hydrolysis and the α,β-unsaturated carboxylic acid formed.[26a] Heating **57** in 6N hydrochloric acid results in hydrolysis of both amino and carboxylate protecting groups.[26] Miller reported that acid hydrolysis of **57** using a mixture of acetic acid and 1N hydrochloric acid at reflux gave an 87% yield of N-CBz-*L*-vinylglycine (**59**).[78] On carrying out this reaction, only moderate yields of the desired compound were obtained, possibly as a result of partial hydrolysis of the CBz-group as well. However, we were able to perform this reaction on a large scale, so workable quantities of product (**59**) became available. No α,β-unsaturated isomer was obtained. Subsequent hydrolysis of the CBz-group in 6N hydrochloric acid yielded *L*-vinylglycine hydrochloride (**60**) with an optical rotation consistent with those reported in the literature (+80.4° [*c*0.54, H_2O], *c.f.* lit. range +78.2 to 83.5°),[26] so the chiral α-centre had survived the sequence without racemisation.

We wished to explore an alternative method of ester hydrolysis of the protected vinylglycine derivative **57** which would proceed under virtually neutral conditions. Such a procedure would not only be of interest in this instance, but generally for the deprotection of esters of acid and/or base sensitive compounds. One attractive option for the conversion of esters to carboxylic acids is the palladium catalysed hydrogenolysis of allylic esters which occurs in the presence of a mild hydride source such as trialkyltin hydride[79] or formate derivatives.[80] This reaction proceeds because of the facile nature of oxidative addition of allyl esters to palladium(0) and the electrophilicity of the resulting π-allylpalladium(II) species.[81]

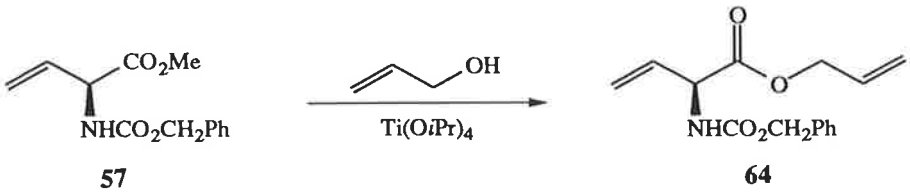
The mechanism of palladium catalysed hydrogenolysis of allyl esters is believed to proceed as shown in *Scheme 2.5*. Oxidative addition of the allyl ester to palladium(0) yields the π-allylpalladium(II) carboxylate (**61**). Exchange of the carboxylate group by a formate anion (from ammonium formate or other suitable formate derivative) (*Path A*) yields **62** and



Scheme 2.5

eliminates the (ammonium) carboxylate salt (*i.e.* the hydrolysed product as a salt).[80] Decarboxylation of the formate yields a hydrido-π-allylpalladium(II) species (**63**) which rapidly undergoes reductive elimination to form propene gas and regenerate the active palladium(0) catalyst. Alternatively, if tin hydride is used as the hydride source a transmetallation occurs between **61** and tin hydride (*Path B*) to form the hydrido-π-allylpalladium(II) intermediate (**63**) and the desired product as a tin carboxylate which readily hydrolyses on workup.[79] The use of a nucleophile results in allylation of the nucleophile accompanying reductive elimination (*Path C*).[81]

To obtain the allyl ester of vinylglycine suitable for palladium catalysed hydrogenolysis, a titanium(IV) catalysed transesterification with allyl alcohol was envisaged.[82] This procedure has previously been applied to amino acid and peptide chemistry and shown to proceed without isomerisation or epimerisation.[82b] Thus, methyl N-CBz-*L*-vinylglycinate (**57**) was converted to its allyl ester (**64**) by heating in allyl alcohol at reflux temperature in the presence of titanium tetraisopropoxide, a mild Lewis acid, resulting in a clean conversion in very good yield without isomerisation to the α,β-unsaturated derivative (*Scheme 2.6*). Hydrogenolysis of the allyl ester

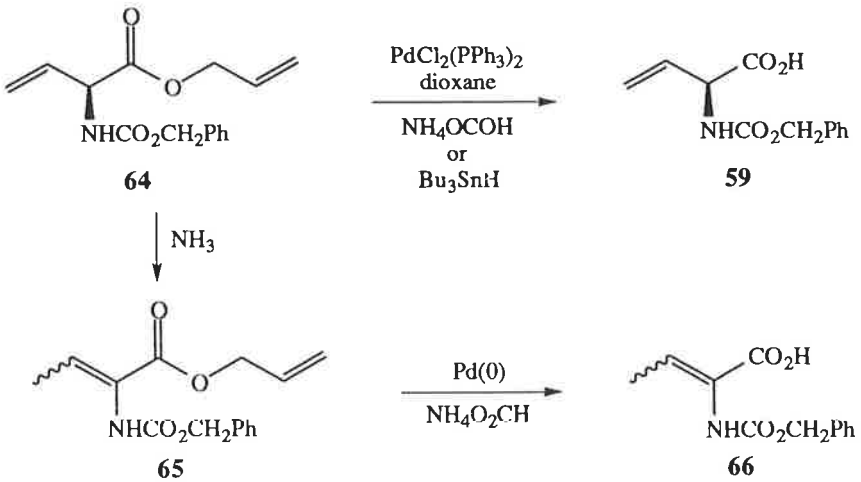


57 **64**

Scheme 2.6

(**64**) with bis(triphenylphosphine)palladium(II) chloride and ammonium formate in dioxane at reflux gave a mixture of N-CBz-vinylglycine (**59**) (53%) and its α,β-unsaturated isomer (**66**) (25%). Presumably this isomer arose from a competing base catalysed double bond migration of allyl N-CBz-vinylglycinate (**64**) with ammonia, formed in an equilibrium amount during the reaction, which resulted in the α,β-unsaturated allyl ester (**65**) which subsequently underwent deesterification (*Scheme 2.7*). The smell of ammonia gas could be detected when the reaction mixture was subjected to t.l.c. analysis. Perhaps formation of **66** could be avoided by substituting formic acid or sodium formate in place of ammonium formate. However, use of tri-*n*-butyltin hydride as the hydride source in the hydrogenolysis reaction (tri-*n*-butyltin hydride, catalytic bis(triphenylphosphine)palladium(II) chloride, dioxane, reflux) resulted in formation of the desired product (**59**) in excellent yield, with no unwanted isomers. The optical rotation of **59** obtained by this method was slightly lower than that of the product obtained by the acid hydrolysis (+13.3°, *c.f.* +13.6°), as was its melting point (126-128°, *c.f.* 128-130°), indicating that only a minimal amount of racemisation may have occurred. Thus, we have developed a complimentary method for deesterification of methyl N-CBz-*L*-vinylglycinate (**57**) in high yield under essentially neutral conditions.

An alternative to ester hydrolysis in controlling the base sensitivity of vinylglycine

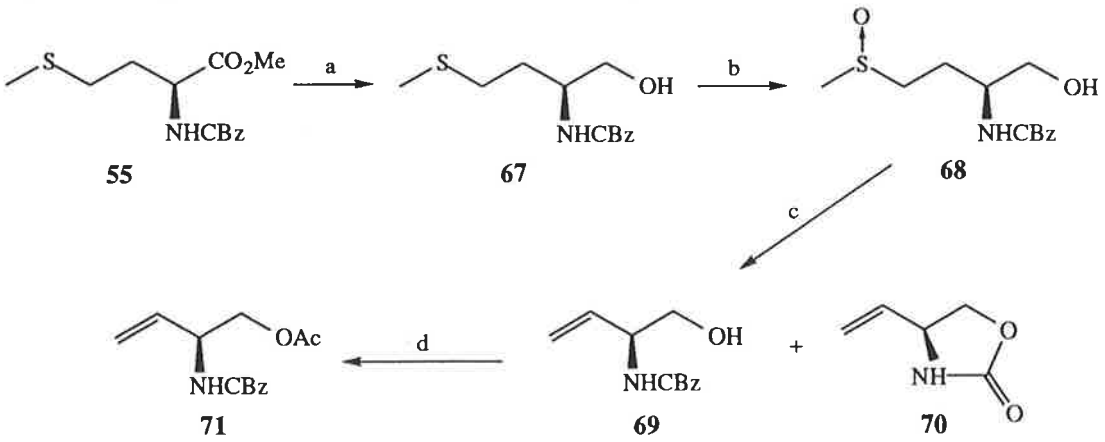


64 **59**

65 **66**

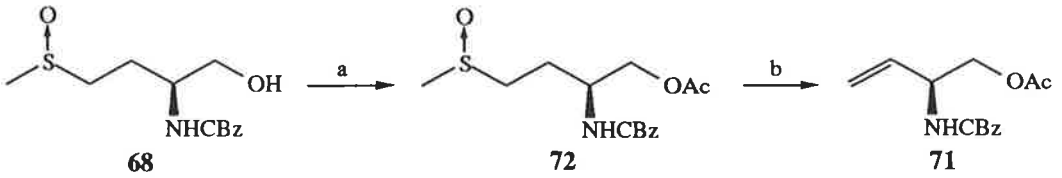
Scheme 2.7

derivatives is the reduction of the carboxylate group to the corresponding alcohol. The reduced form of N-CBz-*L*-vinylglycinate, N-CBz-*L*-2-aminobut-3-enol (**69**), has been prepared in the literature by Ohfune from *L*-methionine[83] by a similar oxidative degradation used by Rapoport for the synthesis of vinylglycine, and we utilised this method with slight variations (*Scheme 2.8*). Reduction of methyl N-CBz-*L*-methionate (**55**) with sodium borohydride in ethanol gave a good yield of the primary alcohol (**67**). Sodium borohydride does not usually reduce carboxylic esters, but presumably does so in this case because of the increased electrophilicity of the carbonyl group resulting from the the presence of the α-CBz-amino group. Reduction with either lithium aluminium hydride or diisobutylaluminium hydride gave lower yields of **67** and unwanted side products were detected by t.l.c. Oxidation of the sulphide (**67**) with sodium periodate gave the sulphoxide (**68**) in excellent yield. Pyrolysis of this sulphoxide could be achieved in solution without the complication of unwanted double bond migration. Thus, heating to 170° in *o*-dichlorobenzene in the absence of any base gave the desired N-CBz-2-aminobut-3-enol (**69**) in moderate yield. The presence of base (calcium carbonate) in the pyrolysis mixture resulted in formation of considerable amounts of oxazolidinone (**70**) which presumably arose by intramolecular alkoxide attack on the CBz-carbonyl group. In order to stop formation of this product we protected the hydroxyl group of **68** as its acetate prior to pyrolysis (*Scheme 2.9*). Without isolation, the crude acetylated product (**72**) was heated to 170° in *o*-dichlorobenzene to yield the CBz-aminobut-3-enyl acetate (**71**) in excellent yield for the two steps. The hydroxy compound (**69**) could be obtained readily from **71** by mild basic hydrolysis (catalytic KOH, methanol, ambient temperature). As a route to **69**, this latter



(a) $NaBH_4$, EtOH, 77%; (b) $NaIO_4$, MeOH, H_2O, 94%; (c) *o*-dichlorobenzene, ($CaCO_3$), 160°, 64%; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 81%.

Scheme 2.8



68 **72** **71**

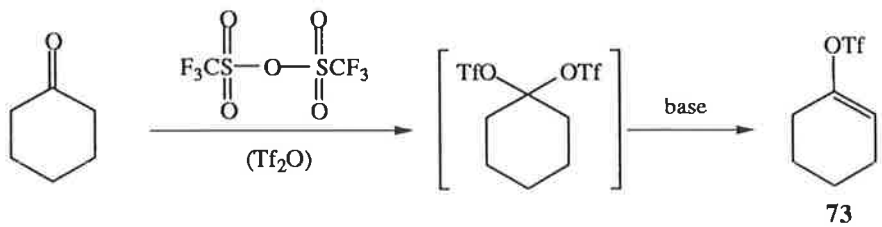
(a) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (b) *o*-dichlorobenzene, 170°. 92% from **68**.

Scheme 2.9

method was far superior in terms of yield and simplicity of preparation. The carboxylate reduced derivatives of vinylglycine obtained by this procedure (**69** and **71**) were optically active crystalline solids, with the optical rotation of the hydroxy compound **69** slightly lower than that reported in the literature (-29.6° [*c*0.69, $CHCl_3$], *c.f.* lit. -32.1° [*c*3.1, $CHCl_3$][83]).

2.3 Synthesis of vinyl triflates and a halide.

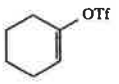
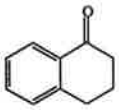
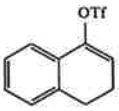
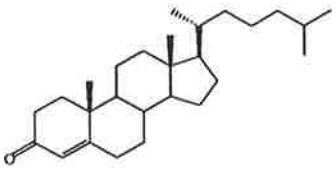
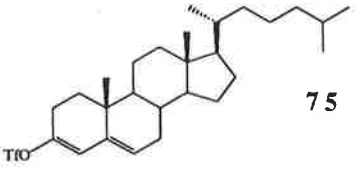
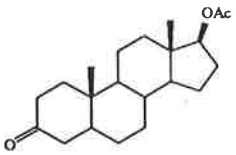
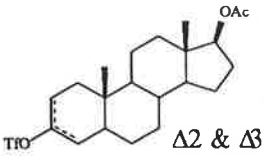
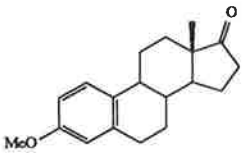
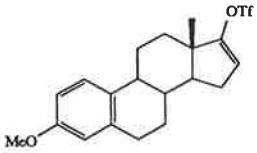
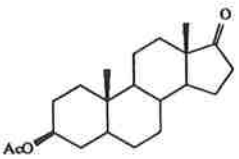
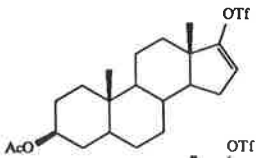
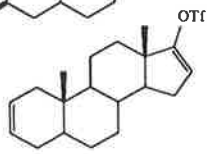
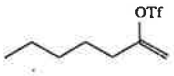
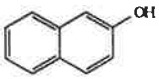
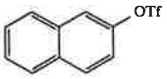
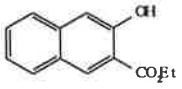
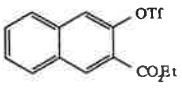
For the palladium catalysed coupling reactions reported in this study we required a variety of organic electrophiles, namely vinyl and aryl halides and trifluoromethanesulphonates. Most halides used were commercially available, but it was necessary to synthesise a number of the triflates as well as a vinyl iodide. These compounds are listed in *Table 2.1*. Vinyl triflates were obtained most commonly from the reaction of a ketone with trifluoromethanesulphonic anhydride (triflic anhydride) and base in dichloromethane at room temperature for a suitable period of time, followed by chromatography and distillation or recrystallisation.[55] In this manner we synthesised a number of cyclohexenyl (entries 1-4) and cyclopentenyl triflates (entries 5 & 6). The base most commonly used was 2,6-di-*tert*-butyl-4-methylpyridine, a sterically hindered non-nucleophilic base, which has been much utilised in vinyl and aryl triflate formation because of its lack of reactivity with triflic anhydride.[84] This allows the anhydride to react with the ketone to form what is proposed to be a geminal ditriflate which reacts with base to eliminate triflic acid (*Scheme 2.10*). However, for the preparation of cyclohex-1-en-1-yl triflate (**73**) (entry 1) we utilised Collins' procedure, in which sodium carbonate is substituted

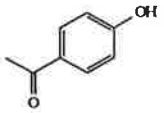
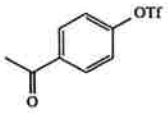
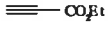


73

Scheme 2.10

Table 2.1 Synthesis of vinyl and aryl triflates and a vinyl halide.

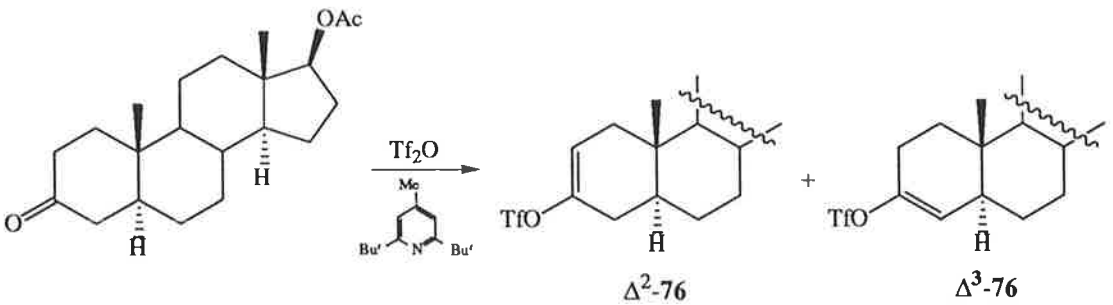
Entry	Substrate	Method[a]	Temp/Time	Product(s)	Yield[b]
1		A	ambient/24h	 **73**	46
2		A	ambient/48h	 **74**	26
3		B	ambient/21h	 **75**	46
4		B	ambient/16h	 Δ2 & Δ3-**76**	31[c]
5		B	ambient/48h	 **77**	69
6		B	ambient/18h	 **78**	33
				 **79**	7
7		C	0°/1.5h	 **80**	93
8		D	reflux/1.5h	 **81**	53
9		D	reflux/1h	 **82**	59
		E	ambient/15h		46

10		F	ambient/4d		**83**	85
11		G	70°/5h		**84**	68

[a] Reactions carried out using the following conditions:
A = Triflic anhydride (2.0 eq), sodium carbonate (2.0 eq), dichloromethane;
B = Triflic anhydride (1.5-2.0 eq), 2,6-di-*tert*-butyl-4-methylpyridine (1.3-2.0 eq), dichloromethane;
C = Triflic acid (0.9 eq), dichloromethane;
D = Triflic anhydride (1.1 eq), sodium hydride (1.0 eq), ether;
E = Triflic anhydride (1.0 eq), pyridine (solvent);
F = N-Phenyltriflimide (1.1 eq), potassium carbonate (1.2 eq), dioxane/water (10:1);
G = Lithium iodide (1.1 eq), acetic acid (solvent).
[b] Yield of pure isolated material.
[c] Mixture of Δ^2 and Δ^3-isomers (84:16).

for the hindered pyridine, which is reported to occur in higher yield.[85]

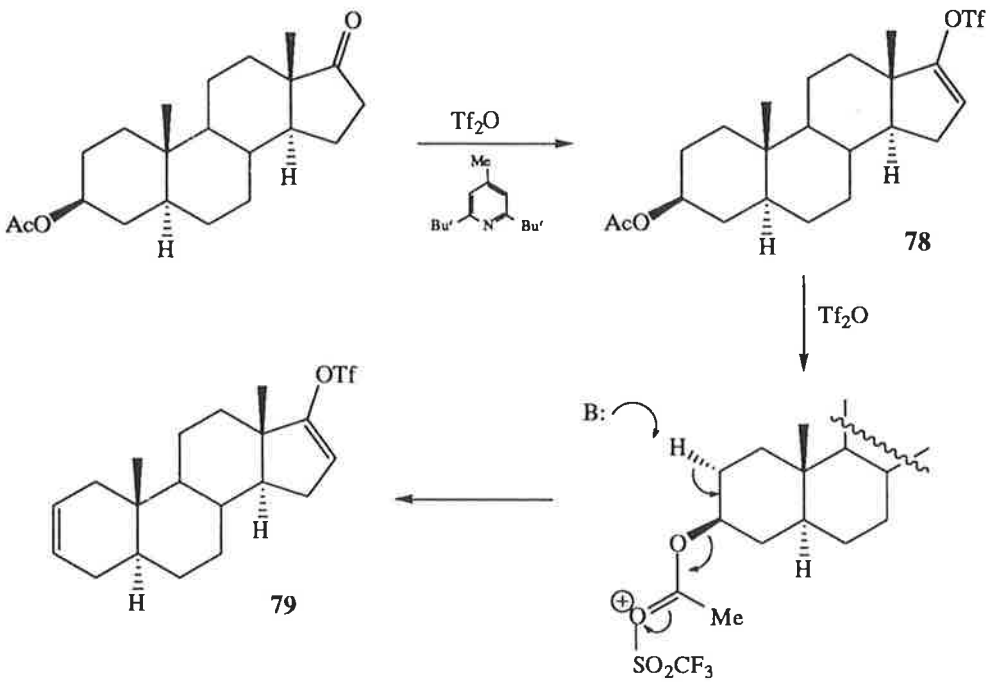
The steroidal triflates (**75**,[86] **76**,[87] **77**[88] & **78**[89]) are known compounds which have been studied extensively in a large number of palladium catalysed reactions, particularly by Cacchi and Ortar.[56,86-90] Reaction of acetyloxyandrosterone with triflic anhydride (entry 4) yielded a *ca* 80:20 mixture of regioisomeric Δ^2 and Δ^3-vinyl triflates (Δ^2 & Δ^3-**76**) which were inseparable by chromatography on silica gel (*Scheme 2.11*). In order to obtain a purer sample, suitable for coupling reactions, we attempted to isomerise Δ^3-**76** to Δ^2-**76** by treating the mixture in dichloromethane in the presence of triflic anhydride and a catalytic amount of triflic acid. This procedure has been used by Cacchi and Ortar for the total isomerisation of Δ^3-cholestenyl triflate to its Δ^2-isomer.[90] However, we were unable to totally convert the minor isomer to the Δ^2-vinyl triflate and only a slightly improved ratio of isomers was obtained (Δ^2:Δ^3-**76** = 84:16). Much decomposition of the vinyl triflates occurred and a low yield of products was obtained. A similar ratio of these vinyl triflates was reported by Cacchi and Ortar (Δ^2:Δ^3-**76** = *ca* 80:20), but it was unclear whether they had attempted a triflic acid catalysed



Scheme 2.11

double bond isomerisation.[87]

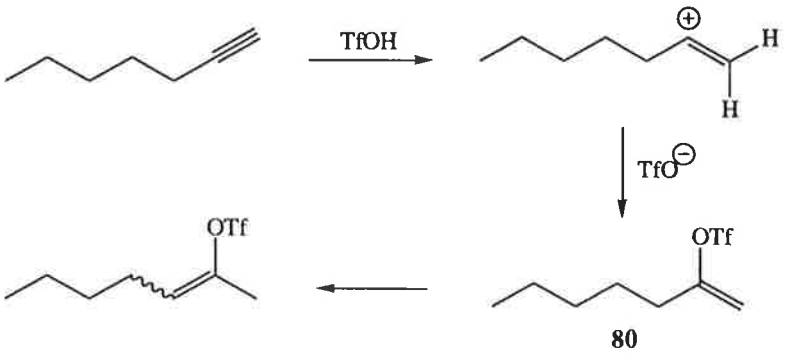
In addition to a low yield of acetyloxyepiandrosteryl triflate (**78**) a by-product from the reaction of acetyloxyepiandrosterone with triflic anhydride (entry 6) was the dehydroacetylated compound (**79**). This presumably arose from reaction of the acetate carbonyl with triflic anhydride, or possibly a trace of triflic acid, followed by elimination of the C2-proton in the presence of base (*Scheme 2.12*). It was presumed from the spectral data that the Δ^2-isomer (**79**) had formed in preference to the Δ^3. This was tentatively assigned on the basis of the observations that in the ^1H and ^{13}C n.m.r. spectra the two cyclohexenyl vinylic protons and the two olefinic carbons (C2 & C3) resonate at almost identical chemical shift values respectively, and that a retro-Diels-Alder fragmentation (loss of butadiene) is evident in the mass spectrum (retro-Diels-Alder reaction of the Δ^3-isomer would not lead to a loss of butadiene). Didehydrosteroidal Δ^2-isomers seem to be more thermodynamically stable than Δ^3-isomers based on the evidence obtained by Cacchi and Ortar for the triflic acid catalysed isomerisation of Δ^3 to Δ^2-vinyl triflates.[90] The elimination of the units of acetic acid during the preparation of vinyl triflate **78**, in addition to the low yields of the other acetylated steroidal triflate (**76**), seems to imply that a less reactive alcohol protecting group than an acetate (*e.g.* methyl ether) may have been preferable .



Scheme 2.12

Hept-1-en-2-yl triflate (**80**) (entry 7) was prepared by the Markovnikov addition of triflic acid to 1-heptyne (*Scheme 2.13*). This is a general method for the formation of vinyl

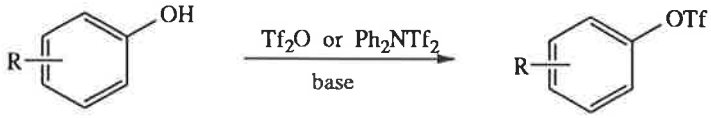
triflates, but is of restricted use because (a) triflic acid will react with most functional groups, (b) the product must contain a vinylic hydrogen atom and (c) regio and stereochemistry problems arise for the reaction of non-terminal alkynes.[55] Thus, reaction of 1-heptyne with less than one equivalent of triflic acid in dichloromethane at ice bath temperature for 90 minutes yielded the desired vinyl triflate (**80**) in good yield after extractive workup and distillation. The use of excess triflic acid resulted in the formation of appreciable amounts of *E* and *Z*-hept-2-en-2-yl triflates which arose by acid catalysed double bond migration to the more substituted double bond.[91]



80

Scheme 2.13

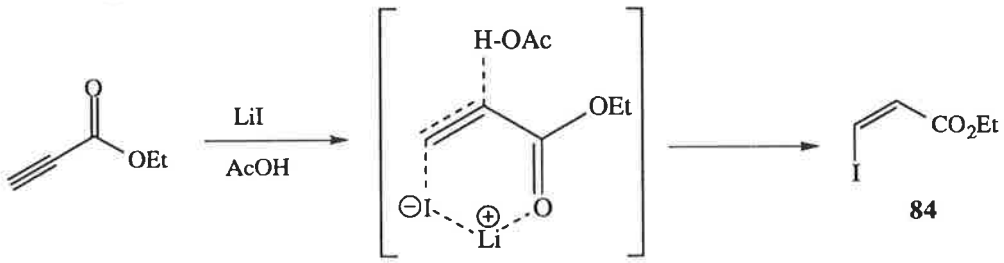
The aryl triflates were prepared from the corresponding hydroxy arenes by reaction with base and a triflating agent (*Scheme 2.14*). β-Naphthol was found to undergo triflation cleanly and in moderate yield when treated sequentially with sodium hydride and triflic anhydride in ether to form naphth-2-yl triflate (**81**) (entry 8).[92a] Using the hindered pyridine as base gave much discolouration and a more troublesome workup.[92b] 3-Carboethoxy-2-naphthyl triflate (**82**) was prepared in moderate yield from 3-carboethoxy-2-naphthol by reaction with triflic anhydride and either sodium hydride or pyridine (entry 9). *p*-Acetylphenyltriflate (**83**) was obtained in good yield by reaction of *p*-acetylphenol with potassium carbonate and N-phenyltriflimide in dioxane and water (entry 10). Use of Stille's procedure for the preparation of **83** (triflic anhydride and pyridine)[93] gave a low yield of product and much decomposition.



Scheme 2.14

The only vinyl halide prepared was ethyl *Z*-3-iodoacrylate (**84**) (entry 11). This vinyl iodide was recently reported in the literature as a suitable substrate for palladium catalysed

coupling reactions and in that study products were found not to have undergone isomerisation to the *E*-isomers.[94] Thus, **84** was prepared by reaction of ethyl propiolate with lithium iodide in acetic acid at 70° for 5 hours (*Scheme 2.15*).[95] Extractive workup yielded a very clean sample of iodoacrylate in good yield. It is reported that the crude reaction mixture can be used for palladium catalysed reactions[94] and initially we attempted a Stille coupling using this procedure (Chapter *3.5.3*). However, a better yield of Stille coupled product was obtained, and less isomeric product was formed, when the vinyl iodide was isolated from the crude reaction mixture prior to coupling.

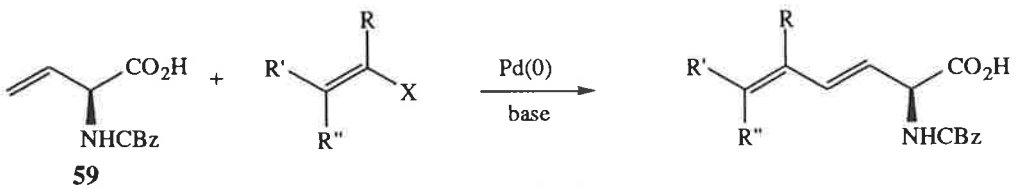


Scheme 2.15

2.4 Heck reactions of N-CBz-*L*-vinylglycine (59)

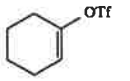
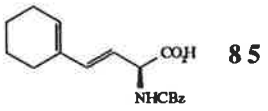
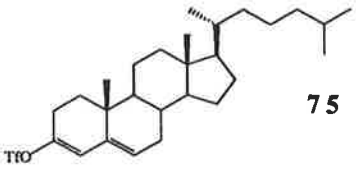
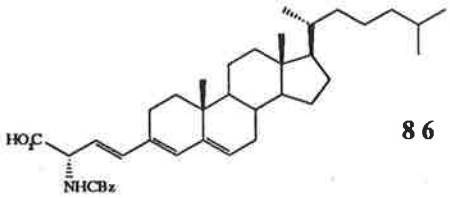
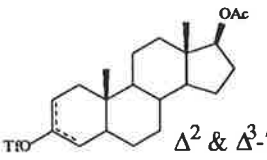
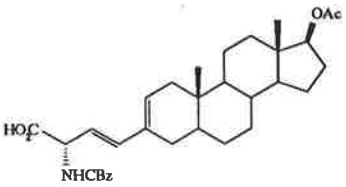
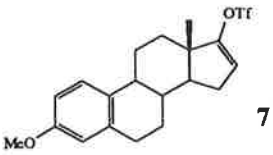
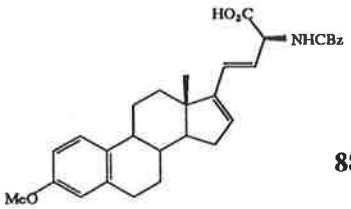
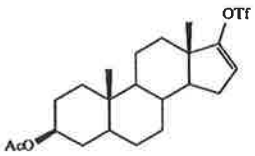
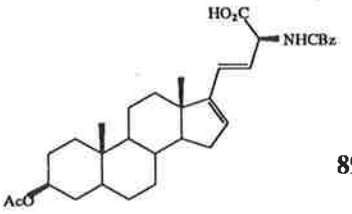
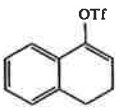
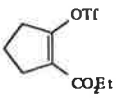
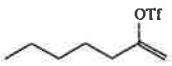
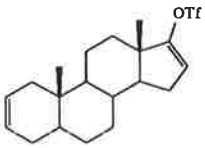
2.4.1 Attempted coupling with vinyl triflates and halides.

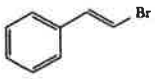
Heck reactions of the general type shown in *Scheme 2.16* were investigated between N-CBz-*L*-vinylglycine (**59**) and a number of vinyl triflates and a vinyl halide as a route to dienyl α-amino acids. Initial studies were undertaken with cyclohexenyl triflate (**73**) and an excess of **59** (*Table 2.2*, entry 1). Under Jeffery conditions (palladium acetate, potassium carbonate, tetra-*n*-butyl ammonium chloride, DMF)[76] instantaneous decomposition of the catalyst to palladium black occurred. The addition of tri-*o*-tolylphosphine, two equivalents relative to palladium, resulted in a far more stable catalyst. Presumably the presence of the carboxylate group of **59** is deleterious to the ligandless palladium(0) catalyst. Gradual heating whilst monitoring the reaction by t.l.c. indicated that the reaction began at *ca* 50° and after an hour at that temperature no vinylglycine remained and one intensely u.v. active spot had appeared in



Scheme 2.16

Table 2.2 Heck reactions between N-CBz-*L*-vinylglycine (**59**) and vinyl triflates and a halide.

Entry	Triflate/halide	Temp./Time	Product	Yield[a]
1	 **73**	50°/1h	 **85**	77
2	 **75**	60°/2h	 **86**	69
3[b]	 Δ^2 & Δ^3-**76**	70°/3h	 **87**	50[c]
4	 **77**	75°/4h	 **88**	54
5	 **78**	85°/1h	 **89**	34
6	 **74**	65°/90min	Not detected	0
7		50°/1h	Not detected	0
8	 **80**	60-75°/2h	Not detected	0
9	 **79**	70°/2h	Not detected	0

10		70°/3h	Not detected	0

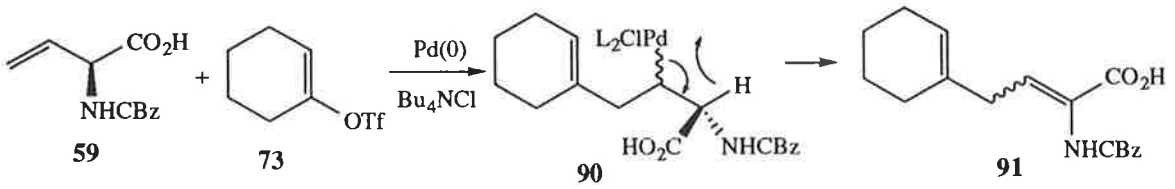
Reactions carried out by heating a mixture of N-CBz-*L*-vinylglycine (1-2 eq), triflate (bromide) (1.0 eq), $Pd(OAc)_2$ (10mol%), $P(o\text{-}Tol)_3$ (20mol%), Bu_4NCl (1.0 eq), and K_2CO_3 (5 eq) in DMF at the temperature and reaction time shown.

[a] Isolated yield of pure material.

[b] 5:1 mixture of Δ^2 and Δ^3-vinyltriflates.

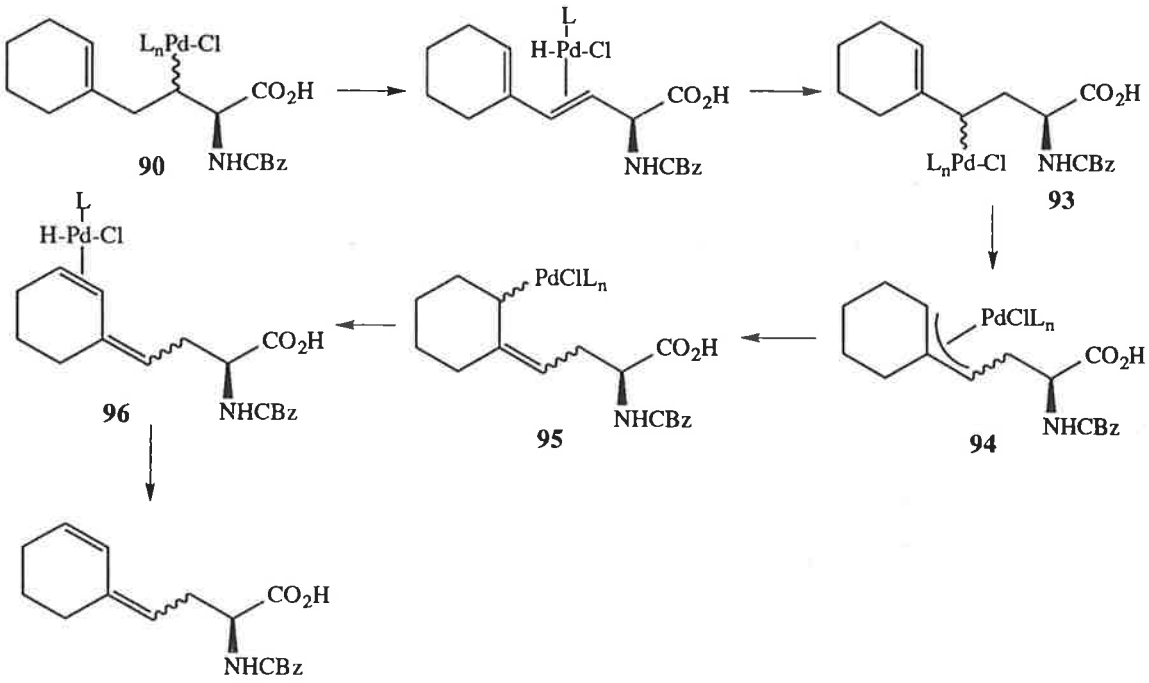
[c] In addition, isomeric material was isolated (26%).

quite a complex mixture. By this stage palladium black had precipitated and generally this signalled the end of all the coupling reactions. Acidic, extractive workup of the reaction mixture followed by flash chromatography on silica gel yielded the coupled product (**85**) in good yield. The spectra obtained for this product were consistent with cyclohexenyl substitution at the terminus of the double bond of the vinylglycine derivative and with *E*-geometry about the β,γ-double bond. The other polar minor products are believed to be double bond isomers of **85**. Characterisation of these minor components was not undertaken owing to the difficulty in obtaining pure samples by flash chromatography. A ^1H n.m.r. spectrum of the mixture of isomers indicated that the compounds contained resonances associated with both the CBz and cyclohexyl moieties, but the olefinic region differed from that of the expected, and obtained, major product (**85**). Unreacted excess vinylglycine (**59**) was recovered from the reaction mixture and since it had obviously not isomerised to the α,β-unsaturated compound under the reaction conditions, presumably any double bond isomeric coupled products arose from palladium catalysed reactions during the catalytic cycle. Two possibilities seem likely. Firstly, *syn*-β-hydride elimination of the organopalladium species (**90**), formed after double bond insertion of vinylglycine derivative into the cyclohexenylpalladium(II) intermediate, may occur with the C2-proton rather than a C4-proton, which would be a favourable process since the double bond formed by elimination in this manner is conjugated with the carboxylate group (**91**) (*Scheme 2.17*). Secondly, isomerisation could occur through readdition of palladium(II)



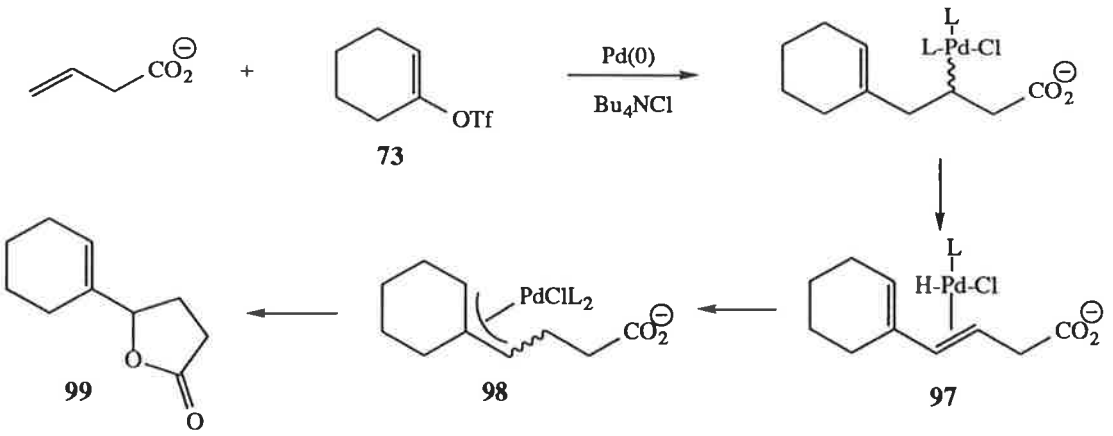
Scheme 2.17

hydride to the double bond of the complexed β-hydride elimination product (**92**) in a 'reverse' manner to form σ-allyl intermediate **93** (*Scheme 2.18*). Rearrangement to a different σ-allyl complex (**95**), *via* a π-allyl complex (**94**), followed by β-hydride elimination would produce the complexed 1,3-diene, **96**. Dissociation, or readdition of palladium hydride followed by β-hydride elimination, could yield a number of 1,3 and 1,4-dienes. The amount of isomeric products was difficult to control and appeared to depend on the particular conditions used for the reaction (*e.g.* how rapidly the solution was heated and to what temperature, exact quantities of reagents, base used, *etc.*), although the yield of the desired product (**85**) was surprisingly consistent (*ca* 70-80%).



Scheme 2.18

Larock has shown that for structurally similar β,γ-unsaturated carboxylic acids, Heck reactions with vinyl triflates may yield γ-vinyl lactones.[96] For example, the coupling of but-3-enoic acid with cyclohexenyl triflate, using a modification of the Jeffery conditions, produced the vinyl lactone **99** in moderate yield (*Scheme 2.19*). Such vinyl lactones are proposed to form by nucleophilic attack of the carboxylate anion onto the π-allyl intermediate (**98**) formed after readdition of palladium(II) hydride in the reverse sense to the initially formed β-hydride elimination product (**97**). Since vinylglycine derivative **59** differs from but-3-enoic acid only by the presence of the α-CBz-amino group, we might have expected some lactone formation from the intermediate **94**, but none was observed. However, we cannot rule out entirely that lactones had not formed, and in some reactions product of this type may account for the low



Scheme 2.19

yield of expected coupled material.

The other vinyl triflates were reacted using the following conditions as the standard general procedure: N-CBz-*L*-vinylglycine (1.0-2.0 eq), vinyl triflate (1.0 eq), palladium acetate (0.1 eq), tri-*o*-tolylphosphine (0.2 eq), potassium carbonate (5 eq) and tetra-*n*-butylammonium chloride (1.0 eq) in DMF under a nitrogen atmosphere was heated and monitored by t.l.c. until the solution blackened or it appeared that no further products were being formed. Acidic, extractive workup followed by flash chromatography yielded the coupled product. Reactions involving steroidal triflates (**75**, **76**, **77** and **78**) all furnished the desired and expected Heck coupled products in low to moderate yields (*Table 2.2*, entries 2-5). Androsteryl triflate (Δ^2-**76**) (entry 3) resulted in a substantial amount of isomeric material, possibly owing, in part, to reaction of Δ^3-**76** (present in *ca* 16%).

Attempts to extend the coupling process to other vinyl triflates (entries 6-9) as well as a vinyl bromide (entry 10) failed. In those reactions no coupled product could be detected or isolated and it appeared as though the triflates and bromide were consumed during the process, possibly by undergoing homocoupling with another molecule of triflate or bromide, or perhaps reduction of some sort, but we did not attempt to isolate these non-polar intermediates. Since vinylglycine derivative **59** is not particularly activated towards Heck addition it seems that only vinyl triflates which are reactive enough to couple will do so. The electrophiles which did not couple may have been less reactive because of steric and electronic factors.

The ^{1}H n.m.r. spectra of some of the coupled products displayed a second set of resonances, slightly offset from the main signals, which is assumed to have been caused by a different conformer of the main product (*Figure 2.1*). These signals were not due to side

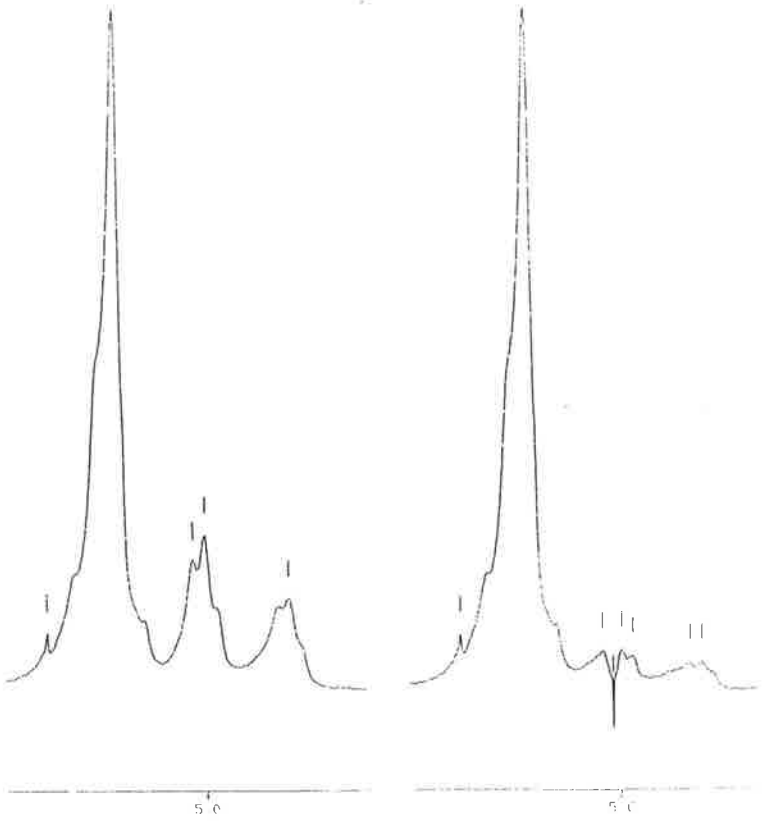


Figure 2.1 Portion of the ^{1}H n.m.r. spectrum of coupled product **85** showing the benzylic methylene and α-methine resonances. All the resonaces are broad and two peaks occur for the α-proton, indicating conformational exchange is occurring on the n.m.r. time scale. The right hand spectrum was obtained by irradiating the major signal of the α-proton. Note that this has the effect of reducing the intensity of the minor α-proton resonance.

products since during decoupling experiments irradiation of the signal of the α-proton of the major conformer caused the disappearance of the correponding resonance of the minor conformer. Conformers could arise from either s-*trans* or s-*cis* arrangements of the diene unit or from either an *E* or *Z* arrangement of the carbamate functional group.

In order to obtain evidence that the Heck reactions were not epimerising the α-centre of the coupled products, the product (**85**) of the reaction between N-CBz-*L*-vinylglycine and cyclohex-1-en-1-yl triflate was analysed by a chiral europium(III) ^{1}H n.m.r. shift experiment. To ascertain the feasibility of such an n.m.r. experiment, N-CBz-*D,L*-vinylglycine (*D,L*-**59**) was used as a trial. The racemic vinylglycine derivative was prepared from *D,L*-vinylglycine hydrochloride (*D,L*-**60**) by N-acylation with benzylchloroformate using Schotten-Baumann conditions. However, addition of a small quantity of the shift reagent, tris[3-(heptafluoromethylhydroxymethylene)-(-)-camphorato]europium(III) [Eu(III)(hfc)$_3$], to a dilute solution of *D,L*-**59** in $CDCl_3$ caused dramatic coalescing of all the proton signals. Since this was probably the effect of the carboxylic acid towards Eu(III) we decided to derivatise the

vinylglycine as its methyl ester. This was simply and cleanly performed by treating a dichloromethane solution of *D,L*-**59** with excess diazomethane. This occurred without isomerisation of the double bond. When sufficient Eu(hfc)$_3$ had been added to the n.m.r. tube, splitting of the methyl protons was achieved (*Figure 2.2*). Two pairs of methyl resonances were observed (at δ3.88/3.89 and δ4.30/4.35). The formation of four, rather than two, diastereomeric europium(III) complexes is known for N-CBz-amino acid dervatives in chiral Eu(III) n.m.r. shift experiments.[97] Presumably this arises because of *E* and *Z*-arrangements of the carbamate functional group.

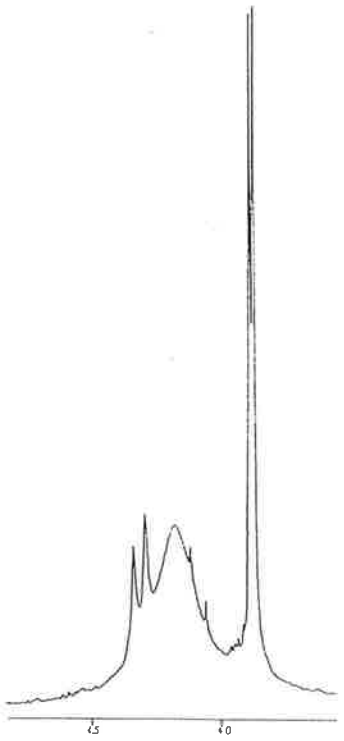
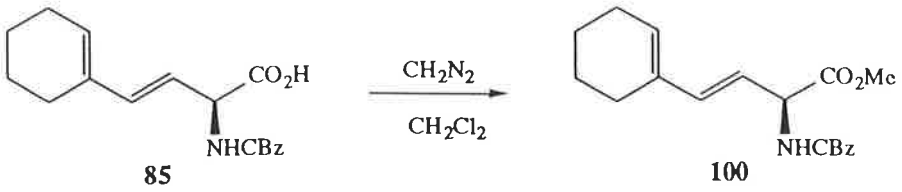


Figure 2.2. Effect of Eu(hfc)$_3$ shift reagent on racemic N-CBz-vinylglycine. The portion of the spectrum shown is that of the the methyl ester resonances of the diastereomeric complexes.

The europium(III) induced separation of the methyl signals on the model having been achieved, the shift experiment was undertaken with the methyl ester of coupled product **85**. The racemic and chiral esters (**100**) were prepared cleanly with diazomethane (*Scheme 2.20*) and no double bond migration occurred. The result of the two chiral shift experiments may be seen in *Figure 2.3*. For the racemic coupled product (*D,L*-**100**), three peaks resulted for the methyl ester resonance (at δ4.56, 4.59 and 4.23 - the latter not split into two distinct signals).



85 **100**

Scheme 2.20

For the 'chiral' coupled product (*L*-**100**) two signals at δ4.51 and 3.99 were obtained; that is, the third signal obtained by splitting of the left hand resonance did not appear. The chemical shift differences of the corresponding signals in the two spectra (*e.g.* δ4.23 *vs* 3.99) were due, possibly, to the differences in concentrations of the two solutions, although the relative concentration of Eu(hfc)$_3$ to diene was the same in both cases. The small peaks immediately to the left of each signal are either impurities in the sample or diastereomeric europium complexes of minor conformers as they seem to be too far removed from the major signals to be the minor diastereomeric complex associated with the other enantiomer, but it is not improbable that this may be the case. If it is assumed that these are associated with the corresponding *D*-coupled product, the ratio of *ca* 10:1 for the two enantiomers would imply an enantiomeric excess of at least 80% in favour of the *L*-isomer.

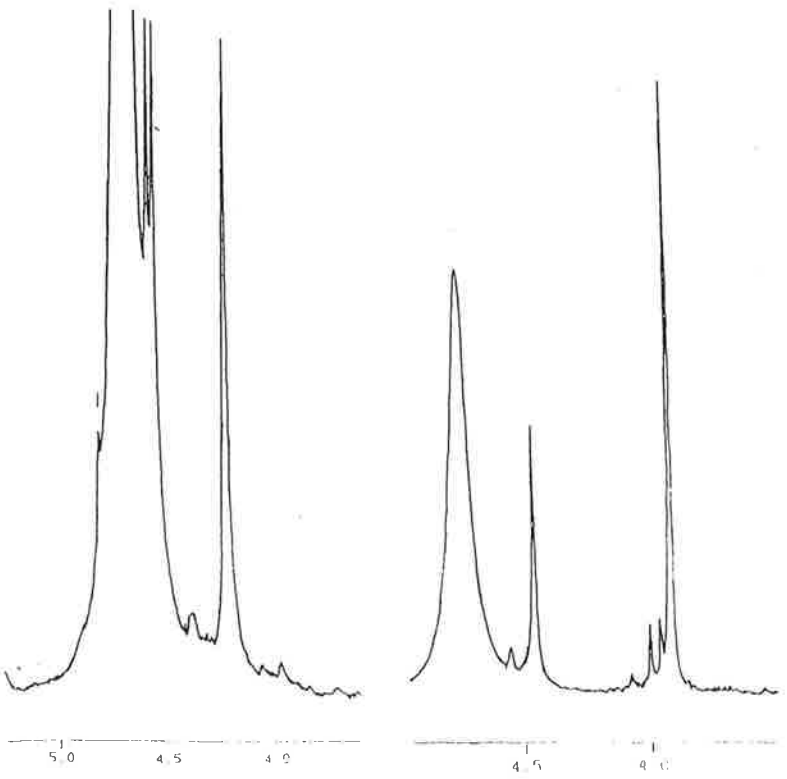
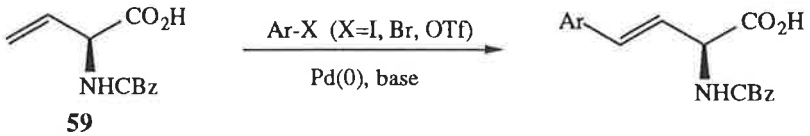


Figure 2.3. Effect of Eu(hfc)$_3$ shift reagent on racemic and chiral **100**. The portion of the spectrum shown is that of the the methyl ester resonances of the diastereomeric complexes.

To summarise, the Heck reactions of N-CBz-*L*-vinylglycine with vinyl triflates and bromide were quite problematic. Only for a select group of vinyl triflates did the reaction proceed at all, and often a number of products were obtained which were difficult to separate by chromatography. For the other vinyl triflates and the vinyl bromide studied no expected coupled product could be detected, although in most cases the vinyl triflate/bromide was totally consumed. The ^{1}H n.m.r. spectra of coupled products were complicated by the presence of what is assumed to be a minor conformer. As expected, little or no racemisation occurred at the α-centre and this was confirmed by a chiral europium(III) ^{1}H n.m.r. shift experiment with the methyl ester of the product obtained by the coupling of cyclohexenyl triflate with both racemic and chiral N-CBz-vinylglycine.

2.4.2 Attempted coupling reactions with aryl triflates and halides.

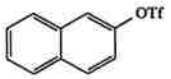
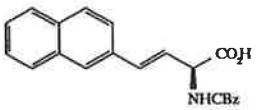
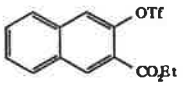
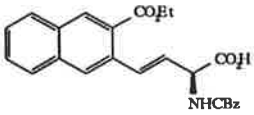
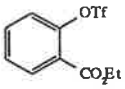
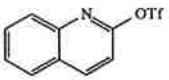
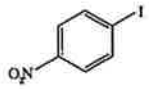
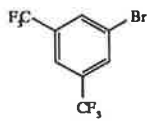
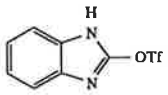
We wished to investigate the scope of Heck reactions of N-CBz-*L*-vinylglycine (**59**) to coupling with aryl halides and triflates of the general type in *Scheme 2.21*. The results of attempted couplings are shown in *Table 2.3*. Reaction with 2-naphthyl triflate (**81**) was undertaken as a model. Attempts at performing the reaction using classical Heck conditions [$Pd(PPh_3)_2Cl_2$, Et_3N, DMF, 100°][70a] gave no product (entry 1). Again, addition of tri-*o*-tolylphosphine was necessary to provide a stable catalyst when coupling using Jeffery conditions [$Pd(OAc)_2$, P(*o*Tol)$_3$, K_2CO_3, Bu_4NCl, DMF] and resulted in the formation of the desired *E*-γ-naphthyl substituted product (**101**) in moderate yield as well as a 21% mixture of α,β-unsturated isomers (*E* & *Z*-**103**) (entry 2). These arose by β-hydride elimination of the C2-hydrogen, rather than one of the two C4-hydrogens, from the diastereomeric intermediate alkylpalladium(II) species (**104**) in the catalytic cycle (*Scheme 2.22*). This is a favourable path to elimination since the double bond formed is conjugated with the carbonyl group. The products (*E* & *Z*-**103**) were assigned the structures shown on the basis of their ^{1}H n.m.r. spectra which displayed for one isomer a vinylic triplet at δ6.96 (1H), an allylic doublet at 4.17 (*J*8.0Hz, 2H) and a broad singlet at 7.06 (NH), and for the other isomer a triplet at δ6.87 (1H),



59

Scheme 2.21

Table 2.3. Heck reactions between N-CBz-*L*-vinylglycine (**59**) and aryl triflates and halides.

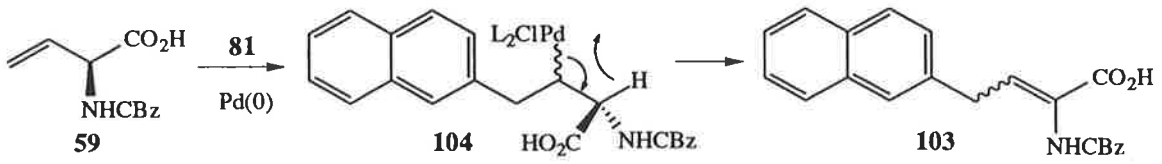
Entry	Triflate/halide	Catalyst system[a]	Temp./Time	Product	Yield[b]
1	 **81**	A	100°/4h	 **101**	0
2		B	40-60°/4h		57[c]
3	 **82**	B	60°/4h	 **102**	8
4		B	70-100°/2h	Not detected	0
5		B	50-80°/8h	Not detected	0
6		C	55°/2h	Not detected	0
7		D	85°/15h	Not detected	0
8		B	80°/2h	Not detected	0
9		B	65°/2h	Not detected	0
10		B	80°/2h	Not detected	0
11		B	80°/1h	Not detected	0
12		A	100°/3h	Not detected	0
		B	80°/4h	Not detected	0

Reactions carried out with the appropriate catalyst system (A, B, C or D) with N-CBz-*L*-vinylglycine (1-2 eq) and aryl triflate (halide) (1.0 eq) in DMF at the temperature and for the reaction time shown.

[a] A = $Pd(PPh_3)_2Cl_2$ (10mol%), triethylamine (5 eq);
B = $Pd(OAc)_2$ (10mol%), P(*o*-Tol)$_3$ (20mol%), Bu_4NCl (1.0 eq), K_2CO_3 (5 eq);
C = $Pd(OAc)_2$ (10mol%), P(*o*-Tol)$_3$ (20mol%), Bu_4NCl (1.0 eq), KOAc (5 eq);
D = $Pd(OAc)_2$ (10mol%), DPPF (20mol%), tributylamine (5 eq), LiCl (3 eq).

[b] Isolated yield of pure material unless otherwise noted.

[c] In addition, isomeric material (*E* & *Z*-**103**) was obtained (21%).



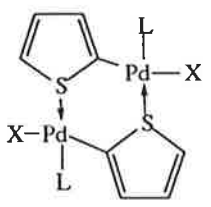
Scheme 2.22

a doublet at 3.63 (*J*6.9Hz, 2H) and a broad singlet at 6.69ppm (1H). We have not assigned absolute stereochemistry to either product, but, by analogy with Rapoport's assignment of α,β-unstaurated amino acid derivatives (*E* & *Z*-**58**),[26a] the former is more likely to be the *E*-isomer based on the higher chemical shift value of the allylic protons.

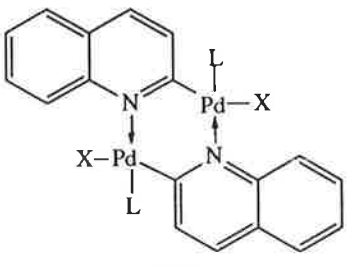
The only other aryl compound from those displayed in *Table 2.3* which underwent a successful Heck reaction was the 3-carboethoxy-2-naphthyl triflate (**82**) which gave a very low yield of the coupled product (**102**) (8%) under modified Jeffery conditions (entry 3). No α,β-unsaturated isomers were detected.

The other aryl halides and triflates listed in *Table 2.3* (entries 4-12) failed to couple to **27**. For example, 2-carboethoxy-1-phenyltriflate yielded no desired products when reacted under similar modified Jeffery conditions to those above, when potassium acetate was substituted as the base, or when a different system [$Pd(OAc)_2$, DPPF, Bu_3N, LiCl, DMF] was utilised (entries 5-7). This last catalyst system has been shown to work for some Heck reactions of aryl triflates which had failed with the Jeffery or classical conditions.[58]

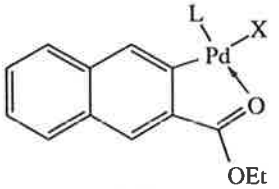
It is possible that some of the organopalladium intermediates form relatively stable dimers or chelates. Similar species have been postulated previously to explain directing effects of heteroatoms in catalytic reactions.[98] Thus, we could be forming intermediates such as **105** or **106**, which are either unreactive towards Heck addition or else follow alternative reaction pathways. The potentially lower reactivity of a chelated intermediate (**107**) may also explain the low yield of coupled product (**102**) from the reaction with 3-ethoxycarbonyl-2-naphthyl triflate when compared to the reaction of 2-naphthyl triflate, but this is no doubt due in part to



105



106



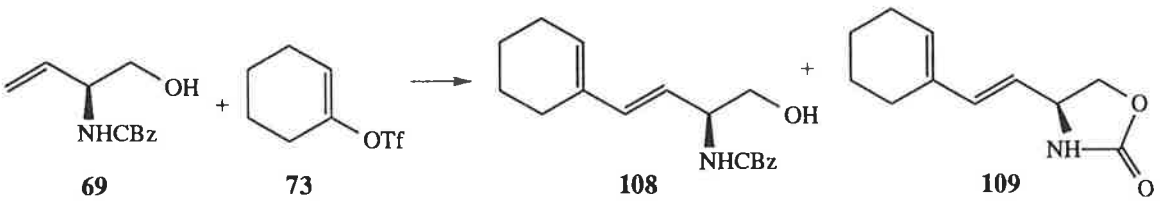
107

steric factors as well.

2.5 Heck reactions of 2-(CBz-amino)-*L*-but-3-enyl acetate (71).

2.5.1 Attempted coupling with vinyl triflates and a halide.

Initially we wished to study the Heck coupling reactions of 2-(CBz-amino)but-3-enol (**69**). Reaction with cyclohexenyl triflate (*Scheme 2.23*) was investigated as a model and under the modified Jeffery conditions [$Pd(OAc)_2$, P(*o*-Tol)$_3$, K_2CO_3, Bu_4NCl, DMF] the reaction proved sluggish and the only product isolated was the oxazolidinone (**109**) in low yield. This suggested that coupling was taking place, but base catalysed cyclisation was a competing process. Repetition of this reaction in the absence of tri-*o*-tolylphosphine and use of potassium acetate as base at *room temperature* gave the desired coupled product (**108**) in low yield, and no cyclisation was observed. The catalyst was stable to these conditions. However, with similar conditions, but at elevated temperature, coupled oxazolidinone was the only product. Although the oxazolidinone is another form of protected amino alcohol, the low yields of coupled product and the decrease in molecular weight upon losing the components of benzyl alcohol (*i.e.* low mass balance) suggested that we should attempt to avoid this cyclisation. Since it seemed that the formation of **109** would be difficult to inhibit merely by modifying the conditions we investigated the reactivity of 2-(CBz-amino)but-3-enyl acetate (**71**) which would not be expected to undergo cyclisation.



69 **73** **108** **109**

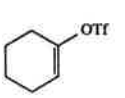
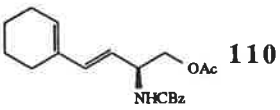
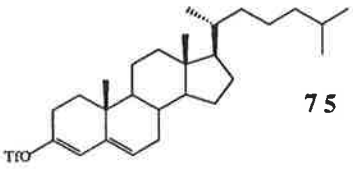
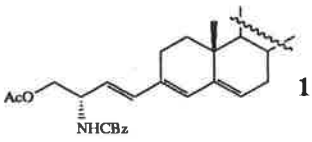
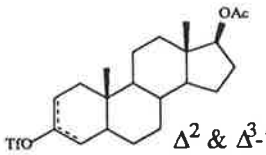
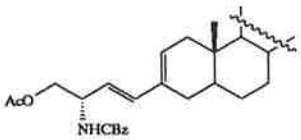
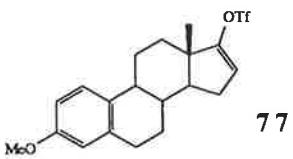
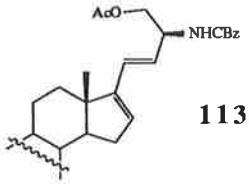
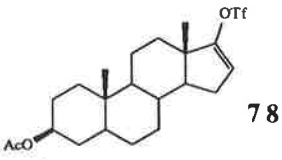
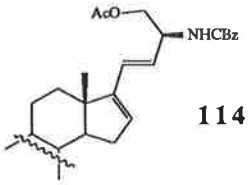
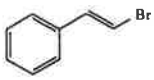
Scheme 2.23

Heck reactions of the acetate (**71**) also did not required tri-*o*-tolylphosphine for catalyst stability. This seems to suggest that the instablility of the palladium catalyst found in *Chapter 2.4* was due to the carboxylic acid and/or the carboxylate anion of N-CBz-*L*-vinylglycine (**59**). Tetra-*n*-butylammonium chloride was unnecessary for the formation of products, but yields were much higher in its presence. This is consistent with Jeffery's observations on the use of solid-liquid phase transfer catalysts in Heck coupling reactions.[78]

All the vinyl triflates which successfully coupled to N-CBz-*L*-vinylglycine (*Chapter*

2.4.1) were reacted with **71** and, again, products were formed (*Table 2.4*). Standard Jeffery conditions [$Pd(OAc)_2$, K_2CO_3, Bu_4NCl, DMF] followed by aqueous extractive workup and flash chromatography on silica gel resulted in moderate to very good yields of the coupled

Table 2.4. Heck reactions between *L*-(2-CBz-amino)but-3-enyl acetate (**71**) and vinyl triflates and halides

Entry	Triflate/halide	Catalyst system[a]	Temp./Time	Product	Yield[b]
1	 **73**	A	65-75°/4h	 **110**	77
		B	75°/4h		43
2	 **75**	A	75°/3h	 **111**	54
		B	60-70°/4h		25
3	 Δ^2 & Δ^3-**76**	A	75°/3h	 **112**	82[c]
		B	75°/4h		31[c]
4	 **77**	A	70-80°/4h	 **113**	83
		B	60-70°/4h		42
5	 **78**	A	75-80°/4h	 **114**	68
6	 **74**	B	80°/5h	Not detected	0
		C	100°/7h		0
7		B	80°/3h	Not detected	0
		C	100°/3h		0

Reactions carried out with the appropriate catalyst system (A, B, or C) with *L*-2-(CBz-amino)but-3-enyl acetate (1.0 eq) and aryl triflate (halide) (1.2-1.5 eq) in DMF at the temperature and for the reaction time shown.

[a] A = $Pd(OAc)_2$ (10mol%), Bu_4NCl (1.0 eq), K_2CO_3 (5 eq);
B = $Pd(OAc)_2$ (10mol%), Bu_4NCl (1.0 eq), KOAc (5 eq);
C = $Pd(PPh_3)_2Cl_2$ (10mol%), triethylamine (5 eq).

[b] Isolated yield of pure material.

[c] A small amount of what is assumed to be the corresponding Δ^3-isomer was observed by t.l.c.

products (**110**-**114**) (*Table 2.4*, entries 1-5, conditions A). Apart from the reaction of androsteryl triflates (Δ^2 & Δ^3-**76**), which resulted in a small amount of separable Δ^3-coupled product, in each case the expected coupled product was observed as the sole new spot in very clean reaction mixture as ajudged by t.l.c. For these coupling reactions excess triflate was used relative to the olefin and the reactions were monitored by t.l.c. until all the olefin had been consumed - if this was not done, chromatographic separation of the product from **71** was often difficult. Reactions carried out in the absence of tetra-*n*-butylammonium chloride and using potassium acetate as base gave substantially lower yields of coupled products (*Table 2.4*, conditions B).

The coupling was also attempted with trans-β-bromostyrene and α-tetralenyl triflate (**74**), two compounds which had failed to react with vinylglycine derivative **59** in *Chapter 2.4.1*. Once again they gave no coupled products using either $Pd(OAc)_2$, KOAc, DMF or $Pd(PPh_3)_2Cl_2$, Et_3N, DMF (entries 6 & 7). The same can be said about the failure of these reactions as was said in *Chapter 2.4.1* (*i.e.* the reactivity of the triflate and bromide has the major effect on whether the reaction proceeds at all).

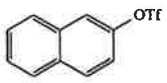
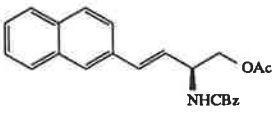
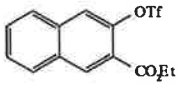
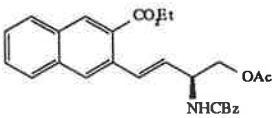
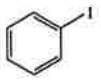
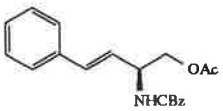
Under appropriate conditions, yields of coupled products were generally higher than those from the corresponding coupling reactions to N-CBz-*L*-vinylglycine (*Chapter 2.4.1*, *Table 2.2*). As all the successful Heck couplings of 2-(CBz-amino)butenyl acetate (**71**) gave solely one isomer which could be purified readily by flash chromatography in high yield, substituted at the terminus of the double bond to form the desired 1,3-dienes (1,3,5-triene in the case of product **111**) as *E* isomers (**110–114**), this is a potentially more useful pathway to unsaturated α-amino acids than that of *Chapter 2.4.1*.

2.5.2 Attempted coupling reactions with aryl/heteroaryl iodides and triflates.

Coupling reactions of *L*-2-(CBz-amino)but-3-enyl acetate (**71**) with the two aryl triflates which successfully coupled with N-CBz-*L*-vinylglycine (**59**), as described in *Chapter 2.4.2*, were initially investigated. Attempted coupling of 2-naphthyl triflate with **71** using the conditions which gave products for the corresponding Heck reactions with vinyl triflates in *Chapter 2.5.1* [*i.e.* $Pd(OAc)_2$, K_2CO_3, Bu_4NCl, DMF or $Pd(OAc)_2$, KOAc, DMF] resulted in no new product formation as ajudged by t.l.c. and the starting olefin was recovered in high

yield (*ca* 75-95%) (*Table 2.5*, entries 1 & 2). However, utilisation of the more traditional Heck reaction conditions [$Pd(PPh_3)_2Cl_2$, Et_3N, DMF, 100°C] gave the coupled product (**115**) in good yield from a very clean reaction mixture. The yield was optimised by using an excess of the triflate and this had the added advantage of removing all traces of **71** which aided chromatographic separation. In this case, an excellent yield of **115** was obtained (entry 3). Using a similar procedure, reaction of 3-carboethoxy-2-naphthyl triflate gave a low yield of the 3-carboethoxy-2-naphthyl coupled product (**116**) was obtained (entry 4), although this yield was four times higher than the coupling reaction of the same triflate with N-CBz-*L*-vinylglycine (*Chapter 2.4.2*, *Table 2.3*). This procedure was also successfully applied to the coupling reaction with iodobenzene (entry 5), an electrophile which failed to couple with N-CBz-*L*-

Table 2.5. Heck reactions between *L*-(2-CBz-amino)but-3-enyl acetate (**71**) and aryl triflates and halides

Entry	Triflate/halide	Catalyst system[a]	Temp./Time	Product	Yield[b]
1	 **81**	A	50-55°/9h	 **115**	0
2		B	80°/5h		0
3		C	100°/7h		84
4	 **82**	C	100°/7h	 **116**	32
5		C	100°/6h	 **117**	86
6		C	100°/6h	Not detected	0

Reactions carried out with the appropriate catalyst system (A, B, or C) with *L*-2-(CBz-amino)but-3-enyl acetate (1.0 eq) and aryl triflate (halide) (2-2.5 eq) in DMF at the temperature and for the reaction time shown.

[a] A = $Pd(OAc)_2$ (10mol%), Bu_4NCl (1.0 eq), K_2CO_3 (5 eq);
B = $Pd(OAc)_2$ (10mol%), Bu_4NCl (1.0 eq), KOAc (5 eq);
C = $Pd(PPh_3)_2Cl_2$ (10mol%), triethylamine (5 eq).

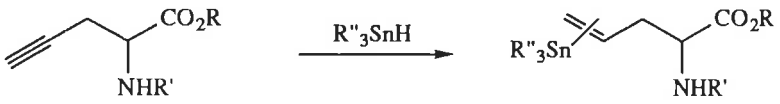
[b] Isolated yield of pure material.

vinylglycine (**59**) under these, or modified Jeffery, conditions. When this procedure was applied to 2-iodothiophene, which also failed to couple with **59** in *Chapter 2.4.2*, no Heck reaction product could be detected by t.l.c. (entry 6). Again, a relatively stable chelated organopalladium(II) intermediate (**105**) may be the cause of its lack of reactivity towards Heck addition to the double bond of **71**.[102]

The yields of the successful arylation reactions of *L*-2-(CBz-amino)but-3-enyl acetate were superior to those of the corresponding reactions of N-CBz-*L*-vinylglycine discussed in *Chapter 2.4.2*. In addition, iodobenzene was successfully coupled to **71** which was not the case for **59**. The reactions were far cleaner and yielded only the expected coupled product. Chromatographic separation of the products was also easier for these coupled products than for the corresponding products obtained in *Chapter 2.4.2*. Of the two vinylglycine derivatives studied in Heck coupling reactions it seems that the acetylated reduced carbonyl compound (**71**) is the preferred one for the synthesis of olefinic amino acid derivatives, provided that a mild method for the conversion from coupled products to amino acids is utilised.

(Tributylstannyl)allylglycine derivatives. Synthesis and reactivity.

As discussed in the introduction, allylglycine and some of its derivatives behave as mechanism based inhibitors for a number of enzymes and are also potentially useful synthetic intermediates for the preparation of chiral molecules. Our aim was to prepare functionally substituted allylglycine derivatives which could be used as potential enzyme inhibitors or as chiral synthons for the construction of more complex molecules. In order to prepare such derivatives, a number of verasatile common intermediates were sought which could be used to elaborate the side chain of the α-aminoacid. Types of intermediates we wished to investigate were allylglycines substituted on the double bond of the α-side chain by a trialkylstannyl moiety. The synthetic versatility of vinylstannanes is well documented, particularly in palladium catalysed[56,99] and electrophilic substitution reactions.[100] We envisaged hydrostannation of a propargylglycine derivative to be an attractive route to the (trialkylstannyl)allylglycine derivatives (*Scheme 3.1*). Racemic propargylglycine derivatives can be easily prepared[101] and readily resolved into *R* and *S*-enantiomers[101,102] and we wished to exploit this process in the preparation of optically active vinylstannanes. Since our chosen path for formation of unsaturated α-amino acid derivatives was *via* side chain modification, and not by formation of one of the four bonds which make up the chiral α-centre, it was important to prepare the (trialkylstannyl)allylglycine derivatives in chiral form without racemisation.

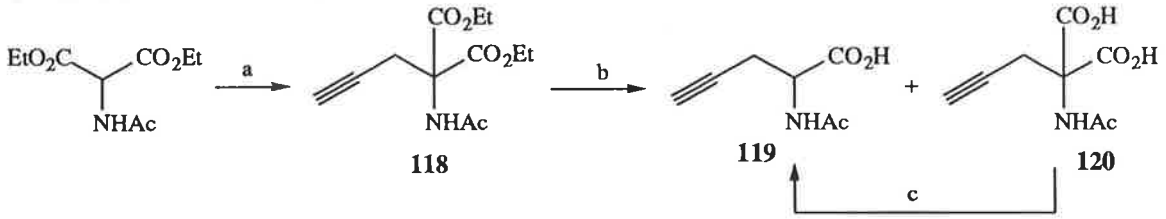


Scheme 3.1

3.1 Propargylglycine derivatives; synthesis and resolution.

Racemic N-acetylpropargylglycine (**119**) was prepared according to Baldwin's procedure which involves alkylation of diethylacetamidomalonate with propargyl bromide in the presence of sodium hydride, followed by saponification and decarboxylation (*Scheme 3.2*).[101a] The alkylation reaction (NaH, propargyl bromide, DMF, 80°, 4h) proceeded cleanly and resulted in an excellent yield of diethylacetamidopropargylmalonate (**118**) (93%). Decarboxylation using Baldwin's method, heating **118** in ethanolic aqueous sodium hydroxide at reflux temperature,[101a] gave after acidic workup the desired product (**119**) as well as the

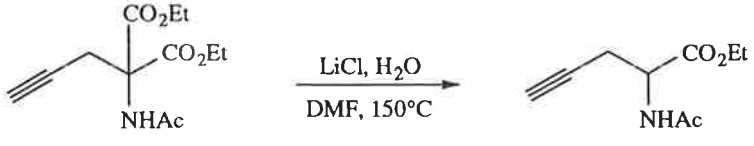
malonic acid (**120**) which formed by hydrolysis without decarboxylation. This mixture was heated in dioxane at reflux for 15 hours to effect total conversion of **120** to N-acetyl-*D,L*-propargylglycine (**119**) in good yield (68% for two steps).



(a) (i) NaH, DMF, 20°C, (ii) propargyl bromide, 80°, 4h;
(b) NaOH, H_2O, EtOH, reflux, 2h;
(c) dioxane, reflux.

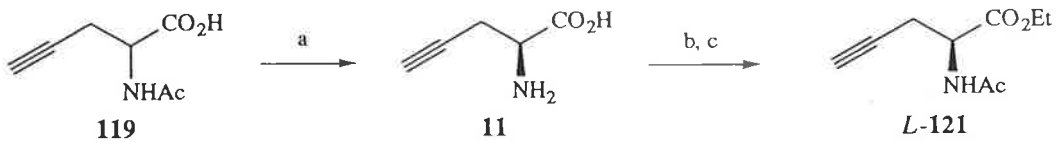
Scheme 3.2

Ethyl N-acetyl-*D,L*-propargylgycinate (**121**) was prepared by Krapcho decarboethoxylation of diethylacetamidopropargylmalonate (**118**) (*Scheme 3.3*). Krapcho decarbalkoxylation is generally carried out by heating a malonate (or β-keto ester) with water and/or a salt (most often lithium chloride) in a high boiling polar, aprotic solvent (normally DMSO), and is reported to proceed cleanly and in high yield.[103] Thus, decarboethoxylation was effected by heating **118** in DMSO at 180° in the presence of lithium chloride (2 eq) and water (1 eq), but the reaction, although fast and clean by t.l.c. (5g consumed within 20 minutes), produced much coloured impurity. In addition, the yield was poor (up to 41%) and removal of traces of DMSO proved laborious when working on a multigram scale. Since the reaction was rapid, we proposed that a lower temperature and more volatile solvent would alleviate those problems. Thus, reactions in water (with LiCl, 2 eq) and in DMF (LiCl, 2 eq; H_2O, 1 eq) were examined as alternatives. No reaction occurred in boiling water. In DMF at 150° the decarboethoxylation reaction proceeded at a much slower rate than it had in DMSO (4-5 hours required for complete conversion of 5-20g), but the amount of discoloration was reduced significantly, and the product (**121**) could be isolated quite easily in moderately good yield (up to 58% after recrystallisation, regularly *ca* 50% on 5-20g scale). Thus, ethyl N-acetyl-*D,L*-propargylglycinate (**121**) was readily available in acceptable yield (54% for two steps) from inexpensive starting materials.



Scheme 3.3

In order to prepare enantiomerically enriched propargylglycine derivatives enzymatic resolution of N-acetyl-*D*,*L*-propargylglycine (**119**) with Acylase I, an *L*-amidoacid acylase isolated from the *aspergillus* species of mushroom[102] was undertaken [Acylase I (8.3 units/mmol), $CoCl_2$ (1mM), pH 7.5-8.0, 35°, 24h]. This produced *L*-propargylglycine (**11**) in good yield (71% of the expected maximum 50% yield), as well as unreacted N-acetyl-*D*-propargylglycine (*D*-**119**) (*Scheme 3.4*). N-Acylation with acetyl chloride and propylene oxide in THF at ambient temperature followed by esterification (ethanol, thionyl chloride, 24h) gave ethyl N-acetyl-*L*-propargylglycine (*L*-**121**) in moderate yield after chromatography and recrystallisation (39% for two steps). This product was optically active and a ^1H n.m.r. shift experiment with chiral Eu(III)(hfc)$_3$ gave an enantiomeric excess of at least 90%, as may be seen in *Figure 3.1* which shows the effect of the shift reagent on the terminal acetylenic proton of the racemic and enantiomerically enriched propargylglycinates.



119 **11** *L*-**121**

(a) Acylase I, $CoCl_2$, pH 7.5-8.0, H_2O, 35°C, 24h;
(b) AcCl, propylene oxide, THF, 25°C, 5h;
(c) $SOCl_2$, EtOH, 25°C, 24h.

Scheme 3.4

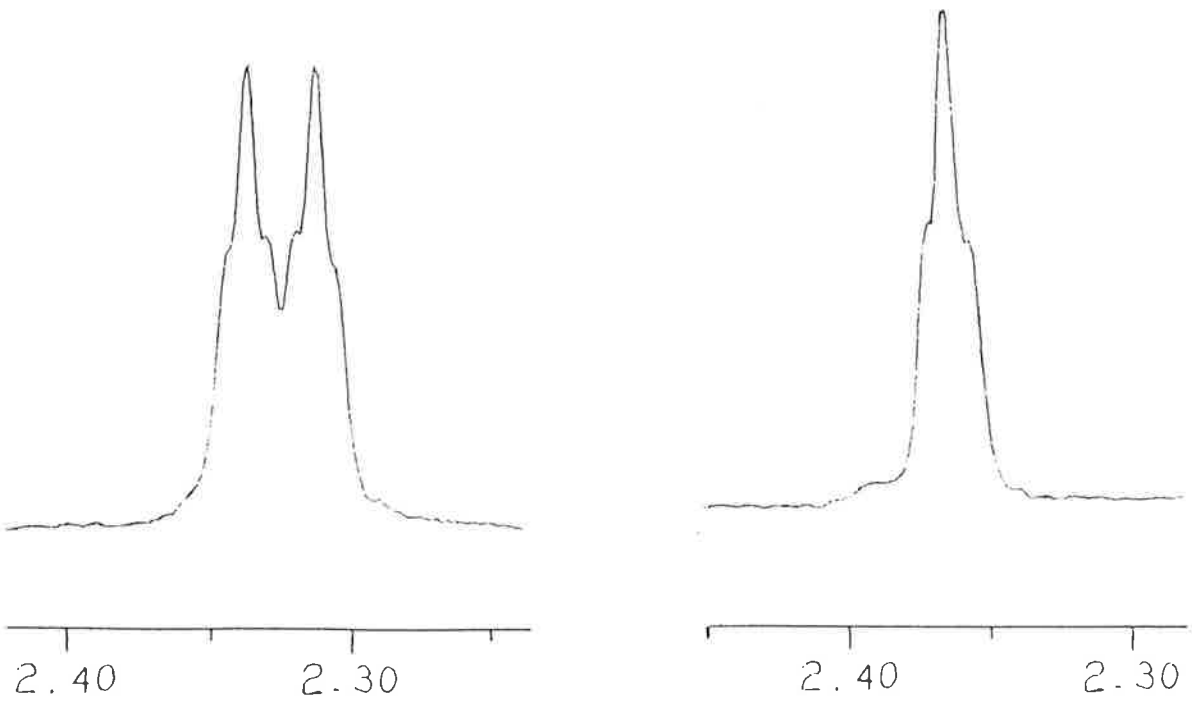
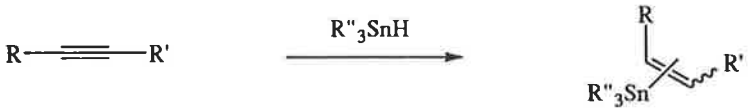


Figure 3.1. Eu(hfc)$_3$ ^1H n.m.r. experiment with racemic and chiral **121**. The portion of the spectrum shown is of the resonances of the terminal acetylenic protons of the diastereomeric complexes.

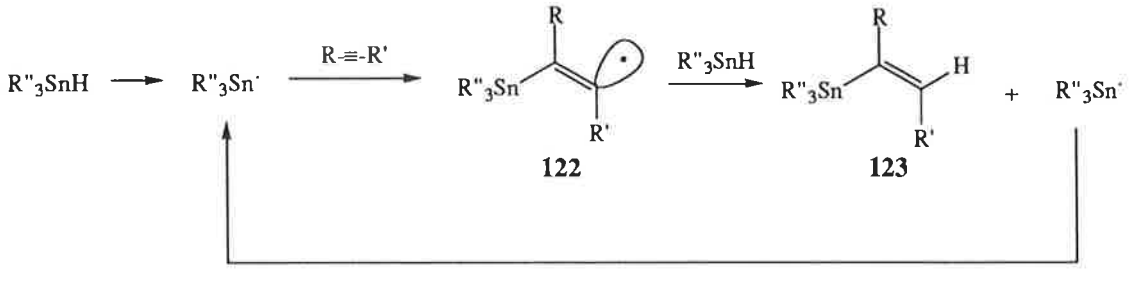
3.2 Hydrostannation reactions. An overview.

Hydrostannation of alkynes (*Scheme 3.5*) has been known for 30 years and is an extremely simple and direct route to vinylstannanes.[100] Radical, ionic and transition metal catalysed versions of the reaction are known and usually proceed with markedly different regio- and stereochemistry. The mechanisms of the different processes are quite well understood and shall now be briefly summarised.

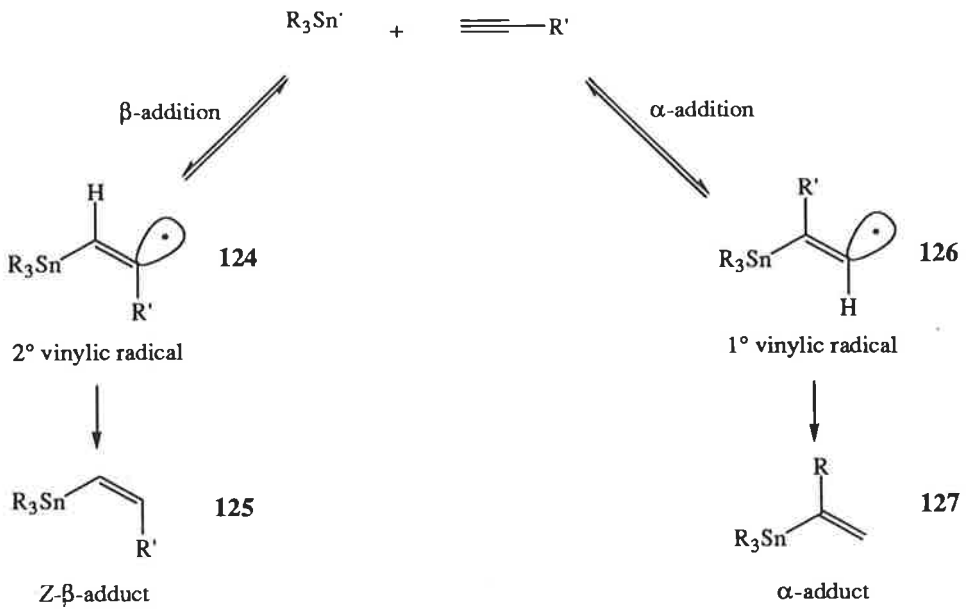


Scheme 3.5

Radical additions: In an extensive study of the hydrostannation of alkynes, Leusink showed that some of these reactions proceed *via* radical intermediates.[104] The reported observations that (*a*) the reaction occurs slowly in the absence of a radical initiator (AIBN), but the rate is rapidly enhanced upon its addition, (*b*) radical inhibitor (galvinoxyl) instantly retards the progress of the reaction, and (*c*) the reaction is not influenced to any great extent by solvent polarity, are all consistent with the notion of intermediacy of trialkylstannyl radicals.[104a] The mechanism is believed to proceed as shown in *Scheme 3.6*. The chain process begins by the formation of a trialkyltin radical from a suitable initiator and trialkyltin hydride. This radical undergoes a reversible *trans*-addition to the alkyne to form a vinylic radical (**122**). Abstraction of a hydrogen atom by this vinyl radical (**122**) from trialkyltin hydride yields a *Z*-substituted vinylstannane (**123**, R'≠H) and this stereoisomer is sometimes observed in practice under non-equilibrating conditions.[104,105] The regiochemistry of this radical addition is often difficult to control for disubstituted alkynes unless electronic and steric effects are particularly dominant. However, for terminal alkynes (R=H), steric effects and, more importantly, the stability of the secondary vinyl radical (**124**) relative to the primary (**126**) (from β and α-addition respectively) results in the formation of the β-adduct (**125**) regioselectively (kinetically, the *Z*-β-vinylstannane) (*Scheme 3.7*).

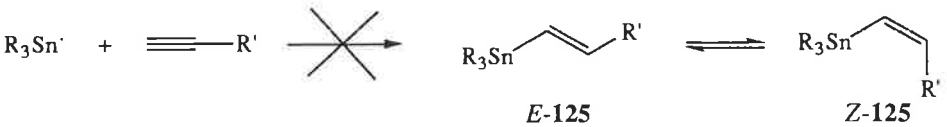


Scheme 3.6

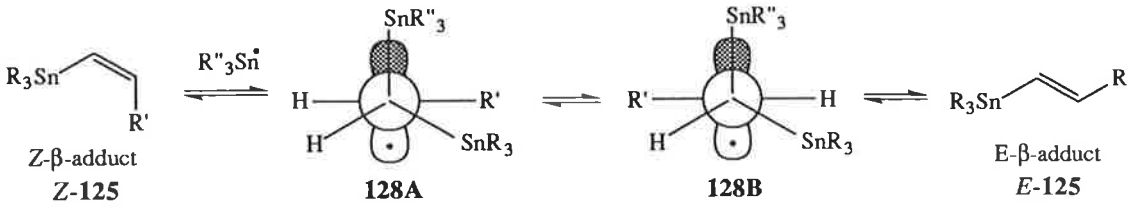


Scheme 3.7

The thermodynamically more stable *E*-isomer (*E*-**125**) does not form by direct reaction of the tin radicals with the alkyne, but by isomerisation of the kinetically formed *Z*-isomer (*Z*-**125**) in the presence of trialkyltin radicals (*Scheme 3.8*).[104b] No *Z* to *E* isomerisation occurs by thermolysis of *Z*-**125** in the presence of either AIBN or trialkytin hydride alone, yet proceeds by heating the mixture with *both* AIBN and trialkystannane. Addition of the radical scavenger, galvinoxyl, inhibits isomerisation. The *Z* to *E* isomerisation is believed to proceed *via* an addition of a trialkyltin radical to the *Z*-vinylstannane to form a geminal bis(trialkylstannyl)alkyl radical (**128**) which may undergo β-scission of one of the two trialkylstannyl groups to reform the carbon-carbon double bond (*Scheme 3.9*). The intermediacy of **128** is inferred from the observation that (*a*) trimethylstannyl group is exchanged for a triethylstannyl group under these conditions and (*b*) in some instances hydrogen abstraction occurs to yield a geminal bis(stannane) as product.[104b] Presumably the geminal bis(stannane) forms in preference to a vicinal bis(stannane), because of partial hyperconjugative stabilisation of the developing carbon centred radical by the 'R3Sn' group. For a bulky substituent, R', the conformation **128B** would be less strained and consequently more highly populated than that of **128A** and, as a result, the *E*-isomer (*E*-**125**) results as the



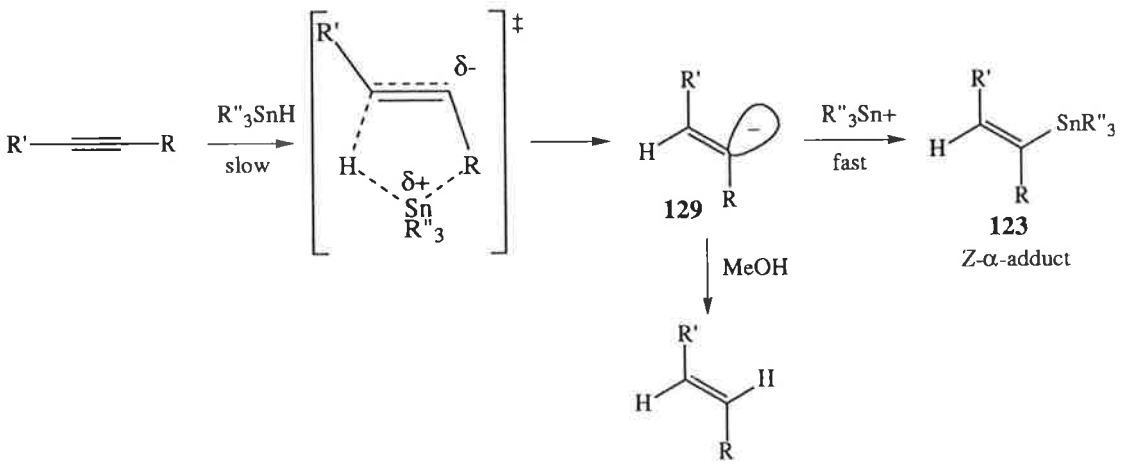
Scheme 3.8



Scheme 3.9

thermodynamic product from β-scission of a trialkylstannyl radical. Total or partial thermodynamic isomerisation is often unavoidable in radical hydrostannation reactions since kinetic conditions (lowest possible temperature, shortest time, minimum initiator and no excess of trialkyltin hydride) are sometimes difficult to achieve, so mixtures of *E* and *Z*-isomers are frequently obtained.[104,105]

Ionic additions: Ionic hydrostannation (*Scheme 3.10*) has been suggested for reactions with electrophilic alkynes.[106] The factors which support an ionic mechanism are: (*a*) the rate of formation of products is enhanced with increasing electron withdrawing ability of the R group (substituent effect); (*b*) reaction rate increases with increased solvent dielectric constant; (*c*) α-adducts form predominantly, which is the reverse situation with respect to radical addition; (*d*) reaction rate is unaffected by addition of either radical inhibitor or initiator; and (*e*) the reactivity sequence of $R"_3SnH$ follows the order of increasing positive inductive effect (ability to stabilise positive charge) of the R" group (*i.e.* $Bu_3SnH>>Et_3SnH>Me_3SnH>Ph_3SnH$) which suggests a significant cationic nature of '$R"_3Sn$' in the transition state.[106b] The mechanism has been postulated based on the above and following observations: (*a*) stereochemical data supports a kinetic *trans*-addition; (*b*) solvent effects do not support a 'hydroboration like' four centred transition state, but instead imply a considerable charge separation in the rate determining step;

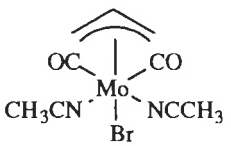


Scheme 3.10

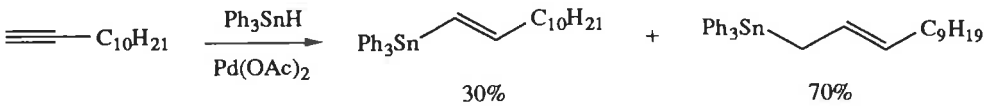
and (*c*) kinetic isotope effect data support hydride transfer in the rate determining step.[106b] The mechanism is believed to involve a slow hydride transfer followed by a fast carbon-tin coupling to form the *Z*-α-adduct (**123**). Any observed isomers (either *E*/*Z*-β-adducts or *E*-α-adduct) are believed to occur from competing radical hydrostannation or isomerisation. The observation that the use of a protic solvent (methanol) for this reaction leads to the overall addition of dihydrogen supports the intermediacy of the vinylcarbanion (**129**).[107]

Metal catalysed addition: Unlike the related metal catalysed hydrosilation reaction,[108] the corresponding hydrostannation of alkynes has not been widely investigated, although a number of independently researched methodology studies have been reported.[109-113] Unfortunately, these studies vary with respect to catalyst, ligands, stannane and substrates used, and thus details such as the prediction of regiochemistry and mechanistic understanding are still difficult. From the areas where these studies do overlap somewhat it is possible to reach some general conclusions.

Transition metal complexes which have been shown to effectively catalyse hydrostannation at or below room temperature are many. Kikukawa discovered that MCl_2L_2 (M=Ni, Pt, Pd; L=PPh_3) and a number of rhodium catalysts are very reactive, with the latter ones giving the best regioselectivity (α:β = *ca* 4:1).[112] Guibé found that $PdCl_2L_2$ [L = PPh_3 and P(*o*-Tol)$_3$] and a molybdenum complex (**130**) were similarly effective, but **130** was preferable for electron rich and sterically hindered alkynes.[109] However, chelating solvent such as THF and up to 40% of the molybdenum complex were found to be necessary, whereas 1mol% of palladium catalyst sufficed in most organic solvents.[109] Oshima found that $Pd(PPh_3)_4$, $PdCl_2(PBu_3)_2$, $Pd(OAc)_2$[P(*p*-MeOPh)$_3$]$_2$ all gave the same isomeric ratio (but conversion and yields were not reported), and that $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2(CH_3CN)_2$ and $Pd(OAc)_2$ were all 'equally effective' (presumably meaning similar conversion and yield, but isomeric ratio was not reported).[113] It is interesting to note that in Oshima's study these last two 'ligandless' catalysts, as well as $PdCl_2$[P(*o*-Tol)$_3$]$_2$, gave *allyl* stannanes predominantly as hydrostannation products *via* double bond migration (*Scheme 3.11*). Oshima is the only one to have reported this anomaly so far.

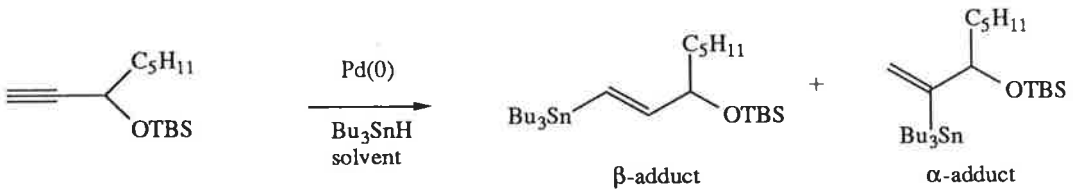


130



Scheme 3.11

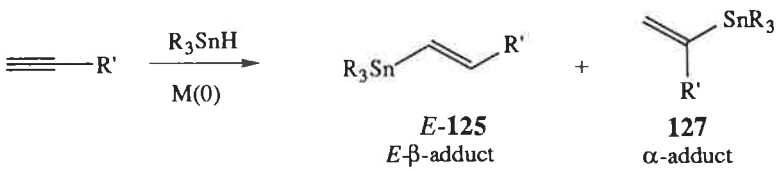
Guibé noted that a less polar solvent resulted in a slightly higher β:α ratio for the reaction of an oct-1-yn-3-ol derivative catalysed by both $Pd(PPh_3)_4$ and molybdenum complex **130** (*Scheme 3.12*).[109] This presumably arises from an increase in coordinative interactions between the metal catalyst and the propargylic oxygen in the transition state as the chelating ability of the solvent is decreased. Oshima studied the same solvents, but found no difference in regioselectivity (perhaps we may speculate that he ignored minor changes), although the nature of the substrate(s) he investigated is unknown.[113] Guibé found there was no significant temperature dependence on the ratio of hydrostannation adducts.[109]



Solvent	α : β
THF	72 : 28
benzene	81 : 19
CH_2Cl_2	87 : 13

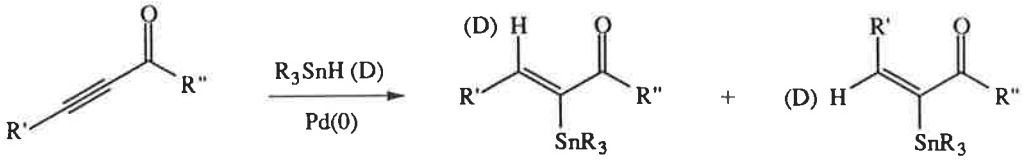
Scheme 3.12

The metal catalysed hydrostannation clearly results in an overall *syn*-addition (a common mechanistic feature in organotransition metal chemistry)[54] of tin and hydrogen to the alkyne. This is inferred from the propensity of formation of *E*-β-adducts, at the exclusion of *Z*-adducts, from terminal alkynes (α-adducts also form) and of *E*-adducts from internal ones (*Scheme 3.13*). Deuterium labelling experiments are also consistent with *syn*-addition.[111] Cochran and Guibé have both noted the formation of '*anti*-addition' isomers for the reaction of conjugated acetylenic ketones, but while Cochran suggests this is the result of a different



Scheme 3.13

mechanism,[110] Guibé believes these products are the result of isomerisation of the first formed *syn*-adduct[109] (*Scheme 3.14*).



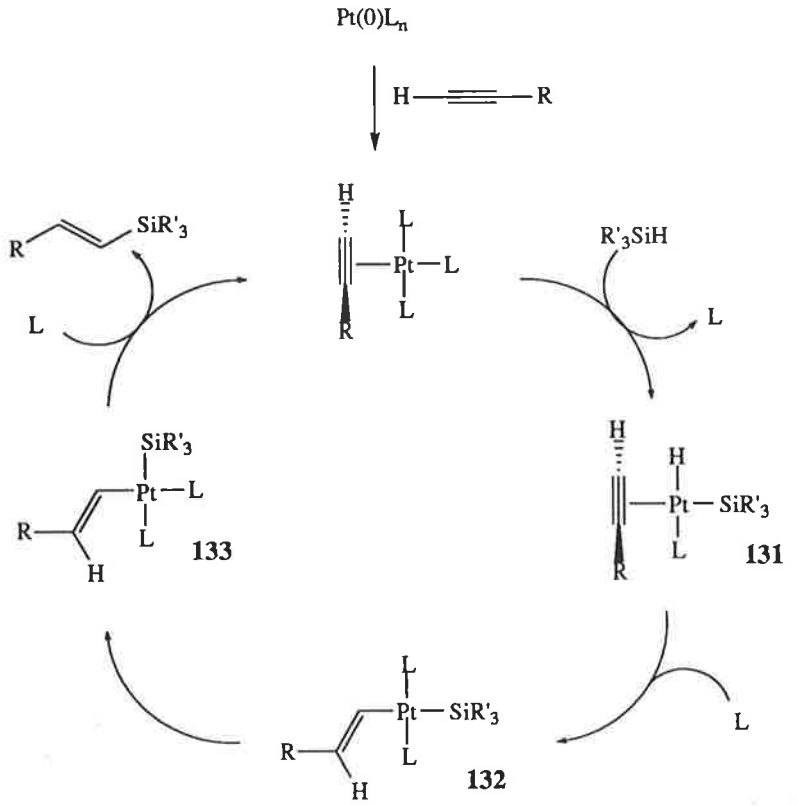
	Z : E
Me_3SnH, R' = Et, R'' = Me	100 : 0
Me_3SnD, R' = H, R'' = Me	50 : 50
Bu_3SnH, R' = *n*Hex, R'' = Me	0 : 100
Bu_3SnH, R' = *n*Bu, R'' = Ph	42 : 58

Scheme 3.14

Although the stereochemistry of the hydrostannation is clearly understood, the regiochemistry is more complex. Rhodium catalysts generally seem to form α-adducts,[112] but other metals are more difficult to categorise. β-Adducts are favoured for terminal alkynes with bulky substituents (steric effect), and α-adducts for some heterosubstituted with electron withdrawing groups (Br, Cl;[109] PhS, PhSe[114]) and for conjugated alkynes (ynones, ynoates, diynes).[109] For most other substituents regioselectivity is difficult to generalise.

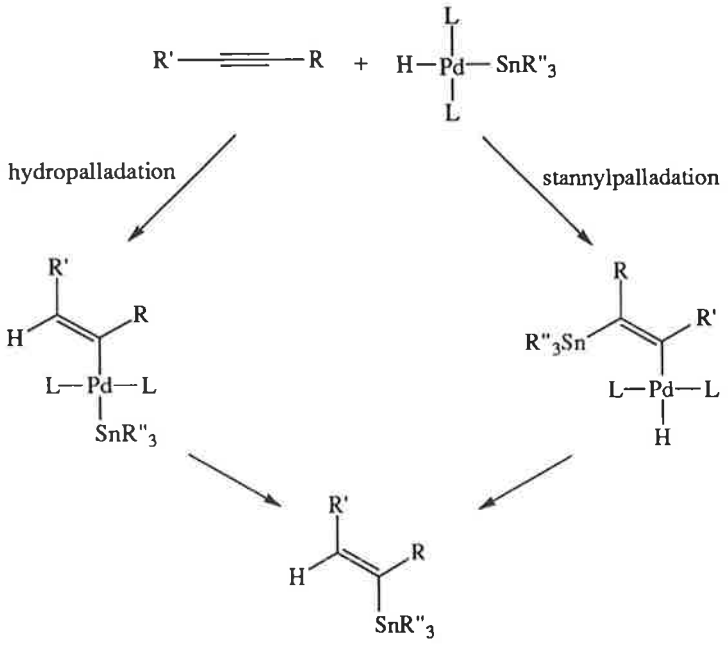
With regard to a mechanism of the hydrostannation we can look at the more studied metal catalysed hydrosilation of alkynes for some ideas.[108] The commonly assumed mechanism for the hydrosilation catalysed by platinum is shown in *Scheme 3.15*.[115] After coordination of the alkyne and oxidative addition of the silane to Pt(0) has occurred, a *trans*-Pt(II)-acetylene π-complex (**131**) is formed preferentially because of the well documented *trans*-effect of silyl ligands. Rotation of the acetylene into the coordinating plane and insertion into the platinum-hydrogen bond forms the σ-vinylplatinum(II) complex (**132**) (in some instances, silylmetallation is proposed as an alternative to hydrometallation[116]). Isomerisation of **132** to *cis*-complex (**133**) followed by reductive migration of the silyl group to the carbon forms the vinylsilane and regenerates the zero-valent catalyst.

It seems as though the extension of this mechanism to the hydrostannation is feasible, with the following observations. Guibé has suggested that the formation of α-adducts from the reaction of alkynes conjugated to electron withdrawing groups (*e.g. Scheme 3.14*) implies that tributyltin hydride behaves as an hydride donor (*c.f.* ionic mechanism) under the influence of the transition metal.[109] This is consistent with a hydropalladation, as opposed to stannylpalladation, of the alkyne during *syn*-addition (*Scheme 3.16*). This may be peculiar to

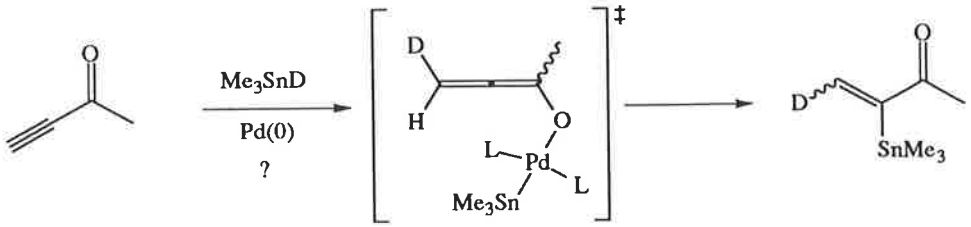


Scheme 3.15

the reaction of conjugated alkynes. In what may be a related reaction, conjugated *alkenes* have been shown to undergo 1,4-addition of tin hydride in the presence of a rhodium catalyst.[117] If the hydrostannation of conjugated acetylenic ketones occurs *via* a 1,4-addition this may explain why Guibé[109] and Cochran[110] saw *anti*-adducts for some of those reactions. For example, the reaction of methyl ethynyl ketone with trimethyltin deuteride and catalytic $Pd(PPh_3)_4$ gave a 1:1

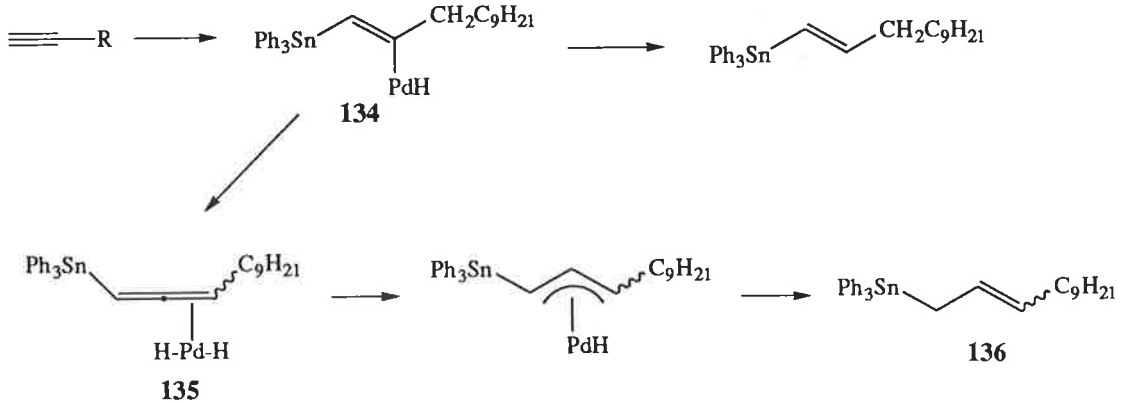


Scheme 3.16



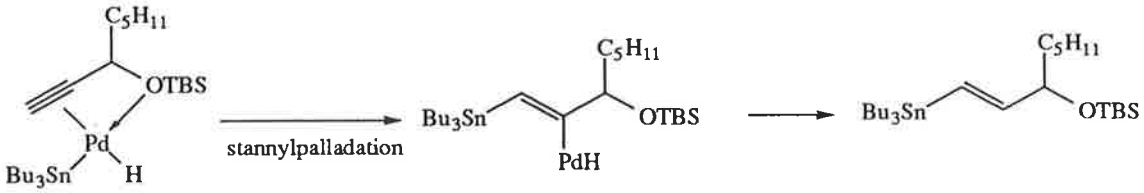
Scheme 3.17

mixture of *E* and *Z*-isomers (*Scheme 3.14*).[110] Perhaps this arises by 1,4-addition to give an Pd(II)-allenolate which tautomerises and reductively eliminates, or *vice versa*, to form a 1:1 mixture of *E* and *Z*-isomers (*Scheme 3.17*). Alternatively, the kinetic product (*syn*-1,2-addition) could isomerise thermally or in the presence of excess tin hydride and palladium. Piers found that structurally similar distannanes isomerise at elevated temperatures.[118] It is difficult to explain the 'anti-addition' based on the limited amount of data. Oshima proposed a mechanism which involves a *syn*-stannylpalladation as the key step.[113] *Syn*-addition of Si-Rh has been used to explain the predominance of *cis*-products in rhodium catalysed hydrosilation reactions.[116] From Oshima's results it is difficult to say why stannylpalladation is favoured over hydropalladation, although the formation of allylstannane in *Scheme 3.11* was rationalised by β-hydride elimination of a stannylpalladation intermediate (**134**) to form a stannylated allene (**135**) which undergoes hydrogenation to form the allylstannane (**136**) (*Scheme 3.18*).[113]



Scheme 3.18

Guibé's observation on the change in regioisomer ratio on changing solvent may support the stannylpalladation argument, since more β-addition occurs when the catalyst chelates to the propargylic oxygen.[109] If a square-planar coordinated intermediate (**137**) is proposed, we may speculate that it is probably more likely for palladium to add to the α-carbon so the tin would only end up on the β-carbon if the reaction were a stannylpalladation (*Scheme 3.19*).



137

Scheme 3.19

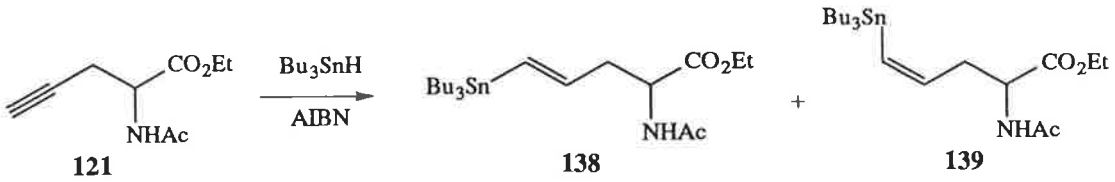
As may be summarised from this brief review of hydrostannation of alkynes, control of regio and/or stereoselectivity is often a complication in these reactions.

3.3 Hydrostannation of ethyl N-acetylpropargylglycinate

We wished to investigate hydrostannation of ethyl N-acetylpropargylglycinate (**121**) as a method for functionalising α-amino acid derivatives through the side chain. Our methodology study began as a search for the methods which would provide isomerically pure α and β-adducts. Radical hydrostannation was expected to yield β-adducts and metal catalysed reaction to yield α and β-adducts (stereoselectively the *E*-β adduct).† Ionic hydrostannation was unexpected since the triple bond of the propargylglycine derivative is not conjugated to electron withdrawing groups.

Initially we investigated the hydrostannation using tri-*n*-butyltin hydride under radical conditions (*Scheme 3.20*). As expected, no reaction occurred with tributyltin hydride in the absence of radical initiator (*i.e.* no ionic reaction). Treatment of ethyl N-acetyl-*D,L*-propargylglycinate (**121**) with an equivalent of tributyltin hydide in the absence of solvent and in the presence of a catalytic amount of AIBN with gradually heating to 100° over a five hour period resulted in an incomplete conversion of the alkyne to products. Periodic addition of further AIBN and tin hydride to the mixture produced more product for a time before the reaction appeared to cease. Hydrostannation products were isolated in poor yield (23%) and **121** was also recovered. ^{1}H n.m.r. spectroscopy showed the product to be the expected result of β-addition and was a mixture of *E* and *Z*-ethyl δ-tributylstannyl-*D,L*-allylglycinates (**138** & **139**). These two isomeric vinylstannanes were easily distinguished in the ^{1}H n.m.r. spectrum. The *E* and *Z*-isomers were assigned on the basis of the magnitude of the vicinal

† Please note that the nomenclature of α and β-hydrostannation adducts (α-adduct is geminally substituted and β is vicinally substituted) is independent to the numbering system of α-amino acids (where the α-carbon is C2, β is C3, γ is C4, δ is C5, *etc.*) For the hydrostannation of the propargylglycine derivative (**121**), the α-adduct places the stannyl moiety on the γ-carbon (C4) and for the β adduct the δ-carbon (C5). The γ/δ-aminoacid nomenclature will herein be used interchangeably for the α/β-adducts respectively.

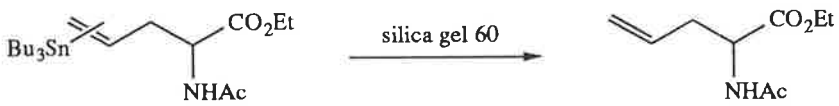


121 138 139

Scheme 3.20

coupling of the vinylic protons (*E*: 18.6Hz, *Z*: 12.6Hz.) Satellites for the $^{117}Sn/^{119}Sn$ to ^{1}H coupling were evident for the vinylic protons. We were unable to separate **138** and **139** by chromatography on silica gel.

Repeating the radical hydrostannation in solvent proved to be a much better procedure. Thus, in toluene at reflux, total conversion of the alkyne (**121**) was observed within 30 minutes. The reaction was very clean by t.l.c. and did not require any further additions of reagents or initiator. No reaction occurred until the toluene reached reflux temperature (initiation period). The hydrostannation also proceeds with similar efficacy in dioxane and this is consistant with the view that radical reactions are generally solvent independent. The products were isolated after crude 'squat' chromatography, to remove non-polar tributyltin containing by-products such as hexabutylditin, in virtually quantitative yield, but still contained minor impurities. Repeated flash chromatography furnished the product mixture (**138** & **139**) in very good yield (84%). The ratio of *Z*-isomer formed depended on the procedure used, but was generally in the region of 5-15%. Chromatography on silica gel 60 seemed to partly decompose these vinylstannanes as the recovery dropped to about 80-90% each time. This was probably due to silica gel induced protolytic cleavage of the tin-carbon bond.[119] However, no allylglycine derivative (**140**) (expected by hydrodestannylation of the vinylstannanes) was ever isolated by chromatography (*Scheme 3.21*).



138, 139 140

Scheme 3.21

The product mixture of isomers is a colourless, clear oil, which is stable to the atmosphere for many months and to distillation at high temperature under reduced pressure (*ca* 200°/0.03mm). We attempted isomerisation of the minor *Z*-isomer (**139**) to the thermodynamically more stable *E*-isomer (**138**) by a number of methods: heating to 250° at

atmospheric pressure (some decomposition) and at 0.03mm (distillation); by heating the product mixture in toluene or dioxane at reflux in the presence of tributyltin hydride and AIBN; and by sun lamp irradiation at reflux in toluene. None of these methods had any significant effect on the proportion of *Z*-isomer present in the mixture. Perhaps we can assume that the ratio obtained is close to the thermodynamic ratio of the two isomers (88:12, **138**:**139**). Clearly, some degree of, or perhaps total, thermodynamic equilibration occurs during the radical hydrostannation reaction at elevated temperature.

Trialkylboranes are useful initiators for producing a number of radicals at low temperatures, sometimes requiring the presence of oxygen.[120] Tin radicals are reported to have been formed at temperatures as low as -78°C.[121] Radicals thus generated have been shown to undergo the addition to triple bonds at or below room temperature under high dilution conditions generally to form a mixture of the *E* and *Z*-substituted double bonds, again by radical induced isomerisation of the kinetically formed *Z*-isomer.[121] We were interested to see what effect the use of this procedure would have on the rate, purity, stereochemistry and yield of the hydrostannation of propargylglycine derivative **121**. Thus, tributylborane (1M THF solution, 0.1 equivalents) was added to a solution of **121** and tributyltin hydride in toluene, stirred under a dry air atmosphere at room temperature and followed by t.l.c. The reaction proceeded slowly and further additions of tributylborane solution were necessary to keep the reaction proceeding. It seems as though the radical chain process would occur for a short period of time after the addition of the borane before termination; perhaps the borane was complexing with the amide and/or ester and this was deleterious to the radical process. The reaction mixture was allowed to stir at room temperature for a total of three weeks and a total of 0.3 equivalents of tributylborane was added. After repeated chromatography the product was isolated in moderate yield (64%) as an oil and n.m.r. analysis showed that it was again the result of β-addition (terminally substituted vinylstannanes) and a 58:42 ratio of *E* and *Z*-isomers (**138** & **139**) was obtained.§ Presumably, the lower temperature of the reaction results in less isomerisation of the kinetic *Z*-isomer by tributyltin radicals than occurs at the higher temperature

§ The ratio was calculated by comparing the relative peak heights of the methylene groups of the tributylstannyl moieties of both isomers in the ^{13}C n.m.r. spectrum. Overlapping signals and $^{117}Sn/^{119}Sn$ satellites in the ^{1}H n.m.r. spectrum prevented an accurate integration of peak areas, so the relative peak heights of the signals obtained from rapidly relaxing carbon nuclei (short T_1) were believed to be a good approximation to the relative abundance of the two isomers.

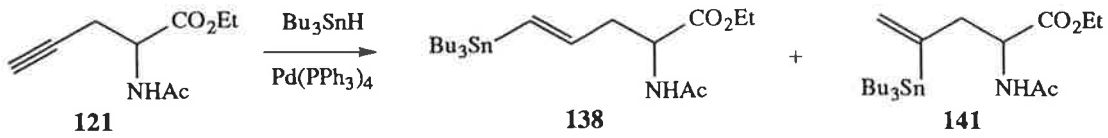
and thus a higher proportion of **139** results in the product mixture. Unfortunately, the hydrostannation is slow at room temperature and this allows the isomerisation to become a competing process.

Formation of tributyltin radicals was also attempted by sun lamp irradiation of tributyltin hydride in a benzene solution of propargylglycinate (**121**). Unfortunately, after 2.5 hours at ambient temperature (up to *ca* 50°), only traces of product could be detected by t.l.c. along with mostly starting material and a number of other products which had not appeared in the other radical reactions, so this method was aborted.

Initiation of tin radicals by ultrasonication was also investigated. This method has been shown to produce radicals at short lived 'hot spots' in solution which undergo addition to alkynes.[122] The kinetic product (*Z*-β-adduct, **125**) is often obtained since radical chain propagation and isomerisation occurs in the cold bulk phase of the solvent (*i.e.* rate of isomerisation is temperature dependant). However, by sonication of a THF solution of **121** and tributyltin hydride in an ultrasonic cleaning bath (low power ultrasound) at ambient temperature (up to *ca* 50°), no product was obtained.

To summarise the results of the radical hydrostannation reactions, we obtained only terminally substituted products (β-adducts, δ-isomers; **138** & **139**) in moderate to very good yields and of varying *Z*:*E* isomeric ratio. We were unable to obtain the *Z* or *E*-isomer exclusively since (*a*) thermodynamic equilibration of the vinylstannanes competed with kinetic product formation, (*b*) the isomers were inseparable by silica gel chromatography and (*c*) attempted isomerisation of the **139** to **138** was unsuccessful. The assumed thermodynamic equilibrium between the two β-adducts contained about 10% of the *Z*-isomer.

Transition metal catalysed hydrostannation was also studied. This was expected to yield two possible products resulting from *syn*-addition in both α and β-manners: *E*-δ-tributylstannyl-*D*,*L*-allylglycinate (**138**) and γ-tributylstannyl-*D*,*L*-allylglycinate (**141**) (*Scheme 3.22*). We chose to use tetrakis(triphenylphosphine)palladium(0) since it has been shown to be an effective hydrostannation catalyst.[110-118] Tributyltin hydride was slowly added dropwise to a stirred solution of $Pd(PPh_3)_4$ (as little as 0.4mol%) and ethyl N-acetyl-*D*,*L*-propargylglycinate (**121**) in benzene at room temperature under a nitrogen atmosphere. The reaction was very fast and, if pure tin hydride was used and the rate of addition was slow



121 **138** **141**

Scheme 3.22

enough to ensure that relatively high concentrations of tin hydride did not result in competitive palladium catalysed formation of hexabutylditin and molecular hydrogen, a total conversion of **121** was observed by t.l.c. immediately after one equivalent has been added. In fact, t.l.c. (ethyl acetate:light petroleum 1:1) indicated that two products were formed at *ca* R_f 0.5, with ΔR_f of about 0.05 (**121** had an R_f of *ca* 0.25 with this eluant). Crude 'squat' chromatography[123] to remove palladium and hexabutylditin resulted in a virtually quantitative yield of the products, and a subsequent number of flash chromatographic purifications gave a clean separation of the two compounds. Again, the recovery was only about 90% for each separation. ^{1}H n.m.r. analysis indicated that the upper spot (58%) was the γ-substituted (**141**) and the lower (15%), the *E*-δ isomer (**138**). The ^{1}H n.m.r. spectrum of the γ-isomer (**141**) was markedly different to that of the δ-isomers - the vinylic methylene protons resonated as broad singlets at δ5.26 and 5.74 and the diastereotopic β-protons as distinct doublets of doublets at 2.51 and 2.79 respectively, all four of these protons with tin satellites. The difference in polarity on t.l.c. is not surprising since the highly bulky tributystannyl group provides a more effective non-polar shield for the ester and amide of the γ-isomer (**141**) than for the δ-isomer (**138**) and hence the γ-isomer binds less strongly to silica gel. The vinylstannane (**141**) was air and temperature stable (distilled at *ca* 200°/0.03mm without decomposition). Since we were unable to obtain a pure δ-isomer (**138** or **139**) by radical hydrostannation, this palladium catalysed route was extremely important as it resulted in the formation of two separable and isomerically pure vinylstannanes (**138** and **141**).

The palladium catalysed hydrostannation was successfully carried out in a number of solvents - benzene, toluene, THF, dichloromethane and acetonitrile. Apart from the reaction in acetonitrile, in which tributyltin hydride is only sparingly soluble, all the reactions proceeded rapidly and cleanly. ^{1}H n.m.r. analysis of the crude reaction mixtures gave very similar spectra for the products in all the solvents studied, and within the bounds of error for the integration of the peaks, no trend was observed with respect to the isomeric ratio and, hence, to the mechanistic implications. Interestingly, the amount of *E*-δ-isomer (**138**) was approximately

30-35% of the crude mixture before chromatography on silica gel, but only *ca* 25% after, indicating that silica induced protolytic cleavage of the Sn-C bond occurs more readily for that isomer than for **141**. This is consistent with the observation that electrophilic substitution generally occurs more readily for vinylstannanes substituted at the β carbon (see *Chapter 4.1*).

To check whether or not the palladium catalysed hydrostannation was occurring with any racemisation at the α-carbon, the enantiomerically enriched propargylglycinate (*L*-**121**) was subjected to the same palladium catalysed hydrostannation conditions. Both the γ and *E*-δ-isomers (*L*-**141** & *L*-**138**) so obtained were optically active and a chiral Eu(III)(hfc)$_3$ ^{1}H n.m.r. shift experiment using **141** confirmed that no racemisation had taken place (*Figure 3.2*).

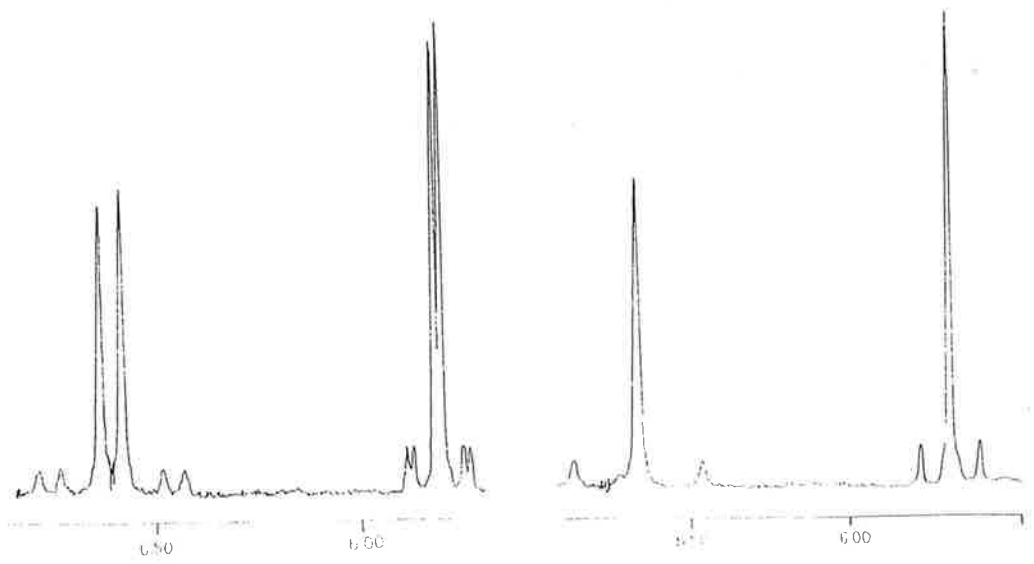
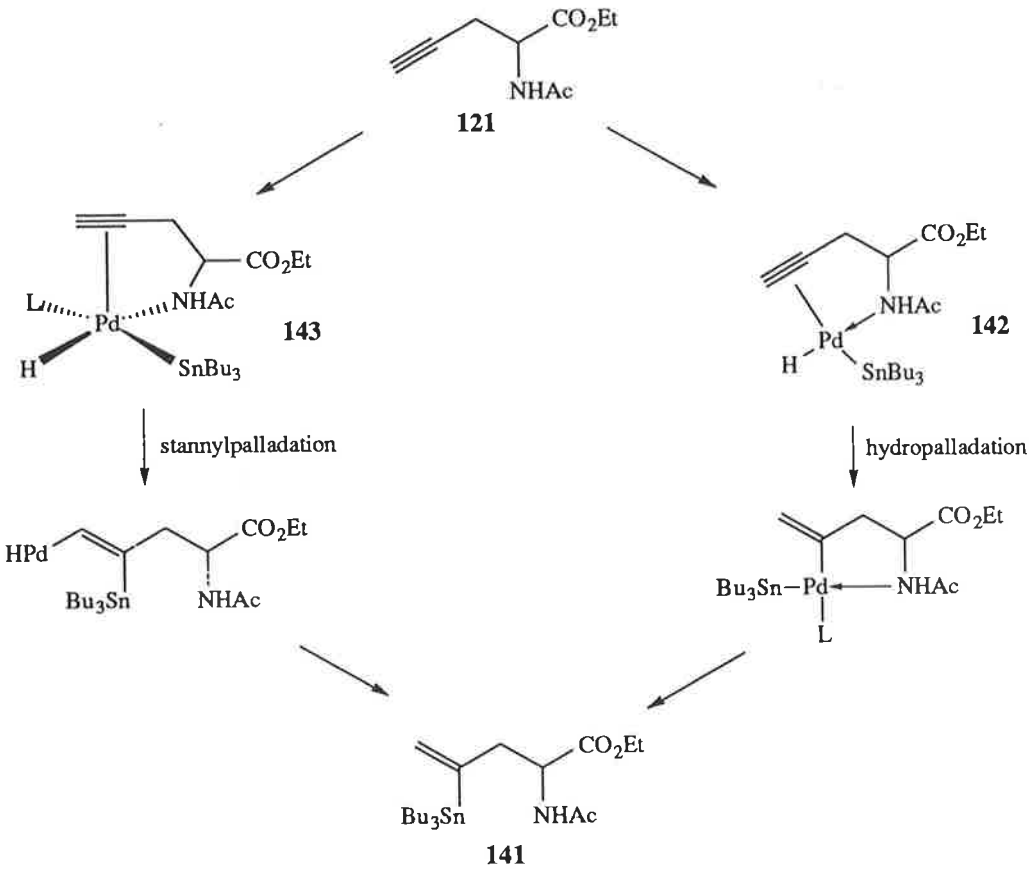


Figure 3.2. Eu(hfc)$_3$ ^{1}H n.m.r. experiment with racemic and chiral **141**. The portion of the spectrum shown is of the resonances of the terminal olefinic protons of the diastereomeric complexes.

Our observation that the α-adduct (γ-isomer) formed selectively is worthy of comment. Since Guibé has invoked the intermediacy of chelated species in the reaction transition states, but did not explain how this affects regioselectivity,[109] we are undoubtably seeing a similar phenomenon for the hydrostannation of **121**. However, he found that more coordination by the substrate in less coordinating solvents to the metal favoured more β-adduct for an oct-1-yn-3-ol derivative (*Scheme 3.12*) whereas we obtained predominantly the α-adduct (**141**) and

detected no solvent effect. Presumably chelation occurs to palladium through the amide nitrogen of **121**. Guibé obtained predominantly β-isomer from the hydrostannation of N,N-dimethylpropargylamine,[109] but this was the only example of an aminoalkyne and the regioselectivity may be due merely to steric effects. It is still difficult to say whether the palladium catalysed hydrostannation results from a *syn*-hydropalladation or *syn*-stannylpalladation (*Scheme 3.16*). For a hydropalladation with chelation, in our case, from the amide nitrogen a square-planar π-complex such as **142** would most likely be the intermediate (*Scheme 3.23*). The rearrangement to the σ-complex whilst retaining ligation of the amide would result in the regioselectivity we observe (α-adduct, **141**, predominates). If a stannylpalladation were invoked then a similar square-planar intermediate would be impossible, but a square pyramidal chelated intermediate (**143**) could result in the preferred α-adduct although chelation by the amide to palladium would be lost during the shift from the π to σ-complex. The mode of addition suggested by Guibé's solvent effect is that of *stannyl*palladation of an intermediate similar to **142** (*i.e.* **137** in *Scheme 3.19*). It would be interesting to see what the effect of a number of strongly chelating nitrogen and phosphorus



Scheme 3.23

containing alkynes of varying chain length mould have on the ratio of hydrostannation adducts. Catalyst relay has been suggested in promoting regio- and stereoselectivity for a number of other reactions.[124]

3.4 Stille coupling reactions. An overview.

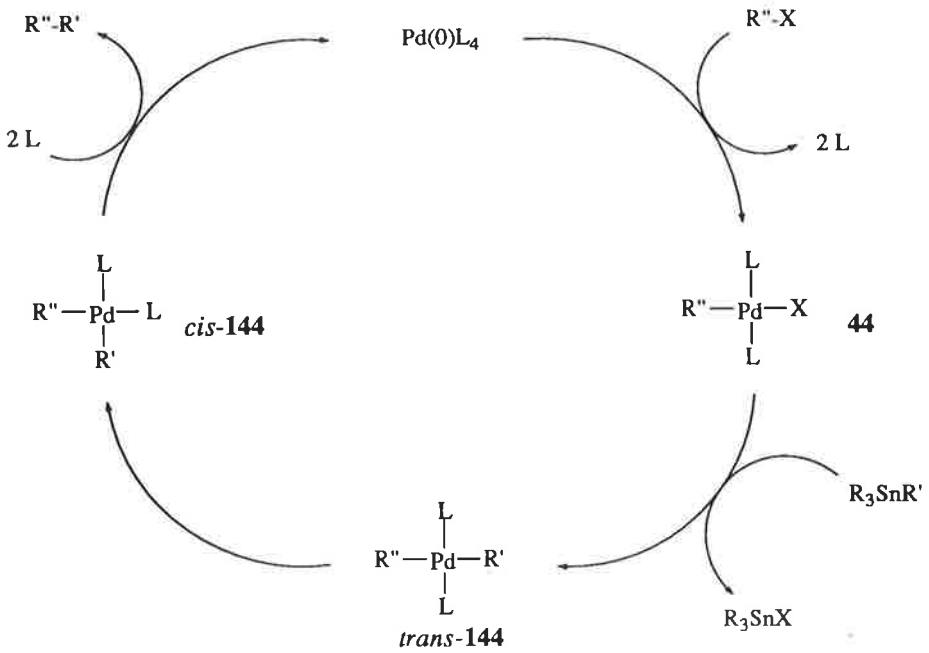
The Stille reaction, the coupling of organostannanes with organohalides and sulphonates (almost always triflates, but other perfluoroalkanesulphonates,[125] fluorosulphonates[126] and *p*-fluorobenzenesulphonates[127] have also proven effective electrophiles) mediated by a zero-valent palladium catalyst, is a particularly effective means of carbon-carbon bond formation (*Scheme 3.24*).[56,99] The coupling is extremely chemoselective and is performed under mild conditions, so almost all functional groups are tolerated. Attention has been focussed recently on developing methodologies for the formation of the precursor stannanes[56,100] and sulphonates[55,126-128] in order to exploit the advantages offered by Stille coupling. A number of palladium catalysts may be used to facilitate the reaction and, although the active catalyst is a palladium(0) species, a wide variety of ligands may be used to modify its stability and reactivity. The rate at which organic groups are exchanged from tin to palladium usually follows the order: alkynyl>alkenyl>aryl>allyl~benzyl>alkyl, so for an organostannane, R_3SnR', where R=alkyl and R' is an unsaturated group, the transfer of the group R' occurs exclusively.

$$R_3Sn—R' \quad + \quad R''—X \quad \xrightarrow{Pd(0)} \quad R'—R'' \quad + \quad R_3SnX$$

Scheme 3.24

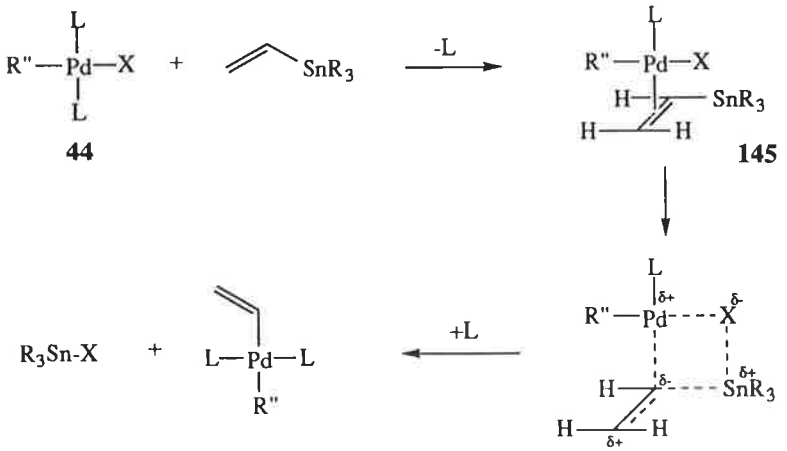
The basic mechanism of the Stille reaction is shown in the following catalytic cycle (*Scheme 3.25*). Oxidative addition of the organohalide or triflate gives the Pd(II) species (**44**). Transmetallation of the labile group, R', from the stannane to palladium occurs with exchange of the halide (triflate in the presence of LiCl) to stannane, producing the bis(organo)palladium(II) complex (**144**) and triorganotin halide. Ligand assisted isomerisation of the initially formed *trans*-complex to *cis*-**144**, followed by reductive elimination, yields the coupled product and reforms the active, zero-valent palladium catalyst.

The oxidative addition and reductive elimination steps have been extensively studied and are quite well understood.[71a] However, intricate mechanistic detail concerning transmetallation



Scheme 3.25

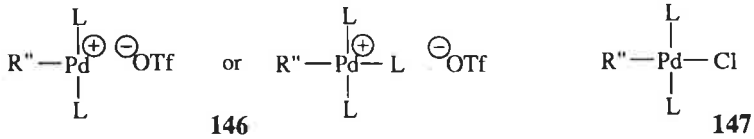
has yet to be determined, although in general terms the step may be considered an electrophilic substitution of a palladium(II) species with a nucleophilic organostannane (essentially an S_E2 mechanism). A study by Farina on the transmetallation of vinylstannanes with palladium(II) intermediates concluded that it initially proceeds with ligand dissociation of **44** and formation of a palladium(II)-organostannane π-complex (**145**) (*i.e.* Pd(II) ligated by a carbon-carbon π-bond of the organostannane) (*Scheme 3.26*).[75] No in-depth study has been reported on the effects of substitution on both the organostannane and organopalladium(II) species. Some insight into these effects has been ascertained from reactions of arylstannanes with *platinum*(II) complexes which have shown that strongly electron donating groups on the aryl ring



Scheme 3.26

dramatically inhibit the rate of transmetallation.[130,132] Crisp and Flynn have shown that the Stille reactions of a 5-trifloxyuridine derivative proceed most rapidly for aryl stannanes bearing strongly electron withdrawing groups (*e.g.* *p*-$CF_3C_6H_4SnMe_3$ reacts *ca* 10 times faster than *p*-$MeOC_6H_4SnMe_3$).[131,132] These results seem to implicate partial negative charge build-up on the aryl ring during transmetallation. This suggests that a degree of cleavage of the carbon-tin bond preceeds carbon-palladium bond formation. For vinylstannanes, the effect of substitution on the double bond has not been conclusively proven. Both electron rich and electron deficient vinylstannanes have been shown to undergo Stille reactions, and it is known that increased steric bulk about the double bond slows down the reaction.[74a] Farina stated[75] that for the different substrates used in Stille reactions, 'the transmetallation proceeds in a fundamentally unique fashion and therefore is subject to unique effects by ligands and additives,' so an all-encompassing picture of the transition state of the transmetallation process has been difficult to formulate.

The effect of varying the substituents on the organohalide or sulphonate has not been conclusively studied, although it seems that increased electrophilicity of the palladium(II) complex formed after oxidative addition results in increased reaction rates. This is borne out by the observation that coordinatively unsaturated catalysts (PdL_n, n<4) are more reactive, although often less stable, than PdL_4.[75,93,133] Also, the rate increase of some vinylpalladium(II) triflates relative to chlorides (formed by addition of lithium chloride to the former complex) has been attributed to the existance of an ion pair (cationic palladium) for the former (**146**) and a covalent Pd-Cl bond for the latter (**147**). The increased electophilicity of **146** is believed to cause of the rate increase.[75] However, most organotriflates have been found unreactive in Stille coupling in the absence of any halide source and the reason for this is not entirely clear.



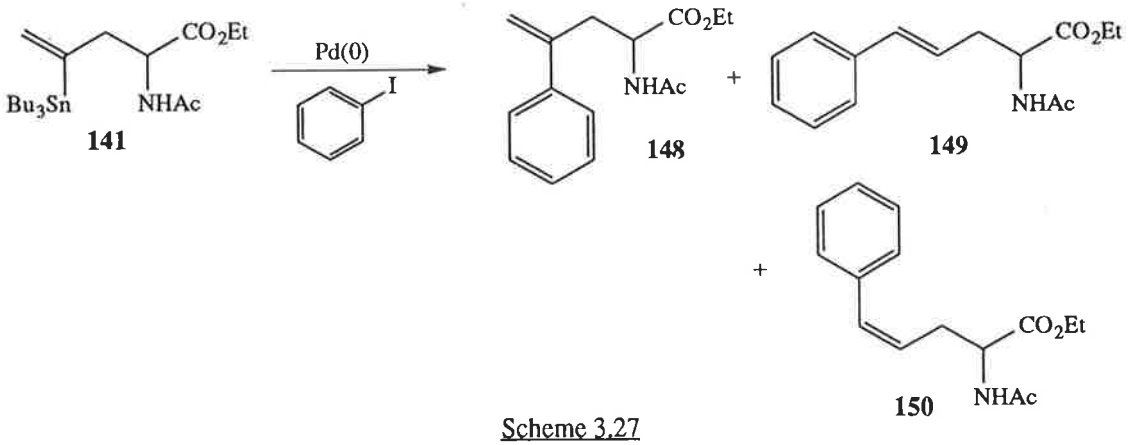
146 **147**

We investigated the utility of the two vinylstannanes **138** and **141**, as coupling partners in Stille reactions as a route to unsaturated α-amino acid derivatives.

3.5 Stille coupling reactions of ethyl N-acetyl-γ-tributylstannylallylglycinate.

3.5.1 Coupling with aryl halides.

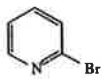
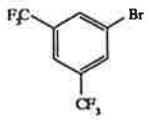
The Stille coupling of the γ-stannane (**141**) with iodobenzene was studied as a model reaction (*Scheme 3.27*). In all reactions 5mol% of catalyst relative to vinyl stannane was used, except where noted. The reaction catalysed by $Pd(PPh_3)_4$ in DMF at 100°C (*Table 3.1*, entry 1) gave a number of different isomeric products: the anticipated γ-phenyl product (**148**) arising from *ipso*-substitution as well as unexpected *E* and *Z*-δ-isomers (**149** & **150**) arising from *cine*-substitution.[134] The δ-*Z*-isomer (**150**) was separable from the other two isomers by flash chromatography, but **148** and **149** were not. The reaction was repeated using a number of different conditions and in all instances the three isomeric products were obtained (*Table 3.1*, entries 1-8). We had initially supposed that the small amounts of δ-substituted isomers (**149** & **150**) had arisen from *ipso*-substitution reaction of small amounts of δ-stannane (**138**) in the starting material, but since a ^1H n.m.r. spectrum confirmed the purity of the γ-stannane *cine*-substitution must have been taking place. Recovery of isomerically pure γ-stannane (**141**) from some of the reaction mixtures suggested that vinylstannanes **138** and **139** were not formed *in situ*.



Scheme 3.27

Farina's study on the effects of ligands on the rate of Stille reactions found that triphenylarsine and trifurylphosphine ligands led to large increases in rate of coupling relative to triphenylphosphine.[75] The use of tetrakis(triphenylarsine)palladium(0) [$Pd(AsPh_3)_4$], prepared *in situ* from tris(dibenzylideneacetone)dipalladium chloroform complex ($Pd_2dba_3.CHCl_3$) and eight equivalents of triphenylarsine ($AsPh_3$), resulted in a more efficient reaction which required a lower temperature for a satisfactory conversion of stannane and a strongly

Table 3.1. Stille coupling between γ-tributylstannylallylglycinate (**141**) and aryl halides

Entry	Substrate	Catalyst[a]	Solvent	Temp./time	% Yield[b]	Ratio of products[c]		
						γ	*E*-δ	Z-δ
1		A	DMF	100°/7h	52[d]	80 **(148)**	10 **(149)**	10 **(150)**
2		A	THF	reflux/90min	0			
3		A	dioxane	reflux/15h	trace	*ni*	*ni*	*ni*
4		B	THF	reflux/15h	56	78	18	4
5		C		reflux/6h	66[d]	52	32	18
6		C[e]		reflux/6h	79	37	38	25
7		C[f]		reflux/15h	54	63	22	15
8		D		reflux/15h	55[d,g]	30	30	10
9		C		reflux/4h	0			
10		C		reflux/20h	56[h]	100 **(151)**	*nd*	*nd*
11		C		reflux/20h	53	54 **(152)**	46 **(153)**	*nd*

Reactions were carried out by heating a mixture of the stannane, substrate and catalyst in the solvent shown for the appropriate length of time.

[a] 5mol% used unless otherwise stated.
A = $Pd(PPh_3)_4$;
B = $Pd(dba)_2$ / $AsPh_3$ (1:4);
C = $Pd_2dba_3.CHCl_3$ / $AsPh_3$ (1:8);
D = $Pd_2dba_3.CHCl_3$ / P(2-furyl)$_3$ (1:8).

[b] Isolated yield.

[c] Calculated from ^1H nmr spectra; *ni*=not isolated, *nd*=not detected; product numbers in parentheses.

[d] Based on recovered vinylstannane.

[e] 10% catalyst.

[f] In addition, triethylamine (3 equivalents) was present.

[g] This product was contaminated with *ca* 30% (2-furyl)-substituted material.

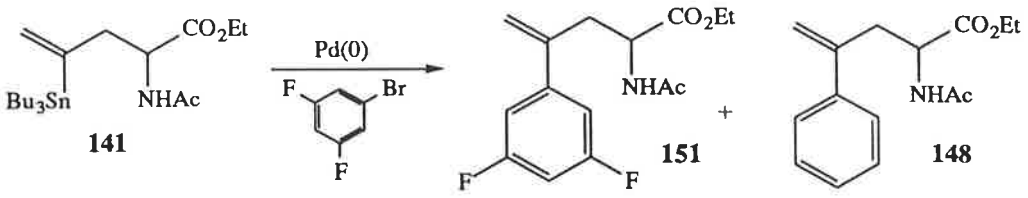
[h] γ-Phenyl substituted product was also obtained (10.4%).

coordinating solvent was unnecessary (*i.e.* THF sufficed). However, this catalyst system produced significantly more *cine*-substitution (entry 5) and increasing the amount of catalyst to 10mol% yielded a product mixture in which the yield of combined *cine*-isomers (**149** & **150**) outweighed the *ipso*-substitution. The exact reason for this effect is unknown, but may be a consequence of the migration of a phenyl group from the arsine catalyst which is discussed below. No significant reaction of the stannane (**141**) occurred at room temperature with $Pd(AsPh_3)_4$ in THF.

The three isomers were easily characterised by the vinylic proton signals in their ^1H n.m.r. spectra. For the γ-phenyl isomer (**148**) the vinylic protons resonated at δ5.02 and 5.25 as broad singlets, whereas the *E*-δ isomer (**149**) had a doublet (δ6.36, *J*15.7Hz) and doublet of triplets (δ5.98, *J*7.4, 15.7Hz) for the C5 and C4-hydrogens respectively and the Z-phenyl (**150**) a doublet (δ6.53ppm, *J*11.6Hz) and doublet of triplets (δ5.50, *J*7.0, 11.7Hz) for those vinylic protons. The resonances of the acetamido methyl group, the ethyl ester methylene and the α-proton were all significantly shifted upfield for 148 relative to **149** and **150** (*ca* 0.17, 0.22 and 0.08 ppm respectively) indicating that those protons are positioned to some extent in the shielding zone of the phenyl ring. The diastereotopic C3-protons were resolved more fully in the ^1H n.m.r. spectrum of **148**, than for **149** and **150**, and were shifted downfield by 0.32 and 0.30ppm respectively, since they lie in the deshielding zone of the aromatic ring.

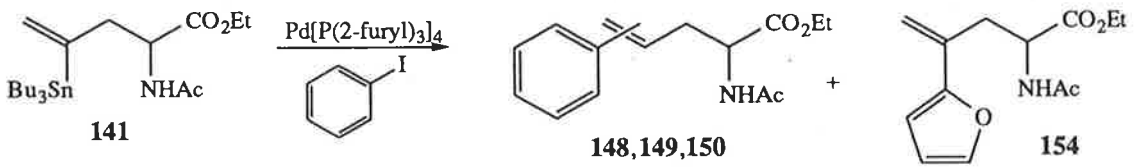
In general, all γ-substituted allylglycine derivatives that are reported in this thesis showed the two diastereotopic C3-hydrogens as distinct doublets of doublets, reflecting the marked conformational restriction imposed by substitution at the γ-carbon. Generally, the C3-hydrogens of δ-isomers appeared as broad multiplets.

The reactions of other aryl halides were investigated using the $Pd(AsPh_3)_4$ in THF system (*Table 3.1*, entries 9, 10, 11). No reaction occurred with 2-bromopyridine and this may be the result of a relatively stable palladium(II) complex forming (*c.f. Chapter 2.4.2*). The addition of lithium chloride did not facilitate this reaction. 3,5-Difluorobromobenzene reacted to give the desired *ipso*-substituted product (**151**) as well as a small amount of γ-phenyl product (**148**) (*Scheme 3.28*). Presumably formation of **148** arose by palladium catalysed transfer of a phenyl group from a triphenylarsine ligand. Transfer of aryl groups from phosphine ligands has previously been observed in Heck[135] and transmetallation reactions

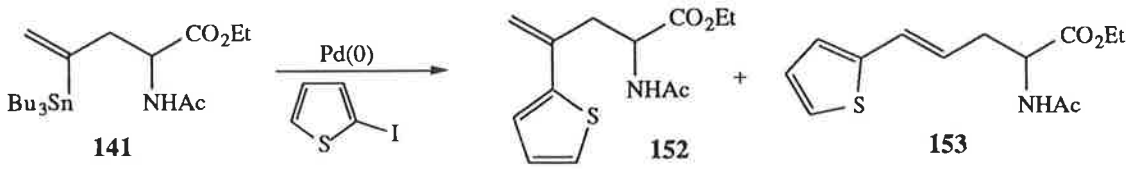


Scheme 3.28

involving a number of transition metals.[136] Indeed, reaction of iodobenzene with 141 in the presence of Pd[P(2-furyl)$_3$]$_4$, preformed from Pd$_2$dba$_3$.CHCl$_3$ and tri(2-furyl)phosphine, gave a small quantity of γ-(2-furyl) product (**154**) as a mixture with the three phenyl substituted products (**148, 149, 150**) (entry 8 & *Scheme 3.29*). The furyl substituted product was tentatively assigned from the ^{1}H n.m.r. spectrum of the mixture because of an extra set of terminal vinylic protons at δ4.91 and 5.53ppm. No *cine*-isomers were observed for the reaction of 3,5-difluorobromobenzene. Reaction of 2-iodothiophene gave an almost 1:1 mixture of γ-(2-thienyl) and *E*-δ-isomers (**152** & **153**) (entry 9 & *Scheme 3.30*). Phenyl substituted products were also formed (t.l.c.) but were separated from the desired products by flash chromatography. In the ^{1}H n.m.r. spectrum the terminal vinylic protons of **152** resonated at similar chemical shifts to those of the structurally similar furyl substituted product and this helped to confirm the structure of **154**



Scheme 3.29

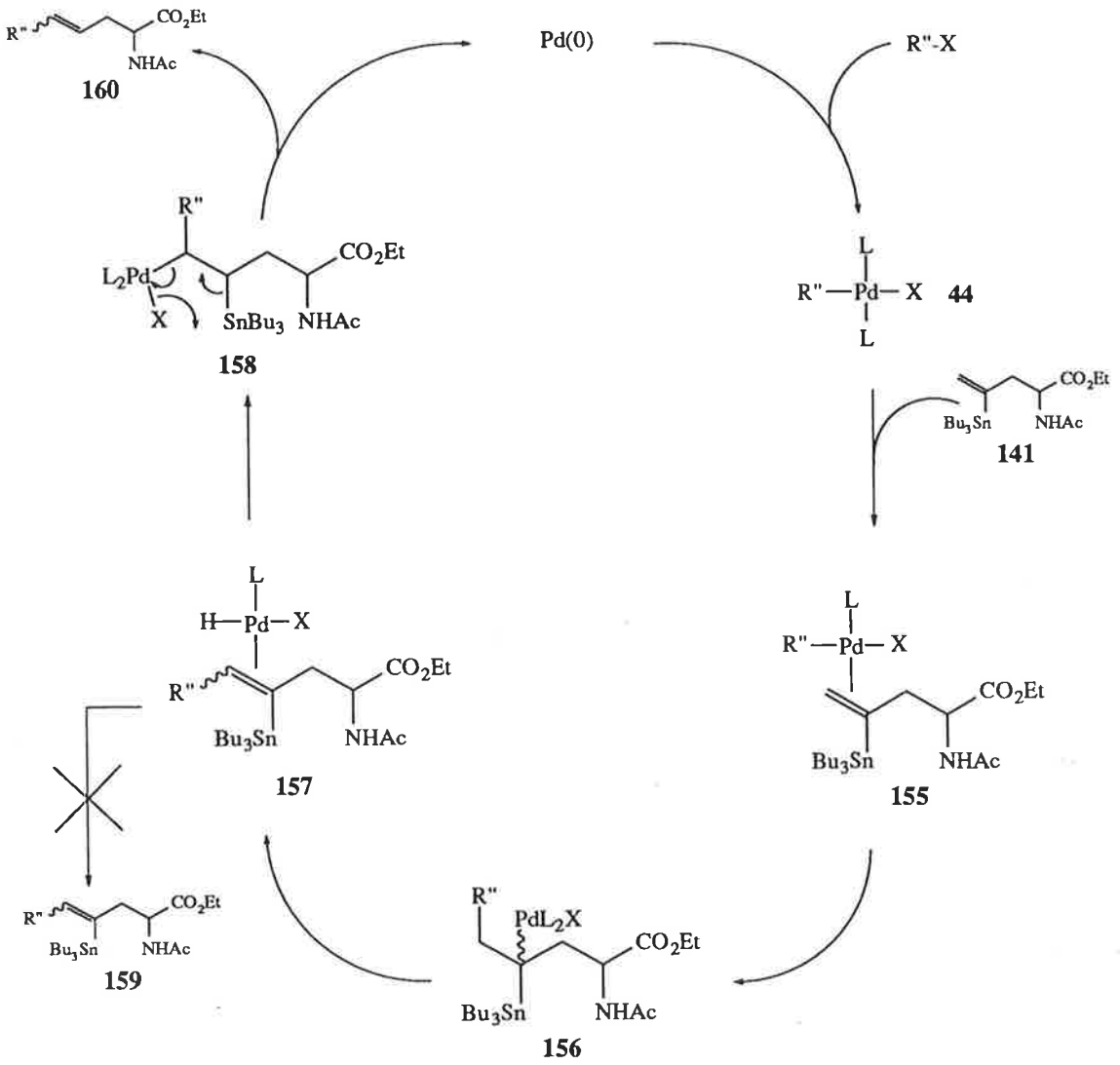


Scheme 3.30

Cine-substitution of vinyl stannanes in Stille reactions has been reported in the literature in only a few instances.[137,138] Kikukawa observed such products in the reaction of vinylstannanes with aryl diazonium salts and proposed a mechanism based on Heck addition to the vinylstannane's double bond rather than transmetallation.[137] Stork later observed similar

results for the coupling of norbornenyl vinylstannanes with iodobenzene.[138] Such stannanes are quite sterically encumbered and perhaps as a result the transmetallation does not occur readily. This allows alternative reaction pathways, such as Heck addition, to take place. In our case, the formation of *cine*-substituted products also may have arisen because the γ-stannane (**141**) is too sterically hindered to undergo an efficient transmetallation owing to the amide and ester functionalities.

The mechanism by which we believe *cine*-substitution arose is shown in *Scheme 3.31*. Complexation of the organopalladium(II) species (**44**) to the vinylstannane π-electrons forms **155** which is proposed to be an intermediate in both Heck[70a] and Stille[75] coupling reactions. A *syn*-addition of the organo and palladium moieties occurs to the double bond to form the unstable diastereomeric palladium(II) intermediates (**156**). *Syn*-β-hydride elimination could theoretically occur with either of the two C5-hydrogens since both eclipsed conformers in the respective transition states are quite crowded, although *E*-**157** seems less strained than *Z*-**157** and of the two probably forms as the major intermediate. Dissociation of these intermediates to produce the substituted stannylallyglycinates (**159**) presumably does not happen since a product of this type was never isolated. When the reaction was repeated in the presence of triethylamine in an attempt to facilitate the dissociation of **157** to **159**, the effect on product distribution was negligible (*Table 3.1*, compare entries 5 & 7). *Syn*-hydropalladation across the double bond in the 'reverse' sense gives the Pd(II) intermediate (**158**). Elimination of Pd(0) and tributyltin halide may then occur in either a *syn* or *anti*-manner. Kikukawa proposed an *anti*-transition state for this step in the coupling of aryl diazonium tetrafluoroborates with vinylstannanes, but fluoride was presumably reacting with the Pd(II) complex intermolecularly.[137] Flynn has proposed a *syn*-elimination proceeding through a five-membered transition state to explain the observed stereochemistry in the *cine* substitution reaction of a 5-(trifloxy)uridine derivative with an α-stannylacrylate, although the presence of excess lithium chloride does not exclude the possibility of an intermolecular reaction.[132] We have observed what we believe to be a *syn*-elimination *via* a five-membered intermediate from a δ-iodo-γ-stannylallylglycine derivative (**283**, see *Chapter 5.3*), and since there is no external source of halide it is possible that we are forming a similar intermediate for the elimination of **158** as well. If the *E*-complex (*E*-**157**) is formed preferentially and a *syn*-elimination occurs

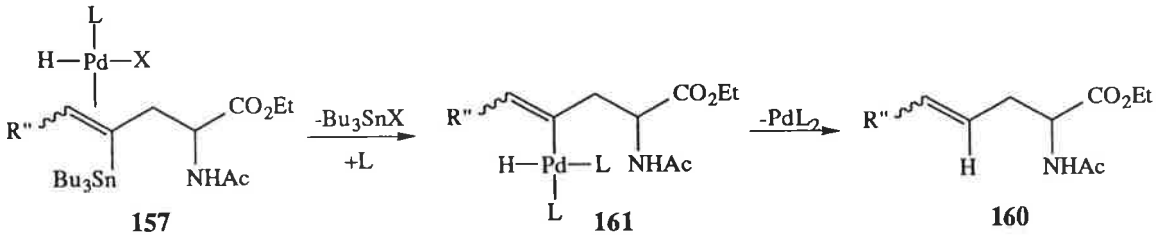


Scheme 3.31

from **158** then the *E*-product (**160**) is the expected major *cine*-substituted isomer, and this is what was observed in practice.

An alternative to the readdition-elimination sequence of *Scheme 3.31* is that the hydridopalladium iodide complexes (*E* & *Z*-**157**) undergo electrophilic substitution (*i.e.* a transmetallation reaction) to form vinylpalladium(II) hydride intermediates (*E* & *Z*-**161**) which reductively eliminate to form *cine*-substituted products (*E* & *Z*-**160**) (*Scheme 3.32*). However, in this case *Z*-**160** would be expected to predominate, but this was not observed.

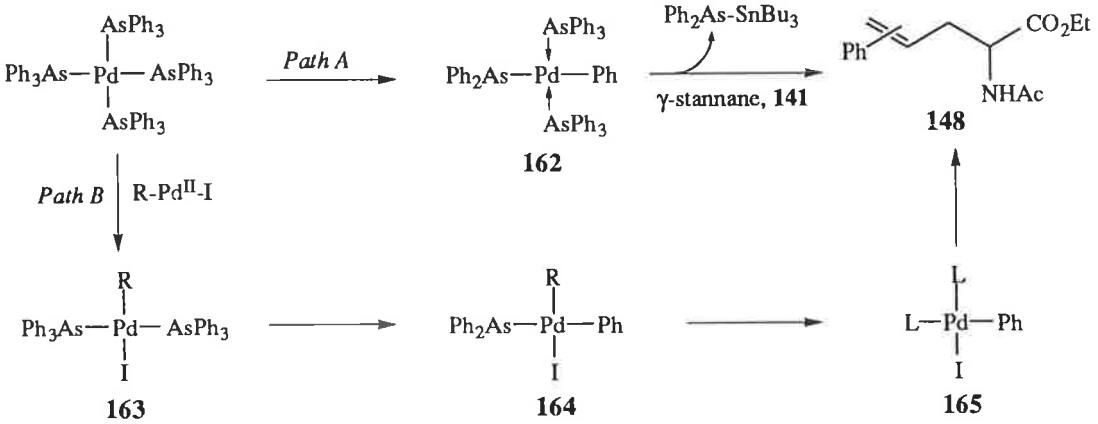
It is interesting to note the effect that the electron density of the aryl group has on the *ipso*:*cine* ratio of the aryl halide Stille reactions. The most electron deficient, 3,5-difluorobromobenzene, gave no *cine* substitution products (entry 10), yet the most electron rich, iodothiophene, gave 46% of **153** (entry 9). Iodobenzene gave up to 50% δ-isomers



Scheme 3.32

(entry 5). If transmetallation is considered as an electrophilic substitution reaction it would be expected to occur more rapidly for more electron deficient Pd(II) complexes. Thus for relatively π-electron rich arylpalladium(II) complexes, such as would be formed after oxidative addition of iodothiophene to Pd(0), transmetallation would occur relatively slowly because of the decreased electrophilicity of palladium(II) so competing processes, such as Heck-addition, become more dominant.

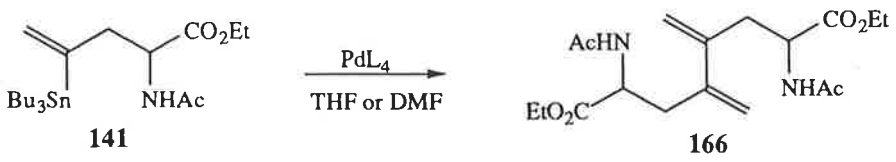
Phenyl substitution from the triphenylarsine ligands may be occurring through oxidative addition of the arsenic-phenyl bond to Pd(0) or Pd(II) intermediates. The corresponding phosphorus-aryl addition to a palladium(0) catalyst has been proposed to explain the formation of aryl exchange products of triarylphosphines in Heck arylation of olefins,[135] as has the oxidative addition to nickel, cobalt and palladium catalysts in transmetallation reactions with aryl lithium and Grignard reagents.[136] Presumably we are encountering transmetallation between a complex such as **162** and the γ-stannane (**141**) to produce the *ipso*-phenyl substituted allylglycine derivative (**148**) and Heck addition to form *cine*-substituted isomers **149** and **150** (*Scheme 3.33, Path A*). (Tributylstannyl)diphenylarsine would be expected to form, but we did not attempt to isolate this by-product. Alternatively (Path B), oxidative addition of the ligand may occur to the Pd(II) intermediate **163** to form Pd(IV) complex **164**.



Scheme 3.33

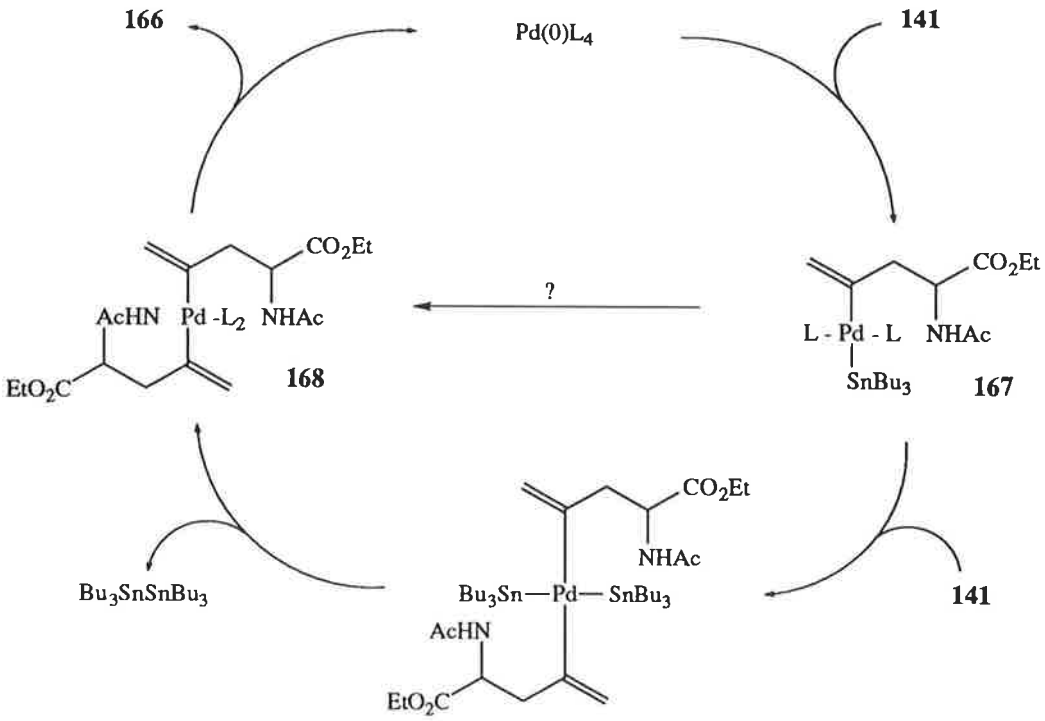
Reductive elimination of Ph_2As-R from **164** yields phenylpalladium(II) iodide which couples with the γ-stannane (**141**). The regioselectivity of phenyl substitution (*cine* or *ipso*) seems to be dependent on the effect of halide source (see *Part 3.5.2*).

When the γ-stannane (**141**) was heated in DMF in the presence of $Pd(PPh_3)_4$, or in THF with $Pd(AsPh_3)_4$, in the absence of any electrophile, total conversion of the starting material resulted and the major product in the crude reaction mixtures were the diastereomeric dimers (*meso* & *dl*-**166**) obtained by homocoupling between the two *ipso*-carbons as a 1:1 mixture (*Scheme 3.34*). The same dimers were also formed by copper nitrate mediated coupling (see *Chapter 3.7*). No phenyl substituted product arising from reaction of a triphenylarsine ligand was observed. Similar palladium catalysed dimerisation reactions have been reported in the literature as requiring a coordinatively unsaturated palladium catalyst and either a strongly coordinating solvent (HMPA)[139] or catalyst reoxidant (*tert*-butylperoxide).[140] The reactive catalyst is reported to be a Pd(II) species, yet this seems dubious for the case of catalytic $PdCl_2(CH_3CN)_2$ in HMPA,[139] since no reoxidant was present and the catalyst would initially have been reduced to Pd(0) by the vinylstannane (presumably forming only a small amount of the dimer). In that case, and also in our example, it is unlikely that Pd(II) is the active catalytic species for the bulk of the reaction, and so it seems necessary to invoke a zero-valent palladium catalyst. Although coordinatively saturated catalysts were used in these reactions, the use of triphenylarsine, a weakly coordinating ligand, allowed the reaction to proceed in a weakly coordinating solvent (THF). Presumably phosphine ligated palladium complexes require a more coordinating solvent (DMF, HMPA[139]). Although we made no extensive study on these reactions, it appears that the mechanism (*Scheme 3.35*) occurs by an initial oxidative adition of the *vinylstannane* to Pd(0) to yield **167**, followed by a transmetallation to form Pd(II) intermediate (**168**) and hexabutylditin. Reductive elimination of **168** would regenerate the zero-valent catalyst and produce the product dimer (**166**). Since no phenyl substituted product (**148**) was detected, arising from reaction of an arsine ligand, such a



141 **166**

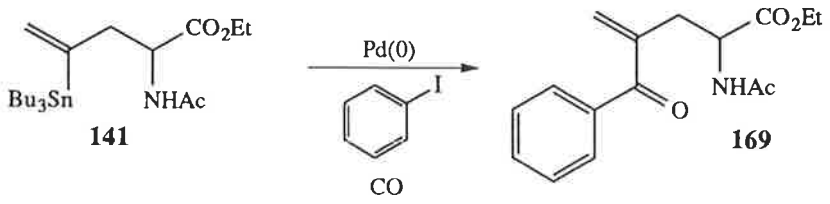
Scheme 3.34



Scheme 3.35

process may require a palladium(II) catalyst (*e.g. Scheme 3.33, Path B*). Small amounts of products arising from homocoupling of either the organostannane or electrophilic starting materials are occasionally observed as side products in a number of Stille reactions.[133,141]

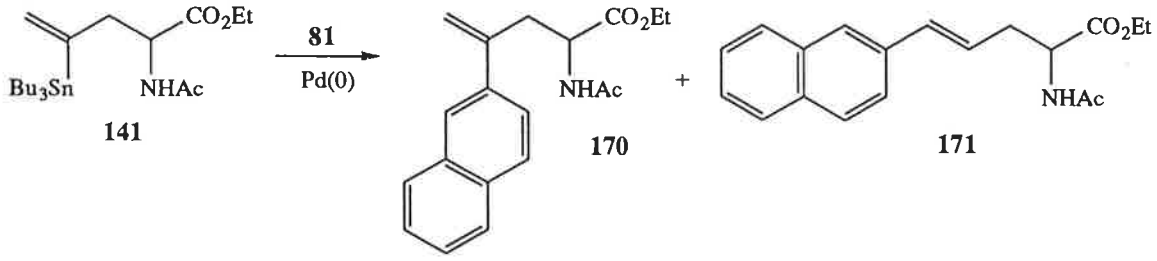
We attempted a carbonylative Stille coupling between the γ-stannane (**141**) and iodobenzene by repeating that reaction under a carbon monoxide atmosphere (*Scheme 3.36*). However, all attempts at forming the product (**169**) failed. $Pd(AsPh_3)_4$ proved to be an inadequate catalyst for these reactions and decomposed rapidly to palladium black in the presence of carbon monoxide. With $Pd(PPh_3)_4$ the reactions also failed to yield **169** and merely resulted in non-carbonylated coupling products (**148**, **149**, **150**). Reactions were attempted in THF and DMF at pressures between 1 and 5 atmospheres of carbon monoxide and at temperatures up to 100°C. Compound **169** was eventually successfully prepared by coupling **141** with benzoyl chloride (see *Part 3.5.5*).



Scheme 3.36

3.5.2 Coupling with aryl triflates.

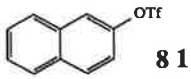
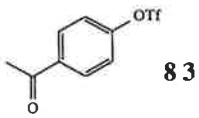
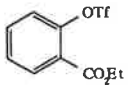
Stille coupling of the γ-stannane (**141**) with aryl triflates was examined and the results are summarised in *Table 3.2*. 2-Naphthyl triflate was initially investigated with a 'workhorse' Stille catalyst system[99] for organotriflates of $Pd(PPh_3)_4$ and LiCl (entry 1). Reaction in DMF at 100°C yielded a mixture of *ipso* and *cine*-substituted isomers: γ-naphthyl and *E*-δ-(2-naphthyl)allylglycinates (**170** & **171**). Repeating this reaction with $Pd(AsPh_3)_4$ and LiCl in THF (entry 2) gave four products - **170** and **171** (slightly more *cine*) as well as the corresponding phenyl substituted products (**148** and **149**) (*Scheme 3.37*). This clearly shows the effect that the ligands have on the product distribution (*i.e.* triphenylarsine transfers a phenyl group in the presence of palladium, but triphenylphosphine does not). Although lithium chloride is reported as being necessary for the coupling reactions of aryl triflates[56,75,99] we investigated the reaction without this additive to see whether the phenyl substitution leading to by-products **148** and **149** was occurring through a non-transmetallative process. To our surprise, in the absence of lithium chloride the reaction (entry 3) resulted in a better yield of γ-naphthyl substituted product (**170**), a stable catalyst and total regiospecificity! The products obtained were only *ipso*-substituted: the γ-naphthyl and the γ-phenylallylglycinates (**170** & **148**). Reaction with less catalyst gave proportionally less phenyl substituted product (entry 4). This is, to the best of our knowledge, the first example of a Stille reaction of an *aryl* triflate occurring without the necessity for the presence of a halide source.



Scheme 3.37

In order to determine the scope of the reaction between the γ-stannane (**141**) and other aryltriflates we investigated the coupling of *p*-acetylphenyltriflate (**83**) in the presence and absence of lithium chloride. Farina had used **83** as a model representative aryl triflate in the study of ligand effects and found that with all the ligands investigated the Stille reaction with vinyl and allyltributyltin occurred only in the presence of lithium chloride, even in NMP as solvent.[75] Reaction of **83** with 141 in the presence of $Pd(AsPh_3)_4$ and LiCl in THF (entry 5)

Table 3.2. Stille coupling between γ-tributylstannylallylglycinate (**141**) and aryl triflates

Entry	Substrate	Catalyst[a]	Time	% Yield[b]	Ratio of products[c]			
					γ	*E*-δ	γ-Ph (**148**)	*E*-δ-Ph (**149**)
1	 **81**	A[d]	2h	70	85 (**170**)	15 (**171**)	*nd*	*nd*
2		B	4h	64	65	13	19	3
3		C	9h	67	86	*nd*	14	*nd*
4		C[e]	15h	74	93	*nd*	7	*nd*
5	 **83**	B	24h	69	95 (**172**)	5 (**173**)	*ni*	ni
6		C	15h	37[f,g]	100		*ni*	*ni*
7		C	15h	0[g]			*nd*	*nd*
8		C	24h	0[g]			*nd*	*nd*

Reactions carried out in THF at reflux unless otherwise stated.

[a] 5mol% used unless otherwise stated:
A = $Pd(PPh_3)_4$ / LiCl;
B = $Pd(AsPh_3)_4$ / LiCl;
C = $Pd(AsPh_3)_4$.

[b] Isolated yield.

[c] Ratio determined by ^1H nmr spectroscopy; *ni*=not isolated, *nd*=not detected; product numbers in parentheses.

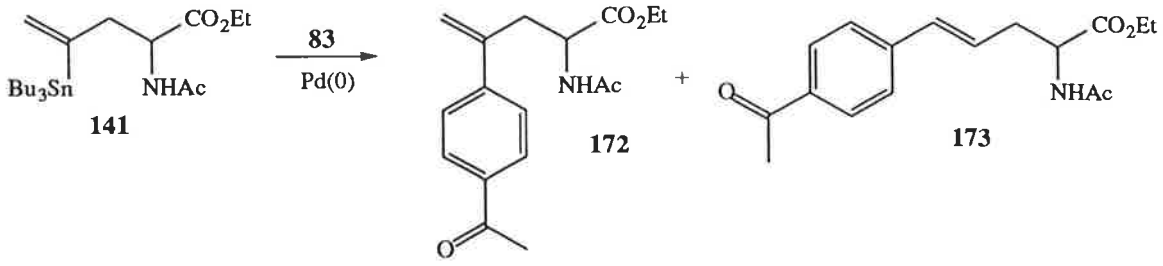
[d] DMF solvent, 100°C.

[e] 3mol% catalyst.

[f] Based on recovered vinylstannane.

[g] Catalyst unstable.

gave the expected *ipso*-substituted γ-isomer (**172**) and a small amount of *E*-δ-isomer (**173**) (*Scheme 3.38*). Repeating the reaction in the absence of lithium chloride (entry 6) gave only the transmetallation product (**172**). However, the catalyst was unstable under these conditions and often conversion of **141** was incomplete. This coupling was unexpected based on Farina's results.[75] The transfer of a phenyl group from an arsine ligand also occurred, but the two products (**172** & **148**) were separable by flash chromatography.



Scheme 3.38

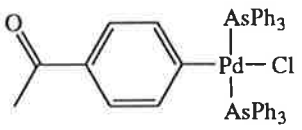
Reaction of 2-carboethoxy-1-phenyl triflate with **141** yielded no coupled product using the $Pd(AsPh_3)_4$ catalyst in THF in the presence or absence of lithium chloride (entries 7 & 8). Presumably the intermediate palladium(II) species is too sterically hindered and stabilised intramolecularly by the *o*-carbonyl oxygen to undergo successful coupling.

Since reactions of iodobenzene and iodothiophene, and 2-naphthyl and *p*-acetylphenyl triflates in the presence of lithium chloride, produced various amounts of δ-substituted allylglycine derivatives, yet in the absence of lithium chloride the two triflates yielded only the expected γ-substitutied isomers, formation of *cine*-substituted products seems to depend on the presence of a halide. The addition of lithium chloride changes the nature of the palladium(II) intermediate formed by oxidative addition of organotriflate to palladium(0). Organotriflates form an ion pair with a cationic palladium(II) (**146**), whereas organohalides form an intermediate with a more covalent bond between palladium and the halide (**44**) (*page 67*). In the presence of lithium chloride **146** forms a palladium(II) chloride (**147**) and lithium triflate. Ion pair intermediates (**146**) were for many years thought to be unreactive in Stille reactions with organostannanes[56] and although the exact role of the chloride ion is still not certain, its presence may facilitate carbon-tin bond cleavage. In some instances it has been observed that lithium chloride retards coupling of vinyl triflates.[75,142] If Stille coupling is considered as an electrophilic substitution reaction, then the more electron deficient the palladium(II) intermediate, the greater would be the rate of transmetallation. This argument was used in *Part 3.5.1* to explain the different amounts of *cine*-substitution obtained from coupling of the various arylhalides. The ion pair (**146**) would be more electrophilic than **147** and we observed transmetallation as the exclusive pathway for coupling of aryl triflates in the absence of lithium chloride. The more electron rich complex (**147**) might have undergone Heck-addition to the vinylstannane as a competing process because of its relatively lower electrophilicity and, consequently, *cine* substituted products were obtained. A third alternative is that the Heck-

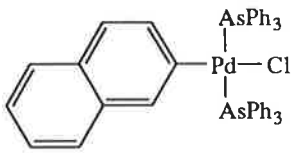
addition is somehow facilitated by the presence of a halide. Since the reaction's discovery lithium chloride has been found to be necessary in almost all Stille couplings of aryl and vinyl triflates with organostannanes in the presence of phosphine stabilised palladium catalysts, so our mechanistic proposal may be peculiar to catalysts stabilised by weakly donating ligands such as triphenylarsine.

On the basis of our results it is curious that Farina did not observe reaction of *p*-acetylphenyl triflate (**83**) with tributylvinylstannane in the absence of lithium chloride.[75] Perhaps this has something to do with the choice of solvent, N-methylpyrrolidinone, stabilising the cationic intermediate, although he suggests that a more polar solvent facilitates formation of the ion pair. Possibly the catalyst was unstable under those conditions. Lithium chloride was found to be unnecessary for the coupling of *vinyltriflates* and Farina used a similar rationale to the one we have proposed, on the basis of increased electrophilicity of a cationic palladium(II) intermediate relative to a covalent one, to explain this observation.[75]

For the reactions with $Pd(AsPh_3)_4$ in which lithium chloride had been added (*Table 3.2*, entries 2 & 5) the coupling of *p*-acetylphenyl triflate (**83**) resulted in substantially less *cine*-substitution than did the coupling of 2-naphthyl triflate (**81**). This is consistant with the proposal that the more electrophilic palladium(II) intermediate will transmetallate more effectively since *p*-acetylphenylpalladium(II) chloride (**174**) is presumably more electron deficient at palladium than is **175**.



174



175

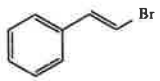
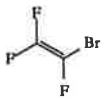
We can conclude that the effects of both lithium chloride and electron density of the aryl group have on product distribution imply the necessity of an electron deficient palladium(II) intermediate for successful transmetallation leading to *ipso*-substitution of the γ-stannylallylglycinate (**141**) in Stille coupling.

3.5.3. Coupling with vinyl halides.

On the basis of the conclusions drawn in *Part 3.5.2* with respect to electron density and the presence of halide, the reaction of vinyl halides with **141** could be expected to yield

substantial *cine*-substituted isomeric product in addition to the expected *ipso*-substitution. Indeed, this was the case (*Table 3.3*). *E*-β-Bromostyrene gave *predominantly* the *cine*-substituted *E,E*-δ-substituted product (**177**) and a minor amount of γ-styryl product (**176**) when reacted under our standard conditions (*Scheme 3.39*). Such a preference for *cine*-substitution was not observed for any other Stille reaction of **141**. Presumably, the adduct formed from oxidative addition (**182**) is quite electron rich at the palladium atom and hence

Table 3.3 Stille coupling between γ-tributylstannylallylglycinate (**141**) and vinyl halides

Entry	Substrate	Catalyst[a]	Time	% Yield[b]	Ratio of products[c]			
					γ	*E*-δ	γ-Ph (**148**)	*E*-δ-Ph (**149**)
1		A	15h	68	8 (**176**)	79 (**177**)	10	3
2		B[d]	3h	47	71	*nd*	29	*nd*
3		C	15h	91	100	*nd*	*nd*	*nd*
4[e]	 **84**	A	15h	70	65 (**178**) 10 (**179**)	18 (**180**) 7 (**181**)	*ni*	*ni*
5[f]		A[d]	6h	94[g]	44 26	22 8	*ni*	*ni*
6		A	24h[h]	0			*nd*	*nd*
7		A	15h[h]	0			*nd*	*nd*

Reactions carried out with 5mol% of catalyst in THF at reflux unless otherwise stated.

[a] A = $Pd(AsPh_3)_4$;
B = $Pd(AsPh_3)_4$ / Ag_2CO_3;
C = $PdCl_2(CH_3CN)_2$.

[b] Isolated yield.

[c] Ratio determined by ^1H nmr spectroscopy; *ni*=not isolated, *nd*=not detected; product numbers in parentheses.

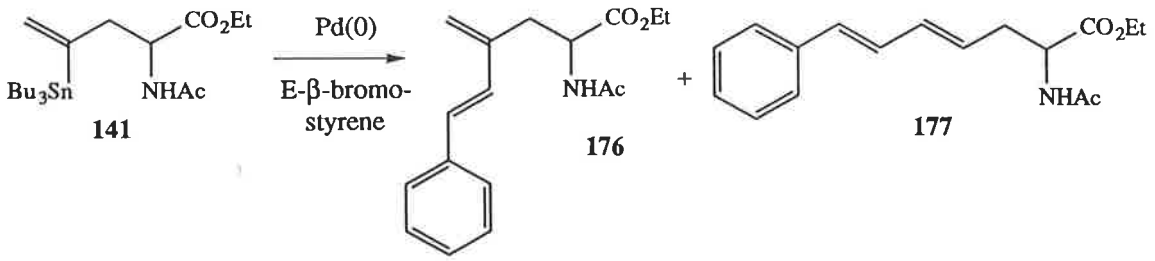
[d] Catalyst decomposed.

[e] Isolated vinyl iodide.

[f] Vinyl iodide reacted as crude reaction mixture: acetonitrile, acetic acid, lithium chloride.

[g] Based on recovered vinylstannane.

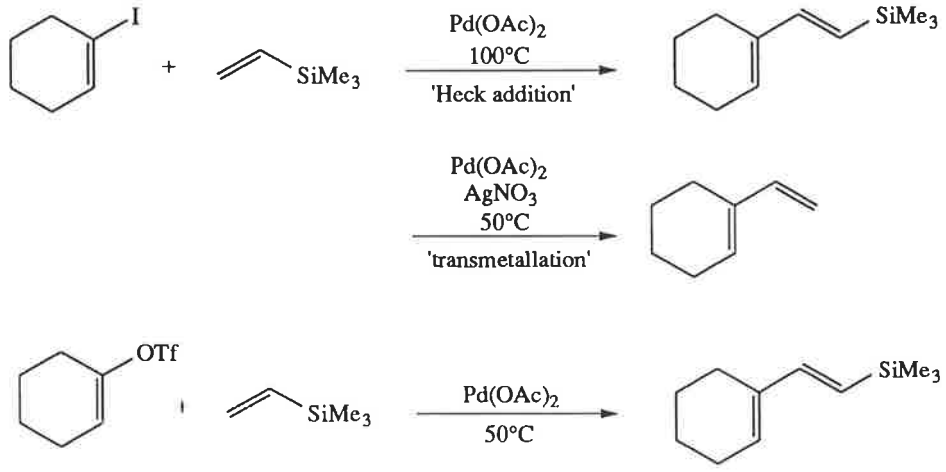
[h] Heated at 70-80° in sealed tube.



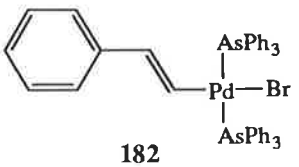
Scheme 3.39

Heck-addition products (*cine*-substitution) are favoured in relation to transmetallation ones.

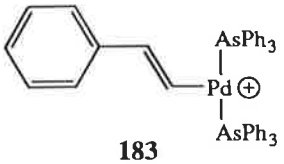
In an attempt to obtain more transmetallation product (*ipso*-substitution), the reaction was repeated in the presence of silver nitrate as a halide abstractor. This procedure has previously been used in Heck reactions of vinyl*silanes* with vinyl and aryl halides where unexpected transmetallation-like products were eliminated by the addition of silver salts (*Scheme 3.40*).[143,144] The corresponding Heck reactions of vinyl *triflates* with vinylsilanes did not give 'transmetallation' products, so similar ion pair palladium(II) complexes were proposed as intermediates of the two reactions.[144] Although we are unaware of any previous use of silver salts in *Stille* reactions we postulated that coupling of organohalides in the presence of silver(I) would lead mainly, or exclusively, to *ipso*-substitution because the cationic intermediate (*e.g.* **183**) would be more electrophilic than **182** and consequently would undergo transmetallation more efficiently. Thus reaction of *E*-β-bromostyrene with γ-stannane in the presence of $Pd(AsPh_3)_4$ and silver nitrate in THF at reflux resulted in decomposition of the catalyst to palladium black before total conversion of **141** was effected and gave a low yield of a mixture of γ-styryl and γ-phenyl products (**176** & **148**) (entry 2 and *Scheme 3.41*). No *cine* substituted products were observed. Again, **148** is formed by phenyl substitution from a



Scheme 3.40

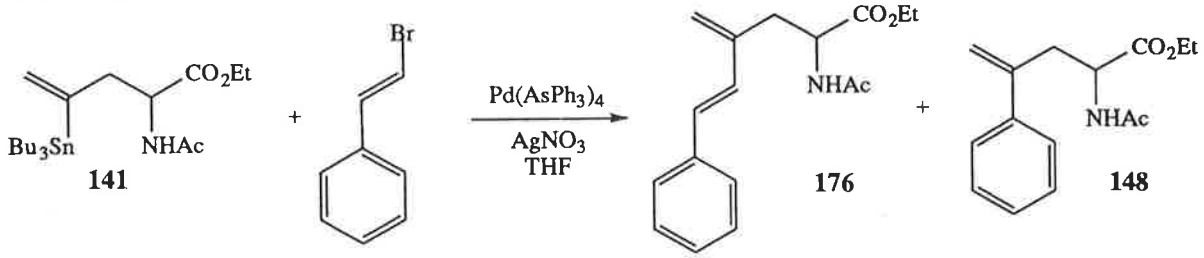


182



183

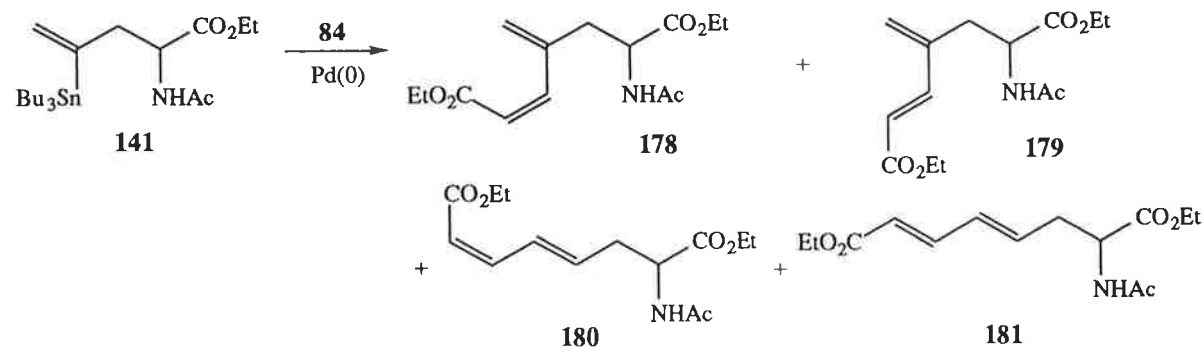
triphenylarsine ligand, a process independent of halide. This reaction shows that Heck addition to a vinylstannane can be suppressed by the addition of silver salts and confirms that halide bound to palladium(II) in the transition state is an important prerequisite for *cine*-substitution. However, catalyst instability may limit the utility of this process for reactions catalysed by $Pd(AsPh_3)_4$.



Scheme 3.41

Reaction of *E*-β-bromostyrene with **141** using the optimal conditions developed by Stille for vinylstannanes [$PdCl_2(CH_3CN)_2$, DMF, room temperature, entry 3][133] gave an excellent yield of the desired γ-styryl product (**176**). Although no study was made with this catalyst system with other substrates, it may well be preferable to other catalyst systems for the Stille reactions of organohalides with the γ-stannane (**141**).

Ethyl *Z*-2-iodoacrylate (**84**) reacted with **141** to yield two *ipso* (**178, 179**) and two *cine* substituted (**180, 181**) isomers (*Scheme 3.42*). These isomers were inseparable and were clearly assigned on the basis of their ^1H n.m.r. coupling constants. When the vinyliodide was prepared from ethyl propiolate (with lithium iodide and acetic acid in acetonitrile,[94] see *Chapter 2.3*) then the stannane and catalyst added to the crude reaction mixture, more *cine* (**180, 181**)



Scheme 3.42

and *ipso-E*-isomers (**179**) were obtained (entry 4) than when **84** was cleanly isolated beforehand (entry 5). The greater amount of *Z* to *E* isomerisation was presumably the effect of acetic acid in the Stille reaction mixture and the greater *cine*-substitution may have resulted from the effect of solvent (acetonitrile rather than THF) or from the presence of excess lithium iodide. Less *cine*-substitution occurred for reactions of **84** than of bromostyrene, possibly because the intermediate Pd(II) species is more electron deficient owing to the presence of the strongly π-electron withdrawing carboxyl group and consequently is better suited to transmetallation. Presumably, addition of silver nitrate to the reaction mixture or use of $PdCl_2(CH_3CN)_2$ as catalyst would have resulted in transmetallation becoming the predominant, or exclusive, pathway.

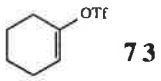
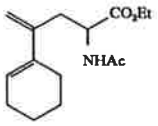
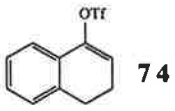
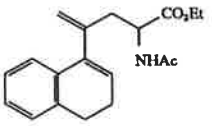
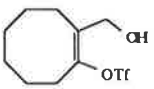
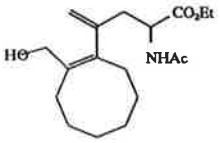
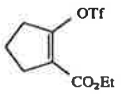
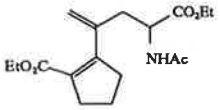
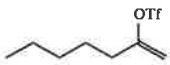
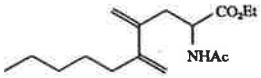
Reactions of both vinylbromide and trifluorovinylbromide (entries 5 & 6) produced no product. Even though the reactions were carried out in a sealed apparatus, the volatility and solubility of these reagents may be the reason for the unreactivity, since both are gases at atmospheric pressure and room temperature so their concentration in solution may have been too low.

3.5.4 Coupling with vinyl triflates.

Vinyl triflates proved to be very good substrates for the Stille reactions of the γ-stannane (**141**) (*Table 3.4*). All coupled successfully and stereospecifically in good to excellent yields with the $Pd(AsPh_3)_4$ catalyst in THF without the need for addition of lithium chloride. This result was expected based on our reactions of the aryl triflates and Farina's results for the reaction of vinyl triflates, although he found the necessity of a coordinating solvent (NMP) for reaction to take place.[75] Catalyst stability was excellent and the reaction mixtures remained clear and light yellow (the colour of the $Pd(AsPh_3)_4$ complex in solution) throughout the reaction. The reactive species in the transmetallation step is believed to be a strongly electrophilic cationic palladium(II) intermediate. No *cine*-substitution products were observed although in some instances small amounts of unidentified product were obtained, possibly double bond isomers.

The low yield of coupled product (**186**) for the reaction of hydroxymethylcyclooctenyl triflate (entry 3) may be due to the diminished reactivity of the Pd(II) intermediate towards transmetallation because of the weakly coordinating hydroxyl group.

Table 3.4. Stille coupling between γ-tributylstannylallyglycinate (**141**) and vinyl triflates

Entry	Substrate	Time	% Yield[a]	Product	
1	 **73**	2h	79[b]		**184**
2	 **74**	7h	98		**185**
3		15h	44[b]		**186**
4		6h	91		**187**
5	 **80**	6h	91[b]		**188**

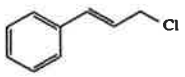
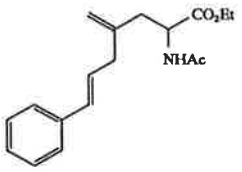
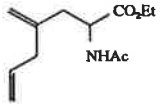
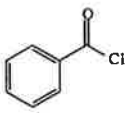
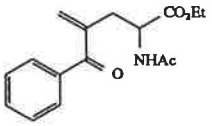
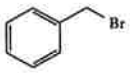
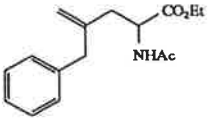
Reactions carried out with 5mol% of $Pd(AsPh_3)_4$ in THF at reflux.
[a] Isolated yield.
[b] Small quantity of unknown impurity present in sample.

3.5.5 Coupling with miscellaneous halides.

Reaction of some miscellaneous halides was also undertaken and the results were extremely satisfying (*Table 3.5*). Thus, reaction of allyl halides (cinnamyl chloride & allyl bromide), benzoyl chloride and benzyl bromide with the γ-stannane (**141**) gave the desired products from *ipso*-substitution in good to quantitative yields (1,4-dienes [**189** & **190**], α,β-unsaturated ketone [**169**] and γ-benzylallylglycinate [**191**]). No isomers resulting from double bond migration were observed by ^1H n.m.r. spectroscopy. The 1,4-dienes were clearly assigned by the presence of the doubly allylic methylene groups at δ2.97 and 2.70 respectively and the expected splitting pattern and *trans*-coupling between the C6 and C7 vinylic protons (*e.g.* **189**: δ6.20, *dt*, C6; **190**: δ5.70, *ddt*, C6).

Although these reactions were with halides, no products arising from *cine*-substitution were observed. Presumably the palladium(II) intermediates are more electron deficient than the corresponding vinyl and aryl intermediates, or as Farina stated,[75] 'transmetallation proceeds in

Table 3.5. Stille coupling between γ-tributylstannylallylglycinate (**141**) and miscellaneous organohalides

Entry	Substrate	Time	% Yield[a]	Product	
1		6h	99		**189**
2		15h	80		**190**
3		2h	69		**169**
4		1h	100		**191**

Reactions carried out with 5mol% of $Pd(AsPh_3)_4$ in THF at reflux.
[a] Isolated yields for single non-optimised runs.

a fundamentally unique fashion.' The π-allyl complexes formed from the allyl halides and the benzoylpalladium(II) chloride complex from benzoyl chloride would be quite electron deficient at the metal centre so transmetallation would be expected to predominate. Benzylpalladium(II) bromide is presumably more electron deficient than styrylpalladium(II) bromide (**182**), for instance, because of the absence of π-electrons on carbons bonded to palladium.

In order to prove that these Stille reactions were not occurring with concomitant racemisation at the α-centre, we repeated one of the reactions using the enantiomerically enriched γ-stannane (*L*-**141**). We chose the reaction of *p*-acetylphenyltriflate (**83**) with $Pd(AsPh_3)_4$ in the absence of lithium chloride (*Table 3.2*, entry 6) since this had given a clean product (**172**) with no unwanted isomers or by products. Thus, a ^1H n.m.r. shift experiment with $Eu(hfc)_3$ on the products of both racemic and chiral reaction products gave the spectra shown in *Figure 3.3*. The section of the spectra shown is of the peaks associated with the vinylic protons of the diastereotopic europium complexes. Clearly, the proportion of the *D*-enantiomer in '*L*'-**172** is about the same as it is in the starting material ('*L*'-**141**) (*Chapter 3.3*,

Figure 3.2), so we may safely conclude that these Stille reactions indeed proceed without significant racemisation at the α-centre.

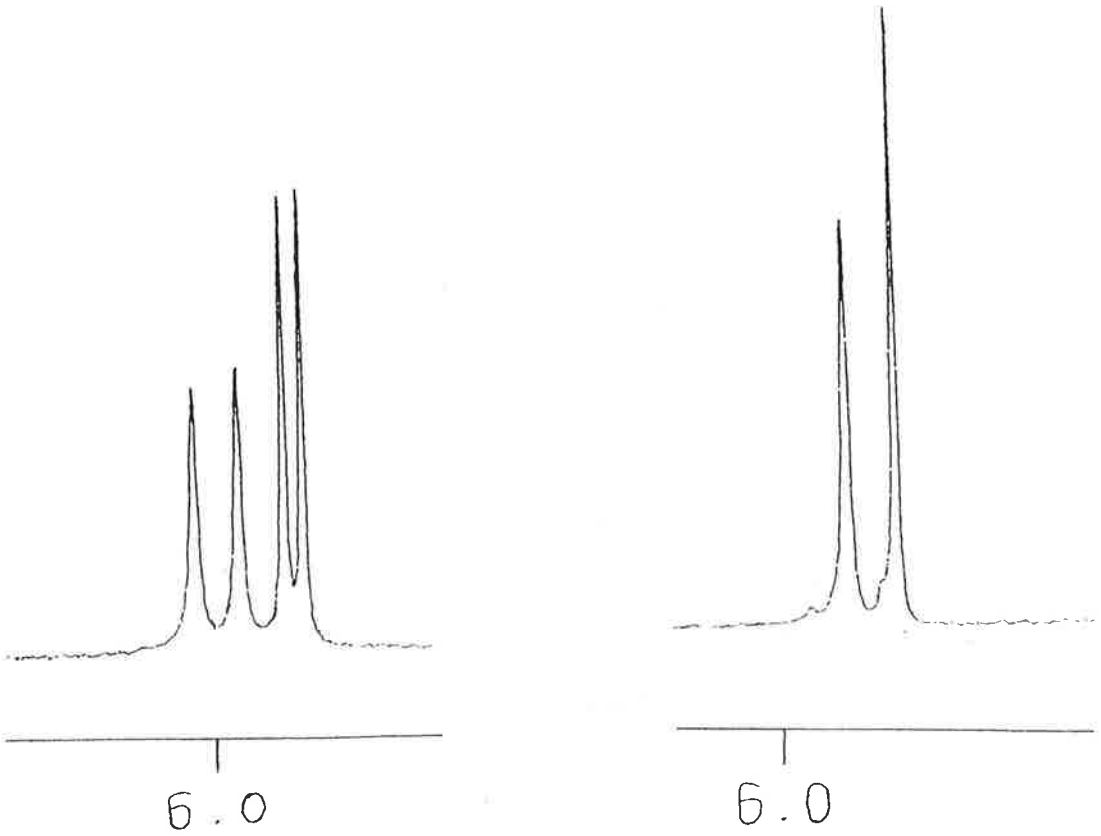


Figure 3.3. Eu(hfc)$_3$ ^{1}H n.m.r. experiment with racemic and chiral **172**. The portion of the spectrum shown is of the resonances of the terminal olefinic protons of the diastereomeric complexes.

To summarise the reactions of various organohalides and triflates, we noticed a number of interesting phenomena: (*a*) *cine*-substitution occurred, by Heck addition to the vinylstannane, for electron rich palladium(II) complexes more readily than for electron deficient ones; (*b*) *cine*-substitution could be supressed by addition of silver nitrate; (*c*) aryl and vinyl triflates coupled in the absence of lithium chloride; (*d*) triphenylarsine transferred a phenyl group in almost all reactions, but the product(s) (**148**, **149**, **150**) could be separated by chromatography in many instances. The reactions of vinyl triflates, allyl and benzyl halides and an acid chloride worked extremely well and only gave the expected, *ipso*-substituted γ-isomers. Reaction of vinyl and aryl halides require other catalyst systems for the best results. Aryl triflates gave *ipso*-substitution when reacted in the absence of lithium chloride, yet catalyst stability may be a problem in some of those cases. As expected, the reactions proceed without racemisation at the α-centre.

3.6 Stille coupling reactions of *E*-ethyl N-acetyl-δ-tributylstannylallylglycinate

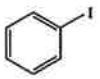
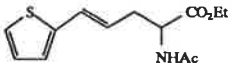
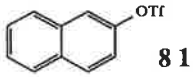
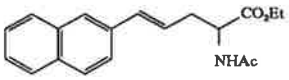
Stille coupling reactions were carried out on *E*-δ-tributylstannylallylglycinate (**138**) with a selection of the organohalides and triflates which had successfully coupled with the γ-stannane (**141**) (*Chapter 3.5*). All reactions were performed using 5mol% of the catalyst obtained by reacting tris(dibenzylideneacetone)dipalladium chloroform complex with triphenylarsine in THF [*i.e.* $Pd(AsPh_3)_4$]. Generally these reactions proceeded to give good to excellent, non-optimised yields of the expected *ipso*-substituted products (aryl alkenes, 1,3 and 1,4-dienes, *etc*).

3.6.1 Coupling with aryl halides and an aryl triflate.

The reaction with aryl halides (*Table 3.6*, entries 1 & 2) gave the desired coupled products (**149** & **153**) in good yields. The products were contaminated with 7 and 8% of their respective γ-isomers (**148** & **152**). These isomers were most likely formed by *ipso*-substitution of a small amount of γ-stannane (**141**) present in the sample of **138** as an impurity which had not been separated totally by flash chromatography. If the reason for *cine*-substitution of the γ-stannane (**141**) was because steric hindrance retarded the efficiency of transmetallation and hence Heck addition became a viable alternative process, we might expect that the less sterically encumbered *E*-δ-stannane (**138**) would be less likely to undergo *cine*-substitution. The ^1H n.m.r. spectra of the *E*-δ and γ-regioisomers were consistent with the proposed structures; the region between δ4.5 and 6.7ppm contained the clearest information about the isomers. Both **149** and **153** gave doublets with *trans* coupling constants (**149**: δ6.37, *J*15.7Hz; **153**: δ6.52, *J*15.6Hz) for their respective C5 protons, and doublets of triplets for the C4 protons (**149**: δ6.04, *J*7.4, 15.7Hz; **153**: δ5.83, *J*7.4, 15.6Hz). The corresponding γ-isomers (**148** & **152**) gave broad singlets for the two C5 protons in the region δ4.8-5.5ppm (see *Chapter 3.5.1*).

The only aryltriflate coupled was 2-naphthyl triflate (**81**) which was reacted both in the presence and absence of lithium chloride. With lithium chloride present the Stille reaction gave a low yield of coupled product (**171**) (entry 3). Even though the γ-stannane (**141**) reacted with two aryl triflates in the absence of lithium chloride, we were unsure whether **138** would react similarly under those conditions since this may have been due somehow to steric hindrance. However, **138** also reacted with **81** in the absence of lithium chloride and gave the product

Table 3.6 Stille coupling between *E*-δ-tributylstannylallyglycinate (**138**) and aryl halides and triflates

Entry	Substrate	Time	% Yield[a]	Product	
1		15h[b]	83[c]		**149**
2		3h	74[d]		**153**
3	 **81**	5h[e]	29[f]		**171**
4	"	4h	76	"	"

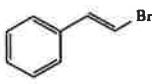
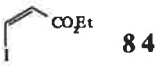
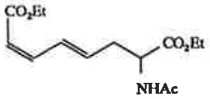
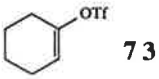
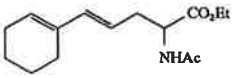
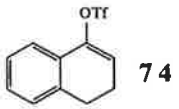
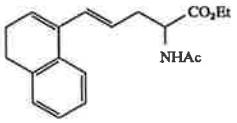
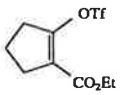
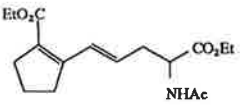
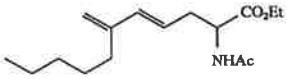
Reactions carried out with 5mol% of $Pd(AsPh_3)_4$ in THF at reflux unless otherwise stated.
[a] Isolated yield.
[b] Heated at 40° overnight then at reflux temperature for one hour.
[c] 92:8 mixture of *E*-δ:γ-isomers.
[d] 93:7 mixture of *E*-δ:γ-isomers.
[e] Heated at 50° in the presence of lithium chloride (2 eq).
[f] 95:5 mixture of *E*-δ:γ-isomers.

(**171**) in good yield (entry 4). The catalyst was not stable in this reaction and precipitated palladium black within two hours. However, this is an interesting result as it shows that Stille coupling of aryl triflates with quite sterically unencumbered vinylstannanes can occur without the addition of a halide source and may be quite general for a variety of stannanes, although catalyst instability may be a limiting factor in some reactions.

3.6.2 Coupling with vinyl halides and triflates.

Stille reactions of **138** with vinyl halides and triflates are summarised in *Table 3.7*. Reactions of *E*-β-bromostyrene and ethyl *Z*-2-iodoacrylate (**84**) (entries 1 and 2) gave good yields of the expected products from *ipso*-substitution (**177** & **180**), although the product obtained from reaction of *E*-β-bromostyrene contained a minor impurity of unknown composition (*ca* 5%, probably isomeric). These two vinyl halides were both compounds which had resulted in considerable *cine*-substitution in the corresponding coupling reactions of **141** (*Section 3.5.3*), but with **138** no *cine*-substituted products were observed. Iodoacrylate (**84**)

Table 3.7. Stille coupling between *E*-δ-tributylstannylallylglycinate (**138**) and vinyl halides and triflates

Entry	Substrate	Time	% Yield[a]	Product	
1		15h	75[b]		**177**
2	 **84**	45h[c]	84		**180**
3	 **73**	4h	47		**192**
4	 **74**	12h	53[d]		**193**
5		12h	93		**194**
6	 **80**	2h	58[e]		**195**

Reactions carried out with 5mol% of $Pd(AsPh_3)_4$ in THF at reflux unless otherwise stated.
[a] Isolated yield.
[b] *ca* 10% unknown isomeric product obtained.
[c] Room temperature.
[d] *ca* 90:10 mixture of *E*-δ:γ-isomers.
[e] *ca* 95:5 mixture of *E*-δ:γ-isomers.

was purified prior to its Stille reaction which occurred with **138** at *room temperature* over two days. Only the *E*,*Z*-isomer (**180**) was obtained. The partial *Z* to *E* isomerisation of the products from the coupling of **84** with **141** may have occurred because that coupling reaction had been carried out at reflux and was possibly a palladium catalysed process. That **84** coupled so readily with the *E*-δ-stannane at room temperature shows that **138** is quite reactive in Stille reactions which is consistent with the observation that no *cine*-substitution occurred for this vinylstannane.

The reactions with vinyl triflates gave moderate to excellent yields of the expected *E*-δ-substituted products (entries 3-6). Again, all these triflates reacted with **138** without the need

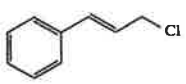
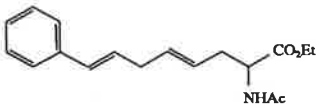
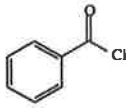
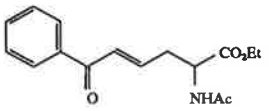
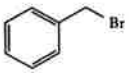
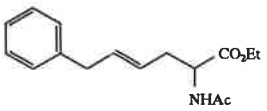
for the addition of lithium chloride. The ^{1}H n.m.r. spectra obtained for **193, 194** and **195** showed the presence of small amounts of their respective γ-isomers (**185, 187, 188**). Since *cine*-substitution was not observed in the reactions of organotriflates with the γ-stannane (**141**) in the absence of lithium chloride (*Parts 3.5.2* and *3.5.4*) it is unlikely that *cine*-substitution occurred with **138**, so γ-isomers were most likely the result of small amounts of γ-stannane present in the starting material undergoing *ipso*-substitution. No phenyl substituted product (**149**) was isolated from any of these reactions, but small quantities may have formed which were separated from the major products by chromatography.

3.6.3 Coupling with miscellaneous halides.

Reactions of cinnamyl chloride, benzoyl chloride and benzyl bromide with *E*-δ-stannane (**138**) (*Table 3.8*, entries 1, 2 & 3) yielded the expected *ipso*-substituted products (**196, 197** and **198**) in good to excellent yields using the standard conditions of 5mol% of $Pd(AsPh_3)_4$ in THF. Benzoyl chloride reacted with **138** under these conditions within minutes at room temperature. The intermediate benzoylpalladium(II) chloride must be extremely electrophilic and this allowed for mild Stille coupling conditions. The three products all contained a small amount of their corresponding γ-substituted products (**189, 169, 191**) which arose from reaction of a small amount of γ-stannane present in the sample of **141** since these halides had resulted only in *ipso*-substitution when coupled to **138**. No other double bond isomers were detected. The structures were assigned on the basis of the ^{1}H n.m.r. spectra: **196** gave the expected coupling pattern for the four vinylic protons (δ6.37, *d*, C8; 6.16, *dt*, C7; 5.59, *dt*, C5, 5.39, *dt*, C4) with two *E*-double bonds (*J*15.2 and 16.0Hz respectively) as well as the doubly allylic methylene as a triplet at δ2.90; **197** showed a doublet (δ6.95) and doublet of doublets (δ6.92) for the vinylic protons with a *trans* coupling constant (15.7Hz); and **198** was clearly no other double bond isomer since both vinylic protons appeared as doublets of triplets at δ5.67 and 5.40 with a *trans* coupling (15.1Hz) between the two.

The *E*-δ-tributylstannylallylglycinate (**138**) reacted with every halide and triflate studied to yield the desired products arising from *ipso*-substitution. Small amounts of γ-substituted products arose by *ipso*-substitution of a trace of γ-stannane (**141**) present in the sample of **138**

Table 3.8. Stille coupling between *E*-δ-tributylstannylallyglycinate (**138**) and miscellaneous organohalides

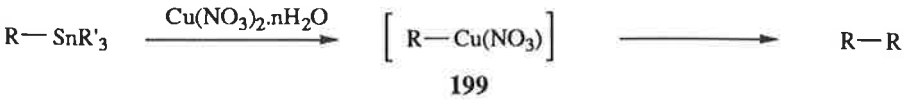
Entry	Substrate	Time	% Yield[a]	Product	
1		6h	96[b]		**196**
2		0.5h[c]	80[b]		**197**
3		1.5h	68[b]		**198**

Reactions carried out with 5mol% of $Pd(AsPh_3)_4$ in THF at reflux unless otherwise stated.
[a] Isolated yield.
[b] *ca* 95:5 mixture of *E*-δ:γ-isomers.
[c] Room temperature.

which had not been totally separated by chromatography. Yields of coupled products were generally good to excellent, making this reaction one of general use in the synthesis of unsaturated α-amino acid derivatives. The naphthyl triflate (**81**) and vinyl triflates coupled without the addition of lithium chloride, and this seems a general reaction when the coupling is carried out using $Pd(AsPh_3)_4$ as catalyst.

3.7 Copper(II) nitrate mediated dimerisation of stannylallylglycinates.

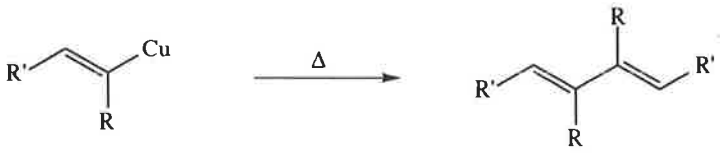
An interesting reaction of organostannanes is the homocoupling reaction which occurs in the presence of copper(II) nitrate (*Scheme 3.43*). This mild process, developed by Kyler, forms symmetrical dimerisation products resulting from carbon-carbon bond formation between the two *ipso*-carbons of the organostannane.[145] When applied to alkynylstannanes the reaction is an alternative to the somewhat similar copper mediated Glaser and Eglinton procedures for the synthesis of diynes.[146] However, Kyler's dimerisation reaction also yields symmetrical dienes and biaryls (*c.f.* the Ullmann reaction[147]) from vinyl and aryl stannanes respectively. The reaction has only been observed to proceed when mediated by copper(II) nitrate and requires the use of non-aqueous solvent even though copper nitrate *hydrate* is a suitable catalyst.[145]



Scheme 3.43

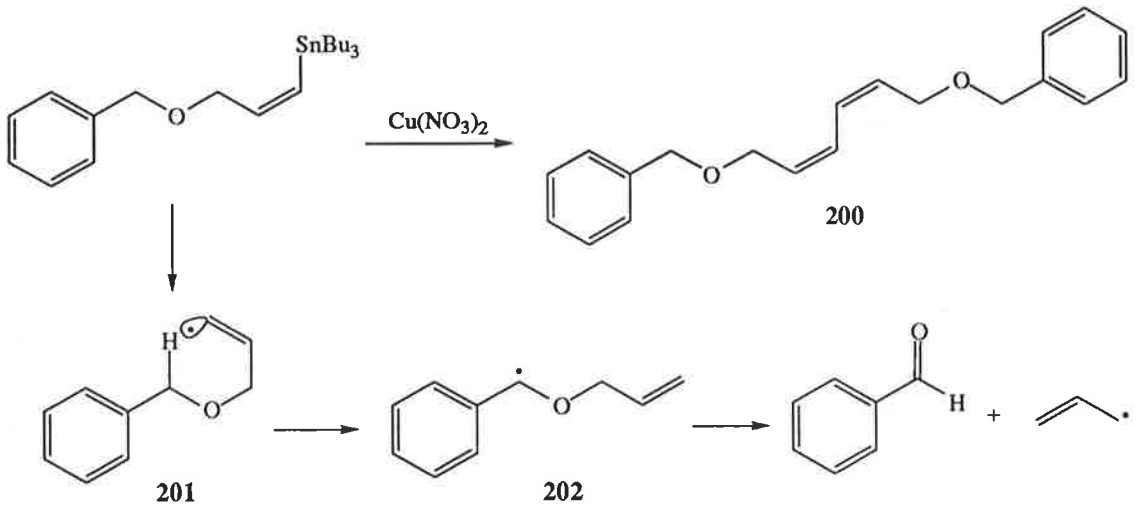
The mechanism of the dimerisation is still open to speculation, but is believed to proceed initially by a transmetallation of the organostannane by the copper(II) salt to form an organocopper(II) intermediate, **199**.[145] The accepted mechanisms of Glaser and Eglinton reactions assume the intermediacy of a copper acetylide which oxidises to an acetylenic radical then undergoes either radical-radical coupling or reaction with another molecule of copper acetylide to form the 1,3-diyne (*Scheme 3.44*). Whitesides, in a study of the thermal decomposition of vinyl copper(I) species to 1,3-dienes and copper metal (*Scheme 3.45*), a reaction which may be similar to the dimerisation of the vinylstannanes, ruled out the possibility of vinylic radicals as intermediates in those reactions by showing that they are not conformationally stable (*i.e.* both *E* and *Z*-2-bromo-2-butenes were reduced by tributyltin hydride to the same ratio of *E* and *Z*-but-2-enes), yet the corresponding vinyl copper(I) compounds dimerise stereospecifically.[148] He concluded that the most plausible mechanism for the thermal decomposition was the reaction between two molecules of vinyl copper(I) intermediate without the formation of any discrete radicals.[148] However, no definite transition state structure could be determined based on this information. Kyler has suggested that radicals may form in the copper mediated dimerisation of organostannanes because of the observation of hydrogen abstraction products in some instances, but accepts that Whitesides' results seem to disprove this mechanism for the reaction of vinylstannanes.[145] A point which was not considered by Kyler which seems to dismiss a vinylic radical intermediate is that the reaction of *Z*-benzyloxypropenylstannane proceeds to give a good yield of the *Z*,*Z*-1,3-diene (**200**), yet

Scheme 3.44



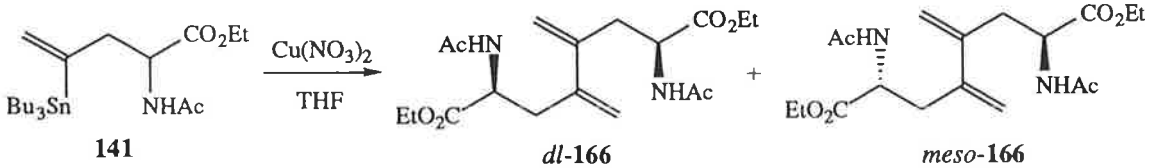
Scheme 3.45

the intermediacy of a long-lived *Z*-vinylic radical (**201**) in this reaction would most likely result in an intramolecular 1,6-hydrogen migration to form a stabilised benzylic radical (**202**) which may undergo β-scission to form benzaldehyde and allyl radical (*Scheme 3.46*). These are facile processes in radical chemistry.[149] This, as well as the documented conformational instability of vinyl radicals,[150] seems to rule out a free radical mechanism for the vinylstannane dimerisation reactions.



Scheme 3.46

We investigated this reaction with the γ and *E*-δ-tributylstannylallylglycinates (**138** & **141**) for the preparation of novel, conformationally restricted, symmetrical, unsaturated amino acid dimers. Thus reaction of the γ-stannane (**138**) with copper(II) nitrate hydrate in THF at room temperature for one hour gave a moderate yield of the diastereomeric homocoupled dienes as a *ca* 1:1 mixture of *dl* and *meso*-compounds (*dl* & *meso*-**166**) (*Scheme 3.47*). These diastereomers were inseparable by flash chromatography on silica gel and the ^{1}H n.m.r. spectrum of the mixture showed four singlets for the terminal olefinic hydrogens, two singlets for each diastereomer at δ4.94, 4.98, 5.17 and 5.19. The olefinic region of this spectrum is shown in *Figure 3.4*. In order to show that this reaction did not proceed with any racemisation at the α-centre, the enantiomerically enriched γ-stannane (*L*-**141**) was subjected to similar reaction conditions. An optically active product was obtained and ^{1}H n.m.r. showed this to be



141 *dl*-**166** *meso*-**166**

Scheme 3.47

predominantly the one diastereomer which was clearly *S,S*-**166**. Since the amount of *D*-**141** present in the sample of *L*-**141** was small, statistically we would expect the proportion of *meso*-dimer (*meso*-**166**) present in the product mixture to be approximately twice this fraction (*i.e.* we obtained *ca* 5% *meso*-**166** from *ca* 2.5% *D*-**141**).

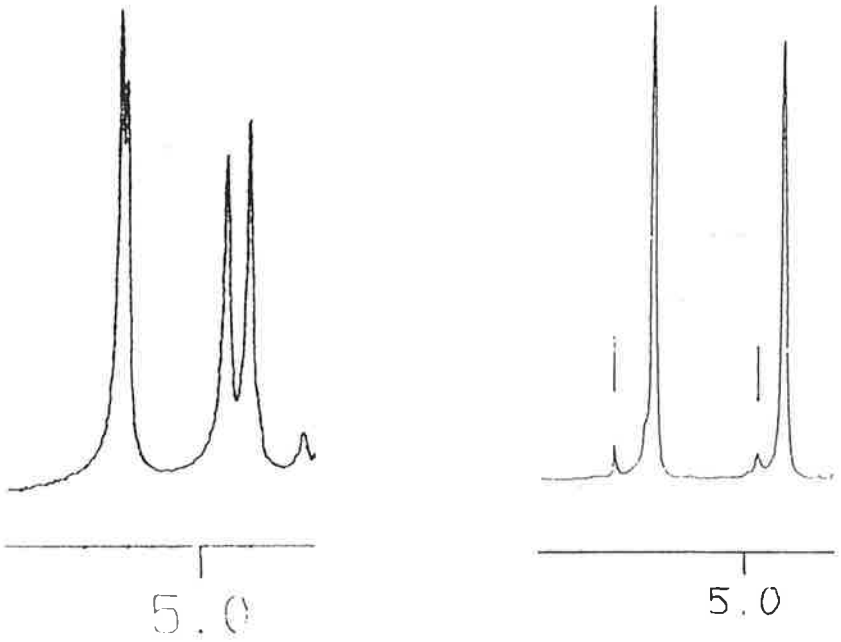
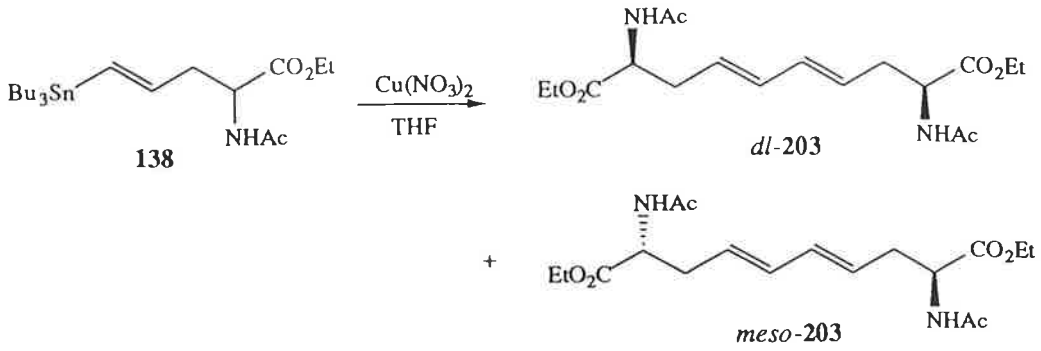


Figure 3.4. ^{1}H n.m.r. spectra of the diastereomeric dimers (*meso* & *dl*-**166**) obtained by copper nitrate catalysed dimerisations of racemic and enantiomerically enriched vinylstannanes **141**. The region shown is that of the vinylic proton resonances.

The corresponding reaction with the *E*-δ-stannane (**138**) was carried out under similar conditions to those described above (*Scheme 3.48*). This time a low yield of *E,E*-dimers (*dl* & *meso*-**203**) was obtained and gave a complex ^{1}H n.m.r. spectrum from which it was not possible to determine the diastereomeric ratio of products, but presumably it was *ca* 1:1 (*dl*:*meso*), since the effects of the chiral centre three carbons removed from, and *trans* to, the site of bond formation would be negligible. As a consequence, the effects of the chiral centres on the relative chemical shifts of the protons of the two diastereomers in the ^{1}H n.m.r. spectum would be insignificant and not surprisingly the diastereomers were not resolved. When repeated with enantiomerically enriched *E*-δ-stannane (*L*-**138**) an optically active product was obtained (*S,S*-**203**) which also gave a complex ^{1}H n.m.r. spectrum. Although *S,S*-**203** has a C2 axis of symmetry, carbons 4 and 7 as well as 5 and 6 are not *magnetically* equivalent and



Scheme 3.48

hence second order splitting patterns are observed (*Figure 3.5*). This is an example of an AA'XX' coupling system.[151] The ^{13}C n.m.r. spectra of both *S,S*-**166** and *S,S*-**203** were consistent with the degree of symmetry present in those molecules (five aliphatic, two olefinic and two carbonyl signals).

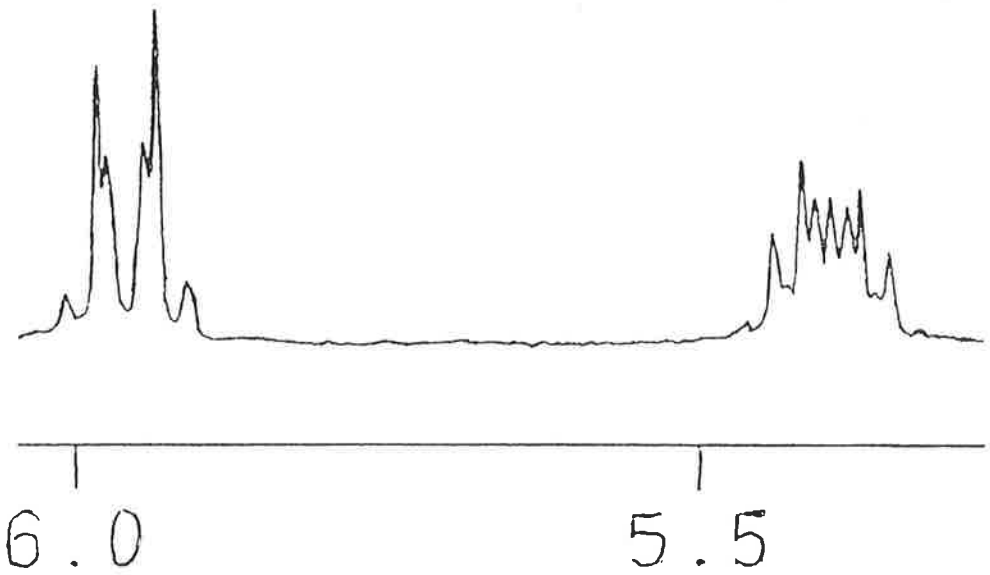


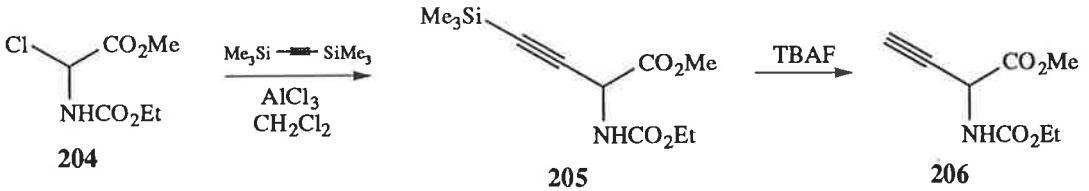
Figure 3.5. ^{1}H n.m.r. spectrum of the dimer *S,S*-**203** obtained by copper nitrate catalysed dimerisation of enantiomerically enriched vinylstannane **138**. The region shown is that of the vinylic proton resonances and displays a AA'XX' coupling system.

3.8 An attempted route to stannylated vinylglycine derivatives.

Obtaining vinylglycine derivatives substituted on the double bond by a tributylstannyl moiety was a more difficult task than was forming analogous allylglycine derivatives. The hydrostannation route required an ethynylglycine derivative and, as mentioned in the introduction, such compounds have rarely been synthesised. We utilised Metcalf's

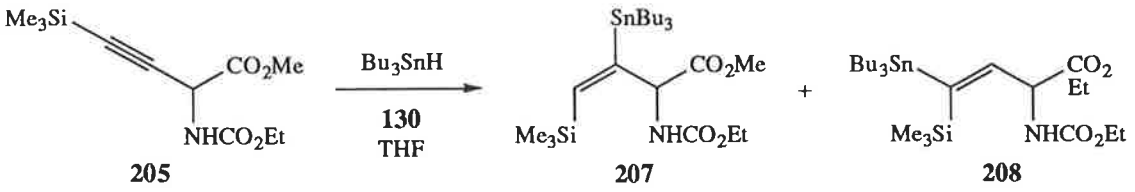
alkynylation of an α-chloroglycine derivative as the chosen route.[24c,d] A number of ethynylglycine derivatives are reported as having been synthesised using this procedure.

Methyl N-carboethoxy-α-chloroglycinate (**204**) was prepared from urethane and glyoxylic acid hydrate in good yield in three steps following a literature procedure.[152] Friedel-Crafts alkynylation of **204** with bis(trimethylsilyl)acetylene in the presence of aluminium chloride in dichloromethane followed by extractive workup and distillation produced the trimethylsilylethynylglycine derivative (**205**) (*Scheme 3.49*). This compound was unstable to chromatography on silica gel 60. Attempted desilation of **205** using the conditions reported by Williams, reaction with TBAF in THF at -78° followed by an acidic quench at that temperature,[24a] resulted in complete consumption of the trimethylsilylalkyne (**205**) within minutes, but no desilated product (**206**) was isolated either by chromatography or distillation. A ^{1}H n.m.r. spectrum of the crude product showed no sign of the ethynylglycine (**206**). Williams had prepared a number of ethynylglycine derivatives using this procedure,[24a] so it is not known why we were unable to obtain **206**. We did not pursue the synthesis of a desilated ethynylglycine derivative beyond this point, but presumably the use of suitable amino and carboxylate protecting groups may permit the formation of such a compound by this attractive route.



Scheme 3.49

Although we were unable to obtain a desilated ethynylglycine derivative we investigated hydrostannation of **205**. Under radical conditions, a complex mixture of products was obtained with much decomposition. No vinylstannanes were isolated. Palladium catalysed hydrostannation using $Pd(PPh_3)_4$ yielded no product and only starting materials were observed by t.l.c. This is perhaps not unexpected since hydrostannation of trimethylsilylalkynes has not been reported to occur under palladium(0) catalysis.[109] However, molybdenum complex **130** has been shown to catalyse those reactions effectively.[109] Thus, reaction of **205** in THF at reflux in the presence of **130** and tributyltin hydride yielded two new products in an otherwise clean reaction mixture (*Scheme 3.50*). The molybdenum catalyst, which did not appear to



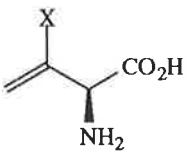
Scheme 3.50

convert tin hydride to hexabutylditin, eventually decomposed. The two new products were isolated by flash chromatography and were found to be the regioisomers **207** and **208** in yields of 23 and 16% respectively. The structures were assigned based on the splitting pattern of the vinylic and α-hydrogens in the ^{1}H n.m.r. spectra. For **207** the vinylic proton resonated as a singlet with tin satellites (*J*87.9Hz) and the α-proton as a broad doublet (coupled to NH). **208** gave a doublet with satellites (*J*98.6Hz) and a multiplet for its vinylic and α-protons respectively. The stereochemistry was tentatively assigned as depicted based on the expected *syn*-addition of tin and hydrogen. Mitchell has reported the preparation of 1-trimethylsilyl-1-trimethylstannyl-1-alkenes and 1-trimethylsilyl-2-trimethylstannyl-1-alkenes by a number of procedures.[153]

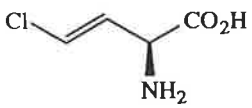
Although these are interesting compounds we did not investigate their reactivity in iododestannylation, iododesilation or Stille coupling reactions.

Iodoallylglycine derivatives. Synthesis and reactivity

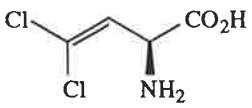
Vinyl halides, and in particular vinyl iodides, are probably the most versatile functional groups in terms of the number of different palladium catalysed reactions in which they participate.[54] Vinyl bromides are slightly less reactive, but participate in most of the same reactions.[54] Vinyl triflates have, in recent years, become increasingly popular as alternatives and/or complements to halides[128] and are in some instances more easily prepared.[55] We wished to prepare amino acid derivatives which incorporated a vinyl iodide or vinyl triflate functional group in the α-side chain. A number of halogenated vinyl and allylglycine derivatives have been reported in the literature. These include β-chloro, fluoro and bromo vinylglycines (**8**),[17] *E*-δ-chlorovinylglycine (**209**),[154] γ,γ-dichlorovinylglycine (210),[155] β,γ,γ-trifluorovinylglycine (**211**)[32] and γ-substituted-γ-iodovinylglycines (**212**).[24a] Allylglycines substituted by halogens include γ-chloro and bromoallylglycines (**10**)[19] and γ-methyl-δ,δ-dichloroallylglycines (**213**).[156] These unsaturated α-amino acids have mostly been prepared as potentially biologically active molecules rather than as synthetic intermediates, although Leanna has recently reported bromoallylglycine derivative (**214**) as a versatile reagent which underwent a number of transformations of the α-side chain including some transition metal catalysed reactions (Stille and Suzuki coupling, carbomethoxylation).[68] Bromo and chloroallylglycines have also been utilised in the synthesis of small peptides which act as renin inhibitors.[157]



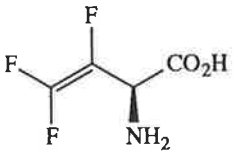
8



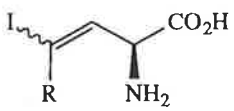
209



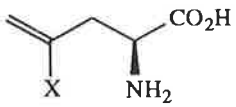
210



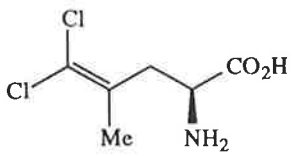
211



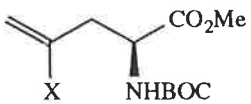
212



10



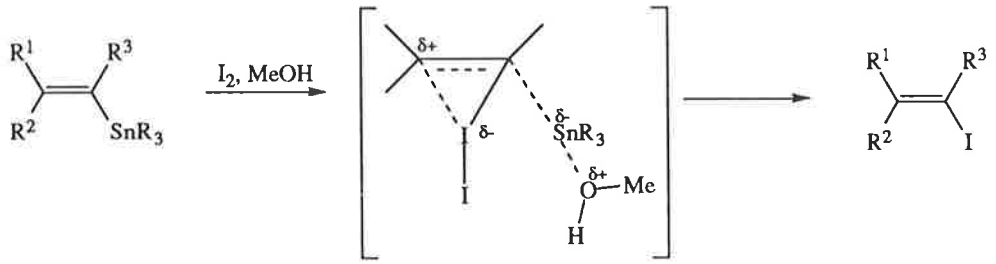
213



214

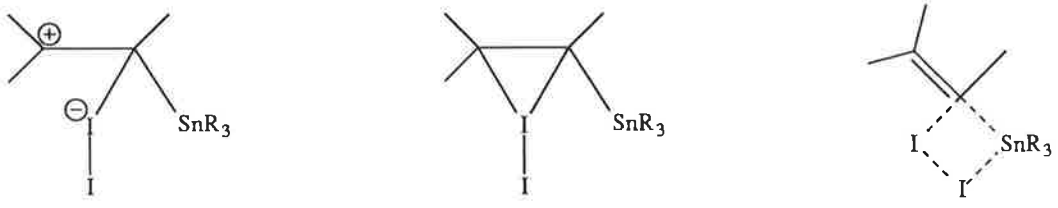
Vinyl iodides are commonly prepared by a number of methods. These include (*a*) the stereospecific reaction of iodine with vinyl organometallic species (commonly alkyne hydrostannation,[100] hydroalumination[158] and hydroboration[159] adducts); (*b*) the addition of hydrogen iodide to alkynes (generally non-stereoselective);[160] (*c*) the non-stereoselective reaction of ketone hydrazones with iodine and base;[161] (*d*) the reaction of ketones with iodoform and chromium(II) chloride[162] and (*e*) Wittig reactions of halomethylene triphenylphosphoranes with aldehydes and ketones.[163] Since we had been able to prepare and cleanly separate the γ and *E*-δ-tributylstannylallylglycinates (**141** & **138**), these seemed logical precursors to the corresponding isomerically pure vinyl iodides.

The reaction of vinylstannanes with electrophiles generally occurs with retention of olefin stereochemistry.[100] A number of electrophiles have been used, such as halogens (Br_2, I_2, NBS), protons (AcOH, HCl, silica gel) and nitro compounds. A commonly cited mechanism for iododestannylation is that which Nasielski proposed to occur *via* an intermediate (**215**), somewhere between the two extremes of the open (**216**) and closed (**217**) transition states (*Scheme 4.1*).[164] Increased substitution at the β-carbon atom (by R^1 and R^2 = alkyl) increased the rate of iododestannylation consistent with the open transition state featuring a positively charge centred at the β-carbon. However, this discrete intermediate (**216**, S_E1 mechanism) was disregarded on the basis that free rotation would occur about the α,β-bond and stereospecificity would not result. The three membered cyclic closed transition state (**217**) would explain the observed stereospecificity, but is inconsistent with the observed rate increase



215

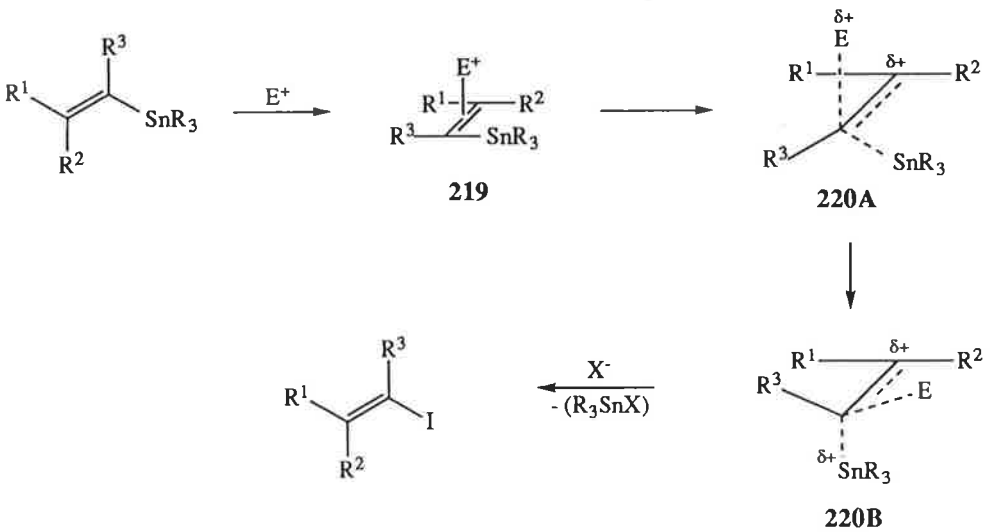
Scheme 4.1



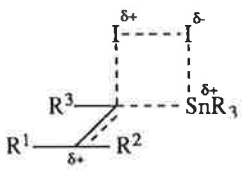
216 **217** **218**

with substitution at the β-carbon. Nasielski ruled out the possibility of a four centred transition state such as **218** for the same reason.[164]

The formation of a three membered intermediate in order to retain double bond configuration seems unnecessary when *proto*destannylation is considered. These reactions also occur stereospecifically, yet no closed transition state such as **215** or **217** is possible. Cochran has suggested an S_E2 mechanism to explain this result (*Scheme 4.2*).[165] The electrophile (*e.g.* proton, iodine) coordinates initially to the π-electrons of the carbon-carbon double bond (**219**); carbon-electrophile bond formation occurs to form **220A** with conconcurrent carbon-tin bond cleavage. Positive charge build up at the β-carbon is partially hyperconjugatively stabilised by the overlap with the carbon-tin bond (the β-effect) and bond formation and breakage continues with rotation about the α,β-carbon-carbon bond to maximise this effect (forming **220B**). The destannylated product is formed by counter ion assisted elimination of R_3SnX (X=halogen, *etc*). At no time does free rotation occur about the carbon-carbon bond so the product retains the initial stereochemistry of the vinylstannane. For the reaction in which iodine acts as the electrophile, a four centred intermediate (**221**) with partial charge build up on the β-carbon seems a likely transition state.



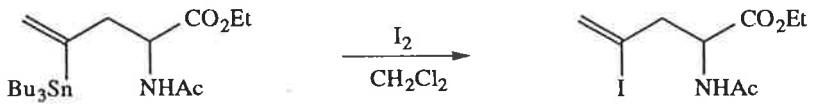
Scheme 4.2



221

4.1 Formation of iodoallylglycine derivatives by iododestannylation of tributylstannylallylglycinates.

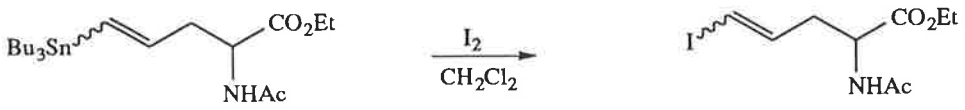
Addition of an equivalent or slight excess of iodine to a dichloromethane solution of γ-stannylallylglycinate (**141**) resulted in the complete consumption of the vinylstannane within 45 minutes and clean formation of vinyl iodide (**222**) and tributyltin iodide (*Scheme 4.3*). γ-Iodoallylglycine derivative (**222**) was obtained as an oil in 82% yield after an aqueous fluoride wash (to convert tributyltin iodide to the polymeric tributyltin fluoride)[166] and chromatography on silica gel. This compound (**222**) was air stable and could be distilled at high temperature (*ca* 200°/0.02mm) without significant decomposition, although some discolouration to pale orange occurred upon standing for a few days, but without noticable decomposition by t.l.c. and ^{1}H n.m.r. spectroscopy.



141 **222**

Scheme 4.3

The *E* and *Z*-δ-stannylallylglycinates (**138** & **139**) were reacted under the same conditions: *E*-δ-tributylstannylallylglycinate (**138**) (obtained from the palladium catalysed hydrostannation) gave only the *E*-δ-vinyl iodide (**223**) in 84% yield (*Scheme 4.4*), another clear, viscous, stable oil which discoloured slightly to pale orange upon standing . Reaction of the δ-stannane mixture obtained from AIBN initiated radical addition (an 88:12 ratio of **138** to **139**) gave an 84:16 mixture of **223** and **224**, and the 58:42 mixture of vinylstannanes obtained from tributylborane initiated reaction gave a 57:43 ratio of vinyl iodides. These results clearly indicate the regio and stereospecificity of the reactions. The vinyl iodides, **223** and **224**, were, like their corresponding stannanes, inseparable by silica gel chromatography and attempts at isomerising the 84:16 mixture totally to the thermodynamically more stable *E*-isomer through high temperature distillation or reaction with either iodine and hydroiodic acid were



138, 139 **223, 224**

Scheme 4.4

unsuccessful. Thus, we were unable to obtain pure samples of **223** or **224** from the iododestannylation of the radical hydrostannation adducts (**138** & **139**). However, we were able to prepare the racemic *E*-δ-iodide (**223**) and γ-iodide (**222**) as pure regioisomers by iododestannylation of the palladium catalysed hydrostannation adducts (**138** and **141**).

In order to determine whether the iododestannylation reactions resulted in any racemisation at the α-centre, the enantiomerically enriched *E*-δ and γ-stannanylallylglycinates (*L*-**138** & *L*-**141**) were reacted separately with iodine. Both products (*L*-**223** & *L*-**222**) were optically active and a $Eu(hfc)_3$ ^1H n.m.r. shift experiment with racemic and chiral **222** proved that little or no racemisation had occurred (*Figure 4.1*).

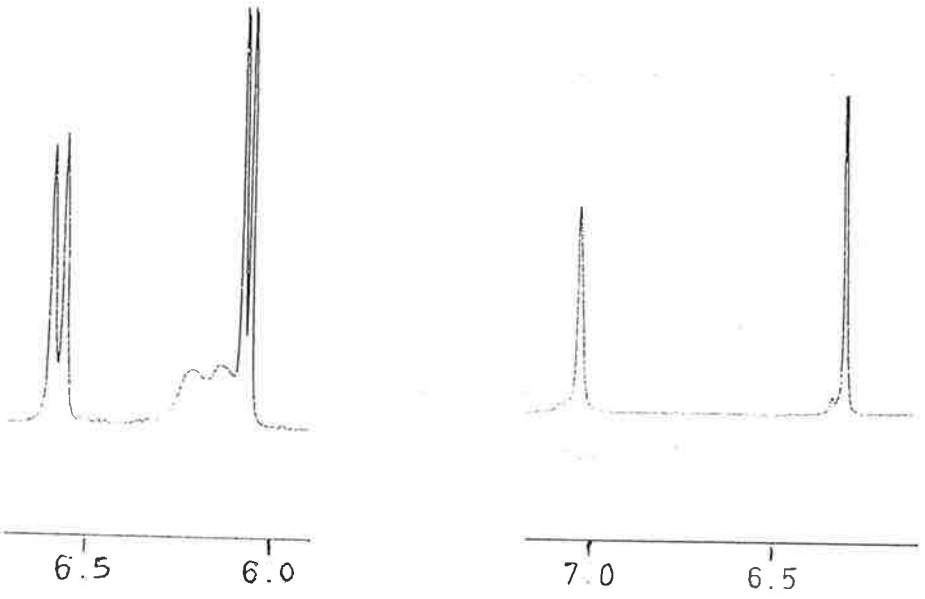
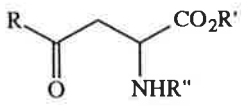


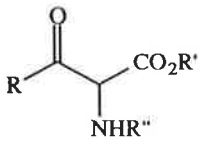
Figure 4.1. $Eu(hfc)_3$ ^1H n.m.r. experiment with racemic and chiral **222**. The portion of the spectrum shown is of the resonances of the terminal olefinic protons of the diastereomeric complexes.

4.2 An attempted route to a trifloxyallylglycine derivative.

Vinyl triflates are commonly prepared from ketones and, to a lesser extent, aldehydes by the action of base and a triflating agent (see *Chapter 2.3*).[55] This procedure often occurs regio and stereoselectively. If this procedure were applied to the synthesis of vinyl and allylglycine derivatives, precursors such as **225** and **226** would be required. However, we did not persue this route because of the possibility of reactions of amino and carboxyl protecting groups, as well as the possibilities of racemisation and double bond migration under the basic reaction conditions. Another method for vinyl triflate formation is the Markovnikov



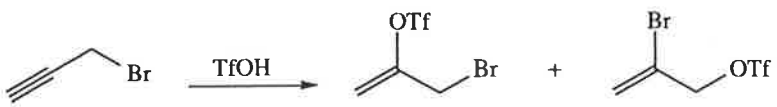
225



226

addition of triflic acid to a terminal alkyne in which the α-adduct is preferentially formed.[55] Initial attempts at using this method of triflation with both the propargylmalonate (**118**) and propargylglycinate (**121**) derivatives not surprisingly resulted only in decomposition.

We believed that an allylating reagent substituted by a trifloxy group on the double bond would be an interesing reagent to prepare. Such a compound would be structurally similar to the commercially available 1,3 and 2,3-dihalopropenes and would theoretically be a convenient precursor to a number of vinyl triflates and in particular a triflated allylglycine derivative *via* alkylation of the sodium salt of diethylacetamidomalonate with subsequent decarboethoxylation. Indeed, this is similar to the route used by Leanna for the preparation of the γ-bromoallylglycine derivative, **214**.[68] We believed that Markovnikov addition of triflic acid to propargyl bromide would be an expeditious route to a vinyl triflate allylating reagent (**227**). The reaction was attemped in a number of solvents (pentane, dichloromethane, chloroform), and also without solvent, and the result was the formation of two products in low to moderate yield and in varying ratios: the expected vinyl triflate (**227**) and the isomeric vinylbromide (**228**) (*Scheme 4.5*). These two isomers were characterised by their ^{1}H n.m.r. spectra in which both the allylic singlet and vinylic doublets were positioned upfield for **227** relative to **228**. Much discoloration occured in these reactions and presumably polymeric products were also obtained. The yield of the two isomers was optimised to 53% by adding propargyl bromide to a triflic acid solution in chloroform, avoiding an aqueous acid or base wash and directly distilling the crude mixture. However, this yielded the vinyl bromide (**228**) as the major product. The yield and ratio of isomers was very much dependent on the reaction conditions.

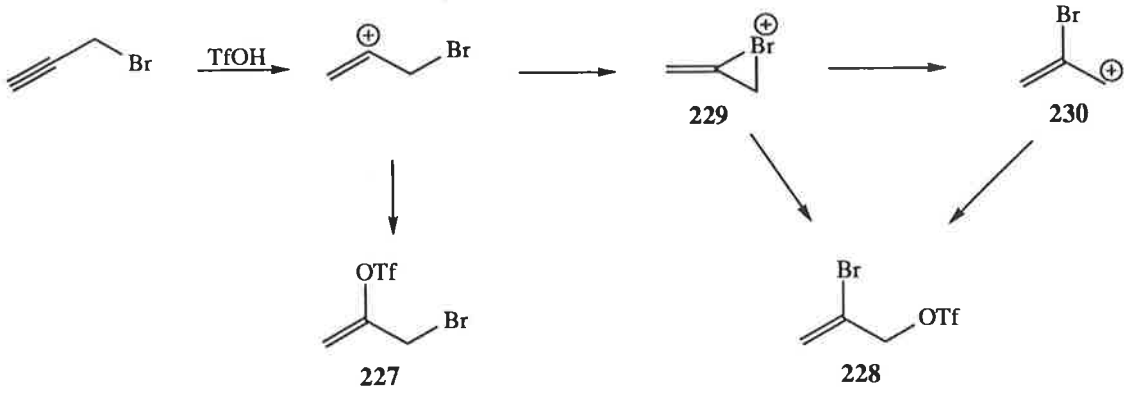


227 228

Scheme 4.5

Presumably **228** arose from an intermediate bromonium ion (**229**) or allyl cation (**230**) which forms after protonation of the triple bond and intramolecular attack by the bromine atom

on the vinyl cation (*Scheme 4.6*). The allylic carbon of **229** or **230** is subsequently attacked by the triflate anion to yield the allyl triflate. The vinyl triflate (**227**) is probably formed by triflate anion addition to the vinyl cation.



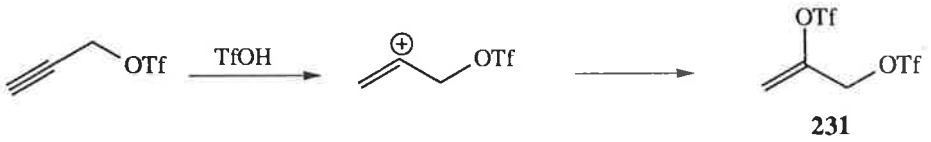
Scheme 4.6

The reaction was repeated in deuteriochloroform with various amounts of triflic acid (between 0.5 and 2.0 equivalents) and monitored by ^{1}H n.m.r. This showed that the formation of the unwanted isomer (**228**) occurred at a rate similar to that of the vinyl triflate (**227**) (constant ratio of *ca* 57:43, unchanged over time) and the ratio of products was independent of triflate concentration. It was confirmed that **228** was not formed by acid catalysed isomerisation of **227** by treating the purified vinyl triflate with triflic acid in an n.m.r. tube from which some discoloration and presumably polymerisation occurred, but no vinylbromide was detected. Curiously, the n.m.r. tube experiments gave very clean spectra and only minor traces of other products were observed even though the solutions were black and opaque.

Allyl triflates are extremely electrophilic and react rapidly with pyridine at room temperature to form N-allylpyridinium triflate salts whereas allyl bromides are stable under similar conditions.[167] We were able to utilise this reactivity as a means of separating the mixture of the vinylbromide. Thus, addition of pyridine to the reaction mixture, as a means of destroying **228** as well as quenching excess triflic acid, then an aqueous wash to remove pyridinium salts and distillation of the residue resulted in a low yield (17%) of desired 3-bromo-2-(trifluoromethanesulphonyloxy)prop-1-ene (**227**). Even though the yield was poor, large quantities of **227** were obtained because of the ease of preparation and the ready availability of the reagents.

We envisaged that an alternative to the formation of the unwanted isomer was to attempt the reaction of propargyl *triflate* with triflic acid. In this case, addition of triflate anion to either

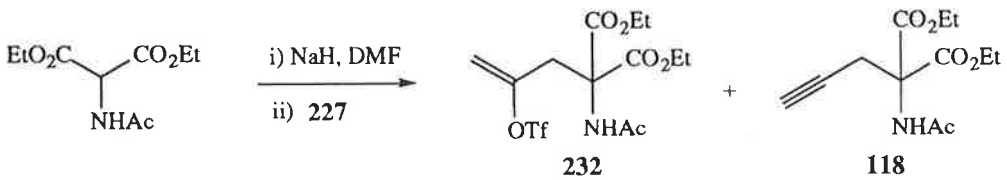
a vinyl or allyl cation would theoretically form the same product (**231**) (*Scheme 4.7*). Propargyl triflate was prepared from propargyl alcohol according to a literature procedure.[167] Interestingly, propargyl triflate was resistant to triflic acid and no product could be observed in an n.m.r. tube experiment. No intermediate cationic intermediate was observed, and addition of tetraethylammonium bromide to the reaction in an attempt to react any transient carbocation merely led to conversion of propargyl triflate to propargyl bromide. Perhaps the very strong inductive electron withdrawing ability of the trifluoromethanesulphonate group significantly reduces the electron density of the acetylene and disfavours protonation, or that the sulphonyl group preferentially protonates. The latter case is unlikely since the trifluoromethane sulphonate moiety is amongst the poorest of bases, and such a protonated sulphonate would presumably protonate the alkyne intramolecularly.



231

Scheme 4.7

Alkylation of the sodium salt of diethylacetamidomalonate with **227** in DMF at ambient temperature for 4 hours furnished a low yield of the desired vinyl triflate (**232**) as well as appreciable quantities of the propargylmalonate derivative (**118**) (*Scheme 4.8*). These products were difficult to separate by chromatography on silica gel owing to their similar R_f's, but it was possible to remove the last traces of **118** by fractional recrystallisation. Presumably **118** was formed by elimination of triflic acid from either the allylating agent (**227**) or the alkylated product (**232**) in the presence of the sodium salt of diethylacetamidomalonate. We were unable to avoid the formation of **118** and coupled with the low yield of vinyl triflate (**232**) and the difficulty in separating the two we decided to abort this route to a trifloxyallylglycine derivative. We had prepared the vinyl iodides (**222** & **223**) very easily in the meantime so these were invesigated as substrates for a number of common palladium catalysed processes, nameiy Heck, Stille and terminal alkyne coupling and carboethoxylation reactions.



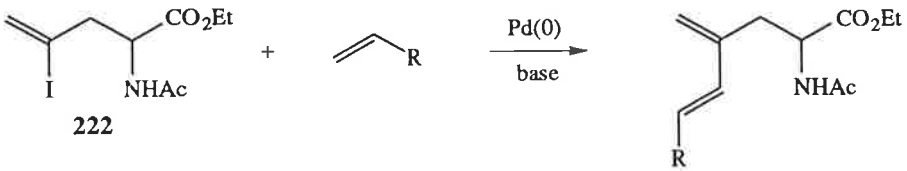
232 **118**

Scheme 4.8

4.3 Heck reactions of ethyl N-acetyl-γ-iodoallylglycinate

As part of our study of the reactivity of the two vinyl iodides (**222** & **223**) we investigated their reactivity in Heck coupling with a number of alkenes. We had hoped that these Heck reactions would be a more general method for the formation of unsaturated amino acid derivatives than were the Heck couplings of the two vinylglycine derivatives (**59** & **71**) investigated in *Chapter 2*, since **222** and **223** could theoretically couple with many *activated* alkenes under a variety of catalyst systems. This method may be an expedient route to a number of dienes which are difficult to prepare *via* Stille coupling methodology of either vinyl stannanes (**141** & **138**) or vinyliodides (**222** & **223**) because the halide, triflate or stannane coupling partners are relatively inaccessible. Nevertheless, the different methods are alternatives and we wished to investigate the complementary nature of the processes and their relative scopes and limitations. The proposed and generally accepted mechanism of the Heck reaction was discussed in *Chapter 2.1*.

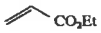
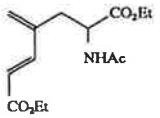
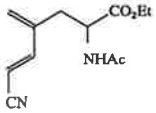
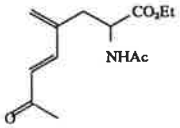
Reactions of the general type as shown in *Scheme 4.9* were investigated. The alkenes chosen as coupling partners were the electron deficient ethyl acrylate, acrylonitrile and methyl vinyl ketone. Ethyl acrylate was investigated as a model alkene (*Table 4.1*, entries 1-4). Using the Jeffery conditions (entry 1), similar to those which had proven effective for the coupling of the vinylglycine derivatives (**59** & **71**) with vinyl triflates, all the vinyl iodide (**222**) was consumed but only a low yield of coupled product (**179**) was obtained. The use of the traditional Heck catalyst system (entry 2) gave a more stable catalyst and a higher yield. The product (**179**) gave an identical ^{1}H n.m.r. spectrum to that obtained for the *cine*-substituted isomer which had resulted from the coupling of γ-stannane (**141**) and *Z*-ethyl iodoacrylate (**84**) (*Chapter 3.5.3*).



Scheme 4.9

The use of silver salts in Heck reactions of vinyl halides was developed by Hallberg[143,144] and Overman[168] and has been shown to improve the rate and yield of the coupling and the isomeric purity of the products. The presence of silver salts results in the

Table 4.1. Heck coupling between ethyl N-acetyl-γ-iodoallyglycinate (**222**) and alkenes.

Entry	Alkene	Catalyst[a]	Temp./Time	Product		Yield[b]
1		A	70-80°/5h		**179**	29
2		B	90°/3h			41
3		C	60-90°/4h			44
4		C[c]	reflux/15h			44
5		A	70°/15h		**233**	0
6		B	60-100°/3h			27
7		B	100°/4h		**234**	-[d]
8		C[c]	reflux/15h			-[d]

Reactions carried out with alkene (*ca* 10 eq) and catalyst system A, B or C at the temperature and time shown (in DMF unless otherwise noted).

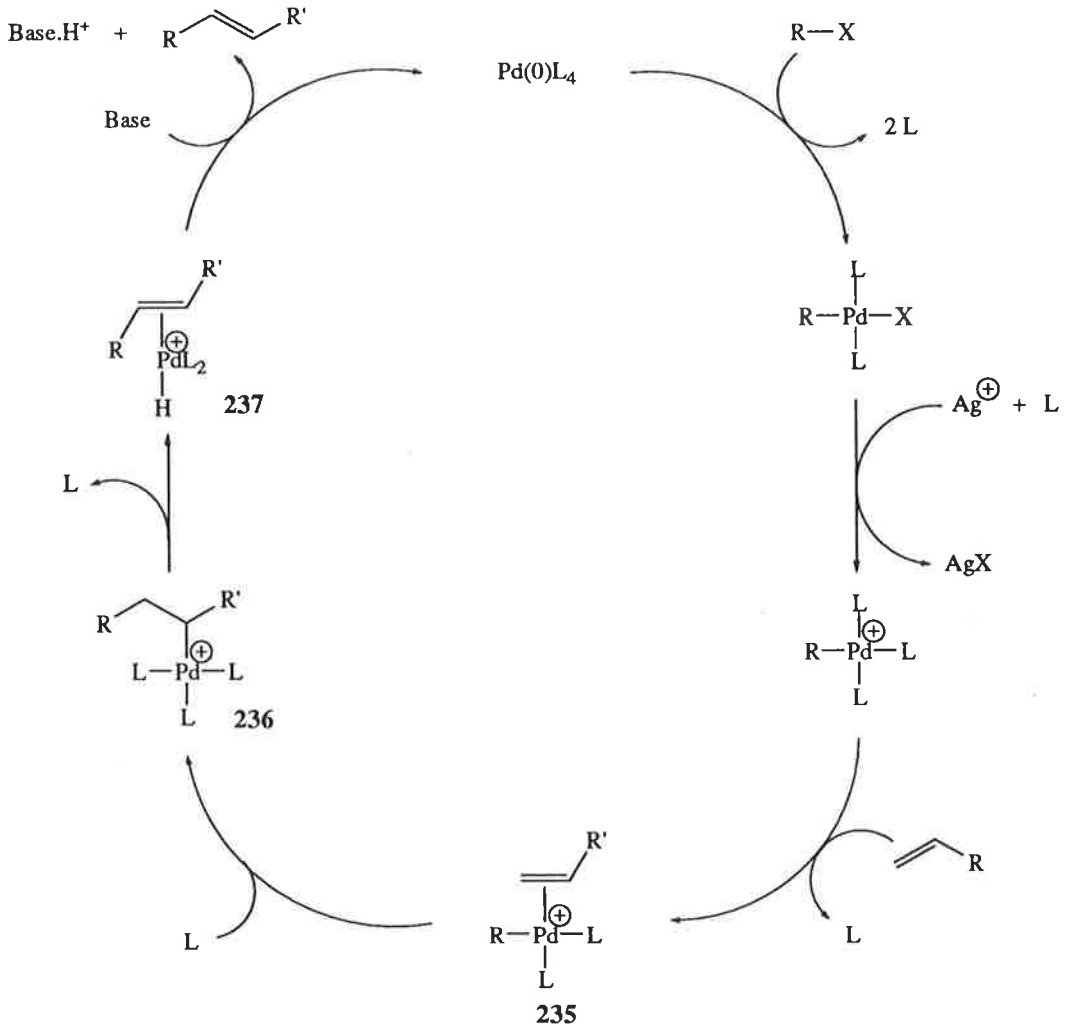
[a] A = $Pd(OAc)_2$ (5mol%), K_2CO_3 (5 eq), Bu_4NCl (1.0 eq);
B = $PdCl_2(PPh_3)_2$ (5mol%), Et_3N (2 eq);
C = $Pd(OAc)_2$ (5mol%), Ag_2CO_3 (1.5 eq).

[b] Isolated yield.

[c] THF solvent.

[d] The isolated product contained a significant amount of an aromatic impurity.

formation of cationic palladium(II) intermediates in the catalytic cycle (see *Chapter 3.5.3*). After oxidative addition of the vinyl halide to palladium(0) and abstraction of the halide by silver(I), the cationic Pd(II) species forms a tight π-complex with the alkene (**235**) followed by alkene insertion into the palladium-carbon bond (*Scheme 4.10*). Reductive elimination of this intermediate (**236**) forms a cationic hydridopalladium(II) alkene π-complex (**237**) which is not prone to readdition of H-Pd to the alkene and this is believed to be the cause of suppression of



Scheme 4.10

isomerisation. Presumably **237** is very unstable in the presence of base and the active palladium(0) catalyst and coupled product are formed. We investigated the use of Overman's catalyst system [$Pd(OAc)_2$, Ag_2CO_3][168] on the reaction with ethyl acrylate (entries 3 & 4) and found that it was acceptable in both DMF and THF as solvents. The yields were similar to those obtained using the other catalyst systems. The use of THF is unusual for successful Heck coupling which normally requires a coordinating solvent such as DMF or acetonitrile.[70]

The reaction was extended to the other alkenes. Acrylonitrile gave no product when reacted under the Jeffery conditions (entry 5), but gave a low yield of the expected 1,3-diene (**233**) when coupled using the more traditional conditions (entry 6). Freshly distilled methyl vinyl ketone coupled with **222** under both the traditional (entry 7) and silver carbonate (entry 8) conditions, but a pure product (**234**) could not be isolated after flash chromatography. The product obtained in both cases contained an aromatic impurity which was not characterised.

The origin of this material is unknown, but it could not have been a triphenylphosphine derivative since none was used in entry 8 and such derivatives were not seen for any other reaction undertaken in this study. Perhaps Diels-Alder reaction or an electrocyclic ring closure somehow occurs with **234** followed by aromatisation. Methyl vinyl ketone is notorious for polymerisation under the conditions of Heck reactions,[70] and **234** may also have undergone polymerisation.

In order to determine whether these Heck reactions were occurring with any degree of racemisation at the α-centre, the reaction of ethyl acrylate was repeated with the enantiomerically enriched vinyl iodide (*L*-**222**) using the conditions of entry 2 of *Table 4.1*. Optically active product was obtained in 48% yield. As can be seen from the ^{1}H n.m.r. spectra of the diasteriomeric Eu(hfc)$_3$ complexes of the racemic and 'chiral' products, little, if any, isomerisation had taken place in the coupling process (*Figure 4.2*).

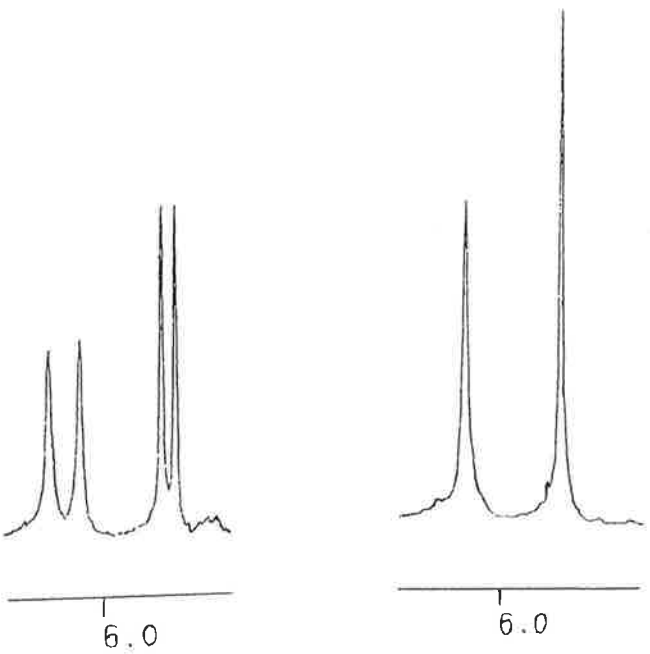


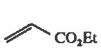
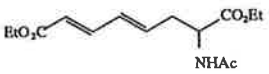
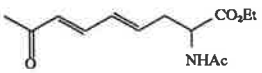
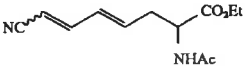
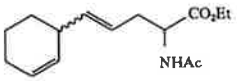
Figure 4.2. Eu(hfc)$_3$ ^{1}H n.m.r. experiment with racemic and chiral **179**. The portion of the spectrum shown is of the resonances of the terminal olefinic protons of the diastereomeric complexes.

The products from these reactions would most probably be better prepared *via* Stille coupling with the γ-stannane (**141**) with the relevant *E*-vinyl iodides (which are known compounds[169]). The advantages offered by these Heck reactions are few, and the synthesis of **222** from the vinyl stannane (**141**) seems unnecessary for the synthesis of **179**, **233** and **234**.

4.4 Heck reactions of *E*-ethyl δ-iodoallylglycinate

The reactions attempted for the γ-iodide (**222**) were repeated with the *E*-δ-iodide (**223**) and in addition coupling with cyclohexene was also studied. Overman's conditions of palladium acetate and silver carbonate in THF[168] with excess alkene were used in all cases. Generally the reactions proceeded to give good yields of coupled products (*Table 4.2*). In all cases the reactions were very clean as ajudged by t.l.c. with just one new spot formed. Ethyl acrylate and methyl vinyl ketone reacted cleanly to furnish the expected coupled products (**181** & **238**) as *E,E*-isomers in good yields (entries 1 & 2). Acrylonitrile gave a moderate yield of product which turned out to be a 58:42 mixture of 6-*E* and 6-*Z*-isomers (*E* & *Z*-**239**) (*i.e.* isomers about the bond which is formed by β-hydride elimination). The corresponding reaction of acrylonitrile with the γ-iodide (**222**) gave only the *E*-isomer (**233**) (*Table 4.1*, entry 6) although a different catalyst and solvent were used in that case. Acrylonitrile is known to produce various amounts of *Z*-isomers as products in a number of Heck reactions.[170] This could be because the nitrile moiety is stabilised to some extent in the more sterically hindered

Table 4.2. Heck coupling between *E*-ethyl N-acetyl-δ-iodoallylglycinate (**223**) and alkenes.

Entry	Alkene	% Yield[a]	Product	
1		73		**181**
2		78		**238**
3		69		**239**[b]
4		43[c]		**240**

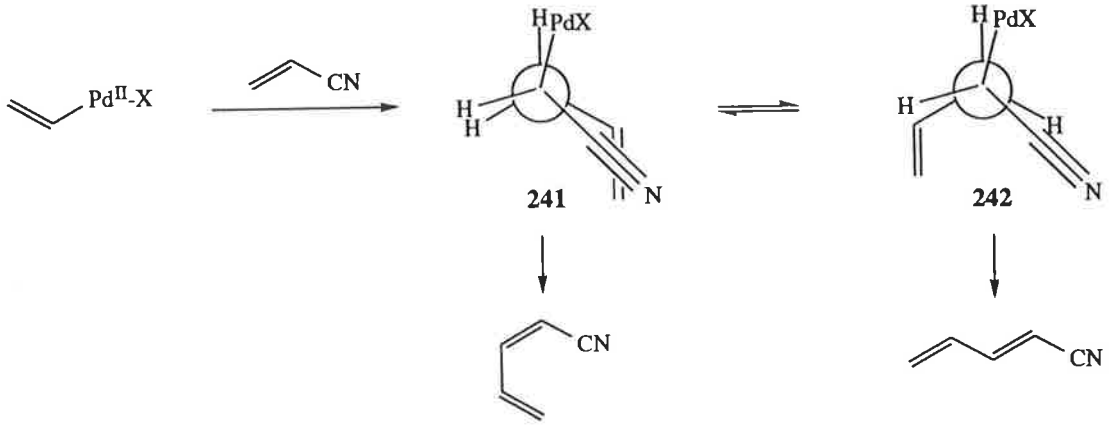
Reactions carried out with 5mol% of $Pd(OAc)_2$, alkene (*ca* 10 eq) and silver carbonate (1.5 eq) in THF at reflux overnight (*ca* 15h).

[a] Isolated yield.

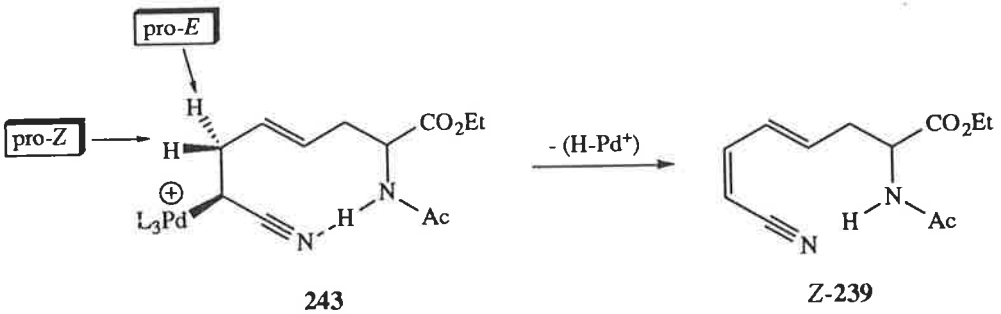
[b] Ratio of *E*:*Z* = *ca* 1:1.

[c] Isomeric mixture, probably diastereomeric 1,4-dienes.

eclipsed conformation (**241** rather than **242**) by π-π interactions with either an olefinic or aryl substituent (*Scheme 4.11*). β-Hydride elimination from **241** would produce the *Z*-isomer. In our example, hydrogen bonding between the nitrile and the amide hydrogen might stabilise the molecule into an eclipsed conformation (**243**) from which the *Z*-isomer would form (*i.e.* *Z*-**239**). No such hydrogen bonding is possible for the intermediates in the corresponding reaction of the γ-iodide (**222**) with acrylonitrile and, indeed, no *Z*-isomer was observed. Steric factors no doubt outweigh any stability gained by π-π interactions in that reaction.

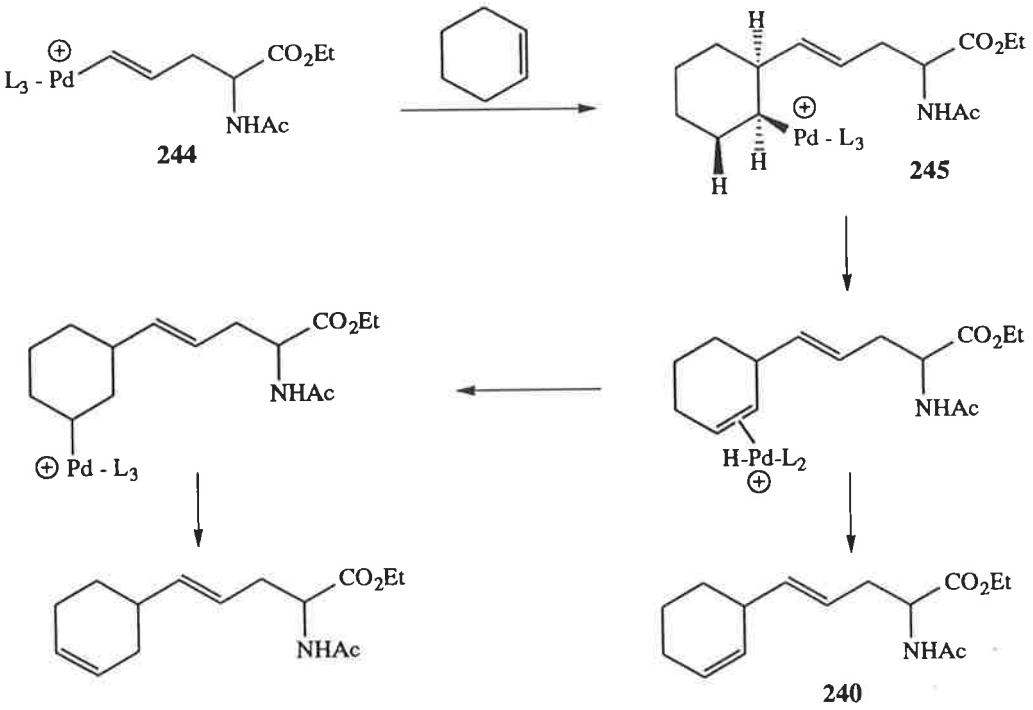


Scheme 4.11



Scheme 4.12

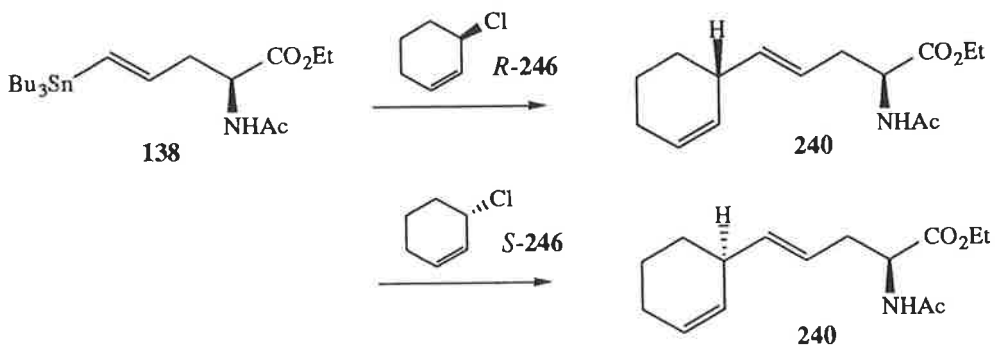
Cyclohexene was also investigated as a coupling partner (entry 4). Under the standard conditions a low yield of product was obtained which was a complex, inseparable mixture of isomers, which we presume to be the diastereomeric pair of 1,4-dienes (**240**). The ^{13}C n.m.r. spectrum showed the presence of eight olefinic resonances which would support the presence of the two diastereomers. The 1,4-dienes are the expected products as the double bond insertion occurs to the palladium(II) intermediate (**244**) in a *syn*-manner to form the intermediate, **245** (*Scheme 4.13*). *Syn*-β-hydride elimination is then only possible with the one hydrogen of this cyclohexyl intermediate which leads to formation of the 1,4-diene (**240**). Any other double bond isomers which may be present in the product mixture must have



Scheme 4.13

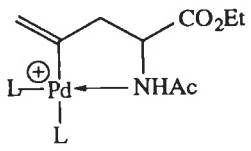
occurred *via* readdition/elimination of H-Pd, although this is unlikely since silver(I) was used in this Heck reaction and is reported to stop this process.[168] The product did not contain any 1,3-diene (**192**) since that compound had been synthesised by Stille coupling of *E*-δ-stannane (**138**) with cyclohexenyl triflate (*Chapter 3.6.2*) and comparison of spectra clearly indicated that **192** was not present in the mixture.

The diastereomers (**240**) would probably be more easily prepared by Stille coupling of chiral *E*-δ-stannane (**138**) with chiral 1-halo-2-cyclohexenes (*e.g. R* and *S*-**246**) (*Scheme 4.14*) since the reactions of allyl halides with vinylstannanes **138** and **141** occurred extremely well (see *Chapters 3.5.5 and 3.6.3*). Stille had shown that 1-halo-2-cyclohexenes react with organostannanes in the presence of a palladium catalyst with inversion of configuration.[171]



Scheme 4.14

The observations gained in this section of the work on the reactivity of the vinyl iodides (**222** & **223**) support the general view that the *E*-δ-iodoallylglycinate (**223**) is the more reactive of the two. The reason for the decreased reactivity of **222** seems to be two-fold. Firstly, **222** is the more sterically hindered of the two iodides and rates of Heck reactions are known to favour the least hindered vinyl halide or triflate. Secondly, the intermediate palladium(II) species resulting from oxidative addition (**247**) may possibly be stabilised intramolecularly by the amide nitrogen or the carbonyl oxygens ligated to the metal. This difference in reactivity was also observed for the Stille couplings of these two iodides (*Chapters 4.5 & 4.6*) and in their reactions with terminal alkynes (*Chapter 4.7*).



247

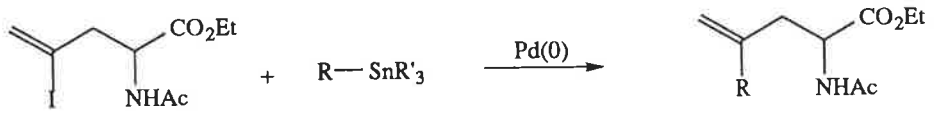
Although the *E*-δ-iodoallylglycinate (**223**) coupled quite well to the olefins in this study, particularly ethyl acrylate and methyl vinyl ketone, problems may arise with respect to isomeric purity of products for other alkenes. Since the Stille couplings of the *E*-δ-stannane proved to be quite an effective route for the synthesis of dienes compared to these Heck reactions, it seems that of the two processes, the Stille methodology is preferable provided that the necessary vinyl halides and triflates can be prepared.

4.5 Stille coupling reactions of ethyl N-acetyl-γ-iodoallylglycinate

The Stille reaction has an inherent advantage over many forms of carbon-carbon bond formation in that the nucleophilic and electrophilic partners in the coupling can be interchanged.[56,99] We explored this complimentarity by carrying out the coupling of iodoallylglycinates (**222** & **223**) with a range of organostannanes as an alternative to the Stille coupling of the two stannylallylglycinates (**141** & **138**) with organo halides and triflates. We hoped these 'reverse' Stille reactions would alleviate some of the problems associated with the reactions described in *Chapters 3.5* and *3.6*, particularly *cine* substitution and phenyl substitution from triphenylarsine ligands. We investigated coupling of the vinyl iodides with a representative sample of vinyl, allyl and phenyl stannanes, a number of which formed the same products as those obtained in *Chapters 3.5* and *3.6* so comparison of the scope of the two

procedures could be made directly. The mechanism of the Stille coupling reaction was discussed in *Chapter 3.4*.

The coupling reactions of the general type shown in *Scheme 4.15* proved to be quite limited in terms of reactivity of the γ-iodoallylglycinate (**222**). The yields obtained for coupled products were variable (*Table 4.3*). For instance, under the conditions developed by Farina which had been used extensively in *Chapters 3.5* and *3.6*,[75] reaction with 2-trimethylstannylpropene yielded no product and unreacted vinyl iodide was recovered (entry 1). Varying the reaction conditions such as the use of DMF as solvent (entry 2) or changing the catalyst to $Pd(CH_3CN)_2Cl_2$ (entry 3) had no effect on the poor reactivity. However, in the reactions with other organostannanes product was isolated in each case (entries 4-7). In some instances, the product could not be separated from **222** by flash chromatography on silica gel. This was a disadvantage since it became difficult to follow the course of those particular reactions by t.l.c.

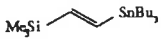
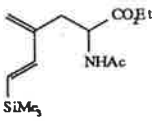
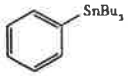
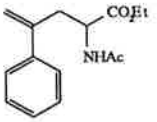
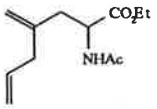
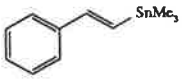


222

Scheme 4.15

Generally the reactions were carried out by the addition of the palladium catalyst to a solution of **222** and organostannane in DMF at room temperature. This caused the solution to turn deep purple in colour, presumably the result of formation of an intermediate palladium(0) or (II) π-complex with the organostannane. After stirring overnight at room temperature the solutions became clear and a pale canary yellow in colour, possibly because of π-coordinated palladium complexes to the coupled product (*i.e.* catalyst did not decompose). Since it was difficult to ascertain whether the reactions had proceeded to completion by t.l.c., the solutions were heated to 80-90° for 1-2 hours by which time palladium black precipitated. Chromatography of the mixtures gave the products as shown in *Table 4.3*. The electron rich *E*-1-(trimethylsilyl)-2-(tributylstannyl)ethylene (entry 4) was a relatively reactive substrate and the coupled product (**248**) was isolated in high yield. Phenyltributylstannane gave a moderate yield of coupled product (**148**) which could not be separated from unreacted vinyl iodide (entry 5). Allyltributylstannane reacted poorly and only a small amount of product (**190**) was obtained as a mixture with recovered vinyl iodide (entry 6). These last two coupled products

Table 4.3. Stille coupling between ethyl N-acetyl-γ-iodoallylglycinate (**222**) and organostannanes.

Entry	Alkene	Catalyst[a]	Temp./Time	Product		Yield[b]
1		A	reflux[c]/15h	Not detected		0
2		A	100°/90min			0
3		B	15°/15h then 90°/2h			0
4		B	15°/15h then 90°/60min		**248**	86
5		B	15°/15h then 90°/2h		**148**	56[d]
6		B	15°/15h then 90°/2h		**190**	7[e]
7		B	15°/15h then 80°/1h	Not detected		0

Reactions carried out with catalyst (A or B) (5mol%), organostannane (2 eq) and vinyliodide (1.0 eq) for the temperature and time shown (in DMF unless otherwise noted).

[a] A = $Pd(AsPh_3)_4$; B = $PdCl_2(CH_3CN)_2$

[b] Isolated yield of pure material unless otherwise noted.

[c] THF solvent.

[d] Mixture with recovered vinyliodide (8%). 61% yield based on recovered starting material.

[e] Mixture with recovered vinyliodide (70%). 23% yield based on recovered starting material.

(**148** & **190**) gave ^1H n.m.r. spectra identical to those obtained for the compounds prepared from coupling stannylallylglycinate (**141**) with iodobenzene and allyl bromide in *Chapter 3.5*. No product could be detected from the reaction of *E*-β-(trimethylstannyl)styrene under these conditions (entry 7).

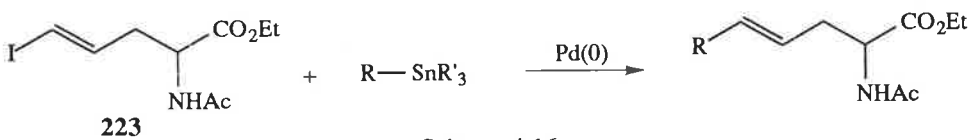
As the products from these 'reverse' Stille reactions (**248**, **148** & **190**) were prepared in low yield and could not adequately be separated from vinyl iodide (**222**), it seems

unnecessary to prepare **222** from the stannane (**141**) in order to prepare compounds of these types. Stille reactions as described in *Chapter 3.5* seem a much better prospect particularly if *cine*-substitution and phenyl substitution can be avoided or minimised by the choice of appropriate conditions.

Since carrying out these reactions, Leanna has reported the results of some coupling reactions of a γ-bromoallylglycine derivative, including a Stille coupling with vinyltributyltin using the workhorse $Pd(PPh_3)_4$ catalyst which gave a γ-(vinyl)allylglycine derivative in moderate yield (63%) (*Introduction, Scheme 1.35*).[68]

4.6 Stille coupling reactions of *E*-ethyl N-acetyl-δ-iodoallylglycinate

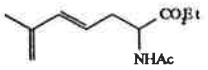
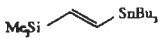
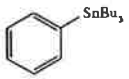
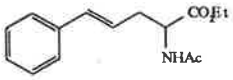
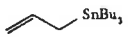
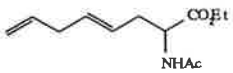
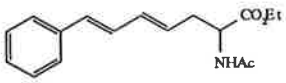
Reactions of the general type shown in *Scheme 4.16* were undertaken with *E*-δ-iodoallylglycinate (**223**) and the same selection of organostannanes as discussed above. Generally, low to moderate yields of coupled products were obtained in all instances. The results are listed in *Table 4.4*. Again, reactions performed with $Pd(AsPh_3)_4$ gave none of the desired products (entries 1 & 5), yet those catalysed by $PdCl_2(CH_3CN)_2$ in DMF were successful (entries 3, 4, 6-8). Using THF rather than DMF gave no desired product (entry 2), so presumably a solvent which coordinates quite strongly to palladium is necessary. Separation of products from unreacted vinyl iodide was often difficult. 2-(Trimethylstannyl)propene reacted quite well with **223** to form **249** (entry 3) whereas no product could be detected or isolated from its Stille reaction with the γ-iodide (**222**) (*Section 4.5*) and this is presumably because the vinyliodide **223** is less sterically demanding. Conversely, a poor yield of product (**250**) was obtained by reaction of *E*-1-(trimethylsilyl)-2-(tributylstannyl)ethylene, which had coupled surprisingly well with **222**, but this was presumably the result of catalyst instability (entry 4).



Scheme 4.16

The products (**149**, **251** & **177**) from coupling of phenyl, allyl and styryl stannanes (entries 5 to 8) were obtained in low yield. Both **149** and **177** had been prepared readily by Stille coupling of *E*-δ-stannane (**138**) with iodobenzene and *E*-β-bromostyrene respectively (*Chapter 3.6*). Presumably the products **249** and **251** would also be more easily prepared by

Table 4.4. Stille coupling between *E*-ethyl N-acetyl-δ-iodoallylglycinate (**223**) and organostannanes.

Entry	Stannane	Catalyst[a]	Solvent	Temp./Time	Product		Yield[b]
1		A	THF	reflux/1h		**249**	0[c]
2		B	THF	37°/15h			0
3		B	DMF	40°/18h			65
4		B[d]	DMF	15°/15h		**250**	23
5		A	THF	reflux/15h		**149**	0
6		B	DMF	15°/15h			31[e]
7		B	DMF	80°/4h		**251**	41[f]
8		B	DMF	40°/17h		**177**	21

Reactions carried out with catalyst (A or B) (5mol%), organostannane (2 eq.) and vinyliodide (1.0 eq) for the temperature and time shown.

[a] A = $Pd(AsPh_3)_4$; B = $PdCl_2(CH_3CN)_2$

[b] Isolated yield of pure material unless otherwise noted.

[c] Recovered vinyl iodide (82%).

[d] Catalyst decomposed.

[e] Mixture with recovered vinyliodide (42%). 53% yield based on recovered starting material.

[f] Mixture with recovered vinyliodide (40%). 68% yield based on recovered starting material.

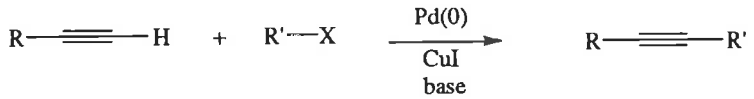
that method.

In terms of the number of stannanes which coupled adequately to **223** and the purity of the isolated products these reactions worked better than the corresponding couplings of the γ-iodide (**222**). This is consistent with the other coupling reactions of these iodides reported in this thesis in which **222** was the less reactive vinyliodide, presumably for reasons of steric hindrance and partial catalyst stability brought about by chelation of either the amide or ester

moieties to the palladium(II) intermediate formed after oxidative addition. As was concluded for the Heck reactions of the vinyl iodides (**222** & **223**) the Stille couplings with organostannanes offer no advantages over the alternative routes discussed in *Chapters 3.5* and *3.6*.

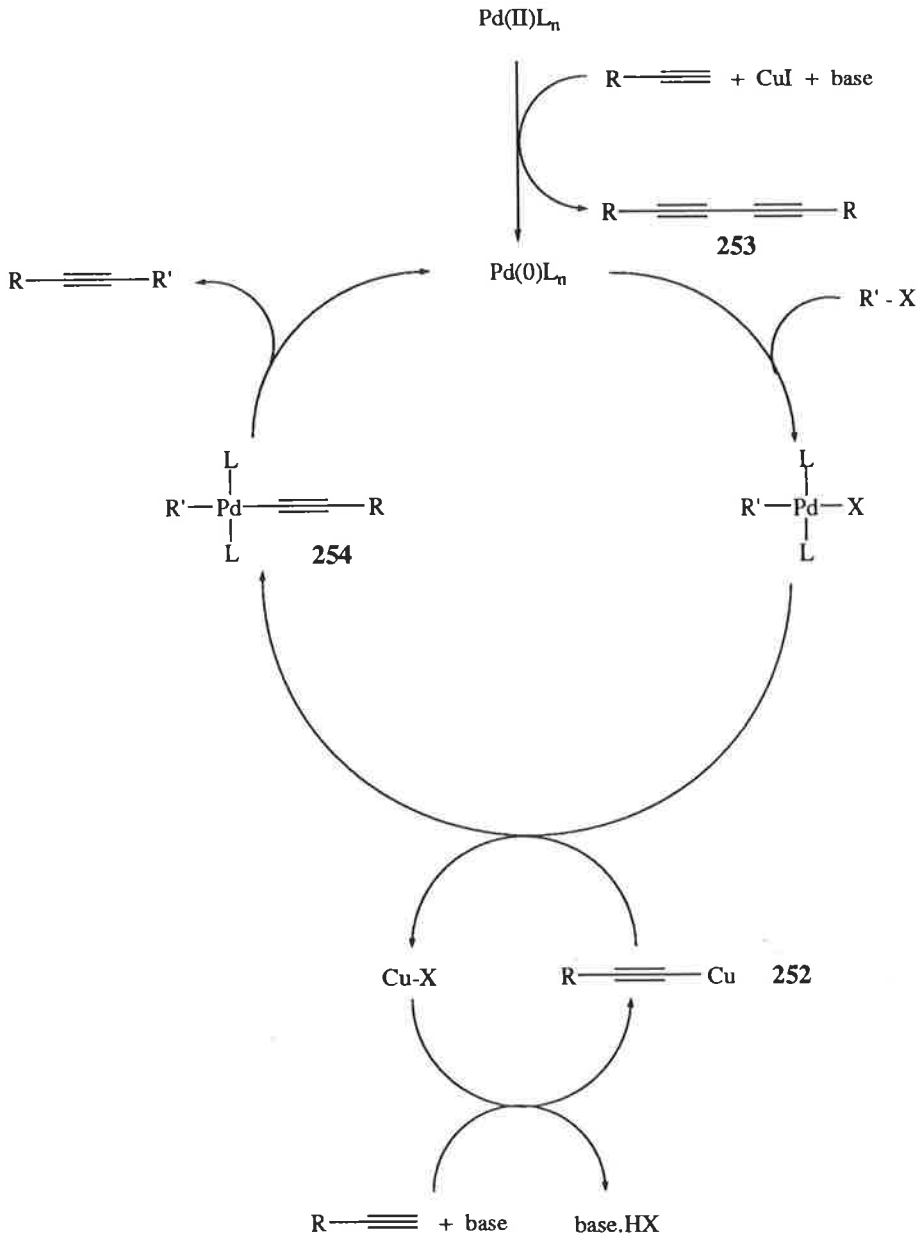
4.7 Coupling of the vinyliodides with terminal alkynes

The organometallic coupling between aryl halides with terminal alkynes (*Scheme 4.17*) has been known for thirty years since Stephens and Castro discovered that copper acetylides react with aryl iodides in pyridine at 120°.[172] Later Cassar[173] and Heck[174] independently found that the reaction of terminal alkynes with aryl and vinyl halides proceeded in the presence of palladium catalysts and base, but again at elevated temperatures in strongly polar solvents. Hagihara observed that the addition of a copper(I) cocatalyst (two equivalents relative to palladium) greatly enhanced the reactivity and permitted the coupling to take place at room temperature.[175] Chen extended the reaction to aryl perfluoroalkylsulphonates[125] and Stille[176] and Cacchi[88] independently investigated the reaction with vinyl triflates. For a successful reaction to occur at room temperature with organo triflates, copper iodide seems essential. This palladium(0)/copper(I) mediated coupling process is one of the most general, mild and selective catalytic processes and has been extensively utilised in organic synthesis.



Scheme 4.17

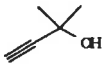
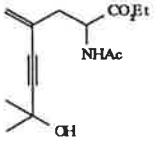
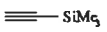
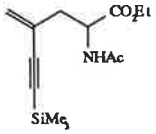
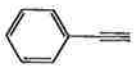
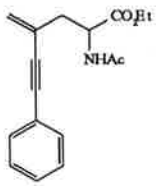
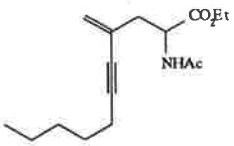
The mechanism is believed to proceed as shown in *Scheme 4.18*.[175] If a palladium(II) precursor to the reactive palladium(0) catalyst is used then this is reduced by the reaction with two equivalents of copper acetylide (**252**) to form a small amount of 1,3-diyne (**253**). Oxidative addition of the organo halide or triflate to the Pd(0) forms an organopalladium(II) halide (triflate) which then undergoes transmetallation with **252** to form an organopalladium(II) acetylide (**254**) and reform copper(I) halide (triflate). Thus, the reaction is catalytic in copper(I) as well as palladium(0). The copper acetylide (**195**) is formed by reaction of the terminal alkyne with copper iodide and base. Reductive elimination from **254** forms the carbon-carbon bond and regenerates the palladium(0) catalyst.



Scheme 4.18

We initially examined the reaction of the γ-iodide (**222**) with a variety of terminal alkynes of varying electron density and the results are shown in *Table 4.5*. All the reactions were performed with $PdCl_2(PPh_3)_2$ (5mol%) and copper(I) iodide (10mol%) in THF at room temperature and monitored by t.l.c. Crystallisation of triethylammonium iodide from the reaction solution also gave a visual indication of the progress of the reaction. Most reactions were complete within one to two hours and produced the enynes (**255, 256, 257, 258**) in good to excellent yields. The products were easily assigned the structures shown because the terminal olefinic protons in the ^1H n.m.r. spectra resonated as singlets in the region δ5.12 to

Table 4.5. Coupling between γ-iodoallyglycinate (**222**) and terminal alkynes

Entry	Substrate	Time	% Yield[a]	Product	
1		1.5h	62		**255**
2		15h	79		**256**
3		15h	97		**257**
4		2h	93		**258**

Reactions carried out with $PdCl_2(PPh_3)_2$ (5mol%), Cu(I) iodide (10mol%), substrate (1.5 eq) and triethylamine (2 eq) in THF at room temperature.
[a] Isolated yield.

5.55 and the infrared spectra showed weak absorbances for the alkynes in the region 2144 to 2212cm^{-1}.

Although it was not expected, to ascertain whether these couplings were proceeding with any degree of racemisation at the α-carbon the reaction of phenylacetylene (entry 3) was repeated using the enantiomerically enriched γ-iodide (*L*-**222**). The products in both instances were examined in $Eu(hfc)_3$ ^1H n.m.r. shift experiments and the regions of the spectra corresponding to the vinylic protons are shown in *Figure 4.3*. Again, no racemisation has occurred in this reaction since the amount of *D*-enantiomer in the product is virtually identical to the amount in the 'chiral' iodide (*Figure 4.1*).

The correponding reactions of *E*-δ-iodoallylglycinate (**223**) were carried out under identical conditions to those used for the coupling reactions above and the results are given in *Table 4.6*. The rates of reaction were much faster than for the corresponding coupling reactions

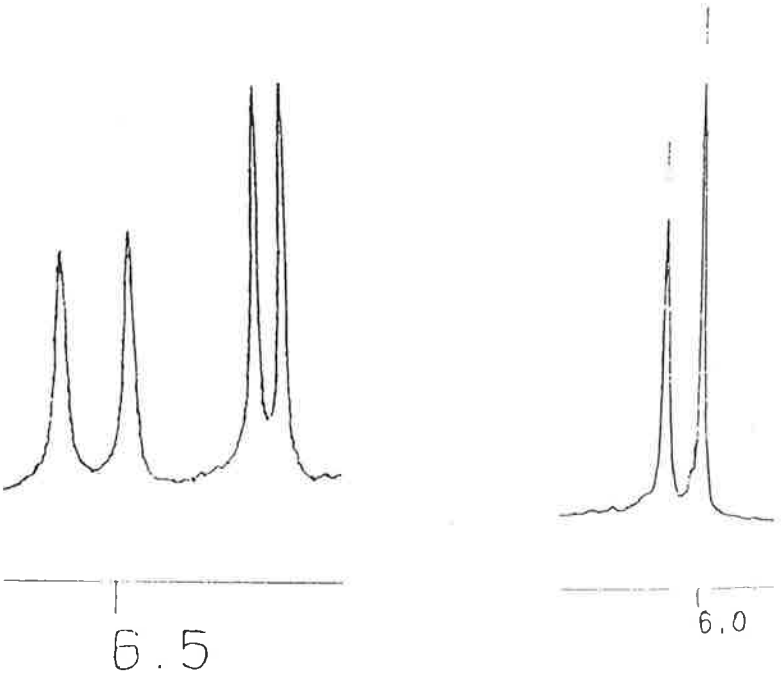
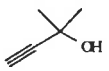
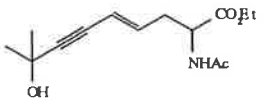
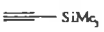
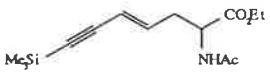
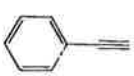
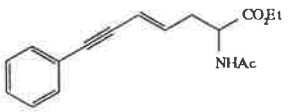


Figure 4.3. Eu(hfc)$_3$ ^{1}H n.m.r. experiment with racemic and chiral **257**. The portion of the spectrum shown is of the resonances of the terminal olefinic protons of the diastereomeric complexes.

Table 4.6. Coupling between *E*-δ-iodoallyglycinate (**223**) and terminal alkynes.

Entry	Substrate	Time	% Yield[a]	Product	
1		15h	98		**259**
2		15h	96		**260**
3		2h	64		**261**
4		15h	80		**262**

Reactions carried out with $PdCl_2(PPh_3)_2$ (5mol%), Cu(I) iodide (10mol%), alkyne (1.5 eq) and triethylamine (2 eq) in THF at room temperature.

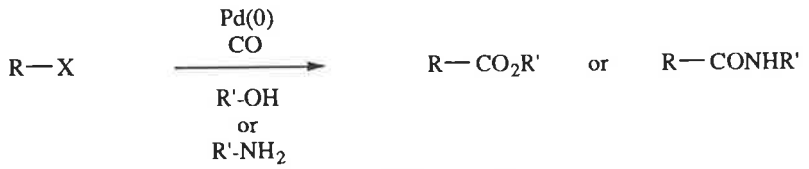
[a] Isolated yield.

of the γ-iodide, and generally triethylammonium iodide precipitated within 5 to 15 minutes, but the reactions were left overnight for convenience. The yields of the 4-en-6-ynes (**259**, **260**, **261**, **262**) were good to excellent and the products were confirmed to have the structures shown by the presence in their ^{1}H n.m.r. spectra of doublets with *trans*-coupling constants (15.7-15.8Hz) in the region δ5.48 to 5.73 for the C5-protons and doublets of triplets for the C4-protons at δ5.86 to 6.02. Infrared spectra confirmed the presence of the alkynes by weak absorbances the region 2132 to 2236cm^{-1}.

These coupling reactions were amongst the simplest and cleanest reactions reported in this thesis and seem to be of total generality in the synthesis of racemic and chiral amino acid derivatives bearing conjugated enynes in the side chain.

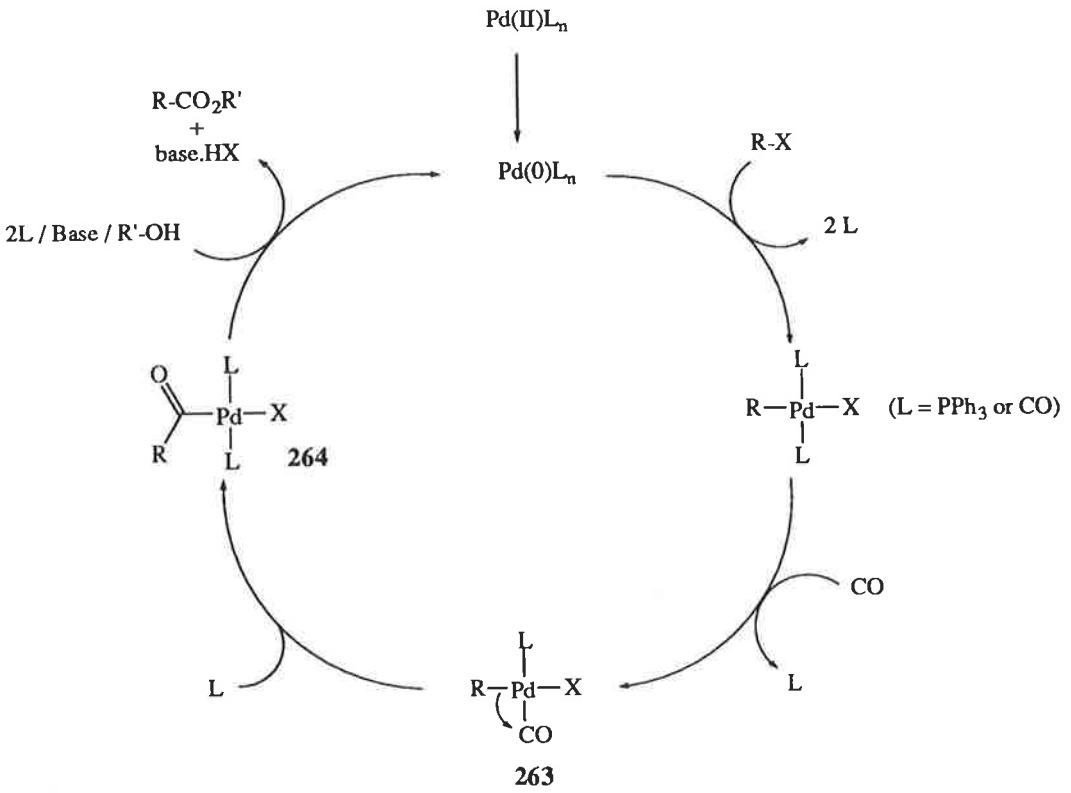
4.8 Carboethoxylation reactions of the iodoallylglycine derivatives.

The palladium catalysed carbonylation of organic halides, triflates and diazonium salts is an extremely effective method for the construction of carboxylic esters, amides and acids (*Scheme 4.19*).[177] It is a safe, mild and catalytic alternative to the use of the highly toxic and volatile nickel tetracarbonyl. The reaction was initially pioneered independently by Heck[178] and Stille[179] for carbonylation of aryl, benzyl and vinyl halides. Matsuda extended the reaction to include aryl diazonium salts,[180] and Dolle[181] and Cacchi[182] investigated independently aryl and vinyl triflates as carbonylation substrates. Intramolecular version of the reaction are an extremely convenient route to aromatic, α-methylene and $\Delta^{\alpha,\beta}$-lactones and lactams.[177,183]



Scheme 4.19

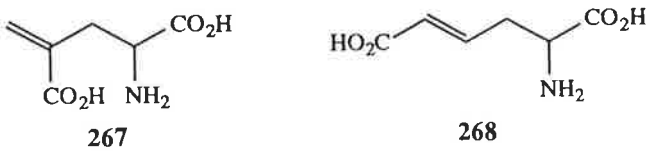
The mechanism of the carbonylation reactions has yet to be fully ascertained, but the following catalytic cycle (for carboalkoxylation of an organohalide) seems plausible (*Scheme 4.20*).[177] Oxidative addition of the organohalide to palladium(0) (formed by reduction *in situ* of a palladium(II) precursor) and ligation of carbon monoxide to palladium(0) occurs to form **263**. Carbonyl insertion occurs by migration of the organic group, R, to carbon monoxide with concomittant carbon-palladium bond formation. This results in an acyl palladium(II)



Scheme 4.20

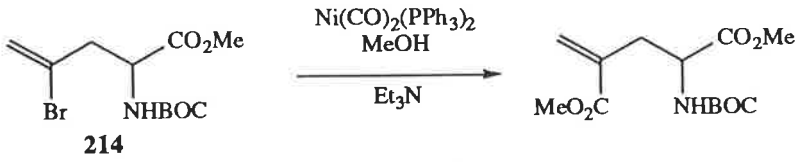
intermediate (**264**) which is susceptible to nucleophilic attack by alcohol in the presence of mild base. The unsaturated ester is formed and the active zero-valent catalyst is regenerated.

We wished to investigate the two vinyl iodides (**222** & **223**) in carbonylative reactions for the formation of α,β-unsaturated esters (**265** & **266**). These products are derivatives of known compounds: 4-methylene glutamic acid (**267**) occurs naturally in a number of plants,[67,68] and 5-amino-2-hexenedioic acid (**268**) which has been investigated as a conformationally restricted amino acid in a few structure-activity studies with respect to neuronal receptor excitation and dihydrofolate reductase inhibition (when incorporated as the amino acid side chain of methotrexate and aminopterin).[184] Leanna has recently reported the carbomethoxylation of a γ-bromallylglycine derivative using a nickel carbonyl catalyst as a route to a 4-methyleneglutamic acid derivative (*Scheme 4.21*).[68]



267 **268**

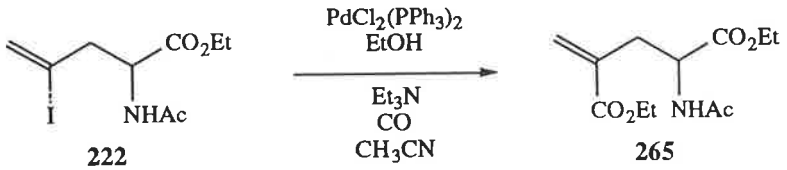
Upon treatment of the γ-iodoallylglycinate (**222**) with $PdCl_2(PPh_3)_2$ and ethanol in the presence of triethylamine under an atmosphere of carbon monoxide in acetonitrile at 60° for 30



214

Scheme 4.21

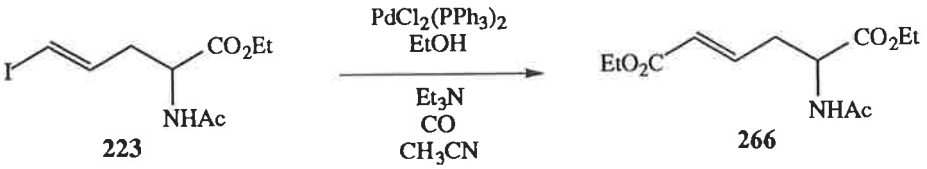
minutes (*Scheme 4.22*), t.l.c. indicated that no vinyl iodide remained and one new spot had formed. This was isolated by flash chromatography in good yield (77%) and the structure confirmed as the expected diethyl N-acetyl-4-methylene glutamate (**265**). ^{1}H n.m.r. showed two broad singlets for the vinylic protons at δ5.61 and 6.21, ^{13}C n.m.r. indicated the presence of an additional carboxylic ethyl ester group (additional resonances at δ14.05, 61.10 and 166.95) and the infrared spectrum confirmed the additional carboxylic carbonyl group (ν1722cm^{-1}).



222 265

Scheme 4.22

The reaction was repeated with the *E*-δ-iodoallylglycinate (**223**) under the same conditions as above and diethyl 5-amido-2-hexenedioate (**266**) was obtained in moderate yield (67%) (*Scheme 4.23*).



223 266

Scheme 4.23

In order to determine if the reactions were occurring with any racemisation at the α-centre, the carboethoxylation was repeated with the enantiomerically enriched γ-iodide (*L*-**222**). As the Eu(hfc)$_3$ ^{1}H n.m.r. shift experiment results depicted in *Figure 4.4* show, little, if any, racemisation had taken place at the α-carbon. This is to be expected since the reaction is chemoselective and mild enough to leave the α-hydrogen untouched.

Although not investigated, this methodology would also be a convenient route to natural products such as the 4-methyleneglutamates (**269**) which are found in peanuts and tulips and other plants.[185]

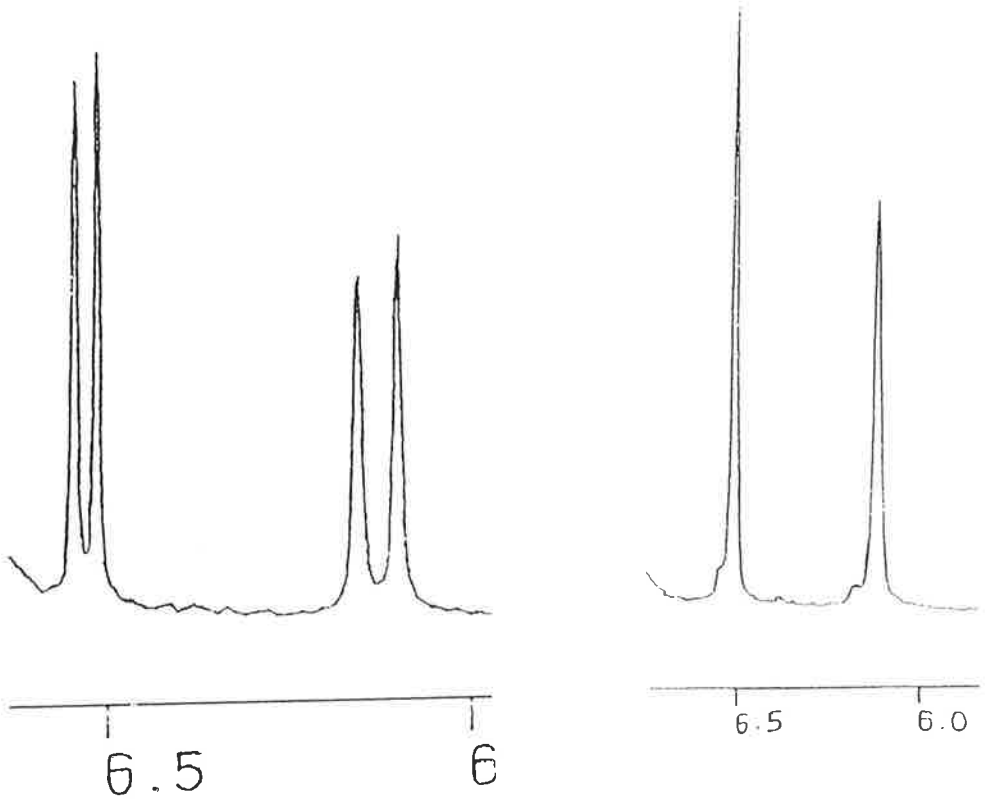
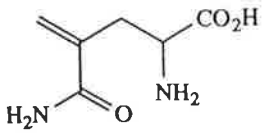


Figure 4.4. Eu(hfc)$_3$ ^{1}H n.m.r. experiment with racemic and chiral **265**. The portion of the spectrum shown is of the resonances of the terminal olefinic protons of the diastereomeric complexes.

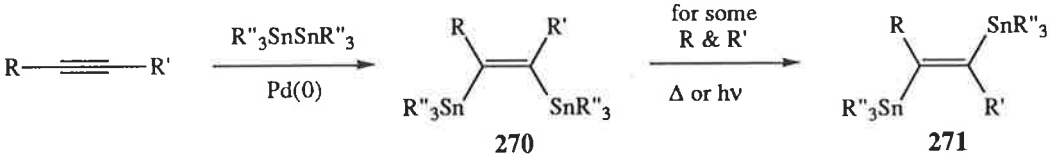


269

Ethyl *cis*-N-acetyl-γ,δ-bis(trimethylstannyl)allylglycinate. Synthesis and reactivity.

5.1 Hexamethylditin addition to ethyl N-acetylpropargylglycinate.

The synthesis of distannylated alkenes has only recently been explored.[118,186,187] These compounds are extremely interesting molecules because of the potential difference in reactivity of the individual stannyl moieties.[187] Although a number of distannanes have been prepared their reactivity has yet to be fully investigated.[187] In addition to hydrostannantion of the propargylglycine derivative (**121**) (*Chapter 3.3*) we investigated the addition of a ditin to this alkyne. This reaction (*Scheme 5.1*), which was developed independently by both Mitchell[186] and Piers,[118] is catalysed by palladium(0) and yields the kinetic *cis*-vinyl ditin adduct (**270**) although some *cis*-vinyl ditins formed from conjugated alkynes readily isomerise thermally to *trans*-adducts (**271**).[118] Best results are obtained when terminal alkynes and hexamethylditin are utilised, although non-terminal alkynes and more hindered ditins (*e.g.* hexabutylditin) may be coupled under more forcing conditions.[188] Reactions carried out with neat mixtures of the reagents generally proceed better than those in solvents.[186] The addition of ditins to allenes[189] and 1,3-dienes[99] has also been reported.

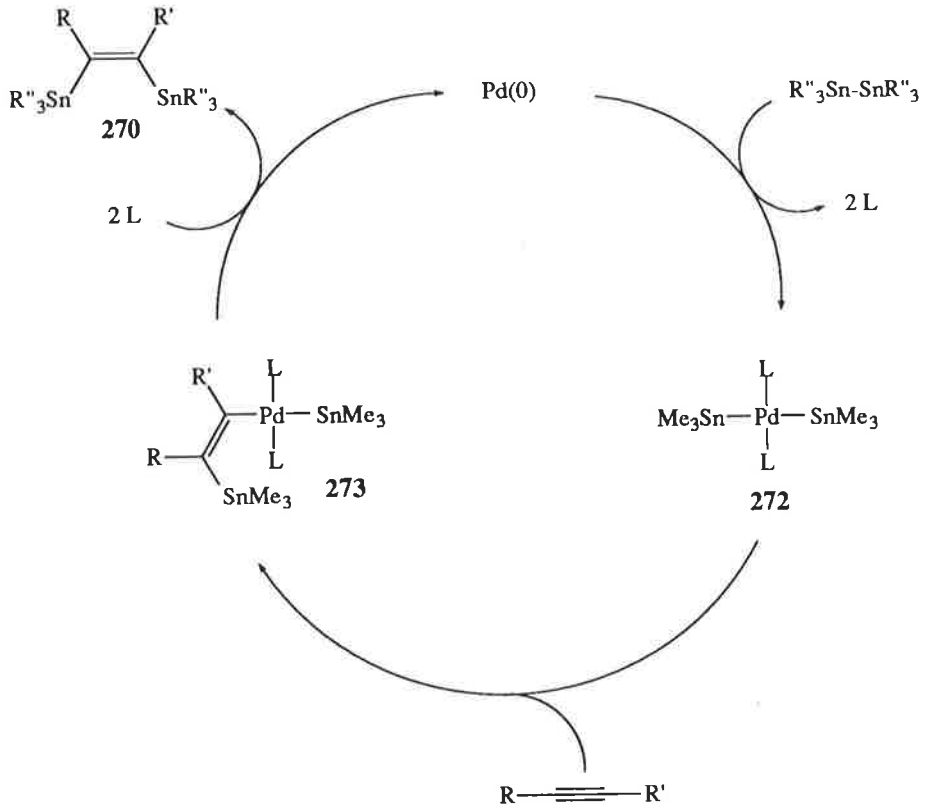


270 **271**

Scheme 5.1

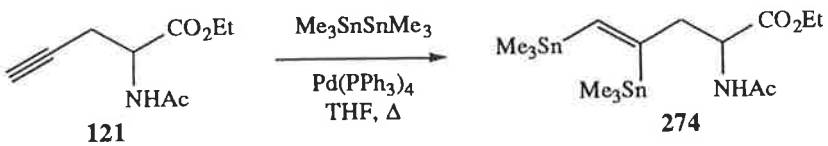
The reaction may proceed through the mechanism shown in *Scheme 5.2*. Oxidative addition of hexamethylditin to palladium(0) forms a palladium(II)-ditin complex (**272**). *Syn*-addition of this species to the alkyne forms a vinyl palladium(II) intermediate (**273**) which undergoes reductive elimination to form the *cis*-vinyl ditin (**270**) and reform the active catalyst.

We wished to prepare a ditin derivative of the propargylglycinate (**121**) in order to explore its reactivity with electrophilic reagents (*i.e.* in iododestannylation and Stille reactions).[187] These reactions would, in theory, be an expeditious route to a number of substituted allylglycine derivatives. Thus, on treating **121** with hexamethylditin in the presence of $Pd(PPh_3)_3$ (5mol%) in THF at reflux (*Scheme 5.3*), a very clean mixture was obtained which comprised only product and starting materials by t.l.c. Unfortunately the catalyst was



Scheme 5.2

unstable to these reaction conditions and precipitated palladium black after about 30 minutes. The *cis*-ditin (**274**) was isolated by flash chromatography on silica gel in moderate yield (49%, 60% based on recovered propargylglycinate) as an oil which was stable to distillation at high temperature under reduced pressure. The stereochemistry was assigned as *cis* based on comparison of the $^{117/119}Sn$-^{1}H coupling constants of the vinylic proton resonance at δ6.57 with the values reported by Mitchell for a series of *cis* and *trans*-vinyl ditins.[186] The coupling constants between this proton and the geminal and vicinal tins were 81 and 182Hz respectively. These compare favourably with Mitchell's ranges for *cis*-compounds of 69-90Hz for $^{2}J_{Sn\text{-}H}$ and 176-214Hz for $^{3}J_{Sn\text{-}H}$; the corresponding *trans*-compounds are reported to give coupling constants in the ranges 96-107 and 104-113Hz respectively.[186]



Scheme 5.3

The reaction was repeated using $Pd(AsPh_3)_4$ as catalyst under the same conditions described above, but decomposition of the catalyst occurred extremely rapidly and only a trace

of product could be detected by t.l.c. Perhaps a catalyst such as $Pd(P[OMe]_3)_4$ would be suitably stable for this ditin addition since it has recently been reported as working efficiently for a number of similar reactions.[99]

Isomerisation of the *cis* to *trans*-ditin (**274** to **275**, *Scheme 5.4*) was attempted by irradiating a neat sample of **274** with a 300W mercury sunlamp at ambient temperature under a nitrogen atmosphere,[186] but this proved unsuccessful and substantial decomposition occurred. As mentioned above, the *cis*-ditin (**274**) was stable to distillation so could not be isomerised at high temperature. Thus, although we were unable to prepare the *trans*-ditin (**275**), the *cis*-isomer (**274**) proved to be an interesting substrate for a number of reactions (*Chapter 5.2* and *5.3*).

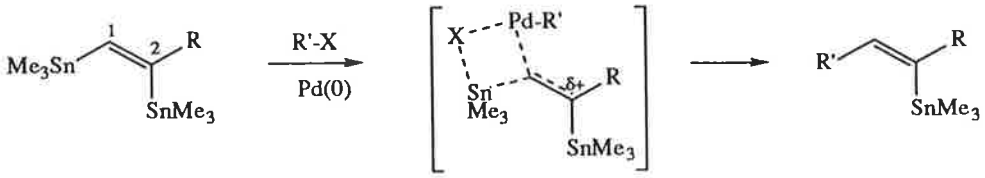
274 **275**

Scheme 5.4

Although the syntheses of a number of 1,2-bis(trimethylstannyl)-1-alkenes have been reported, not much is known about their reactivity. Mitchell has investigated some common vinylstannane reactions with a series of ditins - bromodemethylation, Stille coupling and halodestannylation.[187] It is the two latter reactions which we explored with the ditin **274**.

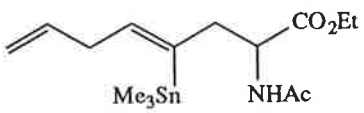
5.2 Stille coupling of *cis*-ethyl N-acetyl-γ,δ-bis(trimethylstannyl)allylglycinate

Mitchell's studies of the mono and bis-Stille coupling reactions have been the only reported to date. Monocoupling has been investigated between a number of vinyl ditins with allyl bromide, benzyl bromide and *p*-chlorotoluene tricarbonylchromium complex (*Scheme 5.5*).[187] The products formed in excellent yield were the result of regioselective and stereospecific coupling of the C1 stannyl moiety.[187] Presumably this regioselectivity arises because of steric effects as well as the S_E2-like mechanism favouring coupling at C1 because the increased substitution at the C2 carbon stabilises partial positive charge build-up at that centre to a greater extent. The second stannane was found to react sluggishly with excess of the electrophile (allyl or benzyl bromide) and low to moderate yields of the *cis*-disubstituted products were obtained.[99]

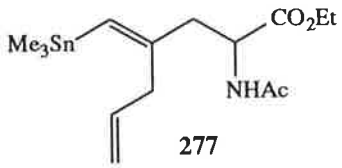


Scheme 5.5

We attempted Stille coupling of *cis*-bis(trimethylstannyl)allylglycine derivative (**274**) with allyl bromide as a model reaction since the regioselectivity of the reaction (*i.e.* formation of **276** or **277**) would be evident from the coupling pattern of both the doubly-allylic methylene protons and the vinylic proton at C5 in the ^{1}H n.m.r. spectrum. Thus, reaction of **276** with

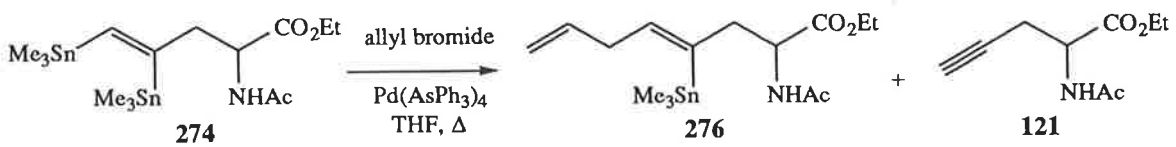


276



277

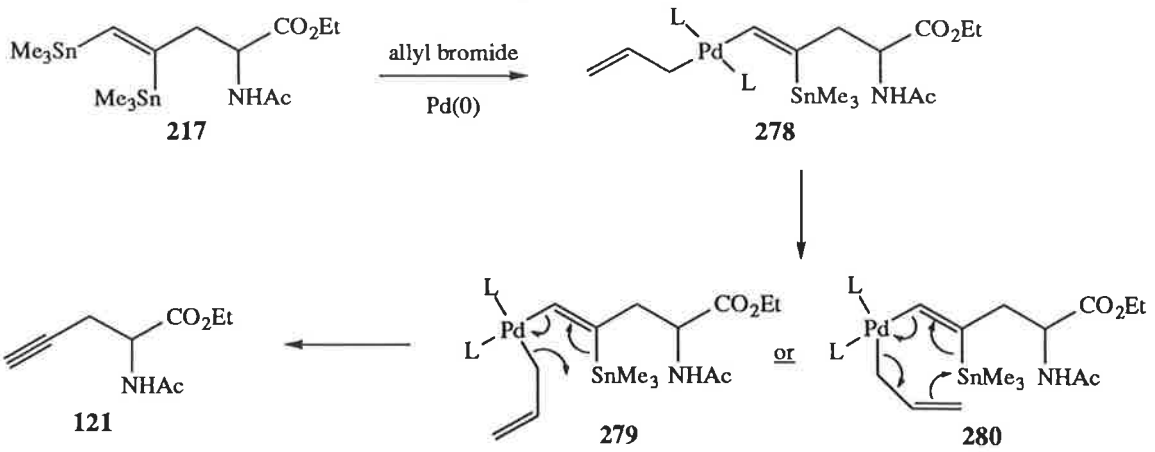
one equivalent of allyl bromide in THF at reflux using the $Pd(AsPh_3)_4$ catalyst, conditions which we had successfully utilised in the couplings of the γ and *E*-δ-stannylallylglycinates (**141** and **138**, *Chapter 3.5* and *3.6*), resulted in a stable catalyst and the formation of two products by t.l.c. These products were isolated cleanly and were characterised as the Stille coupling product (**276**, 36%) arising from reaction of the δ-stannyl moiety as well as the propargylglycinate derivative (**121**, 42%) the result of elimination of both stannyl groups (*Scheme 5.6*).



274 **276** **121**

Scheme 5.6

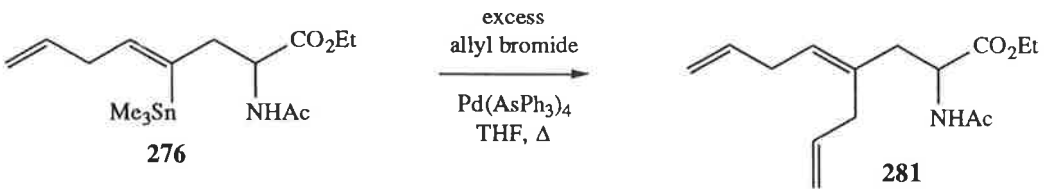
The coupled product (**276**) was assigned the stucture shown because the methylene group at C6 and the vinylic proton at C5 resonated in the ^{1}H n.m.r. spectrum as a broad triplet at δ2.73 and a triplet at 5.93 respectively, whereas a doublet and singlet would have been expected for the corresponding protons of the alternative coupled product (**277**). Also $^{117/119}$Sn satellites were evident at the resonance of the C3-methylene group at δ2.44 and 2.68 (with $^3J_{SnH}$ = *ca* 60Hz), and these were seen for the corresponding methylene protons of the γ-stannane (**141**), but not for the δ-stannanes (**138** and **139**) (*Chapter 3.3*).



217 **278** **121** **279** **280**

Scheme 5.7

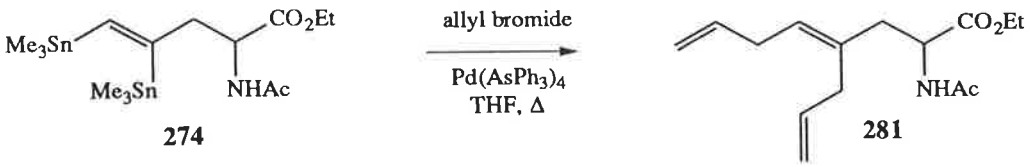
The formation of the propargylglycinate (**121**) was an unexpected result and the mechanism by which it forms is uncertain, but we have proposed a plausible route to this product (*Scheme 5.7*). After oxidative addition and transmetallation the intermediate π-allyl-palladium(II) vinylstannane (**278**) is formed. It is possible that this intermediate undergoes reductive elimination in two ways. The first is the expected carbon-carbon bond forming process proposed for Stille reactions and this yields **276**. The alternative is perhaps an allyl migration from palladium to tin *via* either five or seven membered transition states (**279** or **280**) leading to alkyne formation (**121**) and simultaneous elimination of palladium(0) and allyltrimethylstannane. We did not attempt to isolate the allyltrimethylstannane. Perhaps this reaction is unique to **274**, where elimination may be assisted by the neighbouring amide or ester functional groups, since elimination was not reported by Mitchell as having occurred in any of the coupling reactions of a number of vinyl ditins with allyl bromide, although different catalysts were used.[187] That **121** was not formed by fragmentation of **276** was determined by the coupling of **276** with an excess of allyl bromide under similar conditions as those above (*Scheme 5.8*). In that case, the only product obtained was from Stille coupling (*i.e.* **281**).



276 **281**

Scheme 5.8

Reaction of the vinyl ditin (**274**) with an excess of allyl bromide under the same conditions gave the *cis*-disubstituted product (**281**) in moderate yield (*Scheme 5.9*).

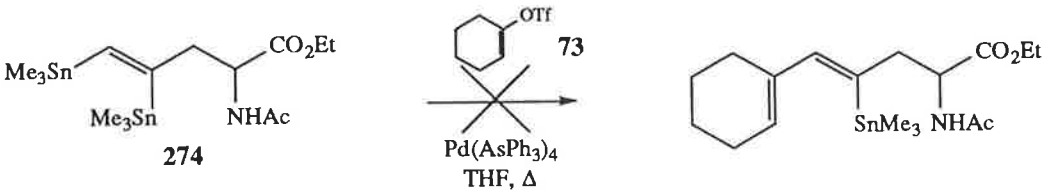


274 **281**

Scheme 5.9

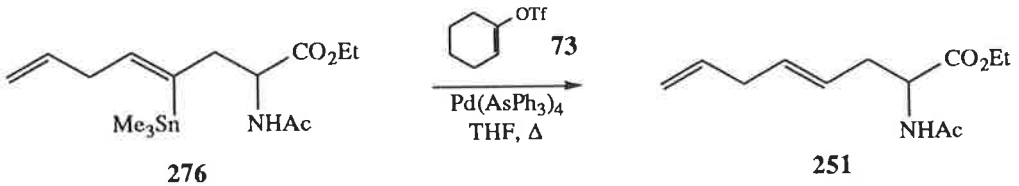
Stereochemistry was tentatively assigned based on the expected stereospecificity of the Stille coupling. The amount of propargylglycine (**121**) appeared, by t.l.c., to be less than that formed when one equivalent of allyl bromide had been used, but it was not isolated. Presumably the direct reductive elimination (**279/280** to **276**) is facilitated by the presence of excess electrophile.

We attempted the coupling reaction of the ditin (**274**) with cyclohexenyl triflate (**73**) (*Scheme 5.10*), but with one equivalent or with a large excess of triflate the reactions, under the same conditions used above (*i.e.* no lithium chloride), produced a complex mixture of many minor products as ajudged by t.l.c. No major product was observed and the reaction was not worked up. We also attempted the coupling of the stannane **276** with this triflate, but again the reaction formed a number of products and the only one which seemed to have been produced in significant amount was found to be the protodestannylated compound (**251**) (30%) (*Scheme 5.11*). This product had a ^{1}H n.m.r. spectrum identical to that obained from coupling of allyltributyltin with *E*-δ-iodoallylglycinate (**223**) (*Chapter 4.6*). The reason **251** formed is unknown, but it is unlikely to have occurred on silica gel during purification since the stannane **276** was never observed to undergo protodestannylation upon chromatographic purification.



274

Scheme 5.10

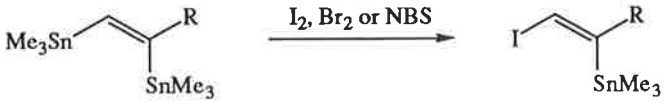


276 **251**

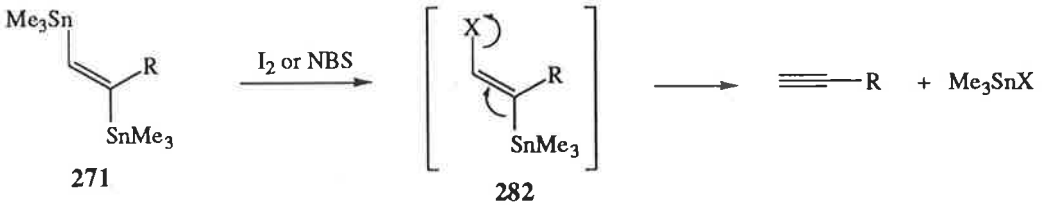
Scheme 5.11

5.3 Iododestannylation of *cis*-ethyl N-acetylbis(trimethylstannyl)allylglycinate

Reaction of *cis*-1,2-bis(trimethylstannyl)-1-alkenes (**270**) with iodine or bromine proceeds regioselectively to form 1-halo-2-trimethylstannyl-1-alkenes as the stereochemically pure *Z*-isomers (*Scheme 5.12*).[187] The chemistry of these interesting synthetic intermediates has yet to be reported. Interestingly, Mitchell observed that the corresponding *trans*-ditins (**271**) were unstable to halodestannylation with iodine or NBS and formed 1-alkynes as major products.[187] Presumably the intermediate *E*-1-halo-2-stannyl-1-alkenes (**282**) form but are unstable at room temperature and readily undergoes antiperiplanar elimination of the elements of trimethyltin halide (*Scheme 5.13*). On the other hand, the *Z*-iodostannylalkenes were found to be quite stable and could be purified by distillation.[187]

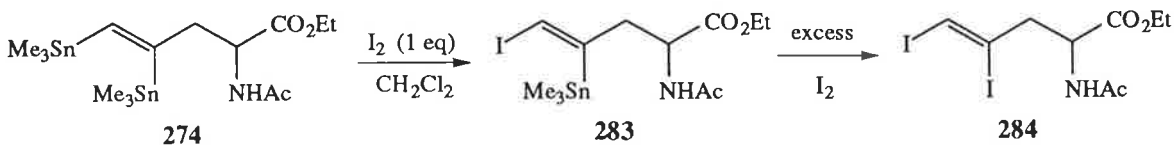


Scheme 5.12



Scheme 5.13

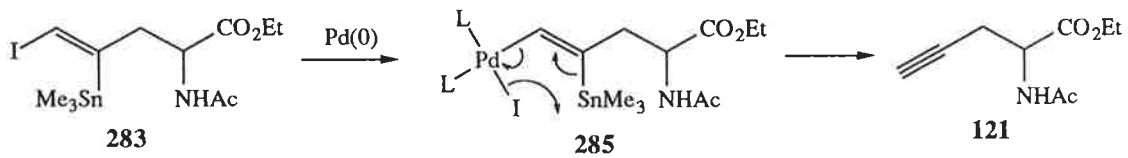
We explored the reaction of the *cis*-vinyl ditin (**274**) with iodine in either dichloromethane or chloroform at room temperature (*Scheme 5.14*). With one equivalent of iodine, the reaction was extremely rapid and the product (**283**) was formed virtually instantly and was isolated in moderate yield (62%). The regio and stereochemistry was tentatively assigned as shown based on the known stereospecificity of the iododestannylation reaction of vinylstannanes, the expected instability of the corresponding *E*-iodostannane and the expected higher reactivity of the δ relative to the γ-stannyl group towards electrophilic substitution. The ^{1}H and ^{13}C n.m.r. spectra were consistent with the data reported by Mitchell for a series of



Scheme 5.14

iodostannyl alkenes (*i.e.* vinylic proton at δ6.77 with satellites, $^3J_{Sn\text{-}H}$=109Hz [*c.f.* lit. $^3J_{SnH}$ = 109-114Hz][187] and olefinic carbons at δ90.6 [protonated, C5; *c.f.* lit. range δ86.7-91.3][187] and 156.8 [quarternary, C4; *c.f.* lit. range of δ147.2-169.2][187]). Reaction of **274** with an excess of iodine in chloroform resulted in much decomposition and a low yield (27%) of diiodide (**284**) was obtained. The stereochemistry was tentatively assigned as *cis* based on the expected stereospecificity of the reaction.

We had initially believed that the *Z*-5-iodo-4-(trimethylstannyl)allylglycinate (**283**) would be a promising substrate for palladium catalysed coupling reactions. However, the observation that propargylglycinate (**121**) formed in the Stille coupling reaction of **274** (*Scheme 5.6*) suggested that the intermediate *Z*-palladium(II) stannylalkene (**285**), formed after oxidative addition of **283** to palladium(0), may also result in this elimination product (*Scheme 5.15*). In order to test this hypothesis, the iodostannylalkene (**283**) was stirred in a THF solution with $Pd(AsPh_3)_4$ (5mol%) at room temperature for 20 minutes (then at reflux for 30 minutes) and a very clean reaction mixture resulted in the formation of propargylglycinate (**121**) in good yield (87%). An intermediate five-membered ring transition state is assumed to be responsible for transfer of the iodide from palladium to tin leading to formation of **121**, trimethyltin iodide and palladium(0). This result seems to rule out most palladium catalysed coupling reactions for this iodostannylalkene (**283**) except perhaps Stille reactions with electrophiles which undergo oxidative addition to palladium faster than does the vinyl iodide (*i.e.* reaction of the stannyl moiety of **283** and not the iodide; *e.g.* Stille coupling with acid chlorides). Again, elimination of this type may be unique to this amino acid derivative for which either the amide or ester groups could lend anchimeric assistance towards cleavage of the tin-carbon bond.



283 **285** **121**

Scheme 5.15

^{1}H and ^{13}C nuclear magnetic resonance (n.m.r.) spectra were recorded using either a Bruker ACP-300 or Bruker CXP-300 spectrometer as dilute solutions in deuteriochloroform, unless otherwise noted. Chemical shift values are given in parts per million (p.p.m.) relative to the internal standard, tetramethylsilane. N.m.r multiplicities are abbreviated as follows: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *quin* = quintet, *m* = multiplet, *br* = broad. Infrared (i.r.) spectra were recorded using a Hitachi 270-30 spectrophotometer as neat films, nujol mulls or chloroform solutions as indicated. I.r. peak shapes are abbreviated as follows: *s* = strong, *m* = medium, *w* = weak, *br* = broad. Electron impact (e.i.) mass spectra and accurate mass measurements were obtained using an AIG-GEC MS3074 spectrometer. Fast atom bombardment (f.a.b.) mass spectra were obtained using a VG ZAB 2HF spectrometer. Optical rotation data were obtained on a Perkin Elmer 141 Polarimeter measured with sodium D light (589nm). Melting points (m.p.) were determined using a Kofler hot stage with a Reichert microscope and are uncorrected. Elemental analyses were determined by Chemical and Micro Analytical Services, Melbourne, Australia.

Thin layer chromatography was carried out on Merck Alufolien Kieselgel 60 PF_{254} plates which were visualised by ultraviolet light (254nm) and by staining with an acidic aqueous solution of ammonium molybdate, a 5% ethanolic solution of phosphomolybdic acid or a 5% ethanolic solution of vanillin followed by development with heat. Flash and 'squat' column chromatographies were carried out using Merck Silica Gel 60 (230-400 mesh) and Merck Silica Gel 60 PF_{254} respectively.

All solvents were distilled prior to use. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium/benzophenone prior to use. Dimethyl formamide (DMF) was distilled from sodium sulphate under reduced pressure and stored over 4Å molecular sieves. Acetonitrile was distilled from calcium hydride and stored over 4Å molecular sieves. Light petroleum refers to the fraction of boiling point 66-69°. Organic extracts were dried with magnesium sulphate.

The following compounds were prepared according to known procedures: tetrakis(triphenylphosphine)palladium,[190] dichlorobis(triphenylphosphine)palladium,[191] dichlorobis(acetonitrile)palladium,[192] tris(dibenzylidine)dipalladium chloroform complex,[193] tri(2-furyl)phosphine,[194] 2,6-di-*t*-butyl-4-methylpyridine,[195] trifluoromethanesulphonic

anhydride,[196] N-phenyltriflimide,[197] 2-{[(trifluoromethyl)sulphonyl]oxy}quinoline,[198] ethyl 2-{[(trifluoromethyl)sulphonyl]oxy}-1-cyclopentene-1-carboxylate,[199] 1-hydroxymethyl-2-{[(trifluoromethyl)sulphonyl]oxy}-1-cyclooctene,[183] ethyl 2-{[trifluoromethyl)sulphonyl]-oxy}benzoate,[200] propargyl trifluoromethanesulphonate,[167] benzimidazole trifluoromethane-sulphonate,[201] ethyl *Z*-2-iodoacrylate,[95] tributyltin hydride,[202] hexamethylditin,[203] trimethyl(2-propenyl)stannane,[204] *E*-1-(trimethylsilyl)-2-(trimethylstannyl)ethene,[205] (β-styryl)trimethylstannane,[206] phenyltributylstannane,[207] allyltributylstannane,[208] N-acetyl-*D,L*-propargylglycine (**119**),[101a] diethyl α-acetamido-α-propargylmalonate (**118**),[101a] methyl *L*-2-[(benzyloxycarbonyl)amino]-4-(methylsulphinyl)butanoate (**56**),[26] and methyl N-ethoxycarbonyl-α-chloroglycinate.[24d] 17β-acetyloxyandrosterone and 3β-acetyloxy-epiandrosterone were prepared by reaction of 17β-androsterone and 3β-epiandrosterone respectively with acetic anhydride, triethylamine and DMAP in dichloromethane; O-methylestrone was prepared from estrone by reaction with methyl iodide and sodium hydride in DMF.

Chapter 2.2

Methyl N-benzyloxycarbonyl-*L*-vinylglycinate (57)

Methyl *L*-2-[(benzyloxycarbonyl)amino]-4-(methylsulphinyl)butanoate (**56**) (7.5g) in a 1 litre round bottom flask was added to an Aldrich™ Kugelrohr preheated to 185° and the pressure quickly reduced to 0.2-0.3mm. The flask was rapidly oscillated (*ca* 100min^{-1}) and the pyrolysate collected in an ice-cooled bulb for 90 minutes (crude yield of 6.6g). Chromatography on silica gel gave the title compound as a light yellow oil [4.2g, 78% based on recovered sulphoxide (0.75g)]. $[\alpha]_D$ = -11.8° (*c*3.0, MeOH) [lit. -11.8° (*c*1.8, MeOH)[26a]]. Other spectroscopic data consistent with literature values.[26a]

N-benzyloxycarbonyl-*L*-vinylglycine (59)

Method 1, Acid hydrolysis: A solution of methyl N-CBz-*L*-vinylglycinate (**57**) (5.0g, 20.1mmol) in 1N hydrochloric acid (40ml) and acetic acid (40ml) was heated at reflux for 90 minutes. The solution was concentrated and the residue extracted with ethyl acetate (4x25ml). The extracts were dried and the solvent evaporated. The yellow solid thus obtained was recrystallised from ethyl acetate/light petroleum to yield two crops of the title compound as

white plates (3.2g, 68%). M.p. 128-130° (lit. 130-131°)[78]; ^{1}H nmr: 4.87 (*br*, 1H, α-H), 5.11 (*s*, 2H, benzylic), 5.23 (*dd*, *J*1.1, 10.2Hz, 1H, C<u>H</u>$_2$=CH), 5.36 (*dd*, *J*1.0, 17.2Hz, 1H, C<u>H</u>$_2$=CH), 5.90 (*br d*, 1H, NH), 5.95 (*ddd*, *J*5.4, 10.3, 17.3Hz, 1H, CH$_2$=C<u>H</u>), 7.34 (*br s*, 5H), 7.77 (*br*, 1H, CO$_2$H); ^{13}C nmr: 55.92 (α-C), 66.57 (Ph<u>C</u>H$_2$), 116.81 (<u>C</u>H$_2$=CH), 127.73, 128.13, 132.60 (CH$_2$=<u>C</u>H), 132.98, 136.04, 155.50 (urethane C=O), 171.87 (<u>C</u>O$_2$H); IR (nujol mull): 3404*m*, 3200-2400(*br*, *m*), 1746*m*, 1730*m*, 1668*s*, 1538*m*, 1418*w*, 1342*w*, 1254*m*, 1204*m*, 1180*w*, 1090*m*, 992*m*, 938*m*, 776*w*, 730*m*, 696*w*; MS: 236 ([M+H]$^+$, 32%), 235 (M$^+$, 23, calc. for $C_{12}H_{13}NO_4$: 235.0845, found: 235.0835), 217 ([M-H$_2$O]$^+$, 10), 190 ([M-CO$_2$H]$^+$, 100), 174 (36), 146 (65), 108 (71), 91 (88); $[\alpha]_D$= +13.3° (*c*1.48, CHCl$_3$) (measured prior to recrystallisation); Calc. for $C_{12}H_{13}NO_4$: C 61.27%, H 5.57, N 5.95. Found: C 61.18, H 5.37, N 5.80. $[\alpha]_D$ = +13.6° (*c*1.70, CHCl$_3$). Hydrolysis of **59** in 6N hydrochloric acid solution at reflux for 60 minutes gave *L*-vinylglycine hydrochloride (**60**); $[\alpha]_D$ = +80.4° (*c* 0.54, H$_2$O) [lit. +78.5°, (*c*1.9, H$_2$O)].[26a]

N-benzyloxycarbonyl-*L*-vinylglycine (59)

Method 2, <u>Palladium catalysed hydrogenolysis</u>: A solution of allyl N-benzyloxycarbonyl-*L*-vinylglycinate (**64**) (108mg, 0.39mmol) and bis(triphenylphosphine)palladium chloride (28mg, 0.039mmol) was brought to reflux in dioxane. Tri-*n*-butyltin hydride (114mg, 0.39mmol) was added dropwise *via* syringe to the boiling solution. After 10min the black solution was cooled, the dioxane removed *in vacuo*, and the residue chromatographed on silica gel (eluant:- ethyl acetate: light petroleum:acetic acid - 10:10:1) to yield N-CBz-*L*-vinylglycine (**27**) (86mg, 93%) which was recrystallised from ethyl acetate/light petroleum to give white flakes. M.p. 126-128° (lit. 130-131°);[78] spectral data as for product obtained using *Method 1* above.

Allyl N-benzyloxycarbonyl-*L*-vinylglycinate (64)

To a stirred solution of methyl N-benzyloxycarbonyl-*L*-vinylglycinate (**57**) (200mg, 0.80mmol) in allyl alcohol (10ml) under a nitrogen atmosphere was added titanium tetraisopropoxide (106µl, 0.36mmol) *via* syringe. The solution was heated at 65-70° for 30h. A further charge of titanium tetraisopropoxide (500µl, 1.68mmol) was added to the warm solution and heating continued for another 24h. The solution was acidified with 1N

hydrochloric acid solution and extracted with dichloromethane. The extracts were washed with saturated brine and the solvents evaporated to an orange oil. Chromatography on silica gel gave the title compound as a clear oil (184mg, 83%). B.p. *ca* 150°/0.045mm (Kugelrohr); ^{1}H nmr: 4.65 (*d*, *J*5.5Hz, 2H), 4.96 (*br*, 1H, α-H), 5.13 (*s*, 2H, benzylic), 5.20-5.41 (*m*, 4H, $C\underline{H}_2$=CH), 5.50 (*br*, 1H, NH), 5.90 (*m*, 2H, CH_2=C$\underline{H}$); ^{13}C nmr: 56.19 (α-carbon), 66.21 ($CO_2\underline{C}H_2$), 67.12 (Ph$\underline{C}H_2$), 117.78 ($\underline{C}H_2$=CH), 118.88 ($\underline{C}H_2$=CH), 128.08, 128.50, 131.30 (CH_2=$\underline{C}$H), 132.34 (CH_2=$\underline{C}$H), 136.15, 155.49 (urethane C=O), 173.67 (ester C=O); IR (neat): 3352(*br*, *m*), 3032*w*, 2948*w*, 1724*s*, 1646*w*, 1516*s*, 1458*m*, 1334*m*, 1272*w*, 1240*w*, 1190*w*, 1048*m*, 1028*w*, 990*m*, 936*m*, 776*w*, 740*m*, 700*m*; MS: 276 ([M+H]$^+$, 11%), 275 (M$^+$, 7, calc. for $C_{15}H_{17}NO_4$: 275.1158, found: 275.1171), 232 (6), 214 (3), 190 (51), 146 (20), 91 (100), 41 (58); $[\alpha]_D$ = -8.9° (*c*0.56, $CHCl_3$).

_L_-2-[(benzyloxycarbonyl)amino]-4-(methylsulphyl)butanol (67)

Sodium borohydride (1.27g, 33.6mmol) was added to methyl N-CBz-*L*-methioninate (**55**) (10.0g, 33.6mmol) in dry ethanol (50ml) at 0°C. The reaction was monitored by t.l.c. and further sodium borohydride (2x1.0g, 2x26.5mmol) was added at hourly intervals. When the t.l.c. indicated no ester remained (*ca* 4h), dilute hydrochloric acid was added, the ethanol evaporated *in vacuo* and the residual aqueous phase extracted with dichloromethane. The extracts were dried and the solvent evaporated to give a thick oil which crystallised from ethyl acetate/light petroleum to yield fine white crystals (6.96g, 77%). M.p. 72.5-73°; ^{1}H n.m.r.: 1.80 (*m*, 2H, C3-H's), 2.09 (*s*, 3H, CH_3S), 2.29 (*s*, 1H, OH), 2.54 (*m*, 2H, C4-H's), 3.63 (*dd*, *J*5.0, 11.0Hz, 1H, C1-H), 3.68 (*dd*, *J*3.8, 11.0Hz, 1H, C1-H), 3.82 (*m*, 1H, C2-H), 5.09 (*s*, 2H, benzylic), 5.15 (*br d*, 1H, NH), 7.34 (*m*, 5H); IR (nujol mull): 3320s, 1684s, 1538s, 1318w, 1284m, 1260m, 1232w, 1140w, 1068m, 1038w, 1012w, 752w, 726m, 698m.

_L_-2-[(benzyloxycarbonyl)amino]-4-(methylsulphinyl)butanol (68)

To a solution of *L*-2-[(benzyloxycarbonyl)amino]-4-(methylsulphyl)butanol (**67**) (6.96g, 25.8mmol) in methanol (60ml) was added dropwise a solution of sodium periodate (5.80g, 27.1mmol) in water (30ml) over a 30 minute period, then stirred at room temperature for 2

hours. The thick, white suspension was filtered through a sintered funnel and the solid washed with methanol. The combined methanolic phases were evaporated *in vacuo*, water (*ca* 20ml) was added and the aqueous phase extracted with chloroform (5x50ml.) The extracts were dried and the solvent evaporated to yield a thick oil which solidified on standing (6.95g, 94%). ^{1}H n.m.r.: 2.06 (*m*, 2H, C3-H's), 2.39 (*s*, 3H, CH_3S), 2.54 (*s*, 1H, OH), 2.77 (*t*, *J*7.4Hz, 2H, C4-H's), 3.69 (*m*, 2H, C1-H's), 3.81 (*m*, 1H, C2-H's), 5.10 (*s*, 2H, benzylic), 5.70 (*br*, 1H, NH), 7.36 (*s*, 5H).

L-2-[(benzyloxycarbonyl)amino]-but-3-enol (69)

A suspension of sulphoxide (**68**) (301mg, 1.05mmol) in *o*-dichlorobenzene (10ml) was heated at 170° for 18h. T.l.c. indicated no sulphoxide remained and a new product had formed. The solvent was evaporated *in vacuo* and the residue chromatographed on silica gel to yield a white solid (149mg, 64%). M.p. 51-52° (lit. 52-53.5°)[83]; ^{1}H nmr: 3.06 (*br*, 1H, OH), 3.58 (*br*, 1H, C1-H), 3.67 (*br*, 1H, C1-H), 4.28 (*br*, 1H, C2–H), 5.08 (*s*, 2H, benzylic), 5.19 (*d*, *J*10.3Hz, 1H, *cis* C4-H), 5.23 (*d*, *J*16.4Hz, 1H, *trans* C4-H), 5.48 (*br d*, 1H, NH), 5.77 (*ddd*, *J*5.3, 10.4, 16.5Hz, 1H, C3-H), 7.31 (*br s*, 5H); ^{13}C nmr: 54.93 (C2), 64.56 (C1), 66.84 ($PhCH_2$), 116.51 (C4), 128.07, 128.43, 135.07 (C3), 136.07, 136.15, 156.41 (C=O); IR (neat): 3700-3100(*br*, *s*), 3064*w*, 2944*w*, 1698*s*, 1530(*br*, *s*), 1458*m*, 1414*w*, 1342*m*, 1252(*br*, *m*), 1072(*br*, *m*), 928*m*, 778*w*, 738*m*, 698*m*; $[\alpha]_D$ = +30.4° (*c*0.84, $CHCl_3$) [lit: -32.1° (*c*3.1, $CHCl_3$)[83]]

L-2-[(benzyloxycarbonyl)amino]-but-3-enyl acetate (71)

To a solution of *L*-2-[(benzyloxycarbonyl)amino]-4-(methylsulphinyl)-butanol (**68**) (6.95g, 24.4mmol), acetic anhydride (3.45ml, 36.5mmol) and triethylamine (5.09ml, 36.5mmol) in chloroform (125ml) was added 4-dimethylaminopyridine (0.60g, 4.28mmol.) The solution was stirred for 60min then washed with 1N hydrochloric acid, dried and the chloroform evaporated to yield a thick oil (8.63g). A portion (600mg) was dissolved on *o*-dichlorobenzene (10ml) and heated at 170° for 24h. The solvent was removed *in vacuo*, and the residue chromatographed on silica gel to yield the title compound (411mg, 92%.) Recrystallisation from dichloromethane/light petroleum gave fine white needles. M.p. 54-56°; ^{1}H nmr: 1.95 (*s*,

3H), 4.06 (*m*, 2H, C1-H's), 4.43 (*br*, 1H, C2–H), 4.94-5.07 (*br*, 1H, NH), 5.04 (*s*, 2H, benzylic), 5.15 (*d*, *J*10.6Hz, 1H, *cis* C4-H), 5.20 (*d*, *J*17.6Hz, 1H, *trans* C4-H), 5.71 (*ddd*, *J*5.4, 10.6, 17.5Hz, 1H, C3-H), 7.29 (*br s*, 5H); ^{13}C nmr: 20.68 (CH_3), 52.20 (C2), 65.53 (C1), 66.89 (Ph$\underline{C}H_2$), 116.87 (C4), 128.12, 128.16, 128.49, 134.35 (C3), 136.20, 155.69 (urethane C=O), 170.86 (acetate C=O); IR (nujol mull): 3332*s*, 1730*s*, 1696*s*, 1540*s*, 1348*w*, 1302*w*, 1276*w*, 1250*m*, 1110*w*, 1088*w*, 1044*w*, 964*w*, 928*w*, 740*w*, 698*w*; MS: 264 ($[M+H]^+$, 4%), 263 (M^+, 6, calc. for $C_{14}H_{17}NO_4$: 263.1158, found: 263.1144), 203 ($[M-AcOH]^+$, 24), 190 ($[M-CH_2OAc]^+$, 99), 146 (99), 91 (100), 43 (100); microanalysis: calc. for $C_{14}H_{17}NO_4$: C 63.86%, H 6.51, N 5.32. Found: C 63.97, H 6.55, N 5.34; $[\alpha]_D$= -43.2° (*c*0.94, $CHCl_3$). A portion of **71** (100mg, 0.38mmol) was stirred in methanol (10ml) containing potassium hydroxide (1mg, 0.018mmol) at room temperature. After 8h, some acetate remained (t.l.c.) so further potassium hydroxide (3mg, 0.054mmol) was added and the solution stirred for a further 3 days. The methanol was evaporated, the residue taken up into dichloromethane and washed with water. The organic phase was dried and the solvent evaporated. Flash chromatography on silica gel gave the alcohol **69** (69mg, 82%) which had $[\alpha]_D$ = -29.6° (*c*0.69, $CHCl_3$) [92% optical purity based on lit. value of -32.1° (*c*3.1, $CHCl_3$)[83].

Chapter 2.3

3,4-Dihydronaphth-1-yl trifluoromethanesulphonate (α-tetralenyl triflate) (74)

Reaction of α-tetralone with triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine gave the title compound as a fragrant, clear oil (26%). B.p. (Kugelrohr): *ca* 90°/0.04mm; ^{1}H nmr: 2.48 (*br*, 2H), 2.86 (*t*, *J*7.7Hz, 2H), 6.03 (*br s*, 1H, vinylic proton), 7.00-7.50 (*m*, 4H); ^{13}C nmr: 22.17, 26.70, 116.47 & 120.70 (central peaks of *q*, $\underline{C}F_3$, J_{CF}319Hz), 117.78, 121.09, 126.82, 127.69, 129.10, 136.15; IR (neat): 3068*w*, 3024*w*, 2936*m*, 2836*w*, 1652*m*, 1604*w*, 1488*m*, 1456*w*, 1422*s*, 1362*m*, 1338*m*, 1248*m*, 1216*s*, 1142*s*, 1058*m*, 1014*s*, 902*s*, 848*m*, 826*m*, 808*m*, 762*s*, 738*m*, 702*m*, 622*m*, 600*m*; MS: 278 (M^+, 78%), 145 ($[M-CF_3SO_2]^+$, 100), 129 (22), 128 (18), 127 (13), 117 (22), 115 (21).

Cholesta-3,5-dien-3-yl trifluoromethanesulphonate (75)

Triflic anhydride (1.31ml, 2.2g, 7.8mmol) was added *via* syringe to a solution of (+)-4-

cholestenone (2.0g, 5.2mmol) and 2,6-di-*t*-butyl-4-methylpyridine (1.7g, 8.3mmol) in dichloromethane (20ml). The solution was stirred for 6h at room temperature, by which time t.l.c. analysis indicated some enone remained so further charges of triflic anhydride (0.43ml, 0.73g, 2.6mmol) and base (0.57g, 2.8mmol) were added and the mixture stirred for a further 15h. The solvent was evaporated and pentane was added to the residue. Filtration of the pyridinium salt, evaporation of the pentane from the filtrate and chromatography of the residue on silica gel gave an off white solid. Recrystallisation from methanol/ethyl acetate/water gave the title compound as a white solid (1.3g, 46%). M.p. 124-126° (lit. 125-126°)[86] ^{1}H nmr: 0.68 (*s*, 3H), 0.84 (*d*, *J*6.8Hz, 6H), 0.89 (*d*, *J*6.4Hz, 3H), 0.93 (*s*, 3H), 0.50-2.70 (*m*, 41H), 5.55 (*m*, 1H, C6-H), 5.96 (*s*, 1H, C4-H); ^{13}C nmr: 11.93, 18.60, 18.67, 21.15, 22.54, 22.80, 23.93, 24.14, 25.54, 27.99, 28.18, 31.57, 31.93, 33.73, 35.74, 36.12, 39.47, 39.57, 47.67, 56.05, 56.65, 120.53, 125.41, 126.37, 146.90 (C-OTf); IR (nujol mull): 1660*w*, 1636*w*, 1420*s*, 1310*w*, 1246*s*, 1204*s*, 1146*s*, 1054*s*, 1004*m*, 920*s*, 902*s*, 870*w*, 832*w*, 788*w*, 740*w*, 660*w*, 608*m*; MS: 516 (M^+, 16%, calc. for $C_{28}H_{43}F_3O_3S$: 516.2885, found: 516.2875), 384 (19), 383 ([M-CF_3SO_2]$^+$, 21), 229 (15), 43 (100); $[\alpha]_D$= -70.1° (*c*0.75, $CHCl_3$).

17β-acetyloxyandrost-2-en-3-yl trifluoromethanesulphonate (Δ^2-**76**)

Reaction of 17β-acetyloxyandrosterone with triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine gave the title compound, as a mixture with its Δ^3-regioisomer. Stirring the mixture of isomers in dichloromethane (10ml) in the presence of triflic acid (one drop) and triflic anhydride (1ml) for 5 days followed by a basic wash and flash chromatography yielded a white solid (31%) (86:14 Δ^2:Δ^3 isomers). M.p. 116-119°; ^{1}H nmr: 0.75 (*s*, 6H), 1.98 (*s*, 3H), 0.65-2.40 (*m*, 20H), 4.54 (*t*, *J*8.2Hz, 1H), 5.33 (*s*, Δ^3-isomer, C4-H, 16%), 5.60 (*br d*, Δ^2-isomer, C2-H, 84%); ^{13}C nmr: Major isomer:- 11.52, 11.96, 20.65, 21.06, 23.42, 27.42, 27.99, 30.90, 31.97, 35.15, 36.74, 38.34, 42.10, 42.45, 50.51, 53.22, 82.63, 116.35 & 120.61 (central peaks of *q*, CF_3, J_{CF}321Hz), 116.98 (C-OTf), 147.54 (CH=COTf), 171.08; IR (nujol mull): 1734*s*, 1700*w*, 1464*s*, 1408*s*, 1246*s*, 1198*s*, 1154*w*, 1140*s*, 1036*s*, 1006*w*, 900*m*, 892*m*, 866*s*, 622*m*; MS: 464 (M^+, 9%, calc. for $C_{22}H_{31}F_3O_5S$: 464.1844, found: 464.1838), 449 ([M-Me]$^+$, 1), 404 ([M-AcOH]$^+$, 59), 389 ([M-AcOH-Me]$^+$, 50), 331

([M-CF_3SO_2]$^+$, 68), 271 (77), 262 ([M-C_4H_6OTf]$^+$, 68), 202 ([C_4H_5OTf]$^+$, 86), 201 (100); $[\alpha]_D$= +31.2° (*c*0.60, $CHCl_3$).

Trifluoromethyl 3-methoxyestra-1,3,5(10),16-tetraen-17-sulphonate (77)

Reaction of 3-O-methylestrone with triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine gave the title compound as a thick oil (69%). ^{1}H nmr: 1.00 (*s*, 3H), 1.2-2.5 (*m*, 11H), 2.87 (*m*, 2H), 3.78 (*s*, 3H), 5.61 (*m*, 1H, C<u>H</u>=COTf), 6.64 (*d*, *J*2.6Hz, 1H), 6.72 (*dd*, *J*2.8, 8.5Hz, 1H), 7.21 (*d*, *J*8.7Hz, 1H); ^{13}C nmr: 15.31, 25.79, 26.72, 28.35, 29.43, 32.69, 36.66, 44.16, 45.05, 53.50, 55.18, 111.47, 113.88, 114.46 (<u>C</u>H=COTf), 116.46 & 120.69 (central peaks of *q*, <u>C</u>F_3, J_{CF}319Hz), 125.95, 132.10, 137.65, 157.56, 159.28 (<u>C</u>-OTf); IR (neat): 2924*s*, 2850*s*, 1628*m*, 1612*m*, 1576*w*, 1504*s*, 1466*m*, 1424*s*, 1378*m*, 1310*m*, 1284*m*, 1244*s*, 1212*s*, 1144*s*, 1072*m*, 1056*s*, 1036*m*, 966*w*, 918*s*, 860*s*, 822*m*, 766*w*, 720*w*, 606*m*; MS: 416 (M$^+$, 100%, calc. for $C_{20}H_{23}F_3O_4S$: 416.1269, found: 416.1282), 283 ([M-CF_3SO_2]$^+$, 23), 199 (15), 173 (21), 160 (35); $[\alpha]_D$= +65.3° (*c*0.59, $CHCl_3$).

3β-Acetyloxyepiandrost-16-en-17-yl trifluoromethanesulphonate (78)

Reaction of 3β-acetyloxyepiandrosterone with triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine gave the title compound as a white solid (33%). ^{1}H nmr: 0.65-0.81 (*m*, 1H), 0.81 (*s*, 3H), 0.91 (*s*, 3H), 0.85-1.10 (*m*, 2H), 1.10-1.70 (*m*, 14H), 1.70-1.80 (*m*, 1H), 1.80-2.00 (*m*, 1H), 1.97 (*s*, 3H), 2.10-2.20 (*m*, 1H), 4.64 (*tt*, *J*5.0, 11.3Hz, 1H), 5.51 (*dd*, *J*1.7, 3.2Hz, 1H); ^{13}C nmr: 12.07, 15.23, 20.41, 21.39, 27.30, 28.15, 28.45, 30.66, 32.57, 33.36, 33.86, 35.63, 36.38, 44.75, 54.06, 54.50, 73.41, 114.41 (<u>C</u>H=COTf), 120.62, 159.22 (CH=<u>C</u>OTf), 170.64; IR (nujol mull): 1738*s*, 1630*w*, 1462*s*, 1244*s*, 1214*s*, 1144*s*, 1074*m*, 1050*m*, 1026*m*, 930*m*, 914*m*, 870*m*, 850*m*, 820*m*; MS: 464 (M$^+$, 1%), 449 ([M-Me]$^+$, 10, calc. for $C_{21}H_{28}F_3O_5S$: 449.1610, found: 449.1643), 403 (49), 388 (100), 349 (16), 334 (16), 313 (27), 253 (27), 239 (27); $[\alpha]_D$ = +10.5° (*c*0.61, $CHCl_3$) (lit. +7°).[89]

Androst-2,16-dien-17-yl trifluoromethanesulphonate (79)

Reaction of 3β-acetyloxyepiandrosterone with triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine gave the title compound as a white solid (7%). ^{1}H nmr: 0.76 (*s*, 3H), 0.95 (*s*,

3H), 0.75-2.25 (*m*, 18H), 5.51-5.62 (*m*, 3H, vinylic protons); ^{13}C nmr: 11.54, 15.21, 20.11, 28.33, 28.49, 30.19, 30.56, 32.66, 33.49, 34.47, 39.39, 41.56, 44.73, 54.20, 54.35, 114.43 (CH=COTf), 116.42 & 120.67 (central peaks of *q*, CF_3, J_{CF}320Hz), 125.64, 125.80, 159.36 (C-OTf); IR (nujol mull): 3020*m*, 1656*w* (vinyl triflate C=C), 1630*m* (C=C), 1424*s*, 1300*m*, 1244*s*, 1216(*s*, *br*), 1144*s*, 1082*m*, 1066*s*, 1046*m*, 902*m*, 912*m*, 926*m*, 866*s*, 844*m*, 820*m*, 666*m*, 608*s*; MS: 404 (M^+, 11%, calc. for $C_{20}H_{27}F_3O_3S$: 404.1633, found: 404.1620), 389 ([M-Me]$^+$, 26), 350 ([M-C_4H_6]$^+$, retro-Diels-Alder fragmentation, 35), 350 ([M-C_4H_6-Me]$^+$, 91), 121 (26), 105 (61), 91 (100), 79 (78); $[\alpha]_D$= +58.8° (*c*0.46, $CHCl_3$).

3-(Carboethoxy)naphth-2-yl trifluoromethanesulphonate (82)

The title compound was prepared (46%) according to the general procedure of reference 55 (Method I) to yield the title compound as a pale brown solid. M.p. 111-114° (light petroleum). ^1H nmr: 1.44 (*t*, *J*7.3Hz, 3H), 4.48 (*q*, *J*7.2Hz, 2H), 7.61 (*m*, 2H), 7.70 (*s*, 1H), 7.84 (*d*, *J*8.1Hz, 1H), 7.94 (*d*, *J*7.9Hz, 1H), 8.60 (*s*, 1H); ^{13}C nmr: 14.08, 62.12, 116.70 & 120.95 (central peaks of *q*, CF_3, J_{CF}320Hz), 120.87, 127.40, 127.66, 127.98, 129.03, 129.63, 131.35, 134.65, 134.83, 163.94; IR (nujol mull): 1720*s*, 1630*w*, 1600*w*, 1510*w*, 1484*w*, 1422*s*, 1368*m*, 1292*s*, 1248*s*, 1202*s*, 1146*s*, 1052*s*, 1014*s*, 924*s*, 894*m*, 880*m*, 828*m*, 776*m*, 760*m*, 720*m*, 656*m*, 624*w*; MS: 348 (M^+, 46%, calc. for $C_{14}H_{11}F_3O_5S$: 348.0279, found: 348.0290), 303 ([M-EtO]$^+$, 17), 215 ([M-CF_3SO_2]$^+$, 37), 170 (46), 143 (100), 115 (49), 114 (49).

Chapter 2.4

The following procedure is representative of all the coupling reactions of N-CBz-*L*-vinylglycine (**59**):

***L*-[2-(benzyloxycarbonylamino)]-4-cyclohex-1-en-1-ylbut-3-enoic acid (85)**

A mixture of tetra-*n*-butylammonium chloride (76mg, 0.27mmol), palladium(II) acetate (5.0mg, 0.022mmol), tri-*o*-tolylphosphine (13mg, 0.043mmol), cyclohex-1-en-1-yl triflate (**73**) (52mg, 0.23mmol), potassium carbonate (155mg, 1.1mmol) and N-CBz-*L*-vinylglycine (**59**) (57mg, 0.24mmol) was heated at 50° for 6h in DMF (3ml). T.l.c. showed no olefin remained and a new intensely u.v. active spot had appeared. Dilute hydrochloric acid (50ml)

was added to the cooled solution which was then extracted with ether (5x50ml). The combined ether extracts were dried and the solvent evaporated. The residue was flash chromatographed on silica gel, gradient eluting with 30-50% ethyl acetate/light petroleum then 0.5-2% acetic acid in 50% ethyl acetate/light petroleum, to yield the title compound as a thick oil (59mg, 77%). ^{1}H nmr: *Major conformer* 1.50-1.75 (*m*, 4H), 2.00-2.20 (*m*, 4H), 4.95 (*br t*, 1H, α-proton), 5.12 (*s*, 2H), 5.52 (*m*, 2H, vinylic & NH), 5.81 (*br s*, 1H), 6.32 (*d*, *J*15.4Hz, 1H), 7.32 (*m*, 5H). *Minor conformer* 4.80 (*br*, 1H), 5.74 (*br s*, 1H), 6.27 (*d*, 1H, obscurred by major isomer); ^{13}C nmr: 22.22, 22.28, 24.29, 25.84, 55.71, 67.20, 118.64, 128.12, 128.46, 131.87, 134.44, 136.06, 137.16, 155.68, 174.62; IR ($CHCl_3$): 3450*w*, 2936*m*, 3040*w*, 2870*w*, 1722*s*, 1580*w*, 1504*m*, 1456*m*, 1425*w*, 1340*m*, 1218*m*, 1190*w*, 1140*w*; MS: 315 (M^+ - not detected), 269 ([M-HCO_2H]$^+$, 0.5%, calc. for $C_{17}H_{19}NO_2$: 269.1416, found: 269.1409), 179 (4), 151 (10), 108 (98), 107 (92), 91 (100). (FABMS): 316 ([M+H]$^+$); $[\alpha]_D$= +38.5° (*c*0.59, $CHCl_3$). Treatment of a dichloromethane solution of this coupled product (**85**) with excess ethereal diazomethane yielded methyl *L*-[2-(benzyloxycarbonylamino)]-4-cyclohex-1-en-1-ylbut-3-enoate (**100**) (84%). ^{1}H nmr: 1.50-1.65 (m, 4H), 2.00-2.10 (m, 4H), 3.72 (s, 3H), 4.88 (m, 1H, α), 5.08 (s, 2H, benzylic), 5.40-5.47 (m, 2H, NH & C3-H), 5.77 (br, 1H, cyclohexenyl vinylic), 6.26 (d, J15.6Hz, 1H, C4-H), 7.32 (s, 5H); ^{13}C nmr: 22.20, 22.26, 24.28, 25.84, 52.63, 55.80, 67.00, 118.93, 128.10, 128.47, 131.88, 134.40, 136.99 (NB: one aromatic overlapping), 155.71, 171.51; MS: 329 (M^+, <0.5%), 305 (9), 270 ([M-CO_2Me]$^+$, 16, calc. for $C_{17}H_{20}NO_2$: 270.1494, found: 270.1489), 225 (26), 194 (45), 177 (76), 107 (67), 91 (100, 67 (72).

***L*-[2-(benzyloxycarbonylamino)]-4-(cholesta-3,5-dien-3-yl)-but-3-enoic acid (86).** Reaction of N-CBz-*L*-vinylglycine (**59**) (0.64mmol) with triflate **75** (0.43mmol) for 2h at 60° gave the title compound as a thick oil (69%). ^{1}H nmr: 0.67 (*s*, 3H), 0.83 (*d*, *J*6.6Hz, 3H), 0.84 (*d*, *J*6.4Hz, 3H), 0.85 (*s*, 3H), 0.89 (*d*, *J*6.5Hz, 3H), 0.90-2.30 (*m*, 26H), 4.87 (*br*, 1H, α-proton - minor conformer present at δ4.81 [*ca* 25%]), 4.99 (*d*, *J*12.1Hz, 1H, diastereotopic benzylic proton), 5.08 (*d*, *J*12.0Hz, 1H, diastereotopic benzylic proton), 5.45 (*br s*, 1H), 5.59 (*dd*, *J*15.3, 6.0Hz, 1H), 5.76 (*br*, 1H, NH), 5.87 (*br s*, 1H), 6.27 (*d*, *J*15.3Hz, 1H), 7.26 (*m*, 5H), 8.70 (*br*, 1H, CO_2H); ^{13}C nmr: 11.94, 18.71, 19.08, 20.79,

21.10, 21.87, 22.54, 22.81, 23.87, 24.14, 27.97, 28.23, 31.67, 32.07, 33.39, 35.08, 35.80, 36.16, 39.47, 39.75, 42.42, 48.08, 56.18, 56.85, 67.07, 120.41, 126.07, 128.07, 128.45, 131.62, 132.11, 135.92, 136.13, 142.00; IR ($CDCl_3$): 3440*w*, 2940*s*, 2864*s*, 3600-2250(*br*, *m*), 1712*s*, 1628*w*, 1504*m*, 1468*w*, 1428*w*, 1382*w*, 1336*w*, 1250*m*, 1058*m*, 964*m*; MS: 601 (M^+ - not present), 557 ($[M-CO_2]^+$, 4%, calc. for $C_{38}H_{55}NO_2$: 557.4233, found: 557.4249), 511 (1), 493 (2), 466 (2), 450 (2), 449 (2), 350 (3), 335 (7), 108 (100), 91 (88), 79 (92), 44 (96); $[\alpha]_D$= -36.0° (*c*0.30, $CHCl_3$).

***L*-[2-(benzyloxycarbonylamino)]-4-(17β-acetyloxyandrost-2-en-3-yl)-but-3-enoic acid (87).** Reaction of N-CBz-*L*-vinylglycine (**59**) (0.34mmol) with triflate **76** (0.31mmol) for 3h at 70° gave the title compound as a thick oil (50%). ^{1}H nmr: 0.72 (*s*, 3H), 0.78 (*s*, 3H), 0.80-1.80 (*m*, 17H), 2.04 (*s*, 3H), 1.80-2.20 (*m*, 3H), 4.58 (*t*, *J*8.2Hz, 1H), 4.96 (*br t*, 1H, α-proton - minor conformer at 4.81ppm), 5.12 (*br s*, 2H), 5.40-5.60 (*m*, 2H), 5.70 (*br s*, 1H), 6.30 (*d*, *J*15.5Hz, 1H), 7.35 (*m*, 5H); ^{13}C nmr: 11.89, 12.02, 20.48, 21.20, 23.49, 27.47, 28.57, 29.37, 31.24, 34.90, 35.31, 36.84, 40.51, 41.16, 42.48, 50.61, 53.72, 67.24, 82.94, 128.14, 128.52, 130.74, 132.53, 136.62, 155.50, 171.48; IR (KBr disc): 3336(*m*, *br*), 2924*s*, 1734*s*, 1512*m*, 1456*w*, 1378*w*, 1342*w*, 1248*s*, 1044*s*, 968*m*, 776*w*, 740*w*, 698*m*; MS: 549 (M^+ - not present), 532 ($[M-OH]^+$, 0.1%), 503 ($[M-HCO_2H]^+$, 0.1), 446 (0.2), 441 (0.2), 370 (4), 328 (3), 256 (3), 202 (4), 179 (6), 151 (18), 108 (67), 107 (57), 91 (81), 88 (100). FABMS: 550 ($[M+H]^+$); $[\alpha]_D$= +86.9° (*c*0.57, $CHCl_3$).

***L*-[2-(benzyloxycarbonylamino)]-4-[(3-O-methyl)estr-16-en-17-yl)-but-3-enoic acid (88).** Reaction of N-CBz-*L*-vinylglycine (**59**) (0.64mmol) with triflate **77** (0.425mmol) for 4h at 75° gave the title compound as a thick oil (54%). ^{1}H nmr: 0.88 (*s*, 3H), 1.20-2.5 (*m*, 11H), 2.87 (*m*, 2H), 3.78 (*s*, 3H), 4.98 (*m*, 1H, α-proton - minor conformer at 4.83ppm), 5.13 (*m*, 2H, diastereotopic benzylic protons), 5.48 (*br d*, 1H, NH), 5.70-5.95 (*m*, 2H), 6.33 (*d*, *J*16.1Hz, 1H), 6.63 (*d*, *J*2.5Hz, 1H), 6.71 (*dd*, *J*2.6, 8.5Hz, 1H), 7.18 (*d*, *J*8.5Hz, 1H), 7.33 (*m*, 5H); ^{13}C nmr: 16.03, 26.52, 27.63, 29.67, 31.11, 35.27, 37.08, 44.14, 46.46, 55.18, 56.29, 56.38, 111.37, 113.78, 126.02, 128.16, 128.16, 128.53, 131.69, 132.52,

133.61, 137.90, 151.21, 157.36; IR (nujol mull): 3320(*m*,*br*), 1712*s*, 1610*w*, 1502*m*, 1344*w*, 1254*m*, 1048*m*, 968*w*, 774*w*, 722*w*, 698*w*; MS: 501 (M^+ - not present), 457 ([M-CO_2]$^+$, 10%, calc. for $C_{30}H_{35}NO_3$: 457.2617, found: 457.2630), 393 (10), 366 (10), 322 (24), 108 (100), 91 (97). FABMS: 502 ([M+H]$^+$); $[\alpha]_D$ = +64.4° (*c*0.86, $CHCl_3$).

***L*-[2-(benzyloxycarbonylamino)]-4-(3β-acetyloxyepiandrost-16-en-17-yl)-but-3-enoic acid (89).** Reaction of N-CBz-*L*-vinylglycine (**59**) (0.17mmol) with triflate **78** (0.21mmol) for 1h at 80-85° gave the title compound as a foam (34%). ^{1}H nmr: 0.60-0.75 (*br*, 1H), 0.81 (*s*, 6H), 0.82-1.98 (*m*, 17H), 1.99 (*s*, 3H), 2.00-2.15 (*m*, 2H), 4.65 (*m*, 1H, AcOC<u>H</u>), 4.75 & 4.90 (2x*br*, total 1H, α-protons of two different conformers, *ca* 1:1), 5.03 (*d*, *J*13.0Hz, diastereotopic benzylic proton of conformer #1), 5.08 (*s*, diastereotopic benzylic proton of conformer #2), 5.09 (*s*, diastereotopic benzylic proton of conformer #2), 5.15 (*d*, *J*13.0Hz, diastereotopic benzylic proton of conformer #1), 5.47 (*br d*, NH of one conformer), 5.63 & 5.70 (2x*br s*, steroidal C16 vinylic protons of two conformers), 5.70-5.85 (*m*, C3 vinylic proton and NH of other conformer), 6.22 & 6.25 (2x*d*, C4 vinylic protons, *J*15.5 & 15.6Hz respectively), 7.23-7.35 (*m*, 5H); ^{13}C nmr: 12.12, 15.97, 21.02, 21.44, 27.35, 28.40, 31.28, 31.68, 33.76, 33.91, 35.17, 35.58, 36.44, 44.72, 46.21, 54.52, 57.03, 66.97, 67.16, 73.75, 121.05, 127.76, 128.11, 128.50, 129.05, 131.64, 170.98; IR ($CDCl_3$): 3444*w*, 3032*w*, 2932*s*, 2852*m*, 1722*s*, 1504*m*, 1454*w*, 1418*w*, 1370*w*, 1346*w*, 1256*s*, 1154*w*, 1132*w*, 1062*m*, 1028*m*, 964*m*; MS: 549 (M^+, <0.5%), 505 ([M-CO_2]$^+$, 1, calc. for $C_{32}H_{43}NO_4$: 505.3192, found: 557.3213), 449 (10), 446 (10), 404 (48), 489 (94), 305 (52), 105 (100); $[\alpha]_D$= +73.3° (*c*0.18, $CHCl_3$).

***L*-[2-(benzyloxycarbonylamino)]-4-(2-naphthyl)-but-3-enoic acid (101)**

Reaction of N-CBz-*L*-vinylglycine (**59**) (0.43mmol) with triflate **81** (0.21mmol) for 4h at 40-60° gave the title compound as an amorphous white solid (57%). ^{1}H nmr: 5.02 (*br*, 1H, α-proton), 5.08 (*s*, 2H), 5.99 (*br d*, 1H, NH), 6.35 (*dd*, *J*5.5, 15.8Hz, 1H), 6.76 (*d*, *J*15.9Hz, 1H), 7.21-7.80 (*m*,12H); ^{13}C nmr: 55.31, 65.76, 122.73, 124.18, 125.22, 125.53, 125.80, 126.77, 127.13, 127.35, 127.61, 131.29, 132.14, 132.58, 132.85, 171.34; IR (nujol mull): 3600-2400(*m*, *br*), 3296*m*, 1728*s*, 1680*s*, 1532*m*, 1334*w*, 1252*m*, 1062*m*, 1014*w*, 966*m*,

820*m*, 734*m*, 696*w*, 652*w*; MS: 361 (M^+ - not present), 253 ([M-$PhCH_2OH$]$^+$, 9%), 209 (16), 180 (26), 141 (30), 108 (60), 69 (100). (FAB): 362 ([M+H]$^+$); $[\alpha]_D$= +35.8° (*c*0.11, MeOH).

***L*-[2-(benzyloxycarbonylamino)]-4-(3-carboethoxy-2-naphthyl)-but-3-enoic acid (102).** Reaction of N-CBz-*L*-vinylglycine (**59**) (0.64mmol) with triflate **82** (0..43mmol) for 4h at 60° gave the title compound as a thick oil (8%). ^{1}H nmr: 1.29 (*t*, *J*7.1Hz, 3H), 4.28 (*q*, *J*6.9Hz, 2H), 4.95-5.25 (*m*, 3H, α & benzylic methylene protons), 5.81 (*br d*, 1H, NH), 6.10 (*m*, 1H, C3-H), 7.10-7.30 (*m*, 6H, phenyl & C4-H's), 7.30-7.50 (*m*, 3H), 7.60-7.80 (*m*, 2H), 8.32 (*s*, 1H); ^{13}C nmr: 14.21, 55.97, 61.36, 67.19, 125.11, 126.69, 127.06, 127.70, 128.10, 128.45, 128.66, 131.79, 131.88, 132.89, 134.05, 134.72, 136.04, 155.92, 167.33, 174.52; IR ($CHCl_3$): 3550-2400(*m*, *br*), 3432*m*, 2980 (*m*, *br*), 1716*s*, 1630*w*, 1502*s*, 1458*m*, 1398*w*, 1334*w*, 1282(*s*, *br*), 1174*m*, 1134*m*, 1062(*s*, *br*), 962*w*, 912*w*; MS: 433 (M^+ - not present), 386 (1%), 368 (5), 326 (5), 317 (6), 305 (20), 197 (16), 181 (18), 149 (32), 108 (52), 91 (100). (FAB): 434 ([M+H]$^+$); $[\alpha]_D$= +7.5° (*c*0.19, $CHCl_3$).

Chapter 2.5

***L*-[2-(benzyloxycarbonylamino)]-4-(cyclohex-1-en-1-yl)but-3-enol (108)**

A mixture of tetra-*n*-butylammonium chloride (62mg, 0.223mmol), palladium(II) acetate (5mg, 22μmol), cyclohex-1-en-1-yl triflate (57mg, 0.248mmol), potassium acetate (110mg, 1.12mmol) and *L*-2-(CBz-amino)but-3-enol (**69**) (54mg, 0.244mmol) was stirred in dry DMF (5ml) at ambient temperature under a nitrogen atmosphere for two hours. Water (30ml) was added and the aqueous phase extracted with ether (3x50ml). The combined organic extracts were dried and the solvent evaporated. Flash chromatography of the residue eluting with ethyl acetate/light petroleum (1:1) yielded the title compound as a thick oil (19mg, 28%). ^{1}H nmr: 1.61 (*m*, 4H), 2.09 (*m*, 4H), 3.66 (*m*, 2H, C1-H's), 4.43 (*m*, 1H, C2-H), 5.11 (*s*, 2H, benzylic), 5.18 (*br d*, *J*7.9Hz, 1H, NH), 5.43 (*dd*, *J*6.3, 15.8Hz, 1H, C3-H), 5.75 (*br*, 1H, cyclohexenyl vinylic), 6.22 (*d*, *J*15.9Hz, 1H, C4-H), 7.34 (*s*, 5H); ^{13}C n.m.r.: 22.39 (two overlapping signals), 24.46, 25.83, 55.01, 65.54, 66.91, 121.71, 128.11, 128.50, 130.70, 134.31, 135.94, 136.39 (NB: one aromatic overlapping), 156.39.

(*S*)-(*E*)-4-[2-(cyclohex-1-en-1-yl)ethenyl]oxazolidin-2-one (109)

Reaction at elevated temperature with the above conditions yielded the title compound as a thick oil after chromatography. ^{1}H nmr: 1.64 (*m*, 4H), 2.13 (*m*, 4H), 4.05 (*dd*, *J*6.8, 8.2Hz, 1H, C1-H), 4.42 (*br q*, 1H, C2-H), 4.53 (*t*, *J*8.3Hz, 1H, C1-H), 5.40 (*br*, 1H, NH), 5.44 (*dd*, *J*7.9, 15.5Hz, 1H, C3-H), 5.82 (*br*, 1H, cyclohexenyl vinylic), 6.20 (*d*, *J*15.6Hz, 1H, C4-H).

The following procedure is representative of all the coupling reactions of *L*-2-(CBz-amino)but-3-enyl acetate (**71**) with vinyl triflates:

***L*-[2-(benzyloxycarbonylamino)]-4-(cyclohex-1-en-1-yl)but-3-enyl acetate (110).** A mixture of tetra-*n*-butylammonium chloride (106mg, 0.38mmol), palladium(II) acetate (8.5mg, 0.038mmol), cyclohex-1-en-1-yl triflate (**73**) (131mg, 0.57mmol), potassium carbonate (262mg, 1.9mmol) and *L*-2-(CBz-amino)but-3-enyl acetate (**71**) (100mg, 0.38mmol) was heated in DMF (3ml) at 65° for 60min in a nitrogen atmosphere. T.l.c. showed that some diene had formed, but much of the olefin remained, so the reaction mixture was heated to 75° and stirred at that temperature for 3 more hours. The mixture was cooled, water added (50ml) and extracted with ether (5x50ml). The combined extracts were dried and the solvent evaporated. The residue was subjected to flash chromatography on silica gel, gradient eluting with 20-30% ethyl acetate/light petroleum to yield the title compould as a thick oil (101mg, 77%). ^{1}H nmr: 1.45-1.65 (*m*, 4H), 1.94 (*s*, 3H), 1.90-2.10 (*m*, 4H), 4.04 (*d*, *J*5.0Hz, 2H), 4.45 (*br*, 1H, α-proton), 5.03 (*s*, 2H), 4.90-5.15 (*br*, 1H, NH), 5.32 (*dd*, *J*15.8, 6.2Hz, 1H), 5.68 (*br s*, 1H), 6.14 (*d*, *J*15.8Hz, 1H), 7.28 (*m*, 5H); ^{13}C nmr: 20.70, 22.28, 24.28, 25.74, 51.94, 65.97, 66.75, 120.98, 128.05, 128.42, 130.79, 134.54, 135.77, 136.28, 155.62, 170.88; IR (neat): 3332*m*, 3028*w*, 2928*m*, 2832*w*, 1726*s*, 1650*w*, 1532*s*, 1234(*br*, *s*), 1050(*br*, *s*), 970*m*, 740*m*, 698*m*; MS: 343 (M^+, 0.2%, calc. for $C_{20}H_{25}NO_4$: 343.1784, found: 343.1799), 283 ([M-AcOH]$^+$, 2), 270 ([M-CH_2OAc]$^+$, 8), 226 (8), 192 (12), 148 (5), 107 (10), 91 (100); $[\alpha]_D$= -7.5° (*c*0.56, $CHCl_3$).

***L*-[2-(benzyloxycarbonylamino)]-4-(cholesta-3,5-dien-3-yl)but-3-enyl acetate (111).** Reaction of *L*-2-(CBz-amino)but-3-enyl acetate (**71**) (0.27mmol) with triflate **75** (0.40mmol) for 3h at 75° gave the title compound as a thick oil (54%). ^{1}H nmr: 0.63 (*s*, 3H),

0.79 (*d*, *J*6.5Hz, 3H), 0.80 (*d*, *J*6.7Hz, 3H), 0.84 (*s*, 3H), 0.85-2.20 (*m*, 29H), 1.96 (*s*, 3H), 4.07 (*br d*, *J*4.9Hz, 2H), 4.50 (*br*, 1H, α-proton), 4.95-5.04 (*br*, 1H, NH), 5.41 (*dd*, *J*6.2Hz, 1H, partially obscurred), 5.44 (*br*, 1H), 5.86 (*s*, 1H), 6.18 (*d*, *J*15.8Hz, 1H), 7.29 (*m*, 5H); ^{13}C nmr: 11.97, 18.66, 19.06, 20.77, 21.04, 21.94, 22.52, 22.78, 23.77, 24.12, 27.96, 28.18, 29.65, 31.67, 32.05, 33.42, 35.14, 35.74, 36.11, 39.44, 39.68, 42.39, 48.13, 56.06, 56.81, 65.97, 66.87, 122.41, 125.88, 128.13, 128.49, 131.51, 131.72, 135.02, 136.28, 142.01, 155.70, 170.98; IR ($CHCl_3$): 3448*m*, 2948*s*, 2864*m*, 1724*s*, 1630*m*, 1504*s*, 1468*m*, 1384*m*, 1368*w*, 1240*s*, 1050*s*, *br*), 966*m*; MS: 629 (M^+ - not present), 569 ([M-AcOH]$^+$, 2%, calc. for $C_{39}H_{55}NO_2$: 569.4233, found: 569.4218), 478 (2), 434 (3), 322 (3), 180 (9), 112 (21), 91 (47), 57 (100); $[\alpha]_D$= +1.0° (*c*0.80, $CHCl_3$).

***L*-[2-(benzyloxycarbonylamino)]-4-(17β-acetyloxyandrost-2-en-3-yl)but-3-enyl acetate (112).** Reaction of *L*-2-(CBz-amino)but-3-enyl acetate (**71**) (0.29mmol) with triflate **76** (0.43mmol) for 3h at 75° gave the title compound as a thick oil (82%). ^{1}H nmr: 0.72 (*s*, 3H), 0.79 (*s*, 3H), 0.80-2.20 (*m*, 20H), 2.03 (*s*, 3H), 2.04 (*s*, 3H), 4.12 (*br d*, *J*4.7Hz, 2H), 4.55 (*br*, 1H, α-proton), 4.58 (*t*, *J*8.0Hz, 1H), 5.05-5.15 (*br*, 1H, NH), 5.11 (*s*, 2H), 5.40 (*dd*, *J*15.9, 6.1Hz, 1H), 5.65 (*br*, 1H), 6.20 (*d*, *J*15.7Hz, 1H), 7.35 (*m*, 5H); ^{13}C nmr: 11.83, 11.97, 20.42, 20.76, 21.14, 23.44, 27.42, 28.55, 29.37, 31.19, 34.86, 35.25, 36.78, 40.40, 41.13, 42.41, 50.55, 53.68, 65.98, 66.77, 82.79, 121.27, 128.08, 128.45, 129.48, 133.33, 135.00, 135.20, 136.31, 155.65, 170.92, 171.21; IR ($CHCl_3$): 3448*w*, 2916*m*, 2848*w*, 1726*s*, 1650*w*, 1504*m*, 1456*m*, 1378*m*, 1258*s*, 1042*m*, 970*w*; MS (EI): 577 (M^+), 517 ([M-AcOH]$^+$, calc. for $C_{33}H_{43}NO_4$: 517.3192, found: 517.3210), 504 ([M-CH_2OAc]$^+$), 460; $[\alpha]_D$= +45.8° (*c*1.37, $CHCl_3$).

***L*-[2-(benzyloxycarbonylamino)]-4-(3-methoxyestra-1,3,5(10),16-tetraen-17-yl)but-3-enyl acetate (113)**

Reaction of *L*-2-(CBz-amino)but-3-enyl acetate (**71**) (0.32mmol) with triflate **77** (0.48mmol) for 4h at 70-80° gave the title compound as a thick oil (83%). ^{1}H nmr: 0.87 (*s*, 3H), 1.30-2.40 (*m*, 11H), 2.03 (*s*, 3H), 2.86 (*m*, 2H), 3.77 (*s*, 3H), 4.15 (*m*, 2H), 4.54 (*br*, 1H, α-proton), 5.08 (*br*, 1H, NH), 5.13 (*s*, 2H), 5.73 (*dd*, *J*6.2, 16.0Hz, 1H, partially obscurred), 5.74 (*br*, 1H), 6.21 (*d*, *J*16.2Hz, 1H), 6.63 (*d*, *J*2.6Hz, 1H), 6.71 (*dd*, *J*2.7, 8.5Hz, 1H),

7.19 (*d*, *J*8.6Hz, 1H), 7.35 (*m*, 5H); ^{13}C nmr: 15.94, 20.72, 26.49, 27.58, 29.61, 30.98, 35.24, 37.04, 44.09, 46.38, 52.25, 55.09, 56.33, 65.83, 66.82, 111.32, 113.71, 116.84, 123.89, 125.95, 127.65, 128.10, 128.46, 130.28, 132.66, 136.27, 137.84, 151.68, 155.65, 157.32, 170.87; IR ($CHCl_3$): 3448*m*, 3000*w*, 2932*m*, 2856*w*, 1728*s*, 1610*m*, 1502*s*, 1458*m*, 1376*m*, 1238*s*, 1038*s*, 968*m*; MS: 529 (M^+, 6%, calc. for $C_{33}H_{39}NO_5$: 529.2828, found: 529.2813), 514 ($[M-Me]^+$, 4), 469 ($[M-AcOH]^+$, 52%), 456 ($[M-CH_2OAc]^+$, 15), 421 (26), 378 (50), 361 (44), 227 (100), 147 (74), 91 (70), 79 (69); $[\alpha]_D$= +55.3° (*c*1.03, $CHCl_3$).

***L*-[2-(benzyloxycarbonylamino)]-4-(3β-acetyloxyepiandrost-16-en-17-yl)but-3-enyl acetate (114).** Reaction of *L*-2-(CBz-amino)but-3-enyl acetate (**71**) (0.17mmol) with triflate **78** (0.25mmol) for 4h at 75-80° gave the title compound as a foam (68%). ^1H nmr: 0.70 (*m*, 1H), 0.79 (*s*, 1H), 0.81 (*s*, 1H), 0.85-1.00 (*m*, 2H), 1.10-1.96 (*m*, 15H), 1.98 (*s*, 6H), 2.06 (*m*, 1H), 4.09 (*m*, 2H), 4.48 (*br*, 1H, α-proton), 4.65 (*tt*, *J*5.0, 11.2Hz, 1H), 4.99 (*br d*, 1H, NH), 5.08 (*s*, 2H), 5.63 (*dd*, *J*6.1, 16.1Hz, 1H), 5.65 (*br d*, 1H), 6.12 (*d*, *J*16.2Hz, 1H), 7.29 (*m*, 5H); ^{13}C nmr: 12.12, 15.96, 20.74, 21.05, 21.44, 27.36, 28.40, 31.21, 31.68, 33.77, 33.93, 35.20, 35.54, 36.45, 44.73, 46.22, 52.25, 54.52, 57.04, 65.86, 66.85, 73.60, 123.73, 127.73, 128.13, 128.49, 130.42, 136.28, 151.60, 155.65, 170.69, 170.90; IR ($CDCl_3$ solution): 3444*w*, 3032*w*, 2932*s*, 2848*m*, 1726*s*, 1648*w*, 1506*s*, 1454*m*, 1374*m*, 1340*w*, 1252*s*, 1154*w*, 1132*w*, 1046*m*, 1026*m*, 966*w*; MS: 577 (M^+, 1%, calc. for $C_{35}H_{47}NO_6$: 577.3403, found: 577.3351), 576 ($[M-H]^+$, 1), 561 ($[M-CH_4]^+$, 0.6%), 515 (17), 503 (6), 459 (9), 457 (11), 441 (13), 426 (15), 425 (19), 408 (17), 107 (91), 89 (96), 31 (100); $[\alpha]_D$= +4.4° (*c*0.29, $CHCl_3$).

The following procedure is representative of all the coupling reactions of *L*-2-(CBz-amino)but-3-enyl acetate (**71**) with aryl triflates and iodides:

***L*-[2-(benzyloxycarbonylamino)]-4-phenylbut-3-enyl acetate (117)**

A mixture of bis(triphenylphosphine)palladium(II) chloride (13.3mg, 0.019mmol), iodobenzene (50μl, 91mg, 0.45mmol), triethylamine (133μl, 96mg, 0.95mmol) and *L*-2-(CBz-amino)but-3-enyl acetate (**71**) (50mg, 0.19mmol) was heated at 100° for 6h in DMF (3ml)

under a nitrogen atmosphere. 1N Hydrochloric acid (50ml) was added to the cooled mixture which was then extracted with ether (5x50ml). The combined extracts were dried and the solvent evaporated. The residue was flash chromatographed on silica gel, gradient eluting with 20-30% ethyl acetate/light petroleum, to yield the title compound as an amorphous white solid (55.3mg, 86%). An analytical sample was obtained after recrystallisation from dichloromethane/light petroleum. M.p. 96-98° (needles from dichloromethane/light petroleum); ^{1}H nmr: 2.03 (*s*, 3H), 4.18 (*br d*, 2H), 4.68 (*br*, 1H), 5.13(*s*, 2H), 5.10-5.20 (*br*, 1H), 6.10 (*dd*, *J*6.1, 16.0Hz, 1H), 6.59 (*d*, *J*16.0Hz, 1H), 7.22-7.36 (*m*, 10h); ^{13}C nmr: 20.74, 52.03, 65.81, 66.96, 125.49, 126.46, 127.92, 128.18, 128.50, 128.54, 132.14, 136.06, 136.19, 155.67, 170.91; IR (nujol mull): 3304*m*, 1728*s*, 1688*s*, 1546*s*, 1278*s*, 1260*s*, 1066*m*, 1042*m*, 970*m*, 756*m*, 730*w*, 698*m*; MS: 339 (M^+ - not present), 279 ([M-AcOH]$^+$, 3%, calc. for $C_{18}H_{17}NO_2$: 279.1259, found: 279.1264), 266 ([M-CH_2OAc]$^+$, 52), 222 (58), 188 (99), 171 (51), 160 (48), 91 (100); $[\alpha]_D$=+20.2° (*c*0.24, $CHCl_3$); Calc. for $C_{20}H_{21}NO_4$: C 70.78%, H 6.24, N 4.13. Found: C 70.78, H 6.48, N 4.20.

L-[2-(benzyloxycarbonylamino)]-4-(2-naphthyl)but-3-enyl acetate (115)

Reaction of *L*-2-(CBz-amino)but-3-enyl acetate (**71**) (0.19mmol) with triflate **81** (0.38mmol) for 7h at 100° gave the title compound as a white solid (84%). ^{1}H nmr: 2.01 (*s*, 3H), 4.08-4.22 (*m*, 2H), 4.70 (*br*, 1H), 5.12 (*s*, 2H), 5.25 (*br d*, *J*6.6Hz, 1H), 6.18 (*dd*, *J*6.0, 15.9Hz, 1H), 6.71 (*d*, *J*15.9Hz, 1H), 7.20-7.52 (*m*, 9h), 7.64-7.77 (*m*, 3H); ^{13}C nmr: 20.72, 52.08, 65.77, 66.93, 123.29, 125.80, 125.98, 126.27, 126.43, 126.67, 127.57, 127.92, 128.15, 128.47, 132.09, 132.19, 132.99, 133.35, 133.47, 136.18, 155.71, 170.90; IR ($CHCl_3$): 3448*m*, 3028(*m*, *br*), 1726*s*, 1504*s*, 1458*m*, 1240(*s*, *br*), 1052(*m*, *br*), 968*m*; MS: 389 (M^+, 3%, calc. for $C_{24}H_{23}NO_4$: 389.1627, found: 389.1606), 329 ([M-AcOH]$^+$, 33), 316 ([M-CH_2OAc]$^+$, 29), 272 (38), 255 (26), 238 (79), 91 (100); $[\alpha]_D$ =+28.3° (*c*0.22, $CHCl_3$)

L-[2-(benzyloxycarbonylamino)]-4-(3-ethoxycarbonyl-2-naphthyl)but-3-enyl acetate (116). Reaction of *L*-2-(CBz-amino)but-3-enyl acetate (**71**) (0.19mmol) with triflate **82** (0.38mmol) for 7h at 100° gave the title compound as a thick oil (32%). ^{1}H nmr: 1.38 (*t*, 3H, *J*7.2Hz), 2.02 (*s*, 3H), 4.23 (*m*, 2H), 4.71 (*br*, 1H), 5.11 (*s*, 2H), 5.22 (*br d*, 1H), 6.02

(*dd*, *J*5.6, 15.7Hz, 1H), 7.06 (*m*, 8H), 7.75-7.85 (*m*, 3H), 8.42 (*s*, 1H); ^{13}C nmr: 14.32, 20.79, 51.99, 61.16, 65.72, 66.94, 126.63, 126.80, 126.96, 127.55, 127.64, 128.14, 128.39, 128.50, 128.69, 131.78, 134.58, 134.76, 136.28, 155.74 (urethane carbonyl), 167.13 (ethyl ester carbonyl), 171.01 (acetate carbonyl); IR ($CHCl_3$): 3444*m*, 2988(*m*, *br*), 1722*s*, 1628*w*, 1504*s*, 1458*m*, 1384*w*, 1368*m*, 1334*w*, 1272(*s*, *br*), 1134*m*, 1060(*s*, *br*), 966*m*, 914*w*; MS: 461 (M^+, 0.5%, calc. for $C_{27}H_{27}NO_6$: 461.1838, found: 461.1811), 401 ($[M\text{-}AcOH]^+$, 4, calc. for $C_{25}H_{23}NO_4$: 401.1627, found: 401.1631), 388 ($[M\text{-}CH_2OAc]^+$, 4), 344 (6), 220 (27), 155 (24), 91 (100); $[\alpha]_D$ = +9.9° (*c*0.24, $CHCl_3$).

Chapter 3.1

Ethyl N-acetyl-*D*,*L*-propargylglycinate (121)

Diethyl-α-acetamido-α-propargylmalonate (**118**) (10.0g, 39.2mmol), lithium chloride (3.32g, 78.3mmol) and water (0.71ml, 39.2mmol) were added to DMF (100ml) and heated at 150-160° (oil bath temperature) for 4h. Solvents were evaporated in vacuo and the light brown residue taken up in ether (100ml) and washed with water (5x20ml). The aqueous washings were back extracted into ether (2x20ml). The combined organic phases were dried and the solvent evaporated. Residual DMF was evaporated under high vacuum. The solid residue was recrystallised from dichloromethane/light petroleum to yield the title compound as white needles (4.15g, 58%). M.p. 69-71°; ^1H nmr: 1.23 (*t*, *J*7.1Hz, 3H), 1.97 (*t*, *J*2.6Hz, 1H), 2.00 (*s*, 3H), 2.70 (*dd*, *J*4.7, 2.6Hz, 2H), 4.18 (*m*, 2H), 4.66 (*dt*, *J*4.6, 7.9Hz, 1H), 6.40 (*br*, 1H); ^{13}C nmr: 13.99, 22.31, 22.96, 50.48, 61.80, 71.38, 78.42, 169.76, 170.28; IR (nujol mull): 3312*m*, 3264*m*, 1728*s*, 1634*s*, 1554*s*, 1346*m*, 1308*w*, 1280*w*, 1232*m*, 1200*s*, 1056*m*, 1026*m*, 672*m*; MS: 183 (M^+, 7%, calc. for $C_9H_{13}NO_3$: 183.0895, found: 183.0903), 145 (24, $[M\text{-}CH_2CCH]^+$), 110 (64, $[M\text{-}CO_2Et]^+$), 102 (58), 74 (20), 68 (100), 43 (64); Analysis: calc. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65; found: C, 58.68; H, 6.77; N, 7.38. Enantiomerically enriched propargylglycine derivative was prepared according to the literature method[102] {$[\alpha]_D$= +97.7° (*c*0.52, $CHCl_3$)}. Chiral Eu(III)$(hfc)_3$ n.m.r. shift experiment showed an enantiomeric excess of approximately 90%.

Chapter 3.3

AIBN initiated radical hydrostannantion:

A solution of ethyl N-acetyl-*D,L*-propargylglycine (**121**) (3.05g, 16.6mmol) and AIBN (5mg) in toluene (30ml) was degassed by a stream of dry nitrogen. Tributyltin hydride (6.7ml, 25.0mmol) was added and the solution heated at reflux for 30 minutes. The solution was cooled and the solvent evaporated. 'Squat column' chromatography of the residue gave a slightly impure product (7.6g, *ca* 96%). A portion (3.6g) was purified by flash chromatography to yield the hydrostannation product (3.15g, 84%). By ^{1}H n.m.r. this product was a mixture of *E* and *Z* isomers of 5-(tributylstannyl)allylglycinate (**138** & **139**) (ratio 88:12).

Tributylborane initiated radical hydrostannantion.

Tributylborane (1.0M in THF, 0.55ml, 0.55mmol) was added *via* syringe to a solution of ethyl N-acetyl-*D,L*-propargylglycine (**121**) (1.00g, 5.46mmol) and tributyltin hydride (1.62ml, 6.00mmol) in dry toluene. The solution was stirred at room temperature open to the dry atmosphere. Two further charges of tributylborane (2x0.5ml) were added after 1 and 15 hours. The reaction was left for a total of three weeks after which time the solvent was evaporated. Crude 'squat column' chromatography gave a slightly impure product (1.94g, 75%) a portion (0.5g) of which was purified by flash chromatography to yield the hydrostannation product (433mg, 64%). By ^{1}H n.m.r. this product was a mixture of *E* and *Z* isomers of 5-(tributylstannyl)allylglycinate (**138** & **139**) (ratio 58:42).

Palladium catalysed hydrostannantion:

Tributyltin hydride (1.62ml, 6.00ml) was added *via* syringe over a ten minute period to a degassed solution of ethyl N-acetyl-*D,L*-propargylglycine (**121**) (1.0g, 5.46mmol) and tetrakis(triphenylphosphine)palladium(0) (25mg, 0.022mmol) in benzene under nitrogen the stirred for five minutes at ambient temperature. The solvent was evaporated and the residue subjected to 'squat column' chromatography to yield a slightly impure mixture of *E*-δ-stannane (**138**) and γ-stannane (**141**) (2.5g, *ca* 96%). These two isomers were obtained pure by repeated flash chromatography gradient eluting with 20-50% ethyl acetate/light petroleum (**141**: 58%, **138**: 15%)

Ethyl (*E*)-N-acetyl-*D*,*L*-5-(tri-*n*-butylstannyl)allylglycinate (138)

b.p. *ca* 200°/0.03 mm Hg; ^{1}H nmr: 0.80-0.90 (*m*, 15H), 1.15-1.25 (*m*, 9H), 1.30-1.50 (*m*, 6H), 1.95 (*s*, 3H), 2.55 (*m*, 2H), 4.13 (*q*, *J*7.1Hz, 2H), 4.58 (*dq*, *J*5.9, 7.5Hz, 1H), 5.73 (*dt*, *J*5.6, 18.7Hz, 1H), 5.99 (*d*, *J*18.6Hz, 1H), 6.00 (*br d*, 1H); ^{13}C nmr: 9.33 ($\underline{C}H_2Sn$ (with Sn-C satellites, $^1J_{SnC}$=329Hz)), 13.63 ($\underline{C}H_3(CH_2)_3Sn$), 14.13 ($\underline{C}H_3CH_2O$), 23.03 ($\underline{C}H_3CON$), 27.17 ($\underline{C}H_2CH_2Sn$ (with Sn-C satellites, $^2J_{SnC}$=54Hz)), 28.99 ($\underline{C}H_2CH_2CH_2Sn$ (with Sn-C satellites, $^3J_{SnC}$=21Hz)), 40.35, 51.53, 61.29, 133.98 (CH=CHSn), 141.93 (CH=CHSn), 169.49, 172.89; IR (neat): 3288*m*, 3064*w*, 2952*s*, 2924*s*, 2868*m*, 2840*m*, 1746*s*, 1656*s*, 1600*w*, 1548*s*, 1466*m*, 1376*m*, 1198*s*, 1030*m*, 864*m*; MS: ; 475 (M^+ (major isotope with ^{119}Sn), 5%, calc. for $C_{28}H_{41}NO_3{}^{119}Sn$: 475.2108, found: 475.2094), 418 ([M-Bu]$^+$, major isotope, 100), 360 (7), 343 (5), 303 (10), 288 (7). Repetition of the palladium catalysed hydrostannantion with enantiomerically enriched propargylglycine (*L*-**121**) yielded the optically active product (*L*-**138**) (7%). $[\alpha]_D$ = +33.5° (*c*1.10, $CHCl_3$).

Ethyl (*Z*)-N-acetyl-*D*,*L*-5-(tri-*n*-butylstannyl)allylglycinate (139)

^{1}H nmr: 0.83 (*m*, 15H), 1.22 (*m*, 9H), 1.40 (*m*, 6H), 1.95 (*s*, 3H), 2.40-2.60 (*m*, 2H), 4.13 (*m*, 2H), 4.61 (*m*, 1H, α), 5.97 (*d*, *J*12.6Hz, 1H), 6.00 (*br*, 1H, NH), 6.31 (*ddd*, *J*6.4, 7.3, 12.6Hz, 1H); ^{13}C nmr: 10.13 ($\underline{C}H_2Sn$, with satellites), 13.62 ($\underline{C}H_3(CH_2)_3Sn$), 14.12 ($\underline{C}H_3CH_2O$), 23.03 ($\underline{C}H_3CON$), 27.29 ($\underline{C}H_2CH_2Sn$, with satellites), 29.13 ($\underline{C}H_2(CH_2)_2Sn$, with satellites), 38.92 (beta C), 51.46 (alpha C), 61.43 ($CH_3\underline{C}H_2O$), 133.62 (CH=CHSn), 141.70 (CH=CHSn), 169.62 (C=O), 171.85 (C=O).

Ethyl N-acetyl-*D*,*L*-4-(tri-*n*-butylstannyl)allylglycinate (141).

b.p. *ca* 200°/0.03 mm Hg; ^{1}H nmr: 0.80-1.05 (*m*, 15H), 1.25-1.40 (*m*, 9H), 1.40-1.60 (*m*, 6H), 2.00 (*s*, 3H), 2.51 (*dd*, *J*9.2, 14.1Hz, 1H), 2.79 (*dd*, *J*5.1, 14.1Hz, 1H), 4.19 (*q*, *J*7.2Hz, 2H), 4.48 (*m*, 1H), 5.26 (*br s*, 1H, (with Sn-H satellites, $^3J_{SnH}$=58Hz)), 5.74 (*br s*, 1H, (with Sn-H satellites, $^3J_{SnH}$=127Hz)), 5.89 (*d*, *J*7.0Hz, 1H); ^{13}C nmr: 9.58 ($\underline{C}H_2Sn$, (with Sn-C satellites, $^1J_{SnC}$=328Hz)), 13.61 ($\underline{C}H_3(CH_2)_3$), 14.07 ($\underline{C}H_3CH_2O$), 22.89 ($\underline{C}H_3CON$), 27.29 ($\underline{C}H_2CH_2Sn$, (with Sn-C satellites, $^2J_{SnC}$=59Hz)), 28.93 ($\underline{C}H_2CH_2CH_2Sn$, (with Sn-C satellites, $^3J_{SnC}$=20Hz)), 43.42, 51.99, 61.21, 128.74

(CH_2=CSn), 150.04 (CH_2=CSn), 169.63, 172.31; IR (neat): 3284*m*, 3032*w*, 2952*s*, 2924*s*, 2868*m*, 2848*m*, 1748*s*, 1656*s*, 1548*s*, 1464*m*, 1446*m*, 1376*s*, 1296*m*, 1270*m*, 1222*m*, 1192*s*, 1162*m*, 1028*m*, 920*m*, 864*w*; MS: 475 (M^+ (major isotope ^{119}Sn), 1%, calc. for $C_{21}H_{41}NO_3{}^{119}Sn$: 475.2108, found: 475.2125), 418 (100, $[M\text{-}Bu]^+$ (major isotope)), 416 (75), 343 (15), 178 (13); Analysis: calc. for $C_{21}H_{41}NO_3Sn$: C, 53.19; H, 8.71; N, 2.95; found: C, 52.95; H, 8.88; N, 2.85. Repetition of the palladium catalysed hydrostannantion with enantiomerically enriched propargylglycine (*L*-**121**) yielded the optically active product (*L*-**141**) (49%). $[\alpha]_D$ = +22.3° (*c*1.04, $CHCl_3$).

Chapter 3.5

Ethyl 2-acetamido-4-phenylpent-4-enoate (148)

Tris(dibenzylidineacetone)palladium(0) chloroform complex (4.8mg, 5.3μmol) and triphenylarsine (13mg, 42μmol) were stirred in dry THF under a nitrogen atmosphere for 10 minutes by which time the solution had become canary yellow in colour. Iodobenzene (35μl, 0.136mmol) and ethyl N-acetyl-*D*,*L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) were added and the solution heated at reflux for 6 hours then cooled to room temperature. Aqueous potassium fluoride (10%, 30ml) was added and the aqueous phase extracted with diethyl ether (4x30ml). The combined organic extracts were dried and the solvent evaporated. Flash chromatography of the residue on silica gel, gradient eluting with a mixture of ethyl acetate and light petroleum (30-50%), gave a mixture of isomers (29mg, 66% based on recovered vinylstannane (**141**) [20%]) consisting of the title compound and *E* and *Z*-5-phenylallylglycinates (**149** & **150**) (ratio 52:32:18). **148**: ^1H nmr: 1.14 (*t*, *J*7.1Hz, 3H), 1.77 (*s*, 3H), 2.90 (*dd*, *J*6.3, 14.2Hz, 1H), 3.00 (*dd*, *J*5.9, 14.1Hz, 1H), 3.88 (*dq*, *J*7.2, 10.7Hz, 1H), 3.97 (*dq*, *J*7.1, 10.7Hz, 1H), 4.59 (*br dt*, *J*6.1, 7.7Hz, 1H), 5.02 (*br s*, 1H), 5.25 (*d*, *J*1.2Hz, 1H), 5.88 (*br d*, 1H), 7.10-7.35 (*m*, 5H); ^{13}C nmr: 14.00, 22.86, 37.60, 51.65, 61.32, 116.35, 126.27, 127.74, 128.33, 140.29, 143.90, 169.46, 171.64, ; IR (neat): 3284 (*br s*), 3056*w*, 2980*w*, 2928*w*, 1742*s*, 1656*s*, 1548*s*, 1498*w*, 1446*m*, 1376*m*, 1300*w*, 1200*s*, 1134*w*, 1028*m*, 906*w*, 780*m*, 704*m*; MS: 261 (M^+, 6%, calc. for $C_{15}H_{19}NO_3$: 261.1365, found: 261.1356), 218 (5), 215 (4), 178 (14), 146 (31), 129 (100), 102 (83), 43 (89).

Ethyl 2-acetamido-4-(3,5-difluorophenyl)pent-4-enoate (151)

Reaction of ethyl N-acetyl-*D,L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) and 3,5-difluorobromobenzene (36µl, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 20h yielded after workup the title compound as a thick oil (35.3mg, 56%). The product was contaminated with phenyl substituted product (**151**) (6.5%). ^1H nmr: 1.16 (*t*, *J*7.2Hz, 3H), 1.84 (*s*, 3H), 2.84 (*dd*, *J*6.3, 14.2Hz, 1H), 2.93 (*dd*, *J*5.7, 14.1Hz, 1H), 3.95 (*dq*, *J*7.2, 10.8Hz, 1H), 4.03 (*dq*, *J*7.1, 10.8Hz, 1H), 4.58 (*br q*, *J*7.6Hz, 1H), 5.10 (*s*, 1H), 5.31 (*d*, *J*0.6Hz, 1H), 6.10 (*br d*, 1H), 6.65 (*tt*, *J*2.3, 8.8Hz, 1H), 6.84 (*m*, 2H); ^{13}C nmr: 13.93, 22.77, 37.42, 51.40, 61.48, 102.94 (*t*, *J*25.6Hz), 109.19 (*d*, *J*25.5Hz), 141.93, 143.71, 162.86 (*dd*, *J*12.6, 248.1Hz), 169.53, 171.48; IR (neat): 3288 (*br s*), 3080*w*, 2984*w*, 1736*s*, 1658*s*, 1622*m*,, 1586*m*, 1548*m*, 1446*m*, 1378*m*, 1324*w*, 1302*w*, 1248*w*, 1208*m*, 1118*s*, 1026*m*, 988*m*, 914*w*, 860*m*; MS: 297 (M^+, 85%, calc. for $C_{15}H_{17}NO_3F_2$: 297.1177, found: 297.1172), 237 (15), 223 (23), 182 (46), 165 (62), 102 (100), 43 (69).

Ethyl 2-acetamido-4-(thien-2-yl)pent-4-enoate (152).

Reaction of ethyl N-acetyl-*D,L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) and iodothiophene (35µl, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 20h yielded after workup the title compound and *E*-5-(thien-2-yl)allylglycinate (**153**) as an inseparable mixture (30.1mg, 53%, 54:46 ratio). **152**: ^1H nmr: 1.19 (*t*, *J*7.2Hz, 3H), 1.90 (*s*, 3H), 2.89 (*dd*, *J*6.3, 14.0Hz, 1H), 2.93 (*dd*, *J*6.4, 14.0Hz, 1H), 4.05 (*m*, 2H), 4.67 (*dt*, *J*6.3, 7.8Hz, 1H), 4.92 (*s*, 1H), 5.40 (*s*, 1H), 6.12 (*br d*, *J*7.7Hz, 1H), 6.94 (*dd*, *J*3.7, 5.1Hz, 1H), 7.04 (*dd*, *J*1.1, 3.7Hz, 1H), 7.14 (*dd*, *J*1.0, 5.2Hz, 1H); IR ($CHCl_3$): 3436*m*, 3016*s*, 2932*w*, 1734*s*, 1668*s*, 1510*s*, 1416*w*, 1376*m*, 1342*w*, 1094*w*, 1024*m*, 936*w*, 860*w*; MS: 268 ($[M+H]^+$, 8%, calc. for $C_{13}H_{17}NO_3S$: 267.0929, found: 267.0918), 267 (M^+, 13), 224 (8), 221 (10), 208 (68), 152 (20), 144 (18), 135 (100), 123 (55), 112 (63), 102 (73), 70 (70), 43 (25).

Ethyl 2-acetamido-4-(naphth-2-yl)pent-4-enoate (171)

Reaction of ethyl N-acetyl-*D,L*-4-(tributylstannyl)allylglycinate (**141**) (80mg, 0.169mmol) and 2-naphthyl triflate (**81**) (70mg, 0.253mmol) with 1.5mol% $Pd(AsPh_3)_4$ in THF at reflux for 9h

yielded after workup the title compound as a thick oil (36.4mg, 69%). The product was contaminated with phenyl substituted product (**148**) (5%). ^{1}H nmr: 1.14 (*t*, *J*7.3Hz, 3H), 1.78 (*s*, 3H), 3.06 (*dd*, *J*6.2, 14.2Hz, 1H), 3.14 (*dd*, *J*6.0, 14.2Hz, 1H), 3.92 (*m*, 2H), 4.70 (*br dt*, *J*7.6Hz, 1H), 5.16 (*s*, 1H), 5.45 (*s*, 1H), 6.09 (*br d*, *J*7.6Hz, 1H), 7.40-7.50 (*m*, 3H), 7.70-7.85 (*m*, 4H); ^{13}C nmr: 13.93, 22.84, 37.59, 51.71, 61.31, 116.70, 124.47, 124.94, 126.00, 126.22, 127.41, 127.90, 128.08, 132.75, 133.14, 137.33, 143.58, 169.52, 171.67; IR (neat): 3292 (*s br*), 3056*m*, 2980*m*, 2932*w*, 1736*s*, 1654*s*, 1598*w*, 1546*s*, 1446*m*, 1376*m*, 1344*w*, 1300*w*, 1198*s*, 1136*w*, 1096*w*, 1026*s*, 968*m*, 908*m*, 860*m*, 820*m*, 752*m*, 732*w*, 704*w*; MS: 311 (M^+, 6%, calc. for $C_{19}H_{21}NO_3$: 311.1521, found: 311.1512), 252 (10), 217 (6), 214 (4), 188 (31), 179 (31), 146 (25), 129 (93), 102 (86), 88 (63), 86 (100), 49 (96), 43 (94).

Ethyl 2-acetamido-4-(*p*-acetylphenyl)pent-4-enoate (172)

Reaction of ethyl N-acetyl-*D*,*L*-4-(tributylstannyl)allylglycinate (**141**) (40mg, 0.084mmol) and *p*-acetylphenyl triflate (34mg, 0.127mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 15h yielded after workup the title compound as a thick oil (18.7mg, 37%). ^{1}H nmr: 1.17 (*t*, *J*7.2Hz, 3H), 1.82 (*s*, 3H), 2.55 (*s*, 3H), 2.95 (*dd*, *J*6.3, 14.2Hz, 1H), 3.04 (*dd*, *J*6.3, 14.1Hz, 1H), 3.98 (*m*, 2H), 4.60 (*br q*, *J*7.6Hz, 1H), 5.16 (*s*, 1H), 5.38 (*d*, *J*0.8Hz, 1H), 5.96 (*br d*, J7.4Hz, 1H), 7.43 (*m*, 2H), 7.88 (*m*, 2H); ^{13}C nmr: 13.91, 22.74, 26.46, 37.51, 51.41, 61.31, 117.99, 126.31, 128.35, 136.07, 142.92, 144.75, 169.48, 171.48, 197.46; IR ($CHCl_3$): 3436*m*, 1734*s*, 1680*s*, 1604*m*, 1506*m*, 1404*w*, 1378*m*, 1360*w*, 1268*m*, 1218*s*, 1138*w*, 1016*w*, 956*w*, 914*w*, 848*w*; MS: 303 (M^+, 14%, calc. for $C_{17}H_{21}NO_4$: 303.1471, found: 303.1459), 259 (6), 256 (6), 243 (16), 230 (16), 229 (14), 188 (28), 171 (44), 160 (20), 115 (18), 102 (54), 43 (100). Reaction of ethyl N-acetyl-*L*-4-(tributylstannyl)allylglycinate (*L*-**141**) (100mg, 0.211mmol) under identical conditions yielded *L*-**172** (25.6mg, 40%). $[\alpha]_D$ = +56.6° (*c*0.26, $CHCl_3$).

Ethyl *E*-2-acetamido-4-methylene-6-phenylhex-5-enoate (176)

To a solution of ethyl N-acetyl-*D*,*L*-4-(tributylstannyl)allylglycinate (**141**) (80mg, 0.169mmol) and *E*-β-bromostyrene (100µl, 0.781mmol) in DMF (2ml) under a nitrogen atmosphere was

added bis(acetonitrile)palladium(II) chloride (2.2mg, 8.5μmol) and the resultant mixture stirred at ambient temperature for 16h. Aqueous potassium fluoride (10%, 30ml) was added and the aqueous phase extracted with diethyl ether (4x30ml). The combined organic extracts were dried and the solvent evaporated. Flash chromatography of the residue on silica gel, gradient eluting with a mixture of ethyl acetate and light petroleum (30-50%), gave the title compound as a thick oil (44.2mg, 91%). ^{1}H n.m.r.: 1.27 (*t*, *J*7.2Hz, 3H), 1.98 (*s*, 3H), 2.79 (*dd*, *J*6.2, 14.1Hz, 1H, C3-H), 2.86 (*dd*, *J*5.8, 14.1Hz, 1H, C3-H), 4.17 (*m*, 2H), 4.81 (*dt*, *J*7.8, 6.5Hz, 1H, C2-H), 5.06 (*br s*, 1H), 5.25 (*br s*, 1H), 6.20 (*br d*, *J*7.6Hz, 1H, NH), 6.70 (*d*, *J*16.4Hz, 1H), 6.78 (*d*, *J*16.4Hz, 1H), 7.20-7.45 (*m*, 5H); MS: 287 (M^+, 13%, calc. for $C_{17}H_{21}NO_3$: 287.1521, found: 287.1506), 260 (22), 228 (68), 188 (32), 155 (55), 131 (91), 44 (100).

Ethyl (Z)-2-acetamido-4-methylene-6-(carboethoxy)hex-5-enoate (178)

Reaction of ethyl N-acetyl-*D*,*L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) and ethyl *Z*-3-iodoacrylate (57mg, 0.253mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 15h yielded after workup the title compound in an isomeric mixture with **179**, **180** and **181** (42mg, 70%, ratio 65:18:10:7). **178**: ^{1}H nmr: 1.17 (*t*, *J*7.1Hz, 3H), 1.21 (*t*, *J*7.1Hz, 3H), 1.93 (*s*, 3H), 2.66 (*dd*, *J*5.7, 14.0Hz, 1H), 2.72 (*dd*, *J*5.9, 14.1Hz, 1H), 4.08 (*m*, 4H), 4.63 (*dt*, *J*8.3, 5.8Hz, 1H), 5.04 (*s*, 1H), 5.08 (*s*, 1H), 5.70 (*d*, *J*12.1Hz, 1H), 6.34 (*d*, *J*12.1Hz, 1H), 7.01 (*br d*, *J*8.2Hz, 1H); IR (neat): 3292 (*m br*), 3064*w*, 2980*m*, 2932*w*, 1740*s*, 1658*s*, 1548*s*, 1446*w*, 1376*m*, 1274*w*, 1182*s*, 1096*w*, 1028*m*, 968*w*, 920*w*, 860*w*, 824*w*; MS: 283 (M^+, 3%, calc. for $C_{14}H_{21}NO_5$: 283.1419, found: 283.1406), 238 (3), 237 (3), 224 (7), 210 (5), 209 (3), 196 (8), 195 (17), 168 (13), 167 (7), 164 (01), 139 (63), 122 (33), 102 (73), 43 (100).

Ethyl 2-acetamido-4-(cyclohex-1-en-1-yl)pent-4-enoate (184)

Reaction of ethyl N-acetyl-*D*,*L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) and cyclohex-1-en-1-yl triflate (**73**) (58mg, 0.253mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 2h yielded after workup the title compound as a thick oil (44mg, 79%). ^{1}H nmr: 1.20 (*t*, *J*7.1Hz, 3H), 1.45-1.70 (*m*, 4H), 1.92 (*s*, 3H), 2.07 (*m*, 4H), 2.57 (*dd*, *J*7.4,

14.0Hz, 1H), 2.68 (*dd*, *J*6.2, 13.9Hz, 1H), 4.08 (*m*, 2H), 4.58 (*br q*, *J*6.3Hz, 1H), 4.75 (*br s*, 1H), 4.98 (*br s*, 1H), 5.89 (*br*, 1H), 6.03 (*br d*, 1H); ^{13}C nmr: 14.02, 21.90, 22.64, 22.92, 25.74, 25.97, 36.25, 51.68, 61.12, 112.06, 125.34, 134.98, 143.44, 169.58, 172.24; IR (neat): 3288 (*br s*), 3064*w*, 2980*w*, 2928*s*, 2852*w*, 1742*s*, 1656*s*, 1548*s*, 1448*m*, 1376*m*, 1296*w*, 1192 (*br s*), 1136*w*, 1028*m*, 920*w*, 896*w*, 854*w*, 802*w*; MS: 265 (M^+, 7%, calc. for $C_{15}H_{23}NO_3$: 265.1678, found: 265.1668), 222 (8), 206 (50), 177 (15), 148 (23), 133 (100), 121 (33), 102 (57), 91 (43), 43 (74).

Ethyl 2-acetamido 4-(3,4-dihydronaphth-1-yl)pent-4-enoate (185)

Reaction of ethyl N-acetyl-*D*,*L*-4-(tributylstannyl)allylglycinate (**141**) (103mg, 0.217mmol) and α–tetralenyl triflate (**74**) (88mg, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 7h yielded after workup the title compound as a thick oil (66.5mg, 98%). ^{1}H nmr: 1.16 (*t*, *J*7.3Hz, 3H), 1.91 (*s*, 3H), 2.28 (*m*, 2H), 2.74 (*m*, 3H), 2.88 (*dd*, *J*5.4, 13.7Hz, 1H), 3.98 (*m*, 1H), 4.07 (*m*, 1H), 4.60 (*br q*, *J*6.4Hz, 1H), 5.14 (*br s*, 1H), 5.17 (*d*, *J*2.0Hz, 1H), 5.98 (*t*, *J*4.4Hz, 1H), 6.12 (*br d*, 1H), 7.05-7.20 (*m*, 4H); ^{13}C nmr: 13.90, 22.84, 22.98, 27.90, 37.33, 51.45, 61.19, 118.20, 124.63, 126.31, 127.00, 127.56, 133.25, 136.42, 139.36, 143.95 (N.B. one aromatic overlapping), 169.43, 171.79; IR (neat): 3284 (*br s*), 3060*m*, 2980*w*, 2932*m*, 2828*m*, 1736*s*, 1654*s*, 1544*s*, 1486*w*, 1450*m*, 1376*m*, 1298*m*, 1096*s*, 1130*m*, 1024*s*, 910*m*, 774*m*, 742*m*; MS: 314 ($[M+H]^+$, 6%, calc. for $C_{19}H_{24}NO_3$: 314.1756, found: 314.1765), 286 (6), 268 (4), 254 (6), 225 (6), 208 (12), 197 (10), 181 (61), 169 (47), 165 (33), 145 (100), 43 (49).

Ethyl 2-acetamido-4-(2-[hydroxymethyl]cyclooct-1-en-1-yl)pent-4-enoate (186)

Reaction of ethyl N-acetyl-*D*,*L*-4-(tributylstannyl)allylglycinate (**141**) (103mg, 0.217mmol) and 2–(hydroxymethylene)cyclooct-1-en-1-yl triflate (94mg, 0.326mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 15h yielded after workup the title compound as a thick oil (31mg, 44%). ^{1}H nmr: 1.23 (*t*, *J*7.2Hz, 3H), 1.30-1.60 (*m*, 8H), 1.96 (*s*, 3H), 2.18 (*m*, 2H), 2.30 (*m*, 2H), 2.55 (*dd*, *J*6.8, 14.4Hz, 1H), 2.72 (*dd*, *J*4.3, 14.4Hz, 1H), 4.00-4.20 (*m*, 4H), 4.56 (*d*, *J*2.4Hz, 1H), 4.61 (*m*, 1H), 4.96 (*br d*, *J*2.3Hz, 1H), 6.55 (*br d*, *J*8.4Hz, 1H); ^{13}C nmr: 14.07, 22.98, 26.14, 26.75, 27.51, 28.27, 28.30, 29.28, 37.17, 51.33,

60.80, 61.65, 118.31, 123.79, 137.00, 143.17, 170.29, 172.44; IR (neat): 3284 (*br s*), 3072*w*, 2920*s*, 2848*m*, 1736*s*, 1656*s*, 1550*s*, 1470*w*, 1448*m*, 1376*m*, 1298*m*, 1208*m*, 1186*m*, 1130*w*, 1004*s*, 912*m*, 732*m*; MS: 323 (M^+, 2%, calc. for $C_{18}H_{29}NO_4$: 323.2097, found: 323.2105), 305 ([M-H_2O]$^+$, 5), 262 (11), 259 (14), 246 (49), 232 (27), 218 (14), 217 (17), 190 (32), 179 (29), 173 (43), 165 (43), 161 (60), 145 (49), 91 (52), 43 (100).

Ethyl 2-acetamido-4-(2-[carboethoxy]cyclopent-1-en-1-yl)-pent-4-enoate (187)

Reaction of ethyl N-acetyl-*D,L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) and 2–(carboethoxy)cyclopent-1-en-1-yl triflate (91mg, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 6h yielded after workup the title compound as a thick oil (62mg, 91%). ^{1}H nmr: 1.16 (*t*, *J*7.1Hz, 3H), 1.21 (*t*, *J*7.2Hz, 3H), 1.78 (*m*, 2H), 1.94 (*s*, 3H), 2.30-2.60 (*m*, 4H), 2.65 (*dd*, *J*5.6, 14.3Hz, 1H), 2.75 (*dd*, *J*5.8, 14.4Hz, 1H), 4.03 (*m*, 2H), 4.10 (*q*, *J*7.1Hz, 2H), 4.58 (*dt*, *J*5.7, 8.1Hz, 1H), 4.94 (*s*, 1H), 4.95 (*s*, 1H), 7.18 (*br d*, 1H); ^{13}C nmr: 13.92, 14.05, 21.71, 22.77, 34.06, 36.52, 38.78, 50.56, 60.15, 61.15, 117.06, 129.87, 140.55, 155.78, 165.97, 170.17, 171.61; IR (neat): 3300 (*br s*), 3076*w*, 2976*s*, 1740*s*, 1708*s*, 1656*s*, 1544*s*, 1446*m*, 1374*s*, 1254 (*s br*), 1192 (*s br*), 1138*m*, 1032*s*, 910*w*, 860*w*, 770*m*; MS: 323 (M^+, 29%, calc. for $C_{17}H_{25}NO_5$: 323.1733, found: 323.1723), 278 (8), 236 (17), 235 (21), 178 (100), 151 (25), 134 (21), 43 (33).

Ethyl 2-acetamido-4,5-(dimethylene)decanoate (188)

Reaction of ethyl N-acetyl-*D,L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) and hept-1-en-2-yl triflate (**80**) (78mg, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 6h yielded after workup the title compound as a thick oil (54mg, 91%). ^{1}H nmr: 0.82 (*t*, *J*6.7Hz, 3H), 1.10-1.15 (*m*, 6H), 1.20 (*t*, *J*7.2Hz, 3H), 1.92 (*s*, 3H), 2.15 (*t*, *J*6.8Hz, 2H), 2.57 (*dd*, *J*7.4, 14.2Hz, 1H), 2.69 (*dd*, *J*5.9, 14.1Hz, 1H), 4.10 (*m*, 2H), 4.60 (*dt*, *J*6.1, 7.5Hz, 1H), 4.89 (*s*, 1H), 4.93 (*s*, 1H), 5.09 (*s*, 1H), 5.10 (*d*, *J*0.9Hz, 1H), 6.06 (*br d*, 1H); ^{13}C nmr: 13.95, 14.02, 22.42, 22.90, 28.06, 31.60, 33.91, 36.68, 51.58, 61.19, 112.57, 115.09, 142.66, 146.80, 169.56, 172.15; IR (neat): 3280 (*s br*), 3080*w*, 2952*s*, 2928*s*, 2856*w*, 1744*s*, 1654*s*, 1594*w*, 1546*s*, 1466*m*, 1376*m*, 1298*w*, 1264*w*, 1188*s*, 1128*w*, 1028*m*, 896*s*; MS: 281 (M^+, 9%, calc. for $C_{16}H_{27}NO_3$: 281.1991, found: 281.1999), 238

(20), 207 (17), 166 (31), 149 (96), 102 (100), 93 (66), 43 (94).

Ethyl 2-acetamido-4-benzoylpent-4-enoate (169)

Reaction of ethyl N-acetyl-*D,L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) and benzoyl chloride (37μl, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 2h yielded after workup the title compound as a thick oil (42mg, 69%). ^{1}H nmr: 1.26 (*t*, *J*7.2Hz, 3H), 1.96 (*s*, 3H), 2.92 (*dd*, *J*7.9, 13.8Hz, 1H), 3.00 (*dd*, *J*5.1, 13.8Hz, 1H), 4.18 (*m*, 2H), 4.72 (*m*, 1H), 5.79 (*s*, 1H), 6.04 (*s*, 1H), 6.71 (*br d*, 1H), 7.45 (*m*, 2H), 7.56 (*m*, 1H), 7.73 (*d*, *J*7.4Hz, 2H); ^{13}C nmr: 14.02, 22.93, 34.26, 52.41, 61.47, 128.18, 129.63, 130.27, 132.41, 136.96, 143.03, 169.86, 171.47, 197.93; MS: 289 (M^+, 13%, calc. for $C_{16}H_{19}NO_4$: 289.1314, found: 289.1304), 245 (13), 229 (37), 215 (44), 183 (40), 173 (50), 155 (65), 105 (60), 102 (100), 77 (60), 43 (79).

Ethyl (*E*)-2-acetamido-4-methylene-7-phenyl-hept-6-enoate (189)

Reaction of ethyl N-acetyl-*D,L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) and cinnamyl chloride (48mg, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 6h yielded after workup the title compound as a thick oil (63mg, 99%). ^{1}H nmr: 1.26 (*t*, *J*7.2Hz, 3H), 2.03 (*s*, 3H), 2.46 (*dd*, *J*8.3, 14.1Hz, 1H), 2.62 (*dd*, *J*5.7, 14.1Hz, 1H), 2.97 (*d*, *J*7.0Hz, 2H), 4.20 (*q*, *J*7.2Hz, 2H), 4.77 (*dt*, *J*8.2, 5.8Hz, 1H), 4.91 (*s*, 1H), 4.98 (*s*, 1H), 6.21 (*dt*, *J*7.0, 15.8Hz, 1H), 6.34 (*br d*, 1H), 6.46 (*d*, *J*15.8Hz, 1H), 7.20-7.40 (*m*, 5H); ^{13}C nmr: 13.98, 22.82, 38.69, 38.88, 50.51, 61.27, 114.44, 125.94, 127.03 (with shoulder), 128.36, 131.98, 137.13, 142.98, 169.75, 172.25; IR ($CHCl_3$): 3444*m*, 2988*m*, 2932*w*, 1734*s*, 1674*s*, 1598*w*, 1508*s*, 1448*m*, 1396*s*, 1344*w*, 1224 (*br m*), 1184*m*, 1128*m*, 1022*m*, 970*m*, 908*m*; MS: 301 (M^+, 3%, calc. for $C_{18}H_{23}NO_3$: 301.1678, found: 301.1667), 242 (55), 169 (100), 157 (50), 140 (31), 129 (23), 105 (18), 102 (30), 91 (28), 43 (43).

Ethyl 2-acetamido-4-methylenehept-6-enoate (190)

Reaction of ethyl N-acetyl-*D,L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) and allyl bromide (27μl, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 15h

yielded after workup the title compound as a thick oil (38mg, 80%). ^{1}H nmr: 1.20 (*t*, *J*7.2Hz, 3H), 1.93 (*s*, 3H), 2.32 (*dd*, *J*8.3, 14.1Hz, 1H), 2.48 (*dd*, *J*5.8, 14.1Hz, 1H), 2.70 (*d*, *J*6.9Hz, 2H), 4.10 (*q*, *J*7.2Hz, 2H), 4.62 (*dt*, *J*5.8, 8.1Hz, 1H), 4.76 (*br s*, 1H), 4.81 (*m*, 1H), 4.98 (*m*, 1H), 5.03 (*m*, 1H), 5.70 (*ddt*, *J*6.9, 9.4, 17.5Hz, 1H), 6.13 (*br d*, 1H); ^{13}C nmr: 14.01, 22.88, 38.56, 39.83, 50.52, 61.29, 114.27, 116.81, 135.35, 142.77, 169.72, 172.28; IR (neat): 3284*br*, 3076*m*, 2980*m*, 2928*w*, 1744*s*, 1656*s*, 1548*s*, 1438*m*, 1376*m*, 1300*w*, 1198*s*, 1132*w*, 1026*m*, 914*m*; MS: 225 (M^+, 100%, calc. for $C_{12}H_{19}NO_3$: 225.1365, found: 225.1357), 183 (4), 179 (4), 166 (6), 165 (7), 151 (14), 110 (18), 102 (16), 93 (20), 43 (26).

Ethyl 2-acetamido-4-methylene-5-phenylpentanoate (191)

Reaction of ethyl N-acetyl-*D*,*L*-4-(tributylstannyl)allylglycinate (**141**) (100mg, 0.211mmol) and benzyl bromide (38µl, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 1h yielded after workup the title compound as a thick oil (58mg, 100%). ^{1}H nmr: 1.24 (*t*, *J*7.2Hz, 3H), 1.98 (*s*, 3H), 2.33 (*dd*, *J*8.3, 14.1Hz, 1H), 2.49 (*dd*, *J*5.6, 14.2Hz, 1H), 3.36 (*br s*, 2H), 4.16 (*m*, 2H), 4.74 (*dt*, *J*8.3, 5.6Hz, 1H), 4.85 (*s*, 1H), 4.89 (*s*, 1H), 6.25 (*br d*, 1H), 7.15-7.35 (*m*, 5H); ^{13}C nmr: 13.93, 22.77, 38.00, 42.01, 50.47, 61.22, 115.12, 126.17, 128.24, 128.88, 138.57, 143.68, 169.73, 172.23; IR (neat): 3284 (*br s*), 3060*w*, 3024*w*, 2980*w*, 2928*w*, 1742*s*, 1656*s*, 1600*w*, 1548*s*, 1440*m*, 1376*m*, 1196 (*s br*), 1028*m*, 904*m*, 740*m*, 702*m*; MS: 275 (M^+, 10%, calc. for $C_{16}H_{21}NO_3$: 275.1521, found: 275.1511), 215 (58), 143 (59), 142 (47), 131 (42), 102 (97), 91 (51), 43 (100).

Chapter 3.6.

Ethyl (*E*)-2-acetamido-5-phenylpent-4-enoate (149)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-(tributylstannyl)allylglycinate (**138**) (100mg, 0.211mmol) and iodobenzene (35µl, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at 40° for 15h then at 60° for 1h yielded after workup an isomeric mixture of products consisting of the title compound and the 4-phenylallylglycinate (**148**) as a thick oil (45.5mg, 83%, ratio 92:8). ^{1}H nmr: 1.25 (*t*, *J*7.2Hz, 3H), 1.99 (*s*, 3H), 2.68 (*m*, 2H), 4.19 (*m*, 2H), 4.72 (*br q*, *J*7.7Hz, 1H), 6.04 (*dt*, *J*7.4, 15.7Hz, 1H), 6.33 (*br d*, *J*7.6Hz, 1H), 6.37 (*d*, *J*15.7Hz, 1H), 7.20-7.35 (*m*, 5H);

^{13}C nmr: 14.12, 23.01, 35.75, 51.89, 61.43, 123.47, 126.08, 127.45, 128.44, 133.82, 136.65, 169.75, 171.77; IR ($CHCl_3$): 3436*m*, 2988*m*, 1736*s*, 1674*s*, 1604*w*, 1510*s*, 1448*w*, 1378*m*, 1344*w*, 1024*m*, 968*m*; MS: 261 (M^+, 6%, calc. for $C_{15}H_{19}NO_3$: 261.1365, found: 261.1356), 202 (77), 129 (100), 117 (60), 102 (60), 43 (89).

Ethyl (*E*)-2-acetamido-5-(thien-2-yl)pent-4-enoate (153)

Reaction of ethyl *E*-N-acetyl-*D,L*-5-(tributylstannyl)allylglycinate (**138**) (85mg, 0.179mmol) and 2-iodothiophene (30µl, 0.269mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 3h yielded after workup an isomeric mixture of products consisting of the title compound and the 4-thienylallylglycinate (**152**) as a thick oil (36mg, 74%, ratio 93:7). ^1H nmr: 1.22 (*t*, *J*7.0Hz, 3H), 1.97 (*s*, 3H), 2.62 (*m*, 2H), 4.16 (*m*, 2H), 4.67 (*dt*, *J*5.7, 7.7Hz, 1H), 5.83 (*dt*, *J*7.4, 15.6Hz, 1H, C4-H), 6.27 (*br d*, *J*7.6Hz, 1H, NH), 6.52 (*d*, *J*15.6Hz, 1H, C5-H), 6.84 (*d*, *J*3.4Hz, 1H), 6.89 (*dd*, *J*3.5, 5.2Hz, 1H), 7.07 (*d*, *J*5.1Hz, 1H); ^{13}C nmr: 14.12, 22.05, 35.60, 51.89, 61.51, 123.13, 124.00, 125.26, 126.93, 127.20, 141.72, 169.75, 171.67; IR ($CHCl_3$) 3436*m*, 2988*m*, 1734*s*, 1672*s*, 1512*s*, 1438*w*, 1399*w*, 1378*m*, 1344*m*, 1024*m*, 958*m*, 856*m*; MS: 267 (M^+, 10%, calc. for $C_{13}H_{17}NO_3S$: 267.0929, found: 267.0918), 208 (100), 135 (68), 123 (58), 102 (29), 43 (39).

Ethyl (*E*)-2-acetamido-5-(naphth-2-yl)pent-4-enoate (171)

Reaction of ethyl *E*-N-acetyl-*D,L*-5-(tributylstannyl)allylglycinate (**138**) (40mg, 0.084mmol) and 2-naphthyl triflate (35mg, 0.127mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 4h yielded after workup the title compound as a white solid (20mg, 76%). Mp: 126-127° (CH_2Cl_2/light petroleum); ^1H nmr: 1.25 (*t*, *J*7.2Hz, 3H), 2.00 (*s*, 3H), 2.73 (*m*, 2H, C3-H's), 4.21 (*m*, 2H), 4.76 (*dt*, *J*5.8, 7.7Hz, 1H, α), 6.15 (*br*, 1H, NH, overlapping with *dt*, *J*7.4, 15.7Hz, 1H, C4-H), 6.57 (*d*, *J*15.7Hz, 1H), 7.41 (*m*, 2H, aromatic), 7.51 (*dd*, *J*1.6, 8.7Hz, 1H), 7.64 (*br s*, 1H), 7.75 (*m*, 3H); ^{13}C nmr: 14.20, 23.16, 36.02, 52.00, 61.57, 123.36, 123.89, 125.84, 126.00, 126.26, 127.60, 127.86, 128.17, 132.89, 134.06, 134.17, 145.37, 169.74, 171.83; IR (nujol mull): 3280*m*, 1746*s*, 1650*s*, 1552*s*, 1304*w*, 1266*w*, 1214*s*, 1182*m*, 1130*m*, 1024*m*, 960*m*, 896*w*, 860*m*, 808*m*, 746*m*, 720*w*; MS: 311 (M^+, 2%, calc. for $C_{19}H_{21}NO_3$: 311.1521, found: 311.1530), 252 (47), 223 (5), 179 (100), 167 (85), 165 (26), 152 (21), 102 (13), 43 (23); Calc. for $C_{19}H_{21}NO_3$: C 73.29, H 6.80, N 4.50;

found: C 73.37, H 6.78, N 4.32.

Ethyl (*E*,*E*)-2-acetamido-7-phenylhepta-4,6-dienoate (177)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-(tributylstannyl)allylglycinate (**138**) (100mg, 0.211mmol) and E-β-bromostyrene (41μl, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 15h yielded after workup the title compound as a thick oil (45mg, 75%). ^{1}H nmr: 1.28 (*t*, *J*7.2Hz, 3H), 2.02 (*s*, 3H), 2.64 (*m*, 2H), 4.21 (*m*, 2H), 4.70 (*dt*, *J*5.8, 7.8Hz, 1H), 5.65 (*dt*, *J*7.5, 15.0Hz, 1H), 6.25 (*dd*, *J*10.4, 15.2Hz, 1H), 6.28 (*br*, 1H), 6.48 (*d*, *J*15.7Hz, 1H), 6.73 (*dd*, *J*10.2, 15.7Hz, 1H), 7.20-7.40 (*m*, 5H); ^{13}C nmr: 14.13, 23.04, 35.58, 51.87, 61.47, 126.17, 127.46, 127.53, 128.16, 128.50, 131.84, 134.44, 136.93, 169.76, 171.73; IR ($CHCl_3$) 3432 (*br m*), 3012*m*, 1736*s*, 1672*s*, 1510*m*, 1450*w*, 1378*m*, 1342*w*, 1236*m*, 1024*w*, 926*w*, 858*w*, 666*m*; MS: 287 (M^+, 1%, calc. for $C_{17}H_{21}NO_3$: 287.1521, found: 287.1509), 260 (4), 228 (18), 202 (4), 188 (7), 154 (22), 131 (36), 114 (51), 102 (43), 72 (100), 43 (43), 42 (96).

Ethyl (*E*,*Z*)-2-acetamido-7-(carboethoxy)hepta-4,6-dienoate (180)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-(tributylstannyl)allylglycinate (**84**) (85mg, 0.179mmol) and ethyl *Z*-3-iodoacrylate (**84**) (49mg, 0.215mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at ambient temperature for 45h yielded after workup the title compound as a thick oil (43mg, 84%). ^{1}H nmr: 1.18 (*t*, *J*7.2Hz, 3H), 1.20 (*t*, *J*7.1Hz, 3H), 1.93 (*s*, 3H), 2.55 (*br dt*, *J*6.9, 14.4Hz, 1H), 2.64 (*br dt*, *J*6.2, 14.5Hz, 1H), 4.08 (*q*, *J*7.1Hz, 2H), 4.12 (*m*, 2H), 4.62 (*br dt*, 1H, α), 5.54 (*d*, *J*11.3Hz, 1H, C7-H), 5.83 (*dt*, *J*7.5, 15.3Hz, 1H, C4-H), 6.32 (*br d*, *J*7.8Hz, 1H), 6.43 (*t*, *J*11.3Hz, 1H, C6-H) 7.33 (*ddd*, *J*0.7, 11.3, 15.2Hz, 1H, C5-H); ^{13}C nmr: 14.01, 14.10, 22.92, 35.67, 51.51, 59.86, 61.53, 117.20, 130.15, 137.30, 143.75, 166.10, 169.83, 171.46; IR ($CHCl_3$): 3432 (*br m*), 2984*m*, 2932*w*, 1736*s*, 1666*s*, 1512*m*, 1378*m*, 1096*w*, 1022*w*, 858*w*; MS: 284 ($[M+H]^+$, 16%), 283 (M^+, 14, calc. for $C_{14}H_{21}NO_5$: 283.1419, found: 283.1408), 238 (22), 237 (19), 224 (51), 210 (11), 195 (86), 140 (43), 102 (56), 43 (100).

Ethyl (*E*)-2-acetamido-4-(cyclohex-1-en-1-yl)pent-4-enoate (192)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-(tributylstannyl)allylglycinate (**138**) (80mg, 0.169mmol)

and cyclohex-1-en-1-yl triflate (**73**) (47mg, 0.202mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 4h yielded after workup the title compound as a white solid (21mg, 47%). Mp: 87-89°; ^{1}H nmr: 1.22 (*t*, *J*7.0Hz, 3H), 1.50-1.65 (*m*, 4H), 1.97 (*s*, 3H), 2.00-2.05 (*m*, 4H), 2.51 (*br t*, 2H, C3-H's), 4.15 (*m*, 2H), 4.60 (*br q*, 1H, α), 5.28 (*dt*, *J*7.3, 15.6Hz, 1H), 5.63 (*br s*, 1H, cyclohexenyl vinylic), 6.01 (*d*, *J*15.5Hz, 1H), 6.03 (*br*, 1H, NH); ^{13}C nmr: 14.16, 22.32, 22.41, 23.15, 24.42, 25.70, 35.63, 52.07, 61.37, 118.73, 129.16, 135.12 (quarternary olefinic), 137.73, 169.66, 171.40; IR (nujol mull): 3253*m*, 3068*w*, 1746*s*, 1638*s*, 1556*s*, 1464*s*, 1340*m*, 1194*s*, 1130*m*, 1100*w*, 1028*w*, 970*m*, 948*w*; MS: 265 (M^+, 1%, calc. for $C_{15}H_{23}NO_3$: 265.1678, found: 265.1668), 206 (7), 177 (3), 133 (12), 121 (4), 102 (5), 91 (7), 79 (5), 43 (7), 32 (100), 31 (28), 29 (64).

Ethyl (*E*)-2-acetamido-5-(3,4-dihydronaphth-1-yl)pent-4-enoate (193)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-(tributylstannyl)allylglycinate (**138**) (88mg, 0.186mmol) and α-tetralenyl triflate (**74**) (75mg, 0.269mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 12h yielded after workup the title compound as a thick oil (29.7mg, 53%). ^{1}H nmr: 1.21 (*t*, *J*7.1Hz, 3H), 1.96 (*s*, 3H), 2.21 (*m*, 2H), 2.50-2.70 (*m*, 4H), 4.14 (*q*, *J*7.0Hz, 2H), 4.65 (*dt*, *J*5.8, 7.8Hz, 1H), 5.75 (*dt*, *J*7.4, 15.5Hz, 1H), 6.02 (*br t*, *J*4.6Hz, 1H), 6.17 (*br d*, *J*7.7Hz, 1H), 6.27 (*br d*, *J*15.4Hz, 1H), 7.05-7.20 (*m*, 4H); ^{13}C nmr: 14.15, 23.07, 23.11, 28.04, 35.89, 52.02, 61.49, 123.60, 124.66, 126.20, 126.34, 126.94, 127.59, 132.43, 133.98, 135.47, 136.47, 169.63, 171.89; IR ($CHCl_3$) 3436 (*br m*), 2988*m*, 2932*w*, 1736*s*, 1674*s*, 1510*s*, 1446*w*, 1378*s*, 1344*w*, 1240*m*, 1180*w*, 1150*w*, 1022*m*, 910*w*; MS: 313 (M^+, 13%, calc.for $C_{19}H_{23}NO_3$: 313.1678, found 313.1669), 268 (10), 254 (13), 225 (15), 181 (85), 145 (35), 141 (40), 128 (35), 102 (65), 86 (55), 84 (90), 70 (45), 43 (100).

Ethyl (*E*)-2-acetamido-5-(2-[carboethoxy]cyclopent-1-en-1-yl)pent-4-enoate (194). Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-(tributylstannyl)allylglycinate (**138**) (87mg, 0.183mmol) and 2-(carboethoxy)cyclopent-1-en-1-yl triflate (77mg, 0.269mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 12h yielded after workup the title compound as a thick oil (55mg, 93%). ^{1}H nmr: 1.19 (*t*, *J*7.2Hz, 3H), 1.21 (*t*, *J*7.2Hz, 3H), 1.76 (*br quin*, *J*7.6Hz, 2H), 1.94 (*s*, 3H), 2.45-2.70 (*m*, 6H), 4.05-4.20 (*m*, 4H), 4.61 (*br q*, 1H), 5.70 (*dt*, *J*7.4,

15.7Hz, 1H), 6.22 (*br d*, *J*7.8Hz, 1H), 7.24 (*d*, *J*15.8Hz, 1H); ^{13}C nmr: 14.02, 14.20, 21.06, 22.97, 33.96, 34.04, 36.05, 51.70, 59.76, 61.43, 128.92, 129.09, 130.95, 151.09, 165.68, 169.75, 171.57; IR ($CHCl_3$) 3432 (*m br*), 2984*m*, 1734*s*, 1674*s*, 1512*m*, 1468*w*, 1446*w*, 1376*m*, 1342*w*, 1258*s*, 1022*m*, 860*w*; MS: 323 (M^+, 4%, calc. for $C_{17}H_{25}NO_5$: 323.1733, found: 323.1723), 278 (9), 264 (20), 235 (32), 204 (12), 189 (23), 165 (15), 162 (17), 134 (20), 117 (17), 105 (20), 102 (34), 43 (100), 29 (46).

Ethyl (*E*)-2-acetamido-6-(methylene)undec-4-enoate (195)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-(tributylstannyl)allylglycinate (**138**) (100mg, 0.211mmol) and hept-1-en-2-yl triflate (**80**) (78mg, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 2h yielded after workup the title compound as a thick oil (34.4mg, 58%). ^{1}H nmr: 0.85 (*t*, *J*6.7Hz, 3H), 1.15-1.45 (*m*, 9H), 1.97 (*s*, 3H), 2.09 (*br t*, *J*7.3Hz, 2H), 2.53 (*m*, 2H), 4.15 (*m*, 2H), 4.62 (*dt*, *J*5.7, 7.8Hz, 1H), 4.87 (*br s*, 2H, both vinylic H's), 5.47 (*dt*, *J*7.4, 15.7Hz, 1H), 6.05 (*d*, *J*15.7Hz, 1H), 6.06 (*br*, 1H, NH); ^{13}C nmr: 14.02, 14.14, 22.48, 23.13, 27.72, 31.70, 31.91, 35.76, 51.96, 61.44, 114.86, 122.48, 136.30, 145.70, 169.63, 171.84; IR (neat) 3288 (*m br*), 3072*w*, 2952*w*, 2928*m*, 2856*m*, 1744*s*, 1656*s*, 1544*s*, 1440*m*, 1376*s*, 1344*w*, 1300*w*, 1192*s*, 1132*m*, 1028*m*, 970*m*, 888*m*; MS: 281 (M^+, 10%, calc. for $C_{16}H_{27}NO_3$: 281.1991, found: 281.1980), 238 (7), 235 (11), 222 (21), 208 (16), 193 (17), 166 (86), 149 (26), 137 (29), 102 (100), 193 (62), 43 (67).

Ethyl (*E*,*E*)-2-acetamido-8-phenylocta-4,7-dienoate (196)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-(tributylstannyl)allylglycinate (**138**) (85mg, 0.179mmol) and cinnamyl chloride (37µl, 0.269mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 6h yielded after workup the title compound as a thick oil (52mg, 96%). ^{1}H nmr: 1.25 (*t*, *J*7.1nmr, 3H), 2.00 (*s*, 3H), 2.52 (*m*, 2H), 2.90 (*br t*, *J*6.5Hz, 1H), 4.17 (*q*, *J*7.1Hz, 1H), 4.18 (*q*, *J*7.0Hz, 1H), 4.64 (*dt*, *J*5.8, 7.8Hz, 1H), 5.39 (*dt*, *J*7.0, 15.3Hz, 1H), 5.59 (*dt*, *J*6.5, 15.2Hz, 1H), 6.16 (*dt*, *J*6.4, 16.0Hz, 1H), 6.23 (*br d*, *J*7.7Hz, 1H), 6.37 (*d*, *J*15.9Hz, 1H), 7.15-7.35 (*m*, 5H); ^{13}C nmr: 14.06, 22.98, 35.28, 35.66, 51.88, 61.28, 124.84, 125.84, 126.94, 128.08, 128.37, 130.60, 132.52, 137.33, 169.58, 171.83; IR (neat) 3288 (*br m*), 3056*w*, 3024*w*, 2980*w*, 1736*s*, 1656*s*, 1598*w*, 1546*s*, 1496*w*, 1438*m*, 1376*m*,

1198*m*, 1132*m*, 1028*m*, 970*s*, 744*m*, 696*m*; MS: 301 (M^+, 9%, calc. for $C_{18}H_{23}NO_3$: 301.1678, found: 301.1667), 256 (3), 242 (7), 228 (4), 187 (9), 169 (17), 168 (19), 145 (29), 142 (23), 141 (26), 105 (40), 102 (49), 91 (49), 86 (71), 84 (100), 57 (57), 43 (83).

Ethyl (*E*)-2-acetamido-6-oxo-6-phenylpent-4-enoate (197)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-(tributylstannyl)allylglycinate (**138**) (100mg, 0.211mmol) and benzoyl chloride (37µl, 0.316mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at ambient temperature for 48h yielded after workup the title compound as a thick oil (49mg, 80%). ^1H nmr: 1.20 (*t*, *J*7.1Hz, 3H), 1.96 (*s*, 3H), 2.74 (*dt*, *J*6.4, 14.8Hz, 1H), 2.80 (*dt*, *J*5.5, 14.7Hz, 1H), 4.14 (*q*, *J*7.2Hz, 2H), 4.74 (*br q*, 1H), 6.61 (*br d*, *J*7.6Hz, 1H), 6.85 (*dt*, *J*6.3, 15.7Hz, 1H), 6.88 (*d*, *J*15.8Hz, 1H), 7.40 (*br t*, *J*7.4Hz, 2H), 7.50 (*br t*, *J*7.3Hz, 1H), 7.84 (*d*, *J*8.2Hz, 2H); ^{13}C nmr: 14.02, 22.90, 35.14, 51.25, 61.70, 128.42, 128.46, 128.74, 132.85, 137.16, 142.39, 169.92, 171.18, 189.95; IR (neat) 3292 (*m br*), 3060*w*, 2980*w*, 1736*s*, 1666*s*, 1624*w*, 1596*w*, 1578*w*, 1546*m*, 1450*m*, 1376*m*, 1292*w*, 1226*m*, 1134*m*, 1096*w*, 1022*m*, 860*w*, 762*w*, 696*m*; MS: 289 (M^+, 6%, calc. for $C_{16}H_{19}NO_4$: 289.1314, found: 289.1310), 288 (3), 245 (13), 242 (22), 173 (19), 156 (69), 146 (94), 145 (41), 105 (100), 102 (63), 77 (59), 43 (97).

Ethyl (*E*)-2-acetamido-6-phenylhex-4-enoate (198)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-(tributylstannyl)allylglycinate (**138**) (85mg, 0.179mmol) and benzyl bromide (32µl, 0.269mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 95min yielded after workup the title compound as a thick oil (34mg, 68%). ^1H nmr: 1.23 (*t*, *J*7.2Hz, 3H), 1.97 (*s*, 3H), 2.48 (*br dt*, *J*6.8, 14.1Hz, 1H, C3-H), 2.54 (*br dt*, *J*6.1, 14.1Hz, 1H, C3-H), 3.32 (*d*, *J*6.7Hz, 2H, C6-H's), 4.15 (*q*, *J*7.2Hz, 2H), 4.63 (*br dt*, *J*5.8, 7.7Hz, 1H, α–H), 5.40 (*dt*, *J*7.3, 15.1Hz, 1H, C4-H), 5.67 (*dt*, *J*6.8, 15.1Hz, 1H, C5-H), 6.15 (*br d*, *J*7.2Hz, 1H), 7.10-7.35 (*m*, 5H); ^{13}C nmr: 14.04, 22.96, 35.23, 38.92, 51.86, 61.32, 124.77, 126.00, 128.32, 133.87, 140.07, 169.55, 171.85; IR (neat) 3284 (*br s*), 3064*w*, 3024*w*, 2984*w*, 2932*w*, 1736*s*, 1656*s*, 1548*s*, 1498*m*, 1378*m*, 1344*w*, 1198*m*, 1096*m*, 972*m*, 860*w*, 750*m*, 700*m*; MS: 275 (M^+, 6%, calc. for $C_{16}H_{21}NO_3$: 275.1521, found: 275.1513), 230 (3), 216 (73), 202 (15), 187 (9), 170 (10), 169 (8), 160 (52), 145 (54), 143 (30), 142 (69), 131 (24), 125 (52), 102 (80), 91 (76), 43 (100).

Chapter 3.7

Diethyl (*S*,*S*)-2,7-diacetamido-4,5-dimethylenesuberate (166)

Copper(II) nitrate hydrate (127mg, 0.527mmol) was added to a solution of ethyl N-acetyl-*L*-4-(tributylstannyl)allylglycinate (*L*-**141**) (250mg, 0.527mmol) in dry THF (2ml). The mixture was stirred at ambient temperature for 60 minutes. Ethyl acetate was added and the organic phase washed with ammonium hydroxide solution (5%, 50ml) and water (50ml), then dried and the solvent evaporated. Flash chromatography of the residue gradient eluting with 0-5% methanol in dichloromethane yielded the title compound as a white solid, contaminated by a small amount of *meso* compound (33mg, 34%). M.p. 153-154° (dichloromethane/light petroleum); $[\alpha]_D$ = +60.7° (*c*0.28, $CHCl_3$); ^1H nmr: 1.24 (*t*, *J*7.0Hz, 3H, ester CH_3), 1.94 (*s*, 3H, acetyl CH_3), 2.67 (*dd*, *J*6.2, 14.3Hz, 1H, C3-H), 2.81 (*dd*, *J*5.1, 14.2Hz, 1H, C3-H), 4.06 (*dq*, *J*7.1, 10.7Hz, 1H, diastereotopic ester CH), 4.16 (*dq*, *J*7.0, 10.7Hz, 1H, diastereotopic ester CH), 4.65 (*m*, 1H, α-H), 4.94 (*s*, 1H, vinylic H), 5.17 (*s*, 1H, vinylic H), 6.74 (*br d*, *J*8.5Hz, 1H, NH); ^{13}C nmr: 14.02, 22.79, 36.20, 51.08, 61.43, 116.87 ($\underline{C}H_2$=C), 141.06 (CH_2=$\underline{C}$), 169.88, 172.36; IR (nujol mull): 3368*m*, 1728*s*, 1682*s*, 1598*w*, 1538*m*, 1294*m*, 1266*w*, 1230*m*, 1200*m*, 1160*m*, 1118*w*, 1020*m*, 916*m*; MS: 368 (M^+, 1%, calc. for $C_{18}H_{28}N_2O_6$: 368.1947, found: 368.1962), 348 (2), 341 (2), 313 (3), 256 (6), 236 (7), 223 (27), 182 (18), 102 (22), 32 (100). *meso*-**166**: ^1H nmr (similar to above with following exceptions): 2.44 (*br dd*, 1H, C3-H), 2.83 (*br dd*, 1H, C3-H), 4.98 (*s*, 1H, vinylic H), 5.19 (*s*, 1H, vinylic H). Reaction of racemic ethyl N-acetyl-*D*,*L*-4-(tributylstannyl)allylglycinate (**141**) (485mg, 0.966mmol) and copper(II) nitrate hydrate (225mg, 0.966mmol) in THF for 60min yielded on workup the product (184mg, 52%) as an inseparable 1:1 mixture of *meso* and *dl*-diastereomers.

(*S*,*S*)-(*E*,*E*)-diethyl 2,9-bis(acetamido)sebacate (*dl*-203)

Reaction of (*E*)-ethyl N-acetyl-*L*-5-(tributylstannyl)allylglycinate (*L*-**138**) (200mg, 0.422mmol) and copper(II) nitrate hydrate (102mg, 0.422mmol) in dry THF (2ml) at ambient temperature for 1 hour yielded on workup, optically active title compound as a thick oil (29.1mg, 37%). $[\alpha]_D$ = +90.4° (c0.29, $CHCl_3$); ^1H nmr: 1.20 (*t*, *J*7.0Hz, 6H), 1.94 (*s*, 6H), 2.48 (*m*, 4H, C3 & C8-H's), 4.12 (*m*, 4H), 4.57 (*br dt*, *J*5.9, 7.7Hz, 2H, C2 & C9-H's), 5.40 (*m*, 2H, C4 and C7-H's, AA'XX' second order system), 5.96 (*m*, 2H, C5 and C6-

H's, AA'XX' system), 6.14 (*br* d, 2H, *J*7.7Hz, NH's); ^{13}C nmr: 14.10, 23.00, 35.40, 51.88, 61.40, 126.70, 133.48, 169.64, 171.70; IR ($CHCl_3$): 3444*w*, 1736*s*, 1676*s*, 1504*m*, 1380*m*, 1346*w*, 1212*s*, 992*w*; MS: 368 (M^+, 1%, calc. for $C_{18}H_{28}N_2O_6$: 368.1947, found: 368.1944), 340 (1), 327 (1), 323 (1), 309 (2), 263 (7), 179 (5), 157 (7), 143 (7), 130 (12), 102 (29), 88 (21), 69 (26), 43 (100). Reaction of racemic (*E*)-ethyl N-acetyl-*D,L*-5-(tributylstannyl)allylglycinate (**138**) (382mg, 0.805mmol) and copper(II) nitrate hydrate (233mg, 1.00mmol) in THF at ambient temperature for 3h yielded on workup the product (117mg, 39%) as an inseparable 1:1 mixture of *meso*-**203** and *dl*-**203**.

Chapter 3.8

Methyl 2-ethoxycarbonylamino-4-(trimethylsilyl)but-3-ynoate (205)

Finely ground aluminium chloride (1.73g, 13.0mmol) was added slowly to a solution of methyl N-carboethoxy-α-chloroglycinate (**204**) (2.5g, 12.8mmol) and bis(trimethylsilyl)acetylene (2.2g, 12.9mmol) in dichloromethane (20ml) at such a rate to avoid excessive heating. The reaction mixture was stirred at room temperature for 15 hours. Water (25ml) was added carefully and the aqueous phase extracted with dichloromethane (2x20ml). The combined extracts were dried and the solvent evaporated. The residue was distilled by kugelrohr to yield a clear, colourless viscous oil (2.41g, 73%). B.p.: 150-160°/0.3mm (lit. 100°/0.15mm)[24d]; ^{1}H nmr: 0.10 (*s*, 9H), 1.20 (*t*, *J*7.2Hz, 3H), 3.76 (*s*, 3H), 4.09 (*q*, *J*7.2Hz, 2H), 5.08 (*d*, *J*8.4Hz, 1H), 5.38 (*br d*, 1H); ^{13}C nmr: -0.47, 14.40, 46.39 (α), 53.27, 61.57, 89.98 (acetylenic), 97.67 (acetylenic), 155.46, 168.29; IR (neat): 3320*m*, 2956*m*, 2180*w* (acetylenic), 1758*s*, 1720*s*, 1526*s*, 1440*w*, 1372*w*, 1316*m*, 1250*s*, 1058*s*, 846*s*, 760*m*; MS: 257 (M^+, 0.5%, calc. for $C_{11}H_{19}NO_4Si$: 257.1083, found: 257.1091), 233 (0.3), 225 (0.3), 198 (15), 147 (1), 133 (2), 126 (2), 99 (3), 95 (4), 93 (7), 73 (4), 32 (36), 31 (100), 29 (24); FAB MS: 258 (M+H, 4%), 93 (100).

Methyl (*E*)-2-ethoxycarbonylamino-3-(tributylstannyl)-4-trimethylsilylbut-3-enoate (207); methyl (*E*)-2-ethoxycarbonylamino-4-(tributylstannyl)-4-trimethylsilylbut-3-enoate (208). Tributyltin hydride (125μl, 0.466mmol) was added dropwise to a degassed solution of methyl 2-ethoxycarbonylamino-4-trimethylsilylbut-3-ynoate

(**205**) (100mg, 0.389mmol) and π-allyldicarbonylbis(acetonitrile)molybdenum(II) bromide (14mg, 38.9μmol) in THF (20ml) then the solution was heated to reflux for 2 hours. Further tributyltin hydride (200μl, 0.744mmol) was added and the heating continued for 15 hours. The solvent was evaporated and the residue subjected to flash chromatography gradient eluting with 0-20% ethyl acetate in light petroleum to yield the seperable title compounds as clear viscous oils (**207**: 46.2mg, 23%; **208**: 34.0mg, 16%). **207**: ^{1}H nmr: 0.18 (*s*, 9H), 0.74-0.95 (*m*, 15H), 1.20 (*t*, *J*7.0Hz, 3H), 1.22-1.45 (*m*, 12H), 3.70 (*s*, 3H), 4.06 (*q*, *J*7.1Hz, 2H), 5.15 (*br d*, *J*6.3Hz, 1H), 5.37 (*br*, 1H, NH), 6.05 (*s*, 1H, plus Sn-H satellites: $^{3}J_{SnH}$=87.9Hz); ^{13}C nmr: 0.26, 10.41 ($\underline{C}H_2Sn$), 13.67 ($\underline{C}H_3(CH_2)_3Sn$), 14.58 ($\underline{C}H_3CH_2O$), 27.28 ($\underline{C}H_2CH_2Sn$), 28.90 ($\underline{C}H_2(CH_2)_2Sn$), 52.45, 60.96 (α), 61.08, 150.30 ($\underline{C}H$=C), 155.30 (NH$\underline{C}$O), 161.17 (CH=$\underline{C}$), 171.64 ($\underline{C}O_2Me$); IR (neat): 3436*w*, 2952*s*, 2924*s*, 2868*w*, 2848*w*, 1730*s*, 1556*w*, 1496*s*, 1378*w*, 1324*m*, 1246*m*, 1198*w*, 1062*m*, 856*s*, 774*w*; MS: 548 ([M-H]$^{+}$, <0.5%), 534 ([M-CH3]$^{+}$, <0.5), 491 ([M-C4H10]$^{+}$, 100), 393 (13), 178 (20), 73 (47). **208**: ^{1}H nmr: 0.17 (*s*, 9H), 0.73-0.98 (*m*, 15H), 1.15-1.29 (*m*, 9H), 1.30-1.45 (*m*, 6H), 3.69 (*s*, 3H), 4.07 (*q*, *J*7.1Hz, 2H), 4.96 (*br*, 1H, alpha), 5.22 (*br*, 1H, NH), 6.09 (*d*, *J*8.5Hz, 1H, plus satellites: $^{3}J_{SnH}$ = 98.6Hz); ^{13}C nmr: 1.13, 10.61, 13.64, 14.51, 27.22, 28.93, 52.45, 58.01 (α), 61.11, 146.49 (overlapping olefinic carbons), 155.39, 171.53; IR (neat): 3364*s*, 2952*s*, 2868*w*, 1732*vs*, 1570*w*, 1504*s*, 1464*w*, 1378*w*, 1320*m*, 1246*m*, 1054*s*, 928*w*, 836*s*, 780*m*, 686*m*; MS: 549 (M^{+}, 3%, calc. for $C_{23}H_{47}NO_4Si^{120}Sn$: 549.2296, found: 549.2277), 492 ([M-Bu]$^{+}$, 95), 445 (83), 418 (80), 393 (48), 321 (100), 306 (70), 291 (66), 234 (53), 179 (58), 177 (55), 85 (78), 73 (64), 57 (80), 41 (77), 29 (81).

Chapter 4.1

Ethyl N-acetyl-*D,L*-4-iodoallylglycinate (222)

Iodine (0.80g, 3.16mmol) was added to a solution of ethyl N-acetyl-*D,L*-4-(tributylstannyl)allylglycinate (**141**) (1.5g, 3.16mmol) in dichloromethane (20ml). The deep purple mixture was stirred under nitrogen for 90 minutes, then the solvent was evaporated. The residue was taken up in ether and washed with 10% potassium fluoride solution (50ml) and the aqueous phase was extracted with ether (4x40ml). The combined organic extracts were dried and the solvent evaporated. Flash chromatography of the residue gradient eluting with

40-50% ethyl acetate/light petroleum yielded the title compound (0.81g, 82%). ^{1}H nmr: 1.18 (*t*, *J*7.1Hz, 3H), 1.92 (*s*, 3H), 2.75 (*dd*, *J*7.6, 14.7Hz, 1H), 2.86 (*dd*, *J*5.3, 14.8Hz, 1H), 4.09 (*q*, *J*7.1Hz, 2H), 4.61 (*dt*, *J*5.5, 7.7Hz, 1H), 5.72 (*d*, *J*1.4Hz, 1H), 6.02 (*d*, *J*1.3Hz, 1H), 6.61 (*br d*, J7.6Hz, 1H); ^{13}C nmr: 13.92, 22.74, 46.40, 51.52, 61.50, 103.03 ($\underline{C}$=CH_2), 129.32 (C=$\underline{C}H_2$), 169.89, 170.84; IR (neat): 3280*s*, 3064*m*, 2980*m*, 2932*w*, 1740*s*, 1660*s*, 1548*s*, 1432*m*, 1376*m*, 1276*w*, 1222*m*, 1192*w*, 1148*m*, 1026*s*, 908*s*, 732*m*; MS: 311 (M^+, 100%, calc. for $C_9H_{14}NO_3I$: 311.0018, found: 311.0030), 293 (2), 269 (5), 265 (5), 237 ([M-HCO_2Et]$^+$, 5), 195 (9), 183 (82), 110 (9), 102 (7), 68 (11), 43 (23). Repetition of the reaction with enantiomerically enriched vinylstannane (*L*-**141**) using identical conditions gave the optically active product (*L*-**222**). $[\alpha]_D$ = +32.6° (*c*0.47, $CHCl_3$).

Ethyl *E*-N-acetyl-*D,L*-5-iodoallylglycinate (223)

Reaction of ethyl (*E*)-N-acetyl-*D,L*-5-(tributylstannyl)allyglycinate (**138**) (0.18g, 0.377mmol) with iodine (0.10g, 0.396mmol) in CH_2Cl_2 for 60min yielded on workup the title compound as a clear oil (99mg, 84%). ^{1}H nmr: 1.15 (*t*, *J*7.2Hz, 3H), 1.90 (*s*, 3H), 2.40 (*m*, 2H), 4.07 (*m*, 2H), 4.50 (*dt*, *J*6.0, 7.7Hz, 1H), 6.05 (*d*, *J*14.3Hz, 1H), 6.30 (*dt*, *J*7.5, 14.4Hz, 1H), 6.72 (*br d*, *J*7.7Hz, 1H); ^{13}C nmr: 13.97, 22.72, 38.13, 50.91, 61.37, 78.58 (CH=CHI), 139.76 (CH=CHI), 169.81, 171.04; IR (neat): 3288*s*, 3052*m*, 2980*m*, 2932*w*, 1736*s*, 1660*s*, 1544*s*, 1436*m*, 1376*m*, 1342*w*, 1298*w*, 1272*m*, 1200*s*, 1128*m*, 1028*s*, 946*s*, 860*w*, 734*m*; MS: 311 (M^+, 2%, calc. for $C_9H_{14}NO_3I$: 311.0018, found: 311.0009), 265 (2), 252 ([M-$AcNH_2$]$^+$, 19), 238 ([M-CO2Et]$^+$, 20), 196 (40), 184 (41), 167 (7), 144 (12), 125 (24), 102 (100), 97 (51), 74 (31), 43 (26). Repetition of the reaction with enantiomerically enriched vinylstannane (*L*-**138**) using identical conditions gave the optically active product (*L*-**223**). $[\alpha]_D$ = +68.1° (*c*0.50, $CHCl_3$).

Ethyl Z-N-acetyl-*D,L*-5-iodoallylglycinate (224)

Reaction of a 58:42 mixture of isomeric (*E*) and (Z)-ethyl N-acetyl-*D,L*-5-(tributylstannyl)allyglycinates (**138** & **139**) (192mg, 0.405mmol) with iodine (93mg, 0.365mmol) in CH_2Cl_2 (15ml) for 90min yielded on workup an inseperable mixture of *E* and *Z*-ethyl N-acetyl-*D,L*-5-iodoallylglycinates (**223** & **224**) as a clear oil (88mg, 70%, ratio

57:43). **224**: ^{1}H nmr: 1.18 (*t*, *J*7.1Hz, 3H), 1.92 (*s*, 3H), 2.51 (*m*, 1H, partially obscurred by *E* isomer, C3-H), 2.57 (*m*, 1H, C3-H), 4.08 (*m*, 2H), 4.63 (*dt*, *J*5.6, 6.9Hz, 1H), 6.07 (*m*, 1H, obscurred by *E* isomer resonance, C4-H), 6.29 (*d*, *J*7.4Hz, 1H, C4-H), 6.49 (*br d*, 1H, NH); ^{13}C nmr: 13.97, 22.90, 37.36, 50.67, 61.60, 85.98 (CH=<u>C</u>HI), 135.36 (<u>C</u>H=CHI), 169.83, 171.29.

<u>Chapter 4.2</u>

2-[(Trifluoromethyl)sulphonyl]oxy-3-bromoprop-1-ene (227)

Triflic acid (2.32ml, 26mmol) was added dropwise under a nitrogen atmosphere over a 5 minute period to a stirred solution of propargyl bromide (2.0ml, 26mmol) in chloroform (30ml) at 0°C. The ice bath was removed and the dark solution was stirred at ambient temperature for 60 minutes then pyridine (5ml) was added cautiously. The solution was washed with water (50ml) and dilute hydrochloric acid (2x50ml). The organic phase was dried and the solvent evaporated. The residue was distilled by kugelrohr to yield the title compound as a non-viscous oil (1.20g, 17%). B.p.: *ca* 100°/15mm; ^{1}H nmr: 4.00 (s, 2H, CH_2Br), 5.32 (*d*, *J*3.9Hz, 1H), 5.36 (*d*, *J*3.8Hz, 1H); ^{13}C nmr: 27.90 (<u>C</u>H_2Br), 108.60 (<u>C</u>H_2=C), 116.33 & 120.57 (central peaks of CF_3 quartet, J_{CF}320Hz), 150.80 (CH_2=<u>C</u>); IR (neat): 1662*m*, 1424*s*, 1232*s*, 1142*s*, 1118*w*, 964*s*, 890*s*, 782*w*, 716*w*, 670*m*, 612*m*; MS: 270/268 (M^+, 1%, calc. for $C_4H_4{}^{79}BrF_3SO_3$: 267.9017, found: 267.9004), 189 ([M-Br]$^+$, 60), 137/135 ([M-SO_2CF_3]$^+$, 5), 121/119 ([M-OTf]$^+$, 15), 93 (29), 69 (25), 59 (47), 42 (77), 39 (100), 28 (45), 27 (55), 26 (25). Without the addition of pyridine, certain amounts of 2-bromo-3-trifloxypropene (**228**) were obtained. **228**: ^{1}H nmr: 4.07 (*s*, 2H), 5.38 (*d*, 1H, *J*4.0Hz), 5.44 (*d*, 1H, *J*3.9Hz).

Diethyl α-[2-(trifluoromethanesulphonyloxy)prop-1-en-3-yl]-α-(acetamido) malonate (232). Sodium hydride (80% dispersion in mineral oil, 20mg, 0.669mmol) was washed with light petroleum then DMF (3ml) was added. Diethyl acetamidomalonate (200mg, 0.743mmol) was added and the reaction stirred at room temperature for 15 minutes. 2-Trifluoromethanesulphonyloxy-3-bromoprop-1-ene (**227**) (161mg, 0.743mmol) was added and the reaction mixture stirred at 50° for 5 hours. The solvent was evaporated in vacuo and the

residue flash chromatographed twice eluting with 20-50% ethyl acetate in light petroleum. The product obtained contained diethyl N-acetylpropargylmalonate (**118**, *ca* 10%), but this was removed by fractional crystallisation from dichloromethane/light petroleum to yield the title compound as white needles (19mg, 6%). M.p.: 86-88°; ^{1}H n.m.r.: 1.24 (*t*, *J*7.2Hz, 6H), 2.01 (*s*, 6H), 3.46 (*s*, 2H, C3-H's), 4.22 (*dq*, *J*7.1, 10.8Hz, 2H, ester methylene H), 4.26 (*dq*, *J*7.2, 10.7Hz, 2H, ester methylene H), 4.98 (*d*, *J*3.5Hz, 1H), 5.17 (*d*, *J*3.5Hz, 1H), 6.86 (*br*, 1H, NH); ^{13}C n.m.r.: 13.82 (ester methyl), 22.80 ($\underline{C}H_3CO$), 37.64 (C3), 63.31 (ester methylene), 64.51 (C2), 108.62 (C5), 118.44 (*q*, *J*320Hz, CF_3), 151.77 (C4), 166.72, 169.42; IR (nujol mull): 3268*m*, 1746*s*, 1642*s*, 1514*m*, 1422*m*, 1306*m*, 1256*w*, 1210*s*, 1184*w*, 1132*m*, 1012*m*, 954*m*, 922*m*, 912*m*, 890*m*, 852*m*, 716*m*; MS: 405 (M^+, 4%), 360 (2), 332 (2), 290 (23), 272 (17), 256 (13), 174 (10), 102 (14), 43 (100); HRMS: calc. for $C_{13}H_{18}F_3NO_8S$: 405.0705, found: 405.0718.

Chapter 4.3

Ethyl (*E*)-2-acetamido-4-methylene-6-(carboethoxy)hex-5-enoate (179)

A mixture of ethyl N-acetyl-*D,L*-4-iodoallylglycinate (**222**) (40mg, 0.129mmol), ethyl acrylate (100µl, 0.923mmol), triethylamine (36µl, 0.257mmol) and bis(triphenylphosphine)palladium(II) chloride (4.5mg, 6.4µmol) in DMF was heated at 90° for 3h under a nitrogen atmosphere, then cooled to room temperature. Water (30ml) was added and the aqueous phase extracted with ether (4x50ml). The organic extracts were dried and the solvent evaporated. Flash chromatography of the residue gradient elution with mixtures of ethyl acetate and light petroleum (25-45%) gave the title compound as a thick oil (15mg, 41%). ^{1}H nmr: 1.24 (*t*, *J*7.1Hz, 3H), 1.25 (*t*, *J*7.1Hz, 3H), 1.96 (*s*, 3H), 2.65 (*dd*, *J*6.2, 14.1Hz, 1H), 2.73 (*dd*, *J*6.5, 14.0Hz, 1H), 4.13 (*m*, 2H), 4.14 (*q*, *J*7.0Hz, 2H), 4.71 (*dt*, *J*6.5, 7.8Hz, 1H), 5.29 (*s*, 1H), 5.45 (*s*, 1H), 6.98 (*d*, *J*15.9Hz, 1H), 6.04 (*br d*, *J*7.8Hz, 1H, NH), 7.25 (*d*, *J*16.0Hz, 1H); ^{13}C nmr: 14.07 ($OCH_2\underline{C}H_3$), 14.22 ($OCH_2\underline{C}H_3$), 23.05, 34.39, 51.19, 60.50 ($O\underline{C}H_2$), 61.69 ($O\underline{C}H_2$), 119.10, 126.01, 139.59 (quarternary olefinic), 145.41, 166.81 (conjugated $\underline{C}O_2Et$), 169.64, 171.67; IR ($CDCl_3$): 3444*m*, 2980*m*, 2936*w*, 1736*s*, 1712*s*, 1678*s*, 1634*m*, 1606*w*, 1512*s*, 1448*m*, 1376*m*, 1312*m*, 1278*s*, 1188*s*, 1034*s*, 986*m*; MS: 283 (M^+, <0.5%, calc. for $C_{14}H_{21}NO_5$: 283.1420, found: 283.1397), 212 (3),

170 (3), 127 (6), 102 (5), 86 (22), 84 (33), 49 (40), 32 (65), 31 (100), 29 (44). Reaction of the enantiomerically enriched vinyliodide (*L*-**222**) using identical conditions yielded the optically active product (*L*-**179**). $[\alpha]_D$ = +24.6° (*c*0.18, $CHCl_3$).

Ethyl (*E*)-2-acetamido-4-methylene-6-cyanohex-5-enoate (233)

Reaction of ethyl N-acetyl-*D,L*-4-iodoallylglycinate (**222**) (40mg, 0.129mmol), acrylonitrile (100µl, 1.52mmol), triethylamine (36µl, 0.257mmol) and 5mol% bis(triphenylphosphine)palladium(II) chloride in DMF at 60-100° for 3h gave on workup the title compound as a thick oil (8.3mg, 27%). ^{1}H nmr: 1.24 (*t*, *J*7.3Hz, 3H), 1.98 (*s*, 3H), 2.65 (*d*, *J*6.6Hz, 2H), 4.16 (*m*, 2H), 4.64 (*br q*, *J*7.1Hz, 1H), 5.32 (*s*, 1H), 5.43 (*s*, 1H), 5.64 (*d*, *J*16.6Hz, 1H), 6.12 (*br d*, *J*7.0Hz, 1H, NH), 6.98 (*d*, *J*16.6Hz, 1H); ^{13}C nmr: 14.14, 23.06, 34.19, 51.17, 61.90, 117.82 (CN), 126.86, 139.30, 150.73, 151.31, 169.75, 171.36; IR ($CHCl_3$): 3436*w*, 2220*w* (CN), 1736*s*, 1672*s*, 1504*m*, 1378*m*, 1280*w*, 970*w*; MS: 236 (M^+, 0.5%, calc. for $C_{12}H_{16}N_2O_3$: 236.1161, found: 236.1152), 177 (2), 165 (9), 123 (20), 102 (16), 86 (18), 84 (28), 49 (33), 43 (100), 32 (39), 31 (95), 29 (90).

Chapter 4.4

Ethyl (*E,E*)-2-acetamido-7-(carboethoxy)hepta-4,6-dienoate (181)

A solution of ethyl (*E*)-N-acetyl-*D,L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol) in dry THF was degassed by a stream of nitrogen. Ethyl acrylate (100µl, 0.923mmol), palladium(II) acetate (1.4mg, 6.5µmol) and silver carbonate (53mg, 0.194mmol) were added and the flask covered with aluminium foil. The mixture was heated to reflux for 19h then cooled to room temperature. Water (30ml) was added and the aqueous phase extracted with ethyl acetate (3x50ml). Flash chromatography of the residue gradient eluting with mixtures of ethyl acetate in light petroleum (30-45%) yielded the title compound as a thick oil (27mg, 73%). ^{1}H nmr: 1.24 (*t*, *J*7.0Hz, 3H), 1.25 (*t*, *J*7.2Hz, 1H), 1.99 (*s*, 3H), 2.60 (*m*, 1H), 2.70 (*m*, 1H), 4.16 (*m*, 2H), 4.67 (*dt*, *J*5.7, 7.6Hz, 1H), 5.78 (*d*, *J*15.4Hz, 1H), 5.91 (*dt*, *J*7.4, 15.1Hz, 1H), 6.08 (*br d*, *J*7.7Hz, 1H), 6.17 (*ddd*, *J*0.7, 11.0, 15.1Hz, 1H, C5-H), 7.17 (*dd*, 1H, *J*10.9, 15.4Hz, 1H, C6-H); ^{13}C nmr: 14.20 ($OCH_2\underline{C}H_3$), 14.25 ($OCH_2\underline{C}H_3$), 23.18, 35.79, 51.64, 60.38 ($O\underline{C}H_2$), 61.78 ($O\underline{C}H_2$), 121.13, 131.97, 136.41, 143.62, 166.91 (conjugated ester

CO), 169.71, 171.45; IR ($CDCl_3$): 3420*m*, 2970*m*, 1730*s*, 1700*s*, 1672*s*, 1618*w*, 1500*m*, 1368*m*, 1340*w*, 1300*w*, 1260*m*, 1198*w*, 1024*m*, 996*m*; MS: 284 ($[M+H]^+$, 1%, calc. for $C_{14}H_{22}NO_5$: 284.1498, found: 284.1503), 238 (2), 224 (5), 210 (4), 195 (11), 188 (13), 158 (11), 142 (11), 116 (17), 114 (22), 102 (46), 72 (43), 43 (100).

Ethyl (*E*,*E*)-2-acetamido-8-oxonona-4,6-dienoate (238)

Reaction of ethyl (*E*)-N-acetyl-*D*,*L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol), methyl vinyl ketone (100µl, 1.20mmol), silver carbonate (53mg, 0.194mmol) and 5mol% $Pd(OAc)_2$ at reflux in THF overnight yielded on workup the title compound as a thick oil (25.5mg, 78%). ^1H nmr: 1.21 (*t*, *J*7.2Hz, 1H), 1.96 (*s*, 3H), 2.21 (*s*, 3H, methyl ketone), 2.57 (*br dt*, *J*7.3, 14.5Hz, 1H), 2.67 (*br dt*, *J*7.0, 14.5Hz, 1H), 4.14 (*m*, 2H), 4.65 (*br q*, 1H, alpha), 5.98 (*dt*, *J*7.5, 15.0Hz, 1H, C4-H), 6.01 (*d*, *J*15.6Hz, 1H, C7-H), 6.17 (*dd*, *J*10.7, 15.1Hz, 1H, C5-H), 6.24 (*br d*, 1H, NH), 6.99 (*dd*, *J*10.6, 15.7Hz, 1H, C6-H); ^{13}C nmr: 14.12, 23.03, 27.09 (methyl ketone CH_3), 35.86, 51.55, 61.70, 130.13, 132.22, 137.59, 141.58, 169.81, 171.36, 198.71 (ketone C=O); IR ($CHCl_3$): 3420*m*, 2970*m*, 1732*s*, 1606*vs*, 1588*w*, 1500*m*, 1372*m*, 988*m*, 900*w*; MS: 254 ($[M+H]^+$, 18%, calc. for $C_{13}H_{20}NO_4$: 254.1392, found: 254.1396), 206 (9), 194 (7), 188 (8), 165 (26), 145 (16), 102 (39), 72 (33), 43 (100).

(*E*,*E*) and (*E*,*Z*)-Ethyl-2-acetamido-7-cyanohexa-4,6-dienoates (239)

Reaction of ethyl (*E*)-N-acetyl-*D*,*L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol), acrylonitrile (100µl, 1.52mmol), silver carbonate (53mg, 0.194mmol) and 5mol% $Pd(OAc)_2$ at reflux in THF overnight yielded on workup the title compounds as an inseparable mixture (21.1mg, 69%, ratio 58:42). ^1H nmr: (***E*,*E***)-**239**: 1.23 (*t*, *J*7.0Hz, 1H), 1.98 (*s*, 3H), 2.59 (*m*, 1H, beta), 2.74 (*m*, 1H, beta), 4.19 (*m*, 2H), 4.67 (*m*, 1H, alpha), 5.26 (*d*, *J*16.1Hz, 1H, C7-H), 6.02 (*dt*, *J*7.5, 15.1Hz, 1H, C4-H), 6.15 (*ddd*, *J*0.7, 10.8, 15.1Hz, 1H, C5-H; overlapping with *br*, 1H, NH), 6.90 (*dd*, *J*10.7, 16.1Hz, 1H, C6-H); (***E*,*Z***)-**239**: 1.25 (*t*, *J*7.2Hz, 1H), 1.99 (*s*, 3H), 2.59 (*m*, 1H), 2.74 (*m*, 1H), 4.19 (*m*, 2H), 4.67 (*m*, 1H), 5.15 (*d*, *J*10.8Hz, 1H), 5.94 (*dt*, *J*7.3, 15.2Hz, 1H, C4-H), 6.15 (*br*, 1H, NH), 6.53 (*ddd*, *J*0.9, 11.0, 15.1Hz, 1H, C5-H), 6.74 (*t*, *J*10.9Hz, 1H, C6-H); IR ($CHCl_3$): 3420*m*, 2976*m*, 2212*s* (CN), 1734*s*, 1672*s*, 1640*w*, 1596*w*, 1394*s*, 1374*m*, 1340*m*, 1018*m*, 984*m*, 942*w*,

900*w*, 850*w*; MS: 236 (M^+, 7%, calc. for $C_{12}H_{16}N_2O_3$: 236.1161, found: 236.1166), 177 (25), 163 (11), 144 (22), 121 (53), 102 (86), 94 (19), 93 (19), 74 (31), 43 (100).

Diastereotopic ethyl 2-acetamido-5-(cyclohex-2-en-1-yl)pent-4-enoates (240)

Reaction of ethyl (*E*)-N-acetyl-*D,L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol), cyclohexene (100µl, 0.987mmol), silver carbonate (53mg, 0.194mmol) and 5mol% $Pd(OAc)_2$ at reflux in THF overnight yielded on workup the title compound as a thick oil (25.5mg, 78%). ^1H n.m.r.: 1.23 (t, J7.1Hz, 3H), 1.30 (m), 1.49 (m), 1.60 (m), 2.44 (m, 2H, C3-H's), 2.68 (m), 4.14 (br q, 2H), 4.57 (br q, 1H, C2-H), 5.25 (br dt, 1H, C4-H), 5.38-5.50 (m), 5.61 (br s), 5.67 (m), 6.02 (br d, J7.2Hz, 1H); ^{13}C n.m.r.: 14.20, 20.33, 20.41, 23.16, 24.66, 24.95, 28.62, 29.13, 31.31, 35.41, 36.51, 38.18, 52.00, 61.39, 121.51, 122.62, 125.88, 126.89, 127.85, 127.85, 128.41, 139.35, 140.40; IR ($CHCl_3$): 3420m, 2980m, 2920m, 2850w, 1732s, 1668s, 1498s, 1432w, 1376m, 1342m, 1018w, 968m, 902w, 854w; MS: 266 (M+H, 44%, calc. for $C_{15}H_{24}NO_3$: 266.1756, found: 266.1758), 206 (41), 102 (100).

Chapter 4.5

Ethyl (*E*)-2-acetamido-4-methylene-6-(trimethylsilyl)hex-5-enoate (248)

A solution of ethyl N-acetyl-*D,L*-4-iodoallylglycinate (**222**) (40mg, 0.129mmol) and (*E*)-1-(trimethylsilyl)-2-(tributylstannyl)ethylene (99mg, 0.257mmol) in DMF (2ml) was degassed with a stream of nitrogen. Bis(acetonitrile)palladium(II) chloride (1.7mg, 6.4µmol) was added and the dark purple solution was stirred at ambient temperature overnight. After 15h the canary yellow solution was heated at 90° for 60min by which time palladium black had precipitated. Potassium fluoride solution (10%, 30ml) was added and the aqueous phase extracted with ether (3x50ml). The organic extracts were dried and the solvent evaporated. Flash chromatography of the residue yielded the title compound as a thick oil (31mg, 86%). ^1H nmr: 0.37 (*s*, 9H), 1.22 (*t*, *J*7.2Hz, 3H), 2.59 (*dd*, *J*6.9, 14.2Hz, 1H), 2.72 (*dd*, *J*5.7, 14.2Hz, 1H), 4.11(*m*, 2H), 4.65 (*br q*, 1H, alpha), 5.00 (*s*, 1H), 5.11 (*s*, 1H), 5.88 (*d*, *J*19.2Hz, 1H), 6.01 (*br d*, *J*7.6Hz, 1H), 6.47 (*d*, *J*19.2Hz, 1H); ^{13}C nmr: -1.36 ($\underline{C}H_3Si$), 14.07, 23.03, 33.25, 51.50, 61.33, 119.20 ($C=\underline{C}H_2$), 129.85, 142.17 ($\underline{C}=CH_2$), 144.98, 169.57, 171.98; IR ($CHCl_3$): 3450*m*, 2900*m*, 1732*s*, 1670*s*, 1576*w*, 1504*m*, 1176*m*, 1238*m*, 1016*w*, 988*m*, 880*s*, 840*w*;

MS: 283 (M^+, 14%, calc. for $C_{14}H_{25}NO_3Si$: 283.1604, found: 283.1611), 268 ([M-$Me^·$]$^+$, 13), 241 (4), 240 (4), 224 ([M-$AcNH_2$]$^+$, 4), 210 ([M-CO_2Et]$^+$, 19), 168 (13), 102 (41), 75 (31), 73 (43), 43 (38), 18 (100). Reaction of enantiomerically enriched vinyliodide (*L*-**222**) using an identical procedure yielded the optically active product (*L*-**248**) (41%). $[\alpha]_D$ = +24.7° (*c*0.15, $CHCl_3$).

Ethyl 2-acetamido-4-phenylpent-4-enoate (148)

Reaction of ethyl N-acetyl-*D,L*-4-iodoallylglycinate (**222**) (40mg, 0.129mmol) and phenyl tributylstannane (94mg, 0.257mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at ambient temperature for 15h then 90° for 2h gave after workup the title compound (56%) contaminated with unreacted and inseparable vinyliodide (**222**) (8%) (*i.e.* 61% yield of **148** based on recovered starting material). ^{1}H n.m.r. spectrum identical to that obtained for product of Stille coupling of γ-stannane (**141**) with iodobenzene in *Chapter 3.5.1*.

Ethyl 2-acetamido-4-methylenehept-6-enoate (190)

Reaction of ethyl N-acetyl-*D,L*-4-iodoallylglycinate (**222**) (40mg, 0.129mmol) and allyl tributylstannane (80μl, 0.257mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at ambient temperature for 15h then 90° for 2h gave after workup the title compound (7%) contaminated with unreacted and inseparable vinyliodide (**222**) (70%) (*i.e.* 23% yield of **190** based on recovered starting material). ^{1}H n.m.r. spectrum identical to that obtained for product of Stille coupling of γ-stannane (**141**) with allylbromide in *Chapter 3.5.5*.

Chapter 4.6

Ethyl (*E*)-2-acetamido-6-methylhepta-4,6-dienoate (249)

Reaction of ethyl (*E*)-N-acetyl-*D,L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol) and prop-1-en-2-yl trimethylstannane (53mg, 0.257mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at ambient temperature for 18h gave after workup the title compound as a thick oil (19mg, 65%). ^{1}H nmr: 1.22 (*t*, *J*7.1Hz, 3H), 1.76 (*br s*, 3H, C6-Me), 1.97 (*s*, 3H), 2.55 (*m*, 2H), 4.15 (*m*, 2H), 4.62 (*dt*, *J*5.8, 7.9Hz, 1H), 4.86 (*br s*, 1H), 4.88 (*br s*, 1H), 5.43 (*dt*, *J*7.4, 15.5Hz, 1H), 6.11 (*br*, 1H, NH, masked by doublet), 6.13, (*d*, *J*15.6Hz, 1H); ^{13}C nmr: 14.12,

18.47 (6-CH_3), 23.10, 35.61, 51.95, 61.42, 116.09, 123.26, 136.87, 141.35 (C=CH_2), 169.66, 171.80; IR ($CHCl_3$): 3430*m*, 2970*m*, 1732*s*, 1670*s*, 1600*w*, 1498*s*, 1432*w*, 1374*m*, 1340*m*, 1120*w*, 1014*w*, 962*m*, 884*m*; MS: 226 ($[M+H]^+$, 23%, calc. for $C_{12}H_{20}NO_3$: 226.1443, found: 226.1453), 179 (10), 166 (52), 152 (10), 137 (29), 102 (63), 93 (100), 43 (50).

Ethyl (*E*,*E*)-2-acetamido-7-(trimethylsilyl)hepta-4,6-dienoate (250)

Reaction of ethyl (*E*)-N-acetyl-*D,L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol) and (*E*)-1-(trimethylsilyl)-2-(tributylstannyl)ethylene (74mg, 0.193mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at ambient temperature for 15 minutes decomposed the catalyst and gave after workup the title compound as a thick oil (8.5mg, 23%). ^1H nmr: 0.02 (*s*, 9H), 1.23 (*t*, *J*7.2Hz, 3H), 1.97 (*s*, 3H), 2.53 (*m*, 2H), 4.16 (*m*, 2H), 4.62 (*dt*, *J*5.7, 7.7Hz, 1H), 5.50 (*dt*, *J*7.4, 15.1Hz, 1H), 5.74 (*d*, *J*18.4Hz, 1H), 6.05 (*dd*, *J*10.1, 15.2Hz, 1H), 6.07 (*br d*, 1H, NH, masked by previous *dd*), 6.40 (*dd*, *J*10.0, 18.4Hz, 1H); ^{13}C nmr: -1.41, 14.15, 23.13, 35.26, 51.82, 61.54, 127.45, 133.82, 137.26, 143.21, 169.77, 171.74; IR ($CHCl_3$): 3426*m*, 2900*m*, 1736*s*, 1662*s*, 1508*m*, 1374*m*, 1236*m*, 1012*w*, 858*m*, 838*m*; MS: 283 (M^+, 7%, calc. for $C_{14}H_{25}NO_3Si$: 283.1604, found: 283.1597), 268 (6), 224 (21), 210 (9), 209 (9), 188 (14), 168 (20), 106 (47), 102 (100), 74 (74), 72 (68), 43 (96).

Ethyl (*E*)-2-acetamido-5-phenylpent-4-enoate (149)

Reaction of ethyl (*E*)-N-acetyl-*D,L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol) and phenyl tributylstannane (94mg, 0.257mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at ambient temperature for 15h gave after workup the title compound (31%) contaminated with unreacted and inseparable vinyliodide (**223**) (42%) (*i.e.* 53% yield of **149** based on recovered starting material). ^1H n.m.r. spectrum identical to that obtained for product of E-δ-stannane (**138**) with iodobenzene in *Chapter 3.6.1.*

Ethyl (*E*)-2-acetamidooctadien-4,7-oate (251)

Reaction of ethyl (*E*)-N-acetyl-*D,L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol) and allyl tributylstannane (80μl, 0.257mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at 80° for 4h gave

after workup the title compound (41%) contaminated with unreacted and inseparable vinyliodide (**223**) (40%) (*i.e.* 68% yield of **251** based on recovered starting material). ^{1}H n.m.r. spectrum identical to that obtained for product of coupling between stannane (**138**) and allylbromide in *Chapter 3.6.3*.

Ethyl (*E*,*E*)-2-acetamido-7-phenylhepta-4,6-dienoate (177)

Reaction of ethyl (*E*)-N-acetyl-*D*,*L*-5-iodoallylglycinate (**223**) (30mg, 96.4μmol) and E-β-(trimethylstannyl)styrene (51mg, 0.193mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at 40° for 17h gave after workup the title compound (6mg, 21%). ^{1}H n.m.r. spectrum identical to that obtained for product of coupling between *E*-δ-stannane (**138**) with E-β-bromostyrene in *Chapter 3.6.2*.

Chapter 4.7

Ethyl 2-acetamido-4-methylene-7-hydroxy-7-methyloct-5-ynoate (255)

To a solution of ethyl N-acetyl-*D*,*L*-4-iodoallylglycinate (**222**) (40mg, 0.129mmol), 2-methyl but-3-yn-2-ol (19μl, 0.193mmol) and triethylamine (36μl, 0.256mmol) in dry THF (2ml) was added bis(triphenylphosphine)palladium(II) chloride (4.5mg, 6.5μmol) and copper(II) iodide (2.5mg, 12.9μmol). The mixture was stirred at room temperature under a nitrogen atmosphere for 90min. Water (20ml) was added and the aqueous phase extracted with ethyl acetate (3x25ml). The combined organic extracts were dried and the solvent evaporated. The residue was subjected to flash chromatography on silica gel gradient eluting with a mixture of ethyl acetate and light petroleum (60-75%) to yield the title compound as a thick oil (21mg, 62%). ^{1}H nmr: 1.23 (*t*, *J*7.2Hz, 3H), 1.46 (*s*, 3H, diasteriotopic methyl), 1.47 (*s*, 3H, diasteriotopic methyl), 1.98 (*s*, 3H), 2.53 (*dd*, *J*7.5, 14.3Hz, 1H), 2.67 (*dd*, *J*5.2, 14.2Hz, 1H), 3.48 (*br*, 1H, OH), 4.15 (*q*, *J*7.1Hz, 2H), 4.80 (*m*, 1H, α), 5.19 (*d*, *J*1.2Hz, 1H), 5.33 (*d*, *J*1.2Hz, 1H), 6.34 (*br d*, *J*8.3Hz, 1H); ^{13}C nmr: 14.08, 23.09, 31.13 (diasteriotopic CH_3), 31.26 (diasteriotopic CH_3), 38.99, 51.03, 61.57, 64.94 (COH), 80.85 (C≡C), 95.81 (C≡C), 124.24 ($\underline{C}H_2$=C), 125.86 (CH_2=$\underline{C}$), 170.08, 171.77; IR (neat): 3292 (*vs*, *br*), 3080*w*, 2980*m*, 2928*w*, 2212*w*, 1736*s*, 1660*s*, 1544*s*, 1440*m*, 1376*m*, 1222 (*s*, *br*), 1024*m*, 954*w*, 910*w*, 860*w*, 754*w*; MS: 267 (M^+, <1%), 249 ($[M-H_2O]^+$, 15, calc. for $C_{14}H_{19}NO_3$: 249.1365, found: 249.1361), 176 (23), 134 (69), 102 (54), 43 (100); FAB: 268 (M+H).

Ethyl 2-acetamido-4-methylene-6-(trimethylsilyl)hex-5-ynoate (256)

Reaction of ethyl N-acetyl-*D*,*L*-4-iodoallylglycinate (**222**) (40mg, 0.129mmol) and trimethylsilyl acetylene (27µl, 0.194mmol) for 15h at ambient temperature yielded on workup the title compound as a thick oil (28.8mg, 79%). ^{1}H nmr: 0.12 (*s*, 9H), 1.22 (*t*, *J*7.2Hz, 3H), 1.95 (*s*, 3H), 2.57 (*dd*, *J*6.2, 14.0Hz, 1H), 2.63 (*dd*, *J*5.3, 14.0Hz, 1H), 4.13 (*m*, 2H), 4.67 (*m*, 1H, α), 5.24 (*s*, 1H), 5.44 (*s*, 1H), 6.27 (*br d*, *J*7.3Hz, 1H); ^{13}C nmr: -0.23 (Me_3Si), 14.01, 23.04, 38.44, 51.52, 61.38, 95.30 (C≡C), 104.51 (C≡C), 125.97 (CH_2=C), 126.20 (CH_2=C), 169.56, 171.19; IR (neat): 3284 (*s*, *br*), 3068*w*, 2956*m*, 2144*m*, 1746*s*, 1658*s*, 1548*s*, 1440*w*, 1376*m*, 1250*m*, 1210*m*, 1134*w*, 1026*m*, 874*w*, 842*s*, 760*m*, 700*w*; MS: 281 (M^+, 26%, calc. for $C_{14}H_{23}NO_3Si$: 281.1447, found: 281.1454), 266 (M^+-Me·, 32), 248 (16), 212 (47), 208 (68), 207 (63), 192 (26), 166 (58), 150 (37), 123 (42), 102 (100), 73 (63), 43 (95).

Ethyl 2-acetamido-4-methylene-6-phenylhex-5-ynoate (257)

Reaction of ethyl N-acetyl-*D*,*L*-4-iodoallylglycinate (**222**) (42mg, 0.134mmol) and phenyl acetylene (21µl, 0.194mmol) for 15h at ambient temperature yielded on workup the title compound as a thick oil (37.8mg, 97%). ^{1}H nmr : 1.21 (*t*, *J*7.2Hz, 3H), 2.01 (*s*, 3H), 2.71 (*dd*, *J*6.0, 14.0, 1H), 2.79 (*dd*, *J*5.3, 13.9Hz, 1H), 4.14 (*m*, 2H), 4.78 (*br q*, 1H, α), 5.31 (*br s*, 1H), 5.50 (*d*, *J*1.3Hz, 1H), 6.57 (*br d*, *J*7.1Hz, 1H), 7.28 (*m*, 3H), 7.38 (*m*, 2H); ^{13}C nmr: 13.99, 22.71, 38.74, 51.64, 61.69, 88.40 (C≡C), 90.39 (C≡C), 122.45 (quarternary aromatic), 125.17 (CH_2=C), 125.80 (CH_2=C), 128.30, 128.50, 131.39; IR (neat): 3288 (*m*, *br*), 3060*w*, 2980*w*, 2928*w*, 2200*w* (C≡C), 1736*s*, 1656*s*, 1546*s*, 1492*w*, 1444*m*, 1376*m*, 1270*w*, 1200*s*, 1070*m*, 912*w*, 756*m*, 692*m*; MS: 285 (M^+, 42%, calc. for $C_{17}H_{19}NO_3$: 285.1365, found: 285.1376), 257 (17), 226 (50), 212 (36), 170 (92), 129 (39), 102 (78), 45 (56), 43 (100). Reaction of ethyl N-acetyl-*L*-4-iodoallylglycinate (*L*-**222**) (40mg, 0.129mmol) under identical conditions yielded *L*-**257** (33.9mg, 91%). $[\alpha]_D$ = +56.9° (*c*0.34, $CHCl_3$).

Ethyl 2-acetamido-4-methylene-undec-5-ynoate (258)

Reaction of ethyl N-acetyl-*D*,*L*-4-iodoallylglycinate (**222**) (40mg, 0.129mmol) and 1-heptyne (26µl, 0.194mmol) for 2h at ambient temperature yielded on workup the title compound as a

thick oil (33.5mg, 93%). ^{1}H nmr: 0.83 (*t*, *J*6.6Hz, 3H), 1.21 (*t*, *J*7.2Hz, 3H), 1.27 (*m*, 4H), 1.46 (*m*, 2H, $C\underline{H}_2CH_2C{\equiv}C$), 1.95 (*s*, 3H), 2.20 (*t*, *J*7.1Hz, 2H, $C\underline{H}_2C{\equiv}C$), 2.53 (*dd*, *J*6.5, 13.9Hz, 1H), 2.59 (*dd*, *J*5.2, 13.9Hz, 1H), 4.12 (*m*, 2H), 4.66 (*br q*, 1H, α), 5.12 (*s*, 1H), 5.27 (*s*, 1H), 6.22 (*br d*, *J*7.5Hz, 1H); ^{13}C nmr: 13.84, 14.04, 19.17, 22.06, 22.95, 28.21, 31.00, 39.11, 51.38, 61.31, 79.85 (C≡C), 91.71 (C≡C), 123.46 ($\underline{C}H_2$=C), 126.44 (CH_2=$\underline{C}$), 169.69, 171.46; IR (neat): 3288 (*m*, *br*), 3068*w*, 2928*s*, 2856*w*, 2212*w*, 1744*s*, 1656*s*, 1546*s*, 1440*m*, 1376*m*, 1200*m*, 1134*w*, 1026*m*, 904*w*; MS: 279 (M^+, 26%, calc. for $C_{16}H_{25}NO_3$: 279.1834, found: 279.1839), 236 (26), 220 (23), 208 (31), 206 (45), 164 (69), 147 (40), 123 (57), 102 (71), 43 (100).

Ethyl 2-acetamido-8-hydroxy-8-methylnon-4-en-6-ynoate (259)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-iodoallylglycinate (**223**) (43.1mg, 0.139mmol) and 2-methyl but-3-yn-2-ol (19μl, 0.194mmol) for 15h at ambient temperature yielded on workup the title compound as a thick oil (36.4mg, 98%). ^{1}H nmr: 1.22 (*t*, *J*7.1Hz, 3H), 1.45 (*s*, 6H), 1.97 (*s*, 3H), 2.54 (*m*, 2H, β), 2.28 (*br*, 1H, OH), 4.14 (*q*, *J*7.1Hz, 1H), 4.15 (*q*, *J*7.2Hz, 1H), 4.61 (*br q*, 1H, α), 5.48 (*dd*, *J*0.7, 15.8Hz, 1H), 5.86 (*dt*, *J*7.5, 15.8Hz, 1H), 6.35 (*br d*, *J*7.7Hz, 1H); ^{13}C nmr: 14.10, 22.00, 31.24 ($\underline{C}H_3COH$), 35.50, 51.50, 61.67, 65.17 (COH), 79.64 (C≡C), 93.88 (C≡C), 113.30 (C=C), 137.09 (C=C), 170.01, 171.49; IR (neat): 3296 (*vs*, *br*), 3068*w*, 2980*m*, 2928*w*, 1736*s*, 1656*s*, 1548*s*, 1438*m*, 1378*s*, 1302*w*, 1216*s*, 1168*m*, 1136*m*, 1096*w*, 1026*m*, 954*s*, 860*m*; MS: 269 (M^+, <1%), 250 ($[M\text{-}OH]^+$, 3), 249 ($[M\text{-}H_2O]^+$, 4, calc. for $C_{14}H_{19}NO_3$: 249.1365, found: 249.1361), 206 (10), 203 (9), 176 (15), 161 (24), 134 (40), 106 (27), 102 (62), 43 (100).

Ethyl *E*-2-acetamido-7-(trimethylsilyl)hept-4-en-6-ynoate (260)

Reaction of ethyl *E*-N-acetyl-*D*,*L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol) and trimethylsilyl acetylene (27μl, 0.194mmol) for 2h at ambient temperature yielded on workup the title compound as a thick oil (35.1mg, 96%). ^{1}H nmr: 0.12 (*s*, 9H), 1.23 (*t*, *J*7.0Hz, 3H), 1.97 (*s*, 3H), 2.55 (*m*, 2H, β), 4.16 (*q*, *J*7.1Hz, 1H), 4.17 (*q*, *J*7.1Hz, 1H), 4.62 (*dt*, *J*5.5, 7.7Hz, 1H), 5.50 (*d*, *J*15.7Hz, 1H), 5.96 (*dt*, *J*7.4, 15.8Hz, 1H), 6.18 (*br d*, *J*7.6Hz, 1H); ^{13}C nmr: -0.23 (CH_3Si), 14.10, 23.07, 35.53, 51.44, 61.68, 94.35 (C≡C), 102.80 (C≡C),

113.86 (C=C), 138.31 (C=C), 169.74, 171.37; IR (neat), 3292 (*s, br*), 3064*w*, 2956*m*, 2900*w*, 2132*m*, 1742*s*, 1656*s*, 1544*s*, 1436*w*, 1376*m*, 1250*m*, 1194*m*, 1134*m*, 1082*m*, 1026*m*, 956*m*, 846*s*, 760*m*, 700*w*, 656*w*; MS: 282 (M^+, 2%, calc. for $C_{14}H_{23}NO_3Si$: 281.1447, found: 281.1454), 266 (M^+-CH_4, 5), 222 (14), 207 (23), 206 (16), 193 (12), 178 (20), 166 (21), 150 (20), 136 (14), 102 (100), 73 (60), 43 (100).

Ethyl *E*-2-acetamido-7-phenylhex-4-en-6-ynoate (261)

Reaction of ethyl *E*-N-acetyl-*D,L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol) and phenyl acetylene (21µl, 0.194mmol) for 2h at ambient temperature yielded on workup the title compound as a thick oil (23.7mg, 64%). ^{1}H nmr: 1.27 (*t*, *J*7.0Hz, 3H), 2.01 (*s*, 3H), 2.64 (*m*, 2H, β), 4.20 (*m*, 2H), 4.68 (*dt*, *J*5.6, 7.7Hz, 1H, α), 5.73 (*dt*, *J*1.3, 15.7Hz, 1H), 6.02 (*dt*, *J*7.6, 15.7Hz, 1H), 6.15 (*br d*, *J*7.8Hz, 1H), 7.25-7.30 (*m*, 3H), 7.35-7.40 (*m*, 2H); ^{13}C nmr: 14.20, 23.16, 35.79, 51.61, 61.75, 87.25 (C≡C), 89.30 (C≡C), 113.89 (C=C), 123.03 (quarternary aromatic), 128.22, 128.29, 131.44, 137.20 (C=C), 169.74, 171.45; IR ($CDCl_3$): 3420*m*, 2976*m*, 2236*m* (C≡C), 1736*s*, 1670*s*, 1590*w*, 1500*s*, 1440*w*, 1370*m*, 1340*m*, 1300*w*, 1210*m*, 1130*w*, 1010*m*; MS: 285 (M^+, 2%, calc. for $C_{17}H_{19}NO_3$: 285.1365, found: 285.1360), 252 (10), 238 (11), 226 (8), 196 (36), 184 (42), 144 (8), 141 (16), 125 (22), 105 (24), 102 (100), 97 (30), 86 (36), 84 (42), 43 (98).

Ethyl 2-(acetamido)dodec-4-en-6-ynoate (262)

Reaction of ethyl *E*-N-acetyl-*D,L*-5-iodoallylglycinate (**223**) (40mg, 0.129mmol) and 1-heptyne (26µl, 0.194mmol) for 2h at ambient temperature yielded on workup the title compound as a thick oil (28.9mg, 80%). ^{1}H nmr: 0.85 (*t*, *J*7.0Hz, 3H), 1.24 (*t*, *J*7.1Hz, 3H), 1.25-1.35 (*m*, 4H), 1.40-1.52 (*m*, 2H), 1.98 (*s*, 3H), 2.22 (*t*, *J*7.0Hz, 1H, diastereotopic C<u>H</u>C≡C), 2.23 (*t*, *J*7.0Hz, 1H, diastereotopic C<u>H</u>C≡C), 2.54 (*m*, 2H, β), 4.17 (*m*, 2H), 4.61 (*dt*, *J*5.5, 7.7Hz, 1H), 5.48 (*br d*, *J*15.7Hz, 1H), 5.80 (*dt*, *J*7.4, 15.7Hz, 1H), 6.09 (*br d*, *J*7.6Hz, 1H); ^{13}C nmr: 13.92, 14.15, 19.23, 22.14, 23.13, 28.31, 31.02, 35.50, 51.58, 61.63, 78.28 (C≡C), 90.54 (C≡C), 114.38 (C=C), 135.35 (C=C), 169.69, 171.50; IR (neat): 3280 (*br, s*), 3060*w*, 2950*w*, 2930*s*, 2860*m*, 2210*w* (C≡C), 1740*s*, 1660*s*, 1540*s*, 1462*w*, 1436*w*, 1376*m*, 1200 (*m, br*), 1020*m*, 750*w*, 856*w*; MS: 279 (M^+, 15%, calc. for

$C_{16}H_{25}NO_3$: 279.1834, found: 279.1839), 252 (4), 250 (3), 236 (12), 220 (57), 206 (33), 191 (27), 164 (62), 163 (57), 147 (45), 105 (73), 102 (57), 99 (58), 79 (67), 77 (80), 75 (78), 60 (83), 55 (92), 43 (100).

Chapter 4.8

Diethyl N-acetyl 4-methyleneglutamate (265)

Carbon monoxide was bubbled through a solution of ethyl N-acetyl-*D,L*-4-iodoallylglycinate (**222**) (40mg, 0.129mmol), ethanol (100µl, 1.70mmol), and triethylamine (22µl, 0.154mmol) in acetonitrile (2ml) for 5 minutes. Tetrakis(triphenylphosphine)palladium(0) (11.1mg, 9.6µmol) was added and the reaction mixture stirred at 60° for 60 minutes under 1 atmosphere of carbon monoxide (balloon). The solution was cooled and the solvent evaporated *in vacuo*. The residue was subjected to flash chromatography on silica gel to yield the title compound as a thick oil (25.7mg, 77%). ^{1}H nmr: 1.21 (*t*, *J*6.9Hz, 3H), 1.26 (*t*, *J*7.1Hz, 3H), 1.94 (*s*, 3H), 2.67 (*dd*, *J*7.8, 14.0Hz, 1H), 2.75 (*dd*, *J*5.4, 14.0Hz, 1H), 4.04-4.22 (*m*, 4H), 4.64 (*dt*, *J*5.4, 7.7Hz, 1H), 5.61 (*s*, 1H), 6.21 (*s*, 1H), 6.40 (*br d*, *J*6.9Hz, 1H); ^{13}C nmr: 14.05 (both $\underline{C}H_3CH_2O$), 22.95, 34.41, 52.07, 61.10 (CH_2O), 61.39 (CH_2O), 128.43 ($\underline{C}H_2$=C), 135.93 (CH_2=$\underline{C}$), 166.95 (conjugated $\underline{C}O_2Et$), 169.75, 171.53; MS: 257 (M^+, 2%, calc. for $C_{12}H_{19}NO_5$: 257.1263, found: 257.1260), 214 (2), 212 (1), 211 (1), 202 (2), 184 (25), 170 (8), 142 (18), 102 (63), 96 (19), 68 (7), 43 (16), 32 (100), 31 (40), 29 (83). The reaction was repeated with the enantiomerically enriched vinyl iodide (*L*-**222**) using identical conditions to yield the optically active product (*L*-**265**): $[\alpha]_D$ = +21.0° (*c*0.26, $CHCl_3$).

Ethyl (*E*)-2-acetamido-5-(carboethoxy)pent-4-enoate (266)

Reaction of ethyl (*E*)-N-acetyl-*D,L*-5-iodoallylglycinate (**223**) (60mg, 0.193mmol), ethanol (100µl, 1.70mmol), and triethylamine (32µl, 0.231mmol) in acetonitrile (2ml) with 5mol% $Pd(PPh_3)_4$ in acetonitrile under 1 atmosphere of carbon monoxide for 3h at 80° yielded after workup the title compound as a thick oil (33mg, 67%). ^{1}H nmr: 1.21 (*t*, *J*7.2Hz, 6H), 1.96 (*s*, 3H), 2.61 (*br dtt*, 1H), 2.68 (*br dtt*, 1H), 4.11 (*q*, *J*7.1Hz, 2H), 4.13 (*m*, 2H), 4.66 (*br dt*, *J*5.7, 7.6Hz, 1H), 5.80 (*dt*, *J*1.2, 15.6Hz, 1H), 6.33 (*br d*, *J*7.5Hz, 1H), 6.72 (*dt*, *J*7.4Hz, 15.6Hz); ^{13}C: 14.04, 14.09, 22.97, 34.63, 51.20, 60.36, 61.75, 124.86, 141.97, 165.73

(conjugated $\underline{C}O_2Et$), 169.80, 171.12; IR (neat): 3296*m*, 3064*w*, 2984*m*, 2936*w*, 1722*s*, 1656*s*, 1542*m*, 1448*w*, 1374*m*, 1266*m*, 1184*s*, 1096*w*, 1034*m*, 982*w*, 862*w*; MS: 257 (M^+, 1%, calc. for $C_{12}H_{19}NO_5$: 257.1263, found: 257.1255), 214 (3), 212 (2), 211 (2), 184 (18), 170 (16), 144 (15), 142 (89), 114 (11), 102 (54), 96 (24), 43 (20), 29 (100).

Chapter 5.1

Ethyl (*cis*)-2-acetamido-4,5-bis(trimethylstannyl)pent-4-enoate (274)

Tetrakis(triphenylphosphine)palladium(0) (8.0mg, 6.9μmol) was added to a solution of ethyl N-acetyl-*D,L*-propargylglycinate (**121**) (92mg, 0.502mmol) and hexamethylditin (165mg, 0.504mmol) in dry THF (3ml). The solution was degassed with a stream of nitrogen then heated to reflux under a nitrogen atmosphere. After 5 hours further hexamethylditin (100mg, 0.305mmol) and $Pd(PPh_3)_4$ (10mg, 8.7μmol) was added and the solution heated at reflux overnight the cooled to room temperature. The solvent was evaporated and the residue subjected to flash chromatography, gradient eluting with 30-75% ethyl acetate in light petroleum, to yield the title compound as a clear oil (126mg, 49%; 60% based on recovered unreacted **121** [17mg, 18%]). ^1H nmr: 0.07 (*s*, 9H), 0.14 (*s*, 9H), 1.17 (*t*, *J*7.2Hz, 3H), 1.88 (*s*, 3H), 2.45 (*dd*, *J*8.5, 12.9Hz, 1H), 2.78 (*dd*, *J*6.1, 13.0Hz, 1H), 4.05 (*m*, 2H), 4.46 (*br q*, *J*7.7Hz, 1H), 6.57 (*s*, 1H, with Sn-H satellites: $^3J_{SnH}$=182Hz, $^2J_{SnH}$=81Hz); ^{13}C nmr: -7.93 (with Sn-C satellites: $^1J_{SnC}$=337Hz), -7.43 (with satellites: $^1J_{SnC}$=326Hz), 14.05, 22.83, 49.75, 51.80, 61.02, 148.43 (Sn$\underline{C}$H=CSn), 162.42 (SnCH=$\underline{C}$Sn), 169.46, 172.19; IR (neat): 3288(*br*, *m*), 3070*w*, 2980*m*, 2912*m*, 1746*s*, 1656*s*, 1546*s*, 1442*w*, 1376*m*, 1262*w*, 1186*s*, 1126*m*, 1032*m*, 770*s*, 712*w*; MS (EI, listed peaks are for major ^{120}Sn isotope): 513 (M^+, not present), 495 ($[M-CH_3]^+$, 40%), 422 (3), 348 (67), 234 (8), 165 (100), 135 (32), 68 (13), 43 (28), 32 (18).

Chapter 5.2

Ethyl (*Z*)-2-acetamido-4-(trimethylstannyl)octa-4,7-dienoate (276)

A mixture of tris(dibenzylidineacetone)dipalladium chloroform complex (2,5mg, 2.5μmol) and triphenylarsine (6.0mg, 19.6μmol) was stirred in dry THF (2ml) for 5 minutes. Ethyl (*cis*)-N-acetyl-4,5-bis(trimethylstannyl)allylglycinate (**274**) (50mg, 97.9μmol) and allyl bromide

(8.5µl, 97.9µmol) were added. The mixture was stirred at ambient temperature for 60 minutes, then at reflux for 4 hours.and then cooled to room temperature. Water (30ml) was added and the aqueous phase extracted with dichloromethane (3x30ml). The combined extracts were dried and the solvent evaporated. Flash chromatography of thr residue, gradient eluting with 30-40% ethyl acetate/light petroleum yielded the title compound (16mg, 36%) as a white solid. Ethyl N-acetylpropargylglycinate (**121**) (15mg, 42%) was also obtained and its spectra were identical to those obtained for the authentic material. **276**: M.p.: 80-81°; ^{1}H nmr: 0.19 (*s*, 9H, with Sn-H satellites: $^1J_{SnH}$=53.2Hz), 1.23 (*t*, *J*7.1Hz, 3H), 1.90 (*s*, 3H), 2.44 (*dd*, *J*8.3, 13.3Hz, 1H, with satellites: $^3J_{SnH}$=*ca* 60Hz), 2.68 (*dd*, *J*5.9, 13.3Hz, 1H, with satellites), 2.73 (*br t*, 2H, C6-H's), 4.09 (*dq*, *J*7.0, 10.8Hz, 1H), 4.14 (*dq*, *J*7.2, 10.8Hz, 1H), 4.48 (*dt*, *J*5.9, 8.2Hz, 1H, α), 4.96 (*m*, 1H, *cis* HCH=CH), 4.99 (*m*, 1H, *trans* HCH=CH), 5.71 (*ddt*, *J*6.3, 10.3, 16.9Hz, 1H, CH_2=CH), 5.82 (*br d*, *J*7.7Hz, 1H, NH), 5.93 (*t*, *J*7.3Hz, 1H); ^{13}C nmr: -8.23, 14.12, 23.08, 38.65 (C6), 43.28 (C3), 52.30 (C2), 61.23, 115.38 (CH_2=CH), 136.45 (CH_2=CH), 140.01 (CH=CSn), 141.69 (CH=CSn), 169.42, 172.32; IR (nujol mull): 3302*s*, 3080*w*, 1758 & 1748*s* (C=O, Fermi resonance), 1654*s*, 1558*s*, 1308*w*, 1262*m*, 1220*s*, 1190*s*, 1138*w*, 1012*m*, 906*w*, 774*m*, 720*m*; MS (listed peaks are for major ^{120}Sn isotope): 389 (M+, not present), 388 ([M-H]$^+$, 1%), 374 ([M-CH_3]$^+$, 52, calc. for $C_{14}H_{24}NO_3{}^{120}Sn$: 374.0778, found: 374.0795), 300 (31), 224 (22), 165 (50), 136 (31), 89 (31), 43 (100).

Ethyl (*E*)-2-acetamido-4-(prop-1-en-2-yl)octa-4,7-dienoate (281)

Reaction of ethyl (*cis*)-N-acetyl-4,5-bis(trimethylstannyl)allylglycinate (**274**) (100mg, 0.196mmol) and allyl bromide (85µl, 0.979mmol) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 15 hours yielded on workup the title compound as a thick oil (24mg, 46%). ^{1}H nmr: 1.22 (*t*, *J*7.2Hz, 3H), 1.94 (*s*, 3H), 2.27 (*dd*, *J*8.2, 13.8Hz, 1H), 2.49 (*dd*, *J*5.8, 13.7Hz, 1H), 2.69-2.77 (*m*, 4H, doubly allylic CH_2's), 4.12 (*m*, 2H), 4.60 (*dt*, *J*5.8, 8.1Hz, 1H), 4.90-5.06 (*m*, 4H, CH_2=C), 5.26 (*br t*, *J*7.3Hz, 1H, C5-H), 5.66 (*ddt*, *J*6.4, 10.2, 16.9Hz, 1H), 5.71 (*ddt*, *J*6.3, 10.2, 17.0Hz, 1H), 5.94 (*br d*, *J*7.6Hz, 1H, NH); ^{13}C nmr: 14.08, 23.01, 32.07, 33.96, 39.63, 50.80, 61,30, 114.87 (CH_2=C), 116.04 (CH_2=C), 127.53 (CH=C$(CH_2)_2$), 133.04 (CH=C$(CH_2)_2$), 135.14 (CH_2=CH), 136.44 (CH_2=CH), 169.59, 172.47; IR (neat): 3280 (*br*, *m*), 3078*w*, 2982*m*, 2932*w*, 1742*s*, 1658*s*, 1546*s*, 1442*m*,

1378*m*, 1190*m*, 1134*w*, 1026*w*, 996*w*, 916*m*; MS: 265 (M^+, 1%, calc. for $C_{15}H_{23}NO_3$: 265.1678, found: 265.1681), 224 (21), 220 (33), 205 (90), 192 ([M-$^{\cdot}CO_2Et]^+$, 21), 165 (52), 28 (100).

Ethyl *E*-2-acetamidoocta-4,7-dienoate (251)

Reaction of vinylstannane **276** (29mg, 75μmol) and cyclohex-1-en-1-yl triflate (100μl, large excess) with 5mol% $Pd(AsPh_3)_4$ in THF at reflux for 5 hours produced a number of products by t.l.c. The major product was obtained by flash chromatography to yield the title compound as a thick oil (5.1mg, 30%). ^1H n.m.r.: 1.24 (*t*, *J*7.0Hz, 3H), 1.98 (*s*, 3H), 2.47 (*m*, 2H, C3-H's), 2.71 (*br t*, 2H, C6-H's), 4.15 (*m*, 2H, ester methylene), 4.59 (*dt*, *J*5.7, 7.8Hz, 1H, C2-H), 4.94-5.00 (*m*, 2H, C8-H's), 5.28 (*dt*, *J*7.2, 15.2Hz, 1H), 5.50 (*dt*, *J*6.5, 15.2Hz, 1H), 5.74 (*ddt*, *J*6.4, 10.5, 16.9Hz, 1H, C7-H), 5.99 (*br d*, *J*6.8Hz, 1H, NH).

Ethyl N-acetylpropargylglycinate (121) (by Pd(0) catalysed elimination of trimethyltin iodide from 283). Tris(dibenzylidineacetone)dipalladium chloroform complex (3.1mg, 3.0μmol) and triphenylarsine (7.4mg, 24.2μmol) were stirred in dry THF under nitrogen for 5 minutes. Ethyl (*Z*)-2-acetamido-4-(trimethylstannyl)-5-iodopent-4-enoate (**283**) (41mg, 86.5μmol) was added and the solution stirred at ambient temperature for 20min, then at reflux overnight and then cooled to room temperature. Water (30ml) was added and the aqueous phase extracted with ethyl acetate (3x30ml). The combined organic extracts were dried and the solvent evaporated. Flash chromatography, gradient eluting with 40-50% ethyl acetate/light petroleum yielded the title compound (13.8mg, 87%). Spectroscopic data was identical to that obtained for the authentic material (*Chapter 3.1*).

Chapter 5.3

Ethyl (*Z*)-2-acetamido-4-(trimethylstannyl)-5-iodopent-4-enoate (283)

Iodine (53.7mg, 0.212mmol) was added to a solution of (*cis*)-ethyl-N-acetyl-4,5-bis(trimethylstannyl)allylglycinate (**274**) (100mg, 0.196mmol) in dichloromethane (10ml). After 15 minutes at ambient temperature, water (20ml) was added. The aqueous phase was extracted with dichloromethane (2x5ml) and the combined organic extracts dried and the solvent

evaporated. Flash chromatography of the residue eluting with 50% ethyl acetate in light petroleum yielded the title compound (57.3mg, 62%). ^{1}H nmr: 0.32 (*s*, 9H, with Sn-H satellites: $^2J_{SnH}$=54.9Hz), 1.25 (*t*, *J*7.2Hz, 3H), 1.96 (*s*, 3H), 2.50 (*dd*, *J*7.8, 13.4Hz, 1H, with Sn-H satellites: $^3J_{SnH}$=47.2Hz), 2.63 (*dd*, *J*6.7, 13.4Hz, 1H, with Sn-H satellites: $^3J_{SnH}$=43.6Hz), 4.15 (*m*, 2H), 4.54 (*br q*, 1H, α), 5.90 (*br d*, *J*7.9Hz, 1H), 6.77 (*s*, 1H, with Sn-H satellites: $^3J_{SnH}$=108.8Hz); ^{13}C nmr: -7.30 (with Sn-H satellites: $^1J_{SnC}$=343Hz), 14.22, 23.14, 46.43 (with Sn-H satellites: $^2J_{SnC}$=37.9Hz), 51.47 (α), 61.59, 90.63 (I<u>C</u>H=CSn), 156.80 (ICH=<u>C</u>Sn), 169.43, 171.85; IR (nujol): 3296*m*, 3070*w*, 1752 & 1740 (*s*, Fermi resonance), 1646*s*, 1550*s*, 1282*w*, 1226*m*, 1208*m*, 1182*m*, 1120*w*, 1018*w*, 772*w*; MS: 475 (M^+, not present), 460 ($[M-Me]^+$, 2%, calc. for $C_{11}H_{19}NO_3ISn$: 459.9432, found: 459.9416), 348 (2), 277 (58), 165 (53), 110 (100), 102 (74), 68 (55), 43 (85).

Ethyl (*cis*)-2-acetamido-4,5-diiodopent-4-enoate (284)

Reaction of ethyl (*cis*)-N-acetyl-4,5-bis(trimethylstannyl)allylglycinate (**274**) (100mg, 0.196mmol) with iodine (75mg, 0.295mmol) in chloroform (30ml) for 15h at ambient temperature yielded on workup the title compound as a thick oil (20mg, 23%). ^{1}H nmr: 1.24 (*t*, *J*7.1Hz, 3H), 1.97 (*s*, 3H), 3.06 (*dd*, *J*6.0, 14.7Hz, 1H), 3.16 (*dd*, *J*5.8, 14.6Hz, 1H), 4.16 (*q*, *J*7.2Hz, 2H), 4.69 (*q*, *J*5.9Hz, 1H), 6.02 (*br d*, 1H, NH), 7.20 (*s*, 1H); ^{13}C nmr: 14.17, 23.16, 48.18 (C3), 51.82 (C2), 62.06, 93.37 (I<u>C</u>H=CI), 114.68 (ICH=<u>C</u>I), 169.71, 170.72; IR ($CHCl_3$ solution): 3432*m*, 2988*m*, 1734*s*, 1676*s*, 1504*s*, 1428*w*, 1378*m*, 1342*m*, 1276*w*, 1182*w*, 1020*w*, 858*w*; MS: 437 (M^+, 24%, calc. for $C_9H_{13}I_2NO_3$: 436.8985, found: 436.8975), 401 (61), 363 (21), 321 (42), 311 (48), 310 (92), 235 (42), 153 (100), 110 (59), 101 (39), 75 (71), 73 (77).

1. Barrett, G.C. *Chemistry and Biochemistry of the Amino Acids*, Chapman & Hall: London, **1985**.

2. Greenstein, J.P.; Winitz, M. *Chemistry of the Amino Acids*, Vol. 1-3; Robert E. Krieger: FL, **1984**.

3. Wagner, I.; Musso H. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 816.

4. Roth, H.J.; Kleemann, A.; Beisswenger, T. *Pharmaceutical Chemistry*, Ellis Horwood Ltd., Chichester, **1988**.

5. *Farm Chemicals Handbook*, 72nd edition, Meister Publ. Co., Willoughby, **1986**.

6. Block, R.J.; Bolling, D. *The Amino Acid Composition of Proteins and Foods*, 2nd Edition; Charles C. Thomas, Illinois, 1951.

7. *The Merck Index*, 11th Ed.; Budvardi, S., Ed.; Merck & Co., Inc., Rahway, **1989**.

8. Spatola, A.F. in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, Vol 7, Marcel Dekker, New York, **1983**, 267.

9. Williams, R.M. *Synthesis of Optically Active α-Amino Acids*, Baldwin, J.E., Ed., Organic Chemistry Series, Pergamon Press: Oxford, **1989**.

10. Coppala, G.M.; Schuster, H.F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids* Wiley Interscience: New York, **1987**.

11. (a) Walsh, C. *Enzymatic Reaction Mechanisms,* W.H. Freemann & Co., San Fransisco: **1979**; (b) Walsh, C. *Tetrahedron* **1982**, *38*, 871.

12. (a) Rando, R. *Biochemistry* **1974**, *13*, 3859; (b) Rando, R.R. *Science* **1974**, *185*, 320; (c) Soper, T., Manning, J., Marcotte, P., Walsh, C. *J. Biol. Chem.* **1977**, *252*, 1571.

13. Giovanelli, I.; Owens, L.; Mudd, S. *Biochem. Biophys. Acta* **1971**, *227*, 691

14. Rando, R.; Relyea, R.; Cheng, L. *J. Biol. Chem.* **1976**, *251*, 3306.

15. Cooper A.L.J.; Fitzpatrick, S.M.; Kaufmann, C.; Dowd, P. *J. Am. Chem. Soc.* **1982**, *104*, 332.

16. Chrystal, E.; Bey, P.; Rando, R. *J. Neurochem.* **1979**, *32*, 1501.

17. (a) Thornberry, N.A.; Bull, H.G.; Taub, D.; Greenlee, W.J.; Patchett, A.A.; Cordes, E.H. *J. Am. Chem. Soc.* **1987**, *109*, 7543; (b) Patchett, A.A.; Taub, D.; Weissberger, B.; Valiant, M.E.; Gadebush, H.; Thornberry, N.A. *Antimicrob. Agents Chemother.*

1988, *32*, 319.

18. (a) Lowe, P.N.; Rowe, A.F. *Comp. Biochem. Physiol., B: Comp. Biochem.* **1987**, *88B*, 223; (b) Johnston, M.; Raines, R; Chang, M; Esaki, N. Soda, K.; Walsh, C. *Biochemistry* **1981**, *20*, 4325.

19. Moriguchi, M.; Yoshifumi, H.; Hatanaka, S. *J. Antibiot.* **1987**, *40*, 904; (b) Esaki, N; Takada, H.; Moriguchi, M.; Hatanaka, S.; Tanaka, H.; Soda, K. *Biochemistry* **1989**, *28*, 2111.

20. (a) Washtein, W.; Abeles, R. *Biochemistry* **1977**, *16*, 2485; (b) Abeles, R.H.; Walsh, C.T. *J. Am. Chem. Soc.* **1973**, *95*, 6124; (c) Johnson, M.; Jankowski, D.; Marcotte, P.; Tanaka, H.; Esaki, N.; Walsh, C. *Biochemistry* **1979**, *18*, 4690.

21. (a) Kuroda, Y.; Okuhara, M.; Goto, T.; Iguchi, E.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1980**, *33*, 125; (b) Kuroda, Y.; Okuhara, M.; Goto, T.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1980**, *33*, 132.

22. Cats/rats/baboons (a) Moyanova, S.; Dimov, S.; Popivanov, D. *Acta Physiol. Pharmacol. Bulg.* **1989**, *15*, 47; (b) Meldrum, B.J.; Swan, J.H.; Otterson, O.P.; Storm-Mathisen, J. *Neuroscience* **1987**, *22*, 17; (c) Valin, A.; Voltz, C.; Naquet, R.; Lloyd, K.G. *Brain Res.* **1991**, *538*, 15.

23. Orlowski, M.; Rheingold, D.; Stanley, M. *J. Neurochem.* **1977**, *28*, 349.

24. (a) Williams, R.M.; Aldous, D.J.; Aldous, S.C. *J. Org. Chem.* **1990**, *55*, 4657; (b) Williams, R.M.; Aldous, D.J.; Aldous, S.C. *J. Chem. Soc., Perkin Trans. I* **1990**, 171; (c) Casara, P.; Metcalf, B.W. *Tetrahedron Lett.* **1978**, 1581; (d) Casara, P.J.; Jung, M.; Metcalf, B.W. *U.S. Pat.* 4,260,823, **1981**.

25. Abdulganeeva, S.A.; Erzhanov, K.B. *Russian Chemical Reviews* **1991**, *60*, 676.

26. (a) Azfali-Ardakani, A.; Rapoport, H *J. Org. Chem,* **1980**, *45*, 4817; (b) Carrasco, M.; Jones, R.J.; Kamel, S.; Rapoport, H. *Org. Synth.* **1992**, *70*, 29; (c) Meffre, P.; Vo-Quang, L.; Vo-Quang, Y.; Le Goffic, F. *Synth. Commun.* **1989**, *19*, 3457.

27. Hanessian, S.; Sahoo, S.P. *Tetrahedron Lett.* **1984**, *25*, 1425.

28. Pelliciari, R.; Natalini, B.; Marinozzi, M. *Synth. Commun.* **1988**, *18*, 1715.

29. Bicknell, A.J.; Burton, G.; Elder, J.S. *Tetrahedron Lett.* **1988**, *29*, 3361.

30. Angst, C. *Pure Appl. Chem.* **1987**, *59*, 373.

31. Greenlee, W.J. *J. Org. Chem.* **1984**, *49*, 2632.

32. Castelhano, A.L.; Horne, S.; Taylor, G.J.; Billedeau, R.; Krantz, A. *Tetrahedron* **1988**, *44*, 5451.

33. Shea, R.G.; Fitzner, J.N.; Fankhayser, J.E.; Spaltenstein, A.; Carpino, P.A.; Peevey, R.M.; Pratt, D.V.; Tenge, B.J.; Hopkins, P.B. *J. Org. Chem.* **1986**, *51*, 5243.

34. Schöllkopf, U.; Nozulak, J.; Groth, U. *Tetrahedron* **1984**, *40*, 1409.

35. Williams, R.M.; Zhai, W. *Tetrahedron* **1988**, *44*, 5425.

36. Baldwin, J.E.; Moloney, M.G.; North, M. *Tetrahedron* **1989**, *45*, 6319.

37. Sasaki, N.A.; Hashimoto, C.; Pauley, R. *Tetrahedron Lett.* **1989**, *30*, 1943.

38. Sibi, M.P.; Renhowe, P.A. *Tetrahedron Lett.* **1990**, *31*, 7407.

39. Beaulieu, P.L.; Duceppe, J.-S.; Johnson, C. *J. Org. Chem.* **1991**, *56*, 4196.

40. Suzuki, M.; Nunami,K.-I.; Yoneda, N. *J. Chem. Soc., Chem. Commun.* **1978**, 270.

41. Chari, R.V.J.; Wemple, J. *Tetrahedron Lett.* **1979**, 111.

42. For example: (a) Metcalf, B.W.; Jung, M. *Tetrahedron Lett.* **1977**, *41*, 3689; (b) Aurell, M.J.; Gil, S.; Martínez, P.V.; Parra, M.; Tortajada, A.; Mestres, R. *Synth. Commun.* **1991**, *21*, 1833; (c) Weber, T.; Aeschimann, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365.

43. (a) O'Donnell, M.J.; Bennett, W.D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353; (b) Williams, R.M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075; (c) Schöllkopf, U.; Neubauer, H.-J. *Synthesis* **1982**, 861.

44. Genet, J.P.; Kopola, N.; Juge, S.; Ruiz-Montes, J.; Antunes, O.A.C.; Tanier, S. *Tetrahedron Lett.* **1990**, *31*, 3133, and references cited therein.

45. (a) Easton, C.J.; Scharfbillig, I.M.; Tan, E.W. *Tetrahedron Lett.* **1988**, *29*, 1565; (b) Baldwin, J.E.; Adlington, R.M.; Lowe, C.; O'Neil, I.A.; Sanders, G.L.; Schofield, C.J.; Sweeney, J.B. *J. Chem. Soc., Chem. Commun.* **1988**, 1030.

46. Yamamoto,Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415.

47. Mooiweer, H.H.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron* **1989**, *45*, 4627.

48. Baldwin, J.E.; Flinn, A. *Tetrahedron Lett.* **1987**, *28*, 3605.

49. Baldwin, J.E.; North, M.; Flinn, A.; Moloney, M.G.; *Tetrahedron* **1989**, *45*, 1465.

50. Shaw, K.J.; Luly, J.R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515.

51. Wade, P.A.; Pillayand, M.K.; Singh, S.M. *Tetrahedron Lett.* **1982**, *23*, 4563.

52. Cordi, A.A.; Marinozzi, M.; Lanthorn, T.H.; Monahan, J.B.; Natalini, B.; Pelliciari, R. *Eur. Pat. Appl.* EP 342,558, **1989**.

53. Castelhano, A.L.; Pliura, D.H.; Venuti, M.C. *U.S. Pat.* US 4,970,297, **1990**.

54. (a) Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, London/Orlando, **1985**; (b) Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, California, **1987**; (c) *Transition Metals in Organic Synthesis*, Scheffold, R., Ed.; Modern Synthetic Methods, Otto Salle Verlag, Frankfurt am Main/Verlag Sauerländer, Aarau **1983**; (d) Davies, S.G. *Organotransition Metal Chemistry: Applications to Organic Synthesis*, Pergamon Press, Oxford, **1982**.

55. Stang, P.J.; Hanack, M.; Subramanian, L.R. *Synthesis* **1982**, 85.

56. Stille, J.K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

57. (a) Tsuji, J. *Synthesis* **1990**, 739; (b) Trost, B.M. *Science* **1991**, *254*, 1471.

58. Arcadi, A.; Cacchi, S.; Marinelli, F.; Morera, E.; Ortar, G. *Tetrahedron* **1990**, *46*, 7151, and references cited therein.

59. (a) Carlström, A.-S.; Frejd T. *Acta Chem. Scand.* **1992**, *46*, 163; (b) Carlström, A.-S.; Frejd T. *J. Org. Chem.* **1991**, *56*, 1289.

60. Cutolo, M.; Fiandanese, V.; Naso, F.; Sciacovelli, O. *Tetrahedron Lett.* **1983**, *24*, 4603.

61. Harrington, P.J.; Hegedus, L.S. *J. Org. Chem.* **1984**, *49*, 2657.

62. Jackson, R.F.W.; Wythes, M.J.; Wood, A. *Tetrahedron Lett.* **1989**, *30*, 5941.

63. Kopola, N.; Friess, B.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1989**, *30*, 3963.

64. van der Werf, A.; Kellogg, R.M. *Tetrahedron Lett.* **1988**, *29*, 4981.

65. Itaya, T.; Shimomichi, M.; Osaza, M. *Tetrahedron Lett.* **1988**, *29*, 4129.

66. Yoo, S.-E.; Lee, S.-H.; Yi, K.-Y.; Jeong, N. *Tetrahedron Lett.* **1990**, *31*, 6877.

67. Ouerfelli, O.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfune, Y. *Synlett* **1993**, 409.

68. Leanna, M.R.; Morton, H.E. *Tetrahedron Lett.* **1993**, *34*, 4485.

69. Crisp, G.T.; Robertson, T.A. *Tetrahedron* **1992**, *48*, 3239.

70. (a) Heck, R.F. *Org. React. (N.Y.)* **1982**, *27*, 345; (b) Reissig, H.-U. in Organic Synthesis Highlights, Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohnk, K.; Reissig, H.-U. (Eds); Weinheim/New York, VCH, **1991**; (c) Heck, R.F. in *Comprehensive Organic Synthesis*, Trost, B.M., Ed.; Pergamon Press, Oxford: **1991**, *4*, 833.

71. (a) Stille, J.K. in *The Chemistry of Functional Groups: The Chemistry of the Metal-Carbon bond*, Vol. 2, Hartley F.R. and Patai, S. (Eds); Wiley, New York, **1985**, 625; (b) Alexander, J.J. *ibid*, p339; (c) Cross, R.J. *ibid*, p559

72. Gillie, A.; Stille J.K. *J. Am. Chem. Soc.* **1980**, *102*, 4933.

73. McCrindle, R.; Ferguson, G.; Arsenault, G.J.; McAlees, A.J.; Stephenson, D.K. *J. Chem. Res. Synop.* **1984**, 360.

74. (a) Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* **1986**, *108*, 3033; (b) Stang, P.J.; Kowalski, M.H.; Schiavelli, M.D.; Longford, D. *J. Am. Chem. Soc.* **1989**, *111*, 3347.

75. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

76. Jeffrey, T. *Tetrahedron Lett.* **1985**, *26*, 2667.

77. Botes, D.P.; Tuinmann, A.A.; Wessels, P.L.; Viljoen, C.C.; Kruger, H.; Williams, D.H.; Santikarn, S.; Smith, R.J.; Hammond, S.J. *J. Chem. Soc., Perkin Trans. I* **1984**, 2311.

78. Miller, M.J.; Rajendra, G. *J. Org. Chem.* **1987**, *52*, 4471.

79. Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1982**, *23*, 241.

80. Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613.

81. (a) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361; (b) Godleski, S.A. in *Comprehensive Organic Synthesis*, Trost, B.M., Ed.; Pergamon Press, Oxford: **1991**, *4*, 585; (c) Frost, C.G.; Howarth, J.; Williams, J.M.J. *Tetrahedron Asymmetry* **1992**, *3*, 1089.

82. (a) Weidmann, B.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31; (b) Rehwinkle, H.; Steglich, W. *Synthesis* **1982**, 826.

83. Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1071.

84. Stang, P.J.; Treptow, W. *Synthesis* **1980**, 283.

85. Collins, C.J.; Martinez, A.G.; Alvarez, R.M.; Aguirre, J.A. *Chem. Ber.* **1984**, *117*, 2815.

86. Cacchi, S.; Morera, E.; Ortar, G. *Org. Synth.* **1990**, *68*, 138.

87. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821.

88. Cacchi, S.; Morera, E.; Ortar, G. *Synthesis* **1986**, 320.

89. Harnisch, W.; Morera, E.; Ortar, G. *J. Org. Chem.* **1985**, *50*, 1990.

90. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 2271.

91. Summerville, R.H.; Senkler, C.A.; Schleyer, P.v.R.; Deuber T.E.; Stang, P.J. *J. Am. Chem. Soc.* **1974**, *96*, 1100.

92. (a) see Reference 55, Method J; (b) Crisp, G.T.; Papadopoulos, S. *Aust. J. Chem.* **1988**, *41*, 1711.

93. Echavarren, A.M.; Stille, J.K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

94. Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1992**, *33*, 2535.

95. Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709.

96. Larock, R.C.; Leuck, D.J. *Tetrahedron Lett.* **1988**, *29*, 6399.

97. Toniolo, C.; Bonora, G.M.; Schilling, F.C.; Bovey, F.A. *Macromolecules* **1980**, *13*, 1381.

98. Pfeffer, M. *Pure Appl. Chem.* 1992, 335.

99. Mitchell, T.N. *Synthesis* **1992**, 803.

100. (a) *Chemistry of Tin*, Harrison, P.G., Ed.; Chapman and Hall: New York, **1989**; (b) Pereyre, M.; Quintard, J.P.; Rahm, A. *Tin in Organic Synthesis*, Butterworths: London, **1987**; (c) Omae, I. *Organotin Chemistry* (Journal of Organometallic Chemistry Library 21), Elsevier, **1989**.

101. (a) Baldwin, J.E.; Bradley, M.; Abbott, S.D.; Adlington, R.M. *Tetrahedron* **1991**, *47*, 5309; (b) Leukart, O.; Caviezel, M.; Eberle, A.; Escher, E.; Tun-Kyi, A.; Schwyzer, R. *Helv. Chim. Acta* **1976**, *59*, 2181.

102. Chenault, H.K.; Dahmer, J.; Whitesides, G.M. *J. Am. Chem. Soc.* **1989**, *111*, 6354.

103. Krapcho, A.P.; Weimaster, J.F.; Eldridge, J.M.; Jahngen Jr, E.G.E.; Lovey, A.J.;

Stephens, W.P. *J. Org. Chem.* **1978**, *43*, 138.

104. (a) Leusink, A.J.; Budding, H.A. *J. Organomet. Chem.* **1968**, *11*, 533; (b) Leusink, A.J.; Budding, H.A.; Drenth, W. *J. Organomet. Chem.* **1968**, *11*, 541.

105. Natavi, C.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 820.

106. (a) Leusink, A.J.; Budding, H.A.; Marsman, J.W. *J. Organomet. Chem.* **1967**, *9*, 285; (b) Leusink, A.J.; Budding, H.A.; Drenth, W. *J. Organomet. Chem.* **1967**, *9*, 295.

107. Quintard, J.-P.; Pereyre, M. *J. Organomet. Chem.* **1972**, *42*, 75.

108. (a) Lewis, L.N.; Sy, K.G.; Bryant Jr, G.L.; Donahue, P.E. *Organometallics* **1991**, *10*, 3750; (b) Hiyama, T.; Kusumoto, T. in *Comprehensive Organic Synthesis*, Trost, B.M., Ed.; Pergamon Press, Oxford: **1991**, *8*, 763.

109. Zhang, H.X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

110. Cochran, J.C.; Bronk, B.S.; Terrence, K.M.; Phillips, H.K. *Tetrahedron Lett.* **1990**, *31*, 6621.

111. Miyake, H.; Yamamura, K. *Chem. Lett.* **1989**, 981.

112. Kikukawa, K.; Umekawa, H.; Wada, F.; Matsuda, T. *Chem. Lett.* **1988**, 881.

113. Ichinose, Y.; Oda, H.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3468.

114. Magriotis, P.A.; Brown, J.T.; Scott, M.E. *Tetrahedron Lett.* **1991**, *32*, 5047.

115. Green, M.; Spencer, J.L.; Stone, G.A.; Tsipis, C.A. *J. Chem. Soc. Dalton Trans.* **1977**, 1525.

116. Ojima, I.; Clos, N.; Donovan, R.J.; Ingallina, P. *Organometallics* **1990**, *9*, 3750.

117. Bruno, S.A. *Eur. Pat. Appl.* EP 355,224, 1990; *Chem. Abst.* **1990**, *113*, P97,806e

118. Piers, E.; Skerlj, R.T. *J. Chem. Soc., Chem. Commun.* **1986**, 626.

119. Mook Jr, R.; Sher, P.M. *Org. Synth.* **1988**, *66*, 75.

120. Brown, H.C.; Midland, M.M. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 692.

121. Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1989**, *45*, 923.

122. Nakamura, E.; Machii, D.; Inubushi, T. *J. Am. Chem. Soc.* **1989**, *111*, 6849.

123. Harwood, L.M. *Aldrichemica Acta* **1985**, *18*, 25.

124. (a) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Acta Chem. Scand.* **1993**, *47*, 212; (b) Jackson, W.R.; Moffat, M.R.; Perlmutter, P.; Tasdelen, E.E. *Aust. J. Chem.* **1992**, *45*, 823; (c) Trost, B.M.; Tasker, A.S.; Ruther, G.; Brandes, A. *J. Am. Chem. Soc.* **1991**, *113*, 670.

125. Chen. Q.-Y.; Yang, Z.-Y. *Tetrahedron Lett.* **1986**, *27*, 1171.

126. (a) Roth, G.P.; Fuller, C.E. *J. Org. Chem.* **1991**, *56*, 3493; (b) Roth, G.P.; Shapiro, C. *Tetrahedron Lett.* **1991**, *32*, 4073.

127. Badone, D.; Cecchi, R.; Guzzi, U. *J. Org. Chem.* **1992**, *57*, 6321.

128. Scott, W.J.; McMurray, J.E. *Acc. Chem. Res.* **1988**, *21*, 47.

129. (a) Eaborn, C.; Odel, K.J.; Pidcock, A. *J. Chem. Soc. Dalton Trans.* **1978**, 357; (b) Eaborn, C.; Water, J.A. *J. Chem. Soc.* **1961**, 542.

130. Deacon, G.B.; Gatehouse, B.M.; Nelson-Reed, K.T. *J. Organomet. Chem.* **1989**, *359*, 267.

131 (a) Crisp, G.T.; Macolino, V.; Flynn, B.L. *Nucleosides and Nucleotides* **1991**, *10*, 763; (b) Crisp, G.T.; Flynn, B.L. *Tetrahedron Lett.* **1990**, *31*, 6621.

132. Flynn, B.L. *Ph.D. Thesis*, The University of Adelaide, 1992.

133. Stille, J.K.; Groh, B.L. *J. Am. Chem. Soc.* **1987**, *109*, 813.

134. Dyall, L.K. *Rev. Pure Appl. Chem.* **1958**, *8*, 33.

135. Yamane, T.; Kikukawa, K.; Takagi, M.; Matsuda, T. *Tetrahedron* **1989**, *45*, 923.

136. (a) Kikukawa, K.; Yamane, T.; Ohbe, Y.; Tagaki, M.; Matsuda, T; *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1187; (b) Goel, A.B. *Inorg. Chem. Acta* **1984**, *86*, L77

137. Kikukawa, K.; Umekaw, H.; Matsude, T. *J. Organomet. Chem.* **1986**, *311*, C44.

138. Stork, G.; Richard, C.A. *J. Am. Chem. Soc.* **1990**, *112*, 7399.

139. Tolstikov, G.A.; Miftakhov, M.S.; Danilova, N.A.; Vel'der, Y.L.; Spinkhin, L.V. *Synthesis*, **1989**, 633.

140. Kanemoto, S.; Matsubara, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Chem. Lett.* **1987**, 5.

141. Farina, V.; Roth, G.P. *Tetrahedron Lett.* **1991**, *32*, 4243.

142. Piers, E.; Friesen, R.W.; Keay, B.A. *Tetrahedron* **1991**, *47*, 4555.

143. Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986**, *51*, 5286.

144. Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909.

145. Ghosal, S.; Luke, G.P.; Kyler, K.S. *J. Org. Chem.* **1987**, *52*, 4296.

146. Simándi, L.I. in *The Chemistry of Functional Groups, Supplement C*, part 1; Patai, S., Rappoport, Z., Eds; Wiley, New York, **1983**, 529.

147. Fanta, P.E. *Synthesis*, **1974**, 9.

148. Whitesides, G.M.; Casey, C.P.; Krieger, J.K. *J. Am. Chem. Soc.* **1971**, *93*, 1379.

149. Giese, B. *Radicals in Organic Synthesis: formation of carbon-carbon bonds*, Pergamon Press, Oxford, 1986.

150. Simamura, O. *Top. Stereochem.* **1969**, *4*, 1.

151. Williams, D.H.; Fleming, I. *Spectroscopic methods in organic chemistry*, 4th ed., McGraw-Hill, U.K., **1989**.

152. Bernstein, Z.; Ben-Ishai, D. *Tetrahedron* **1977**, *33*, 881.

153. (a) Mitchell, T.N.; Wickenkamp, R.; Amamria, A.; Dicke, R.; Schneider, U. *J. Org. Chem.* **1987**, *52*, 4868; (b) Mitchell, T.N.; Reimann, W. *J. Organomet. Chem.* **1987**, *322*, 141, 151.

154. Burton, G.; Pearson, M.J. *Eur. Pat. Appl.* EP 209,237, **1987**.

155. Laske, R.; Schoenenberger, H.; Holler, E. *Arch. Pharm. (Weinheim Ger.)* **1989**, *322*, 857.

156. Ego, D.; Beaucourt, J.P.; Pichat, L. *J. Labelled Compd. Radiopharm.* **1986**, *23*, 229.

157. Rosenberg, S.H.; Denissen, J.F. *Eur. Pat. Appl.* EP 456,185, **1991**.

158. Zweifel, G.; Whitney, C.C. *J. Am. Chem. Soc.* **1967**, *89*, 2753.

159. Brown, H.C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786.

160. Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675, and references cited therein.

161. Pross, A.; Sternhell, S. *Aust. J. Chem.* **1970**, *23*, 989.

162. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

163. (a) Smithers, R.H. *J. Org. Chem.* **1978**, *43*, 2833; (b) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 6021 and references cited therein.

164. Baekelmans, P.; Gielen, M.; Malfroid, P.; Nasielski, J. *Bull. Soc. Chim. Belges* **1968**, *77*, 85.

165. Cochran, J.C.; Williams, L.E.; Bronk, B.S.; Calhoun, J.A.; Fassberg, J.; Clark, K.G. *Organometallics* **1989**, *8*, 804.

166. Leibner, J.E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.

167. Vedejs, E.; Engler, D.A.; Mullins, M.J. *J. Org. Chem.* **1977**, *42*, 3109.

168. Abelman, M.M.; Oh, T.; Overman, L.E. *J. Org. Chem.* **1987**, *52*, 4133.

169. (a) Ethyl *E*-3-iodoacrylate: Carpita, A.; Neri, D.; Rossi, R. *Gazz. Chim. Ital.* **1987**, *117*, 481; (b) *E*-3-iodoacrylonitrile: Coe, P.C.; Milner, N.E.; Smith, J.A. *J. Chem. Soc. Perkin Trans. I* **1975**, 654; (c) *E*-4-iodobut-3-en-2-one: Jabri, N.; Alexakis, A.; Normant, J.F. *Tetrahedron* **1986**, *42*, 1369.

170. Melpolder, J.B.; Heck, R.F. *J. Org. Chem.* **1976**, *41*, 265.

171. Sheffy, F.K.; Godschalx, J.P.; Stille, J.K. *J. Am. Chem. Soc.* **1984**, *106*, 4833.

172. Stephens, R.D.; Castro, C.E. *J. Org. Chem.* **1963**, *28*, 3313.

173. Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253.

174. Dieck, H.A.; Heck, R.F. *J. Organomet. Chem.* **1975**, *93*, 259.

175. Sonogashira,K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

176. Scott.W.J.; Peña, M.R.; Swärd, K.; Stoessel, S.; Stille, J.K. *J. Org. Chem.* **1985**, *50*, 2302.

177. Thompson, D.J. in *Comprehensive Organic Synthesis*, Trost, B.M., Ed.; Pergamon Press, Oxford: **1991**, *3*, 1015.

178. (a) Schoenberg, A.; Bartoletti, I.; Heck, R.F. *J. Org. Chem.* **1974**, *39*, 3318; (b) Schoenberg, A.; Heck, R.F. *J. Org. Chem.* **1974**, *39*, 3327.

179. Stille, J.K.; Wong, P.K. *J. Org. Chem.* **1975**, *40*, 532.

180. Nagira, K.; Kikukawa, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1980**, *45*, 2365.

181. Dolle, R.E.; Schmidt, S.J.; Kruse, L.I. *J. Chem. Soc., Chem. Commun.* **1987**, 904.

182. (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109; (b) Cacchi, S.; Ciattini, P.G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931.

183. Crisp, G.T.; Meyer, A.G. *J. Org. Chem.* **1992**, *57*, 6972.

184. (a) McLennan, H.; Hicks, T.P.; Liu, J.R. *Neuropharmacology* **1982**, *21*, 549; (b) Rosowsky, A.; Bader, H.; Forsch, R.A.; Moran, R.G.; Freischeim, J.H. *J. Med. Chem.* **1988**, *31*, 763; (c) Rosowsky, A.; Forsch, R.A.; Moran, R.G.; Freischeim, J.H. *Pteridines* **1991**, *2*, 133.

185. (a) Peoples, M.B.; Pate, J.S.; Atlains, C.A.; Bergersen, F.J. *Plant Physiol.* **1986**, *82*, 946; (b) Ohyama, T. *Nippon Dojo Hiryogaku Zasshi* **1986**, *57*, 300.

186. Mitchell, T.N.; Amamria, A.; Killing, H.; Rutschow, D. *J. Organomet. Chem.* **1986**, *304*, 257;

187. Mitchell, T.N.; Kwekat, K.; Rutschow, D.; Schneider, U. *Tetrahedron* **1989**, *45*, 969.

188. Mitchell, T.N.; Dornseifer, N.M.; Rahn, A. *J. High Pressure Res.* **1991**, *7*, 165.

189. Mitchell, T.N.; Schneider, U. *J. Organomet. Chem.* **1991**, *407*, 319.

190. Coulson, D.R. *Inorg. Synth.* **1972**, *13*, 121.

191. King, A.O.; Negishi, E.-i.; Villani, F.J.; Silveira, A. *J. Org. Chem.* **1978**, *43*, 358.

192. Hartley, F.R.; Murray, S.G.; McAuliffe, C.A. *Inorg. Chem.* **1979**, *18*, 1394.

193. Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnett, J.J.; Ibers, J.A. *J. Organomet. Chem.* **1974**, *65*, 253.

194. Allen, D.W.; Hutley, B.G.; Mellor, M.T.J. *J. Chem. Soc. Perkin II* **1972**, 63.

195. Anderson, A.G.; Stang, P.J. *Org. Synth.* **1981**, *60*, 34.

196. Stang, P.J.; Deuber, T.E. *Org. Synth.* **1974**, *54*, 79.

197. Bair, J.B.; Bergeron, R.; Giga, A.; Skipper, P.L.; Sternbach, D.D.; Waring, J.A. *Org. Prep. Procedures* **1977**, *9*, 173.

198. Crisp, G.T.; Papadopoulos, S. *Aust. J. Chem.* **1989**, *42*, 279.

199. Lipschutz, B.H.; Reuter, D.C.; Ellsworth, E.L. *J. Org. Chem.* **1989**, *54*, 4975.

200. Beyl, V.; Niederprum, H.; Voss, P. *Justus Liebig Ann. Chem.* **1970**, *731*, 58.

201. Crisp, G.T., unpublished results.

202. Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem.* **1967**, *10*, 81.

203. *Organometallic Syntheses*, Vol. 2; Eisch, J.J., King, R.B. (Eds); Academic Press, New York, **1981**, 167.

204. Seyferth, D.; Vaughan, L.G. *J. Organomet. Chem.* **1963**, *1*, 138.

205. Cunico, R.F.; Clayton, F.J. *J. Org. Chem.* **1967**, *41*, 1480.

206. Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* **1983**, *105*, 6129.

207. Gielen, M.; DePoorter, D. *Rev. Silicon, Germanium, Tin Lead Compd.* **1977**, *3*, 9.

208. Keck, G.E.; Enholm, E.J.; Yates, J.B.; Wiley, M.R. *Tetrahedron* **1985**, *41*, 4079.