Synthesis and Diels-Alder Reactions of Chiral 1,3-Dienes

A thesis submitted for the degree of

Doctor of Philosophy

by

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April 1996

dedicated to my late mother, Rosemarie Gebauer

....the whole history of the past 500 years since Copernicus is replete with illustrations of how apparently simple truths turn out to be more complicated than they first appear. And then they have to be revised, and revised again. That, you will recall, is progress in science.

John Maddox. March 1995

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Abstract

1,3-Dienes that were attached to a stereogenic center were synthesised *via* Heck reactions of alkene precursors with a vinyl triflate under phosphine-free conditions. Chloride ions, which are part of the standard protocol for Heck couplings conducted under phospine-free conditions, were replaced by triflate ions as it was found that the former inhibit the reaction. It was proposed that, in the presence of chloride ions, the oxidative addition product was kinetically rather inert to olefin insertion with the alkenes.

The product dienes differed only in the nature of the protecting groups for the allylic amine and homoallylic hydroxyl functionality. These dienes participated in Diels-Alder reactions with maleic anhydride and *N*-phenyl maleimide under mild conditions. A facile rearrangement of the cycloadducts into isoindolones occurred under the reaction conditions. The rate of this rearrangement varied depending on the stereochemistry of these cycloadducts and the nature of the amino protecting group. The relative stereochemistry of the isoindolones was unambigously established from X-ray diffraction analysis and nOe studies of the methyl ester derivatives of the isoindolones. A trend in the π-facial selectivity of the structurally analogous dienes was established: An increase in the size of the hydroxyl protecting groups caused a steadily increasing π-diastereofacial selectivity until a plateau was reached at d.e. = 83 %. Therefore the hydroxyl protecting groups appeared to be involved in the shielding of the 1,3-diene moiety. A conformational model based on the minimisation of 1,3-allylic strain in the dienes was proposed to account for this trend in the π-facial selectivity.

In the second part of this work the transition metal mediated hydrostannation of suitably protected propargylglycine derivatives afforded α-amino acid derivatives featuring a vinylstannane in their side-chain. These vinylstannanes were elaborated *via* a Stille reaction with vinyl bromide. The coupling rate was markedly dependent on the nature of the amino protecting group and its position with regard to the vinylstannane. Under suitable conditions the reaction of the secondary vinylstannane isomer was complete within 30 minutes at 0 °C! It was proposed that the coupling was significantly accelerated due to the chelation of the palladium catalyst during the transmetallation by the imine protected nitrogen of the reactive vinylstannane.

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 available for loan and photocopying.

Signed: Date: 23-4-96

ACKNOWLEGEMENT

I thank my supervisor Dr Geoffrey Crisp for his continuous committment to this project and for his guidance as well as interminable confidence to grant me the freedom to follow my chemical instincts. More importantly I thank Geoff for his friendship and personal support.

To my wife Mary, my deepest thanks, for without her insight and advice on many matters together with her unconditional love and friendship throughout these past years much would not have been possible.

Furthermore to my mother-in-law Anna for her continual encouragement and selfless care I am truly grateful. For their long lasting support and concern for my education I thank my parents Konrad and Gerda.

I thank the Australian Research Council for awarding me with an Australian Post-graduate Award Scholarship and therefore the Australian people for financing my education.

Within the Department of Chemistry I extend my thanks to all those who have contributed to this study, in particular Dr Simon Pyke and Paul Low, for fruitful discussions and Phil Clements, for his assistance in operating the nmr-spectrometers.

Special thanks to Mary for typing large sections of the manuscript and to those that proof-read my thesis: Geoff Crisp, Steven Blanksby and Peter Turner.

To the academic staff of the Organic Chemistry Branch of the Chemistry Department I also extend my thanks for they are largely responsible for my chemical upbringing. In particular I wish to mention Dr David Ward, Dr George Gream and Dr David Hamon. I also would like to thank the current and former members of Lab 4.

I was a privileged to enjoy the company of many good colleagues and friends and can only mention some of them: Tim Bubner, Indu Mahevedan, Suresh Dua, Josephine Newton, Jeff Gore, Adam Meyer, Michael Millan, Peter Turner, Steven Blanksby.

List of Abbreviations

2°	secondary
3°	tertiary
4°	quaternary
$[\alpha]_D$	specific rotation at $\lambda = 589$ nm
ABq	quartet of an AB-spin system
Ac	acyl
AIBN	azobis*iso*-butyronitrile
Anal.	analytical data (chemical micro-analysis)
ar	aryl
ax	axial
Bn, bn	benzyl
Boc	*tert*-butoxycarbonyl
b.p.	boiling point
bs	broad singlet
Bu	butyl
Calcd.	calculated
Cbz	benzoxycarbonyl
COLOC	correlation through long range coupling
conc.	concentrated
COSY	correlation spectroscopy
δ	chemical shift
d	doublet or day
dba	dibenzylidineacetone
d.e.	diastereomeric excess
DEPT	distortionless enhancement polarisation transfer
DMAP	*N',N'*-4-dimethylaminopyridine
DMA	dimethylacetamide
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
fab	fast atom bombardment
FDA	Food and Drug Administration
fid	free induction decay
e.e.	enantiomeric excess
eq	equatorial
h	hour(s)
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
hplc	high pressure liquid chromatography

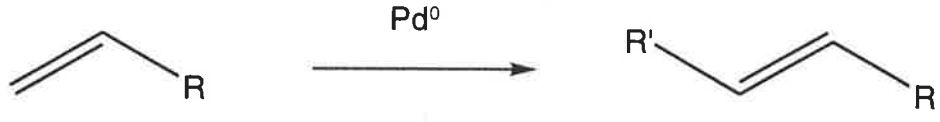
Hz	hertz
ir	infra red
J	coupling constant
λ	wave length
L	ligand
LDA	lithium di*iso*-propylamide
L-DOPA	*L*-3,4-dihydroxyphenylalanine
lit.	literature
LUMO	lowest unoccupied molecular orbital
m	multiplet or milli
M	moles per liter
M^+	molecular ion
Me	methyl
min	minute(s)
m.p.	melting point
mplc	medium pressure liquid chromatography
ms	mass spectrometry
m/z	mass to charge ratio
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser effect
or	optical rotation
Pg	protecting group
ppm	parts per million
R_f	relative retention (with regard to the solvent) on a tlc plate
q	quartet
s	singlet
sat.	saturated
sec	second(s)
sep	septet
t	triplet or time
t	tertiary
t_1-domain	incremented time domain in 2D nmr spectroscopy
t_2-domain	time domain for the actual data acquisition in 2D nmr spectroscopy
T1- relaxation time	longitudinal (or spin-lattice) relaxation time
***t*-hexyl**	**1,1,2-trimethylpropyl**
THF	tetrahydrofuran
tf	trifluoromethanesulfonate
tlc	thin-layer chromatography
t_R	retention time
UV	ultraviolet

Chapter 1: The Heck Reaction

We intended to explore Diels-Alder reactions of chiral 1,3-dienes. The synthesis of the required dienes *via* Heck olefinations of suitable alkenes is discussed in Chapter 1 and the Diels-Alder reactions in Chapter 2.

1.1. Introduction

The Heck reaction[1] is the palladium(0) catalysed substitution of a vinylic hydrogen atom by an aryl or a vinyl group (**Scheme 1**). Since such a transformation is not achievable by any other reaction, the Heck reaction has been recognised as an indispensable tool in the synthesis of alkenes. Alkenes bearing an electron-withdrawing substituent, e.g. acrylic acid esters, react smoothly and regioselectively, since the aryl or vinyl group adds to the electron deficient terminus of the carbon-carbon double bond during olefin insertion (**Scheme 2**).

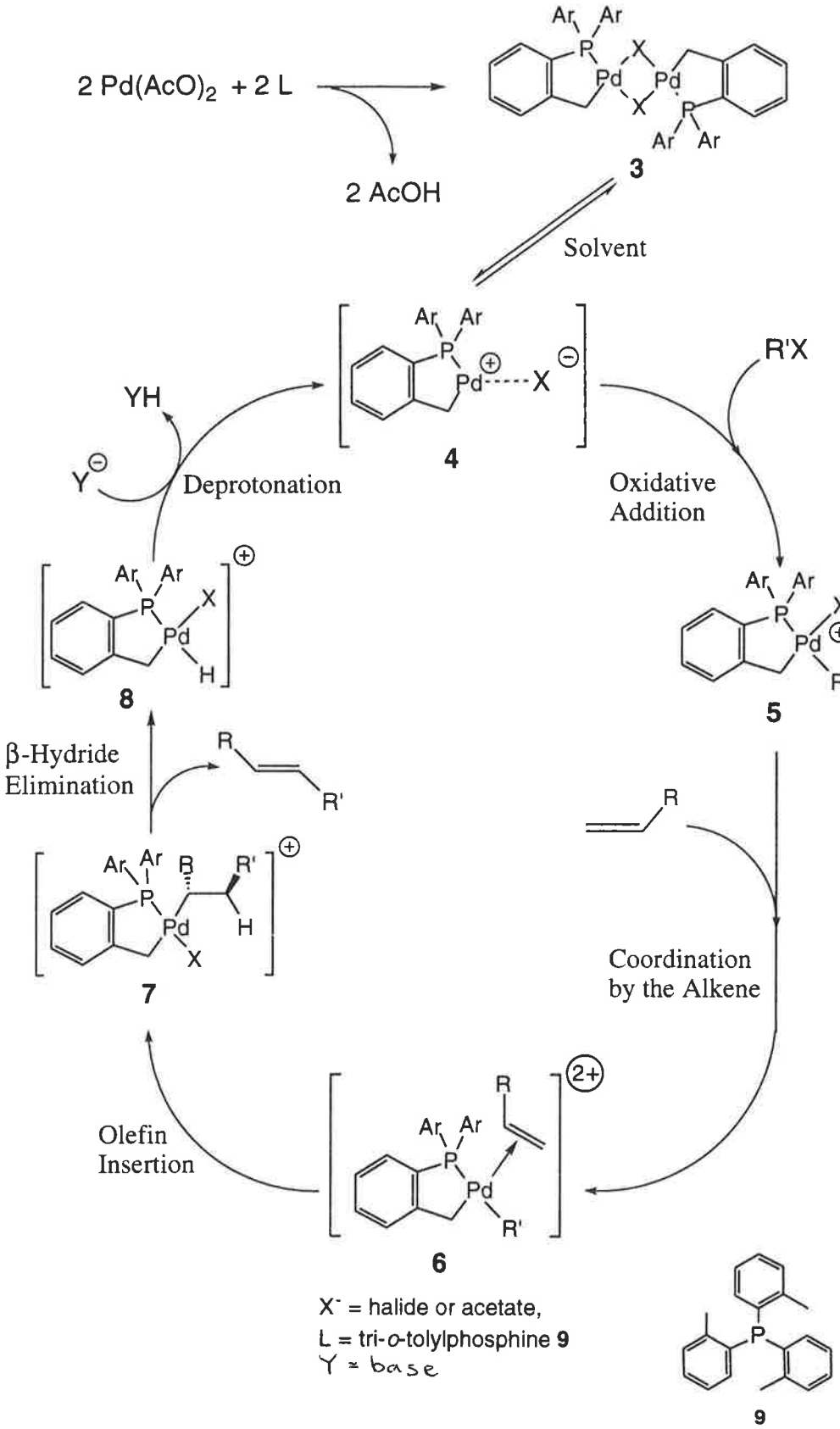


1 **2**

R' = aryl, vinyl
R = aryl, vinyl, alkyl, C=O

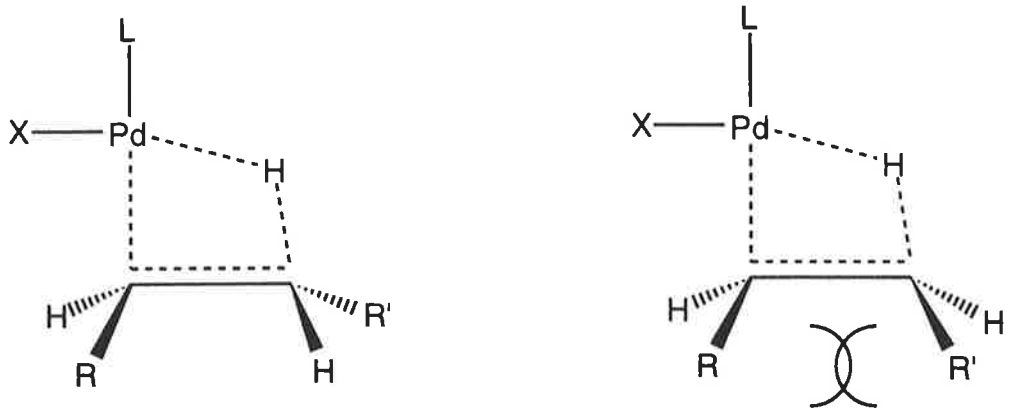
Scheme 1

It has been well established for substrate alkenes **1** bearing a single electron-withdrawing substituent that *E*-alkenes **2** are formed in preference to *Z*- and 1,1-disubstituted alkenes. This selectivity is the combined result of a regioselective addition of a vinyl or aryl palladium complex to the electron-deficient terminus of the alkene (**Scheme 2**, olefin-insertion)[3] and a subsequent *syn* elimination of preferentially one of the two possible hydrogen atoms in the position β to palladium (**Scheme 2**, β-hydride elimination).[4] This facile β-hydride elimination reaction from alkyl palladium(II) complexes proceeds through a four-membered cyclic transition state.[5] It was postulated, that steric interactions in the eclipsed conformation of the transition state **10** that leads to the formation of *E*-alkenes **1** are minimised (**Scheme 3**).



Mechanism proposed for the Heck reaction of aryl halides at reaction temperatures exceeding 100 °C. At ambient reaction temperatures or when triphenylphosphine is substituted by **9** other palladium species than shown here are involved in the catalysis.

Scheme 2



10
Preferred transition state

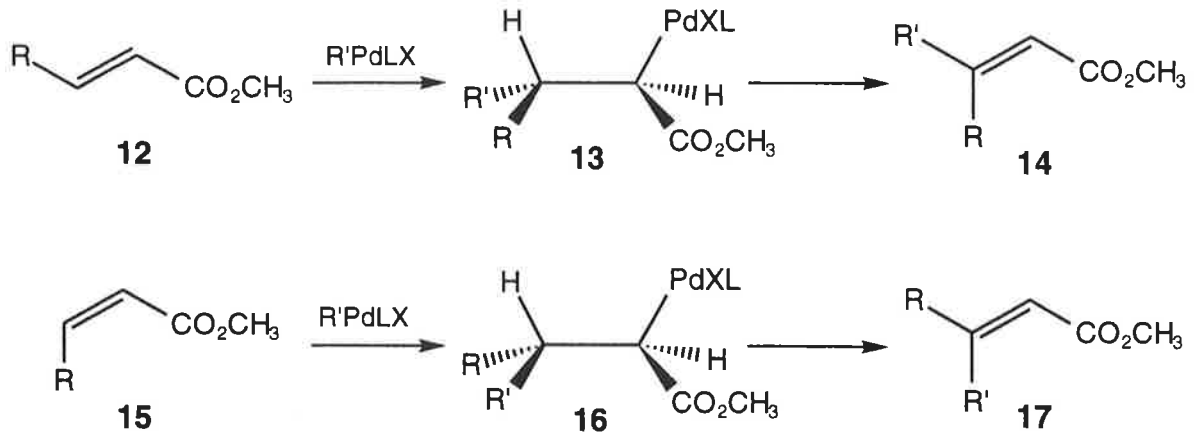
11
Steric interactions exist between the R and R' groups

Alternative transition states during β-hydride elimination of palladium(II) alkyl complexes

Scheme 3

A less pronounced steric bias during the β-hydride elimination is observed when unsymmetrically 1,1-disubstituted alkenes are substrates and a mixture of *E*-and *Z*-alkenes is usually formed. On the other hand only a single isomer of a trisubstituted alkene is formed when 1,2-disubstituted alkenes are employed as substrates, as there is only one hydrogen in the β-position of the intermediate palladium complexes **13** and **16** (**Scheme 4**).

The β-hydride elimination from alkyl palladium(II) complexes does not only have a stereochemical aspect, it furthermore restricts the choice of the electrophile to those that have no hydrogen atom bonded to a sp^3-hybridised carbon in the position β to the leaving group. Aryl and vinyl iodides, and aryl and vinyl triflates have been commonly employed. Aryl and vinyl bromides, in particular those substituted by an electron-withdrawing substituent, also participate in the Heck reaction at higher than ambient reaction temperatures. At reaction temperatures exceeding 60 °C the palladium catalyst is normally stabilised by the addition of tertiary phosphine ligands to the reaction mixture.[1,2] Aryl and vinyl chlorides are inferior substrates in the Heck reaction, nevertheless, efforts are directed at utilising these commercially more viable substrates,[6,7] which are of particular significance to the chemical industry.[7] Traditionally, palladium(II) acetate is used as a convenient and commer-



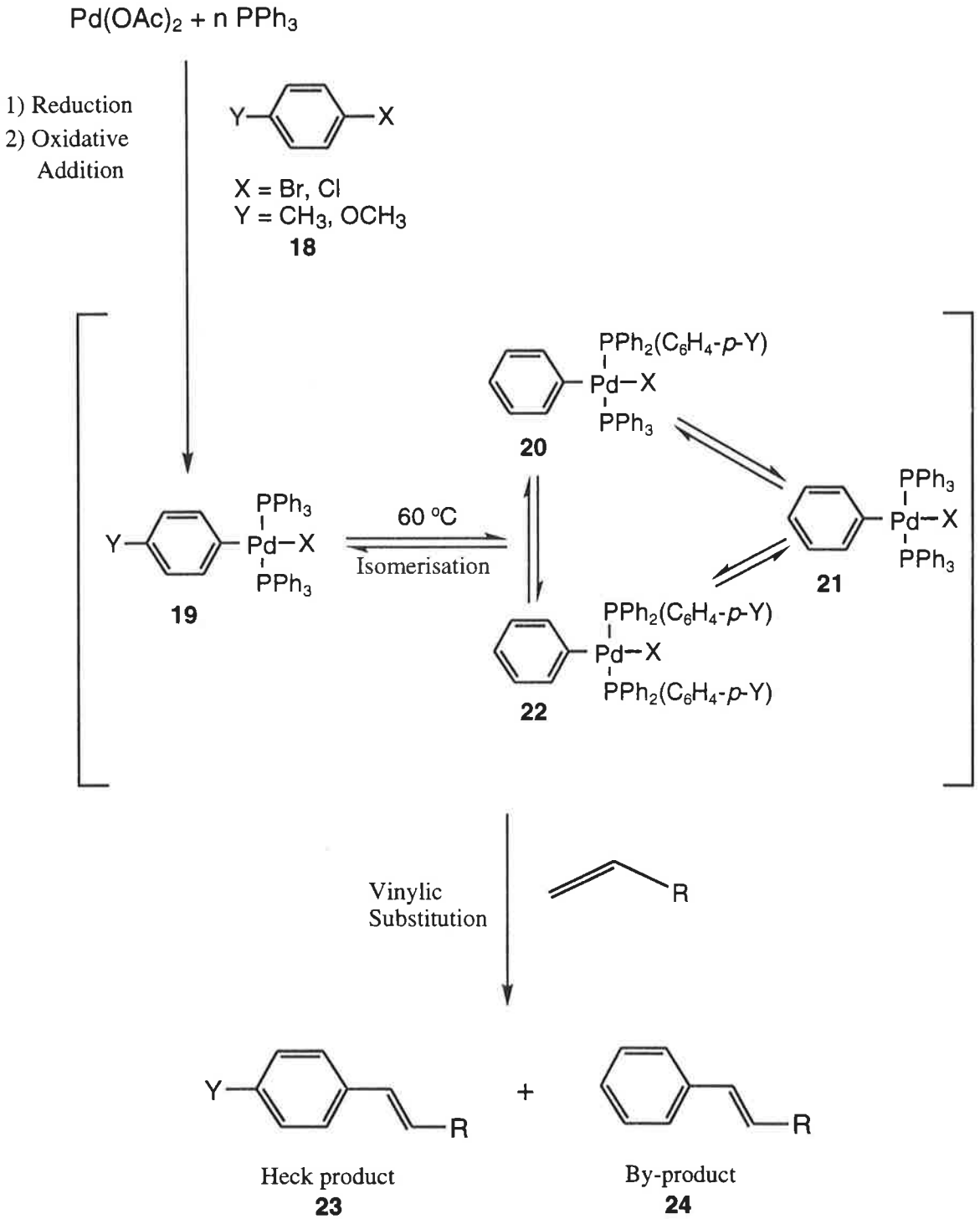
Scheme 4

cially available catalyst precursor, which is reduced by tertiary phosphines to zero-valent palladium.[8]

The effects of tertiary phosphines on the Heck reaction are numerous, although not all of them are beneficial. Primarily, phosphine ligated palladium is stabilised in solution against the premature precipitation of catalytically inactive metallic palladium at elevated temperatures. Secondly, all reactions constituting the catalytic cycle can be affected, in particular, they may be accelerated or decelerated in comparison to the same reaction in the absence of tertiary phosphines. The overall efficacy of the Heck reaction is dependent on both the activity and the stability of the catalyst. A palladium catalyst stabilised by ligation with tertiary phosphines is frequently less efficient than a palladium catalyst formed from palladium(II) acetate *in the absence* of tertiary phosphine ligands. However, the latter has a shorter lifetime and reaction conditions that are optimised for a particular substrate usually represent the best compromise between catalyst stability and activity.

In particular less reactive electrophiles, such as aryl chlorides and electron-rich aryl bromides, require a ligand stabilised palladium catalyst at elevated reaction temperatures. It has been found empirically that tri-*o*-tolylphosphine is a better ligand than triphenylphosphine.[1] Significant amounts of phenyl substituted by-products were observed, in which the phenyl group was derived from the ligand triphenyl-

phosphine. During a scrambling reaction that occurred after the oxidative additon aryl groups bonded to phosphorous were exchanged for aryl groups stemming from the aromatic electrophile employed as the coupling partner (**Scheme 5**).[7,11] This exchange was greatly facilitated by the presence of an electron-donating sub-



Scheme 5

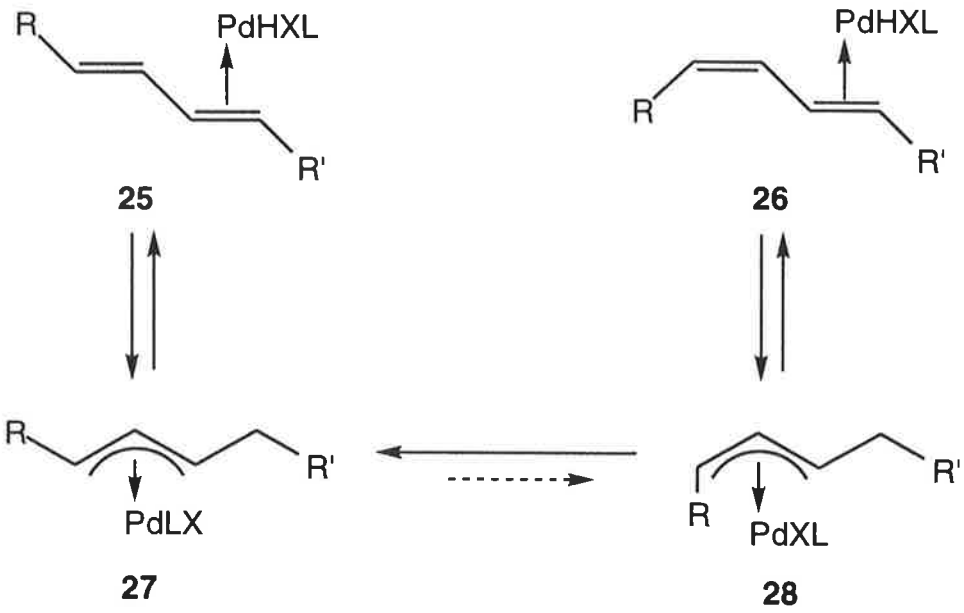
stituent bonded to the aryl moiety that was derived from the aryl halide coupling partner. In addition, reaction temperatures in excess of approximately 100°C promoted the formation of phenyl substituted by-product **24**. When triphenylphosphine was replaced with tri-*o*-tolylphosphine the formation of by-product **24** was suppressed and Heck products derived from electron-rich aryl bromides were formed in high yields. The mechanistic basis of this remarkable effect, which is caused by a seemingly insignificant change in the structure of the tertiary phosphine ligand, is depicted in **Scheme 2**. Marked differences become apparent when the latter mechanism is compared to that commonly found in textbooks, however, evidence for the catalytic activity *and* exceptional thermal stability of the dimeric palladium species drawn in **Scheme 2** has been obtained.[7,10,11] In particular, the structure of palladacycle **3** was elucidated by X-ray diffractional analysis[10] and **3** was proven to be the catalytically active species and exceptionally stable even at a reaction temperature of 150 °C.[7]

At ambient reaction temperatures the palladacycle **3** is *not* formed from palladium(II) acetate and tri-*o*-tolylphosphine. In this situation the mechanism of the Heck reaction is similar to that commonly represented in text-books, except for the fact that mono-ligated tri-*o*-tolylphosphinepalladium(0) dominated the oxidative addition reaction[12] rather than a bi-ligated palladium(0) species as it was observed when triphenylphosphine was employed as a stabilising ligand.[8]

Since the Heck reaction was first reported in 1972, numerous modifications of the original conditions have been devised. In particular, for reactive electrophiles, such as vinyl or aryl iodides, the use of an inorganic base *in the absence of tertiary phosphines*[9] has proven to be very effective.

A particular problem has been the formation of the *same* predominant isomer of a 1,3-diene in the Heck reaction irrespective of whether the vinyl halide has a *Z* or *E*-stereochemistry. Under conditions where the β-hydride elimination was reversible, a facile readdition of palladium hydride to the product 1,3-diene produced isomeric π-allyl palladium complexes, which readily equilibrated (**Scheme 6**).[1] After the β-

hydride elimination of the more stable π-allyl palladium complex **27** the *E,E*-diene **25** was predominantly formed.



An equilibrium between isomeric 1,3-dienes is set up *via* the isomeric π-allyl palladium complexes **27** and **28** when the β-hydride elimination is reversible

Scheme 6

Although to our knowledge no explanation for the increased efficacy of the modified conditions[9] has been offered in the literature, it is conceivable, that anhydrous alkali carbonate in DMF in conjunction with a phase transfer catalyst is a considerably stronger base than the traditionally employed triethylamine. The comparatively rapid deprotonation of palladium hydride species such as **25** and **26** by carbonate ions in DMF may be faster than the formation of π-allyl palladium complexes **27** and **28**.

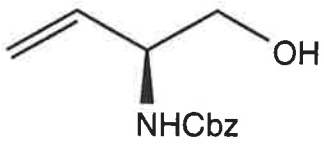
1.2. Aim

We wished to synthesise a variety of acyclic 1,3-dienes *via* the Heck reactions of amenable precursor alkenes. The prominent structural feature of these dienes was a stereogenic center in the allylic position.

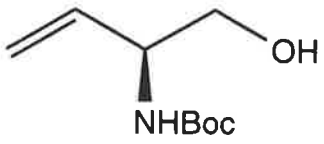
1.2. Results and Discussion

1.2.1. Synthesis of Alkene Precursors

We intended to demonstrate that the Heck olefination was compatible with a variety of hydroxy and amino protecting groups present in the substrate alkene. Therefore a variety of alkenes were prepared as precursors for the Heck reaction by protection of aminobutenols **34** and **35**.



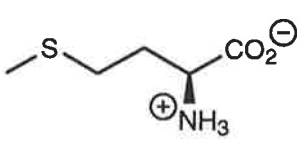
34



35

The synthesis of (2*S*)-2-[*N*-(benzoxycarbonyl)amino]-but-3-en-1-ol **34** and of (2*S*)-2-[*N*-(*tert*-butoxycarbonyl)amino]-but-3-en-1-ol **35** from the corresponding methionine esters **30** and **31** was reported in a communication[13] containing little experimental detail. In particular, the purification of the product alcohols was not described. The procedure has since been modified by replacing lithium aluminium hydride in the reduction of (2*S*)-*N*-benzoxycarbonyl methionine methyl ester **30** with the more convenient sodium borohydride.[14] Unlike ordinary aliphatic esters, *N*-protected α-amino acid methyl estersare readily reduced by sodium borohydride because of their greater susceptibility to nucleophilic attack.

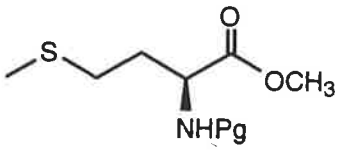
We have further refined the conditions, under which **30** and **31** can be converted into **34** and **35**, using a "one-pot" reduction oxidation sequence on a multi-gram scale. In detail, (*S*)-methionine **29** was esterified in methanol saturated with anhydrous HCl in quantitative yield (**Scheme 7**).[15] (*S*)-Methionine methyl ester hydro-



29

1) Methanol, HCl

2) Benzyl chloroformate or di-*tert*-butyl dicarbonate, ethyl acetate, aqueous K_2CO_3



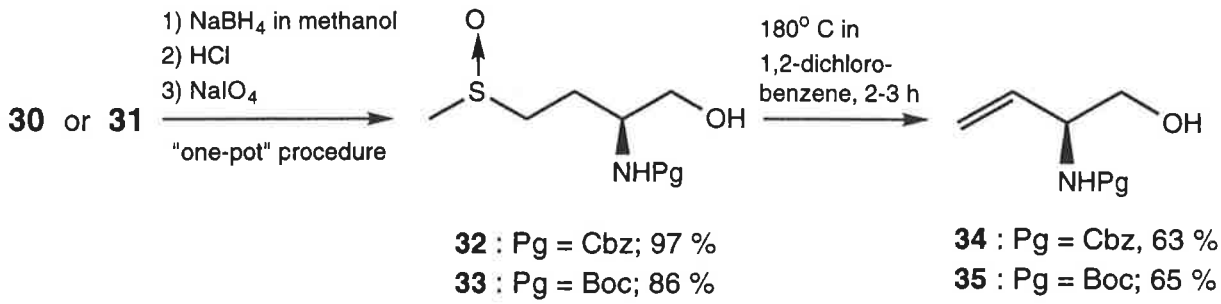
30 : Pg = Cbz; 98 %
31 : Pg = Boc; 88 %

Scheme 7

chloride was converted with benzyl chloroformate in a two phase solvent system into (2*S*)-*N*-benzoxycarbonyl methionine methyl ester **30** in nearly quantitative yield.[15] Following the same procedure[15] (2*S*)-*N*-*tert*-butoxycarbonyl methionine methyl ester **31** was synthesised from (*S*)-methionine methyl ester hydrochloride and di-*tert*-butyl dicarbonate, however, the crude ester **31** was contaminated by a small amount of di-*tert*-butyl dicarbonate. (2*S*)-*N*-*tert*-Butoxycarbonyl methionine methyl ester **31** was obtained in 88 % yield which was determined on the basis of ^{1}H nmr spectroscopic analysis of the crude product. Esters **30** and **31** were used in crude form for the subsequent steps.

Following complete reduction of **30** or **31** by sodium borohydride in methanol, the reaction solution was carefully neutralised by the addition of 10 % HCl (**Scheme 8**). A saturated aqueous solution of sodium periodate was added to the resulting solution and the crude intermediate sulfoxide alcohols **32** and **33** were obtained after extractive work-up in nearly quantitative and 86 % yield, respectively. ^{13}C nmr spectroscopic analysis revealed that these products were essentially pure and consisted of a mixture of diastereomers differing by the relative stereochemistry of the configurationally stable chiral sulfur.

Thermal elimination of methyl sulfinic acid from sulfoxide **32** and **33** in refluxing 1,2-dichlorobenzene according to the literature procedure[13] afforded the homoally-



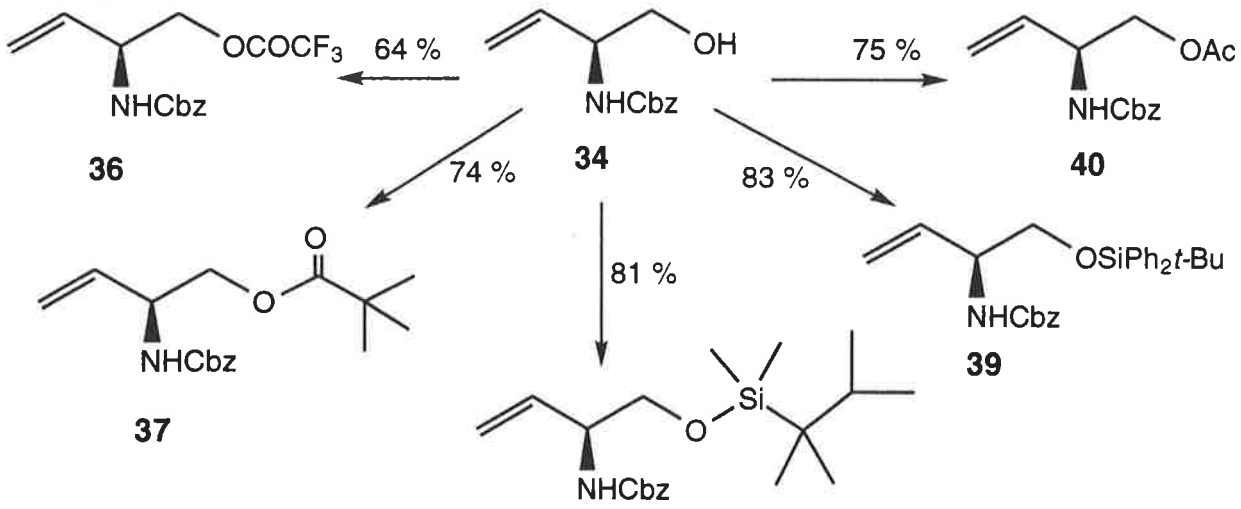
Scheme 8

lic alcohols **34** and **35** in the reported yield of 65 % after chromatography and distillation. Contrary to the literature procedure[13] we found cleaner reaction mixtures without the recommended use of a base to trap the liberated methyl sulfin-

ic acid. During distillation the crude alcohols **34** and **35** decomposed extensively. However, when the crude product was chromatographed prior to the distillation, **34** and **35** were isolated in a satisfactory yield of 63 and 65 %. Attempts to effect the thermal elimination of **33** in the absence of solvent, under conditions reported for the synthesis of optically pure vinyl glycine derivatives,[15] failed as sulfoxide **33** decomposed rapidly and, as a result, the desired alkene **35** was isolated in less than 5 % yield. Aminobutenols **34** and **35** produced by us were of similar optical purity as the compounds reported in the literature,[13] in particular, $[\alpha]_D$ = -34.1° for **34** (lit.:[13] $[\alpha]_D$ = -32.1°) and $[\alpha]_D$ = -26.6° for **35** (lit.:[13] $[\alpha]_D$ = -29.0°).

Protection of the free hydroxyl group of **34** as the acetate raised the yield in the thermal elimination of methyl sulfinic acid from sulfoxide **26** only marginally to 70 % after chromatography and crystallisation.[14]

Esters **37** and **40** were prepared in 74 - 78 % yield by reaction of **34** with the cor-



Scheme 9

responding carboxylic acid chlorides or anhydrides in the presence of pyridine (**Scheme 9**).[16] The trifluoroacetylation of alcohol **34** succeeded in the absence of any pyridine base that are commonly used in the literature in a yield of 64%.[16]

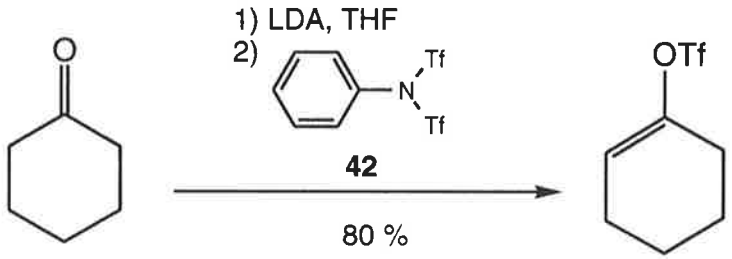
Silyl ethers **38** and **39** were synthesised in 81 and 83 % yield by reacting alcohol

34 with the corresponding silyl chloride in the presence of triethylamine and a catalytic amount of *N*-hydroxy benzotriazole.[17]

Having successfully prepared a series of Cbz protected aminobutenol derivatives, we turned our attention to the vinyl triflate as the second coupling partner in the Heck reaction.

Vinyl triflates are commonly prepared by the triflation of enolisable ketones.[18] Several procedures for the synthesis of triflate **43** from cyclohexanone **41** have been reported that rely on triflic anhydride as the triflating agent. Despite careful experimentation we could not reproduce the yields claimed for **43**. In particular, when sodium carbonate was used as the base, triflate **43** was synthesised in a much lower yield of 23 % than reported (89 %).[19] We repeated this procedure several times under rigorously anhydrous conditions. ^{13}C nmr analysis of the chromatographed product revealed the presence of major quantities of an unknown material which was separated from the desired product by fractional distillation.

Furthermore it was reported that employing 4-methyl-2,6-di-*tert*-butylpyridine as a non-nucleophilic base resulted in good yields of vinyl triflates.[20] However, when we



Scheme 10

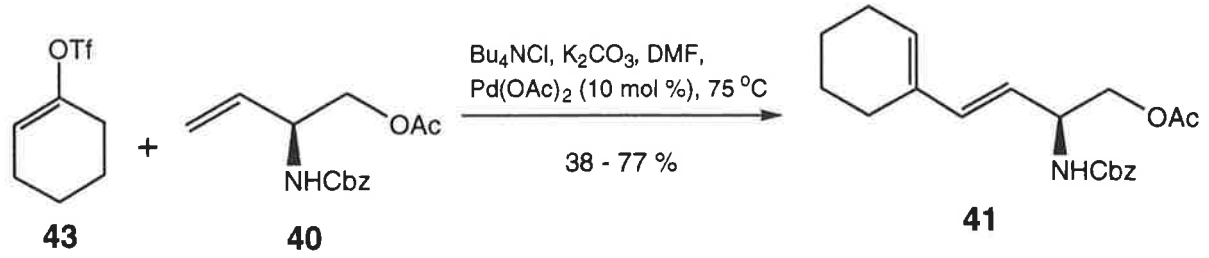
repeated the synthesis of triflate **43** under strictly anhydrous and carefully controlled conditions, a rather complex mixture of compounds was observed by ^{13}C nmr spectroscopic analysis of the crude product. Pure cyclohex-1-enyl triflate **43** was isolated after fractional distillation in 38 % yield, only half of the reported value.[20]

We then turned our attention to commercially available 1,1,1-trifluoro-*N*-phenyl-*N*-

[(trifluoromethyl)sulfonyl]methanesulfonamide **42** as a milder triflating agent. Indeed, pure vinyl triflate **43** was isolated in the reported yield of 80 % following Scott's procedure[21] for the triflation of enolates derived from alkanones (**Scheme 10**).

1.3.2. Synthesis of 1,3-Dienes *via* Heck Reactions

Upon commencement of our study of Diels-Alder reactions we focussed our interest on diene **41**, as it was prepared previously on a small scale.[14] However, we found that yields of **41** were initially low, necessitating chromatographic separation of alkene **40** and diene **41** (**Scheme 11**). After considerable experimentation it was

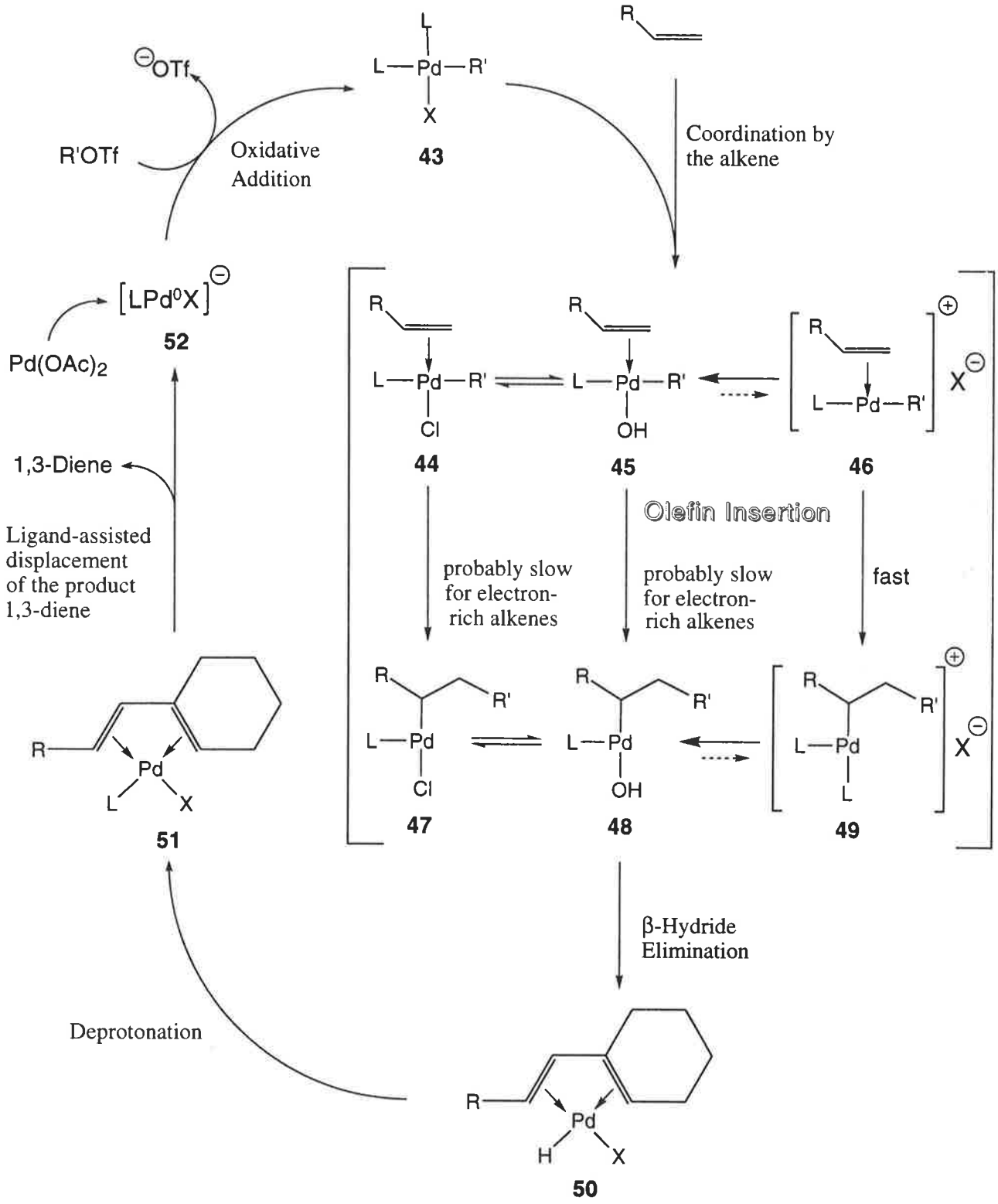


Scheme 11

discovered that the presence of water beneficially influenced the coupling reaction, which is supported by literature precedence.[22] We identified potassium carbonate and tetrabutylammonium chloride as potential sources of moisture. Rigorous drying of these reagents resulted in the slow conversion of alkene **40** and premature deposition of catalytically inactive palladium metal. A good yield for diene **40** of more than 70 % was achieved in experiments on a gram scale when a small amount of water (usually five equivalents with regard to the alkene) was added to the reaction mixture.

The beneficial influence of water in Heck couplings could be explained in terms of a ligand effect. Under the conditions depicted in **Scheme 11**, the catalytically active palladium species were largely ligated to solvent molecules and chloride ions, whilst, in the presence of water, chloride ligands were temporarily displaced by hydroxide ions[23] formed from water and potassium carbonate (**Scheme 12**, e.g. structures **44**, **45**, **47** and **48**). In comparison to a chloride ion a hydroxide ion is a

Mechanism for the Heck Reaction of Vinyl Triflates with Alkenes lacking a Conjugated Electron-withdrawing Group

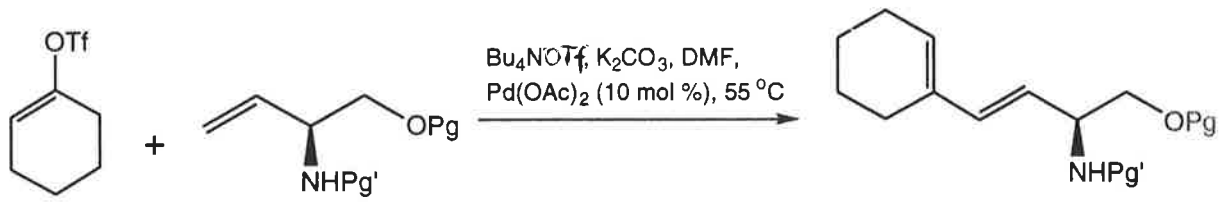


X = ⁻OAc, Cl⁻, ⁻OH; L = a neutral ligand such as a molecule of solvent

Scheme 12

weaker and kinetically more labile ligand for palladium and this may be a key guarantor to a faster and more efficient Heck reaction. Indeed, it has been observed in other palladium catalysed reactions, e.g. the cross-coupling of organoboranes which is commonly referred to as the Suzuki reaction, that a hydroxopalladium complex was a more efficient catalyst than a chloride ligated palladium species.[24] It appears to be a rather general observation that strongly coordinating ligands such as tertiary phosphines or chloride ions have a decelerating effect on the rate of palladium catalysed coupling reactions *of reactive substrates* and should therefore be avoided.

Despite this improvement over the original reaction conditions,[14] a sterically hindered substrate, such as the t-hexylsilyl protected alkene **38**, was only converted to an extent of 47 % before the catalyst suffered decomposition. The isolated yield of t-hexylsilyl protected diene **56** was even lower, as repeated chromatography was necessary due to almost identical retention times of **38** and **56** on silica. As it was the nature of the protecting group of the alkene, that appeared to influence the overall reaction rate, we reasoned that the olefin insertion was the kinetic bottleneck of the catalytic cycle. If the olefin insertion could be accelerated, perhaps the overall efficacy of the Heck coupling could be improved upon. Conceivably the olefin insertion could be accelerated, when *all* halide ions in the reaction mixture were replaced by counter anions which ligate only weakly to palladium. Indeed, when tetrabutylammonium triflate was substituted for tetrabutylammonium chloride as a



43

41: Pg' = Cbz; Pg = $COCH_3$
53: Pg' = Cbz; Pg = H
54: Pg' = Cbz; Pg = $COCF_3$
55: Pg' = Cbz; Pg = $COCMe_3$
56: Pg' = Cbz; Pg = $SiMe_2$*t* hexyl
57: Pg' = Cbz; Pg = $SiPh_2$*t* Bu
58: Pg' = Boc; Pg = H

Scheme 13

phase transfer catalyst (**Scheme 13**), complete conversion of the recalcitrant alkenes **38** and **39** was achieved independently of the presence of water and yields of dienes produced under these conditions were good to excellent (**Table 1**)

Table 1. Results for the Heck Reaction of Alkenes **34** to **40** with Triflate **43** under the Conditions depicted in Scheme 13.

Entry	Alkene	Hydroxyl Protecting Group	Diene	Yield	Elemental Analysis [a] C	H	N
1	**34**	H	**53**	53 %	-0.02	0.05	-0.05
2	**36**	$COCF_3$	**53**	65 %	-0.01	0.03	-0.04
3	**37**	$COCMe_3$	**55**	81 %	-0.22	0.01	-0.21
4	**38**	$SiMe_2$*t*hexyl	**56**	83 %	-0.29	0.09	0.16
5	**39**	$SiPh_2$*t*Bu	**57**	83 %	0.14	0.24	-0.05
6	**40**	$COCH_3$	**41**	80 %	0.05	0.14	0.05
7	**35**	H	**58**	52 %	-0.17	0.04	-0.19

[a] of the chromatographed material. The absolute deviations from the calculated values are listed.

The question arises then, how halide ions inhibit the Heck coupling of vinyl halides with alkenes lacking an activating electron-withdrawing substituent, such as a conjugated carbonyl group. Firstly we speculated that, under the halide ion free reaction conditions, the hydroxovinylpalladium complex **45** was the predominant palladium species, while in the presence of halide ions it was the chloropalladium complex **44** (**Scheme 12**). Both **44** and **45** were presumably in equilibrium when tetrabutylammonium chloride and water were present in the reaction medium. Furthermore, the cationic species **46** could be produced by the dissociation of a chloride or a hydroxide ligand from **44** or **45**. According to this mechanistic scenario the rate of the olefin insertion would be dependent on both the equilibrium concentrations of all three species **44**, **45** and **46** and their reactivity. The high reactivity of cationic palladium(II) complexes such as **46** to olefin insertion is documented with some complexes inserting into electron-rich alkenes at reaction

temperatures as low as -40 °C.[25] A comparatively rapid olefin insertion can be rationalised by the lack of repulsive interactions between a filled molecular orbital of the alkene and the *empty* 5s-orbitals of the cationic palladium species **46**.[26] On the other hand, it has been demonstrated that the coordination of a chloride ion to a palladium(II) complex similar to **44** prevented the olefin insertion of an electron-rich alkene even under forcing conditions.[27] As before, this sluggish olefin insertion can be rationalised by arguments about the involved molecular orbitals. In particular, repulsive interactions between a filled molecular orbital of the alkene and the *filled* 5s-orbitals of the neutral palladium(II) complexes such as **44** led to a high energy barrier for the insertion reaction.[26] To the best of our knowledge no reports about the reactivity of hydroxopalladium(II) species such as **45** to olefin insertion have appeared in the literature. We expect that the neutral hydroxopalladium complex **45** may be characterised by a lack of reactivity similar to its analogue **44**, since both complexes are expected to possess a filled 5s-orbital causing the repulsive interactions with a filled orbital on the electron-rich alkene during the transition state of the olefin insertion.[26]

Given the case that **44** and **45** are of similar reactivity to olefin insertion the question arises, how chloride ions inhibit the olefin insertion. It has been demonstrated in the literature that a cationic palladium species such as **46** is presumably more readily formed from a hydroxopalladium complex **45** rather than from a chloropalladium(II) complex **44** due to the different tendencies of chloride and hydroxide ligands to dissociate.[24] Consequently, in the presence of halide ions (**Scheme 11**), the Heck reaction of non-activated alkenes is hampered due to the formation of a rather inert palladium complex of the type **44**, while under halide ion free conditions (**Scheme 13**) the olefin insertion is accelerated because of the comparatively facile dissociation of a hydroxide ion from complex **45** affording the very reactive cationic palladium species **46**.

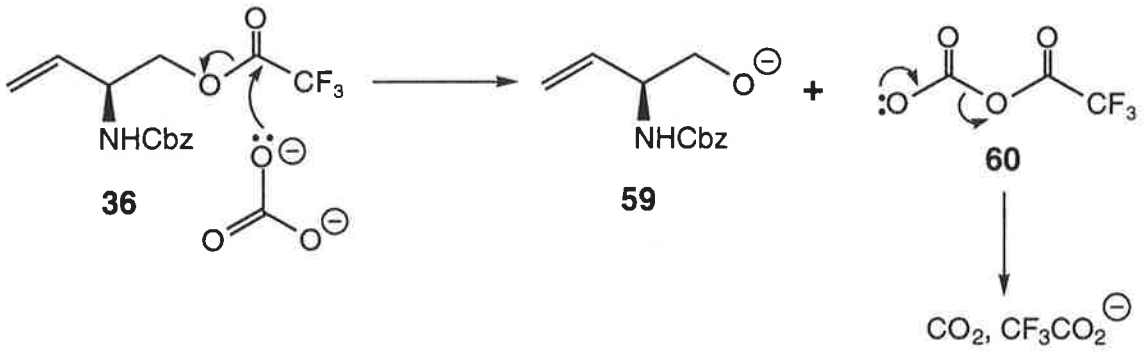
Thus far we have only discussed the olefin insertion as it is the step limiting the overall reaction rate and therefore the overall efficacy of the Heck reaction of non-

activated alkenes with reactive electrophiles. However, a short comment about the oxidative addition[2] of vinyl triflate **43** to the palladium complex **43** (**Scheme 12**) is needed. Recently, it was demonstrated[28] that an acetate coordinated *anionic* palladium complex similar to **43** was the predominant species to participate in the oxidative addition rather than a neutral palladium species as it is frequently assumed in the literature. The anionic palladium(0) species **43** was formed by the reduction of palladium(II) acetate possibly by the solvent or by the alkenes **36** to **40**. Wishing to settle this mechanistic ambiguity, we treated palladium(II) acetate with a solution of an equimolar amount of alkene **40** and potassium carbonate in DMF at 60 °C. After 10 minutes palladium black precipitated, which was an unambigous indication of the reduction of palladium(II) acetate. Unchanged alkene **40** was isolated from the reaction mixture in nearly quantitative yield, which ascertained that, under our improved reaction conditions depicted in **Scheme 13**, palladium(II) acetate was reduced to the zerovalent palladium complex **43** by DMF rather than by the alkene **40**.

On a practical note, the progress of Heck reactions was simply monitored by the change in the colour of the reaction mixture which was originally yellow or orange once the active palladium(0) catalyst was formed at ambient temperature. Towards the end of the reaction the colour progressively darkened. The dark colour was attributed to the aggregation of palladium in solution and the deposition of palladium metal. Monitoring the reaction depicted in **Scheme 11** by ^{1}H nmr spectroscopic analysis revealed that in dark brown reaction mixtures the catalyst was deactivated.

As a sole exception, the trifluoroacetate protecting group was incompatible with the basic conditions of the Heck reaction as the deprotected alcohol diene **53** was obtained in 65 % yield. When the reaction was repeated under anhydrous conditions deprotection of starting alkene **36** was still very facile. It was conceivable that a stoichiometric amount of a nucleophile present in the reaction mixture was required to effect the removal of the trifluoroacetate group. We realised that dimethylamine, which was a decomposition product of DMF, or carbonate ions were

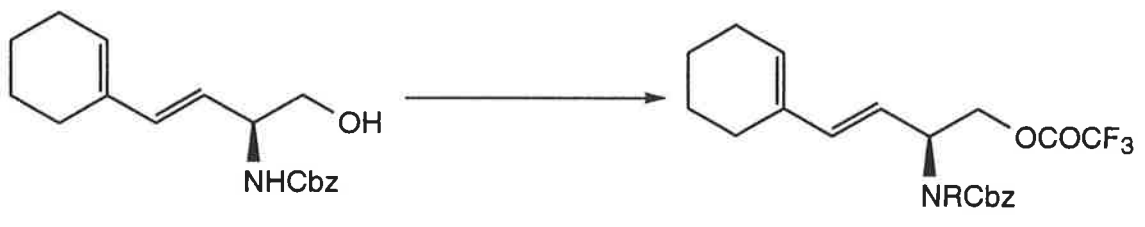
possible candidates. Indeed, alkene **36** was deprotected within several hours by stirring in DMA with a stoichiometric amount of anhydrous potassium carbonate *at ambient temperature* to afford alcohol **34**. We therefore reasoned that alkene **36** was rapidly deprotected as shown in **Scheme 14** by the action of carbonate and that the resulting alkoxide **59** participated in the Heck reaction.



Scheme 14

The exceptional reactivity of the trifluoroacetate as compared to ordinary esters was attributed to the high electrophilicity of the ester carbonyl group of **36** caused by the combined effect of three electron-withdrawing fluorine atoms.

Trifluoroacetate protected diene **54** was amenable by reprotecting diene **53** with trifluoroacetic anhydride *in the absence of any base* (**Scheme 15**). The use of pyridine that is common practice for the introduction of this protecting group[16] was not simply unnecessary, but lead to the formation of diene **61** presumably *via* an intramolecular transfer of a trifluoroacetate group as depicted in **Scheme 16**. The formation of diene **53** bearing a free hydroxyl group during the Heck reaction of **36**

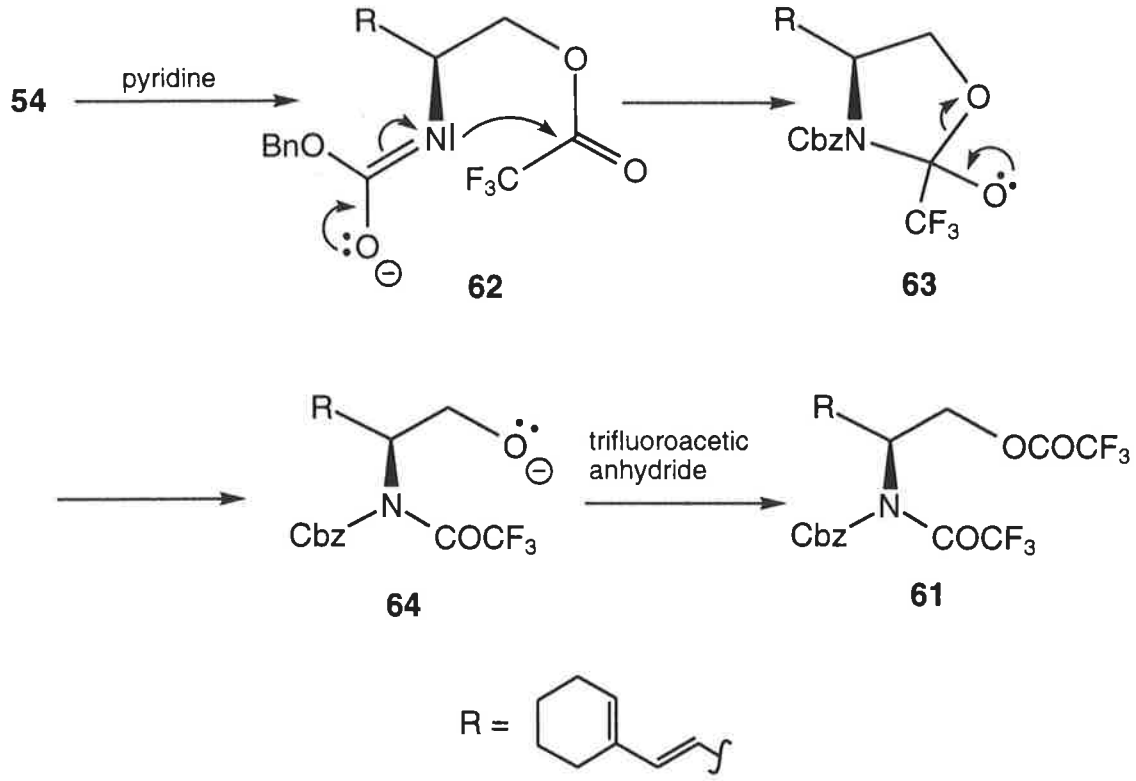


53

54: R = H
61: R = $COCF_3$

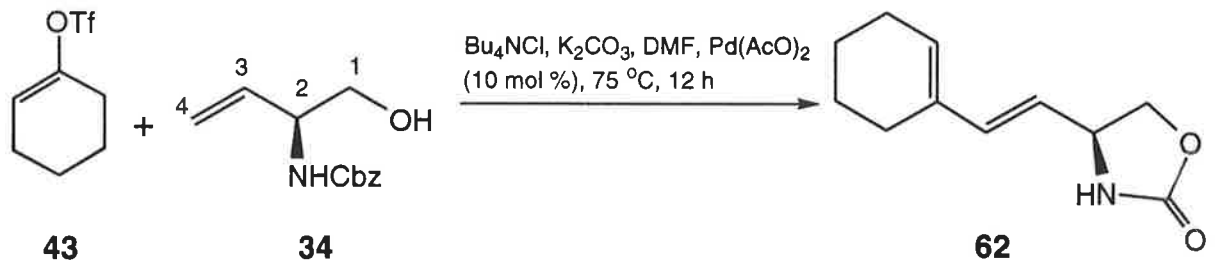
Conditions A: 1.0 equiv. of trifluoroacetic anhydride, pyridine, CH_2Cl_2, 21 % of **61**, 0 % of **54**, 1h.
Conditions B: 1.0 equiv. of trifluoroacetic anhydride, CH_2Cl_2, 66 % of **54**, 0 % of **61**, 1h.

Scheme 15



Scheme 16

intrigued us, as it should now be possible to convert the deprotected aminobutenols **34** and **35** directly into the corresponding dienes **53** and **58**. Previously protection of the free hydroxyl group of alcohol **34** was deemed necessary during the Heck coupling in order to suppress the formation of cyclised diene **62** (**Scheme 17**).[13] Performing the Heck reaction under the milder and more efficient conditions reported here obviated the need for protection of the starting alkenes **34** and **35** as dienes **53** and **58** were obtained in 53 % and 52 % yield, respectively (**Table 1**). On a larger scale it was desirable to decrease the catalyst loading, the amount of tetrabutylammonium triflate and perform the reactions at higher substrate concentrations to avoid the use of excessive amounts of solvent. Repetition of the reaction



43 **34** **62**

Scheme 17

of triflate **43** with alkene **34** with only half of the usual amount of palladium(II) acetate (5 mol%) and of solvent and only a catalytic amount of tetrabutylammonium triflate (10 mol%) still lead to the formation of product diene **53** in 47 % within several hours.

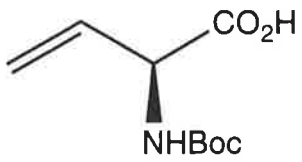
In comparison to alkenes **36** to **40** bearing a protected hydroxyl group, the deprotected aminobutenols **34** and **35** gave a lower yield of the Heck products **53** and **58** (**Table 1**). It was plausible that an intramolecular coordination of the palladium catalyst by the alkoxide group and the carbon-carbon double bond of **59** occurred that may have led to the partial decomposition of alkenes **34**, **35**, **53** and **58** *via* a facile β-hydride elimination of a hydrogen from the carbon bearing the alkoxide group. The aldehydes produced in that way may have decomposed under the reaction conditions. This was consistent with the observation of significant quantities of material remaining at the baseline during chromatography of dienes **53** and **58**.

All product dienes were optically active and we expected no racemisation of the stereogenic center of the substrate alkenes and product dienes to occur during the course of the Heck reaction. Even more base-sensitive substrates have previously be reacted under the conditions depicted in **Scheme 11** and no loss of optical activity was observed.[14]

In summary, we have established reaction conditions under which non-activated and sterically congested alkenes undergo smooth coupling with vinyl triflate **43**. These conditions are furthermore efficacious as they require only equimolar amounts of both coupling partners. By comparison, the original experimental protocol[9] recommended a large molar excess of the alkene. We hope that the conditions described in this work should find application in the Heck reaction of vinyl and aryl triflates with terminal alkenes, which bear no activating electron-withdrawing group in conjugation with the carbon-carbon double bond.

In particular, vinyl glycine derivatives such as **63** are interesting substrates for the elaboration of the side chain *via* a Heck reaction[14,29] to afford α-amino acids with important physiological properties.[30,31] It appears possible that the reaction condit-

ions described in **Scheme 13** may provide a better method than the reported[14] experimental protocol for the Heck reaction of such vinyl glycine derivatives with vinyl and aryl triflates.



63

Furthermore, a rate retarding effect of chloride ions in Heck couplings of non-activated alkenes was observed and rationalised. We wish to propose, that generally Heck reactions of non-activated alkenes conducted in the presence of an inorganic base benefit from replacing the traditionally employed tetrabutylammonium chloride[9] by a halide ion free phase transfer catalyst such as tetrabutylammonium triflate, since such a measure fosters the intermediacy of reactive cationic palladium species.

Chapter 2: The Diels-Alder Reaction

2.1. Introduction

2.1.1. A Historical Perspective

Several examples[31] of the reaction depicted in **Scheme 18** in a general fashion were observed in the literature up to 36 years *before* Otto Diels and Kurt Alder put their claim to the discovery of this transformation,[33] which is today known as the "Diels-Alder reaction".

Scheme 18

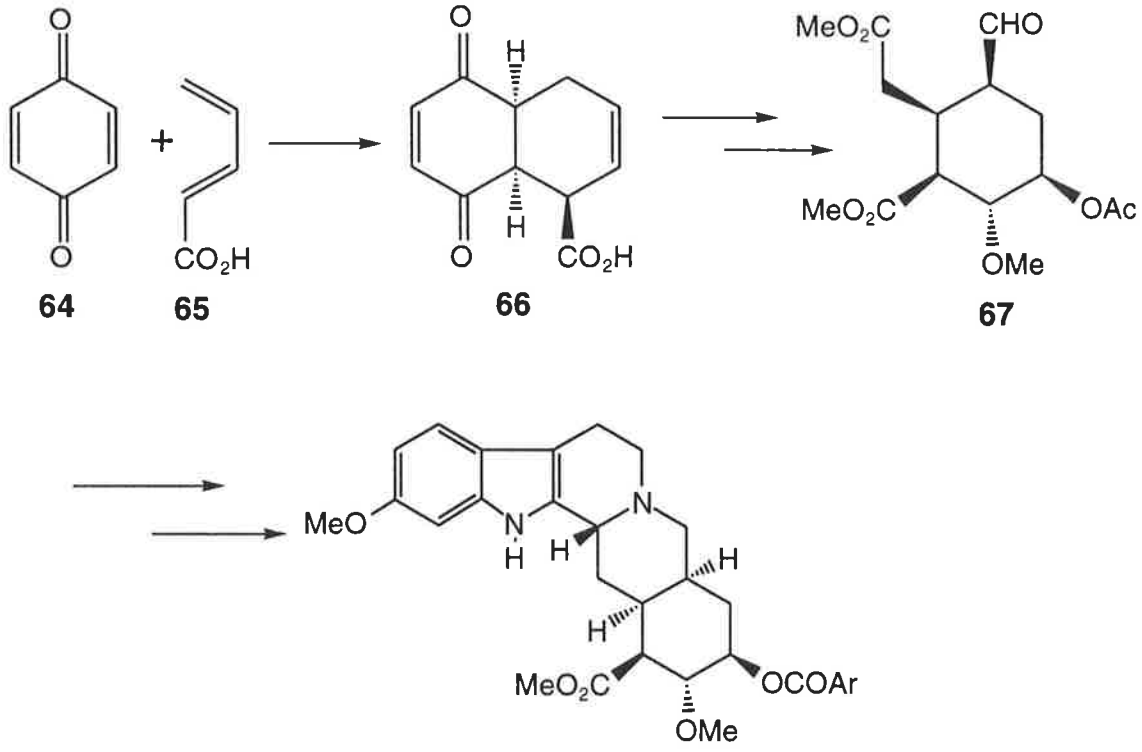
Although it is true, that the Diels-Alder reaction had been *observed* by several researchers, the generality, mechanistic implications and synthetic potential of this transformation were first *recognised* and *exploited* by Diels and Alder:[33]

> "The results of our investigation will not only bear on the discussion of theoretically interesting questions, for example, the strain in polycyclic systems, but are likely to gain greater significance in a practical context. For it appears to us that the possibility of the synthesis of complex compounds closely related to or identical to natural products such as terpenes, sesquiterpenes, perhaps also alkaloids, has been moved to the near prospect."

In 1950 Diels and Alder were jointly awarded the Nobel Prize for Chemistry in recognition of "their discovery and development of the diene synthesis".[34]

Countless examples of natural product syntheses are legion to Diels' and Alder's original prediction of the synthetic potential of this versatile reaction.[35] These became increasingly sophisticated and an early landmark was Woodward's synthesis of reserpine **68** in 1951 which features the formation of three contiguous stereogenic centers in a single step (**Scheme19**).[36]

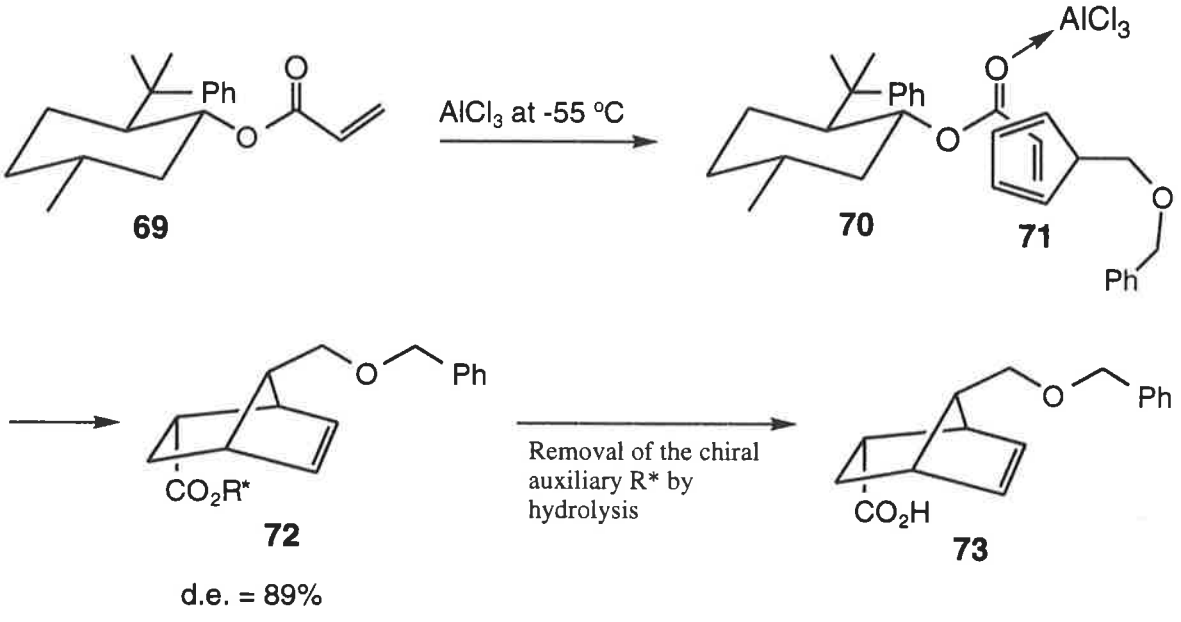
In numerous excellent studies of the Diels-Alder reaction of dienophiles with an at-



Reserpine

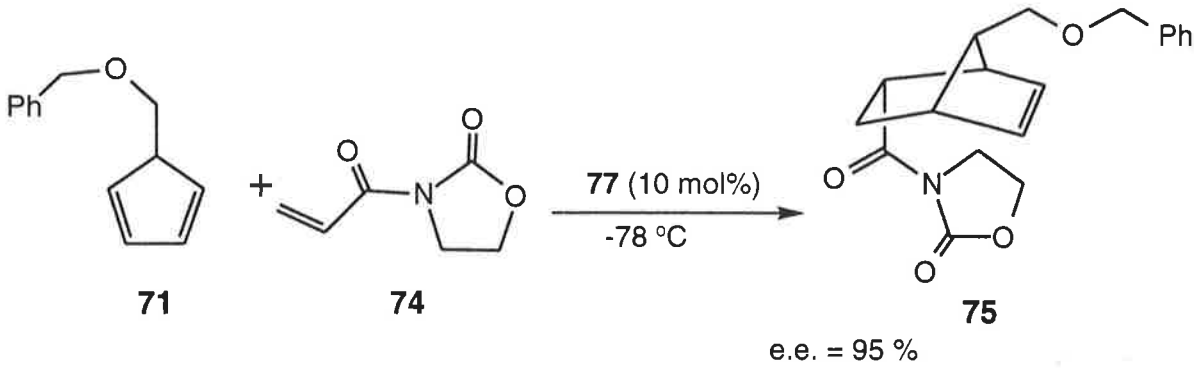
Scheme 19

tached chiral moiety it was demonstrated that enantiomerically enriched or even pure products with the predicted absolute stereochemistry could be synthesised (**Scheme 20**).[37] Perhaps the most sophisticated studies so far are the increasingly



Scheme 20

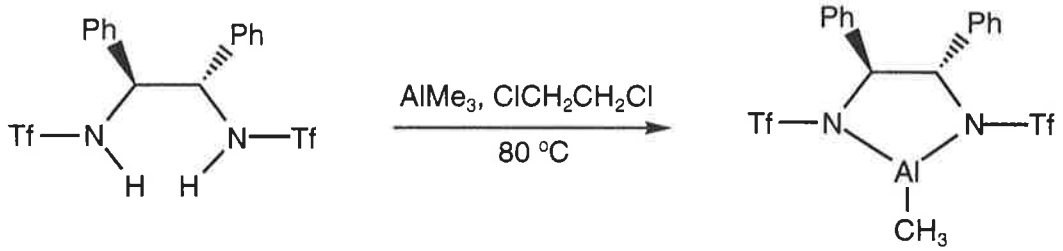
successful applications of optically active Lewis-acid catalysts[38] as well as catalytic antibodies and enzymes,[39] that mediate the conversion of achiral into enantiomerically enriched or even pure compounds (**Scheme 21**). Efforts in the synthesis of enantiomerically pure compounds are primarily motivated by the realisation that strikingly different physiological activities are frequently observed for each enantiomer.[40] Undoubtedly such observations led to the stringent requirement for a separate evaluation of the physiological properties of each enantiomer and the racemic mixture of a potential drug by federal drug licensing agencies (e.g. FDA).[41]



71 **74** **75**

e.e. = 95 %

Preparation of the chiral Lewis acid catalyst **77**:



76 **77**

Scheme 21

2.1.2. The Mechanism of the Diels-Alder Reaction

The Diels Alder reaction is a 4π+2π cycloaddition that proceeds through a concerted reaction. The concertedness of the process was postulated by Alder and others as early as 1937 when it was realised that the formation of two bonds between the diene and the dienophile occurred simultaneously.[43] The obvious alternative and erroronous view of a stepwise bond formation also found advocates[44]

and both views were discussed by Woodward.[45]

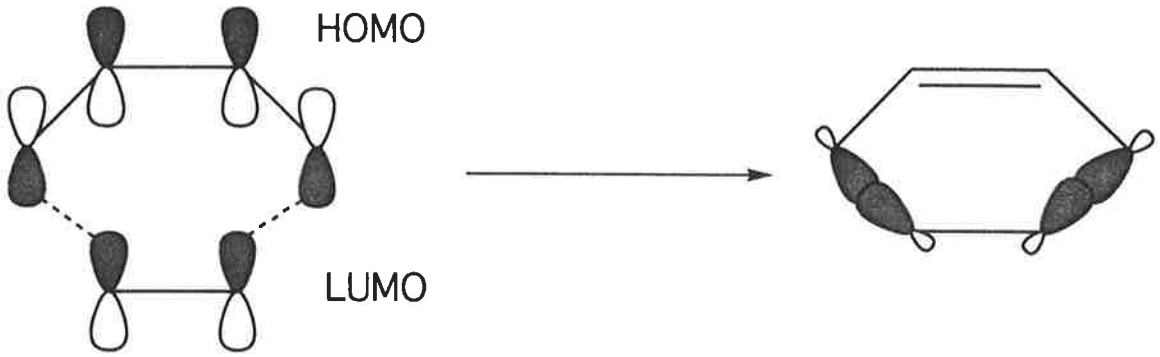
One of the greatest achievements in organic chemistry in modern times was the disclosure of the *principle of orbital symmetry conservation* in the course of *concerted* organic reactions and the postulation of a set of "selection rules" concerning the energetic accessibility of transition states.[46] The application of this theory enabled chemists to rationalise the mechanism of many reactions, including the Diels-Alder reaction, and predict their outcome. Only a very brief discussion of the principle of orbital symmetry conservation with regard to the Diels-Alder reaction shall follow.

The so-called "frontier-orbital approach"[47] is conceptually the most simplified representation of the *principle of orbital symmetry conservation*. According to this approximation only the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of the reactants are considered, as interactions of other molecular orbitals are deemed to contribute insignificantly to the overall energy of the transition state. At the transition state of a Diels-Alder reaction of an electron-rich diene with an electron-deficient dienophile there is an in-phase overlap of the HOMO of the diene and the LUMO of the dienophile in their electronic ground states. The relationship between the phases of the frontier orbitals of the transition state and the newly formed σ-orbitals of the cyclohexene product are identical (**Scheme 22**), or alternatively expressed "conserved". According to the principle of orbital symmetry conservation transition state **78** is *symmetry allowed* and *therefore energetically readily accessible*.

The overwhelming majority of Diels-Alder reactions are stereospecific, or in other words the geometries of substituents of the starting diene and dienophile are retained in the product cyclohexene as the reaction proceeded only through a symmetry allowed transition state.

The geometrical features of transition state **78** include the planarity of the π-electron systems, the coplanar approach of both reactants, the *cisoid* conformation of the diene and the simultaneous formation of both σ-bonds.

A very early observation in the history of the Diels-Alder reaction is the formation of



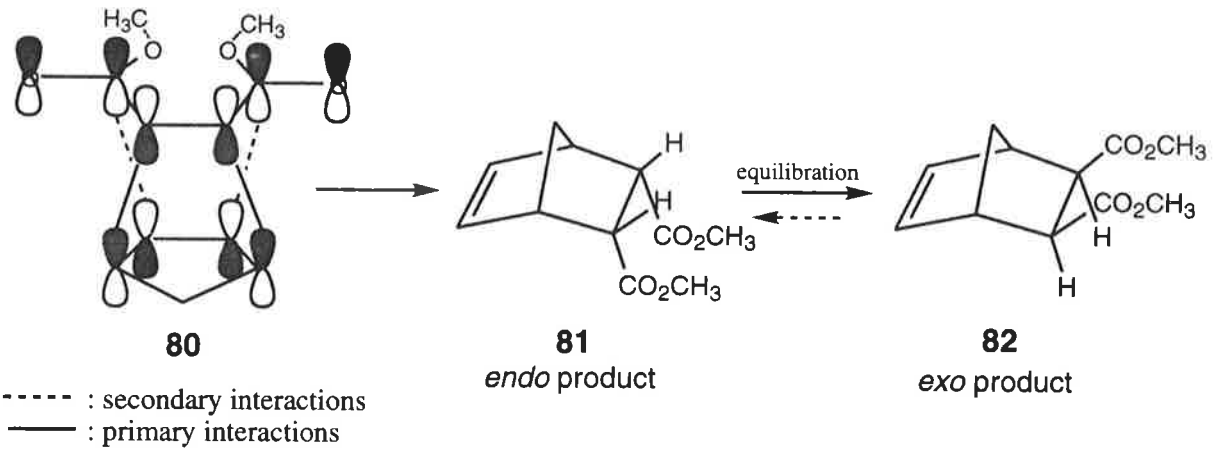
78 **79**

Conservation of orbital symmetry in the Diels-Alder reaction

Scheme 22

a single product when there is a choice of two possible isomers. This selectivity is observed for some dienophiles with conjugated electron-withdrawing substituents. The sterically more compact "*endo*" adduct **81** is formed when the reaction is conducted under kinetic control, while it is frequently the sterically less compact "*exo*" adduct **82**, which is thermodynamically more stable (**Scheme 23**). This stereochemical preference could be rationalised by invoking weaker interaction between regions of the HOMO and LUMO that are distant from the site of bond formation.

The HOMO and LUMO of an alkene attached to an electron withdrawing substituent

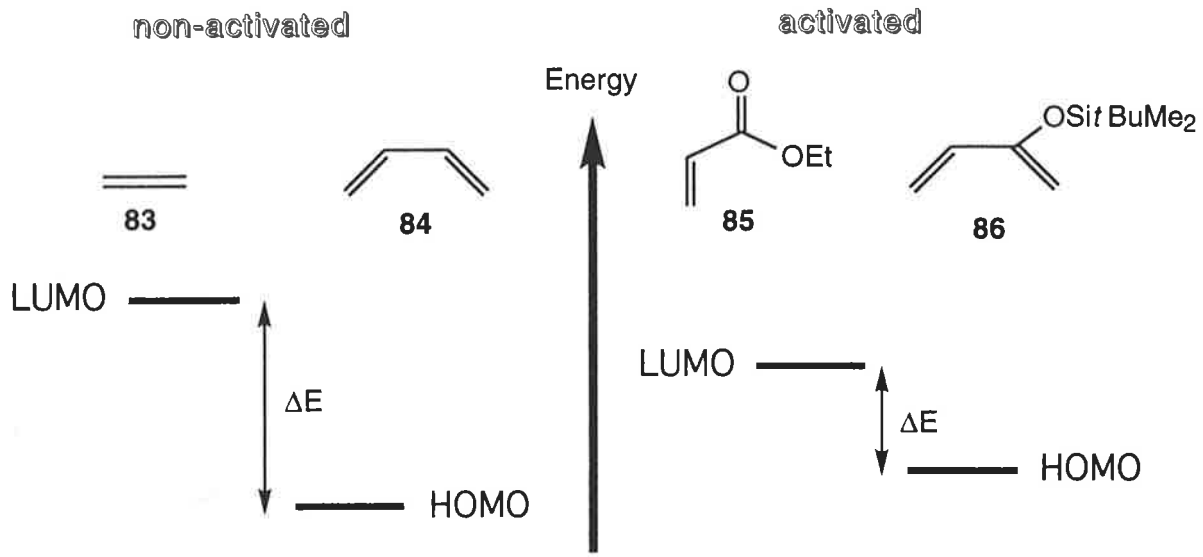


80 **81** *endo* product **82** *exo* product

Secondary interactions of the frontier orbitals lead to the formation of the thermodynamically less stable *endo* product

Scheme 23

are energetically lower than those of the corresponding unsubstituted alkene, whilst the energy of the HOMO and LUMO of the diene are raised by an electron-donating substituent. This situation is illustrated qualitatively in **Scheme 24**. The energy gap ΔE between the HOMO of the diene and the LUMO of the dienophile is reduced as a result of these substitutions leading to a better interaction of the frontier orbitals and consequently to an energetically lower transition state.



The reactivity of dienes and dienophiles is dependent on the substituents

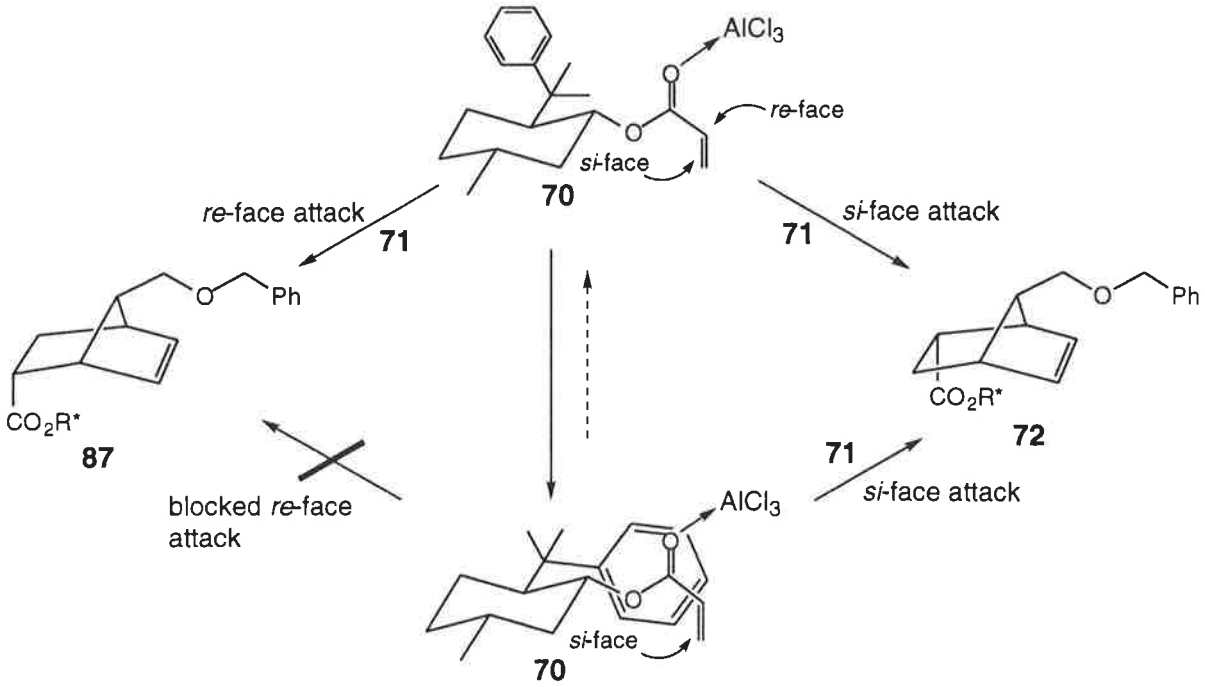
Scheme 24

Recently transition metal induced versions of the Diels-Alder reaction have been developed, which proceed *via* a mechanism that is fundamentally different from the 4π+2π cycloaddition.[48] These reactions offer the prospect of overcoming some of the limitations of the Diels-Alder reaction with regard to the substrates and the stereochemistry of the products.

2.1.3. π-Facial Selectivity of 1,3-Dienes

The term "π-facial selectivity" in the context of a Diels-Alder reaction refers to the dienophile or the diene or both possessing non-equivalent faces of the π-electron system. For example the approach of a dienophile to either the top or bottom face of a diene proceeds through *energetically different* transition state. The products resulting from those alternative approaches are diastereomers. Under kinetic

control, their ratio is dependent on their relative rates of formation and therefore on the difference in the activation energy of the corresponding transition states. For example, product **72** was formed 9 times faster than its diastereomer **87** as the difference in the free energy[49] of the transition states approximated to only 1.3 kcal mol^{-1} (**Scheme 25**).



Conformational control in the Diels-Alder reaction of 8-phenylmenthyl acrylate **70** with 5-benzoxymethyl cyclopentadiene **71** was a prerequiste for good π-facial selectivity.[34c]

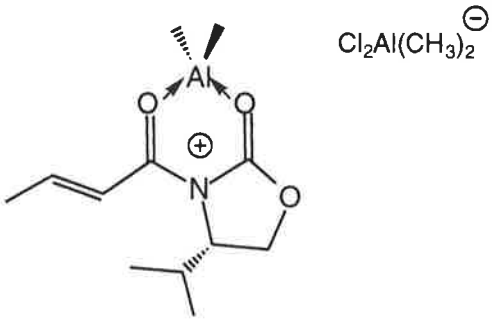
Scheme 25

Therefore the π-facial selectivity is primarily determined by weak interactions that affect the conformation of the transition state. These can include weak π-stacking interaction between the phenyl ring and the acrylate moiety of **70** reducing the frequency of *re*-face attack.[50a]

As previously stated the ambitious goal of producing essentially only one of several possible diastereomers has frequently been achieved by employing alkenes attached to a chiral moiety that imparts a π-facial bias. Far fewer examples of dienes with such a π-facial bias have been investigated and generally their Diels-Alder reactions are considerably less stereoselective.[42] Is there an explanation for this difference? In order to answer this question the molecular parameters that

determine π-facial selectivity have to be considered. For example, a strong π-facial bias of a chiral diene frequently necessitates the presence of a sterically interfering substituent that can prevent an approach by the dienophile to the π-electron system. Furthermore, this substituent should be held in a position to shield *only one* face of the π-electron system *all of the time*. The π-facial selectivity may be disappointingly low if both criteria are not met.

A rather rigid conformation of the necessary type was frequently realised by Lewis-acid coordination (**Scheme 26**)[37b] and/or π-stacking interactions between a relatively electron-rich phenyl substituent and an electron-deficient dienophile (**Scheme 25**). In addition, coordination by the Lewis-acid substantially lowered



88

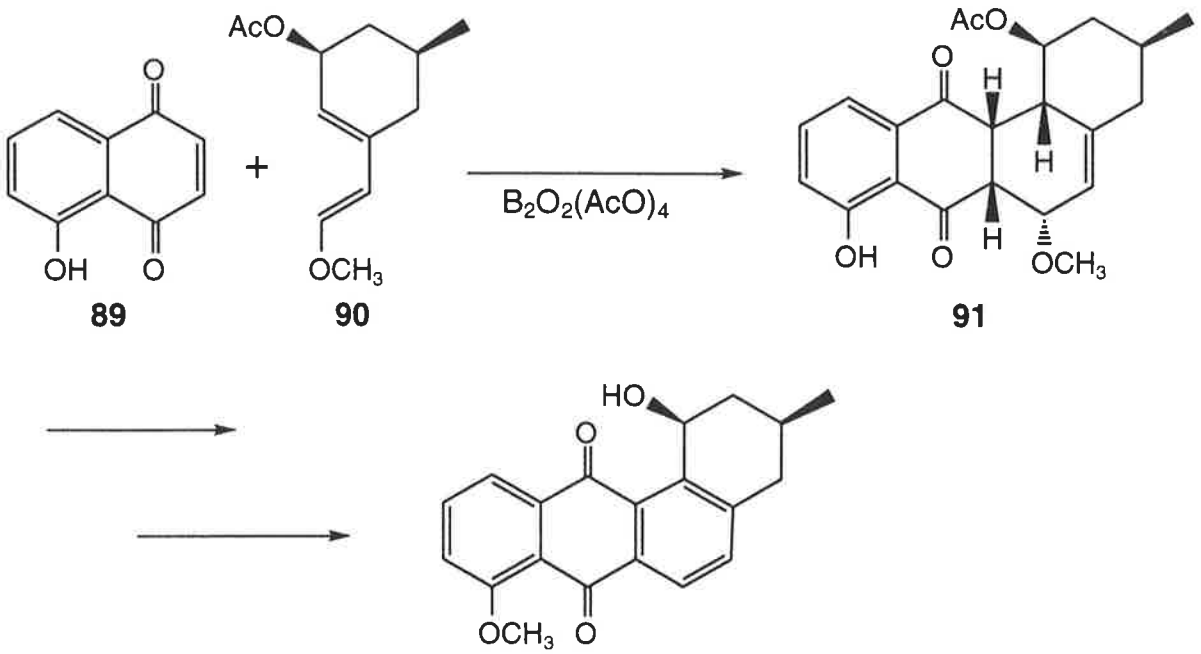
The rotation of the acrylate moiety in **88** was restricted by coordination to Al and steric interactions with the *iso*-propyl substituent that also provided a π-facial bias.

Scheme 26

the energy of the LUMO of the dienophile (*vide supra*) therefore allowing the Diels-Alder reaction to be carried out at a lower reaction temperature (frequently at -78 °C) under excellent kinetic control.

Whereas the synthetic tasks of introducing a sterically interfering substituent into a diene or dienophile are comparable, it is frequently the conformational ambiguity of a diene in the transition state, which contrasts the single reactive conformer of a Lewis-acid coordinated dienophile. A high π-facial selectivity is, however, achieved when the sterically interfering substituent is locked into a spatially defined position relative to the diene moiety. This has to our knowledge been realised twice by coordination of the diene to a Lewis acid.[42b,51] A more frequently employed approach embeds the 1,3-diene moiety and the sterically interfering substituent into

the rigid atom frame of a molecule. For example, reaction of diene **90** with naphthoquinone **89** afforded a single stereoisomer **91** as attested by nmr spectroscopy (**Scheme 27**).[52] The proposed stereochemical assignment of **91** re-



89 **90** **91** **92**

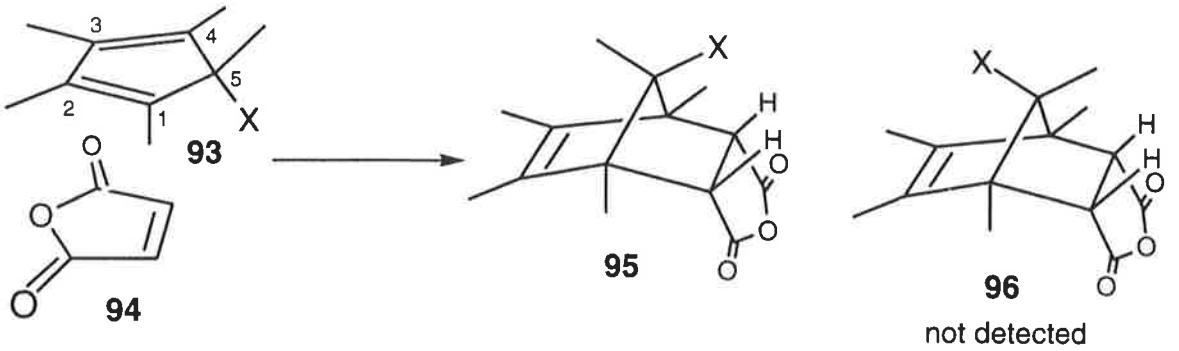
Rubiginone B_1

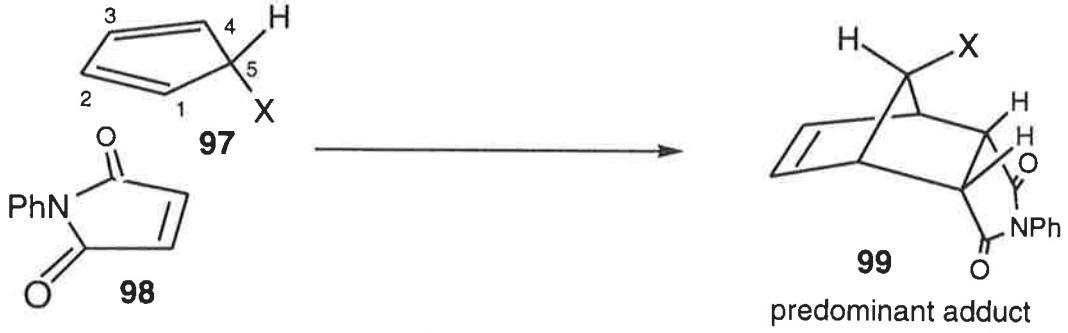
Scheme 27

sted on the dihedral angle dependence of vicinal proton couplings. It was assumed that the acetoxy substituent directed the cycloaddition to the sterically less encumbered face of diene **90**. The excellent π-facial selectivity of diene **90** was, however, immaterial to the subsequent synthesis of the antibiotic rubiginone B_1 **92** because the newly formed ring was aromatised.

2.1.4. Stereo-electronic Effects

A very interesting group of dienes are 5-heteroatom substituted cyclopentadienes, since their π-facial bias was contrary to predictions based on simple steric models. For example permethylated cyclopentadienes **93**[54,55] and cyclopentadienes **97**[53a] reacted with dienophiles *at the sterically more encumbered face of the π-electron system* (**Scheme 28**). Several theories based on the frontier molecular orbital theory were proposed to account for these observations. Two models will now be discussed in further detail.





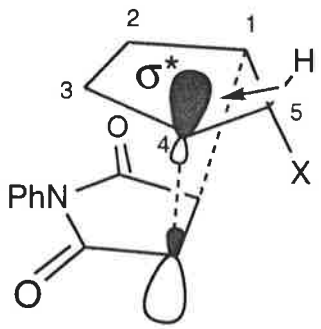
Contrasteric π-facial selectivity of some 5-heteroatom substituted cyclopentadienes

Scheme 28

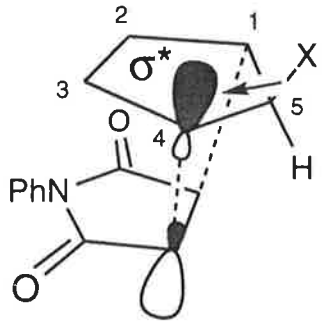
Firstly, it was postulated that hyperconjugational stabilisation of the incipient σ*-orbitals in position 1 and 4 in the transition state **100** overrides the clear steric bias of these dienes (**Scheme 29**).[54] This stabilisation can be a donation of electron density from the σ-orbital of the carbon-carbon bond in position 5 of **97** or, in the case of diene **97**, the carbon-hydrogen bond in the same position. A similar overlap of the incipient σ*-orbitals with the comparatively electron-deficient carbon-heteroatom in position 5 of cyclopentadienes **93** and **97** was less favourable (structure **101**, **Scheme 29**). Such theories about the stabilisation of σ*-orbitals in the transition state of various reactions were proposed by Cieplak[56] and further applied mainly by Fallis to explain the contrasteric π-facial bias of a number of cyclic 1,3-dienes in Diels-Alder reactions.[53,54]

A similar model based on the stabilisation of the incipient σ-bond in the transition state by hyperconjugation of its σ-orbital to the antibonding σ*-orbital of the carbon-heteroatom bond in position 5 of cyclopentadienes such as **93** was proposed by

"Cieplak-Model":



100



101

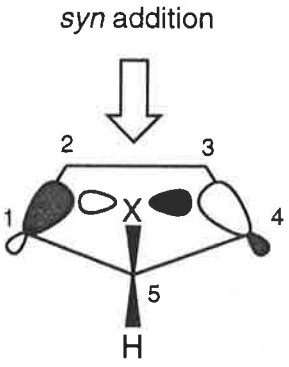
Stabilisation of the incipient σ*-orbitals is more efficient in structure **100** than in the alternative transition state **101** (in each structure only one σ*-orbital is indicated).

Scheme 29

Felkin and Anh.[54] A good discussion of both models was presented in the literature.[55]

Alternatively, the contrasteric π-facial bias of permethylated cyclopentadienes **93** was rationalised by Inagaki on the basis of the orbital mixing rule. According to this theory,[59] the HOMO of the diene was expected to distort inwardly on the same face as the substituent resulting in a non-symmetrical distribution of electron density with regard to the plane of the 1,3-diene unit (**Scheme 30**).[55] Owing to a better overlap with the HOMO in the critical region at C1 and C4, dienophile **94** reacted on the face *syn* to the substituent in position 5 of **102**.

Frontier Molecular Orbital Mixing:

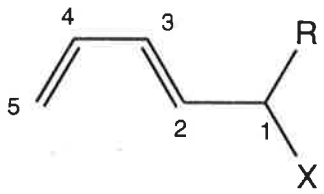


102

The HOMO of the 1,3-diene unit is distorted inwardly on the side *syn* to X due to interactions with a π- or σ-orbital of the substituent X (only a part of the frontier orbital is indicated).

Scheme 30

Stereo-electronic effects such as the hyperconjugational stabilisation of the emerging σ*-orbitals in the transition state were also invoked for the Diels-Alder reaction of *acyclic* dienes of the general type **103** bearing an electron-withdrawing heteroatom in the allylic position.[54] In contrast to the 5-heteroatom substituted cyclopentadienes, the transition state conformation of the heteroatom substituent (X) with regard to the 1,3-diene moiety of **103** is uncertain due to the rotation around the C1C2 bond. Conformational control of this bond rotation *and* a strong π-facial bias of the ensuing energetically favoured transition state conformation were deemed prerequisites for a high diastereoselectivity in the Diels-Alder reaction of dienes **103**. Predictions concerning the π-facial bias of dienes **103** are difficult since the factors that control the reactive conformation have not unequivocally been established.



X = substituent attached *via* N or O to the stereogenic centre
R = aliphatic substituent, may contain heteroatoms in a remote position

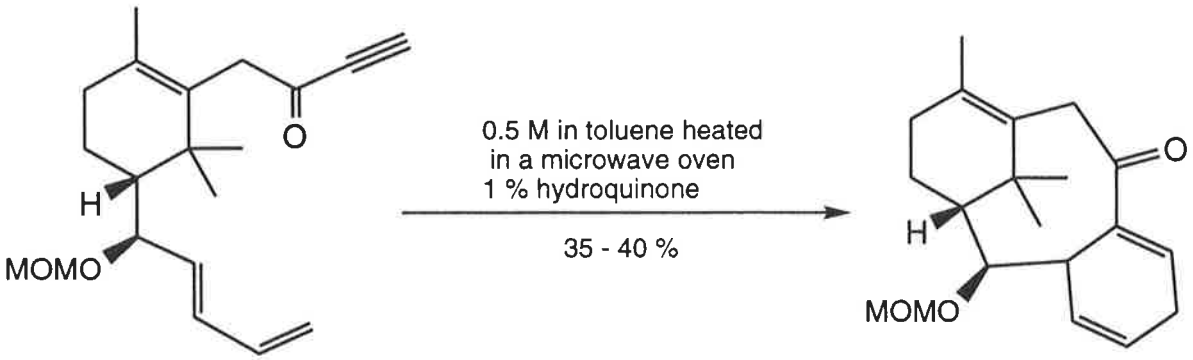
103

It is, however, desirable to disentangle the daunting skein of steric and electronic factors governing the π-facial bias of conformationally flexible dienes, such as **103**. Such knowledge may allow for the careful design of dienes of the general type **103**, in order to maximise the π-facial bias and fully exploit their synthetic potential. Work presented in Chapter 2 will contribute to this goal.

2.1.5. Intramolecular Diels-Alder Reaction

It should be mentioned that *linking diene and dienophile by a chiral tether* is a powerful and frequently employed strategy of ring formation in natural product synthesis (**Scheme 31**). Good to excellent π-facial bias of both the diene and the dienophile moieties are frequently observed with this approach.[35] This method is

also efficacious in terms of atom economy[61] provided the chiral linker arm is an intergal part of the target structure. The length of the linker arm, the position and the nature of the stereogenic centre are among the parameters that determine the stereochemical course of the reaction in a complex fashion.



"MOM": methoxymethyl

104 **105**

Synthesis of the taxane nucleus **105** by an intramolecular Diels-Alder reaction [60]

Scheme 31

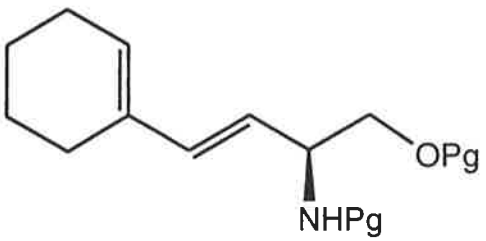
2.2. AIM

We wished to investigate the Diels-Alder reaction of conformationally flexible dienes that were synthesised in chapter 1, in which an asymmetrically substituted carbon is directly linked to the 1,3-diene moiety. In particular, we wished to shed light on the factors that affect their π-facial bias.

2.3. Results and Discussion

2.3.1. Preliminaries

In studying the factors that determine the π-facial selectivity of chiral 1,3-dienes in the Diels-Alder reaction we focussed our interest on dienes of the general type **109** for several reasons.



109

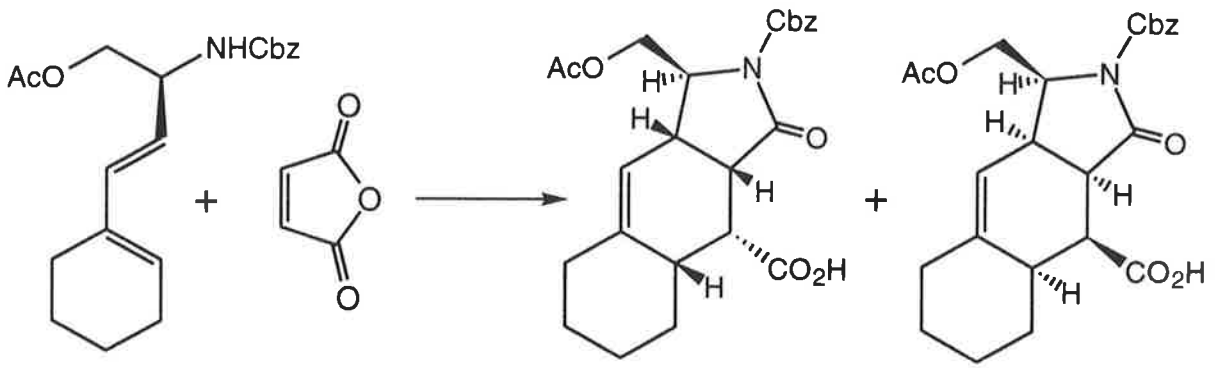
Firstly, differentially protected dienes **109** were readily accessible *via* Heck reactions of amenable precursor alkenes (Chapter 1). Secondly, the influence of two substituents at the stereogenic center of **109** on the π-facial selectivity could be assessed by a simple and systematic variation of the heteroatom protecting groups. Thirdly, owing to the structural similarity of dienes **109**, we expected the products of the Diels-Alder reactions with the same dienophile to be similar in their physical properties, for example similar proton and carbon nmr spectra. Such similarities should facilitate the isolation and structural identification of the Diels-Alder products.

Although all compounds that are introduced in Chapters 1 and 2 showed optical activity, their enantiomeric purity was never determined. One reason for this is that the purpose of this study was an investigation into the π-facial bias of dienes **109** and *not* the synthesis of any particular target molecule in an enantiomerically pure form. Such a study on the π-facial selectivity could have equally well been carried out with racemic chiral compounds. The substrate dienes of the general type **109** were synthesised from optically pure starting material (Chapter 1) and no racemisation was expected to have occurred. This expectation is based on the non-sensitive nature of the chiral carbon atom of dienes **109** and its precursors (Chap-

ter 1), and also on literature precedent[14] where chiral shift experiments have been performed. The thermal Diels-Alder reaction that is central to this chapter is not usually associated with a racemisation of substrates. Consistent with this is that we never observed any evidence for an epimerisation of any of our Diels-Alder adducts.

2.3.2. Initial Investigations in the Diels-Alder Reaction

Firstly, diene **41** was reacted with maleic anhydride **94** in toluene at 110 °C for several hours. As the ^1H nmr spectroscopic analysis of the crude reaction product revealed a significant amount of decomposed material, we attempted to conduct the same reaction in solvent 1,2-dichlorobenzene (Conditions A, **Scheme 32**). The conversion of diene **41** was monitored by tlc analysis of the reaction mixture and found to be considerably faster and also cleaner in refluxing 1,2-dichlorobenzene than in toluene. ^1H nmr spectroscopic analysis of the crude reaction product showed two sets of resonances. The ir spectrum of the crude mixture was consistent with the presence of a carboxylic acid and the absence of an amide hydrogen. Recognising the acidic nature of the products we extracted an ethereal solution of



41 **94** **112a** major product + **113a** minor product

Conditions A: **94** (3 equiv.), a 0.03M solution of **41** in 1,2-dichlorobenzene, 180 °C, 1 h.
Conditions B: **94** (3 equiv.), a 1.0M solution of **41** in CH_2Cl_2, 40 °C,12 h.
Conditions C: **94** (3 equiv.), a 1.0M solution of **41** in $CDCl_3$, 25 °C, 4 days.
Conditions D: **94** (3 equiv.), a 0.45M solution of **41** in $LiClO_4$, 25 °C, 5 h.

Scheme 32

the crude mixture with saturated $NaHCO_3$, the aqueous extracts were then acidified and the precipitate extracted from the aqueous phase with ether. The ^1H nmr spectrum of the crude extracts revealed two sets of resonances identical to those detected before the extraction. At this stage we tentatively assigned the structures **112a** and **113a** to the product carboxylic acids. A detailed structural assignment will be presented in Sections 2.3.4. and 2.3.5..

It was also apparent at this stage that a two-step process had occurred, namely a Diels-Alder reaction of **41** and **94** and an opening of the carboxylic acid anhydride, but not necessarily in that chronological order. The mechanism of this conversion will be discussed shortly.

A hplc assay was developed using a commercial column packed with reversed phase silica in order to analyse the reaction mixture more accurately and allow for a semi-preparative purification of the product carboxylic acids. The co-elution of several compounds present in the crude product was avoided by a careful optimisation of the solvent system.

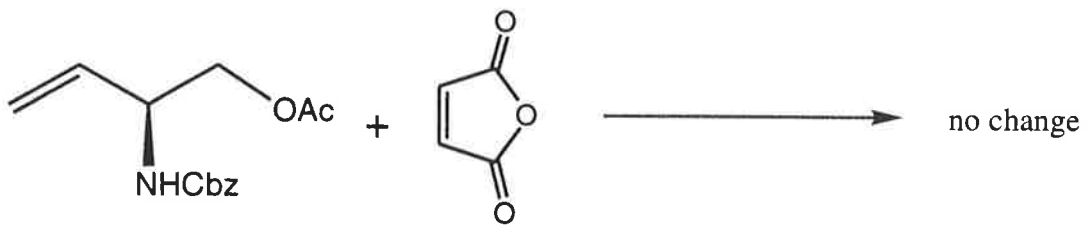
Whilst pure **112a** was isolated in a 30 % yield, only a contaminated sample of the minor product **113a** could be obtained.

We attempted to improve on the low yield of **112a** by reacting a concentrated solution of diene **41** with maleic anhydride **94** in refluxing dichloromethane (Conditions B, **Scheme 32**). ^1H nmr spectroscopic analysis of the crude reaction mixture revealed the same predominant product **112a** as for the reaction conducted at 180 °C. The crude reaction product was extracted with saturated $NaHCO_3$ and the acidified extracts analysed by hplc. This material was markedly cleaner than the crude product obtained from the reaction of the same substrates in refluxing 1,2-dichlorobenzene. The pure carboxylic acid **112a** was obtained in 47 % yield after column chromatography on normal phase silica.

Although it was obvious that the isoindolones were formed by a Diels-Alder reaction and an opening of the carboxylic anhydride moiety, the chronological order of these events was not certain. In order to discuss the π-facial bias of a diene, such as **41**, knowledge of the mechanistic sequence of events was imperative, as the ratio

of isoindolones **112a** to **113a** should provide a measure for the π-facial bias of diene **41**.

Fortunately both mechanistic scenarios were readily distinguished since, under the same conditions, maleic anhydride **94** did not react with alkene **40**, which served as an analogue of diene **41** (**Scheme 33**). These experiments confirmed the ex-



40 **94**

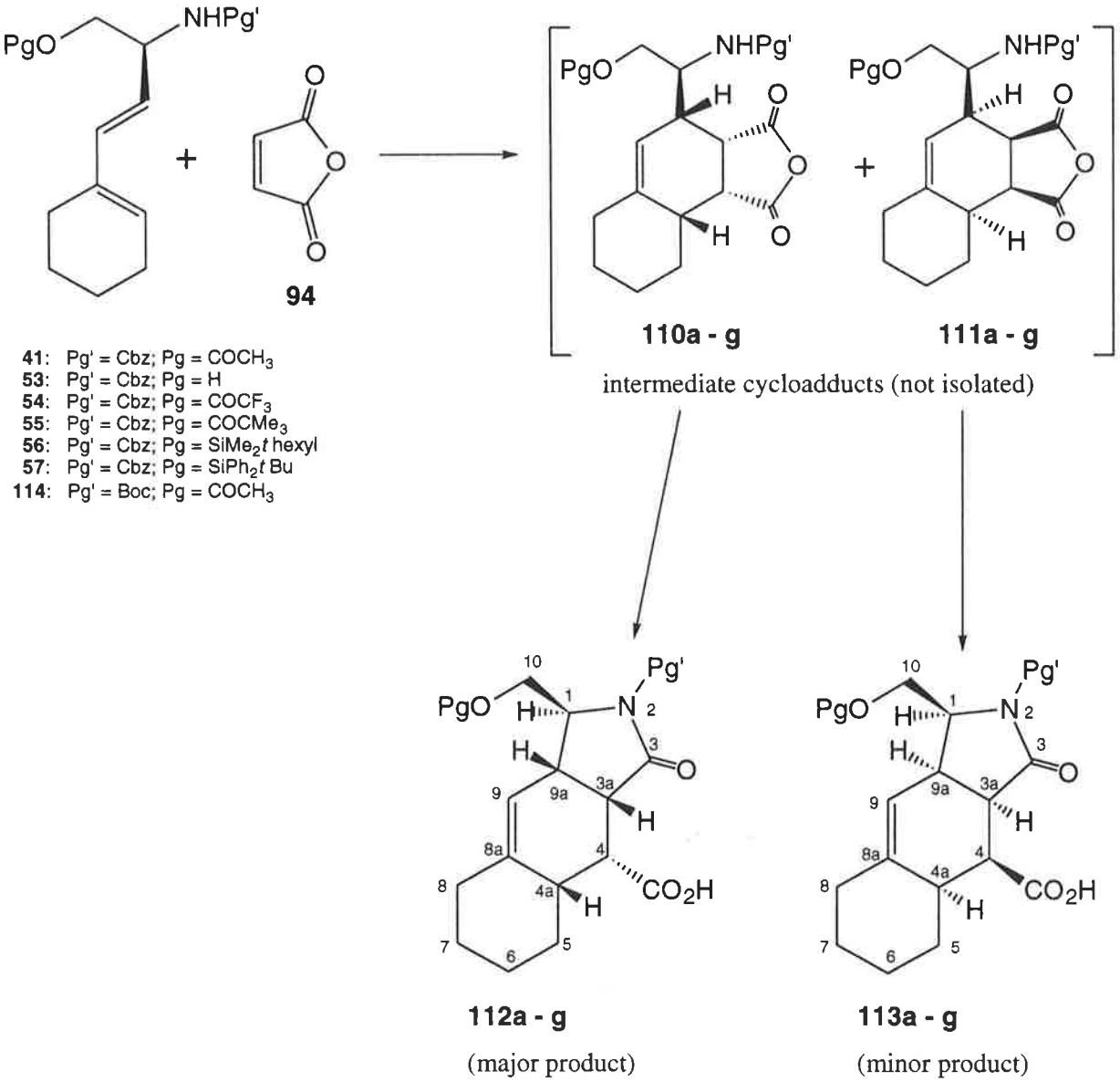
Conditions A and B as described in Scheme 32

Scheme 33

pectation that the Cbz protected nitrogen of **40** and therefore also of diene **41** were inert towards maleic anhydride **94**. It was therefore concluded that an *intermolecular* Diels-Alder reaction had occurred and was followed by a rearrangement of the anhydride of the initial cycloadducts **110a** and **111a** into the thermodynamically more stable carboxylic acid and imide functionality (**Scheme 34**).

During the course of this work the *acid catalysed* rearrangement in a system similar to **110a** was published.[62] As the most obvious structural difference between **110a** and the compound reported in the literature[62] was the presence of the second six-membered ring with the *exo*-cyclic double bond in **110a**, we reasoned that cycloadducts **110a** and **111a** were more constrained. This additional strain may have caused the higher reactivity of the anhydride portion of **110a** and **111a**.

The mechanism of the rearrangement is proposed in **Scheme 35**. It involves a nucleophilic attack by the imine nitrogen atom of the tautomerised carbamate protecting group on the anhydride moiety followed by a proton transfer. Possibly a small amount of cycloadducts **110a** and **111a** formed initially and catalysed the enolisation of the carbamate group.

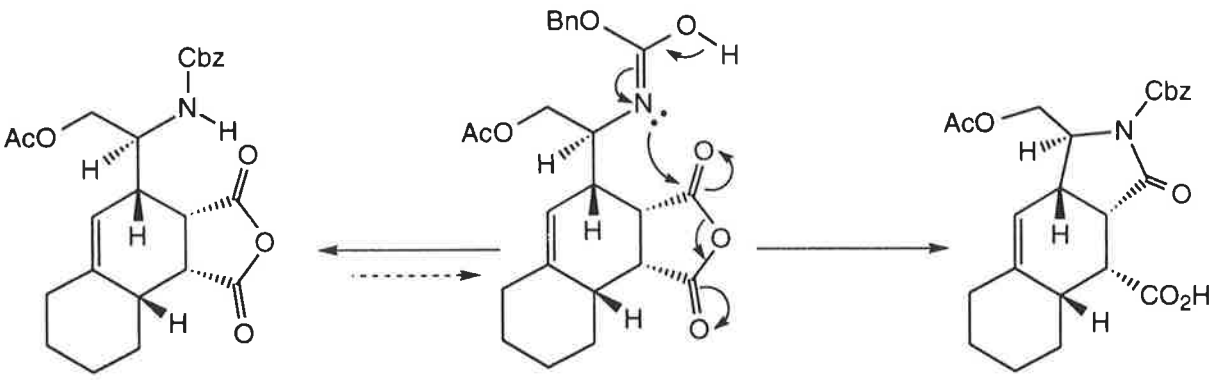


41: Pg' = Cbz; Pg = $COCH_3$
53: Pg' = Cbz; Pg = H
54: Pg' = Cbz; Pg = $COCF_3$
55: Pg' = Cbz; Pg = $COCMe_3$
56: Pg' = Cbz; Pg = $SiMe_2t$ hexyl
57: Pg' = Cbz; Pg = $SiPh_2t$ Bu
114: Pg' = Boc; Pg = $COCH_3$

a: Pg' = Cbz, Pg = $COCH_3$
b: Pg' = Cbz, Pg = OH
c: Pg' = Cbz, Pg = $COCMe_3$
d: Pg' = Cbz, Pg = $COCF_3$
e: Pg' = Cbz, Pg = $OSiMe_2t$ hexyl
f: Pg' = Cbz, Pg = $OSiPh_2t$ Bu
g: Pg' = Boc, Pg = $COCH_3$

Scheme 34

In order to analyse the reaction mixture directly by ^1H nmr spectroscopy, we conducted the reaction of diene **41** with maleic anhydride **94** in $CDCl_3$ at ambient temperature (Conditions C, **Scheme 32**). Although isoindolone **112a** was the



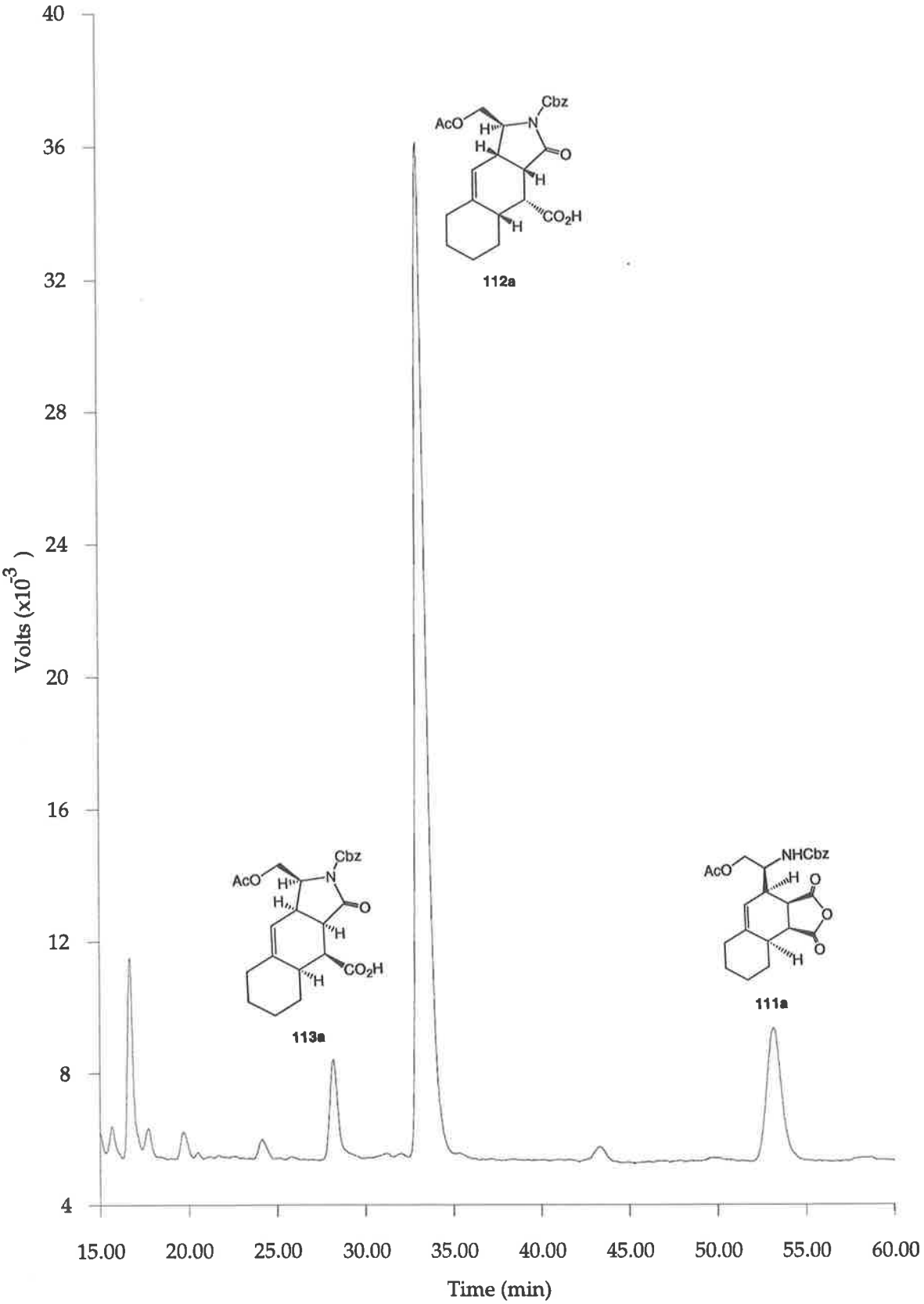
110a **115** **112a**

Scheme 35

major product as before, we were initially not able to reproduce the exact ratio of isomeric isoindolones **112a** and **113a** present in the crude product when the experiment was repeated. In particular, it appeared that extended reaction times led to a decrease in the ratio of isomeric isoindolones.

Clearly, if both initial cycloadducts rearranged rapidly *at a similar rate*, the ratio of isoindolones **112a** and **113a** should remain constant throughout the reaction.
If, however, the rearrangement of the cycloadducts **110a** and **111a** proceeded *at distinctly different rates*, we predicted that in the early stages of the reaction isoindolone **112a** would predominate due to the rapid rearrangement of the initial cycloadduct **110a**, and that, during the further course of the reaction, more of the isomeric isoindolone **113a** would be formed by a slow rearrangement of cycloadduct **111a**.
In order to confirm this conjecture of a marked difference in the rate of rearrangement of the initial cycloadducts **110a** and **111a**, the Diels-Alder reaction of diene **41** with maleic anhydride **94** was repeated (Conditions C, **Scheme 32**) and closely monitored by hplc. Indeed, the initial ratio of **112a** to **113a** was gradually reduced from 33.5 to 1.0 after 12 hours to 13.8 to 1.0 after 4 days of reaction time (**Figure 1**). A late eluting peak due to a non-polar compound was also detected, which decreased in intensity with progressing reaction time. When the reaction mix-

Figure 1. HPLC Analysis of the 12 h old Reaction Mixture depicted in Scheme 32 (Conditions C).



ture was analysed by ^1H nmr spectroscopy it became evident that none of the starting diene **41** remained and could therefore have accounted for the late eluting peak. On the other hand additional signals appeared transiently in the ^1H nmr spectrum. Presumably a reaction intermediate accumulated and gave rise to the late eluting peak. A candidate for such an intermediate was the slowly rearranging cycloadduct **111a**.

By heating the 4 day old reaction mixture overnight at 60 °C the ratio of **112a** to **113a** could be further reduced from 5.2 to 1.0, whilst the intensity of the late eluting peak was even further diminished. However, only refluxing of the crude reaction product in 1,2-dichlorobenzene at 180 °C led to the disappearance of the late eluting peak and, presumably, a complete conversion of the initial cycloadduct **111a**. A quantitative analysis of the ratio of the sum of the peak areas in the chromatograms obtained after varying reaction times was performed. It was revealed that the ratio of isoindolone **113a** and its precursor **111a** with regard to isoindolone **112a** was *constant and therefore independent of the reaction time* (**Equation 1**).

Equation 1. Calculation of the underlying π-facial Selectivity of diene **41** in the Diels-Alder Reaction with Maleic Anhydride **94**.

$$\text{d.e.} = \frac{A(\mathbf{112a}) + A(\mathbf{110a}) - [A(\mathbf{113a}) + A(\mathbf{111a})]}{A(\mathbf{112a}) + A(\mathbf{110a}) + A(\mathbf{113a}) + A(\mathbf{111a})} = (57 \pm 2)\ \%$$

"A": Peak areas of the respective compounds in the chromatograms. A(**110a**) was always assumed to be 0 as **110a** was never detected. For the eight hplc analyses of the reaction mixture (6 h, 12 h, 1 d, 2 d, 3 d, 4 d, after refluxing in $CDCl_3$ for 10 h, and after refluxing in 1,2-dichlorobenzene for 1 h) a constant value was calculated.

This constant relationship is consistent with a slow rearrangement of **111a** as it accumulated during the reaction, whilst the isomeric **110a** rearranged too rapidly in order to be detected. The constant ratio of the peak areas as depicted in **Equation 1** was interpreted as the underlying π-facial selectivity of diene **41** during the Diels-Alder reaction (d.e. = 57 %).

The presence of **111a** as a reaction intermediate may have most convincingly been

confirmed by the isolation of **111a** and the monitoring of the rearrangement into isoindolone **113a**. Unfortunately, **111a** could not be isolated.

An alternative suggestion for the varying ratio of isoindolones **112a** and **113a** could be that, rather than the effects of a rate difference in the rearrangement of the cycloadducts **110a** and **111a**, a direct interconversion of isoindolones **112a** and **113a** was monitored. Such a rationale was ruled out by heating isomerically pure **112a** at 180 °C in 1,2-dichlorobenzene. After the solvent was distilled, only unchanged **112a** was detected by ^{1}H nmr spectroscopic analysis of the crude material.

The suprisingly facile rearrangement of the inferred cycloadduct **110a** could be aided by a favourable rotamer population, whilst in the case of the isomeric cycloadduct **111a** the rotamer required to align the nitrogen atom and the anhydride moiety was presumably less populated possibly due to non-bonding interactions between the substituents on C1 and C9a of **111a**.

When the Diels-Alder reactions of other dienes bearing a Cbz amino protecting group but different hydroxyl protecting groups were investigated (**Scheme 34**), the effects of a similar rate difference in the rearrangement of the intermediate cycloadducts **110c - f** and **111c - f** was observed. In contrast, *both* Boc protected initial adducts **110g** and **111g** rearranged rapidly, which was evidenced by a ratio of isomeric isoindolones **112g** and **113g** that remained constant during the reaction.

2.3.3. The Synthesis of Isoindolones with different Protecting Groups

With the exception of alcohol **112b** and trifluoroacetate **112d** all isoindolones were isolated in isomerically pure form by hplc or column chromatography of the crude Diels-Alder products of various dienes (**Table 2**). Although on the basis of a ^{1}H and ^{13}C nmr spectroscopic analysis of the reaction mixtures isoindolone **112b** was formed when diene **53** was treated with maleic anhydride **94** in $CDCl_3$ at ambient temperature, the isolation of **112b** was thwarted by the presence of significant amounts of unidentified material.

Table 2. The Synthesis of Isoindolones **112** and **113** *via* the Diels-Alder Reaction of various Dienes with Maleic Anhydride **94**

Run	Diene	Amino Protecting Group	Hydroxyl Protecting Group	Conditions[a]	Yield of **112**	Yield of **113**	d.e.[b]
1	**41**	Cbz	$COCH_3$	A	30 %	7 %[c]	46 %
2	**41**	Cbz	$COCH_3$	B	47 %		n.d.
3	**41**	Cbz	$COCH_3$	C	38 %		56 %
4	**41**	Cbz	$COCH_3$	D	42 %		69 %
5	**53**	Cbz	none	C	n.d.		n.d.
6	**54**	Cbz	$COCF_3$	B	n.d.		n.d.
7	**55**	Cbz	$COCMe_3$	A	36 %	9 %	54 %
8	**55**	Cbz	$COCMe_3$	B	55 %		n.d.
9	**55**	Cbz	$COCMe_3$	C	44 %		65 %
10	**56**	Cbz	$SiMe_2$*t*hexyl	A	34 %	15 %[c]	63 %
11	**56**	Cbz	$SiMe_2$*t*hexyl	B	62 %		n.d.
12	**56**	Cbz	$SiMe_2$*t*hexyl	C	46 %		74 %
13	**57**	Cbz	$SiPh_2$*t*Bu	A	39 %	11 %	64 %
14	**57**	Cbz	$SiPh_2$*t*Bu	B	63 %		n.d.
15	**57**	Cbz	$SiPh_2$*t*Bu	C	48 %		76 %
16	**57**	Cbz	$SiPh_2$*t*Bu	D	49 %		83 %
17	**114**	Boc	$COCH_3$	C	18 %		57 %

[a] Reactions were performed under the conditions listed in Scheme 32. [b] "d.e." = diastereomeric excess of **112** over **113**. [c] Only partially purified, "n.d." = not determined.

A pure reference sample of **112b** was synthesised by the acidic hydrolysis of the acetate protected isoindolone **112a** in 96 % yield.

The isolation of isoindolone **112d** was precluded due to the ease with which the trifluoroacetate protecting group hydrolysed during chromatography. Therefore no attempt was made to synthesise **112d** *via* a different route. A set of resonances predominated the ^1H and ^{13}C nmr spectra of the reaction mixture of diene **54** with maleic anhydride **94** in $CDCl_3$ at ambient temperature, and these were assigned to **112d** by comparison with the resonances of isoindolones **112a** and **112c** (Section 2.3.4.).

The most efficient method of isolating the Cbz protected isoindolones **112** was to

perform the Diels-Alder reactions in refluxing CH_2Cl_2 in the presence of activated 4Å molecular sieves. These suppressed the hydrolysis of maleic anhydride **94** during the reaction, and the formation of adducts of the derived maleic acid to the dienes. Although molecular sieves have been implicated in a catalysis of the Diels-Alder reaction,[154] control experiments performed in the absence of molecular sieves, under otherwise identical conditions, proceeded equally fast. The crude reaction mixtures were either extracted with cold saturated $NaHCO_3$ (**112a**, **112c**) and chromatographed or chromatographed without prior extraction. It was most convenient to work the reaction mixtures up as soon as most of the starting diene had been converted, since, at this stage, only a small amount of the isomeric isoindolones **113** had been formed *via* the slow rearrangement of Cbz protected **111**. In this fashion isoindolones **112a**,**c**,**e** and **f** were isolated in yields ranging from 18 to 63%.

For the isolation of the minor Diels-Alder products **113**, dienes were reacted with maleic anhydride **94** in refluxing 1,2-dichlorobenzene in order to increase the relative amount of **113** present in the crude reaction product. When compared to the same reaction performed at ambient temperature, relatively more isoindolone **113** was formed due to an impaired kinetic control at the elevated temperature. It was established that the Diels-Alder reaction of diene **41** with maleic anhydride **94** was under kinetic control and not under thermodynamic control as heating a mixture of isomerically pure isoindolone **112a** at 180 °C showed no evidence of isomerisation. Such an isomerisation may have occurred through a reversible Diels-Alder reaction.

Among the isoindolones only the pivaloyl and the *t*butyldiphenylsilyl protected adducts **113c** and **113f** were isolated in pure form in very modest yields of 9 and 11 %, respectively. The acetate and the *t*-hexyldimethylsilyl protected isoindolones **113a** and **113e** were only partially purified since unidentified impurities with identical retention times complicated chromatography on normal and reverse phase silica. The remaining isoindolones **113b** and **d** containing a free hydroxyl group and a trifluoroacetate group were not isolated as dienes **53** and **54** decomposed

significantly at 180 °C, and no attempt was made to isolate **113g**.

2.3.4. Assignment of the ^{1}H and ^{13}C NMR Spectra of Isoindolones

The most remarkable structural feature of the isoindolones depicted in **Scheme 34** was their rigid cyclic structure, which was reflected in the appearance of the ^{1}H and ^{13}C nmr spectra. Interpretation of scalar proton couplings is a principle tool for obtaining structural information in nmr spectroscopy.[63] In particular, couplings of vicinal protons yield information about the atom framework of a molecule and can often be determined by a simple inspection of the line splitting of well resolved proton resonances or, when this is not possible, by alternative methods.[64]

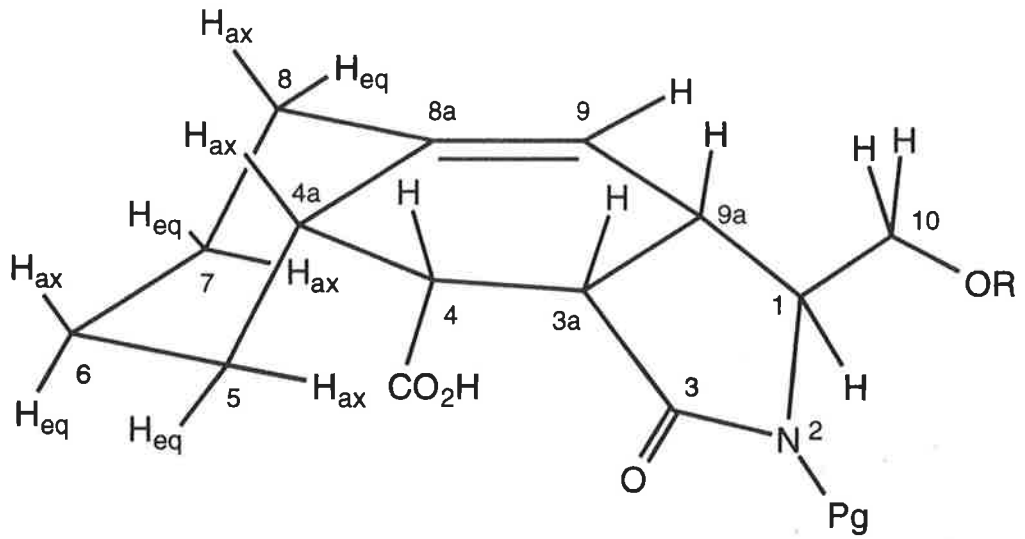
Even proton spectra of small molecules would be intractably complicated if proton coupling would not rapidly attenuate with an increase in the number of bonds that separate the coupled protons. This simple relationship between distance and the strength of the coupling can be strongly modulated in rigid molecules that have fixed dihedral angle due to the Karplus relationship.[65] For example, no couplings may be observed between vicinal protons, whilst long-range couplings between protons separated by 5 bonds may be prominent.[63,68]

With these preliminary remarks in mind, we now assign the ^{1}H and ^{13}C nmr spectra of isoindolones **112** and **113**, which are distinguished by a rigid tricyclic core structure. Isoindolones having the same relative stereochemistry displayed a great similarity in the ^{1}H and ^{13}C nmr data (**Appendix**), as well as H,H COSY[66] and H,C COSY[67] spectra, which were acquired for **112a**, **c**, **e**, **f** and **g** and **113c**, **e**, and **f** (**Appendix**). These similarities aided the spectral assignment, as results obtained from a particular experiment (e.g. selective homonuclear proton decoupling) were easily extended to all isomerically identical isoindolones. For example the spectra of *all* compounds **112** were assigned, even though a particular experiment may have only be performed on a *single* isoindolone in order to aid the assignment.

Firstly, all aromatic, benzylic and olefinic proton and carbon resonances were identified on the basis of their chemical shift.

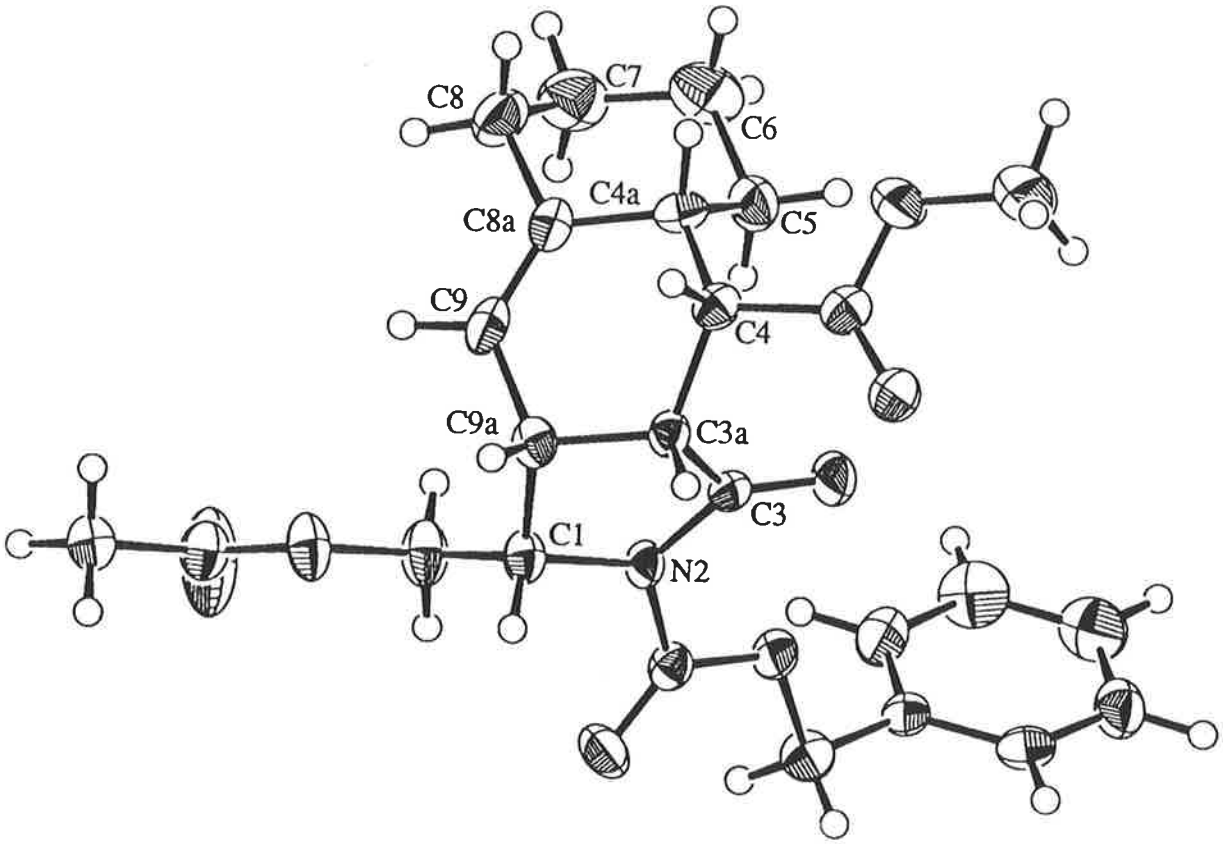
In the case of isoindolones **113** the connectivity of positions 10, 1, 9a, 3a, 4 and 4a could be established partially from the analysis of the multiplet structures of first order spin systems and from the cross-peaks in the H,H COSY 45 spectrum. The observed vicinal coupling between protons H9 and H9a of both pivaloyl protected isoindolones **112c** and **113c** was as small as $J = 1.5$ Hz due to a dihedral angle in the vicinity of 90°. It was measured by selective irradiation of H9a of **112c**, which produced a narrowing of the olefinic resonance from 5 Hz line-width at half height to 3.5 Hz. Even that line-width was still broad for a proton in a fast tumbling molecule and it appeared that further couplings existed to this proton. Those were subsequently identified as allylic couplings by selective irradiation of protons $H8_{ax}$ and H4a, which also led to a sharpened olefinic resonance for both **112c** and **113c**. For the same compounds two homoallylic couplings of $J_{1,5} = 2$ Hz between $H8_{ax}$ and H9a as well as between H4a and H9a were determined in the same fashion. Homoallylic proton couplings through five bonds are documented in the literature[68] and it has been postulated that a rigid collinear allignment of the proton carbon bonds is required. Such a geometrical allignment is indeed observed for the H9aC9a, $H8_{ax}$C8 and H4aC4a bonds of the methyl ester **116** (the synthesis of **116** will be described later) in the crystal structure (**Figure 3**). We expected that the conformation of the tricyclic core structure of *all* isoindolones **112** and **113** in solu-

Figure 2. Three-dimensional Drawing of Isoindolones **112**.



tion would be similar to this solid state structure due its conformational inflexibility. As conformational averaging of vicinal proton coupling constants is not observed in such rigid molecules, the size of the coupling constant was primarily dependant on the fixed dihedral angle between the coupled protons. The Karplus curve[65] describes the dependence of the size of the vicinal proton coupling on the dihedral angle the dihedral angle and reaches a minimum in the proximity of 90°. In fact, a

Figure 3. ORTEP Drawing of Isoindolone **116** analysed by X-ray Diffraction of a single Crystal.



vicinal coupling may not be observed at all when the dihedral angle is in the vicinity of 90°. In selective homonuclear decoupling experiments performed on **112a** and **112g**, in which an adequate digital resolution of the proton signals was ensured (detection limit: $J \approx 0.5$ Hz), no coupling was observed between the vicinal protons H1 and H9a. On the contrary, a coupling of $J = 7$ Hz was measured for the same pair of protons (H1 and H9a) in the isomeric isoindolone **117**. This distinct differ-

ence in the ^{1}H nmr spectroscopic properties of the isomeric isoindolones **112** and **113** provided some evidence in the stereochemical assignment of those isoindolones, which will be discussed in a later paragraph.

As the connectivity between positions 1 and 9a of **112** could not be established *via* proton proton coupling, we resorted to a COLOC experiment,[69] which transfers magnetisation from ^{1}H onto ^{13}C coupled through two or three bonds which is evidenced by a cross-peak between the coupling partners. A COLOC experiment was performed with the methyl ester derivative **117** of isoindolone **112a** and showed a cross-peaks between H9 and carbons in five positions: 1, 3a, 4a, 8 and 9a (**Figures 4** and **5**). Furthermore, H1 and C9a as well as one of the diastereotopic protons H10 and C9a were correlated. Therefore, these results provided unambigous proof of the connectivity between positions 1 and 9a of **117** for which no vicinal proton coupling was observed. It was anticipated that these results were applicable to all isoindolones **112**.

Figure 4. An Expansion of the COLOC Spectrum of Isoindolone **117**

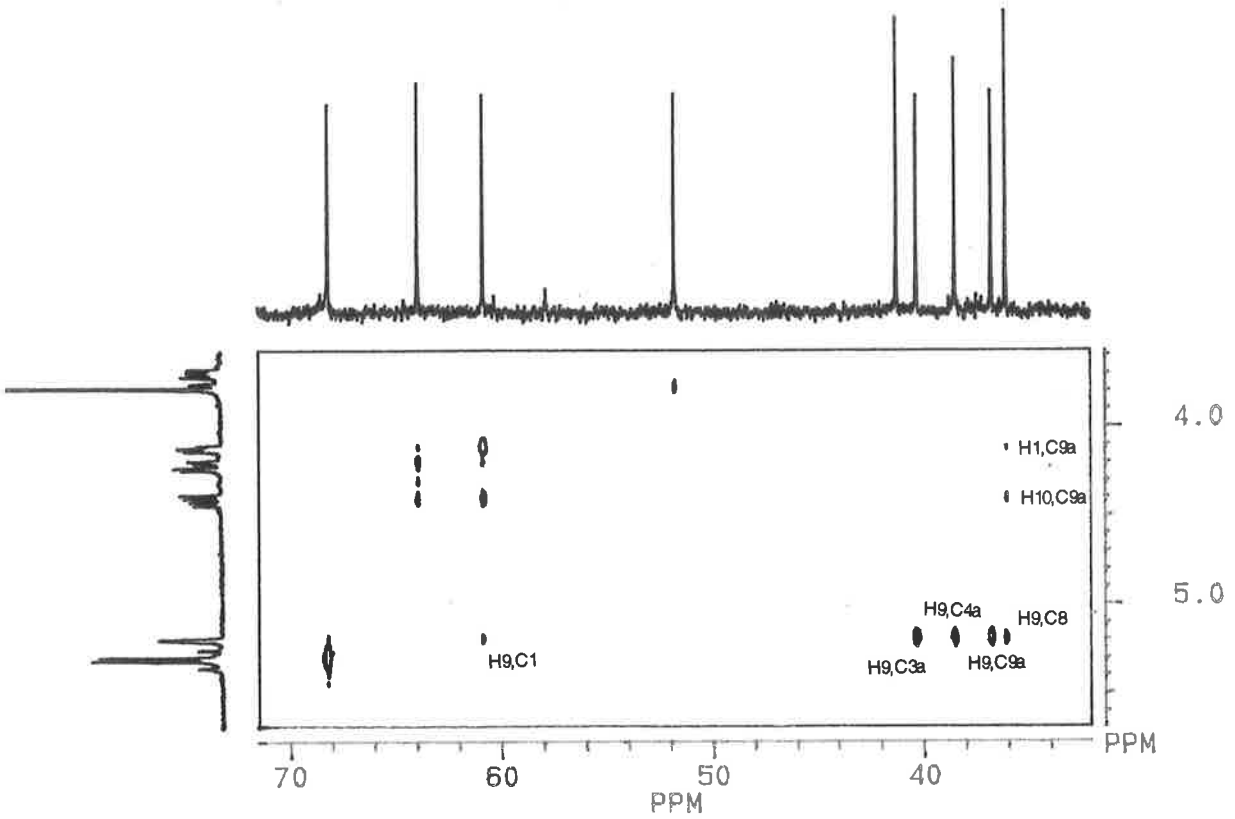
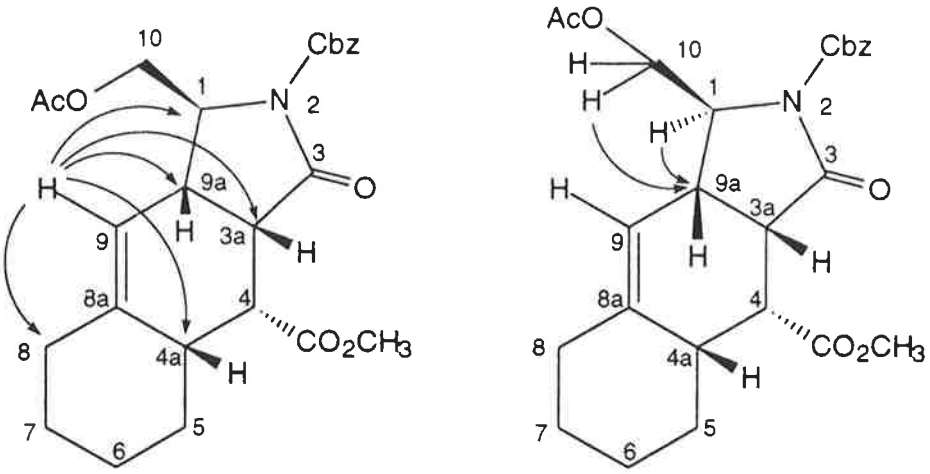


Figure 5. Results of the COLOC Experiment performed on Isoindolone **117**.



The arrows indicate a transfer of magnetisation from a 1H to a 13C spin. Only those transfers are indicated for which the corresponding cross- peak has been marked in the spectrum (see Figure 4).

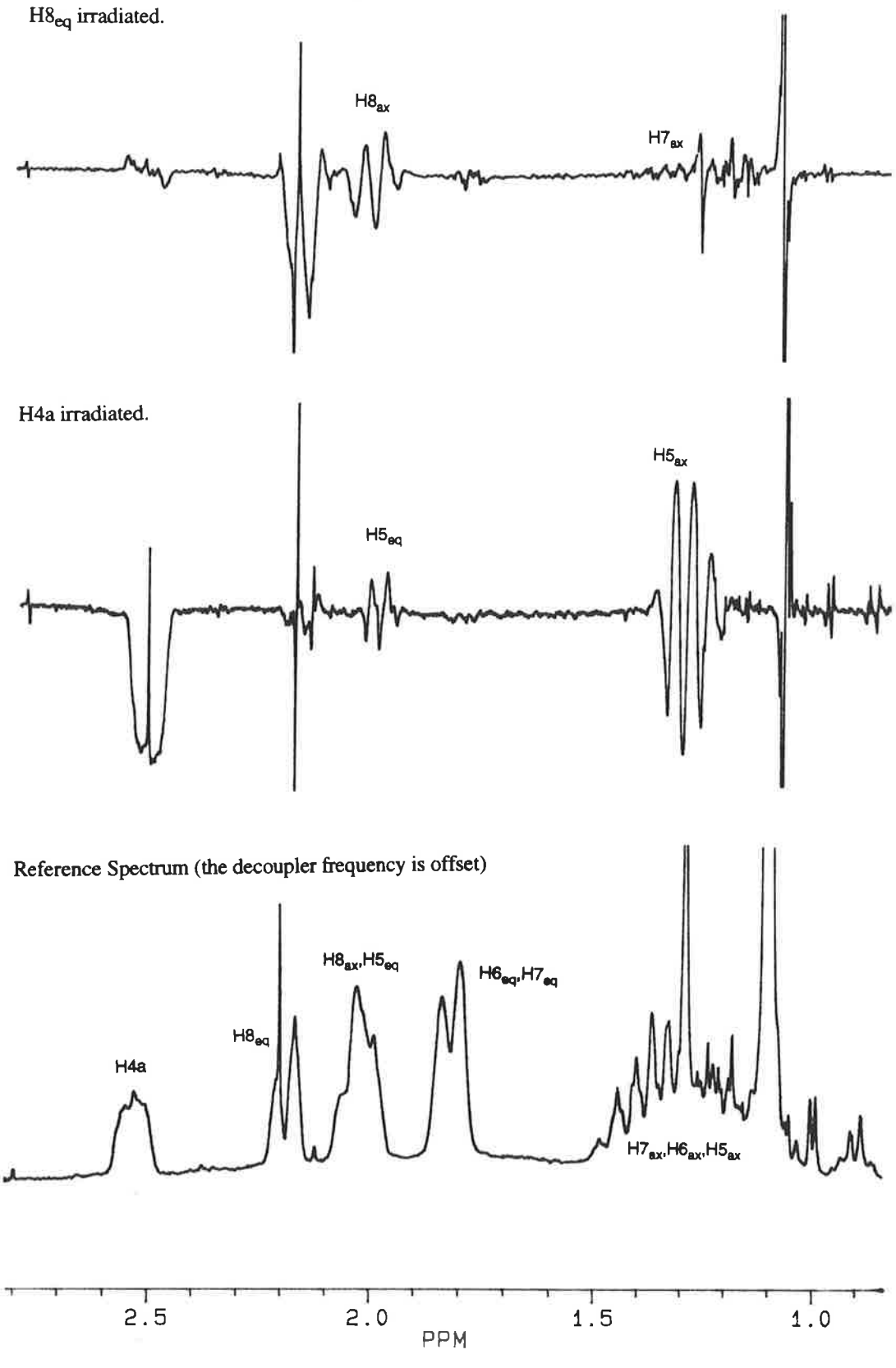
The appearance of protons in positions 5, 6, 7, and 8 was independent of the stereochemistry and practically identical in all isoindolones. At the proton resonance frequency of 300 megahertz all protons of the saturated ring were overlapped in the aliphatic region of the spectrum with the exception of the signals at $\delta = 2.5$ ppm and $\delta = 2.2$ ppm. This allowed for the selective irradiation of the latter two resonances and monitoring the resulting changes in the spectrum by difference spectroscopy.[70]

For example, when H4a of isoindolone **112c** was selectively irradiated, a nOe[71] enhancement of 3% was measured for a signal at $\delta = 2.0$ ppm. This was due to proton $H8_{ax}$, which was therefore in a 1,3-diaxial position as the resonance of the more distant equatorial proton $H8_{eq}$ at $\delta = 2.2$ ppm remained unaltered.

In a decoupling difference experiment selective irradiation of a resonance during the acquisition changes the multiplet structure of the signal of a coupled proton.[70] Subtraction of the decoupled spectrum from the reference spectrum results in a residual signal at the chemical shift of the coupled proton due to the uneven cancellation of the multiplet structures of both spectra. In this fashion selective decoupling of H4a of isoindolone **112f** greatly perturbed the multiplet structure of $H5_{ax}$ ($\delta = 1.3$ ppm, **Figure 6**). A large perturbation, as seen in **Figure 6**, usually results when

the coupling is large as for example in the case of a geminal aliphatic or vicinal di-axial proton pair in a cyclohexane ring adopting a chair conformation.

Figure 6. Decoupling Difference Spectra of Isoindolone **112f**.



Indeed, studies on a model of **112f** indicated a rigid chair conformation of the saturated cyclohexane moiety, which was also observed in the solid state of **116**. An approximate chemical shift of $\delta = 2.0$ ppm was determined for the geminal proton $H5_{eq}$ of **112f** by measuring the position of the second cross-peak of C5 in a H,C COSY spectrum of **112f** (**Appendix**). The signal of $H5_{eq}$ was perturbed to a lesser extend than $H5_{ax}$ by the selective irradiation of H4a in the decoupling difference experiment since an axial-equatorial coupling is significantly smaller than a diaxial coupling in a cyclohexane ring (**Figure 6**).[68]

In the same fashion as protons H5 were identified in the crowded region of the spectrum, protons H7 could be identified by the selective irradiation of $H8_{eq}$ of **112f** in a decoupling difference experiment. The greatest change in the multiplet structure was observed for the geminal proton $H8_{ax}$ ($\delta = 2.0$ ppm, **Figure 6**). However, in this experiment the small changes in the spectrum were more significant. There was a definite, although only small change in the broad signal at $\delta \approx 1.4$ ppm due to a small equatorial-axial coupling to $H7_{ax}$.

By means of a H,C COSY spectrum of **112f** an approximate chemical shift of $\delta = 1.8$ ppm was determined for the geminal proton $H7_{eq}$ of **112f** by measuring the po-sition of the second cross-peak to C7 (**Appendix**).

Although in a vicinal position, this signal ($\delta = 1.8$ ppm) was *not* perturbed by the irradiation of $H8_{eq}$ (**Figure 6**) presumably due to a very small diequatorial coupling (usually 2 Hz$<J_{eq,eq}<$5 Hz).[68]

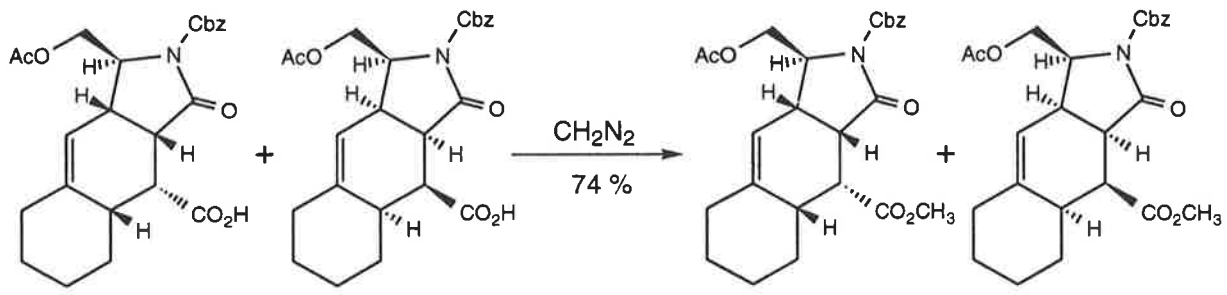
At this stage only resonances arising from the protons and the carbon in position 6 had still to be assigned. The resonances due to H6 overlapped with other proton signals at $\delta = 1.8$ ppm and $\delta = 1.3$ ppm. Whilst the resonance arising from C6 was resolved in the routine ^{13}C nmr spectrum of **112f** ($\delta = 26.8$ ppm) it was overlapped with a cross-peak arising from the *t* butyl group in the H,C COSY spectrum of **112f** due to a lower digital resolution (**Appendix**). We expected to observe two cross-peaks in the H,C COSY spectrum owing to coupling between H6 and C6. Unfortunately, these were obscured by a large cross-peak of the *t*-butyl group. Consistent with this assignment was, however, a doubled cross-peak at $\delta = 1.8/26.8$ ppm and

δ = 1.3/26.8 ppm in the H,C COSY spectrum of the similar t-hexyldimethylsilyl protected isoindolone **112e**, which was in the expected position for H6 and C6. Our assignment of $H6_{ax}$ (δ = 1.3 ppm) and $H6_{eq}$ (δ = 1.8 ppm) was based on ample precedence in the literature, according to which axial protons are comparatively deshielded.[68]

2.3.5. Assignment of the Stereochemistry of Isoindolones

On the basis of Alder's *endo* rule we expected both isoindolones **112a** and **113a** to be derived from *endo* cycloadducts which only differed in the relative stereochemistry at C1 and C9a. From model studies we inferred that only for the isoindolones **112** the dihedral angle spanned by H1 and H9a was close to 90°. We suspected therefore that the major product **112a** had the *trans*-stereochemistry depicted in **Scheme 32** (page 36), while the minor product **113a** had the *cis*-stereochemistry (the terms "*trans*" and "*cis*" refer to protons H1 and H9a being on either opposite faces or on the same face of the five membered ring).

Unequivocal evidence for the stereochemical assignment of **113a** was obtained by the X-ray diffraction analysis of a single crystal of the methyl ester derivative **116** of the minor isoindolone **113a** (**Figure 3**, page 48), which was synthesised as follows. The crude product of the reaction of diene **41** with maleic anhydride **94** in 1,2-dichlorobenzene (Conditions A, **Scheme 32**) was esterified under neutral conditions with diazomethane in a yield of 74 % with regard to diene **41** (**Scheme 36**). During the esterfication no selective kinetic effects were observed since the



112a **113a** **117** **116** (crystalline)

Ratio: 2.6 to 1.0 Ratio: 2.6 to 1.0

Scheme 36

two methyl esters **116** and **117** were produced in the same ratio as the parent carboxylic acids **112a** and **113a**. These ratios were measured by ^{1}H nmr spectroscopy and hplc. When a sample of the crude esters **116** and **117** was dissolved in a minimum amount of methanol, crystals precipitated. Hplc analysis of a solution of a few crystals, of the mother-liquor and of the initially obtained crude product established that a selective and virtually complete crystallisation of the *minor* isomer **116** had occurred.

The solid was recrystallised twice in order to obtain a single crystal suitable for X-ray diffraction analysis.

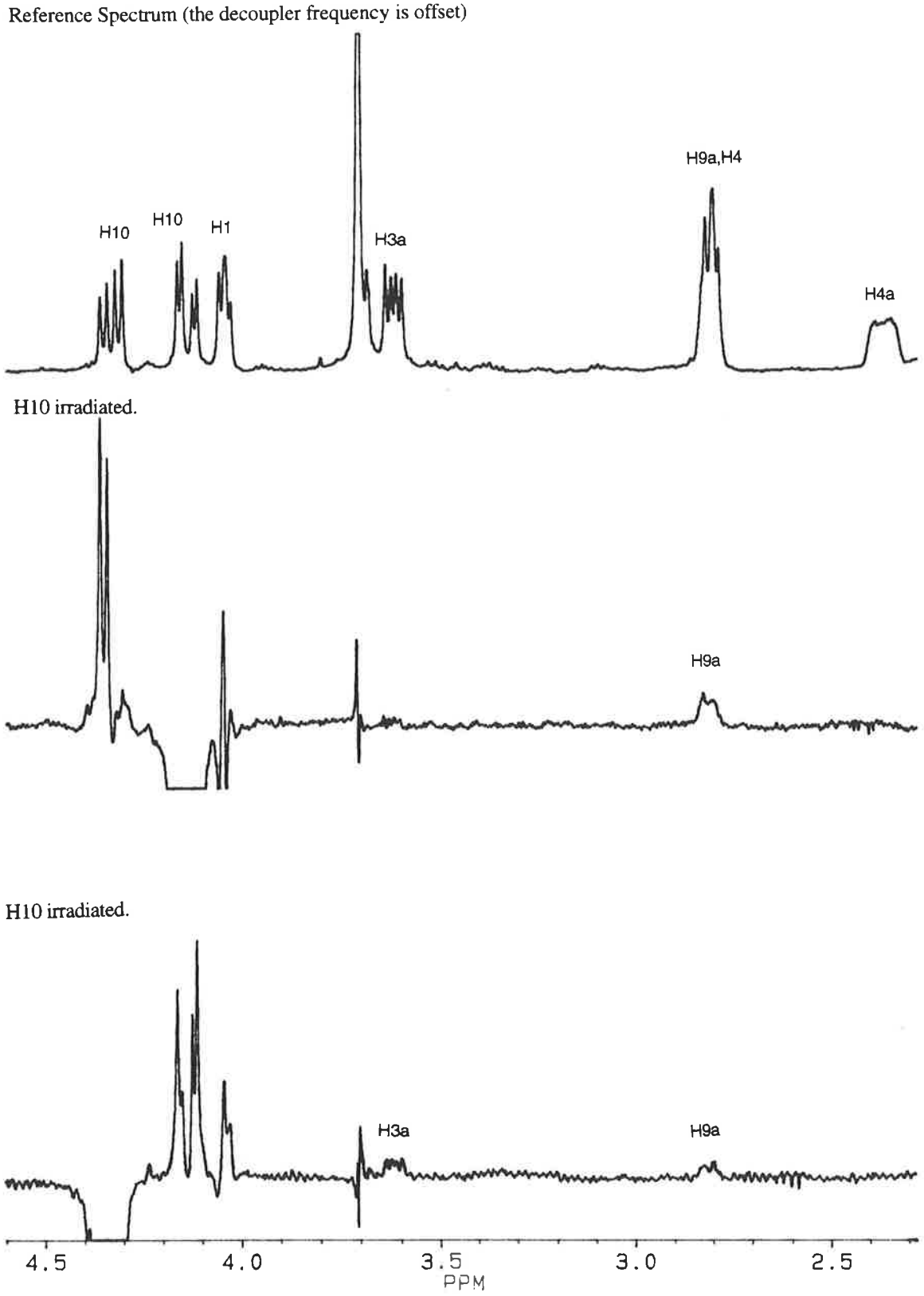
Purification of the mother-liquor by hplc resulted in the isolation of methyl ester **117** in 21 % yield. ^{1}H nmr spectroscopic analysis of this material confirmed that it was identical to the *major* compound present in the crude product of the esterfication reaction. It was evident from the constant isomeric ratios (**Scheme 36**) that no change in the stereochemistry had occurred and we therefore inferred the same stereochemistry for the minor isomers **113a** and **116**.

The first indication of the relative stereochemistry of isoindolone **117** was the absence of any detectable coupling between the vicinal protons H1 and H9a since this indicated a dihedral angle of approximately 90°. On the basis of CPK molecular model studies of isomers of esters **116** and **117** we concluded that a 90° dihedral angle in this position was only concordant with the *trans-endo*-stereochemistry for **117**. This is also in agreement with literature precedence of a study of 1,3-dienes similar to ours where the stereochemistry of the major Diels-Alder adduct was assigned on the basis of X-ray diffraction analysis.[62]

However, we wished to gather independent evidence for the stereochemical assignment of ester **117**. To this end we performed steady-state nOe difference spectroscopy on the methyl ester **117**.[70,71] Selective irradiation of anyone of the diastereotopic protons in position 10 produced nOe enhancements of less than 1 % for H9a and, even more importantly, for H3a (**Figure 7**). These nOes suggested that the acetoxy substituent and H9a and H3a were on the same face of the five-membered ring which was consistent with the assignment of the *trans-endo*-stereo-

chemistry to **117**. Although at least in theory the enhancement of the signal at $\delta = 2.88$ ppm could arise from a nOe for anyone of the overlapping protons H4 and

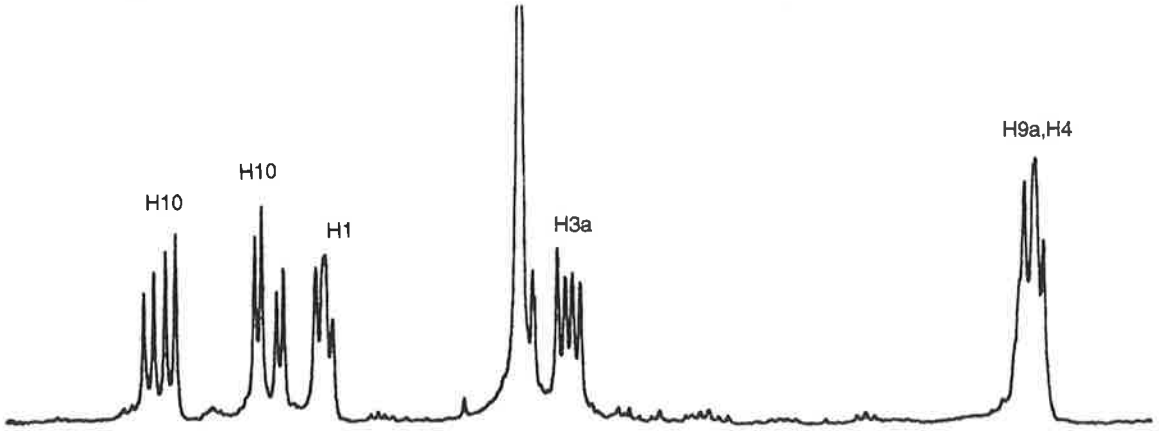
Figure 7. NOE Difference Spectra of Isoindolone **117**.



H9a, it was highly improbable that H4 contributed to the signal enhancement as it was too distant from the irradiated protons H10.

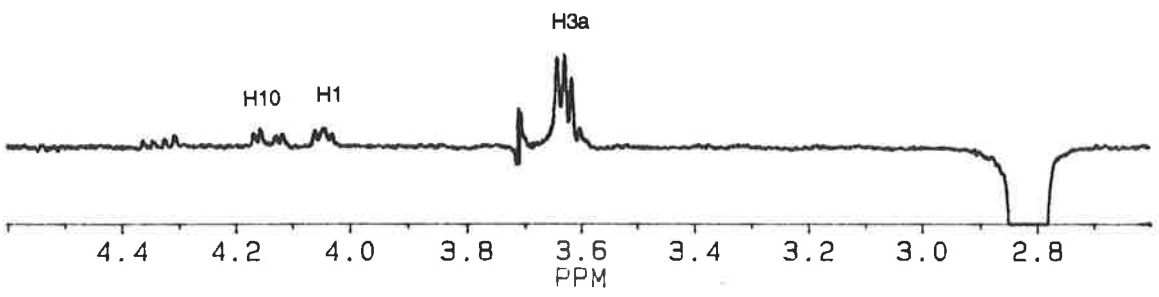
Figure 8. NOE Difference Spectra of Isoindolone **117**.

Reference Spectrum (the decoupler frequency is offset).



H3a irradiated.

H9,4a irradiated.



NOe enhancements of less than 1 % that were complementary to those measured in the previous experiment were observed for H10 upon selective irradiation of H3a or H9a of **117** (**Figure 8**).

The stereochemical assignment was extended to all isoindolones that had similar ^{1}H and ^{13}C nmr spectra. As the ^{1}H and ^{13}C nmr data of isoindolones **112** and **117** was very similar, they were listed for a more convenient comparison in tables (**Appendix**).

2.3.6. The π-facial Selectivity of Dienes in the Diels-Alder Reaction

Bearing in mind that the rearrangement of the minor Cbz protected inferred cyclo-adducts **111a-f** into the corresponding *cis*-isoindolones was slow at ambient temperature (Section 2.3.2.), we ensured their complete conversion by refluxing the crude reaction product, following the complete conversion of the starting diene, in 1,2-dichlorobenzene for 1 hour. Thereafter the ratios of *trans* to *cis*-isoindolones were interpreted as a measure for the π-facial selectivity of the respective dienes. Ratios of isoindolones were determined by hplc, ^{1}H and ^{13}C nmr spectroscopy, and are expressed as the diastereomeric excess (d.e.) of *trans* over *cis*-isoindolone in **Table 2** (page 44).[73] As an exception the π-facial selectivities of the Diels-Alder reactions of the trifluoroacetate protected diene **54** and the unprotected diene **53** was not determined since significant amounts of unidentified products complicated the analysis of the reaction mixture. These unidentified compounds may have been formed by reactions of the free hydroxyl or the trifluoroacetate groups.

The ratio of the pivaloyl protected isoindolones **112c** and **113c** was measured by integration of the well-separated nmr signals of H3a and H10. This method of analysis could not be extended to silyl ether protected isoindolones as the proton signals of isoindolones **112e** and **113e**, as well as those of **112f** and **113f** were overlapped and hplc analysis was unsuccessful. Signal overlap was not usually a problem in ^{13}C nmr spectra owing to the greater chemical shift dispersion and the

tertiary olefinic resonances were well-separated by approximately $\Delta\delta = 4$ ppm in both cases.

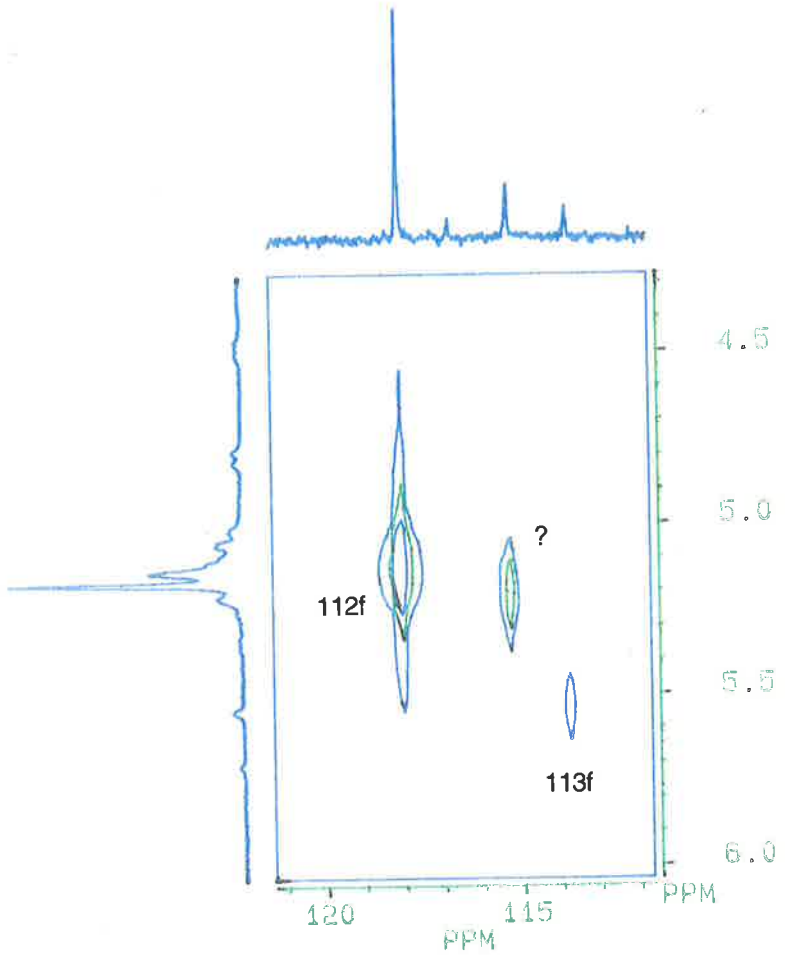
In order to obtain sufficiently accurate isomeric ratios by ^{13}C nmr spectroscopy, nOe enhancements from proton decoupling and the effects of possibly different T1 relaxation times for the compared ^{13}C signals had to be minimised. Applying proton decoupling only during the acquisition time and addition of a relaxation agent (chromium(III) acetylacetonate) were effective measures to suppress nOes from protons onto carbon spins and to accelerate the relaxation of the later. Under these conditions, the T1 relaxation times of the tertiary olefinic ^{13}C spins were measured to be less than 200 milliseconds by the inversion recovery method and a delay period of 2 seconds between scans was deemed adequate for a thermal eqilibrium to re-establish.[76] Fids were *not* multiplied with a window function before a Fourier transformation was performed.

The olefinic section of the ^{13}C nmr spectrum of the crude reaction product of the *t*-butyldiphenylsilyl protected isoindolones **112f** and **113f** revealed the presence of two other minor resonances at $\delta = 116.8$ ppm and at $\delta = 115.2$ ppm. Our assignment of the signal at $\delta = 113.8$ ppm to the *cis*-isoindolone **113f** was supported by a H,C COSY spectrum performed on the same sample that was quantitatively analysed (**Figure 9**). A cross-peak of the latter resonance to a proton at $\delta = 5.5$ ppm and a comparison with the spectra of **113f** that were acquired in the absence of chromium(III) acetylacetonate confirmed that the tertiary olefinic ^{1}H and ^{13}C chemical shift values of **113f** were hardly altered by the presence of the paramagnetic metal complex. The origin of the other minor resonance $\delta = 116.8$ ppm and at $\delta = 115.2$ ppm was not be identified.

The intensity of the tertiary olefinic resonances at $\delta = 118.0$ ppm (**112f**) and at $\delta = 113.8$ ppm (**112f**) was compared in the spectrum of the crude mixture acquired in the presence of chromium(III) acetylacetonate and interpreted as the ratio of **112f** to **113f** (**Figure 10**).

Several trends concerning the π-facial selectivity of dienes in the Diels-Alder reac-

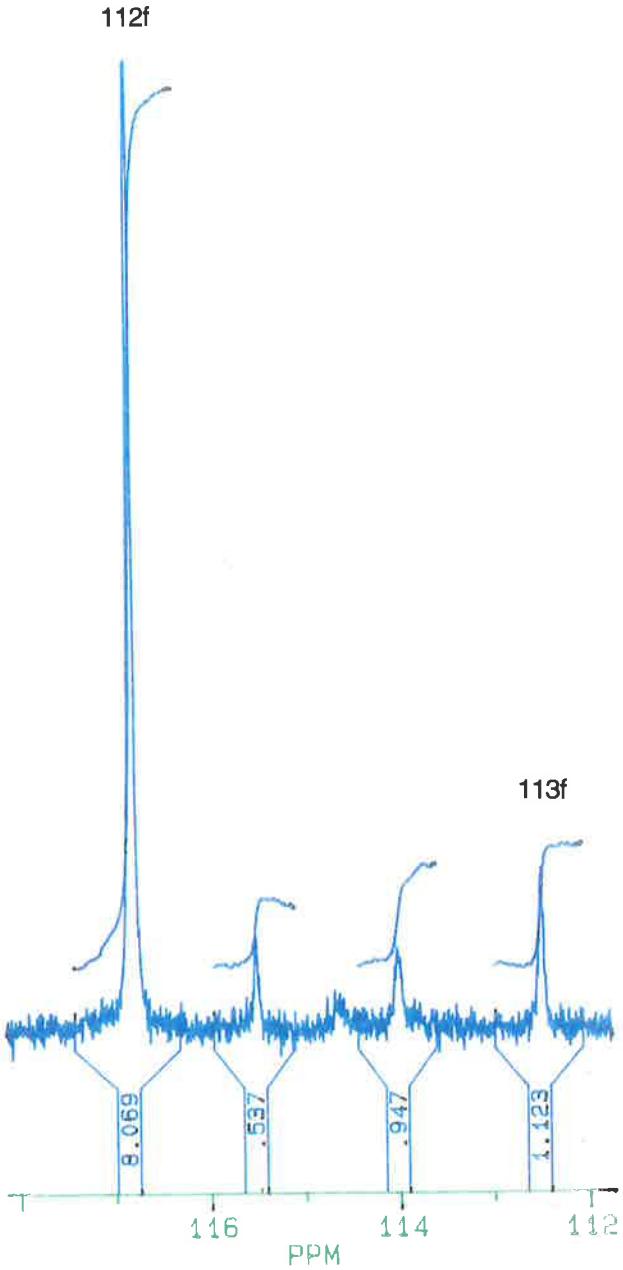
Figure 9. The olefinic region of an H,C COSY spectrum of the crude product obtained from the Diels-Alder reaction of diene **57** with maleic anhydride **94** acquired in the presence of $Cr(acac)_3$.



tion with maleic anhydride **94** can be stated when **Table 2** (page 44) is inspected. Firstly, larger hydroxyl protecting groups led to a gradual increase in the π-facial selectivity of the Diels-Alder reaction. In particular, the acetate protected diene **41** had a lower π-facial selectivity than the pivaloyl protected diene **55** (entries 3 and 9, **Table 2**). A plateau of d.e. ≈ 75 % was reached with the very voluminous silyl ethers **56** and **57** (entries 12 and 15, **Table 2**). These results clearly implicate the hydroxyl protecting group in the steric shielding of the 1,3-diene moiety.

Secondly, the nature of the alkyl portion of the carbamate protecting group appeared to have no influence on the π-facial bias of the investigated dienes (entries 3 and 17, **Table 2**), suggesting that the carbamate group was directed away from the site of reaction in the transition state.

Figure 10. The olefinic region of an ^{13}C spectrum of the crude product obtained from the Diels-Alder reaction of diene **57** with maleic anhydride **94** acquired in the presence of $Cr(acac)_3$.



Thirdly, the π-facial bias of the investigated dienes deteriorated with an increase in the reaction temperature from ambient temperature to 180 °C, as it is expected for a reaction conducted under kinetic control. Nevertheless, a d.e. of approximately 64 % for the reaction of the siloxy protected dienes **56** and **57** indicated that the π-facial selectivity was high even at the elevated temperature (entries 10 and 13, **Table 2**).

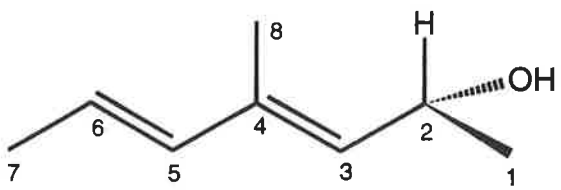
Finally, a change in the reaction solvent from $CDCl_3$ to a saturated ethereal solution of $LiClO_4$ led to a slight increase in the π-facial selectivity (entries 3 and 14 as opposed to entries 4 and 16, **Table 2**). Such an effect has been previously reported.[62,84]

2.3.7. A Model for the π-facial Bias of 1,3-Dienes

A significant number of publications on the Diels-Alder reaction of acyclic chiral dienes have appeared in the literature and several explanations for their π-facial selectivity have been advanced. Essentially all rationales focussed on an identification of the factors stabilising conformations that are accessed by a rotation of the allylic C2-C3 bond as this was expected to be a key-determinant for the π-facial selectivity.

Models based on stereo-electronic factors have successfully been applied to rationalise the π-facial selectivity of *conformationally rigid* dienes such as cyclopentadienes that are substituted with a heteroatom in position 5. Nevertheless, the literature opinion about *which* stereoelectronic factors are of greatest significance still appears divided (Introduction). Significant to this work, however, is the idea that stereo-electronic factors were also implicated in the control of the transition state conformation of acyclic chiral dienes similar to those discussed in this chapter.[54]

A different model was proposed for some acyclic 1,3-dienes in order to explain the π-facial selectivity in Diels-Alder reactions.[77] Dienes bearing a second substituent in the *ortho*-position, such as **118**, belong to this category. These dienes are distinguished from those with only a small hydrogen atom in the same position by a clear conformational preference in the ground state with regard to a rotation of the allylic C2-C3 bond.[77,78]



118

In the preferred C8-H2 eclipsed conformation of **118**, which is depicted above, unfavourable non-bonding interactions between the substituents on C4 and on C2 are minimised to an extent that other rotamers with regard to a rotation around the allylic C2-C3 bond are only sparsely populated. These non-bonding interactions in such systems are commonly referred to as 1,3-allylic strain.[78]

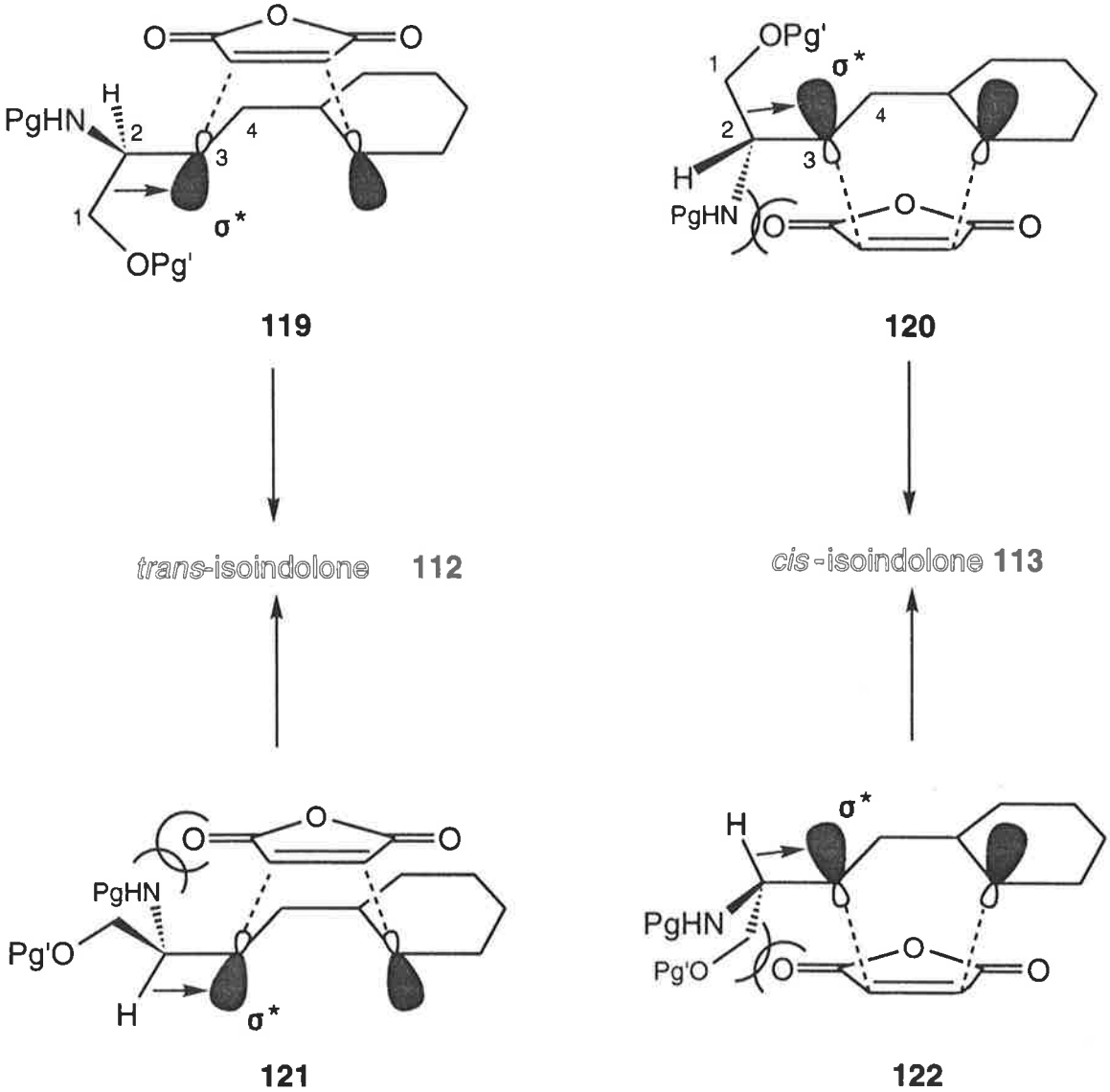
We now wish to discuss these alternative models for the π-facial selectivity of dienes reported in this work.

Stereo-electronic Factors: the "Cieplak Model"

According to the "Cieplak model" (Introduction) certain stabilising orbital interactions *in the transition state* lead to an unexpected degree of conformational control with regard to rotation around the allylic carbon-carbon bond of acyclic 1,3-dienes.[54] In particular, a collinear alignment of the emerging σ*–orbital on C3 with a relatively electron-rich σ-orbital, such as that of the C2-H2 or C1-C2 bond, was required for an effective transfer of electron density (**Scheme 37**).[54,56] Any deviation from this exactly collinear arrangement of the mentioned orbitals led to a less efficient orbital overlap and consequently less hyperconjugational stabilisation of such conformations in the transition state. The alternative collinear alignment of the C2-N bond with the emerging σ*-orbital was unfavourable as the comparatively electron-deficient C2-N bond was less apt to donate electron density. As both faces of the planar π-electron system of diene depicted in **Scheme 37** were non-equivalent, four different transition state conformations emerged that allowed for an efficient stabilisation of one of the emerging σ*-orbitals *via* hyperconjugation (**119-122**).

We posed the question whether the experimentally observed increase in the π-facial selectivity of dienes depicted in **Scheme 37** with an increase in the size of the hydroxyl protecting group (**Table 2**, page 44) could be explained by invoking transition states **119-122**. It was immediately apparent, that structures **119** and **120** were *not* affected by a change in the size of the hydroxyl protecting group, as steric interaction between the hydroxyl protecting group and the dienophile was

Application of the "Cieplak Model" to the Present Study



Donation of electron density into the developing σ*-orbital on C3 was postulated to control the rotation of the C2-C3 bond in the transition state of Diels-Alder reactions of heteroatom substituted dienes according to the "Cieplak model". The Pg' groups of the dienes reported in this study were H, Ac, $COCMe_3$, $SiMe_2$*t*hexyl, $SiPh_2$*t*Bu and Pg were either Boc or Cbz.

Scheme 37

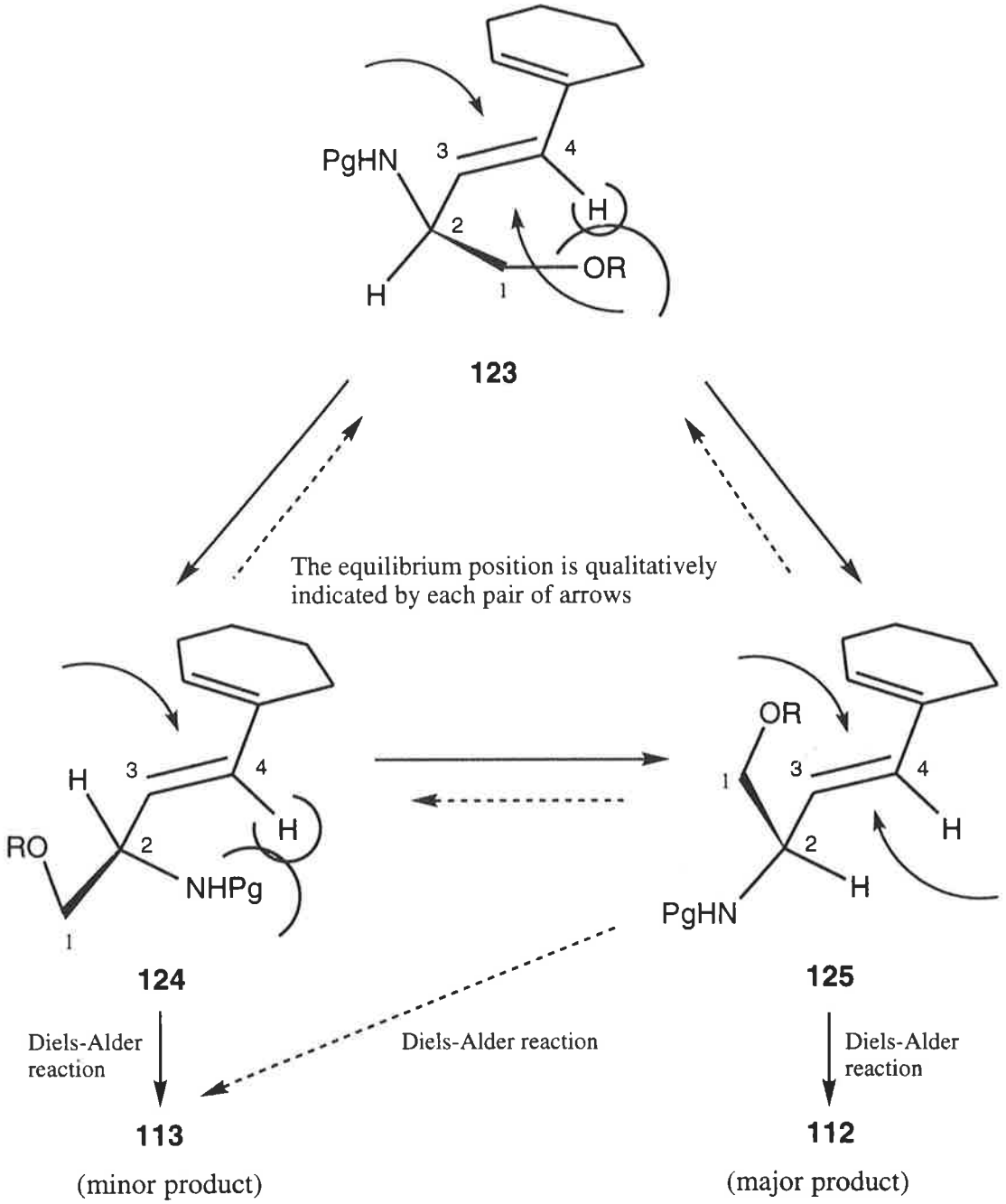
absent. The π-facial selectivity *was*, however, affected by a change in the size of the hydroxyl protecting group and structures **119** and **120** had therefore to be excluded as *major* contributing conformations. On the other hand structures **121** and **122** appeared to be less stable than **119** owing to severe steric interactions between a carbonyl group of maleic anhydride **94** and the carbamate substituent in **121** or the CH_2OPg group in **122**.

It is difficult to see how a model based entirely on conformations **121** and **122** could account for the pronounced increase in the π-facial selectivity with an increase in the size of the hydroxyl protecting group of the diene.

The Minimisation of non-bonding Interactions: 1,3-Allylic Strain

Invoking 1,3-allylic strain as a factor determining the π-facial selectivity of dienes reported in this thesis required a detailed conformational analysis. Fortunately, a considerable amount of work has been published on allylic systems that are comparable to our dienes. For example, nmr spectroscopic evidence[80] and recent *ab initio* molecular orbital calculations[79] revealed that the *eclipsed* conformations of the carbon-carbon double bond with a substituent on the allylic carbon are generally lower in energy than the alternative staggered arrangements. Applying the literature results to our dienes, we could draw three presumed low energy ground-state conformations by rotating the allylic C2-C3 bond that were expected to adequately represent the conformational space (**Scheme 38**). It is interesting to note that conformation **124** is the solid-state conformation of diene **41** (**Appendix**).
The next question we asked concerned the position of the equilibrium between the conformations **123** to **125**. It was predicted that a conformation was relatively more populated when non-bonding interactions between H4 and the eclipsed substituent on the allylic carbon were minimised. As the size of the eclipsed substituent decreases in the order $CH_2OPg > NHCbz > H$, rotamer **125** was most frequently populated followed by **124** and then by **123**. Although we obtained no independent evidence, *ab initio* calculations on closely related systems were published in support of this proposed order of relative stability .[81]

Under the premise that the same order of stability applied for the transition state conformations of dienes depicted in **Scheme 38**, this model predicted the correct stereochemistry for the major Diels-Alder product **112**. In the predominant conformer **125** one face of the planar 1,3 diene unit was shielded against the approach of maleic anhydride **94** by the hydroxyl protecting group, whilst the other face could be accessed leading to the formation of *trans*-isoindolone **112** because the carba-



Factors influencing the rotation of the C2-C3 allylic bond in the ground state may also influence the transition state conformation. Curved arrows indicate the accessible faces of the planar 1,3-diene moiety. The Pg' groups of the dienes reported in this study were H, Ac, $COCMe_3$, $SiMe_2t$hexyl, $SiPh_2t$Bu and Pg were either Boc or Cbz.

Scheme 38

mate group was directed away from the 1,3-diene moiety. This was consistent with dienes **41** and **58** displaying the same π-facial selectivity notwithstanding a change of the amino protecting group from Cbz to Boc (entries 3 and 17, **Table 2**,

page 44). Furthermore, studies on CPK molecular models of diene **41** indicated that the alkyl portion of the carbamate group could not be located in the proximity of the 1,3 diene unit without changing the hybridisation of the imide nitrogen from sp^2 to sp^3 and introducing considerable strain into the molecule.

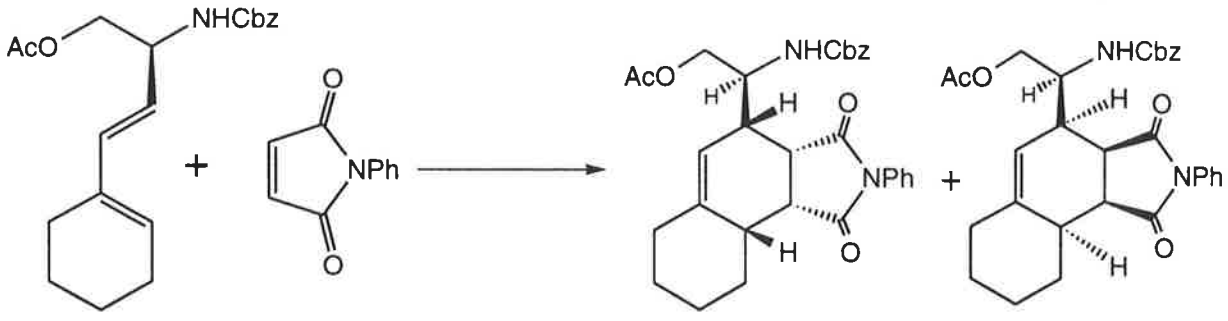
Diene confomation **124** was distinguished by the highest π-facial selectivity in favour of the formation of *cis*-isoindolone **113**. This was a result of the differential steric shielding of the diene moiety exerted by H2 as opposed to the hydroxyl protecting group. However, as conformation **124** was expected to be less frequently accessed during the transition state than **125**, isoindolone **113** was *not* the major reaction product. Diene confomation **123** was presumably least stable and therefore least contributing to the transition state.

Most importantly, this model based on the minimisation of 1,3-allylic strain accounted for the observed increase in the π-facial selectivity with an increase in the size of the hydroxyl protecting group. A larger hydroxyl protecting group was anticipated to lead to a higher π-facial bias of the predominant confomer **125** and therefore to the formation of more *trans* at the expense of *cis*-isoindolone. Small hydroxyl protecting groups, such as the acetate of diene **41**, could easily be in positions removed from the 1,3-diene unit by a rotation around the C1-C2 bond. The hydrogen atom in position 1 was too small to effectively shield the 1,3-diene unit from an incoming reagent in confomer **125**. With larger hydroxyl protecting groups a rotation around the C1-C2 bond became increasingly less efficient in placing the protecting group in a position where it would not shield the 1,3-diene moiety. However, even for the silyl ether protected dienes **56** and **57** a plateau of d.e. = 75 % was apparently approached and a very high diastereoselectivity (e.g. with a d.e. > 95 %) was not observed because *both* diene conformations **124** and **125** (and conformations similar to **124** and **125**) contributed to the transition state. An increase in the steric bulk of the hydroxyl protecting group would also influence the π-facial selectivity of confomation **124**, however, a smaller effect on the overall diastereoselectivity was anticipated since **124** contributed considerably less to the transition state.

When the Diels-Alder reaction of dienes **41** and **57** with maleic anhydride **94** was conducted in ether saturated with $LiClO_4$ coordination of the carbonyl groups of **94** by lithium ions was feasible. Such a coordination would not only have activated **94** towards the cycloadditon by lowering the energy of the LUMO but also made the carbonyl group more sterically demanding by increasing the effective size of the dienophile. Conceivably such an increase in the size of the dienophile led to a better π-facial diastereoselectivity of conformation **125**, as the hydroxyl protecting group provided better steric shielding of the 1,3-diene moiety against the approach of a comparatively larger lithium coordinated dienophile.

2.3.8. Diels-Alder Reaction with *N*-Phenylmaleimide 98

In order to demonstrate that the rearrangement of the initial adducts **110** and **111** (**Scheme 34**, page 39) could be avoided by an appropriate choice of the dienophile, diene **41** was reacted with *N*-phenylmaleimide **98**,[82] which was structurally very similar to a maleic anhydride **94** (**Scheme 39**). The isomeric products **126** and **127** were formed in a ratio of 4.4 to 1.0 which was determined by hplc analysis of the crude reaction mixture and comparison of the intergrals of the resonances at $\delta = 5.50$ ppm and $\delta = 5.60$ ppm in the ^1H nmr spectrum of the crude mixture. As expected the cyclic adducts **128** and **129** showed no propensity to rearrange in a manner analogous to the intial adducts **110a** and **111a** due to the relative stability



41 **98** **126** **127**

(ratio: 4.4 to 1.0 in favour of **126**)
(combined yield: 53 %)

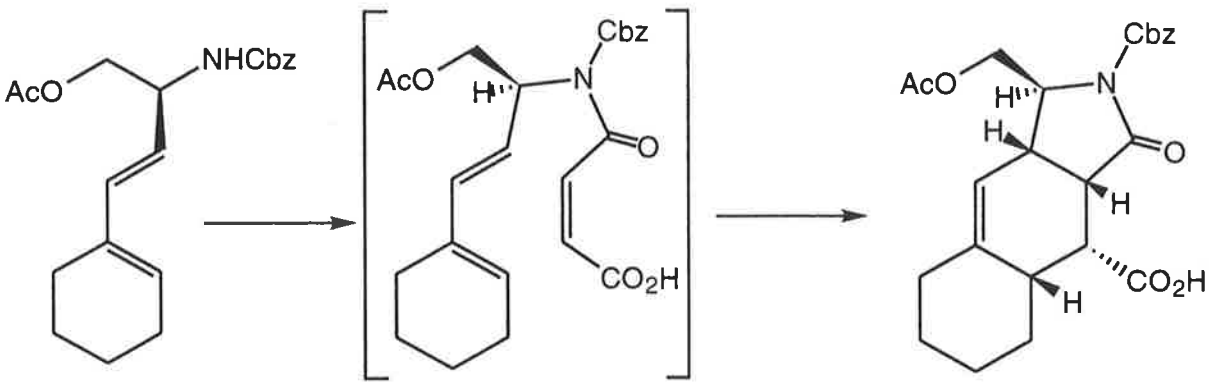
Conditions: **98** (3 equiv.), a 1.0M solution of **41** in $CDCl_3$, 25 °C, 4 d,

Scheme 39

of the imide functionality. On the basis of the structural similarity of the dienophiles **94** and **98** we expected the same sense of π-facial selectivity for diene **41** in Diels-Alder reaction with both dienophiles.[83] Consequently, the stereochemistry of **126** and **127** (**Scheme 39**) was proposed on the basis of the known stereochemistry of cycloadducts **110a** and **111a**. It was interesting to note that the diastereomeric excesses of 54 % was very similar to the value (d.e. = 57 %) determined for the analgous reaction performed with maleic anhydride **94**. Both cycloadducts **126** and **127** were separated by hplc.

2.3.9. The intramolecular Diels-Alder Reaction

Isoindolones **112** and **113** were formed by an *intermolecular* Diels-Alder reaction of the corresponding diene and maleic anhydride **94** (Section 2.3.2.) rather than by an *intramolecular* Diels-Alder reaction. We were interested in exploring the *intramolecular* reaction mode further in order to gauge the effect on the π-facial selectivity. A conceptually simple approach was the acylation of the amide nitrogen of diene **41** with maleic anhydride **94** to form a triene **128**, which was expected to cyclise readily.



41 **128** **112a**

intermediate triene (not isolated)

(major product, yield: 8 %)

\+ several unidentified by-products

Conditions: 1) LDA in THF at -50 °C 2) Maleic anhydride **94**, DMPU, let warm to 0 °C

Scheme 40

In order to promote the acylation of an amide nitrogen, diene **41** was deprotonated at -50 °C and reacted with maleic anhydride **94** (**Scheme 40**). A significant amount of starting diene **41** was still present when the reaction product was analysed by ^{1}H nmr spectroscopy. As we expected triene **128** to be acidic, acidic and neutral reaction products were separated by extraction with saturated $NaHCO_3$. Whilst the only neutral product was unchanged diene **41**, the acidic portion of the reaction product revealed several compounds. *Trans*-isoindolone **112a** was identified, by ^{1}H and ^{13}C nmr spectroscopic and hplc analysis of the crude reaction mixture, as the major component and was subsequently isolated in a very modest yield of 8 %. Furthermore it was evident, that the acetate of **112a** was partially removed as **112b** was isolated from the reaction mixture presumably due to a partial hydrolysis during the extractive work-up. A significant amount of an unknown compound, which appeared to be an isomer (possibly with an *exo*-stereochemistry) of isoindolone **112**, was formed. A sample of this unknown compound could not be isolated in a sufficiently pure form to allow for a complete characterisation. The ^{1}H spectrum of the partially purified material was, however, inconsistent with a triene since only one olefinic signal was observed. In fact none of triene **128** was detected presumably due to a rather rapid intramolecular Diels-Alder reaction that occurred at or below 0 °C (the work-up was performed with cooled reagents).

A careful hplc analysis of the crude acidic extracts revealed that *none* of the diastereomeric *cis*-isoindolone **113a** was present. It may have been the case that the acetate group of **113a** was completely removed and that this was the reason for the absence of **113a**. As the hplc analysis of the crude acidic extracts revealed other unidentified material in minor amounts it may well have been possible that the hydrolysed isoindolone **113b** was formed.

In summary, the intramolecular version of the Diels-Alder reaction of diene **41** with maleic anhydride **94** appeared less selective than the intermolecular version due to the formation of a significant amount of unidentified by-products and was, from a

synthetic viewpoint, not promising. Therefore we did not attempt to improve on the reaction conditions.

2.3.10. Summary

Structurally related 1,3-dienes bound to an asymmetrically substituted carbon atom were treated with maleic anhydride **94** or *N*-phenylmaleimide **98** under a variety of conditions. The initial Diels-Alder adducts **110** and **111** were not isolated as they spontaneously rearranged into isoindolones **112** and **113**. By careful experimentation we established that the rate of these rearrangements was dependent on the relative stereochemistry of the initial cycloadducts and the nature of the carbamate protecting group. The π-facial selectivity of the Diels-Alder reactions was very carefully determined by analysing the isomeric isoindolones by several methods. It was possible to increase in the π-facial selectivity by using larger protecting groups for the homoallylic hydroxyl function and by performing the cycloaddition reaction in the presence of a mild Lewis-acid, such as lithium ions. These effects were rationalised by proposing a model based on steric rather than stereoelectronic effects. As others did before us,[77] we propose that 1,3-allylic strain governs the rotation of the allylic carbon-carbon bond that linked the asymmetrically substituted carbon atom and the 1,3-diene portion. These conformational factors are expected to translate to the transition state and are consequently an important parameter in the asymmetric induction exerted by the stereogenic center.

Chapter 3: The Hydrostannation of Alkynes

We intended to explore the hydrostannation of suitably protected propargylglycine derivatives in order to synthesise α-amino acid derivatives featuring a vinylstannane in their side-chain (Chapter 3), which could further be elaborated *via* Stille reactions (Chapter 4).

3.1. Introduction

Vinylstannanes are useful synthons for a variety of transformations. They can be converted into the corresponding vinyllithium species,[85] which can also be used to generate a variety of vinylorganometallic reagents. In addition, they will react readily with halogens to give vinyl halides.[86] Furthermore, vinylstannanes are frequently employed as coupling partners in Stille reactions.[87,127] The common feature of the transformations of vinylstannanes mentioned thus far is their stereospecificity. In other words, the stereochemistry of products is completely controlled by employing the vinylstannane with the desired stereochemistry. It therefore transpires that the stereoselective preparation of isomerically pure vinyllstannanes is a prime objective in organic synthesis. The most important synthetic methods will be discussed below.

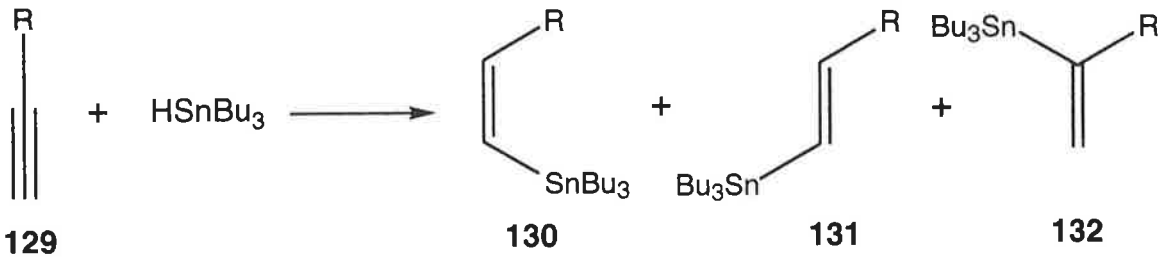
3.1.1. The Hydrostannation of Alkynes

The hydrostannation of terminal and internal alkynes with commercial tributyltinhydride is the most general method of preparing isomeric vinylstannanes.[88]

Other methods which have not been as well exploited include the chromium(III) mediated reaction of dibromomethyltributylstannanes with aldehydes[89] and the metallostannation of alkynes.[90] Whilst the latter methods may be incompatible with substrates that are sensitive to basic or nucleophilic species, the hydrostannantion of alkynes tolerates a wide range of functional groups.

Traditionally the hydrostannation of terminal alkynes has been performed under free radical conditions, e.g. by heating tributyltin hydride with the alkyne in the ab-

sence of solvent.[91] However, more recently, the transition metal catalysed hydrostannation has evolved as an even milder and more general method.[92] Both methods can be complementary with regard to the stereochemistry of the product vinnylstannanes since the free radical induced version generally affords a mixture of *E*- and *Z*-isomers,[91] as compared to a mixture of *E*-1,2-disubstituted and 1,1-disubstituted isomers that are the expected products of the transition metal catalysed version (**Scheme 41**).

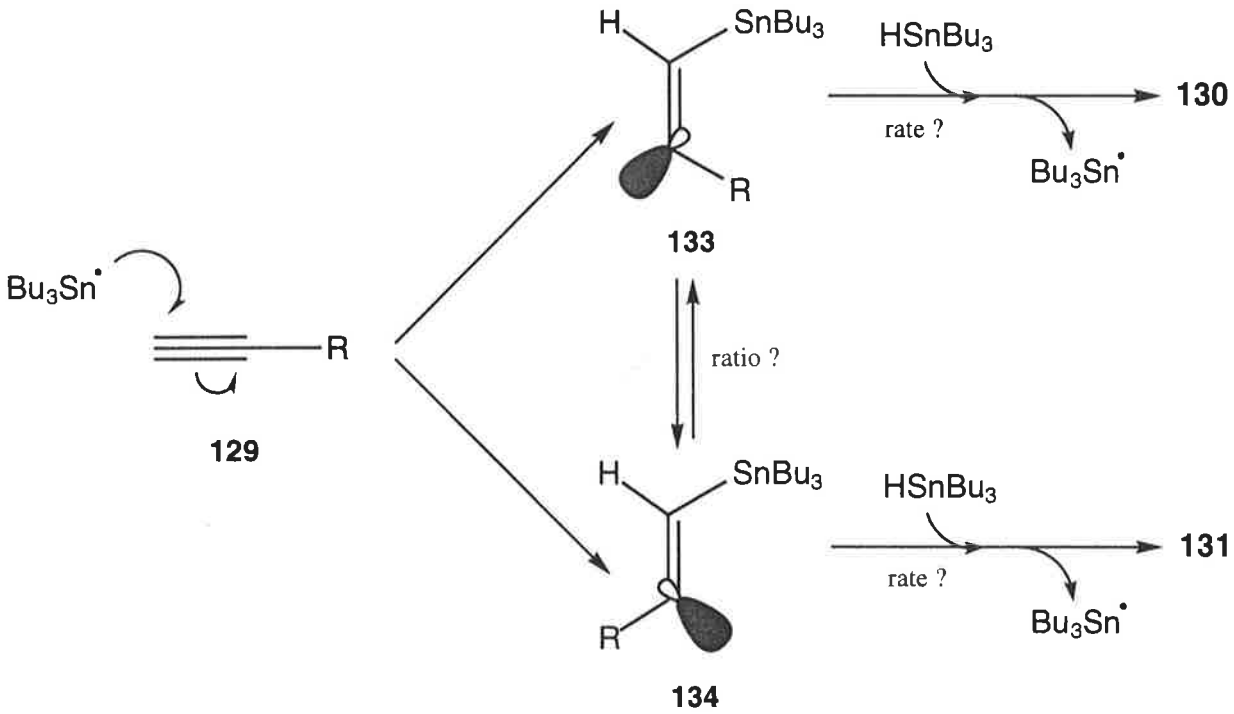


129 **130** **131** **132**

Scheme 41

Under free radical conditions, a tributylstannyl radical adds to the alkyne affording a vinyl radical. An anti-Markownikoff addition is generally observed for radical additions to alkynes and may be the result of the addition to the sterically less encumbered terminus of the carbon-carbon triple bond or the formation of a secondary vinyl radical **133** or **134**, which is more stable than a less substituted primary vinyl radical.[93] A vinyl radical can then abstract a hydrogen atom from a molecule of tributyltin hydride to yield the product vinylstannanes **130** or **131** (**132** is not usually formed) and another tributylstannyl radical, which can propagate the radical chain (**Scheme 42**). In most reactions a mixture of *E*- and *Z*-vinylstannanes is obtained in a ratio that is largely dependent on the reaction conditions and the substrate alkyne.[94] To the best of our knowledge no detailed mechanistic studies have been published. In accordance with the postulated mechanism[94] for the addition of other radicals to alkynes it reasonably can be assumed, however, that the ratio of vinylstannanes is determined by the ratio of the isomeric vinyl radicals **133** and **134** and their relative reactivity in the hydrogen abstraction. Non-substituted isomeric vinyl radicals usually interconvert very rapidly at ambient temperature owing to a

low barrier of inversion in the range of 2 to 3 kcal/mol.[95] This barrier of inversion can, however, be higher for secondary vinyl radicals.[96] It is therefore not clear if the isomeric vinyl radicals **133** and **134** have a sufficiently long life-span for an equilibrium to establish. As neither the ratio of isomeric vinyl radicals nor the individual rates for the hydrogen abstraction are known, a rationalisation of the ratio of vinylstannanes **130** and **131** appears rather speculative. An additional complication is the frequently encountered interconversion of vinylstannanes under the reaction conditions.



Scheme 42

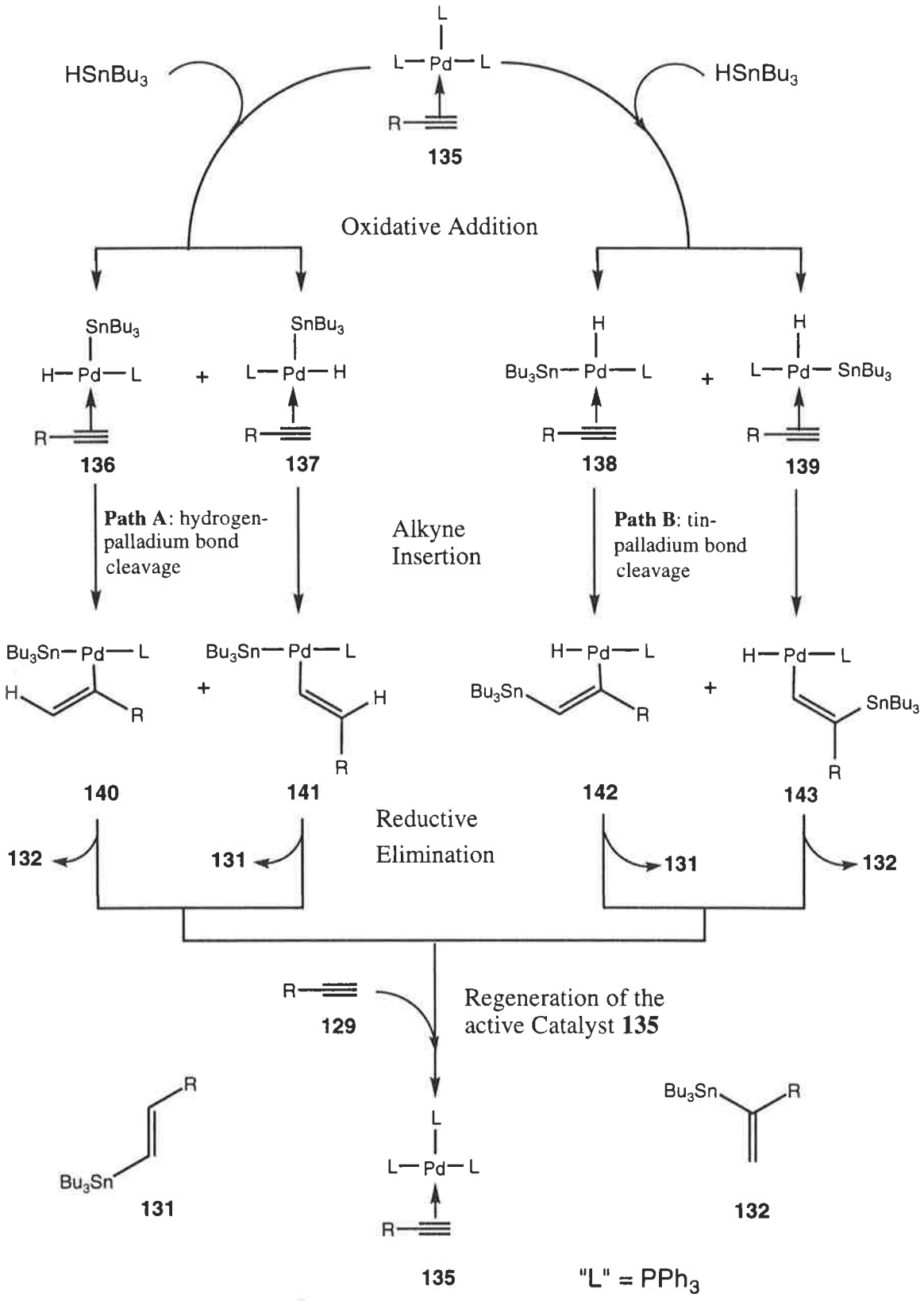
In contrast to the harsh conditions of the hydrostannation induced by free radicals, the hydrostannation of terminal alkynes catalysed by tertiary phosphine stabilised palladium complexes is an instantaneous reaction at ambient temperature.[91] Most functional groups are tolerated with the exception of those that readily undergo an oxidative addition reaction with palladium.

Similarily the mechanism of the transition metal mediated hydrostannation of alkynes has not yet been explored, nevertheless it has been proposed[97] that an oxida-

tive addition[2] of the tin-hydrogen bond of tributyltin hydride to the transition metal is followed by an insertion of the alkyne into the resulting complex[98] and finally a reductive elimination[131] of vinylstannane. The transition metal catalysed hydrostannation of terminal alkynes is, unlike the radical induced version, a *syn*-addition. Consequently *Z*-vinylstannanes **130** are not usually formed. A principle disadvantage of both the free radical induced and the transition metal catalysed hydrostannation of terminal alkynes is the formation of mixtures of isomeric vinylstannanes. In the transition metal catalysed version the regioisomeric vinylstannanes **131** and **132** are usually obtained as a mixture, which requires separation by chromatography. As the chromatographic separation of isomeric vinylstannanes can be difficult and isolated yields of the desired regioisomer low, there has been a continuing attempt to develop regioselective transition metal catalysed reactions. Conceivably the regioselectivity is determined during the insertion of the alkyne into the transition metal complex. In principle, there is a choice of an insertion into the transition-metal-tin or the transition-metal-hydrogen bond of the intermediate complexes **136** to **139**, which is illustrated for palladium as "path A" or "path B" in **Scheme 43**. Both pathways lead to the formation of different vinylstannanes **131** and **132**. In addition, the regioisomeric outcome may be affected by the precise geometry of the intermediate complexes and the orientation of the alkyne during the addition with respect to the rest of the metal complex.

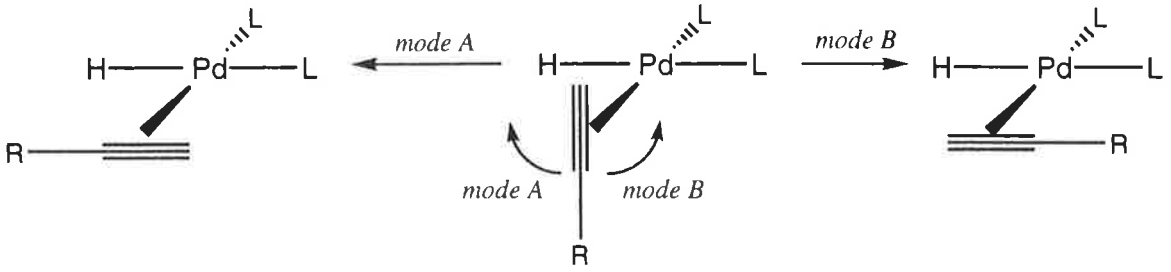
The energetically most favorable orientation of coordinated alkynes in square planar palladium(II) complexes is expected to be with the long axis of the alkyne perpendicular to the plane in which the ligands are located.[99] *Ab initio* calculations revealed that coordinated alkenes and alkynes have to rotate into the plane of the ligands in order to undergo an insertion reaction (**Scheme 44**).[99] This rotation can occur in the complexes **136** and **139** with a clockwise or counterclockwise movement of the alkyne. Considering such a multitude of alternative mechanistic routes it is indeed suprising that, for some terminal alkynes, the transition metal catalysed hydrostannation affords only a single vinylstannane (*vide infra*).[92]

Mechanism of the Palladium catalysed Hydrostannation



This Scheme shows several alternative mechanistic pathways through which the regioisomeric vinylstannanes **131** and **132** may be formed during the hydrostannation of alkynes. Similar pathways can be proposed for the hydrostannation catalysed by other metals.

Scheme 43



144 **145** **146**

From the most stable conformation **145** the alkyne has to rotate into the plane of the ligands in order to insert into the palladium-hydrogen bond. The stereochemical outcome of the insertion of the alkyne is affected.

Scheme 44

It transpires from a number of studies that the regioselectivity is influenced by both the nature of the transition metal and the nature of the ligand,[92] but is primarily dependent on the structure of the substrate alkyne.

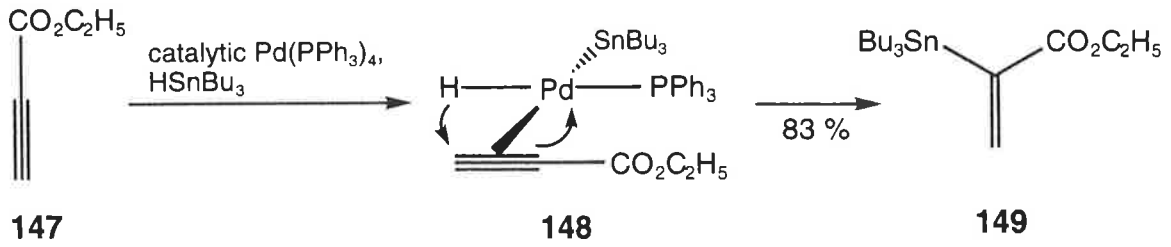
Alkynes that have a strong regiochemical bias fall into 3 categories:

1) those bearing a conjugated substituent that polarises the carbon-carbon triple bond, such as a carbonyl group,[92d,92e,97]
2) terminal alkynes bearing a sterically demanding substituent, such as a trimethylsilyl group,[92a-d]
3) heteroatom substituted alkynes that can coordinate to tin.[92d,92f]

In the following section we wish to discuss the hydrostannation of alkynes belonging to these categories. Each alkyne is representative of its category with regard to the complete regioselectivity for the formation of a single vinylstannane.

Alkynes of the first category were typically propynoic acid esters for which the insertion of the alkyne into the hydrogen-palladium bond of the intermediate complex **148** was postulated.[97] During this insertion the hydride added to the electron-deficient terminus of the carbon-carbon triple bond (**Scheme 45**).

In addition to electronic factors, steric interactions can direct the insertion of the alkyne. Alkynes of the second category had a pronounced steric bias when a tertiary or quartenary carbon atom or a trimethylsilyl group attached to the one terminus and a hydrogen atom attached to the other terminus of the carbon-carbon triple

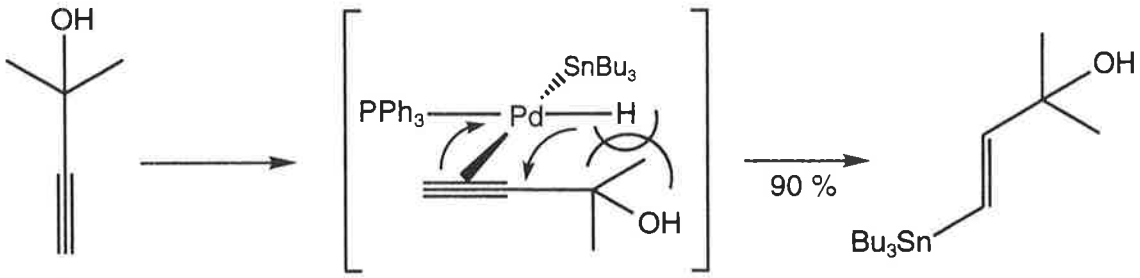


147 148 149

Conditions: $Pd(PPh_3)_4$ (2 mol %), $HSnBu_3$ (1.1 equiv.), benzene, ambient temperature, 15 min.

Scheme 45

bond. It appears feasible that the palladium-hydrogen and the carbon-carbon triple bond aligned in an orientation that minimises non-bonding interactions with the bulky substituent of the alkyne in the insertion reaction (**Scheme 46**).[92a-d]



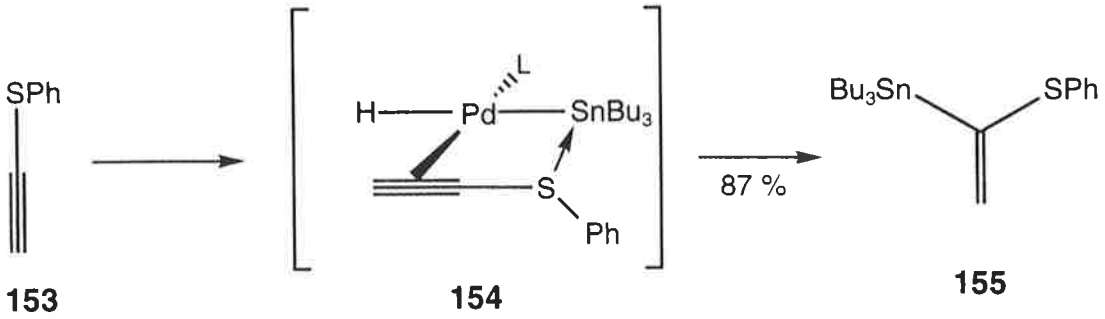
146 147 148

Conditions: $Pd(Ph_3)_4$ (2 mol %), $HSnBu_3$ (1.1 equiv.), THF, ambient temperature, 15 min.

Scheme 46

The essentially complete regioselective formation of 1,1-disubstituted vinylstannanes from alkynes bearing a halide,[92d] sulfide or selenide substituent has been well established (**Scheme 47**).[92f] A convincing rationale implies the coordination of the tin by the heteroatom during the alkyne insertion into the palladium-hydrogen bond. Although this is only a weak interaction since the tin atom in a trialkylstannanes moiety does not readily expand its coordination number,[101,143] it is sufficiently strong to orientate the alkyne with respect to the palladium-hydrogen and palladium-tin bonds in a collinear fashion during the insertion reaction. Coordination of tin by sulfur as depicted in **Scheme 47** was also implicated in the regioselective silylstannation of alkynylsulfides catalysed by palladium.[90b]

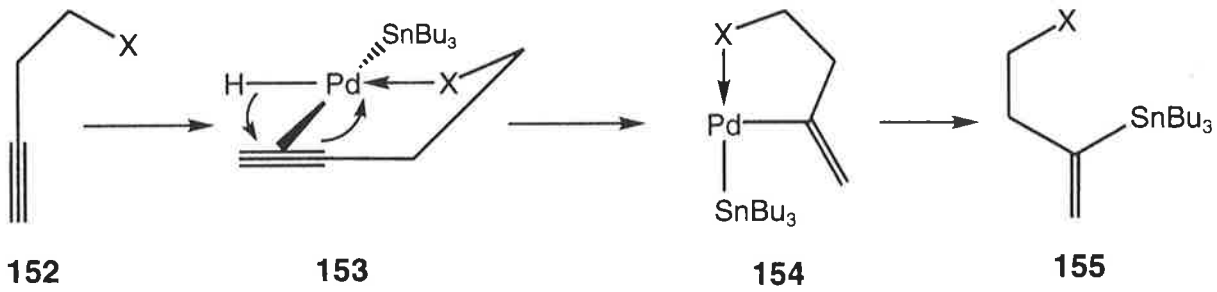
In addition to the alkynes discussed thus far, we envisaged alkynes with a suitable heteroatom in a position remote from the carbon-carbon triple bond that could direct



Conditions: $Pd(Ph_3)_4$ (1 mol %), $HSnBu_3$ (1.05 equiv.), benzene, ambient temperature, 10 min.

Scheme 47

the regiochemistry during the alkyne insertion as illustrated in **Scheme 48**. Although the heteroatom directed hydrostannation of the latter type has not yet successfully been demonstrated,[102] there is ample precedence in the literature of other transition metal mediated reactions that are directed in a stereoselective manner by a heteroatom in a suitable position.[103]



A possible rationale for the envisaged heteroatom (=X) directed hydrostannation of alkynes.

Scheme 48

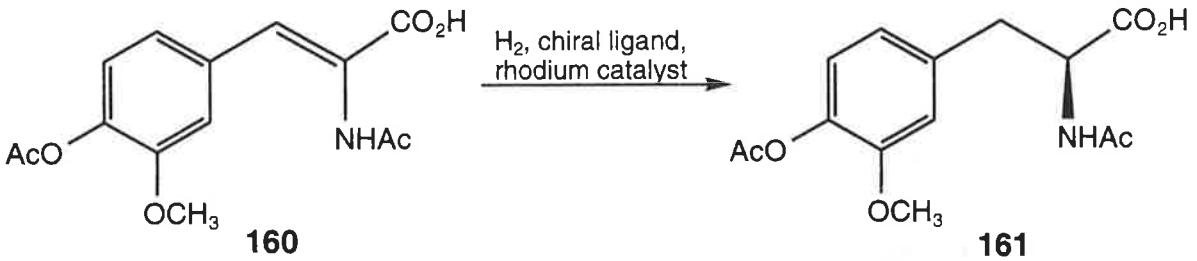
α-Amino acid derivatives were perceived as ideal substrates to test whether or not a heteroatom directed hydrostannation would afford a single regioisomer.

3.1.2. Unsaturated α-Amino Acids

α-Amino acids[104] participate in almost every biological process either in their free form, but more importantly when incorporated into peptides and proteins. Many non-natural α-amino acids that have unsaturated carbon side-chains are irreversible enzyme inhibitors and find employment as mechanistic probes in the exploration of enzyme activity such as the pyridoxal phosphate dependent enzyme

activity.[105] Commonly a covalent bond is formed between a nucleophile present at the catalytic site and the unsaturated carbon-carbon multiple bond of the amino acid.[105]

Unsaturated α-amino acids are furthermore important precursors for the synthesis of more complex non-natural α-amino acids *via* the elaboration of a carbon-carbon multiple bond present in the side-chain. One of the most prominent examples is the asymmetric hydrogenation of α,β-dehydroamino acid derivatives to produce (*S*)-DOPA, a therapeutic agent against the effects of Parkinson's desease. The industrial synthesis of (*S*)-DOPA is a modification of that depicted in **Scheme 49.**[106]



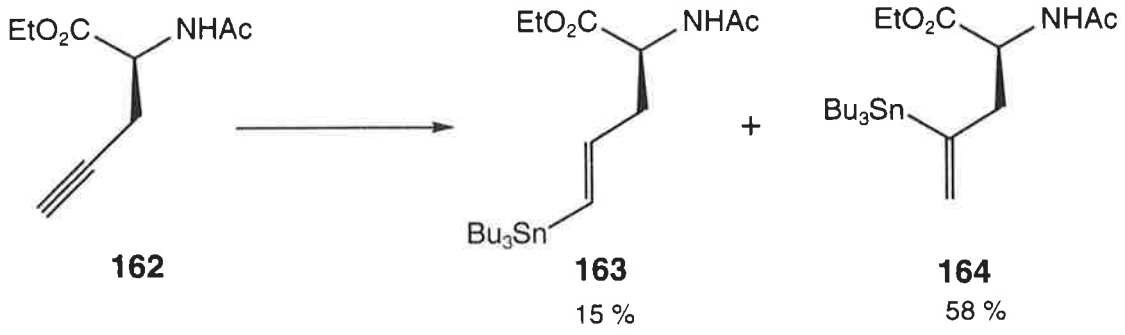
This asymmetric hydrogenation forms the basis for the industrial synthesis of (*S*)-DOPA.

Scheme 49

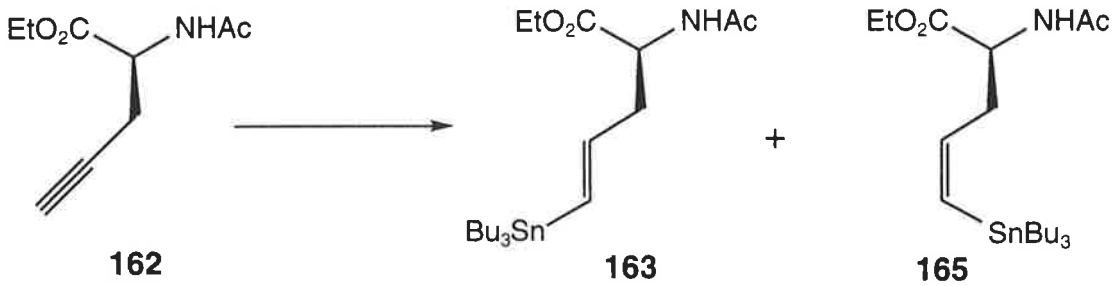
Many methods have been developed for the synthesis of enantiomerically pure unsaturated α-amino acids,[104b] some of which were mediated by transition metals.[107]

Our group introduced the Stille reaction[108] and the palladium catalysed coupling of propargylglycine derivatives[109] to the synthesis of unsaturated α-amino acids as well as expanded on the Heck reaction of vinylglycine derivatives.[14,29]

In particular, the Stille reaction was shown to be a versatile synthetic tool allowing for the preparation of α-amino acids possessing multiple unsaturation in their side-chain. The vinylstannanes required for Stille reactions were synthesised by the palladium catalysed hydrostannation of a propargylglycine derivative.[110] A mixture of regioisomers had then to be separated by repeated chromatography and the individual isomers were isolated in a modest yield (**Scheme 50**).[110] The problem



Conditions: 0.5 mol% of $Pd(PPh_3)_4$, $HSnBu_3$ (1.1 equiv.), benzene, ambient temperature, 5 min.



Conditions: Bu_3B, O_2 (0.3 equiv.), $HSnBu_3$ (1.1 equiv.), toluene, ambient temperature, 3 weeks.

Scheme 50

of repeated chromatography was compounded by the partial protodestannylation of the more reactive *E*-vinylstannane **163** on silica. By contrast, the *Z*-isomer **165** could not be obtained as the radical induced hydrostannation of propargylglycine derivative **162** yielded a mixture of *Z*- and *E*-vinylstannanes **163** and **165** that could not be separated.

It was therefore desirable to develop a synthetic method to *selectively* access any one of the three possible vinylstannes depicted in **Scheme 50**.

3.2. Aim

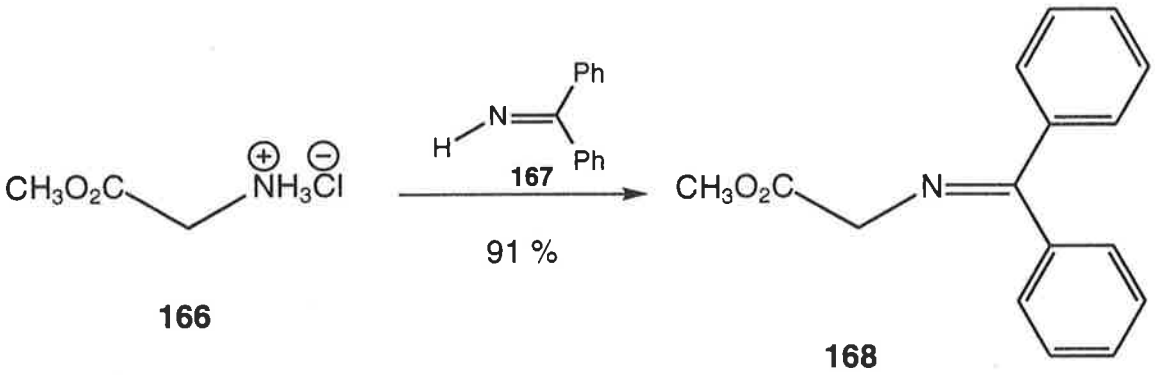
We wished to investigate whether vinylstannanes of the general type **163** and **164** could be synthesised *selectively* by means of a heteroatom directed transition metal catalysed hydrostannation of a suitably protected propargylglycine derivative.

3.3. Results and Discussion

3.3.1. Synthesis of Propargylglycine Derivatives

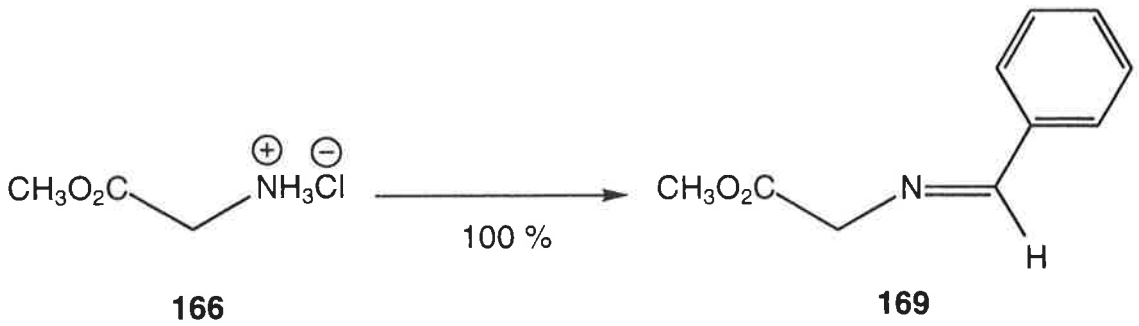
A popular strategy in the synthesis of α-amino acids is to protect the nitrogen of the α-amino group as an imine, primarily because of the ready accessibility of the corresponding imine protected glycine esters, such as **168**, and the ease with which a side-chain is introduced *via* the alkylation of the derived glycine enolates.[111] In addition imine protecting groups are readily hydrolysed by treatment with aqueous acid under very mild conditions.[111,112]

The best method for introducing the diphenylmethylenimine protecting group is *via* a transamination reaction of an amino acid ester hydrochloride salt with diphenylketimine **167** rather than a direct condensation of benzophenone and the free amine.[112,113] Following the literature procedure we were able to produce the imine protected glycine derivative **168** as a crystalline solid in nearly 90 % yield (**Scheme 51**).[112] Diphenylketimine **167** was readily prepared according to the literature procedure and is now also commercially available.[114] Differing from ketones, the more reactive aldehydes can be directly treated with a free amine to afford the derived aldimines. We prepared *N*-benzylidenimine glycine methyl ester **169** in quantitative yield (**Scheme 52**) according to the published procedure.[112] Whilst the aldimine derivative **169** was reported to hydrolyse readily on silica,[111] the diphenylmethylenimine protecting group imparted sufficient stability to chrom-



Conditions : 1.0 equiv. of **167**, CH_2Cl_2, ambient temperature, 12 h.

Scheme 51



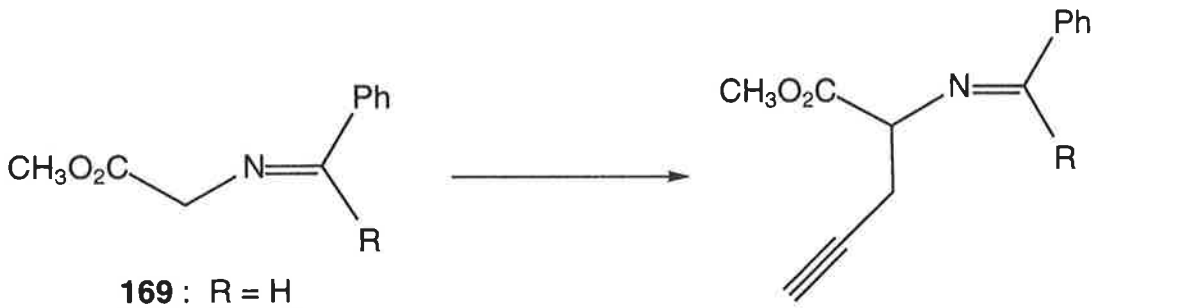
166 **169**

Conditions: Benzaldehyde (1.0 equiv.), CH_2Cl_2, ambient temperature, anhydrous $MgSO_4$, 12 h.

Scheme 52

atography. A purification of glycine derivative **169** was not required for our purposes as the produced material was pure when analysed by ^1H and ^{13}C nmr spectroscopy. However, stability of the amino protecting group during chromatography was a very important issue later in the synthesis when a separation of isomeric (tributylstannyl)allylglycine derivatives was imminent.

In following the general literature procedure for the generation and alkylation of aldimine protected glycine enolates with reactive electrophiles,[111] we were able to produce the propargylglycine derivatives **170** and **171** in excellent yields of 97 and 91 %, respectively (Conditions A, **Scheme 53**). Crude propargylglycine derivative **170** was pure by ^1H and ^{13}C nmr spectroscopy and was not purified further. The successful outcome of these experiments hinged on the use of a fresh batch of n-BuLi in hexanes, as otherwise an intensely red reaction mixture and a



169 : R = H
168 : R = Ph

170 : R = H (Conditions A: 97 %)
171 : R = Ph (Conditions A: 91 %)
(Conditions B: 93 %)

Conditions A : LDA (1.0 equiv.) in THF, DMPU (3 equiv.), propargyl bromide (1.5 equiv.).
Conditions B : NaH (1.0 equiv.) in DMF, propargyl bromide (1.5 equiv.).

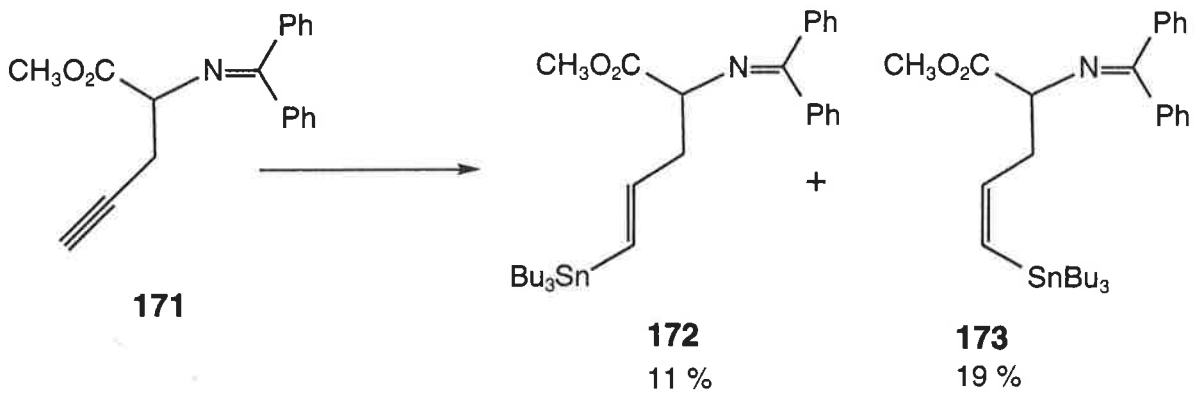
Scheme 53

great number of unidentified resonances in the ^{1}H and ^{13}C nmr spectra of the crude product indicated an extensive decomposition of the reaction mixture. In order to consistently achieve good yields of the propargylglycine derivatives, exactly one equivalent of base with regard to the starting glycine derivative was employed. We have modified the published procedure[111] by substituting the less toxic DMPU[115] for the hazardous co-solvent HMPA.

A good supply of propargylglycine derivative **171** was required for the hydrostannation study, we developed an even more convenient method for the alkylation of glycine derivative **168** with propargyl bromide that relied on the use of sodium hydride in DMF (Conditions B, **Scheme 53**).

3.3.2. Initial Investigations into the Hydrostannation

The hydrostannation of alkynes has frequently been carried out under free radical conditions[92] to afford a mixture of *E*- and *Z*-vinylstannanes. After trial experiments in the radical induced hydrostannation of propargylglycine derivative **171** conducted in refluxing toluene had failed more forcing conditions were applied by heating the reaction mixture to 165 °C in 1,2-dichlorobenzene (**Scheme 54**). Under those conditions, **171** was converted to an extent of 51% into a mixture of *E*-vinylstannane **172** and *Z*-vinylstannane **173** that were separated by mplc. As an isomeric mixture was obtained this reaction was not optimised with regard to the amount of tributyltin hydride that was used.



171

172
11 %

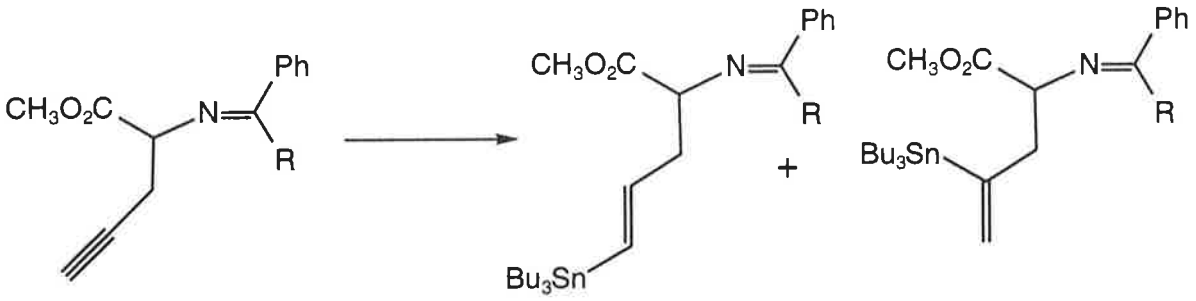
173
19 %

Conditions: AIBN (a catalytic amount), $HSnBu_3$ (1.7 equiv.), 1,2-dichlorobenzene, 165 °C, 30 min.

Scheme 54

The stereochemistry around the carbon-carbon double bond of vinylstannanes **172** and **173** was determined on the basis of the size of the vicinal coupling of the olefinic protons. The ^{1}H nmr spectrum of *Z*-vinylstannane **173** showed two olefinic resonances that were each split with a coupling constant of $J = 13$ Hz indicating a *cis*-stereochemical relationship. On the basis of the appearance of the ^{1}H nmr spectrum vinylstannane **172** was a geometrical isomer of **173**. However, the apparently larger olefinic coupling constant for the *E*-isomer **172** could not be measured directly by inspecting the line-splitting, as the chemical shift separation of two resonances at $\delta = 5.98$ ppm (d) and at $\delta = 5.76$ ppm (dt) was not sufficiently large to allow for a first order analysis of this spin-system.[116]

In stark contrast, the hydrostannation of propargylglycine derivative **171** mediated by $Pd(PPh_3)_4$ was an instantaneous and quantitative reaction at ambient temperature that formed a one to one mixture of the regioisomeric vinylstannanes **172** and **176** (**Scheme 55**) which were separated by mplc. The isomer ratio was determined by comparing the intensities of the olefinic resonances in the ^{1}H nmr spectrum of the vinylstannanes.



170 : R = H
171 : R = Ph

174 : R = H (not isolated)
172 : R = Ph (32 %)

175 : R = H (not isolated)
176 : R = Ph (37 %)

Conditions: 0.5 mol% of $Pd(PPh_3)_4$, $HSnBu_3$ (1.2 equiv.), benzene, ambient temperature, 15 min.

Scheme 55

The ^{1}H nmr spectrum of vinylstannane **176** was diagnostic of a 1,1-disubstituted vinylstannane as the two olefinic resonances at $\delta = 5.67$ ppm and at $\delta = 5.17$ ppm were coupled with a coupling constant of $J = 3$ Hz, which characteristically small for a geminal olefinic coupling constant (-3 Hz $< J < 3$ Hz).[68] Both protons could be assigned as the size of the ^{117}Sn/^{119}Sn to H coupling which was indicated by the

satellite resonances rather different in each case. A coupling of approximately J = 136 Hz for the proton at δ = 5.67 ppm indicated a *trans*-stereochemical relationship relative to the stannyl moiety, whilst the coupling of approximately J = 62 Hz indicated a *cis*-stereochemical relationship for the proton at δ = 5.16 ppm.[117]

A decrease in the reaction temperature from 25 °C to -20 °C produced slightly more of the 4-(tributylstannyl)allylglycine derivative **176**, however, the regioselectivity was still very modest (2 to 1 in favour of **176**).

Hydrostannation of *N*-benzylidenimine protected propargylglycine derivative **170** proceeded smoothly under the same conditions (**Scheme 55**) indicating that the aldimine group of **170** was also compatible with this reaction. A one to one ratio of product stannanes **174** and **175** was determined by ^{1}H nmr spectroscopic analysis of the crude product as described previously. The olefinic region of the spectrum was very similar to that of a mixture of the analogous vinylstannanes **172** and **176**. Anticipating that vinylstannanes **174** and **175** would hydrolyse on silica due to the lability of the aldimine group, we did not attempt to purify **174** and **175**.[111]

Next we wished to improve on the regioselectivity of the hydrostannation by varying the transition metal catalyst. In the following sections the screening of 20 different transition metal derivatives for the hydrostannation of propargylglycine derivative **171** will be described.

3.3.3. The Transition Metal catalysed Hydrostannation of Propargylglycine Derivative 171

Transition metal complexes that were screened in the hydrostannation of propargylglycine derivative **171** were mostly synthesised (**Table 3**). The most frequently screened transition metal was palladium as its triphenylphosphine complexes have firmly been established as efficient catalysts for the hydrostannation of alkynes.[92a-d] We were particularly interested to explore the effect of the size of the ligand on the regioselectivity. Palladium(II) complexes without a stabilising tertiary phosphine

Table 3. Synthesis or Source of the Transition Metal Complexes that were screened for the Hydrostannation of Propargylglycine Derivative **171**.

Entry	Transition metal complex	Source	lit.[a]	Colour	Yield
1	$Pd(PPh_3)_4$[b]	$PdCl_2$, N_2H_4, PPh_3, DMSO	119	canary-yellow	91 %
2	aged $Pd(PPh_3)_4$	$Pd(PPh_3)_4$		red-brown	
3	$PdCl_2(PPh_3)_2$[b]	NaCl, $PdCl_2$, PPh_3	120	yellow	30 %
4	$PdCl_2[P(o\text{-tolyl})_3]_2$	NaCl, $PdCl_2$, $P(o\text{-tolyl})_3$[b]	120	yellow	89 %
5	$PdCl_2[P(CH_3)_3]_2$	$Na_2[PdCl_4]$, $AgNO_3 \cdot PMe_3$[b]	120	yellow	35 %
6	$PdCl_2(PBu_3)_2$	NaCl, $PdCl_2$, PBu_3[b]	120	yellow	76 %
7	$PdCl_2$dppe[b]	NaCl, $PdCl_2$, dppe	120	off-white	45 %
8	$PdCl_2(AsPh_3)_2$	NaCl, $PdCl_2$, $AsPh_3$	120	dark yellow	84 %
9	"$Pd(AsPh_3)_4$" in THF	Pd_2dba_3[b], $AsPh_3$[b]	121	bright yellow	
10	Pd on polyimine[b]	purchased		orange	
11	Pd on polymer supported PPh_3[b]	$Pd(PPh_3)_4$[b], polymer supported PPh_3[b]	122	brown	
12	$PdCl_2(CH_3CN)_2$[b]	purchased	124	yellow	
13	$PdCl_2(PhCN)_2$[b]	purchased	124	yellow	
14	$Pd(OAc)_2$[b]	purchased		red-brown	
15	5 % Pd on carbon[b]	purchased		black	
16	amorphous Pd-metal	$Na_2[PdCl_4]$[b]	123	black	96 %
17	$RhCl(PPh_3)_3$[b]	$RhCl_3$, PPh_3, ethanol	124	burgundy	86 %
18	Cp_2ZrHCl[b]	$ZrCl_2Cp_2$, $LiAlH_4$, ether	125a	white	72 %
19	$NiBr_2(PPh_3)_2$[b]	purchased	157	metallic green	74 %
20	"ligand-free" Ni^0	$NiCl_2$ (orange), $LiAlH_4$, THF		dark solution	86 %
21	$PtCl_2(PPh_3)_2$[b]	purchased	124	white	86 %
22	PPh_3[b]	purchased		white	

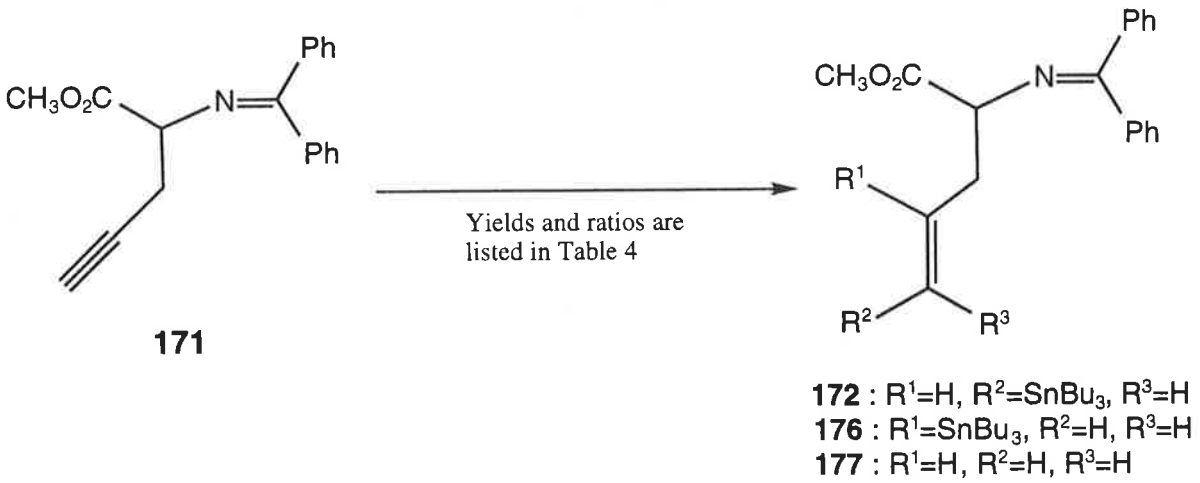
[a] The literature procedure for the preparation is quoted. [b] Available from Aldrich.

were also prepared as they were thought to provide catalysts that may allow for a regioselective hydrostannation that is directed by the imine nitrogen of alkyne **171**.

For a coordination of the imine nitrogen of **171** to the palladium catalyst to occur it was deemed necessary that tertiary phosphines, which interact relatively strongly with palladium, were not present in the reaction mixture.

Anticipating that a heterogenous palladium catalyst could have a different selectivity from its homogenous counterpart, we also screened several heterogenous catalysts.[118] Furthermore, complexes of 5 different transition metals were prepared in order to gauge the effect of the metal centre. We prepared complexes of the late transition metals nickel, palladium, platinum and rhodium as they were previously shown to catalyse the hydrostannation of terminal alkynes.[92] In addition to these catalysts, we wished to assess Cp_2ZrClH as an *early* transition metal complex.

The transition metal complexes listed in Table 3 were screened for the hydrostannation of propargylglycine derivative **171** under essentially identical conditions (**Scheme 56**) and the results are listed in **Table 4.**



171

172 : R^1=H, R^2=$SnBu_3$, R^3=H
176 : R^1=$SnBu_3$, R^2=H, R^3=H
177 : R^1=H, R^2=H, R^3=H

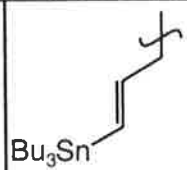
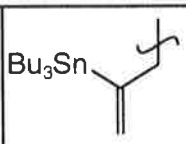
Conditions : $HSnBu_3$ (2.0 equiv.), 5 mol% of the transition metal complex, 2 h, 25 °C.

Scheme 56

In the following discussion we shall first focus on the catalytic activity of these transition metal complexes and then discuss the stereochemical aspects of the hydrostannation.

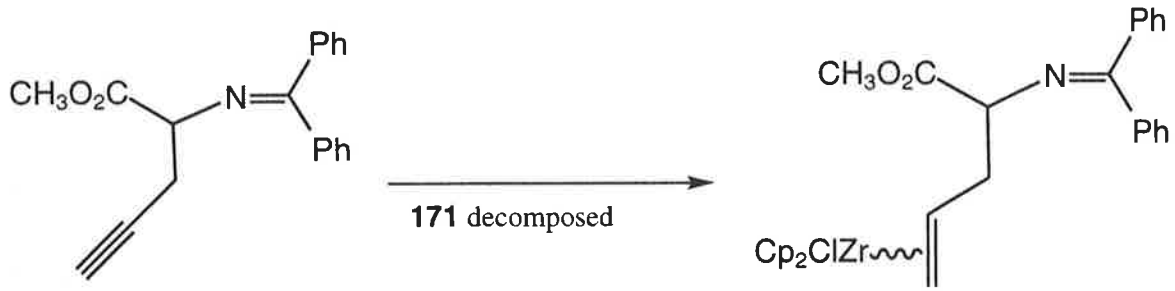
Comparing entries 1 and 3 with entries 17 to 21 in **Table 4** we concluded that palladium complexes were more active catalysts than rhodium, nickel and platinum

Table 4: Results[a] for the Hydrostannation of Propargylglycine Derivative **171**.

Entry	Transition metal complex	 **172**	 **176**	 **171**	 **177**
1	$Pd(PPh_3)_4$	43 %	46 %	0 %	0 %
2	aged $Pd(PPh_3)_4$	23 %	9 %	29 %	28 %
3	$PdCl_2(PPh_3)_2$	35 %	50 %	9 %	0 %
4	$PdCl_2[P(o\text{-tolyl})_3]_2$	30 %	15 %	43 %	30 %
5	$PdCl_2(PMe_3)_2$	3 %	2 %	89 %	2 %
6	$PdCl_2(PBu_3)_2$	24 %	16 %	48 %	0 %
7	$PdCl_2$dppe	15 %	15 %	59 %	3 %
8	$PdCl_2(AsPh_3)_2$	0 %	0 %	92 %	0 %
9	"$Pd(AsPh_3)_4$" in THF	0 %	0 %	88 %	4 %
10	Pd on polyimine	5 %	1 %	33 %	44 %
11	Pd on polymer-supported PPh_3	37 %	38 %	0 %	19 %
12	$PdCl_2(CH_3CN)_2$	21 %	16 %	38 %	21 %
13	$PdCl_2(PhCN)_2$	25 %	11 %	32 %	13 %
14	$Pd(OAc)_2$	25 %	5 %	49 %	16 %
15	10 % Pd on carbon	0 %	0 %	92 %	0 %
16	amorphous Pd-metal	0 %	0 %	91 %	0 %
17	$RhCl(PPh_3)_3$	13 %	8 %	65 %	10 %
18	Cp_2ZrHCl	0 %	0 %	77 %	8 %
19	$NiBr_2(PPh_3)_2$	8 %	8 %	79 %	0 %
20	"ligand-free Ni^0"	28 %	23 %	44 %	0 %
21	$PtCl_2(PPh_3)_2$	8 %	31 %	49 %	4 %
22	PPh_3	0 %	0 %	98 %	0 %

[a] Yields were determined by ^1H nmr analysis of the crude reaction product and an internal standard or by chromatography. Vinylstannanes **172** and **176** were isolated as a mixture by chromatography for entries 1, 2, 3, 4, 5, 11, 12, 20, 21. The reaction conditions are outlined in Scheme 56.

complexes for the hydrostannation of **171**. Cp_2ZrClH did not catalyse the hydrostannation, possibly because the latter complex may have irreversibly reacted with the propargylglycine derivative **171**. Anticipating that a vinylzirconium species **178** may have been a possible product from such a reaction, we attempted to synthesise **178** directly by treating propargylglycine derivative **171** with an equimolar amount of Cp_2ZrHCl (**Scheme 57**).[125b] ^1H and ^{13}C nmr spectroscopic analysis of the crude reaction product revealed, however, a complex mixture of compounds. Apparently the diphenylmethylenimine or the ester protecting group were incompatible with the use of a reactive metal hydride such as Cp_2ZrHCl.



171 **178**
(not detected)

Conditions: Cp_2ZrHCl (1.1 equiv.), CH_2Cl_2, 25 °C, 1h.

Scheme 57

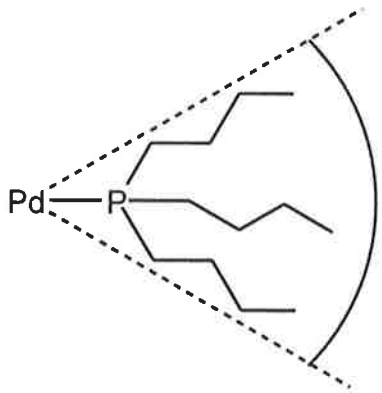
Tertiary phosphine ligands, in particular triphenylphosphine, markedly increased the catalytic activity of palladium (entries 1 and 3, **Table 4**). Palladium complexes, in which stabilising ligands may have been weakly coordinating solvent molecules ("ligand-free" complexes, entries 12 to 14, **Table 4**) were also less active than their tertiary phosphine stabilised counterparts.

To the best of our knowledge no mechanistic studies have been carried out on the metal catalysed hydrostannation of terminal alkynes, therefore we did not attempt to rationalise the increased efficacy of the hydrostannation in the presence of tertiary aromatic phosphines of the propargylglycine derivative **171**, which is presumably a general feature of the palladium mediated hydrostannation of terminal alkynes. As expected, triphenylphosphine did not, in the absence of a metal, catalyse the hydrostannation of the propargylglycine derivative **171** (entry 23, **Table 4**).

Comparing entries 3 to 6 of **Table 4** we concluded that no simple relationship between the cone angle of the tertiary phosphine and the regioselectivity of the hydrostannation existed. The cone angle is defined as a measure of the steric shielding that a metal atom experiences upon binding to the tertiary phosphine (**Figure 11**).[126] In particular, similar ratios of regioisomeric vinylstannanes **171** and **175** were obtained when palladium was stabilised by tri-*o*-tolylphosphine having a very large cone angle or by tributylphosphine, which has a small cone angle (entries 4 and 6, **Table 4**).

Although the regioselectivity varied depending on the tertiary phosphine used, it was in all cases modest. The best results were obtained with $PtCl_2(PPh_3)_2$, which afforded an almost four to one ratio of vinylstannanes **172** and **176** in favour of the 1,1-disubstituted isomer **176** and with a "ligand-free" catalyst derived from palladium(II) acetate, which afforded a five to one ratio in favour of the 1,2-disubstituted *E*-isomer **172** (entries 14 and 21, **Table 4**).

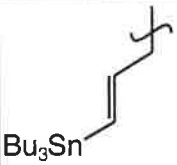
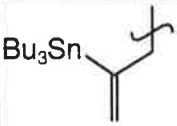
Figure 11. The Definition of the Cone Angle of a Ligand.



It is well established that a completely different product distribution can be obtained by replacing a heterogeneous catalyst with its analogue in solution or *vice versa*.[118] Such a direct comparison was possible in our study when palladium adsorbed on polymer supported triphenylphosphine was substituted for $Pd(PPh_3)_4$ (entries 1 and 11, **Table 4**). Unfortunately, no increase in the the regioselectivity of the hydrostannation of propargylglycine derivative **171** was achieved.

Among the heterogenous palladium species, palladium on carbon and amorphous palladium metal did not catalyse the hydrostannanation of the propargylglycine derivative **171** under the conditions specified in **Scheme 56** (entries 15 and 16, **Table 4**). Palladium on carbon did, however, catalyse the hydrostannation of **171** when more forcing reaction conditions were applied (**Table 5**).

Table 5: The Effect of Piperidine on the Hydrostannation of Propargylglycine Derivative **171**.

Entry	Catalyst and Solvent[a]	 **172**	 **176**	 **171**	 **177**
1	Pd on C, THF	7 %	0 %	28 %	54 %
2	Pd on C, THF piperidine	33 %	5 %	43 %	11 %
3	aged $Pd(PPh_3)_4$, THF	28 %	14 %	0 %	41 %
4	aged $Pd(PPh_3)_4$, THF, piperidine	31 %	18 %	24 %	0 %

[a] Reaction conditions: syringe-pump addition of $HSnBu_3$ at 50 °C over 3 h (8 equiv. for entries 1 and 2; 5 equiv. for entries 3 and 4). Yields of chromatographed compounds are listed.

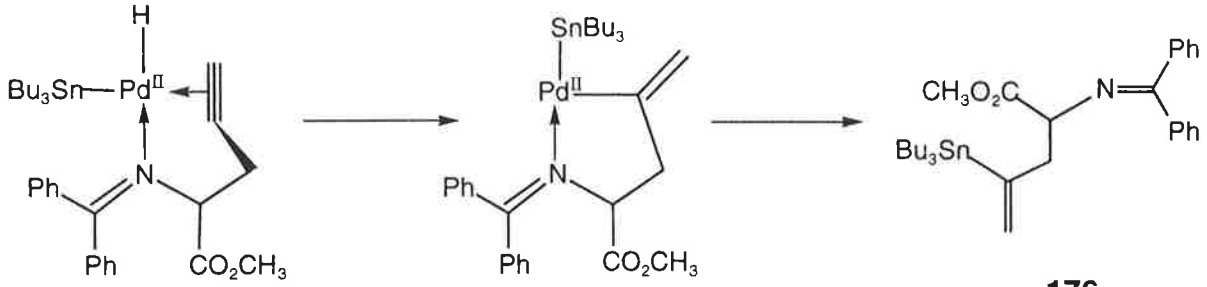
Heterogenous catalysts gave significant amounts of the allylgylcine derivative **177** (**Table 4**). The allylglycine derivative **177** could be derived from propargylglycine **171** by hydrogenation of the alkyne moiety or from vinylstannanes. When we exposed a clean mixture of vinylstannanes **172** and **176** to aged $Pd(PPh_3)_4$ and slowly added tributyltinhydride under the same conditions (**Table 5**), allylglycine derivative **177** was not detected by ^1H nmr spectroscopy of the crude product. Although there was no direct evidence we suggest that an aged batch of $Pd(PPh_3)_4$ promoted the *hydrogenation* of alkyne **171** to allylglycine **177** as a side-reaction (**Table 4**).

The question arises then, which property of the catalyst effects the formation of the

allylglycine derivative **177** as a by-product. A property common to all catalysts promoting this side-reaction was that they were probably oligomeric palladium compounds. Unlike tertiary phosphine stabilised palladium complexes in solution which were presumably monomeric, palladium atoms could be bonded to each other to form aggregates. Such an aggregation may have occurred in solution in the absence of strongly coordinating ligands (entries 12 to 14, **Table 4**) or during the adsorption of several palladium atoms from solution onto the same site of a solid support, as is presumably the case in the commercial synthesis of palladium on carbon and palladium supported by polymeric phosphine. In an aged batch of $Pd(PPh_3)_4$ triphenylphosphine may be depleted due to atmospheric oxidation to give triphenylphosphine oxide. The latter is an inferior ligand and consequently "aged $Pd(PPh_3)_4$" had properties similar to the "ligand-free" catalysts, which are known to aggregate in solution.

We performed the following experiment to corroborate our hypothesis: The hydrostannation of **171** in the presence of "aged $Pd(PPh_3)_4$" was performed in a mixture of THF and piperidine. Interestingly piperidine completely suppressed the hydrogenation of **171**. Presumably the strong ligand piperidine prevented the aggregation of palladium atoms in solution or, alternatively, suppressed the hydrogenation catalysed by oligomeric palladium species directly. In the light of these results the possibility that piperidine supressed the formation of allylglycine **177** by preventing an acid catalysed protodestannylation reaction of vinylstannanes **172** and **176** appeared improbable to us.

The "ligand-free" palladium complexes (entries 12 to 14, **Table 4**) were screened, as it was already mentioned, in order to allow for a possible chelation of palladium by the carbon-carbon triple bond and the imine nitrogen as indicated in complex **179**. We speculated that such a coordination may well result in a high selectivity for the formation of vinylstannane **176**. Unfortunately, the regioselectivity was very modest using $PdCl_2(CH_3CN)_2$ and $PdCl_2(PhCN)_2$ as catalyst precursors and not sufficiently high in the case of $Pd(OAc)_2$ to allow for conclusions as to whether chelation of palladium by **171** occurred or not.



179 **180** **176**

A mechanistic scenario on which we based our expectation of a regioselective hydrostannation.

Scheme 58

In summary, we synthesised propargylglycine derivative **171** in a high yield following modified literature procedures. Propargylglycine **171** was then treated with tributyltinhydride under a variety of conditions to afford the three possible isomers of (tributylstannyl)allylglycine derivatives **172**, **173** and **176**, which were separated by chromatography. A comparative study of a variey of transition metal complexes demonstrated the superior catalytic efficacy of the palladium/triphenylphosphine and platinum/triphenylphosphine systems for the hydrostannation of the propargylglycine derivative **171**. Screening of a variety of tertiary phosphine stabilised palladium complexes revealed that there was no linear dependence of the ratio of regioisomeric (tributylstannyl)allylglycine derivatives **172** and **176** on the steric requirements of the tertiary phosphine ligand. The highest ratio of five to one in favour of *E*-tributylstannylallylglycine derivative **172** was achieved with palladium(II) acetate although this reaction was only moderately efficient. A catalyst derived from $PtCl_2(PPh_3)_2$ mediated the hydrostannation of **171** with the highest selectivity in favour of the regioisomeric 4-(tributylstannyl)allylglycine derivative **176**.

A heteroatom directed and completely regioselective hydrostannation of **171**, as it is discussed in the Introduction, was unfortunately not observed.

Chapter 4: The Stille Reaction

4.1. Introduction

4.1.1. General Aspects

The Stille reaction is the palladium induced coupling of vinyl, aryl, or acetylenic trialkylstannanes with electrophiles (**Scheme 59**).[87,127] Many unsaturated halides,

$$R^1X + R^2SnR^3_3 \xrightarrow{Pd^0} R^1R^2 + XSnR^3_3$$

R^2 = aryl, vinyl, alkynyl
R^3 = butyl, less frequently methyl
R^1X: See Table 6

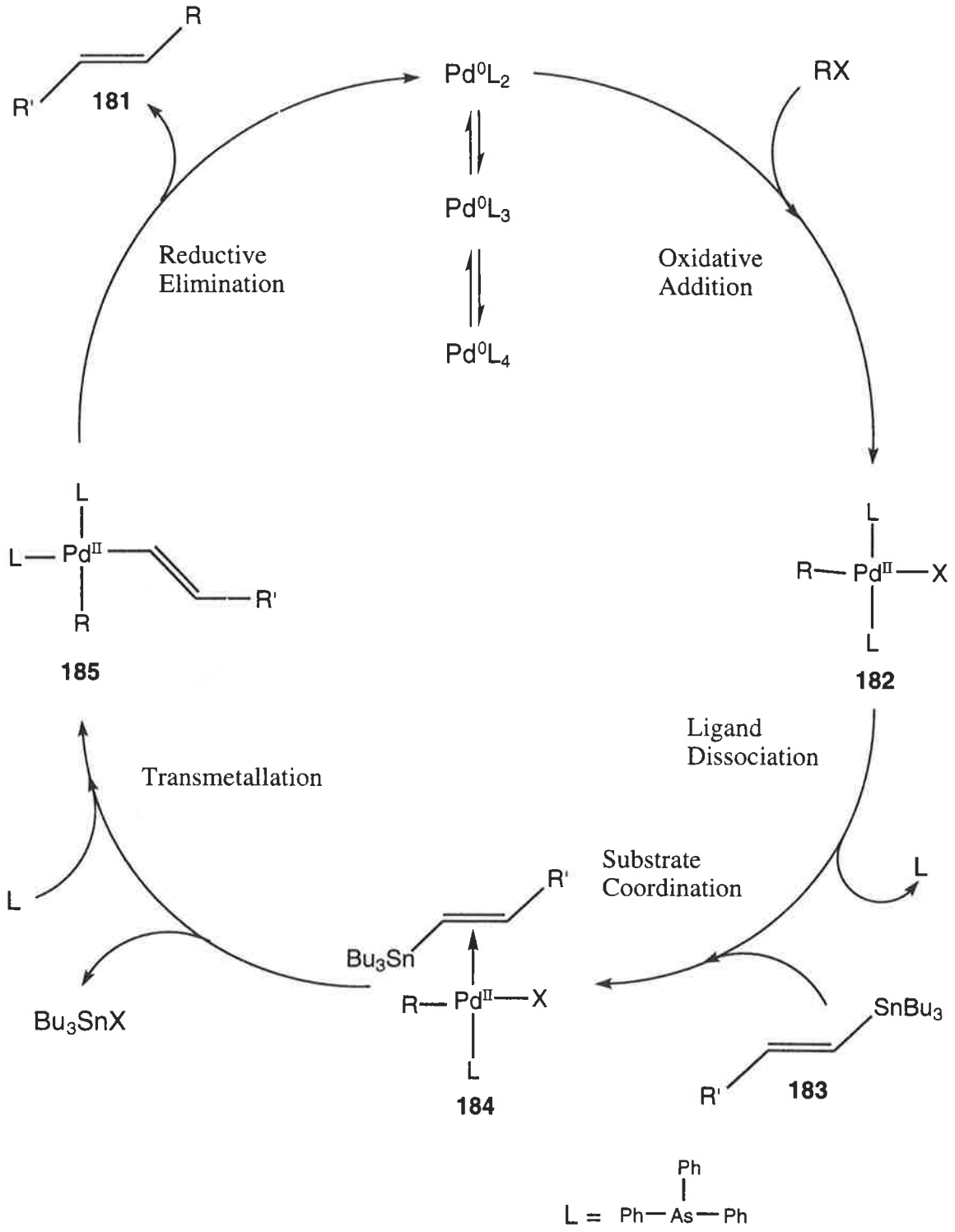
Scheme 59

triflates[128] and fluorosulfonates[129] have been employed as electrophiles (**Table 6**). The mechanism of the Stille reaction[87] involves a triad of elementary reactions, namely the oxidative addition of an electrophile to a zerovalent palladium complex,[2] transmetallation[130] of the resultant divalent palladium complex with an organostannane followed by a reductive elimination[131] to form the product and regenerate the palladium(0) catalyst (**Scheme 60**). The ease of transferring an organic moiety from tin to palladium increases in the approximate order *n*-butyl < methyl < vinyl < aryl < acetylenic with decreasing hybridisation of the carbon-tin bond.[130] A

Table 6. The most frequently employed electrophiles in the Stille reaction.

	acyl	allyl	benzyl	aryl	vinyl	alkynyl
Cl	√					
Br		√	√	√	√	√
I				√	√	√
$OS(O)_2CF_3$				√	√	
$OS(O)_2F$				√		

The Mechanism of the Stille Reaction



The Stille reaction of vinylstannanes under standard conditions (Pd_2dba_3, $AsPh_3$, THF); the coupling of aryl- and alkynylstannanes follows the same mechanism.

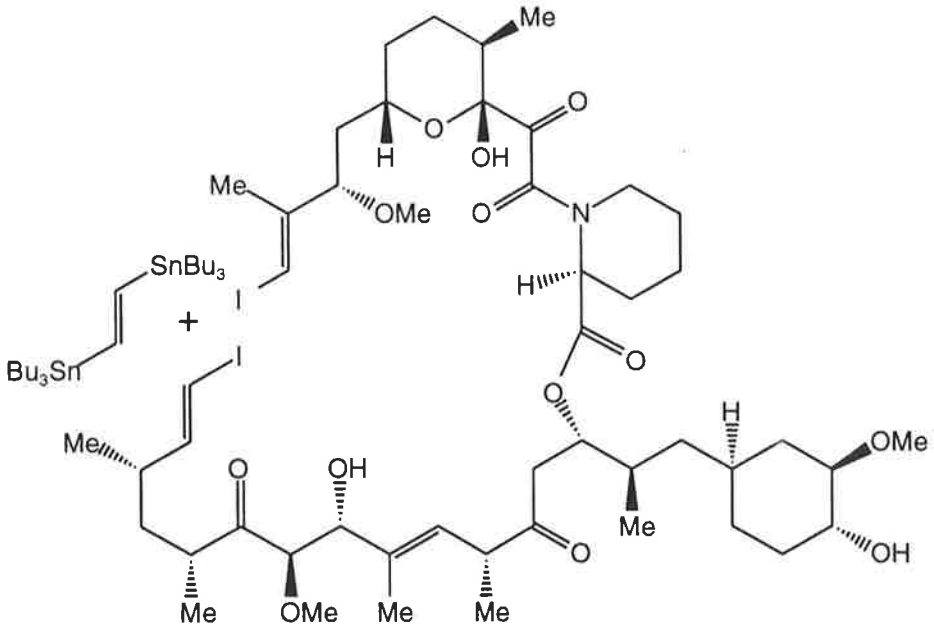
Scheme 60

butyl group is not generally transferred in the presence of an organic moiety bonded to tin through a sp^2-hybridised carbon.[130]

Organostannanes are non-basic and are thus distinguished from many other organometallics that are commonly employed in cross-coupling reactions, such as Grignard reagents,[132] organocopper[133] and organozinc species.[134] Other non-basic organometallic reagents include derivatives of boranes,[135] silanes,[136] and aluminium[137] and zirconium.[138] With the exception of organoboranes, aryl and vinylstannanes are probably the most frequently employed non-basic organometallics in cross-coupling reactions.

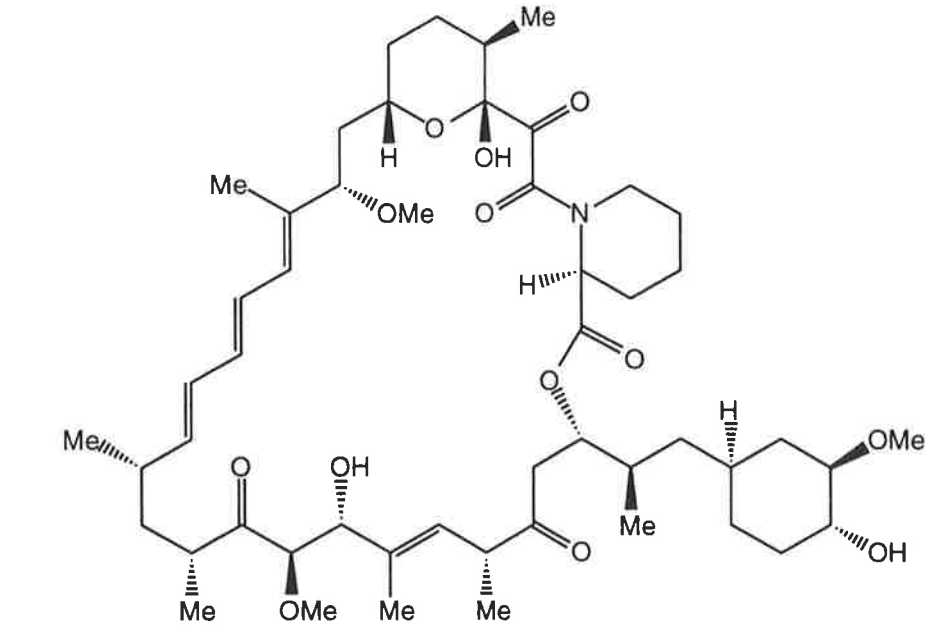
An important stereochemical feature of the Stille reaction is the preservation of the substitution pattern of vinylic precursors. Consequently the outcome of a particular reaction is highly predictable. It is therefore possible to assemble an unsaturated carbon chain in a sterospecific manner from simple vinyl, aryl or alkynyl building blocks. Under the frequently mild conditions, a wide variety of functional groups is tolerated. This was recently highlighted by the total syntheses of the antibiotic rapamycin **187** (**Scheme 61**)[139] and the DNA cleaving reagent dynemicin A.[140] In the synthesis of rapamycin **187** the authors elegantly employed a double Stille reaction as the final step in the synthetic sequence forming a conjugated triene in an all *trans*-configuration and closing the macrocycle. In order to preserve the integrity of the sensitive substrate **187** a reactive "ligand-free" catalyst derived from $PdCl_2(CH_3CN)_2$ was employed and the reaction conducted at ambient temperature. Triethylamine was present in the reaction mixture although it is not a common ingredient in the experimental protocol of Stille reactions.

Advantages of a particular synthetic transformation, such as chemoselectivity, are often intractably intermingled with short-comings, such as a lack of reactivity. The Stille reaction is no exception. Whilst tributylorganotin derivatives are non-basic reagents of negligible nucleophilicity and pronounced stability to purification by chromatography, they lack the high reactivity of organocopper, Grignard and zinc reagents towards transmetallation. Therefore, some effort has been spent on improving the efficacy of the Stille reaction by modifying the reaction conditions. In



186

28 %



Rapamycin

187

Conditions : Di*iso*propylethylamine (1.2 equiv.), $Pd(CH_3CN)_2Cl_2$ (0.2 equiv.), 0.003 M solution of **186** in a 1:1 mixture of DMF and THF, 25 °C, 24 h.

Scheme 61

the single most successful modification of the original conditions a simple substitution of triphenylphosphine with triphenylarsine as a ligand for palladium resulted in an hundred to thousandfold increase in the overall reaction rate.[129]

Convincing kinetic data was presented in evidence for the transmetallation as the rate determing step in the Stille coupling of reactive electrophiles.[129,141] This kinetic data suggested that a ligand dissociation from the palladium complex occurred immediately prior to the transmetallation of the organostannane (**Scheme 62**). Reaction rates were comparatively slow in the presence of an excess of the strongly coordinating triphenylphosphine ligand. As triphenylarsine is a kinetically more labile ligand than triphenylphosphine, the transmetallation was dramatically accelerated. Furthermore, the addition of copper(I) iodide resulted in a fster reaction.[142] This rate effect was shown to arise from the coordination of copper(I) iodide to an excess of triphenylarsine, which facilitated the formation of an undercoordinated palladium species immediately prior to the transmetallation.[142]

Currently, the universally most useful catalytic system for the Stille reaction is a combination of 5 mol% of palladium derived from Pd_2dba_3, triphenylarsine and copper(I) iodide in a ratio of one to four to one.[142]

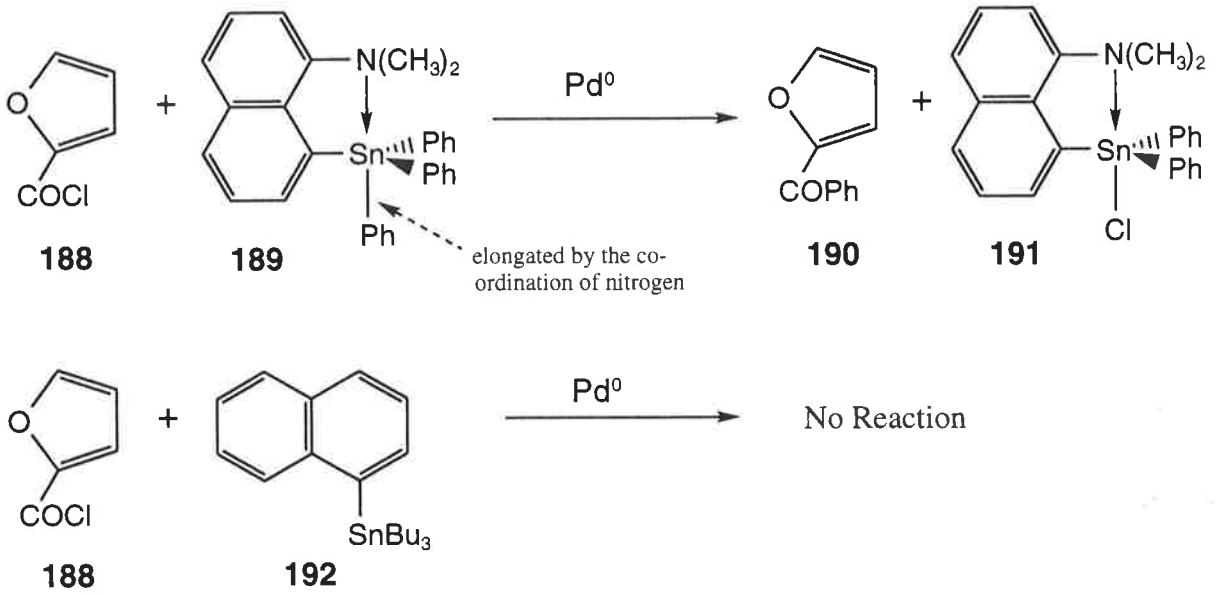
In contrast to these modifications, which have essentially replaced the original protocol of the Stille reaction, another approach to enhance the efficacy of the Stille reaction relies on the use of a reactive stannane. We wish to term this approach the "heteroatom assisted Stille reaction" as it requires the presence of a heteroatom in the organostannane that can coordinate a metal with a free pair of electrons. To our knowledge only two reports have been published before the commencement of this study.[143,144] Since that work is relevant to ours we shall briefly discuss it.

4.1.2. The Heteroatom assisted Stille Reaction

Some arylstannanes that contained a heteroatom in a remote position were found to be exceptionally reactive in the Stille reaction.[143,144] Such an effect of enhanced reactivity as a result of heteroatom coordination is extensively documented for other coupling reactions in the literature, for example, the chelation assisted insertion of

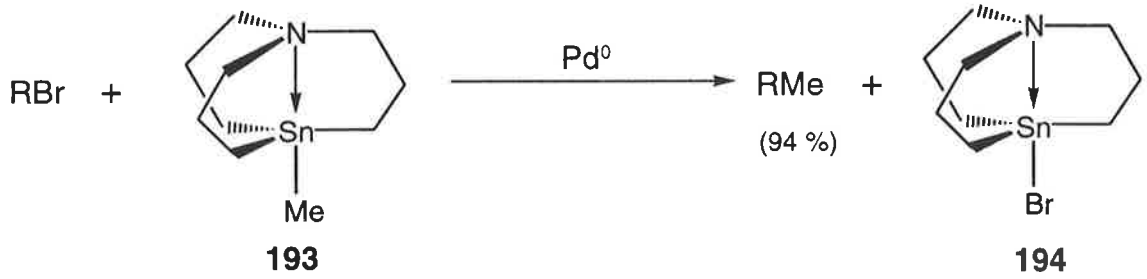
zerovalent nickel into the carbon-sulfur bond,[146] of an iron(II) species into the carbon-bromine bond,[147] of a zerovalent palladium into the tin-silicon,[148] the silicon-silicon[149] and the carbon-tin bond.[150]

The chelation assisted insertion of palladium(II) into the tin-carbon bond was demonstrated with an arylstannane **189** that had a nitrogen atom in the position γ to the tin atom (**Scheme 62**).[143] It was proposed that an intramolecular coordin-



Conditions: 4 mol% of ClPd[C(O)Ph](PPh$_3$)$_2$, THF, 40 °C.

Scheme 62



Conditions: A catalytic amount of dppfPdCl$_2$, 75 °C, 2 h, toluene, RBr = *p*-bromoanisole

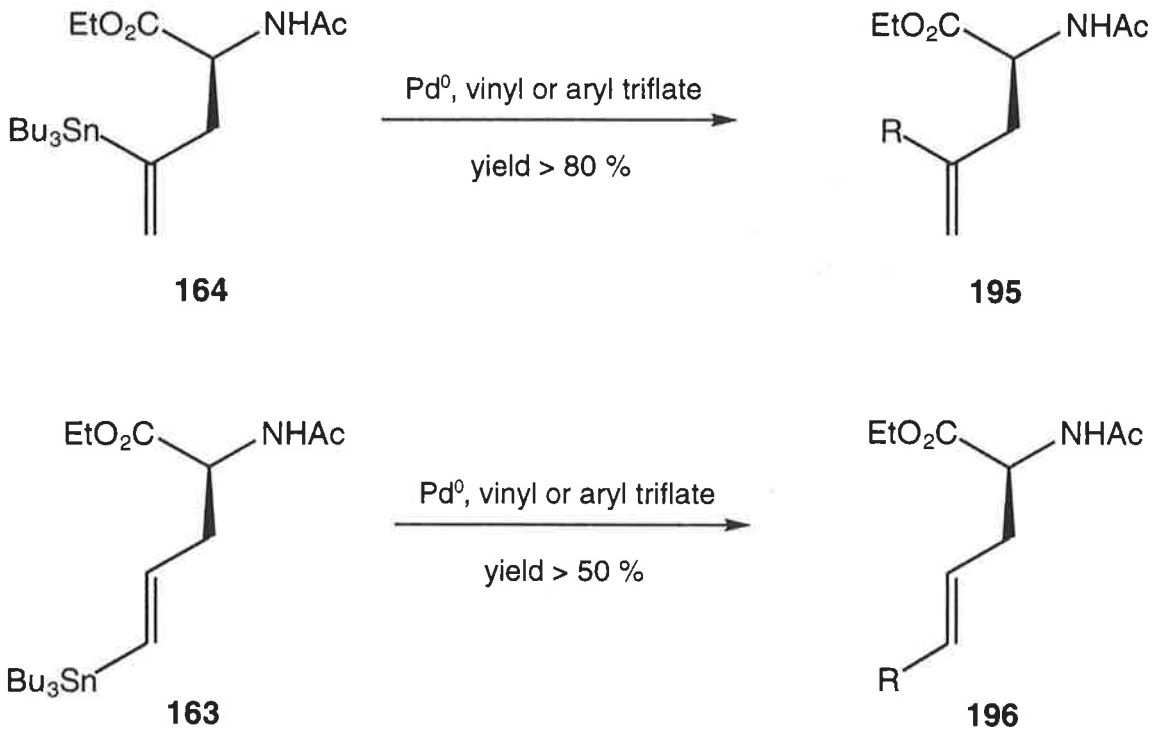
Scheme 63

ation of the tin by the nitrogen atom of **189** was enforced by the rigid naphthyl moiety, which resulted in a weakened carbon-tin bond in a position *trans* to the nitrogen atom and an accelerated transmetallation.[145] The second example of an

unusually reactive organostannane **193** involved the same principle of enforced chelation of the tin atom by a nitrogen atom in the position γ, which resulted in an accelerated transmetallation of a methyl group in a position *trans* to the nitrogen atom (**Scheme 63**).[144]

4.1.3. The Stille Reaction in the Elaboration of the Side-Chains of α-Amino Acids

α-Amino acids featuring a vinylstannane in their side-chain participated in the Stille reaction with a wide range of electrophiles (**Scheme 64**).[108] One of the incentives



Conditions: 5 mol% of Pd_2dba_3, ROTf (1.5 equiv.), R = aryl or vinyl, reflux in THF for several hours. Aryl and vinyl halides couple as well.

Scheme 64

of employing the Stille reaction in the synthesis of potential enzyme inhibiting α-amino acids that feature multiple unsaturation in the side-chain was the mildness of the reaction conditions in particular with regard to the use of non-basic and non-acidic reagents.[104,105] Ideally, the reaction conditions for subsequent manipulations

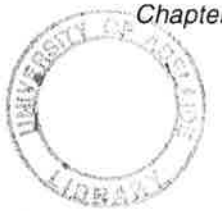
of the α-amino acids, such as a peptide coupling and deprotection, should also be mild in order to preserve an acid or base-sensitive side-chain. In that respect the *N*-acetyl amino protecting group represented a less than ideal choice since reaction conditions for its non-enzymatic removal would be harsh, when compared to the ease of removing the more commonly employed Boc, Cbz and Fmoc protecting groups. This problem is addressed in this work by using the diphenylimine protecting group.

4.2. Aim

We were interested in exploring the Stille reaction of vinnylstannanes analogous to those depicted in **Scheme 64**, in which the amino functionality was protected as the diphenylmethylenimine. In contrast to the acetamido, the diphenylmethylenimine protecting group can be removed under mildly acidic conditions.

Furthermore, we were interested to react the *N*-diphenylmethylenimine protected α-amino acid stannanes **172** and **176** (**Scheme 65**) with vinyl bromide since previously no coupling between this particular electrophile and the related *N*-acetyl protected vinylstannanes **163** and **164** could be induced.[108]

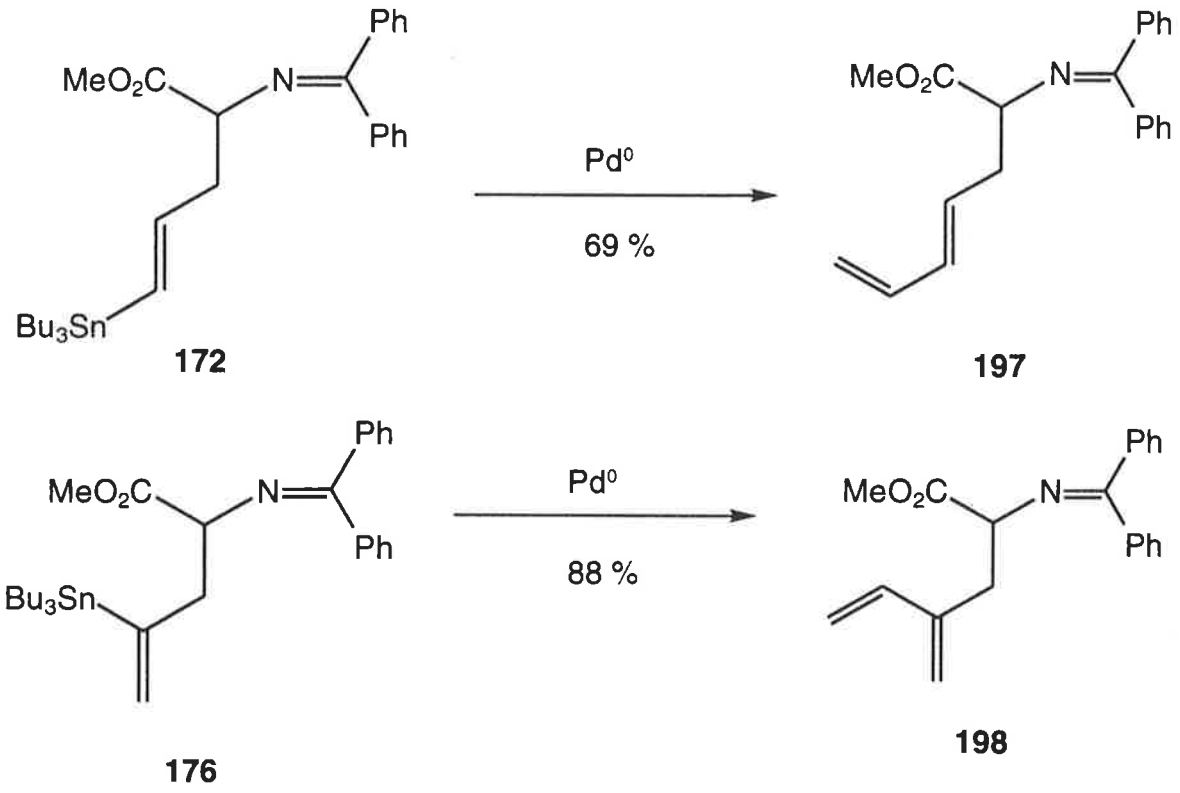
Our greatest interest, however, was the exploration of a heteroatom assisted Stille reaction, which was deemed possible as the imine nitrogen of vinylstannanes **172** and **176** could possibly interact with the palladium catalyst. Ideally, under heteroatom assistance, Stille reactions would be efficiently conducted under even milder than the reported conditions.[108]



4.3. Results and Discussion

4.3.1. The Stille Reaction of α-Amino Acids featuring isomeric Vinylstannanes in their Side-chains

Initially we reacted isomerically pure vinylstannanes **172** and **176** with vinyl bromide in separate reactions to afford dienes **197** and **198** in 69 % and 88 % yield, respectively (**Scheme 65**). Our choice of $PdCl_2(CH_3CN)_2$ as a precursor for the "ligand-free" palladium(0) catalyst was inspired by the reported successful coupling of the analogous stannanes **163** and **164** with *trans*-β-bromostyrene (**Scheme 64**).[108] Under these conditions, the secondary vinylstannane **176** was significantly more reactive than its sterically less encumbered isomer **172**. In fact, we were able to convert vinylstannane **176** completely within 40 minutes at a temperature of 0 °C! We suspected that the extraordinary reactivity of vinylstannane **176** was caused by the assistance of the imine nitrogen. In order to test this hypothesis we carried out a series of competition experiments.



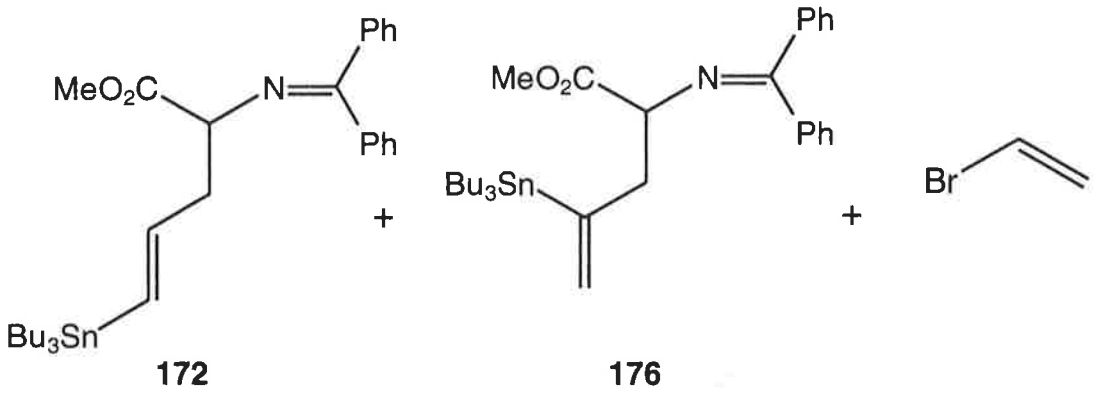
172 **197**

176 **198**

Conditions: 5 mol% of $PdCl_2(CH_3CN)_2$, vinyl bromide (34 equiv.), DMF, 25 °C, 24 h.

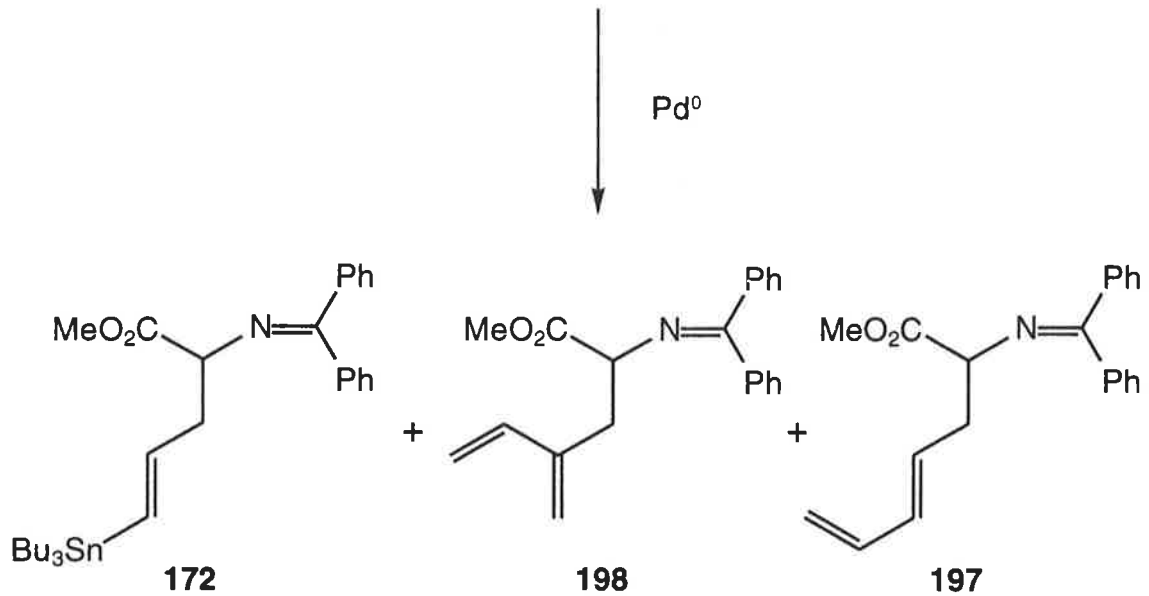
Scheme 65

Firstly, a one to one mixture of vinylstannanes **163** and **164** was treated in DMF with an excess of vinyl bromide in the presence of 5 mol% of $Pd(CH_3CN)_2Cl_2$ at 0 °C (**Scheme 66**). The crude reaction product was analysed by ^1H and ^{13}C nmr spectroscopy. Resonances due to diene **198** and unchanged vinylstannane **172** dominated both spectra. A closer inspection revealed, however, that a small amount of diene **197** was present. The ratio of vinylstannane **172** and its derived product diene **197** was estimated at nine to one in favour of **172** by the integration of the olefinic resonances at $\delta = 5.98$ ppm (**172**) and $\delta = 5.09$ ppm (**197**). As



172 **176**

(A mixture of **172** and **176** in a 1 to 1 ratio)



172 **198** **197**

(yield : 30 %) (combined yield : 51 %)
(ratio : 9 to 1 in favour of **198**)

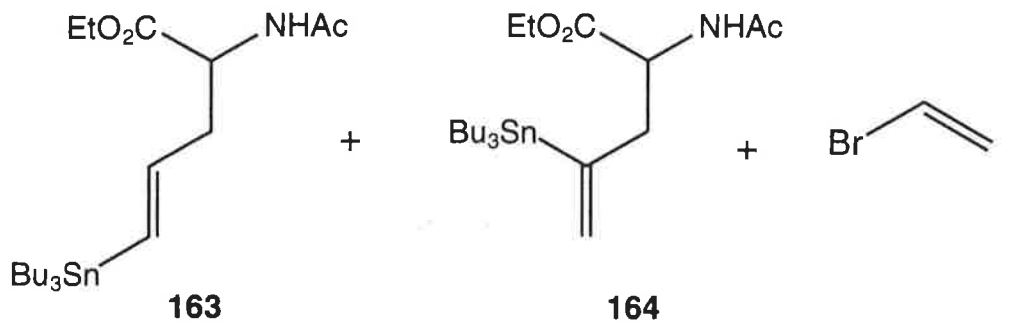
Conditions: See Scheme 65, yields are isolated and based on the combined amount of starting vinylstannanes **172** and **176**.

Scheme 66

stannane **176** was not detected, this ratio was an indication of the relative reaction rates of vinylstannanes **176** and **172**, which was therefore at least 9 times greater for **176** than for **172**. Purification of the reaction mixture by mplc resulted in the isolation of unchanged vinylstannane **172** and a mixture of dienes **197** and **198**.

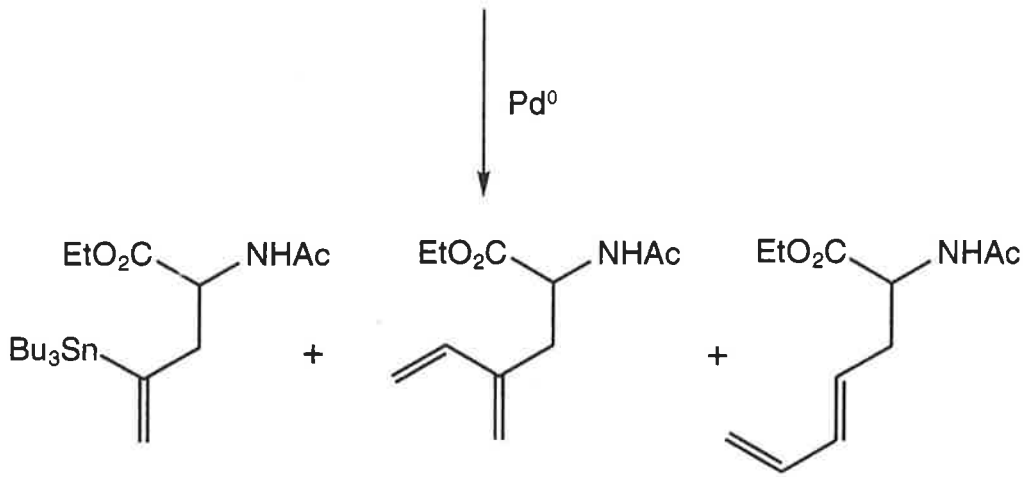
In order to confirm the exceptional reactivity of vinylstannane **176** was influenced by the amino protecting group, we prepared a one to one mixture of *N*-acetyl protected vinylstannanes **163** and **164** according to the literature procedure[110] and treated it with vinyl bromide (**Scheme 67**).

Whilst a significant amount of unchanged vinylstannane **164** was detected when the olefinic region of the ^1H nmr spectrum of the crude product, only a trace amount



163 **164**

(A mixture of **163** and **164** in a 1 to 1 ratio)



164 (20 %) **199** **200**

(combined yield: 36 %)
(ratio: 1.7 to 1.0 in favour of **200**)

Conditions: 5 mol% of $PdCl_2(CH_3CN)_2$, vinyl bromide (30 equiv.), DMF, ambient temperature for 1 d.

Scheme 67

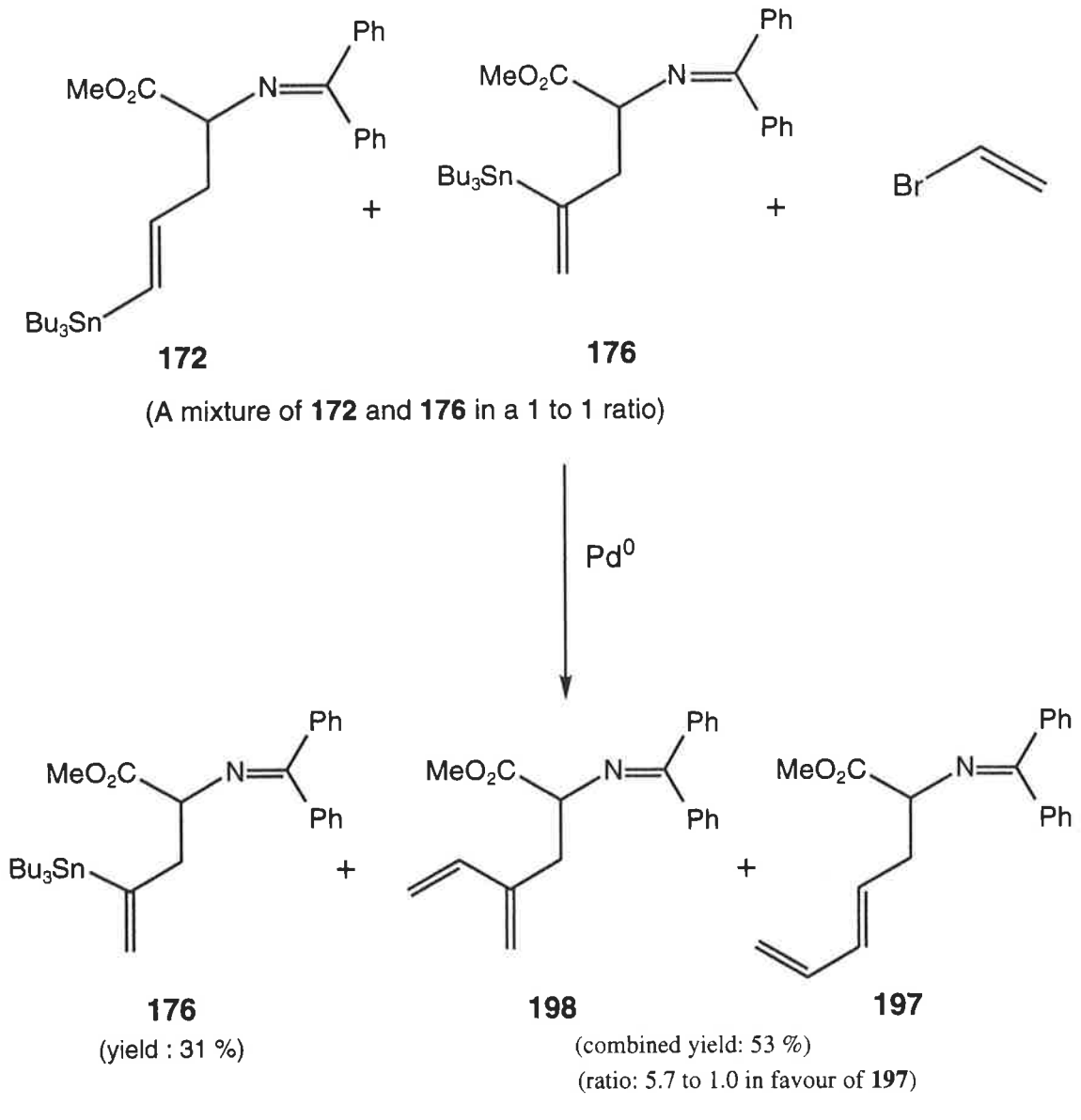
of the isomeric vinylstannane **163** was detected in the ^{13}C nmr spectrum. From this material a mixture of dienes **199** and **200** were isolated by mplc as a mixture in 36 % yield. Their ratio of 1.7 to 1.0 in favour of **200** was determined by comparison of the resonances at $\delta = 5.15$ ppm (**200**) and $\delta = 5.06$ ppm (**199**). Clearly, under these conditions, vinylstannane **163** was more reactive than the isomer **164**, which was recovered in 20 % yield. Hence, with regard to the relative reactivity of the starting isomeric vinylstannanes, the situation found for the *N*-acetyl as compared to the *N*-diphenylmethylenimine protected vinylstannanes was reversed.

These results appeared to implicate the lone pair of electrons on the imine nitrogen of vinylstannane **176** as a cause for its exceptional reactivity in the Stille reaction as all of the valence electrons of the nitrogen of the acetamide **164** were engaged in bonding, which includes the resonance delocalisation of the unpaired pair. We reasoned that the imine nitrogen of **176** was coordinating to the palladium catalyst during the Stille reaction *via* its lone pair of electrons. In a way that has yet to be determined this coordination appeared to facilitate the Stille reaction.

Before a mechanistic rationale will be proposed to account for the observed rate effects, it is illuminating to discuss the results of another experiment.

We treated a one to one mixture of vinylstannanes **172** and **176** with vinyl bromide in the presence of a triphenylarsine ligated palladium catalyst (**Scheme 68**).

^{1}H nmr spectroscopic analysis revealed that even after 48 hours of reaction time the secondary vinylstannane **176**, which was, *in the previous experiments*, more reactive than its isomer **172** was still present in significant quantities in the reaction mixture. By contrast, none of the isomeric stannane **172** could be detected as it was completely converted into diene **197**. Only a relatively small amount of diene **198** could be detected and the ratio of vinylstannane **176** to its derived product diene **198** was estimated by the integration of the olefinic resonances at $\delta = 5.02$ ppm (**198**) and $\delta = 5.16$ ppm (**176**). This ratio of approximately four to one in favour of **176** was an indication for the relative reaction rates of vinylstannanes **172** and **176**. Apparently there was an enormous decline in reactivity of vinylstannane **176** upon substituting a ligated for a "ligand-free" palladium catalyst. This change was



Conditions: 2.5 mol% of Pd_2dba_3, 0.4 equ. of $AsPh_3$, 15 equ. of vinyl bromide, THF, 2 days at ambient temperature, isolated yields are indicated.

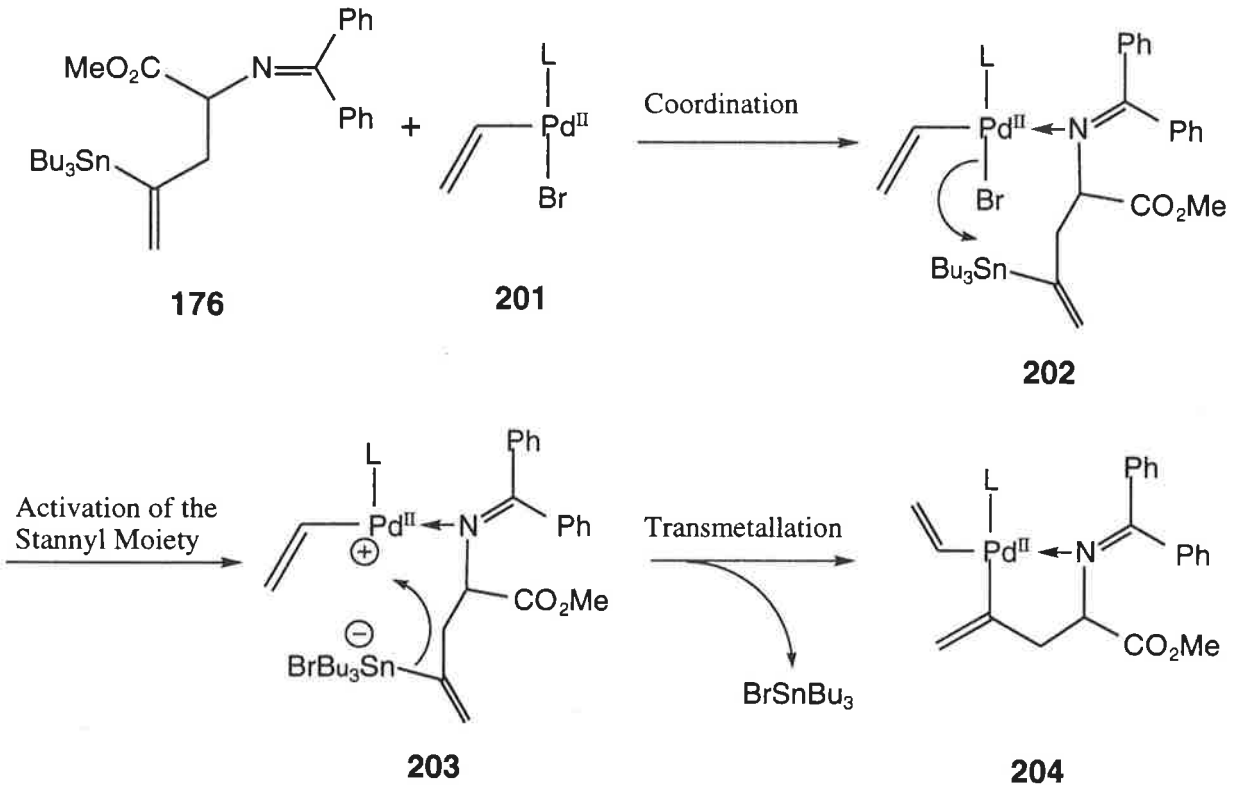
Scheme 68

so marked that, under the catalysis of triphenylarsine ligated palladium, vinylstannane **176** reacted approximately 4 times *slower* than the isomer **172** (**Scheme 68**).

4.3.2. A Mechanistic Model for the "Chelation assisted" Stille Reaction

The mechanism of the Stille reaction consists of the usual triad of oxidative addition, transmetallation and reductive elimination as depicted in **Scheme 60**,

amongst which the transmetallation is the rate-determining step.[127] This also appeared to be the case in the reactions of the α-amino acid vinylstannane derivatives **172** and **176**, since the reaction rate was markedly dependent on the geometry of the double bond as it was determined in the competition experiments. We reasoned that the reaction of vinylstannane **176** with vinyl bromide was remarkably fast *in the absence of strongly coordinating ligands such as triphenylarsine*, because the imine nitrogen of **176** coordinated to the vinylpalladium(II) complex **201** during the transmetallation (**Scheme 69**).

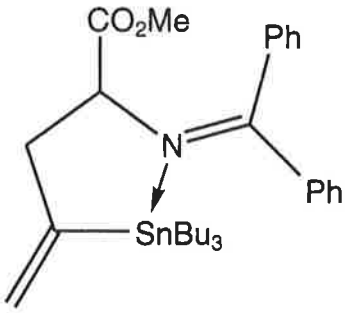


Scheme 69

Coordination of divalent palladium(II) species by an imine nitrogen has often been observed.[151] *In the presence of triphenylarsine* the coupling rate is not markedly accelerated as, under these conditions, potential coordination-sites on palladium are blocked by the ligand. In the light of these results it appeared improbable that an intramolecular coordination of tin by the imine nitrogen as depicted in **Figure 12** caused the great reactivity of stannane **176** in the presence of a "ligand-free"

palladium catalyst. Should such an intramolecular coordination occur we would have expected vinylstannane **176** to be very reactive *independently* of the presence of a strong ligand, which was in a clear contradiction to our observations. In this manner vinylstannane **176** is distinguished from the other unusually reactive stannanes discussed in the introduction to this chapter, in which an intramolecular coordination of tin is enforced by the rigid structure of the stannane.[143,144]

Figure 12. Intramolecular Coordination of Tin by the Imine Nitrogen in stannane **176**.



The question now arises, how coordination of palladium by the imine nitrogen of vinylstannane **176** but not of the isomer **172** accelerated the transmetallation. In order to answer this question the transmetallation has to be discussed in more detail. Studies by Stille have established several facts:[127]

a) The breaking of the carbon-tin bond occurs before the making of the carbon-palladium bond.

b) Arylstannanes transmetallated faster when the aryl moiety was attached to an electron-withdrawing group. This suggested a built-up of negative charge on the tin atom during the transition state.

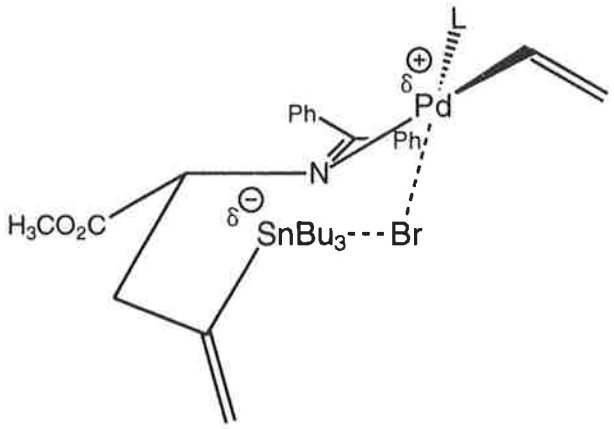
c) The retention of the configuration of the carbon-carbon double bond of vinylstannanes in the coupled products was consistent with an electrophilic substitution of tin by a palladium complex.

d) At some stage during the transmetallation a bond is formed between the tin and halogen atoms.

We speculated that the breaking of the carbon-tin bond may be the highest energy barrier during the transmetallation of most Stille reactions. This is a reasonable expectation as a carbon-tin bond is considerably strong. This process may, however, be assisted by a nucleophilic attack of an halide ion on the stannyl moiety to give a penta-coordinated tin species, such as **203**. Although organotin compounds generally only expand their coordination number from four to five when at least one of the substituents on tin is an electron-withdrawing halogen atom, such a penta-coordinated tin species may be formed *transiently*.[145] The carbon-tin bond would be greatly weakened in a penta-coordinated tin intermediate (e.g. **203**) and it may readily be substituted by an electrophilic palladium(II) complex. Circumstantial evidence does exist for an initial activation of the stannyl moiety by a nucleophilic attack by a halide ion. For example, vinyl triflates do not react with vinylstannanes in the presence of a palladium catalyst *unless* a halide source is present in the reaction mixture.[128] Secondly, triorganovinylsilanes are very similar to vinylstannanes, however, they do not couple as readily with unsaturated electrophiles under the catalysis of palladium.[136] In the presence of a very strong nucleophile, such as fluoride, a smooth reaction ensues, which may be due to an initial activation of the silane by a nucleophilic attack by the fluoride ion.

On the basis of the tentative mechanism for the transmetallation of vinylstannane **176** (**Scheme 69**) it appears, that the formation of the zwitterion **203** would have been energetically unfavoured as it involves the breaking of a palladium-bromine bond. The energy required for this bond cleavage would hardly be compensated by the formation of the relatively unstable anionic penta-coordinated tin species. Consequently structure **203** should have a high energy and be rather a transition state than a true reaction intermediate. The question arises now, which factors stabilise such a zwitterion in the case of stannane **176** as opposed to the isomer **172**? We undertook studies using CPK molecular models for possible transition states of the transfer of a bromide ion from palladium to tin for both stannanes **172** and **176**. For the fast reacting vinylstannae **176** a cyclic transition state could be constructed (**Figure 13**). The features of this transition state are the seven-membered pallada-

Figure 13. Tentative Transition State for the Halide Ion Transfer during the Transmetallation.



cycle in which the positive charge on palladium(II) is stabilised by the coordination to the imine nitrogen. Furthermore, the geometry appears to be ideal for a transfer of the bromide ion from palladium to tin.

By contrast such a cyclic transition state could not be constructed for the less reactive vinylstannane **172** and a transferral of a bromide ion would presumably have required a disruption of the coordination of palladium by the imine nitrogen of vinylstannane **172**.

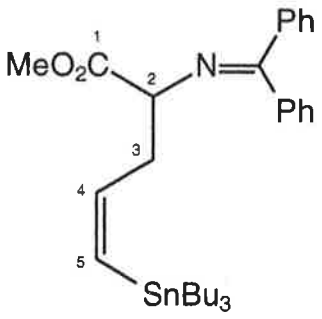
The actual transmetallation of the zwitterion **203** to form the divinyl palladium complex **204** may be a rather rapid process due to the presence of an activated penta-coordinated stannyl moiety (**Scheme 69**). This is also consistent with the observations of previous studies, which stated that a penta-coordinated organotin species transmetallated faster.[143]

In summary, we have shown that the Stillle reaction of the 4-(tributylstannyl)allylglycine derivative **176** was unusually fast and efficient when a "ligand-free" catalyst derived from $Pd(CH_3CN)_2Cl_2$ was employed. Competition experiments support the idea that the diphenylmethylenimine protecting group *actively participated in the reaction* by means of a coordination of the palladium catalyst. A tentative mechanistic rationale for the heteroatom assisted Stille reaction was proposed.

From a synthetic standpoint these results are important as we have now optimised the conditions by which the Stille reaction can be employed to synthesise 4-sub-

stituted allylglycine derivatives *via* the Stille reaction. Stille reactions of vinylstannane **176** represent a short and very mild route into such allylglycine derivatives. There is also no plausible reason why the hydrostannation (Chapter 3) could not be carried out on optically active propargylglycine derivative **171**, which would lead into optically active 4,4-disubstituted allylglycine derivatives.

It remains to be shown whether *Z*-vinnylstannane **173** would also participate in Stille reactions with aryl or vinyl halides under these exceptionally mild conditions. The derived *Z*-allylglycine derivatives would constitute interesting targets possibly as mechanistic probes in the exploration of pyridoxal phosphate dependent enzymes.[105]



173

Conclusions

This methodological study was on the elaboration of the side-chain of α-amino acid derivatives *via* transition metal promoted transformations and the Diels-Alder reaction.

In Chapter 1 markedly improved reaction conditions for the Heck-type coupling of non-activated alkenes with vinyl triflates were developed based on a change of the inorganic ligand of the palladium catalyst. These conditions may be applied in future to the stereo-controlled synthesis of 1,3-dienes under mild conditions.

In the second chapter it was discovered that the heteroatom protecting group that was separated from the 1,3-diene moiety by 4 (!) bonds partially shielded the π-electron system against the attack of a dienophile. The highest π-facial discrimination in the Diels-Alder reaction of these chiral dienes was achieved with bulky silyl ether protecting groups (d.e. = 83 %). An even higher value was presumably precluded due to the conformational diversity of the acyclic chiral dienes in the transition state. We postulate that this diversity may be curtailed and the diastereofacial selectivity lifted by introducing further 1,3-allylic strain into acyclic chiral dienes.

In Chapter 3 a systematic study of a variety of transition metal complexes as catalysts for the hydrostannation of alkynes was undertaken with the aim of increasing the regioselectivity of this process and met with limited success.

Protecting groups are commonly introduced as part of a synthetic strategy to avoid the formation of by-products from the reactions of a particular functional group. We have reversed this principle in Chapter 4 and shown that a suitable amino protecting group present in a remote location in a vinylstannane caused a dramatic acceleration in the coupling rate during a Stille reaction. It was reasoned that the imine protected nitrogen atom acted as a superior internal ligand to the palladium catalyst. Awareness of this new "chelation assisted Stille reaction" may be useful in planning the syntheses of complex natural products that frequently contain both unsaturation and nitrogen functionality.

Experimental

General Experimental Section

Solvents: THF was distilled from sodium/benzophenone, DMF and DMA were dried over activated 4Å molecular sieves and distilled (3 Torr) immediately prior to use. Acetonitrile and $CDCl_3$ were used as supplied. Water was deionised. Other solvents were fractionated through a 30 cm-long column packed with glass helices. When dichloromethane was used as a reaction solvent it was freshly redistilled from phosphorous pentoxide. "Hexane" refers to the fraction of light petroleum boiling between 67 and 69 °C. 1,2-Dichlorobenzene (grade: "purum") was purchased from Fluka and used without further purification.

Chemicals were purchased from Aldrich, Sigma, Fluka or BDH and were reagent grade. The following compounds were synthesised according to the quoted literature procedures: (*S*)-Methionine methyl ester hydrochloride,[15] (*S*)-*N*-benzoxycarbonyl methionine methyl ester **30**,[15] cyclohexen-1-yl triflate **43** (starting cyclohexanone was distilled through a fractionating comumn before use),[21] 2,2'-azobisisobutyronitrile,[155] vinylstannanes **163** and **164**,[110] methyl *N*-diphenylmethylenimine glycinate **168**.[112]

Transition metal complexes: Pd on polyimine, $PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$ and $Pd(OAc)_2$ were purchased. The following complexes were synthesised according to the quoted literature procedures: $PdCl_2(PMe_3)_2$,[119] amorphous Pd-metal,[123] $RhCl(PPh_3)_3$,[124] $NiBr_2(PPh_3)_2$,[157] $PtCl_2(PPh_3)_2$,[124] Cp_2ZrHCl.[125a] The syntheses of $PdCl_2(PBu_3)_2$, $PdCl_2$dppe, $PdCl_2[P(o\text{-tolyl})_3]_2$, $PdCl_2(AsPh_3)_2$ and $PdCl_2(PPh_3)_2$ is described at the end of the Experimental Section.

Reactions were performed under an atmosphere of nitrogen unless otherwise mentioned. Where mentioned reaction mixtures were degassed by performing evacuation/refilling cycles using a vacuum/nitrogen double manifold.

Hplc: The following solvents were employed: acetonitrile (hplc grade), water (purified using the Waters MilliQ filtering system), methanol (reagent grade, fractionally distilled), trifluoroacetic acid (Aldrich). The solvent systems were optimised

according to known procedures.[153] For the preparation of aqueous solvent systems for isocratic elution they were mixed and then degassed by filtration through methanol treated polytetrafluoroethylene (PTFE) membrane. A 25 cm × 10 mm column (Supelco) packed with 1-octadecanol derivatised silica (particle size: 5 µm) was used. A column efficiency of 24336 theoretical plates was determined by the supplier. A flowrate of 4 ml/min was achieved by an ICI LC 1110 pump. The eluant was generally detected at $\lambda = 258$ nm (Cbz derivatives) or at $\lambda = 240$ nm (Boc derivatives) using an ICI LC 1200 UV/VIS detector. The ICI DP800 data processing program was used on a 286 BIOS work station. For greater accuracy peak areas were measured using the manual integration option of the data processing program rather than the automatic integration routine. Equal extinction coefficients at the detection wavelength were assumed for all Cbz derivatives, which was a valid procedure considering that quantitative nmr spectroscopic measurements reproduced the isomeric ratios measured by hplc. Analytical samples were prepared by evaporating the solvent of an aliquot of the reaction mixture, dissolving the residue in a minimum amount of the eluant and filtration through a PTFE membrane.

Fractions obtained from semi-preparative separations were pooled, kept on ice and a few drops of sat. $NaHCO_3$ were added to neutralise trifluoroacetic acid present in the solvent system in order to minimise the hydrolysis of esters. Their purity was checked by hplc analysis of an aliquot of the pooled fraction. Following tenfold concentration under reduced pressure pooled fractions were acidified to pH ≈ 0 by the cautious addition of 10 % HCl. It was immediately extracted four times with ether. The total amount of ether was ten times the volume of the aqueous phase. During the extraction the pH of the aqueous phase was maintained at 0. The combined extracts were washed with a quarter of their volume of 10 % HCl, dried ($MgSO_4$) and the solvent evaporated.

Mplc was performed on a 25 cm × 2.5 cm LiChroprep® column (Merck) packed with silica gel (Si60, particle size 0.040 to 0.063 mm). A constant flowrate of 1

cm/min was achieved by a peristaltic pump and the eluant was generally detected at $\lambda = 258$ nm using an UV detector.

Chromatography was performed, unless otherwise mentioned, on silica gel 60 (particle size 0.040-0.063 mm, Merck) according to the published procedure.[154] A solvent system was chosen that moved the desired compound to $R_f = 0.25$ on a tlc plate. When the crude product was soluble in the eluting solvent (≈10× of the sample weight), it was loaded onto the column as a solution. When the crude material did not dissolve, it was preadsorbed onto silica (≈5 times of the weight of the sample) from a more polar than the eluting solvent system (usually dichloromethane or ethyl acetate). The solvent was completely evaporated until a freely flowing powder was obtained, which was loaded onto the column as a slurry in a minimum amount of the eluting solvent.

Where indicated Florisil (Fluka) was used as the stationary phase. It was activated by heating to 150 °C at a reduced pressure of 0.5 Torr for 1 day.

Basic alumina (Merck, 0.063 to 0.200 mm particle size) was of activity 1.

Nmr spectroscopy

All samples were analysed as solutions in $CDCl_3$ on a Bruker ACP300 spectrometer at a static field strength of 7.05 Tesla (300 megahertz for proton) unless otherwise mentioned. All experiments were performed using quadrature detection and quad images were suppressed by a CYCLOPS phase cycle. Except for nOe measurements all experiments were performed on spinning samples.

^{1}H nmr spectroscopy. Spectra were acquired with a pulse angle of 40° over a range of 3000 Hz and digitised with 16000 datapoints. For quantitative determinations of proton signals a pulse angle of 90° and a relaxation delay of 10 sec between scans was employed. When proton coupling constants were measured with an accuracy of one decimal adequate digital resolution was ensured.

^{13}C nmr spectroscopy. Spectra were acquired with a pulse angle of 72° over a range of 20000 Hz and digitised with 32000 datapoints. Proton decoupling was achieved by the composite pulse sequence WALTZ-16. For the quantitative determination of carbon signals the pulse angle was 90° and 64000 datapoints were used

to digitise a spectral range of 14000 Hz. A radiationless relaxation delay of 2 sec was included. Samples were prepared by dissolving 50-100 mg of compound and 2-4 mg of chromium(III) acetylacetonate in $CDCl_3$.

2D nmr spectroscopy. $^1H,^1H$ and $^1H,^{13}C$ correlated spectra were acquired with quadrature detection in the second dimension, which was brought about by time proportional phase increment. The two dimensional data set was usually multiplied with a shifted sine-bell window function (maximum at t = 0 sec).

Typical parameters for a H,H COSY experiment[66] were: A 45° or 90° acquisition pulse, spectral width = 2300 Hz; acquisition time in the t_2-domain= 0.225 sec, acquisition time in the t_1-domain = 0.112 sec, number of experiments = 256, the t_1-dimension was zerofilled to obtain equal digital resolution in both dimensions. This allowed for symmetrisation with respect to the diagonal of the data set after initial inspection of the unsymmetrised 2D spectrum.

Typical parameters for a H,C COSY experiment[67] were in the t_1-domain (^1H): spectral width = 23000 Hz, acquisition time = 0.112 sec, number of experiments = 128, number of datapoints = 512, in the t_2-domain (^{13}C): spectral width = 12000 Hz, acquisition time = 0.172 sec. Delays were optimised for J = 150 Hz.

Typical parameters for a COLOC experiment[69] were as for H,C COSY experiments although the spectral width in the t_2-dimension was increased to include carbonyl carbons and the delays were optimised for J = 8 Hz.

Difference spectroscopy. Proton resonances well separated from other resonances (by more than 0.2 ppm) were selectively irradiated for 0.8 sec before each scan. A radiationless delay of 2 sec was included. In the reference experiment the decoupler frequency was placed in a region free of resonances and, when possible, the decoupler frequency in the nOe and in the control experiment were positioned symmetrically around the resonance for which an nOe was observed in order to minimise uneven cancellation of signals due to decoupling artefacts. Spectra were digitised with 32000 datapoints.

The irradiation power on the decoupler channel was set to 5 to 25 μWatts for nOe experiments and to 0.05 Watts for decoupling experiments.

Reporting of nmr spectral data: It was assumed that the size of the line splitting of a multiplet was a direct measure of the coupling constants when an analysis of the spin system using a first order approximation appeared justified ($\Delta\delta > 4\times J$). In the case of $\Delta\delta < 4\times J$, the type of multiplet structure of a signal may be reported but not the line-splitting. Coupling constants were determined with a digital resolution of ±0.4 Hz and rounded to the nearest integer.

Infrared spectroscopy (ir): Oils were analysed as a thin film and solids as a nujol mull between sodium chloride plates on a Hitachi 270-30 spectrometer.

Ultraviolet spectroscopy (uv): Compounds were analysed as solutions in ethanol on a Pye-Unicam SP8-100 spectrometer.

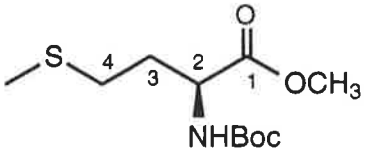
Mass spectroscopy (ms): Fast atom bombardment (fab) mass spectra were acquired on a Vacuum Generators ZAB 2HF reverse sector geometry mass spectrometer equipped with an Ion Tech FAB gun operating with argon gas at an accelerating potential of 6 - 8 kV and a current of 1 mA^2. Electron impact (ei) mass spectra and accurate mass measurements were acquired on the same instrument. The ionising energy was set at 70 eV and the temperature of the ion source was typically 150 °C and the accelerating potential 7 kV.

Microanalysis was carried out by the Chemistry Department of the University of Otago (New Zealand).

Melting points of solids were observed through a Reichert microscope on a hot plate. The temperature was measured with a thermometer fitted and calibrated for the hot plate.

Optical rotations of solutions were measured in a 1 ml sample cuvette on a Perkin-Elmer 141 polarimeter at ambient temperature.

(*S*)-*N*-*tert* Butoxycarbonyl methionine methyl ester (31)[15]



(*S*)-Methionine **29** (0.98 mg, 6.56 mmol) was treated with di-*tert*-butyl dicarbonate (1.58 g, 7.28 mmol) *in lieu of* benzyl chloroformate according to the reported procedure.[15] After the work-up a yellow oil obtained (1.75 g). ^{1}H and ^{13}C nmr spectroscopic analysis of the crude product was consistent with a mixture of **31** and unchanged di-*tert*-butyl dicarbonate. A ratio of 5:1 in favour of **31** was estimated by comparing the intensities of the resonances due to the *tert*-butyl groups. Taking the contaminating di-*tert*-butyl dicarbonate into account, a yield of 88 % was calculated for **31**. The crude product was used for further synthesis.

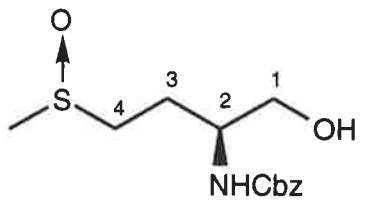
^{1}H nmr δ 5.36 (bd, 1H, NH), 4.21 (m, 1H, H2), 3.75 (s, 3H, OCH_3), 2.55 (t, 2H, H4), 2.15 (m, 1H, H3), 2.10 (s, 3H, SCH_3), 1.94 (m, 1H, H3), 1.45 (s, 9H, Bu).

^{13}C nmr δ 155.1, 146.4, 79.5, 52.5, 52.0, 31.8, 29.7, 28.0, 15.1.

Ir (neat) υ 3350 (NH), 1725, 1698 cm^{-1}.

Ms (ei) *m/z* 263 (M^{+}).

(2*S*)-2-[*N*-(Benzoxycarbonyl)amino]-4-(methylsulphinyl)butanol (32)



(*S*)-*N*-Benzoxycarbonyl methionine methyl ester **30** (59.44 g, 0.224 mol) was placed into a 2L two necked round bottomed flask equipped with an alcohol thermometer. Methanol (400 ml) was added and the contents were magnetically stirred until all of the ester had dissolved. The flask was immersed into an ice bath and

when the temperature of the solution reached 5 °C, of sodium borohydride from a freshly opened batch (11.0 g, 0.30 mol) was quickly added. Temporarily the reaction temperature rose to 30 °C. After stirring for 40 min the temperature reached 5 °C and sodium borohydride (7.4 g, 0.20 mol) was added. Following 20 min the ice bath was removed and stirring continued for 2 h. None of the starting ester **30** was detected by tlc analysis (1:1 ethyl acetate/hexane) of the reaction mixture and methanol (400 ml) was added. The reaction mixture was neutralised by the addition of 10 % HCl in small portions (total: 160 ml), whilst the pH was monitored after each addition. A clear solution resulted and was cooled to 5 °C in an ice bath. An aqueous solution was prepared by stirring sodium periodate (47.9 g, 0.224 mol) in boiling water (200 ml). The resulting solution was cooled to ambient temperature and immediately added to the stirred reaction mixture from a dropping funnel at a rate such as the reaction temperature did not exceed 15 °C. A white solid precipitated and after 30 min the reaction mixture was analysed by tlc (1:9 acetic acid/ethyl acetate). None of the intermediate sulfide remained and the mixture was filtered through a sintered glass funnel. After rinsing the solid with methanol (2×70 ml) the combined filtrates were concentrated to approximately 800 ml and thoroughly extracted with dichloromethane (2×250 ml, then 4×100 ml). The combined extracts were dried ($MgSO_4$) and the solvent evaporated to afford sulfoxide **32** as a light yellow solid (62.01 g, 97 %). The ^1H and ^{13}C nmr spectra of this material were consistent with a clean mixture of diastereomers.

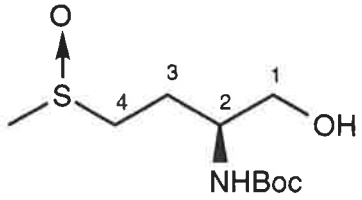
^1H nmr δ 7.31 (bs, 5H, ar), 6.80 (bs, OH), 5.90 (bd, 1H, NH), 5.05 (s, 2H, bn), 3.75 (m, 1H, H2), 3.59 (bs, 2H, H1), 3.08 (m, 2H, H4), 2.84 (s, 3H, SCH_3), 1.96 (m, 2H, H3).

^{13}C nmr δ 156.6 (CO), 136.0 (4° ar), 128.5 128.2, 128.1 (3° ar), 66.8 (bn), 64.5, 64.3 (C1), 52.3, 51.8 (C2), 50.5 (C4), 38.3 (SCH_3), 24.5, 24.4 (C3).

Ir (neat) υ_{max} 3600-3300 (OH, NH), 1696, 1540, 1260, 1070-1000 cm^{-1}.

Ms (e.i.) *m/z* 285 (M^+).

(2*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(methylsulphinyl)butanol (33)



Crude (*S*)-*N*-*tert*-butoxycarbonyl methionine methyl ester **31** (5.79 g, 22.0 mmol) was treated following the procedure for the synthesis of **32**. Crude product **33** was and isolated as a light yellow solid (4.76 g, 86 %). The ^{1}H and ^{13}C nmr spectra of this material were consistent with a clean mixture of diastereomers **33**.

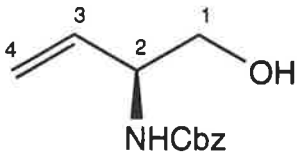
^{1}H nmr δ 5.50 (bd, 1H, NH), 4.03 (m, 1H, H2), 3.70 (bs, OH), 3.63 (m, 2H, H1), 2.81 (m, 2H, H4), 2.60 (s, 3H, SCH_3), 1.99 (m, 2H, H3), 1.44 (s, 9H, $C(CH_3)_3$).

^{13}C nmr δ 156.4 (CO), 79.3 (4^{o}), 64.3, 64.1 (C1), 51.6, 51.1 (C2), 50.9, 50.7 (C4), 38.1 (SCH_3), 24.8, 24.4 (C3).

Ir (neat) υ_{max} 3540 (OH), 3350 (NH), 1705, 1540, 1180, 1070-1010 cm^{-1}.

Ms (ei) *m/z* 251 (M^{+}).

(2*S*)-2-[*N*-(Benzoxycarbonyl)amino]-but-3-enol (34)[13,14]



All procedures were carried out in an efficient fume hood because of the stench of the sulfur containing by-products. Sulfoxide **32** (11.97 g, 42.0 mmol) was refluxed in 1,2-dichlorobenzene (150 ml) for 3 h under an atmosphere of nitrogen. The progress of the reaction was monitored by ^{1}H nmr spectroscopic analysis of an aliquot of the reaction mixture, from which the solvent was evaporated at a reduced pressure of 0.3 Torr. After the singlet at δ = 2.84 ppm ($SOCH_3$ **32**) had disappeared the solvent was distilled from the cooled reaction solution through a 20 cm long vacuum jacketed Vigreux column at a pressure of 0.5 Torr. The residue was chromatographed (45:55 ethyl acetate/hexane) and distilled through a short-path

distillation apparatus, b.p. 140-142 °C (0.02 Torr). Alcohol **34** (5.85 g, 63 %) was obtained as a white solid, m.p. 51-53 °C (lit.[13] 52-53 °C). The nmr spectral data matched the literature data for **34**.[13] Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.38; N 6.33 %. Found: C, 65.14; H, 6.95; N, 6.50 %.

^{1}H nmr δ 7.36 (m, 5H, ar), 5.75 (ddd, *J* = 16 Hz, *J* = 10 Hz, *J* = 5 Hz, 1H, H3), 5.55 (bd, 1H, NH), 5.21 (d, *J* = 16 Hz, 1H, $H4_{pro\text{-}Z}$), 5.17 (d, *J* = 10 Hz, 1H, $H4_{pro\text{-}E}$), 5.07 (ABq, 2H, bn), 4.25 (m, 1H, H2), 3.64 (m, 1H, H1), 3.54 (m, 1H, H1), 3.24 (t, *J* = 6 Hz, 1H, OH).

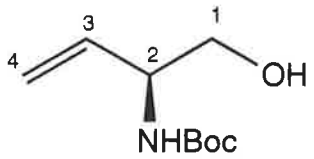
^{13}C nmr δ 156.4 (CO), 136.1 (4° ar), 135.1 (C4), 128.3, 127.9, 127.8 (3° ar), 116.3 (C3), 66.7 (bn), 64.3 (C1), 54.9 (C2).

Ir (nujol mull) υ_{max} 3600-3100 (OH), 1698 (CO), 1252, 1240, 1072 cm^{-1}.

Ms (ei) *m/z* 221 (M^+).

Or ($CHCl_3$, c = 3.1) $[\alpha]_D$ -34.1° (lit.[13] -32.1°).

(2*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-but-3-enol (35)



Crude sulfoxide **33** (4.03 g, 15.3 mmol) was treated following the procedure for the synthesis of **34**. The progress of the reaction was monitored by the disappearance of the singlet at δ = 2.60 ppm ($SOCH_3$ of **33**). The crude product was chromatographed (4:6 ethyl acetate/hexane) and distilled through a short-path distillation apparatus, b.p.: 120-133 °C (0.03 Torr), to afford **35** (1.86 g, 65 %) as a colourless clear oil (a solid with a m.p. of 36-37 °C was reported[13]). Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48 %. Found: C, 57.32, H 9.34, N 7.41 %. The nmr spectral data matched the literature data for **35**.[13]

^{1}H nmr δ 5.82 (ddd, *J* = 16 Hz, *J* = 10 Hz, *J* = 5 Hz, 1H, H3), 5.41 (d, 1H, NH), 5.24 (d, *J* = 16 Hz, 1H, H4$_{pro\text{-}E}$), 5.17 (d, *J* = 10 Hz, 1H, H4$_{pro\text{-}Z}$), 4.18 (m, 1H, H2), 3.86 (t, *J* = 6 Hz, 1H, OH), 3.63 (m, 2H, H1).

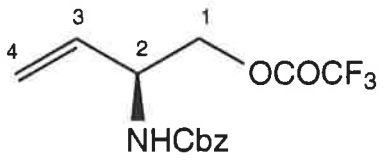
^{13}C nmr δ 155.8 (CO), 135.7 (C4), 115.7 (C3), 64.3 (C1), 54.4 (C2).

Ir (neat) υ_{max} 3600-3100 (OH), 1600, 1520, 1180, 1060 cm^{-1}.

Ms (ei) *m/z* 187 (M$^+$).

Or ($CHCl_3$, c = 1.6) $[\alpha]_D$ -26.6° (lit.[13] -29.0°).

(2*S*)-2-[*N*-(Benzoxycarbonyl)amino]-but-3-enyl trifluoroacetate (36)



To a solution of the alcohol **34** (53.4 mg, 0.242 mmol) in dichloromethane (0.5 ml) at 0 °C was added dropwise from a syringe freshly distilled trifluoroacetic anhydride (56 mg, 0.266 mmol) under a dry atmosphere. After stirring for 1 h the cooling bath was removed and the solvent evaporated. The crude material was chromatographed on Florisil (ether, flowrate: 3.5 cm per min) and **36** obtained (49 mg, 64 %) as a colourless clear oil. Anal. Calcd. for $C_{14}H_{14}NF_3O_4$: C, 53.00; H, 4.45; N, 4.41 %. Found: C, 52.84; H, 4.44; N, 4.74 %.

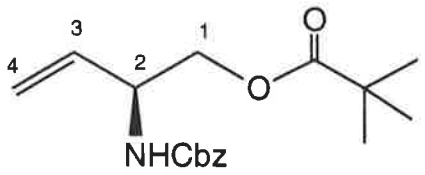
^{1}H nmr δ 7.34 (m, 5H, ar), 5.73 (ddd, *J* = 17 Hz, *J* = 10 Hz, *J* = 6 Hz, 1H, H3), 5.33 (bd, 1H, NH), 5.29 (d, *J* = 17 Hz, 1H, H4$_{pro\text{-}Z}$), 5.24 (d, *J* = 10 Hz, 1H, H4$_{pro\text{-}E}$), 5.09 (ABq, 2H, bn), 4.60 (m, 1H, H2), 4.34 (bd, 2H, H1).

^{13}C nmr δ 157.2 (q, CO_2R), 155.7 (NC(O)O), 136.2 (4° ar), 132.8 (C4), 128.4, 128.2, 128.0 (3° ar), 118.0 (C3), 114.3 (q, $J_{C,F}$ = 286 Hz, CF_3), 67.0 (bn), 68.3 (C1), 51.7 (C2).

Ir (neat) υ_{max} 3325 (NH), 1795, 1700, 1540, 1290, 1230, 1175 cm^{-1}.

Ms (ei) *m/z* 317 (M$^+$).

(2*S*)-2-[*N*-(Benzoxycarbonyl)amino]-but-3-enyl 2',2'-dimethylpropanoate (37)



To a solution of the alcohol **34** (162 mg, 0.733 mmol), pyridine (80 mg, 1.010 mmol) and a small crystal of *N',N'*-dimethyl-4-aminopyridine in dichloromethane (1 ml) at 0 °C freshly distilled 2,2-dimethylpropanoyl chloride (122 mg, 1.010 mmol) was added dropwise from a syringe under a dry atmosphere. After stirring for 12 h dichloromethane (20 ml) was added, the organic phase washed with 1M HCl (5 ml) and the aqueous phase extracted with dichloromethane (7 ml). The combined organic phases were washed with sat. $NaHCO_3$ (5 ml) and water (5 ml), and dried ($MgSO_4$) and the solvent evaporated. The crude material was chromatographed (16:84 ethyl acetate/hexane) and **37** obtained (166 mg, 74 %) as a colourless oil. Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59 %. Found: C, 66.58; H, 7.69; N, 4.62 %.

^{1}H nmr δ 7.34 (m, 5H, ar), 5.75 (ddd, *J* = 16 Hz, *J* = 10 Hz, *J* = 5 Hz, 1H, H3), 5.29 (bd, 1H, NH), 5.25 (d, *J* = 16 Hz, 1H, $H4_{pro\text{-}Z}$), 5.18 (d, *J* = 10 Hz, 1H, $H4_{pro\text{-}E}$), 5.08 (ABq, 2H, bn), 4.52 (m, 1H, H2), 4.14 (dd, 1H, H1), 4.05 (dd, 1H, H1), 1.17 (s, 9H, CH_3).

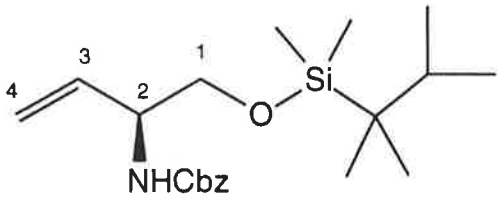
^{13}C nmr δ 178.1 (CO), 155.6 (NC(O)O), 136.2 (4° ar), 134.3 (C4), 128.3, 128.1, 127.9 (3° ar), 116.6 (C3), 66.6 (bn), 65.0 (C2), 52.3 (C2), 38.6 (4°), 26.9 (CH_3).

Ir (neat) υ_{max} 3350 (NH), 1730, 1700, 1695, 1540, 1290, 1240, 1160 cm^{-1}.

Ms (ei) *m/z* 305 (M^+).

Or ($CHCl_3$, c = 2.01) $[\alpha]_D$ -40.8°.

(2*S*)-1-(dimethyl-1',1',2'-trimethylpropyl)siloxy-*N*-(benzoxycarbonyl)-but-3-en-2-yl amine(38)



To a solution of alcohol **34** (999 mg, 4.52 mmol) in DMF (10 ml) were added dimethyl-1,1,2-trimethylpropyl silyl chloride (1.21 g, 6.78 mmol), triethylamine (686 mg, 6.78 mmol) and *N*-hydroxybenzotriazole (122 mg, 0.904 mmol) under an atmosphere of nitrogen. The mixture was stirred for 12 h and partitioned between ether (40 ml) and sat. NH_4Cl (15 ml). The aqueous layer was extracted with ether (20 ml) and the combined organic phases were washed with sat. NH_4Cl (3×15 ml), sat. $NaHCO_3$ (15 ml) and water (15 ml), and dried ($MgSO_4$) and the solvent evaporated. The crude material was chromatographed (12:88 ethyl acetate/hexane) and separated from contaminating dimethyl-1,1,2-trimethylpropyl silyl alcohol (b.p. 35-40 °C at 0.03 Torr) by distillation through a short-path distillation apparatus to yield **38** (1.33 g, 81 %) as a clear and colourless oil, b.p. 110-125 °C (0.03 Torr). Anal. Calcd. for $C_{20}H_{33}NSiO_3$: C, 66.07; H, 9.15; N, 3.85 %. Found: C, 66.08; H, 9.31; N, 4.11 %.

^{1}H nmr δ 7.34 (m, 5H, ar), 5.83 (ddd, J = 17 Hz, J = 10 Hz, J = 5 Hz, 1H, H3), 5.15 (1H, NH), 5.22 (d, J = 17 Hz, 1H, $H4_{pro\text{-}Z}$), 5.15 (d, J = 10 Hz, 1H, $H4_{pro\text{-}E}$), 5.11 (ABq, 2H, bn), 4.25 (m, 1H, H2), 3.68 (dd, 1H, H1), 3.61 (dd, 1H, H1), 1.60 (sep, J = 7 Hz, 1H, $CH(CH_3)_2$), 0.86 (d, 6H, J = 7 Hz, $CH(CH_3)_2$), 0.82 (s, 6H, $SiC(CH_3)_2$), 0.07 (s, 6H, $Si(CH_3)_2$).

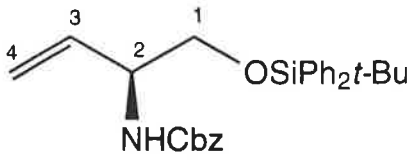
^{13}C nmr δ 155.8 (CO), 136.5 (4° ar), 136.2 (C4), 128.4, 128.0, 128.0 (3° ar), 115.8 (C3), 66.6 (bn), 64.9 (C1), 54.6 (C2), 34.1 (3°), 25.0 (4°), 20.2, 20.1, 18.4, 18.4 (CH_3), -3.7, -3.7 ($Si(CH_3)_2$).

Ir (neat) υ_{max} 3340 (NH), 1720, 1545, 1515, 1270, 1125, 850, 795, 715 cm^{-1}.

Ms (ei) *m/z* 363 (M^+).

Or (CH_2Cl_2, c = 13.54) $[\alpha]_D$ -37.2°.

(2*S*)-1-(Diphenyl*tert*-butyl)siloxy-*N*-(benzoxycarbonyl)-but-3-en-2-yl amine (39)



Alcohol **34** (1.62 g, 7.32 mmol) was treated following the procedure for the synthesis of **38** with diphenyl*tert*-butyl silyl chloride (3.02 g, 11.0 mmol) *in lieu of* dimethyl-1,1,2-trimethylpropyl silyl chloride. Contaminating diphenyl*tert*-butyl silyl alcohol was removed from crude product by distillation (oilbath temperature at 140 °C) through a short-path distillation apparatus, which was externally heated to 120 °C during the distillation, b.p. 90-100 °C (0.02 Torr). The oily residue was chromatographed (11:89 ethyl acetate/hexane) to yield **39** (2.79 g, 83 %) as a colourless oil. Anal. Calcd. for $C_{28}H_{33}NSiO_3$: C, 73.16; H, 7.24; N, 3.05 %. Found: C, 73.32; H, 7.22; N, 2.90 %.

^{1}H nmr δ 7.64-7.31 (m, 15H, ar), 5.84 (ddd, J = 17 Hz, J = 10 Hz, J = 5 Hz, 1H, H3), 5.08 (1H, NH), 5.23 (d, J = 17 Hz, 1H, $H4_{pro\text{-}Z}$), 5.18 (d, J = 10 Hz, 1H, $H4_{pro\text{-}E}$), 5.11 (ABq, 2H, bn), 4.32 (m, 1H, H2), 3.76 (dd, 1H, H1), 3.65 (dd, 1H, H1), 1.04 (s, 9H, $C(CH_3)$).

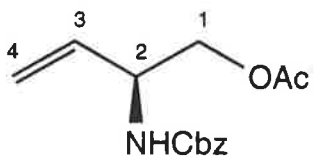
^{13}C nmr δ 155.9 (CO), 136.5, 136.0 (4° ar), 135.6, 135.5 (C4), 133.1, 132.9, 129.8 (ar), 128.5, 128.1, 127.7 (3° ar), 116.0 (C3), 66.7 (bn), 65.9 (C1), 54.7 (C2), 26.8 (4°), 19.3 (CH_3).

Ir (neat) υ_{max} 3330 (NH), 1720, 1535, 1505, 1220, 1110, 810, 740, 700 cm^{-1}.

Ms (ei) *m/z* 459 (M^+).

Or (CH_2Cl_2, c = 11.1) $[\alpha]_D$ +24.8°.

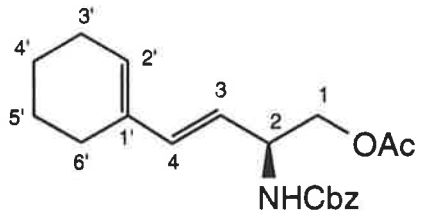
(2*S*)-2-[*N*-(Benzoxycarbonyl)amino]-but-3-enyl acetate (40)



Alcohol **34** (6.39 g, 28.9 mmol) was treated according to the procedure for the synthesis of **37** with freshly distilled acetic anhydride (3.25 g, 31.8 mmol) *inlieu of* 2,2-dimethylpropanoyl chloride. The crude material was chromatographed (1:3 ethyl acetate/hexane) and crystallised (ether/hexane) to afford **40** (5.71 g, 75 %) as a white solid, m.p. 54-56 °C (lit.[14] 54-56 °C). Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32 %. Found: C, 63.60; H, 6.52; N, 5.21 %.

^{1}H nmr δ 7.36 (m, 5H, ar), 5.78 (ddd, *J* = 16 Hz, *J* = 10 Hz, *J* = 5 Hz, 1H, H3), 5.03 (bs, 1H, NH), 5.28 (d, *J* = 16 Hz, 1H, $H4_{pro\text{-}Z}$), 5.23 (d, *J* = 10 Hz, 1H, $H4_{pro\text{-}E}$), 5.12 (ABq, 2H, bn), 4.52 (m, 1H, H2), 4.13 (m, 2H, H1), 2.03 (s, 3H, CH_3).
^{13}C nmr δ 170.5 (CO_2R), 155.6 (NC(O)O), 136.2 (4° ar), 134.3 (C4), 128.3, 128.0, 127.9 (3° ar), 116.7 (C3), 66.7 (bn), 65.4 (C1), 52.1 (C2), 20.5 (CH_3).
Ir (nujol mull) υ_{max} 3332, 1730, 1695, 1540, 1250 cm^{-1}.
Ms (ei) *m/z* 263 (M^+).
Or ($CHCl_3$, c = 0.94) $[\alpha]_D$ -40.1° (lit.[14] -43.2°).

(2*S*,3*E*)-2-[*N*-(Benzoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)-but-3-en-1-yl acetate (41)



A 100 ml Schlenk tube was charged with a magnetic stirring bar, freshly distilled DMF (50 ml), alkene **40** (462 mg, 1.75 mmol), anhydrous potassium carbonate (581 mg, 4.20 mmol), water (126 mg, 7.00 mmol), tetrabutylammonium trifluoromethanesulfonate (686 mg, 1.75 mmol) and 1-cyclohexen-1-yl trifluoromethanesulfonate **43**[21] (595 mg, 2.59 mmol, **43** was a colourless clear liquid of which the purity was checked by ^{13}C nmr spectroscopic analysis of a concentrated sample). Magnetic stirring was commenced and the atmosphere in the reaction vessel was replaced with nitrogen performing four evacuation/refilling cycles using

a double vacuum/nitrogen manifold. Palladium(II) acetate (42 mg, 0.175 mmol) was introduced into the mixture by quickly removing the rubber septum from the Schlenk tube. Another three evacuation/refilling cycles were performed as described before. After stirring the mixture at ambient temperature for 30 min it was heated to 55 °C overnight. A small aliquot of the dark brown reaction mixture was withdrawn and thoroughly mixed with twice its volume of 1M HCl and ether. The organic phase was analysed by a tlc (35:65 ethyl acetate/hexane). None of the starting alkene **40** could be detected. A 20 cm long Vigereux column was fitted to the Schlenk tube and most of the solvent was distilled at a pressure of 1 Torr (oilbath at 40 °C). The residue was partitioned between ether (120 ml) and sat. NH_4Cl (40 ml). The separated aqueous layer was extracted with ether (70 ml) and the combined organic phases were washed with sat. NH_4Cl (2×40 ml), sat. $NaHCO_3$ (40 ml) and water (40 ml). The organic layer was dried ($MgSO_4$) and the solvent evaporated. The crude material was chromatographed (22:78 ethyl acetate/hexane) and **41** was obtained (481 mg, 80 %) as a white solid. Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08 %. Found: C, 70.00; H, 7.44; N, 4.13 %. Recrystallisation from ethyl acetate/hexane furnished crystals suitable for X-ray diffraction analysis; m.p. 66-67 °C. The nmr spectral data matched those reported in the literature.[14]

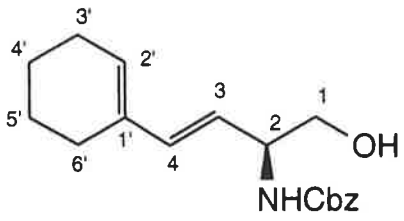
^{1}H nmr δ 7.36 (m, 5H, ar), 6.22 (d, *J* = 16 Hz, 1H, H4), 5.76 (bt, 1H, H2'), 5.41 (dd, *J* = 16 Hz, *J* = 6 Hz, 1H, H3), 5.12 (ABq, 2H, bn), 5.01 (bd, 1H, NH), 4.53 (m, 1H, H2), 4.13 (bd, 2H, H1), 2.10 (bm, 4 H, H3' and H6'), 2.03 (s, 3H, CH_3), 1.66-1.56 (bm, 4 H, H4' and H5').

^{13}C nmr δ 170.6 (CO_2R), 155.5 [NC(O)O], 136.2 (4° ar), 135.6 (C4), 136.3 (C1'), 130.5 (C2'), 128.2, 127.8, 127.8 (3° ar), 120.9 (C3), 66.6 (bn), 65.8 (C1), 51.9 (C2), 25.6, 24.2 (C3' and C4'), 22.2, 22.1 (C4' and C5'), 20.5 (CH_3).

Ms (ei) *m/z* 343 (M^+).

Or ($CHCl_3$, c = 0.56) $[\alpha]_D$ -7.3° (lit.[14] -7.5°).

(2*S*,3*E*)-2-[*N*-(Benzoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)-but-3-en-1-ol (53)



Method 1: Diene **53** was synthesised from alkene **34** (257 mg, 1.16 mmol) according to the procedure for the synthesis of **41**. The reaction mixture had blackened after 5 h and was worked-up as usual. ^{1}H nmr spectroscopic analysis showed that none of the starting alkene **34** was remaining in the crude product which was then chromatographed (1:1 ethyl acetate/hexane) to give diene **53** as a solid (185 mg, 53 %). Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65 %. Found: C, 71.71; H, 7.74; N, 4.60 %. Recrystallisation from isopropanol yielded flat rhombic crystals, m.p. 106-107 °C.

Method 2 (scale-up): The procedure was exactly as described under Method 1 scaling up the reagents as follows: alkene **34** (2.21 g, 10.0 mmol), 1-cyclohexen-1-yl trifluoro methanesulfonate **43** (2.76 g, 12.0 mmol), DMF (100 ml), water (180 mg, 10.0 mmol), tetrabutylammonium trifluoromethanesulfonate (392 mg, 1.0 mmol), potassium carbonate (3.45 g, 25.0 mmol), palladium(II) acetate (112 mg, 0.5 mmol). The crude product was chromatographed and diene **53** was obtained in 47 % yield as a solid.

Method 3: Diene **53** was also synthesised from **36**. The procedure is described under the synthesis of **54** (Method 1).

^{1}H nmr δ 7.35 (m, 5H, ar), 6.21 (d, *J* = 16 Hz, 1H, H4), 5.76 (bt, 1H, H2'), 5.45 (dd, *J* = 16 Hz, *J* = 6 Hz, 1H, H3), 5.26 (ABq, 2H, bn), 5.12 (bd, 1H, NH), 4.79 (m, 1H, H2), 4.46 (t, 1H, H1), 4.06 (dd, 1H, H1), 2.10 (m, 4 H, H3', H6'), 1.64 (bm, 4 H, H4' and H5' and OH).

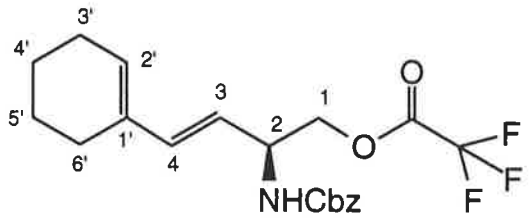
^{13}C nmr δ 156.4 (CO), 136.3 (4° ar), 135.6 (C4), 134.6 (C1'), 132.7 (C2'), 128.5, 128.4, 128.3 (3° ar), 121.7 (C3), 68.5 (bn), 67.7 (C1), 57.4 (C2), 25.9, 24.3 (C3' and C4'), 22.2, 22.2 (C4' and C5').

Ir (nujol mull) υ_{max} 3500 (OH), 3300 (NH), 1670, 1555, 1260, 1092, 1060, 970 cm^{-1}.

Ms (ei) *m/z* 301 (M^+).

Or (CH_2Cl_2, c = 5.00) $[\alpha]_D$ 8.5°.

(2*S*,3*E*)-2-[*N*-(Benzoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)-but-3-en-1-yl trifluoroacetate (54)



Method 1: Alkene **36** (98 mg, 0.309 mmol) was treated following the procedure for the synthesis of **41**. The reaction mixture turned black after 7 h and was worked up. Tlc analysis (1:1 ethyl acetate/hexane) of crude material showed that none of the starting alkene **36** was remaining, but a spot with a retention time significantly lower than **36** was detected. The crude product was chromatographed (1:1 ethyl acetate/hexane) and the *deprotected* diene **53** (61 mg, 65 %) obtained as a solid, m.p. 102-105 °C. Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65 %. Found: C, 71.72; H, 7.72; N, 4.61 %.

Method 2: Alcohol **53** (65 mg, 0.216 mmol) was treated with freshly distilled trifluoroacetic anhydride (54 mg, 0.259 mmol) according to the method described for the synthesis of **36**. The crude material was chromatographed on Florisil (ether, flowrate: 2.5 cm per min) and **54** (57 mg, 66 %) obtained as a white solid, m.p. 77-79 °C. Anal. Calcd. for $C_{20}H_{23}NF_3O_4$: C, 60.30; H, 5.82; N, 3.52 %. Found: C, 60.29; H, 5.85; N, 3.48 %.

^{1}H nmr δ 7.34 (m, 5H, ar), 6.24 (d, J = 16 Hz, 1H, H4), 5.78 (bt, 1H, H2', 5.38 (dd, J = 16 Hz, J = 6 Hz, 1H, H3), 5.10 (s, 2H, bn), 5.10 (bd, 1H, NH), 4.63 (m, 1H, H2), 4.39 (bs, 2H, H1), 2.06 (bm, 4 H, H3' and H6'), 1.70-1.56 (bm, 4 H, H4' and H5').

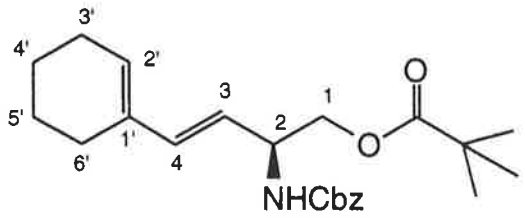
^{13}C nmr δ 157.3 (q, CO_2R), 155.6 (NC(O)O), 136.0 (4° ar), 137.1 (C4), 134.3 (C1'), 131.8 (C2'), 128.5, 128.2, 128.1 (3° ar), 119.1 (C3), 114.3 (q, $J_{C,F}$ = 286 Hz, CF_3), 67.1 (bn), 69.0 (C1), 51.6 (C2), 25.8, 24.2 (C3' and C4'), 22.3, 22.2 (C4' and C5').

Ir (neat) υ_{max} 3350 (NH), 1798, 1700, 1545, 1290, 1235, 1180 cm^{-1}.

Ms (ei) *m/z* 398 (M^+).

Or (CH_2Cl_2, c = 2.62) $[\alpha]_D$: -4.2°.

(2*S*,3*E*)-2-[*N*-(Benzoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)-but-3-en-1-yl 2',2'-dimethylpropanoate (55)



Alkene **37** (156 mg, 0.511 mmol) was treated following the procedure for the synthesis of **41**. After heating for 24 h the dark brown reaction mixture was worked up. The crude product was chromatographed (14:86 ethyl acetate/hexane) and **55** (160 mg, 81 %) obtained as a colourless clear oil. Anal. Calcd. for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63 %. Found: C, 71.44; H, 8.11; N, 3.42 %.

^{1}H nmr δ 7.35 (m, 5H, ar), 6.21 (d, J = 16 Hz, 1H, H4), 5.75 (bt, 1H, H2'), 5.40 (dd, J = 16 Hz, J = 6 Hz, 1H, H3), 5.11 (ABq, 2H, bn), 4.97 (bd, 1H, NH), 4.56 (bm, 1H, H2), 4.13 (ddd, 2H, H1), 2.08 (bm, 4 H, H3' and H6'), 1.67-1.56 (bm, 4 H, H4' and H5'), 1.16 (s, 9H, CH_3).

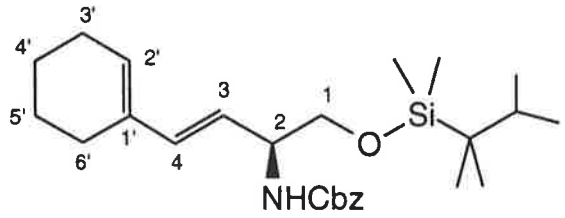
^{13}C nmr δ 178.3 (CO_2R), 155.7 (NC(O)O), 136.4 (4° ar), 135.8 (C4), 134.6 (C1'), 130.7 (C2'), 128.5, 128.1, 128.1 (3° ar), 121.1 (C3), 66.8 (bn), 65.6 (C1), 52.4 (C2), 38.8 (4°), 27.1 (CH_3), 25.8, 24.4 (C3' and C4'), 22.4, 22.3 (C4' and C5').

Ir (neat) υ_{max} 3350 (NH), 1730, 1705, 1545, 1295, 1245, 1165 cm^{-1}.

Ms (ei) *m/z* 385 (M^+).

Or (CH_2Cl_2, c = 2.12) $[\alpha]_D$ 2.6°.

(2*S*,3*E*)-1-(Dimethyl-1',1',2'-trimethylpropyl)siloxy-*N*-(benzoxycarbonyl)-4-(1'-cyclohexen-1'-yl)-but-3-en-2-yl amine (56)



Alkene **38** (217 mg, 0.597 mmol) was treated following the procedure for the synthesis of **41**. After heating for 40 h the brown reaction mixture was worked up. The crude product was chromatographed (8:92 ethyl acetate/hexane) and **56** (220 mg, 83 %) obtained as a colourless clear oil. Anal. Calcd. for $C_{26}H_{41}NO_3Si$: C, 70.38; H, 9.31; N, 3.16 %. Found: C, 70.10; H, 9.40; N, 3.00 %.

^{1}H nmr δ 7.36 (m, 5H, ar), 6.20 (d, *J* = 16 Hz, 1H, H4), 5.72 (bt, 1H, H2'), 5.51 (dd, *J* = 16 Hz, *J* = 7 Hz, 1H, H3), 5.11 (ABq, 2H, bn), 5.09 (bs, 1H, NH), 4.27 (bm, 1H, H2), 3.69 (dd, 1H, H1), 3.59 (dd, 1H, H1), 2.09 (bm, 4 H, H3' and H6'), 1.60 (bm, 4 H, H4' and H5'), 1.57 (m, 1H, C**H**$(CH_3)_2$), 0.86 (d, 6H, *J* = 7 Hz, CH(C**H**$_3)_2$), 0.83 (s, 6H, SiC(C**H**$_3)_2$), 0.07 (s, 6H, Si(C**H**$_3)_2$).

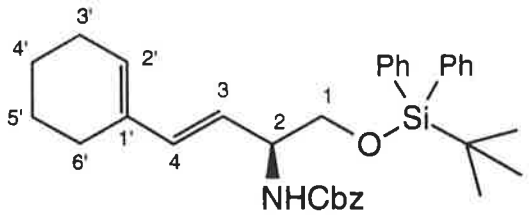
^{13}C nmr δ 155.8 (CO), 136.6 (4° ar), 134.9 (C4), 141.9 (C1'), 129.7 (C2'), 128.4, 128.0, 127.9 (3° ar), 123.1 (C3), 66.5 (bn), 65.4 (C1), 54.4 (C2), 34.1 (3°), 25.7, 25.1 (4°), 24.3 (C3' and C4'), 22.4, 22.3 (C4' and C5'), 20.3, 20.2, 18.5, 18.4 (CH_3), -3.6 ($Si(CH_3)_2$).

Ir (neat) υ_{max} 3350 (NH), 2950, 1720, 1700, 1540, 1510, 1260, 1110, 840, 780, 700 cm^{-1}.

Ms (ei) *m/z* 443 (M^+).

Or (CH_2Cl_2, c = 2.45) $[\alpha]_D$ -3.0°.

(2*S*,3*E*)-1-(Diphenyl*tert*-butyl)siloxy-*N*-(benzoxycarbonyl)-4-(1'-cyclohexen-1'-yl)-but-3-en-2-yl amine (57)



Alkene **39** (203 mg, 0.442 mmol) was treated following the procedure for the synthesis of **41**. After heating for 42 h the brown reaction mixture was worked up. The crude product was chromatographed (7.5:92.5 ethyl acetate/hexane) and **57** (198 mg, 83 %) obtained as a white solid. Anal. Calcd. for $C_{34}H_{41}NSiO_3$: C, 75.65; H, 7.66; N, 2.60 %. Found: C, 75.79; H, 7.42; N, 2.55 %. This material was recrystallised from hexane, m.p. 95-96 °C.

^{1}H nmr δ 7.64-7.31 (m, 5H, ar), 6.19 (d, *J* = 16 Hz, 1H, H4), 5.71 (bt, 1H, H2'), 5.51 (dd, *J* = 16 Hz, *J* = 6 Hz, 1H, H3), 5.11 (ABq, 2H, bn), 5.10 (bd, 1H, NH), 4.36 (bm, 1H, H2), 3.77 (dd, 1H, H1), 3.63 (dd, 1H, H1), 2.10 (bm, 4 H, H3' and H6'), 1.70-1.55 (m, 4 H, H4' and H5'), 1.07 (s, 9H, CH_3).

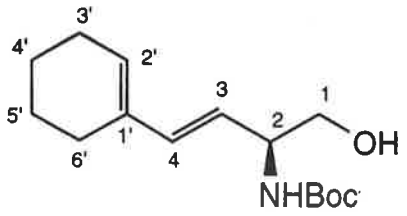
^{13}C nmr δ 155.8 (CO), 136.6, 135.6, 135.5, 135.0, 134.8, 133.2, 133.0, 129.9, 129.7, 127.7, 128.4, 128.0, 127.9, 122.9 (C3), 66.6 (bn), 66.4 (C1), 54.5 (C2), 26.8 (CH_3), 25.8, 24.4 (C3' and C4'), 22.5, 22.4 (C4' and C5'), 19.2 (4°).

Ir (nujol mull) υ_{max} 3350 (NH), 2950, 1700, 1550, 1280, 1250, 1125, 1055 cm^{-1}.

Ms (ei) *m/z* 539 (M^+).

Or (CH_2Cl_2, c = 2.82) $[\alpha]_D$ -22.0°.

(2*S*,3*E*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)-but-3-en-1-ol (58)



Alkene **35** (182 mg, 0.972 mmol) was treated following the procedure for the synthesis of **41**. After heating for 40 h the brown reaction mixture was worked up. ^{1}H nmr spectroscopic analysis showed that none of the starting alkene **35** was remaining in the crude product which was then chromatographed (45:55 ethyl acetate/hexane) to give **58** (143 mg, 52 %) as a white solid. Anal. Calcd. for $C_{15}H_{25}NO_4$: C, 67.38; H, 9.43; N, 5.24 %. Found: C, 67.21; H, 9.47; N, 5.05 %. Recrystallisation of this material from ethyl acetate/hexane furnished a white solid, m.p. 85-86 °C.

^{1}H nmr δ 6.20 (d, *J* = 16 Hz, 1H, H4), 5.74 (bt, 1H, H2'), 5.45 (dd, *J* = 16 Hz, *J* = 6 Hz, 1H, H3), 5.21 (m, 1H, NH), 4.24 (m, 1H, H2), 3.70-3.54 (m, 2H, H1), 3.42 (t, *J* = 6 Hz, OH), 2.10 (m, 4 H, H3' and H6'), 1.65-1.54 (bm, 4 H, H4' and H5'), 1.44 (s, 9H, CH_3).

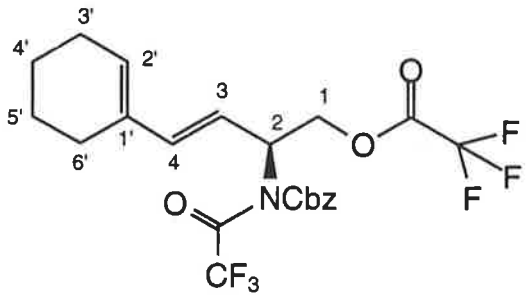
^{13}C nmr δ 155.9 (CO), 135.1 (C4), 134.7 (C1'), 129.9 (C2'), 122.3 (C3), 79.4 (4°), 65.3 (C1), 54.3 (C2), 28.2 (CH_3), 25.6, 24.2 (C3' and C4'), 22.3, 22.2 (C4' and C5').

Ir (nujol mull) υ_{max} 3500-3300 (OH,NH), 1690, 1518, 1300, 1280, 1002, 993 cm-1.

Ms (ei) *m/z* 283 (M^+).

Or ($CHCl_3$, c = 3.90) $[\alpha]_D$ 23.1°.

(2*S*,3*E*)-2-[*N*,*N*-(Benzoxycarbonyltrifluoroacetate)amino]-4-(1'-cyclohexen-1'-yl)-but-3-en-1-yl trifluoroacetate(61)



Alcohol **53** (87 mg, 0.289 mmol) was treated with trifluoroacetic anhydride (67 mg, 0.318 mmol) *in lieu of* 2,2-dimethylpropanoyl chloride following the procedure for the synthesis of **36**. Several compounds were detected by ^{1}H and ^{13}C nmr spec-

troscopic analysis of the crude reaction product, however, the mono-trifluoroacetate **54** was not amongst them. The crude material was chromatographed (13:87 ethyl acetate/hexane) and **61** (30 mg, 21 %) obtained as a colourless clear oil. Anal. Calcd. for $C_{22}H_{21}F_6NO_5$: C, 53.55; H, 4.29; N, 2.84 %. Found: C, 53.50; H, 4.20; N, 3.14 %.

^{1}H nmr δ 7.40 (bs, 5H, ar), 6.34 (d, J = 16 Hz, 1H, H4), 5.84 (bt, 1H, H2'), 5.53 (dd, J = 16 Hz, J = 7 Hz, 1H, H3), 5.32 (m, 1H, H2), 5.29 (ABq, 2H, bn), 4.79 (t, J = 11 Hz, 1H, H1), 4.53 (dd, J = 11 Hz, J = 6 Hz, 1H, H1), 2.15 (m, 2H, H3' or H5'), 2.00 (m, 2H, H3' or H5'), 1.63 (m, 4H, H4' and H5').

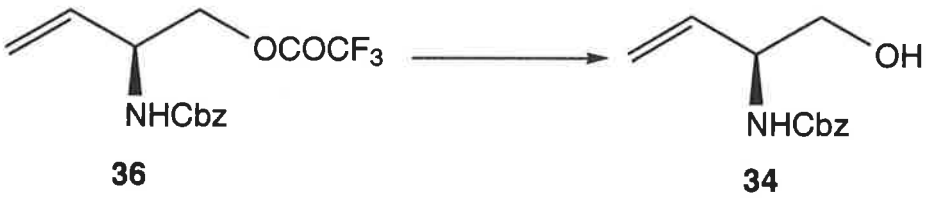
^{13}C nmr δ 160.3 (q, $J_{C,F}$ = 42 Hz, **C**OCF_3), 156.9 (q, $J_{C,F}$ = 42 Hz, **C**OCF_3),152.1 (NC(O)O), 141.3 (C4), 134.4 (4°), 133.6 (4°), 133.4 (C2'), 115.2 (q, $J_{C,F}$ = 288 Hz, CF_3), 115.0 (C3), 114.1 (q, $J_{C,F}$ = 290 Hz, CF_3), 70.5 (C1), 66.1 (bn), 58.4 (C2), 25.9, 24.1 (C3' and C4'), 22.2, 22.1 (C4' and C5').

Ir (neat) υ_{max} 1795, 1770, 1725, 1260, 1225, 1180 cm^{-1}.

Ms (ei) *m/z* 493 (M^+).

Or (CH_2Cl_2, c = 3.30) $[\alpha]_D$ 23.0°.

Cleavage of the trifluoroacetate group of (36)



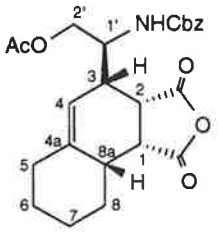
36 **34**

A solution of trifluoroacetate **36** (159 mg, 0.50 mmol) in dry and freshly distilled DMA (20 ml) was treated, under an atmosphere of nitrogen and at ambient temperature, with anhydrous potassium carbonate (70 mg, 0.050 mmol, desiccated at 160 °C and at 0.6 Torr to constant weight). Starting alkene **36** could not be detected by tlc analysis (3:7 ethyl acetate/hexane) of the reaction mixture after 4 h. The solvent was distilled at a pressure of 0.5 Torr and the residue chromatographed (45:55 ethyl acetate/hexane) to afford **34** (104 mg, 94 %).

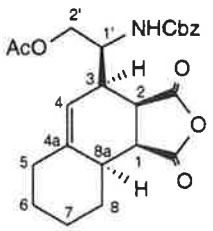
***In situ* generation of the zerovalent palladium catalyst**

A mixture of alkene **40** (115 mg, 0.438 mmol), anhydrous potassium carbonate (145 mg, 1.05 mmol) and palladium(II) acetate (105 mg, 0.437 mmol) in DMF (10 ml) was heated under an atmosphere of nitrogen at 60 °C for 1 h. A metallic mirror formed on the wall of the reaction vessel. The solvent was distilled at a pressure of 1 Torr and the residue worked up in the usual way. Chromatography of the residue furnished starting alkene **40** (107 mg, 93 %).

(1*R*, 2*S*, 3*S*, 8a*R*)-3-[(1'*S*)-2'-Acetoxy-1'-*N*'-(benzoxycarbonyl) aminoethyl]-(1,2,3,5,6,7,8,8a) octahydronaphthalene-1,2-dicarboxylic acid anhydride (110a) and **(1*S*, 2*R*, 3*R*, 8a*S*)-3-[(1'*S*)-2'-acetoxy-1'-*N*'-(benzoxycarbonyl) amino-ethyl]-(1,2,3,5,6,7,8,8a) octahydronaphthalene-1,2-dicarboxylic acid anhydride (111a)**



110a



111a

The cycloadducts **110a** and **111a** were not isolated, but the following experiments infer their intermediacy:

Experiment 1 (Conditions C, Scheme 32): A degassed solution of diene **41** (116 mg, 0.375 mmol) and maleic anhydride **94** (110 mg, 1.122 mmol) in $CDCl_3$ (0.40 ml) was stirred at ambient temperature for 4 d. After 12 h the reaction mixture was analysed by ^1H and ^{13}C nmr spectroscopy. Starting diene **41** and *cis*-isoindolone **113a** were not detected. Resonances due to *trans*-isoindolone **112a** predominated the spectra. Other resonances presumably belonged to the *cis*-cycloadduct **111a** and were not assigned due to considerable signal overlap.

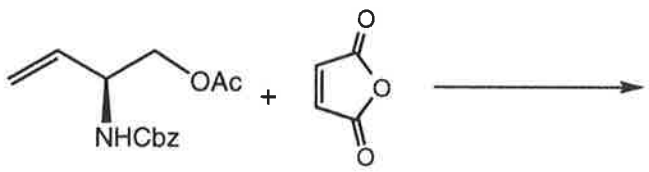
Monitoring the reaction by HPLC after 6h, 12 h, 1 d, 2 d, 3 d and 4 d of reaction time showed the following peaks (relative intensities are listed for the 12 h old reaction

in parenthesis): $t_R = 28.2$ min (**113a**, 3.0 %), $t_R = 33.1$ min (**112a**, 100 %) and $t_R = 53.2$ min (presumably **111a**, 9.0 %). Co-injection with partially purified *cis*-isoindolone **113a** markedly decreased the ratio of the peaks at $t_R = 28.2$ min and at $t_R = 33.1$ min. After 4 d peaks were observed at $t_R = 28.1$ min (**113a**, 7.2 %), $t_R = 33.0$ min (**112a**, 100 %) and $t_R = 52.9$ min (**111a**, 20 %).

$CDCl_3$ (1.0 ml) was added to one half of the reaction mixture and the solution was refluxed for 10 h. The crude product was analysed by hplc and peaks were observed at $t_R = 28.2$ min (**113a**, 19.2 %), $t_R = 33.1$ min (**112a**, 100 %) and $t_R = 53.2$ min (**111a**, 7.3 %).

The solvent was evaporated from the other half of the reaction mixture and the residue was dissolved in 1,2-dichlorobenzene (7 ml). It was refluxed for one 1h and the solvent distilled (0.4 Torr). Two major peaks at $t_R = 28.2$ min (**113a**, 37 %), $t_R = 33.2$ min (**112a**, 100 %) were observed by hplc analysis of the residue. No peaks were observed with a retention time in the range 40-60 min. A ratio of 1.0:3.6 was determined for the resonances at $\delta = 4.46$ ppm (**112a**) and at $\delta = 4.87$ ppm (**113a**) and at $\delta = 3.57$ ppm (**112a**) and at $\delta = 3.39$ ppm (**113a**) in the ^1H nmr spectrum of the crude product which was purified by semi-preparative hplc (355:250:125:6 acetonitrile/water/methanol/trifluoroacetic acid). Isoindolone **112a** (31 mg, 38 %) was obtained as an oil.

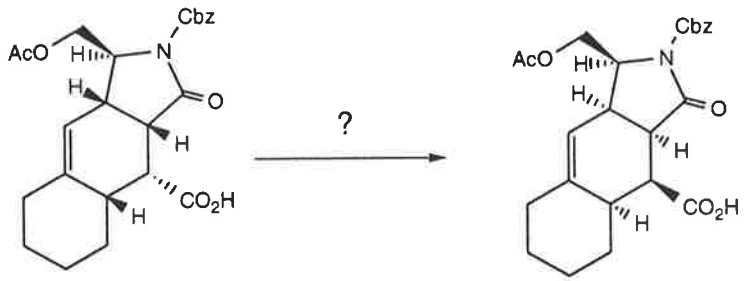
Experiment 2: Attempted reaction between maleic anhydride **94** and alkene **40**



40 **94**

A solution of alkene **40** (145 mg, 0.54 mmol) and maleic anhydride **94** (159 mg, 1.62 mmol) in 1,2-dichlorobenzene (5 ml) was refluxed for 1 h and the solvent distilled (0.5 Torr). ^1H nmr spectroscopic analysis of the crude product was consistent with a mixture of starting **40** and **94**.

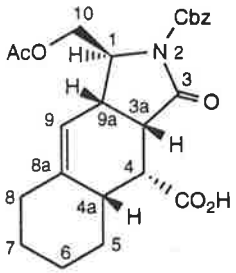
Experiment 3: Attempted equilibration of *trans*-isoindolone **112a**



112a 113a

Isomerically pure *trans*-isoindolone **112a** (31 mg, 70 μmol) was refluxed in 1,2-dichlorobenzene (5.0 ml) for 30 min. The solvent was distilled (0.6 Torr) and the residue analysed by ^{1}H nmr spectroscopy. The ^{1}H spectrum was clean and displayed resonances due to **112a** and 1,2-dichlorobenzene.

(1*S*, 3a*S*, 4*R*, 4a*R*, 9a*S*)-1-(Acetoxy)methyl-2-*N*-benzoxycarbonyl(1,3a,4,4a,5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (112a)



Method 1 (Conditions C, Scheme 32): See Experiment 1 under the synthesis of **110a** and **111a**.

Method 2 (Conditions B, Scheme 32): A degassed mixture of diene **41** (600 mg, 1.747 mmol), activated 4Å molecular sieves (707 mg) and maleic anhydride **94** (514 mg, 5.241 mmol) in dichloromethane (5 ml) was heated at reflux for 1 d. An aliquot (1.0 ml) of the reaction mixture was withdrawn, the solvent evaporated under reduced pressure and the residue analysed by ^{1}H and ^{13}C nmr spectroscopy. Neither starting diene **41** nor *cis*-isoindolone **113a** were detected and resonances due to *trans*-isoindolone **112a** dominated the spectra. The reaction mixture was cooled to ambient temperature, combined with the nmr sample and filtered. Follow-

ing careful washing of the molecular sieves with dichloromethane (3×5 ml) the solvent was evaporated from the combined organic phases and the residue dissolved in ether (100 ml). It was thoroughly extracted with sat. $NaHCO_3$ (3×30 ml). The combined extracts were washed with ether (30 ml) and acidified by slowly adding conc. HCl until the precipitation of a white solid ceased (at pH≤0). It was extracted with ether (3×50 ml), the combined extracts were dried ($MgSO_4$) and the solvent evaporated to yield an amorphous light brown solid (531 mg, 69 %). The crude product was analysed by hplc (355:520:125:6 acetonitrile/water/methanol/trifluoroacetic acid) and the following peaks were observed (relative intensities in parenthesis): $t_R = 20.9$ min (**112b**, 14 %), $t_R = 32.3$ min (unknown, 8 %), $t_R = 33.8$ min (**113a**, 2.5 %), $t_R = 35.3$ min (unknown, 11 %), $t_R = 40.5$ min (**112a**, 100 %). Co-injection with partially purified *cis*-isoindolone **113a** markedly decreased the ratio of the peaks at $t_R = 33.8$ min and at $t_R = 40.5$ min.

The crude product was chromatographed on silica (120:120:12.5 hexane/dichloromethane/acetic acid) to yield pure **112a** (363 mg, 47 %) as a colourless oil. Anal. Calcd. for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17 %. Found: C, 64.97; H, 6.40; N, 2.96 %.

Method 3 (Conditions D, Scheme 32): A degassed mixture of diene **41** (62 mg, 0.181 mmol), lithium perchlorate (213 mg, 2.00 mmol) and maleic anhydride **94** (53 mg, 0.544 mmol) in dry ether (0.40 ml) was stirred at ambient temperature for 5 h until none of the starting diene **41** was detected by tlc analysis (2:3 ethyl acetate/hexane) of the reaction mixture. Ether (8 ml) and 1M HCl (3 ml) were added and the mixture thoroughly shaken. The separated aqueous phase was extracted with ether (2×5 ml), the combined organic phases were washed with 1M HCl (2×3 ml), dried ($MgSO_4$) and the solvent was evaporated. The ^1H and ^{13}C nmr spectra of the crude product showed resonances due to **112a** as the main compound. A solution of the crude product in 1,2-dichlorobenzene (5 ml) was heated at 180 °C for 1 h. Following distillation of the solvent (0.5 Torr) the residue was analysed by ^1H spectroscopy as described for Experiment 1 under the preparation of **110a** and **111a** and

a ratio of 5.5:1.0 in favour of **112a** was determined. Chromatography (120:120:12.5 hexane/dichloromethane/acetic acid) of the crude reaction product afforded pure **112c** (34 mg, 42 %) as an oil.

Method 4 (Scheme 40): To a solution of di*iso*-propylamine (51 mg, 0.506 mmol) in dry THF (3 ml) was added a 2.36M solution of *n*-butyllithium in hexane (195 µl, 0.456 mmol) at -50 °C (dry-ice/acetonitrile cooling-bath). After 10 min of stirring a solution of diene **41** (158 mg, 0.460 mmol) in THF (1 ml) was added followed by a solution of maleic anhydride **94** (135 mg, 1.380 mmol) in a mixture of THF (400 µl) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (177 mg, 1.380 mmol). Both solutions were added rather quickly from a syringe. The colour of the reaction mixture changed from yellow to red upon the addition of maleic anhydride. After the mixture was stirred at -50 °C for 30 min it was allowed to warm to -5 °C over a period of 90 min. The colour of the reaction mixture intensified during this time. It was poured onto ether (50 ml) that had been cooled in a freezer. Ice-cold 1M HCl (30 ml) was added and the two phases were shaken until the red colour disappeared. The separated organic phase was washed with cold 1M HCl (2×10 ml), extracted with ice-cold sat. $NaCO_3$ (2×30 ml), the remaining ethereal solution dried ($MgSO_4$) and the solvent evaporated to afford unchanged diene **41** (54 mg, 34 %). The red aqueous extracts were immediately washed with cold ether (30 ml) and acidified with ice-cold conc. HCl until the red colour disappeared (at pH≤0). The acidic aqueous phase was extracted with cold ether (2×30 ml), the combined organic extracts were dried ($MgSO_4$) in a freezer and the solvent was evaporated to afford an oil (75 mg). ^1H and ^{13}C nmr spectra ($^2H_6$-acetone) were consistent with a mixture of compounds amongst which *trans*-isoindolone **112a** was the major product. Other resonances were also intense, however the lack of olefinic resonances was consistent with the absence of triene **128**. The ^1H nmr spectrum of this sample did not change after leaving the sample for several days at ambient temperature. Hplc analysis (355:520:125:6 acetonitrile/water/methanol/trifluoroacetic acid) of the crude extracted reaction product showed several peaks (relative intensities in parenthesis) at $t_R = 21.6$ min (**112b**, 18.8 %), $t_R = 27.2$ and 27.7 min (unknown,

17.2 %), t_R = 33.6 min (unknown, 45.5 %) and t_R = 42.7 min (**112a**, 100 %). When a partially purified sample of *cis*-isoindolone **113a** was co-injected a pronounced peak at t_R = 36.1 min was observed while the retention times of the other peaks remained unaltered. It was estimated that the detection limit for **113a** was less than 1 % (relative to **112a**). The intensity of the peak at t_R = 21.6 min (**112b**) was markedly enhanced upon co-injection with an authentic sample of pure **112b**. Other peaks were observed that had an area of less than 7 % of the total area of the major peak (**112a**).

Isoindolone **112a** (5 mg, 8 %) was isolated by hplc (with regard to recovered diene **41**) as an oil.

Incomplete nmr spectral data for the compound giving rise to the peak t_R = 33.6 min.

^{1}H nmr ($^2H_6$-acetone) δ 13.2 (bs, 1H, CO_2H), 7.51-7.32 (m, 5H); 5.68 (bs, 1H); 5.28 (ABq, 2H); 4.61 (dt, *J* = 8 Hz, *J* = 5 Hz, *J* = 4 Hz, 1H); 4.49 (dd, *J* = 12.0 Hz, *J* = 5 Hz, 1H); 4.32 (dd, *J* = 12.0 Hz, *J* = 4 Hz); 3.42 (m, 1H), 2.91 (dd, *J* = 14.0 Hz, *J* = 4 Hz, 1H), 2.78 (dd, *J* = 11.0 Hz, *J* = 4 Hz, 1H), 2.63 (m, 1H), 2.25 (bd, 1H), 2.00 ppm (s, 3H), 2.05-1.15 (m).

^{13}C nmr ($^2H_6$-acetone) δ 144.7, 136.8, 129.2, 128.8, 128.7, 117.1, 68.2, 62.0, 57.6, 43.8, 43.0, 36.9, 35.3, 27.4, 32.2, 29.1.

Data for the title compound **112a**

^{1}H nmr δ 13.2 (bs, 1H, CO_2H), 7.42-7.33 (m, 5H, ar), 5.30 (ABq, 2H, bn), 5.18 (bs, 1H, H9), 4.43 (dd, 1H, H10), 4.21 (dd, 1H, H10), 4.13 (m, 1H, H1), 3.65 (dd, 1H, H3a), 3.01 (dd, 1H, H4), 2.91 (m, 1H, H9a), 2.44 (m, 1H, H4a), 2.23 (bd, 1H, $H8_{eq}$), 2.07 (s, 3H, CH_3), 2.0 (m, 1H, $H8_{ax}$), 2.0 (m, 1H, $H5_{eq}$), 1.8 (m, 1H, $H7_{eq}$), 1.8 (m, 1H, $H6_{eq}$), 1.4 (bm, 1H, $H7_{ax}$), 1.3 (bm, 1H, $H5_{ax}$), 1.3 (bm, 1H, $H6_{ax}$).

^{13}C nmr δ 175.6, 175.0 (CO_2H, ring CO), 170.5 (CO_2R), 151.1 (NC(O)O), 146.2 (C8a), 134.9 (4° ar), 128.6, 128.5, 127.9 (3° ar), 116.6 (C9), 68.6 (bn), 63.9 (C10), 61.6 (C1), 43.2 (C4), 40.4 (C3a), 38.6 (C4a), 36.6 (C8), 36.4 (C9a), 31.6 (C5), 29.0 (C6), 26.9 (C7), 20.8 (CH_3).

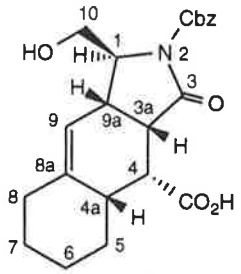
Ir (neat) υ_{max} 3300-2400 (CO_2H), 1795, 1750, 1730, 1700, 1390, 1305, 1230, 1050 cm^{-1}.

Ms (fab) *m/z* 442 (MH^+).

Uv (ethanol) λ_{max} 258 nm ($\varepsilon = 221$).

Or ($CDCl_3$, c = 2.72) $[\alpha]_D$ -61.8°.

(1*S*, 3a*S*, 4*R*, 4a*R*, 9a*S*)-1-(Hydroxymethyl)methyl-2-*N*-benzoxycarbonyl(1,3a,4, 4a,5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (112b)



Method 1 (Conditions C, Scheme 32): A degassed mixture of diene **53** (102 mg, 0.339 mmol) and maleic anhydride **94** (100 mg, 1.017 mmol) in $CDCl_3$ (0.5 ml) was stirred at ambient temperature for 24 h in a sealed vessel. Analysis of the crude reaction mixture by ^1H and ^{13}C nmr spectroscopy revealed the presence of **112b** as the major compound, however, other unidentified resonances were prominent in both spectra. An isolation of the major product **112b** was not attempted.

Method 2: A solution of isoindolone **112a** (56 mg, 0.127 mmol) in a mixture of methanol (6 ml), water (3 ml) and trifluoroacetic acid (1 ml) was stirred at ambient temperature in a vessel open to the atmosphere for 10 h. The solvent was distilled (2.3 Torr) and the residue dissolved in dichloromethane (10 ml). The organic phase was washed with 1M HCl (3 ml), dried ($MgSO_4$) and the solvent evaporated to afford **112b** (45 mg, 96 %) as a colourless oil. Anal. Calcd. for $C_{22}H_{25}NO_6$: C, 71.91; H, 6.86; N, 3.81 %. Found: C, 71.77; H, 6.67; N, 3.60 %.

^1H nmr δ 9.3 (bs, 2H, CO_2H, OH), 7.36 (m, 5H, ar), 5.30 (ABq, 2H, bn), 5.18 (bs, 1H, H9), 4.04-3.68 (m, 3H, H1 and H10), 3.80 (m, 1H, H3a), 3.10 (dd, 1H, H4), 2.98

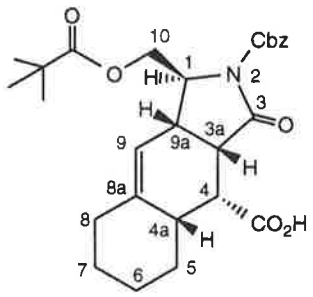
(m, 1H, H9a), 2.46 (m, 1H, H4a), 2.22 (bd, 1H, $H8_{eq}$,), 2.0 (m, 1H, $H8_{ax}$), 2.0 (m, 1H, $H5_{eq}$), 1.8 (m, 1H, $H7_{eq}$), 1.8 (m, 1H, $H6_{eq}$), 1.4 (bm, 1H, $H7_{ax}$), 1.2 (bm, 1H, $H5_{ax}$), 1.2 (bm, 1H, $H6_{ax}$).

^{13}C nmr δ 150.8 (NC(O)O), 145.9 (C8a), 117.4 (C9), 68.3 (bn), 64.7 (C10), 62.8 (C1), 43.2 (C4), 40.6 (C3a), 38.5 (C4a), 36.4 (C8), 36.2 (C9a), 31.5 (C5), 28.9 (C6), 26.8 (C7).

Ir (neat) υ_{max} 3500 (OH), 3300-2400 (CO_2H), 1790, 1745, 1725, 1695 cm^{-1}.

Ms (fab) *m/z* 368 (MH^+).

(1*S*, 3a*S*, 4*R*, 4a*R*, 9a*S*)-1-(2',2'-Dimethylpropanoate)methyl-2-*N*-benzoxycarbonyl(1,3a,4,4a,5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (112c)



Method 1 (Conditions C, Scheme 32): A degassed solution of diene **55** (98 mg, 0.254 mmol) and maleic anhydride **94** (75 mg, 0.763 mmol) in $CDCl_3$ (0.4 ml) was stirred in a sealed vessel at ambient temperature for 24 h. Resonances due to diene **55** and isoindolone **113c** were of a very low intensity in the ^{1}H and ^{13}C nmr spectra of the reaction mixture. The solvent was evaporated and the residue refluxed in 1,2-dichlorobenzene (9 ml). After the solvent was distilled (0.2 Torr) the residue was analysed and a ratio of 4.6:1.0 for the proton resonances at δ = 3.71 ppm (**112c**) and at δ = 3.40 ppm (**113c**) was measured. The crude product was chromatographed (120:120:12.5 hexane/dichloromethane/acetic acid) to afford **112c** (54 mg, 44 %) as an oil.

Method 2 (Conditions B, Scheme 32): A degassed mixture of diene **55** (183 mg, 0.475 mmol), maleic anhydride **94** (140 mg, 1.426 mmol) and activated 4Å molecular sieves (200 mg) was refluxed in dichloromethane (2.0 ml). After 12 h a trace of diene **55** was detected by tlc analysis of the reaction mixture (3:7 ethyl acetate/hexane) which was then cooled to ambient temperature. The molecular sieves were removed and washed with dichloromethane (3×5 ml). The combined organic phases were evaporated and the crude product chromatographed (120:120:12.5 hexane/dichloromethane/acetic acid) to yield **112c** (126 mg, 55 %) as a colourless oil. Anal. Calcd. for $C_{27}H_{33}NO_7$: C, 67.06; H, 6.88; N, 2.90 %. Found: C, 66.72; H, 6.63; N, 2.59 %.

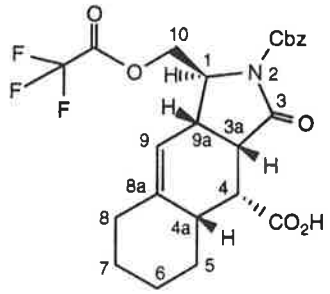
^{1}H nmr δ 12.9 (bs, 1H, CO_2H), 5.33 (ABq, 2H, bn), 5.19 (bs, 1H, H9), 4.46 (dd, 1H, H10), 4.20 (dd, 1H, H10), 4.16 (m, 1H, H1), 3.60 (dd, 1H, H3a), 3.12 (dd, 1H, H4), 2.90 (m, 1H, H9a), 2.49 (m, 1H, H4a), 2.23 (bd, 1H, $H8_{eq}$), 2.0 (m, 1H, $H8_{ax}$), 2.0 (m, 1H, $H5_{eq}$), 1.8 (m, 1H, $H7_{eq}$), 1.8 (m, 1H, $H6_{eq}$), 1.4 (bm, 1H, $H7_{ax}$), 1.2 (bm, 1H, $H5_{ax}$), 1.2 (bm, 1H, $H6_{ax}$), 1.17 (s, 9H, CH_3).

^{13}C nmr δ 177.7, 177.5, 173.3, 150.6 (NC(O)O), 146.3 (C8a), 134.7 (4° ar), 128.7, 128.7, 128.0 (3° ar), 116.5 (C9), 68.9 (bn), 63.7 (C10), 61.2 (C1), 44.7 (C4), 40.6 (C3a), 39.0 (C4a), 38.8 (4°), 36.8 (C8), 36.5 (C9a), 31.6 (C5), 28.9 (C6), 26.8 (C7), 27.1 (CH_3).

Ms (fab) *m/z* 484 (MH^+).

Ir (neat) υ_{max} 3300-2500 (CO_2H), 1795, 1745, 1730, 1700 cm^{-1}.

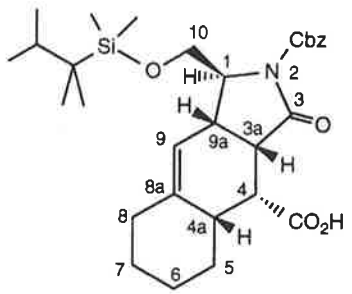
(1*S*, 3a*S*, 4*R*, 4a*R*, 9a*S*)-1-(Trifluoroacetate)methyl-2-*N*-benzoxycarbonyl-(1,3a,4,4a,5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (112d)



A degassed mixture of diene **54** (154 mg, 0.387 mmol) and maleic anhydride **94** (114 mg, 1.161 mmol) in $CHCl_3$ (1.0 ml) was stirred in a sealed vessel at ambient temperature under an atmosphere of nitrogen. The reaction was monitored by ^1H and ^{13}C nmr spectroscopy. After 6 h resonances due to starting diene **54** were detected. A set of resonances predominated both spectra that were similar to the previously characterised isoindolone **112a**. With increasing reaction time these resonances diminished and were not detected after 48 h of reaction time. A large number of unidentified signals were observed. The reaction mixture was not treated further.

^1H nmr δ 5.29 (ABq, 2H, bn), 5.21 (bs, 1H, H9), 4.47 (dd, 1H, H10), 4.52 (dd, 1H, H10), 4.26 (t, 1H, H1), 3.65 (dd, 1H, H3a), 3.03 (dd, 1H, H4), 2.99 (m, 1H, H9a), 2.45 (m, 1H, H4a), 2.25 (bd, 1H, $H8_{eq}$), 2.0 (m, 1H, $H8_{ax}$), 2.0 (m, 1H, $H5_{eq}$), 1.8 (m, 1H, $H7_{eq}$), 1.8 (m, 1H, $H6_{eq}$), 1.4 (bm, 1H, $H7_{ax}$), 1.2 (bm, 1H, $H5_{ax}$), 1.2 (bm, 1H, $H6_{ax}$).
^{13}C nmr δ 146.8 (C8a), 134.7 (4° ar), 129.9, 128.7, 128.5 (3° ar), 116.0 (C9), 68.9 (bn), 67.0 (C10), 60.8 (C1), 43.5 (C4), 40.6 (C3a), 38.9 (C4a), 36.5 (C8), 35.9 (C9a), 31.3 (C5), 29.0 (C6), 27.0 (C7).

(1*S*, 3a*S*, 4*R*, 4a*R*, 9a*S*)-1-[(Dimethyl-1',1',2'-trimethylpropyl)siloxy]methyl-2-*N*-benzoxycarbonyl(1,3a,4,4a,5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (112e)



Method 1 (Conditions C, Scheme 32): Diene **56** (212 mg, 0.479 mmol) was treated with maleic anhydride **94** (141 mg, 1.436 mmol) as described for the synthesis of **112c** (Method 1). After 1,2-dichlorobenzene was distilled the residue was dissolved in $CDCl_3$ (0.5 ml) and chromium(III) acetylacetonate (4 mg, 0.011 mmol)

was added. The T1 relaxation times of the resonances at δ = 117.4 ppm (**112e**) and at δ = 113.0 ppm (**113e**) were estimated by the inversion recovery method.[76] A ^{13}C nmr spectrum was acquired using inverse gated ^{1}H decoupling and a ratio of 6.8:1.0 was determined for these resonances, respectively. Chromatography (140:100:12.5 hexane/dichloromethane/acetic acid) of the crude reaction product afforded **112e** (119 mg, 46 %) as an oil of a light red colour.

Method 2 (Conditions B, Scheme 32): Diene **56** (202 mg, 0.456 mmol) was treated with maleic anhydride **94** (134 mg, 1.368 mmol) as described for the synthesis of **112c** (Method 2). The crude product was chromatographed and **112e** (153 mg, 62 %) obtained as a solid, m.p. 131-135 °C. Anal. Calcd. for $C_{30}H_{43}NSiO_6$: C, 66.51; H, 8.00; N, 2.59 %. Found: C, 66.16; H, 8.27; N, 2.49 %.

^{1}H nmr δ 13.0 (bs, 1H, CO_2H), 5.32 (ABq, 2H, bn), 5.19 (bs, 1H, H9), 3.89 (m, 2H, H1 and H10), 3.73 (dd, 1H, H1 or H10), 3.67 (dd, 1H, H3a), 3.10 (dd, 1H, H4), 2.96 (m, 1H, H9a), 2.46 (m, 1H, H4a), 2.20 (bd, 1H, $H8_{eq}$), 2.0 (m, 1H, $H8_{ax}$), 2.0 (m, 1H, $H5_{eq}$), 1.8 (m, 1H, $H7_{eq}$), 1.8 (m, 1H, $H6_{eq}$), 1.57 (sep, J = 7 Hz, 1H, $CH(CH_3)_2$), 1.4 (bm, 1H, $H7_{ax}$), 1.2 (bm, 1H, $H5_{ax}$), 1.2 (bm, 1H, $H6_{ax}$), 0.87 (d, J = 7 Hz, 6H, $CH(CH_3)_2$), 0.82 (s, 6H, $SiC(CH_3)_2$), 0.06 (s, 6H, $Si(CH_3)_2$).

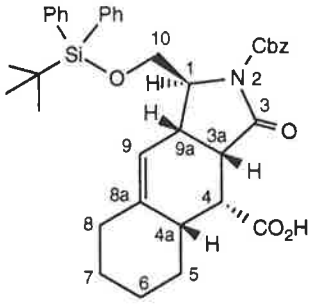
^{13}C nmr δ 178.6, 174.3, 151.0 (NC(O)O), 145.5 (C8a), 134.8 (4° ar), 128.6, 128.6, 128.1 (3° ar), 117.4 (C9), 68.6 (bn), 64.9 (C10), 63.2 (C1), 45.1 (C4), 40.9 (C3a), 39.1 (C4a), 37.0 (C8), 36.5 (C9a), 34.0 (3°), 31.6 (C5), 28.8 (C6), 26.8 (C7), 25.0 (4°), 20.1, 20.1, 18.3, 18.3 (CH_3), -3.8 ($Si(CH_3)_2$).

Ir (nujol mull) υ_{max} 3300-2500 (CO_2H), 1750, 1740, 1715, 1475, 1385, 1300, 1140 cm^{-1}.

Ms (fab) *m/z* 542 (MH^+).

Or (CH_2Cl_2, c = 3.86) $[a]_D$ -60.4°.

(1*S*, 3a*S*, 4*R*, 4a*R*, 9a*S*)-1-[(Diphenyl*tert*-butyl)siloxy]methyl-2-*N*-benzoxy-carbonyl(1,3a,4,4a,5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (112f)



Method 1 (Conditions C): Diene **57** (175 mg, 0.324 mmol) was treated with maleic anhydride **94** (96 mg, 0.974 mmol) as described for the synthesis of **112e** (Method 1). The crude product was analysed as described for **112e**. A ratio of 7.3:1.0 for the carbon resonances at $\delta = 117.2$ ppm (**112f**) and at $\delta = 112.7$ ppm (**113f**) was determined. Chromatography (140:100:12.5 hexane/dichloromethane/acetic acid) of the crude reaction product afforded **112f** (99 mg, 48 %) as a light red coloured oil.

Method 2 (Conditions B): Diene **57** (237 mg, 0.440 mmol) was treated with maleic anhydride **94** (129 mg, 1.319 mmol) as described for the synthesis of **112c** (Method 2). The crude product was chromatographed (140:100:12.5 hexane/dichloromethane/ acetic acid) and **112f** obtained as a colourless oil (177 mg, 63 %). Anal. Calcd. for $C_{38}H_{43}NSiO_6$: C, 71.56; H, 6.80; N, 2.20 %. Found: C, 71.47; H, 6.88; N, 2.19 %.

Method 3 (Conditions D, Scheme 32): Diene **57** (156 mg, 0.289 mmol) was treated with maleic anhydride **94** (85 mg, 0.867 mmol) as described for the synthesis of **112a** (Method 3). After 1,2-dichlorobenzene was distilled, the crude product was analysed as described for **112e**. A ratio of 11.0:1.0 for the carbon resonances at $\delta = 117.1$ ppm (**112f**) and at $\delta = 112.6$ ppm (**113f**) was determined. Chromatography (140:100:12.5 hexane/dichloromethane/acetic acid) of the crude reaction product afforded **112f** in 49 % yield as a light red coloured oil.

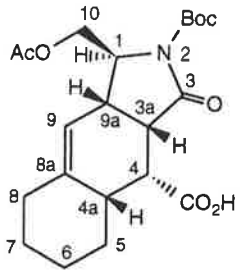
^{1}H nmr δ 13.6 (bs, 1H, CO_2H), 5.24 (ABq, 2H, bn), 5.19 (bs, 1H, H9), 4.10-3.95 (m, 3H, H1 and H10), 3.79 (dd, 1H, H3a), 3.02 (dd, 1H, H4), 2.97 (m, 1H, H9a), 2.45 (m, 1H, H4a), 2.21 (bd, 1H, $H8_{eq}$), 2.0 (m, 1H, $H8_{ax}$), 2.0 (m, 1H, $H5_{eq}$), 1.8 (m, 1H, $H7_{eq}$), 1.8 (m, 1H, $H6_{eq}$), 1.4 (bm, 1H, $H7_{ax}$), 1.2 (bm, 1H, $H5_{ax}$), 1.2 (bm, 1H, $H6_{ax}$), 1.17 (s, 9H, CH_3), 1.07 (s, 9H, CH_3).

^{13}C nmr δ 179.1, 173.7, 150.6 (NC(O)O), 145.6 (C8a), 135.5, 135,4, 134.6 (4° ar), 132.5, 132.2, 130.2, 130.1 (ar), 128.7, 128.6, 128.0 (3° ar), 117.2 (C9), 68.6 (bn), 64.9 (C10), 64.0 (C1), 45.5 (C4), 41.0 (C3a), 39.1 (C4a), 36.9 (C8), 36.4 (C9a), 31.6 (C5), 29.7 (4°), 28.8 (C6), 26.8 (CH_3), 26.7 (C7).

Ir (neat) υ_{max} 3300-2500 (CO_2H), 1780, 1735, 1700, 1380, 1295, 1100, 720, 695 cm^{-1}.

Ms (fab) *m/z* 638 (MH^+).

(1*S*, 3a*S*, 4*R*, 4a*R*, 9a*S*)-1-(Acetoxy)methyl-2-*N*-*tert*-butoxycarbonyl(1,3a,4,4a, 5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (112g)



A solution of diene **114** (116 mg, 0.375 mmol) and maleic anhydride **94** (110 mg, 1.122 mmol) in $CDCl_3$ (0.40 ml) was stirred in a sealed vessel at ambient temperature. When the reaction mixture was analysed by ^{1}H nmr spectroscopy after 4 h, the ratio of the resonances at δ = 4.45 ppm (**112g**) and δ = 4.88 ppm (**113g**) was 3.6:1.0. This ratio was confirmed by hplc analysis (355:520:125:3 acetonitrile/water/methanol/trifluoroacetic acid) of the crude reaction product. Analysis of the reaction mixture in the same fashion after 8, 12 and 24 h revealed that this ratio did not change. Following 24 h the solvent was evaporated and the residue chromatographed (47:47:6 dichloromethane/hexane/acetic acid) to furnish **112g** (28 mg,

18 %) as a colourless solid, m.p.: 144-146 °C. Anal. Calcd for $C_{21}H_{29}NO_7$: C, 61.90; H, 7.17; N 3.44 %. Found: C, 61.59; H, 6.96; N, 3.36 %.

^{1}H nmr δ 14.1 (bs, 1H, CO_2H), 5.21 (bs, 1H, H9), 4.46 (dd, 1H, H10), 4.23 (dd, 1H, H10), 4.08 (m, 1H, H1), 3.53 (dd, 1H, H3a), 3.15 (dd, 1H, H4), 2.89 (m, 1H, H9a), 2.50 (m, 1H, H4a), 2.27 (bd, 1H, $H8_{eq}$), 2.10 (s, 3H, $C(O)CH_3$), 2.0 (m, 1H, $H8_{ax}$), 2.0 (m, 1H, $H5_{eq}$), 1.8 (m, 1H, $H7_{eq}$), 1.8 (m, 1H, $H6_{eq}$), 1.55 (s, 9H, $C(CH_3)$), 1.4 (bm, 1H, $H7_{ax}$), 1.3 (bm, 1H, $H5_{ax}$), 1.3 (bm, 1H, $H6_{ax}$), 1.17 (s, 9H, CH_3).

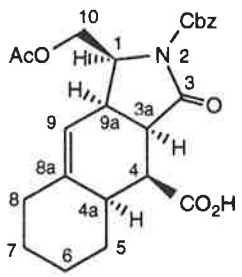
^{13}C nmr δ 178.0, 173.9, 170.4, 149.0 (NC(O)O), 146.0 (4° olefinic), 135.1 (4° ar), 128.4, 128.2, 127.8 (3° ar), 116.7 (C9), 84.9 (**C**(CH_3)), 68.1 (bn), 63.8 (C10), 62.1 (C1), 45.2 (C4), 40.6 (C3a), 39.0 (C4a), 36.5 (C8), 36.3 (C9a), 31.6 (C5), 28.9 (C6), 27.9 (C(**C**H_3), 26.7 (C7), 20.4 (C(O)**C**H_3).

Ir (nujol mull) υ_{max} 3200-2400 (CO_2H), 1775, 1745, 1700, 1620, 1580, 1405, 1300, 1240, 1150, 1040, 980 cm^{-1}.

Ms (fab) *m/z* 408 (MH^+).

Or (CH_2Cl_2, c = 0.65) $[\alpha]_D$ -55.6°.

(1*S*, 3a*R*, 4*S*, 4a*S*, 9a*R*)-1-(Acetoxy)methyl-2-*N*-benzoxycarbonyl(1,3a,4,4a,5,6, 7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (113a)



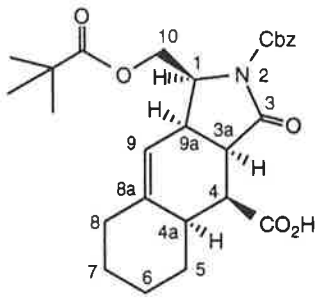
Conditions A (Scheme 32): A degassed mixture of diene **41** (500 mg, 1.456 mmol) and maleic anhydride **94** (428 mg, 4.368 mmol) was refluxed in 1,2-dichloro-benzene (50 ml) for 1 h. an aliquot (5 ml) of the reaction mixture was withdrawn, the solvent distilled (0.5 Torr) and the residue analysed by ^{1}H and ^{13}C nmr spectros-copy. Starting diene **41** was not detected and two sets of resonances (**112a** and **113a**) predominated each spectrum. The ratio of the resonances at δ = 3.57 ppm

(**112a**) and at $\delta = 3.39$ ppm (**113a**) was 2.6:1.0. The reaction mixture was cooled to ambient temperature and combined with the nmr sample. Approximately half of the solvent was distilled (0.3 Torr) and ether (70 ml) added to the concentrated reaction mixture. It was thoroughly extracted with sat. $NaHCO_3$ (3×30 ml). The combined extracts were immediately washed with ether (30 ml) and acidified to pH≤0 by the slow addition conc. HCl. It was extracted with ether (3×50 ml) and the solvent evaporated from the combined extracts to yield a brown oil (430 mg, 67 %), which was analysed by hplc (355:520:125:6 acetonitrile/water/methanol/-trifluoroacetic acid). The following peaks were observed (relative intenses in parenthesis): $t_R = 33.4$ min (unknown, small), $t_R = 34.8$ min (**113a** 37 %), $t_R = 36.6$ min (unknown, small), 41.9 min (**112a**, 100 %). 40 mg of the crude product were submitted to hplc (355:250:125:6 acetonitrile/water/methanol/trifluoroacetic acid). From the main fraction pure **112a** (18 mg, 30 %) was isolated as a colourless oil. A minor fraction contained a mixture of compounds amongst which **113a** (4 mg, 7 %) was predominant.

^{1}H nmr δ 13.3 (bs, 1H, CO_2H), 7.42-7.33 (m, 5H, ar), 5.29 (ABq, 2H, bn), 5.21 (bs, 1H, H9), 4.87 (dd, $J = 11$ Hz, $J = 4$ Hz, 1H, H10), 4.33 (ddd, $J = 9$ Hz, $J = 7$ Hz, $J = 4$ Hz, 1H, H1), 4.19 (dd, $J = 11$ Hz, $J = 9$ Hz, 1H, H10), 3.37 (m, 1H, H3a), 3.1 (overlapped with signals of impurities, 2H, H9a and H4), 2.49 (m, 1H, H4a), 2.24 (bd, 1H, $H8_{eq}$), 2.03 (s, 3H, CH_3), 2.2-1.1 (m, 7H, remaining ring protons).

^{13}C nmr δ 175.3, 174.3, 170.4 (CO), 151.2 (NC(O)O), 146.2 (C8a), 135.3, 128.7, 128.5, 128.4 (ar), 112.0 (C9), 67.7 (bn), 60.6 (C10), 56.8 (C1), 43.6 (C4), 41.1 (C3a), 38.0 (C4a), 36.6 (C8), 33.9 (C9a), 31.0 (C5), 28.6 (C6), 26.5 (C7), 20.7 (CH_3).

(1*S*, 3a*R*, 4*S*, 4a*S*, 9a*R*)-1-(2',2'-Dimethylpropanoate)methyl-2-*N*-benzoxycarbonyl(1,3a,4,4a,5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (113c)



Conditions A (Scheme 32): Diene **55** (141 mg, 0.366 mmol) was treated with maleic anhydride **94** (107.8 mg, 1.099 mmol) in refluxing 1,2-dichlorobenzene (12 ml) for 1 h. The reaction mixture was allowed to cool, the solvent distilled (0.4 Torr) and the residue analysed by ^{1}H nmr spectroscopy. A ratio of 3.2:1.0 was measured for the proton resonances at $\delta = 3.71$ ppm (**112c**) and at $\delta = 3.40$ ppm (**113c**). Chromatography (120:120:12.5 hexane/dichloromethane/acetic acid) of the crude product afforded pure **112c** (63 mg, 36 %) in the main fraction. Title compound **113c** (16 mg, 9 %) was isolated as a colourless oil from a minor fraction. Anal. Calcd. for $C_{27}H_{33}NO_7$: C, 67.06; H, 6.88; N, 2.90 %. Found: C, 66.89; H, 6.92; N, 2.77 %.

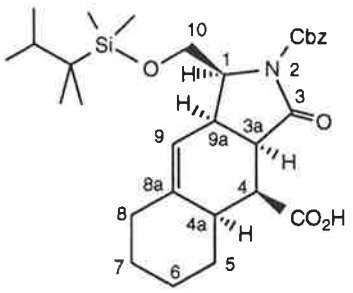
^{1}H nmr δ 11.9 (bs, 1H, CO_2H), 7.41 (m, 5H, ar), 5.29 (ABq, 2H, bn), 5.12 (bs, 1H, H9), 4.76 (dd, $J = 11$ Hz, $J = 4$ Hz, 1H, H10), 4.39-4.26 (m, 2H, H1 and H10), 3.30 (dd, $J_{3a,9a} = 7$ Hz, $J_{3,4} = 4$ Hz, 1H, H3a), 3.19 (dd, $J_{4,4a} = 7$ Hz, $J_{4,3a} = 4$ Hz, 1H, H4), 3.08 (m, 1H, H9a), 2.53 (m, 1H, H4a), 2.24 (bd, 1H, $H8_{eq}$), 2.2-1.1 (m, 7H, remaining ring protons), 1.16 (s, 9H, CH_3).

^{13}C nmr δ 178.6, 173.2 (CO), 151.3 (NC(O)O), 147.4 (CH=**C**), 135.4 (4° ar), 128.7, 128.5, 128.5 (3° ar), 111.8 (C9), 68.9 (bn), 60.8 (C10), 57.8 (C1), 43.3 (C4), 41.4 (C3a), 38.9 (C4a), 38.9 (4°), 37.2 (C8), 35.0 (C9a), 31.4 (C5), 28.9 (C6), 27.1 (C7), 27.0 (CH_3).

Ir (neat) υ_{max} 3300-2500 (CO_2H), 1780, 1750, 1725, 1700 cm^{-1}.

Ms (fab) *m/z* 484 (MH^+).

(1*S*, 3a*R*, 4*S*, 4a*S*, 9a*R*)-1-[(Dimethyl-1',1',2'-trimethylpropyl)siloxy]methyl-2-*N*-benzoxycarbonyl(1,3a,4,4a,5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (113e)



Conditions A (Scheme 32): Diene **56** (168 mg, 0.379 mmol) was treated with maleic anhydride **94** (112 mg, 1.138 mmol) as described for the synthesis of **113c**. Exactly half of the crude reaction product was analysed by ^{13}C nmr spectroscopy in the presence of chromium(III) acetylacetonate as described for **112e** (Method 1). A ratio of 4.4:1.0 for the carbon resonances at δ = 117.4 ppm (**112f**) and at δ = 113.1 ppm (**113f**) was determined.

The remaining half of the crude product was submitted to chromatography (140:100:12.5 hexane/dichloromethane/acetic acid). From the main fraction pure **112e** was isolated in a yield of (34 mg, 34 %), while a minor fraction yielded the title compound **113e** (15 mg, 15 %) as an oil which was contaminated by some unidentified material. Further purification by hplc was attempted but failed.

^{1}H nmr δ 14.3 (bs, 1H, CO_2H), 7.35 (m, 5H, ar), 5.46 (bs, 1H, H9), 5.25 (ABq, 2H, bn), 4.29 (dd, J = 10 Hz, J = 4 Hz, 1H, H10), 4.08 (ddd, J = 10 Hz, J = 6 Hz, J = 4 Hz, 1H, H1), 3.64 (t, J = 10 Hz, 1H, H10), 3.25 (dd, $J_{3a,9a}$ = 7 Hz, $J_{3,4}$ = 4 Hz, 1H, H3a), 3.14 (dd, $J_{4,4a}$ = 7 Hz, $J_{4,3a}$ = 4 Hz, 1H, H4), 3.05 (overlapped with signals of impurities, 1H, H9a), 2.47 (m, 1H, H4a), 2.19 (bd, 1H, $H8_{eq}$), 2.2-1.1 (m, 7H, remaining ring protons), 1.57 (sep, J=7 Hz, 1H, C**H**$(CH_3)_2$), 0.87 (d, J=7 Hz, 6H, $CH(CH_3)_2$), 0.83 (s, 6H, $SiC(CH_3)_2$), 0.06 (s, 6H, $Si(CH_3)_2$).

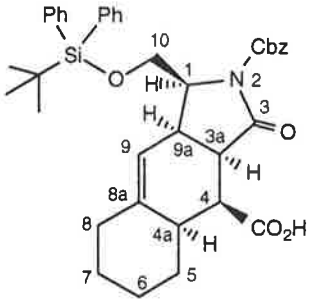
^{13}C nmr δ 178.5, 173.2 (CO), 151.0 (NC(O)O), 146.3 (CH=**C**), 134.6 (4° ar), 128.7, 128.5, 128.4 (3° ar), 113.0 (C9), 68.9 (bn), 60.5 (C10), 59.5 (C1), 44.4 (C4), 41.5

(C3a), 39.1 (C4a), 37.1 (C8), 34.6 (C9a), 34.0 (3°), 31.5 (C5), 29.0 (C6), 27.0 (C7), 25.0 (4°), 20.1, 20.1, 18.3, 18.3 (CH_3), -3.7 ($Si(CH_3)_2$).

Ir (neat) υ_{max} 3300-2500 (CO_2H), 1740, 1715 cm^{-1}.

Ms (fab) *m/z* 542 (MH^+).

(1*S*, 3a*R*, 4*S*, 4a*S*, 9a*R*)-1-[(Diphenyl*tert*-butyl)siloxy]methyl-2-*N*-benzoxy-carbonyl(1,3a,4,4a,5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (113f)



Conditions A (Scheme 32): Diene **57** (231 mg, 0.406 mmol) was treated with maleic anhydride **94** (118 mg, 1.208 mmol) as described for the synthesis of **113e**. Exactly half of the crude reaction product was analysed by ^{13}C nmr spectroscopy in the presence of chromium(III) acetylacetonate as described for **112e** (Method 1). A ratio of 4.6:1.0 for the carbon resonances at δ = 117.2 ppm (**112f**) and at δ = 112.9 ppm (**113f**) was determined.

The remaining half of the crude product was chromatographed (140:100:12.5 hexane/dichloromethane/acetic acid) and pure **112f** (50 mg, 39 %) was isolated as an oil from the main fraction, while pure **113f** (14 mg, 11 %) was obtained as an oil from a minor fraction eluting after the main fraction. Anal. Calcd. for $C_{38}H_{43}NSiO_6$: C, 71.56; H, 6.80; N, 2.20 %. Found: C, 71.34; H, 6.81; N, 2.17 %.

^{1}H nmr δ 13.8 (bs, 1H, CO_2H), 7.65-7.25 (m, 15H, ar), 5.51 (bs, 1H, H9), 5.10 (ABq, 2H, bn), 4.45 (dd, J = 10 Hz, J = 5 Hz, 1H, H10), 4.11 (m, 1H, H1), 3.72 (t, J = 10 Hz, 1H, H10), 3.28-3.18 (m, 3H, H3a and H4 and H9a), 2.52 (m, 1H, H4a), 2.15 (bd, 1H, $H8_{eq}$), 2.2-1.1 (m, 7H, remaining ring protons), 1.07 (s, 9H, CH_3).

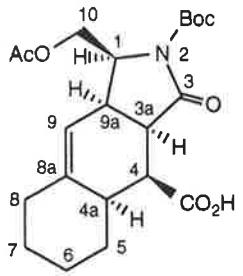
^{13}C nmr δ 178.9, 173.4 (CO), 150.9 (NC(O)O), 146.7 (CH=**C**), 135.5, 135.5, 134.3, 132.9, 132.8, 130.1, 130.0, 128.6, 128.4, 128.4, 127.9 (3° ar), 112.7 (C9), 68.9 (bn), 60.4 (C10), 60.7 (C1), 45.0 (C4), 41.6 (C3a), 39.2 (C4a), 37.0 (C8), 34.7 (C9a), 31.6 (C5), 29.8 (4°), 28.8 (C6), 26.9 (C7), 26.9 (CH_3).

Ir (neat) υ_{max} 3300-2500 (CO_2H), 1795, 1760, 1730, 1280, 1120, 1000, 740, 700 cm^{-1}.

Ms (fab) *m/z* 638 (MH^+).

Or (CH_2C_2, c = 0.46) $[a]_D$ -3.26°.

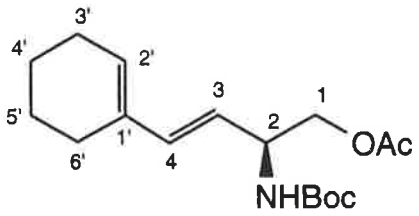
(1*S*, 3a*R*, 4*S*, 4a*S*, 9a*R*)-1-(Acetoxy)methyl-2-*N*-*tert*-butoxycarbonyl(1,3a,4,4a, 5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylic acid (113g)



The crude reaction product that was obtained during the synthesis of **112g** was analysed by ^{1}H and ^{13}C nmr spectroscopy. From these spectra only two resonances of **113g** were not overlapped with signals of **112g**. No attempt was made to synthesise and isolate **113g** according to the usual method.

^{1}H nmr δ 4.88 (dd, 1H, H10), 3.41 (dd, 1H, H3a).

(2*S*, 3*E*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)-but-3-en-1-yl acetate (114)

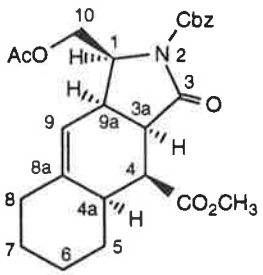


Alcohol **58** (132 mg, 0.466 mmol) was treated with freshly distilled acetic anhydride (58 mg, 0.559 mmol) *in lieu of* 2,2-dimethylpropanoyl chloride following the

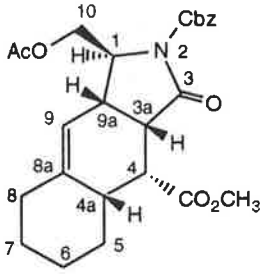
procedure for the synthesis of **37**. After chromatography (17:83 ethyl acetate/hexane) of the crude product acetate **58** (117 mg, 89 %) was isolated as a colourless clear oil. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N 4.53 %. Found: C, 65.70; H, 8.87; N, 4.51 %.

^{1}H nmr δ 6.20 (d, *J* = 16 Hz, 1H, H4), 5.76 (bt, 1H, H2'), 5.41 (dd, *J* = 16 Hz, *J* = 6 Hz, 1H, H3), 4.76 (bs, 1H, NH), 4.47 (m, 1H, H2), 4.10 (d, 1H, H1), 2.11 (bm, 4 H, H3' and H6'), 2.06 (s, 3H, CH_3), 1.70-1.57 (m, 4 H, H4' and H5'), 1.45 (s, 9H, *t*Bu).
^{13}C nmr δ 170.8 (ester CO), 155.1 (NC(O)O), 135.4 (C4), 130.4 (C1'), 134.6 (C2'), 121.4 (C3), 79.4 (**C**$(CH_3)_3$), 66.1 (C1), 51.2 (C2), 28.2 (C(**C**$H_3)_3$), 25.7, 24.3 (C3' and C6'), 22.3, 22.2 (C4' and C5'), 20.7 (C(O)**C**H_3).
Ir (neat) υ_{max} 3339, 1725, 1695, 1530, 1250 cm^{-1}.
Ms (ei) *m/z* 309 (M^+).
Or ($CHCl_3$, c = 2.90) $[\alpha]_D$ +2.71°.

Methyl (1*S*, 3a*R*, 4*S*, 4a*S*, 9a*R*)-1-(acetoxy)methyl-2-*N*-benzoxycarbonyl(1,3a, 4,4a,5,6,7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylate (116) and **methyl (1*S*, 3a*S*, 4*R*, 4a*R*, 9a*S*)-1-(acetoxy)methyl-2-*N*-benzoxycarbonyl(1,3a, 4,4a,5,6, 7,8,9a)-nonahydrobenzo[f]isoindol-3-one-4-carboxylate (117)**



116



117

A solution of diene **41** (500 mg, 1.456 mmol) and maleic anhydride **94** (428 mg, 4.368 mg) was refluxed in 1,2-dichlorobenzene (50 ml) as described for the synthesis of **113a**. The solvent was distilled (0.5 Torr) and the residue extracted with sat. $NaHCO_3$ as described for **113a**.
The crude acidic extracts (826 mg) were dissolved in ether (50 ml) and cooled to

-10 °C in a conical flask. To this stirred solution an ethereal solution of diazomethane[155] was slowly added until the yellow colour just persisted. A few drops of acetic acid were added to discolour the solution. The solvent was evaporated, the residue dissolved in methanol (12 ml) and filtered through a 3 cm deep pad of reversed phase silica (elution with 100 ml of methanol). After the solvent was evaporated from the filtrate the residue was dissolved in ethyl acetate (5 ml) and filtered through a 4 cm deep pad of tlc grade silica (elution with 150 ml of ethyl acetate). The solvent was evaporated from the filtrate to give a brown oil (491 mg, 74 % with regard to diene **41**). A ratio of 2.7:1.0 was determined for the resonances at $\delta = 3.69$ ppm (**117**) and $\delta = 3.46$ ppm (**116**) by ^{1}H nmr spectroscopic analysis of the crude product. Two peaks were detected at $t_R = 10.9$ min (**116**, 36 %) and $t_R = 12.1$ min (**117**, 100 %) by hplc analysis of the crude product (3:7 water/ methanol, flowrate: 5 ml).

The crude product was dissolved in a minimum amount of hot methanol (≈2 ml) and the solution allowed to stand at ambient temperature for 1 h. The mother-liquors were removed with a pipette and the remaining crystals washed with ice-cold methanol (1 ml) and dried to yield ester **116** (54 mg, 8 % with respect to diene **41**), m.p. 193-202 °C. A few crystals were dissolved in a minimum amount of methanol and analysed by hplc. The chromatogram showed essentially a single peak at $t_R = 10.9$ min. Co-injection of a solution of the crystals and a solution of the crude reaction product markedly enhanced the intensity of the smaller peak at $t_R = 10.9$ min. When an aliquot of the methanolic filtrate was analysed the relative intensity of the peaks was changed: $t_R = 10.9$ min (**116**, 3 %) and $t_R = 12.1$ min (**117**, 100 %). The ^{1}H nmr spectrum of the residue obtained by evaporation of the mother-liquors showed only *trans*-isoindolone **117**.

Ester **117** (158 mg, 21 % with respect to diene **41**) was obtained as a colourless oil by semi-preparative hplc of the mother-liquors. Attempted crystallisation from a variety of solvents was unsuccessful. Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N 3.07 %. Found: C, 65.68; H, 6.62; N, 2.98 %.

Recrystallisation of **116** from methanol and subsequent slow crystallisation from hot ethanol (≈1 ml) furnished crystals suitable for X-ray crystallographic analysis, m.p. 202-203 °C. Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N 3.07 %. Found: C, 65.75; H, 6.42; N, 2.95 %.

Data for isoindolone **116**

^{1}H nmr δ 12.2 (bs, 1H, CO_2H), 7.44-7.31 (m, 5H, ar), 5.28 (ABq, 2H, bn), 5.21 (bs, 1H, H9), 4.86 (dd, J = 10 Hz, J = 4 Hz, 1H, H10), 4.30 (ddd, J = 9 Hz, J = 7 Hz, J = 4 Hz, 1H, H1), 4.19 (dd, J = 10 Hz, J = 9 Hz,, 1H, H10), 3.78 (s, 3H, OCH_3), 3.46 (dd, J = 8 Hz, J = 4 Hz, 1H, H3a), 3.12 (m, 1H, H9a), 2.92 (dd, J = 6 Hz, J = 4 Hz, 1H, H4), 2.46 (m, 1H, H4a), 2.23 (bd, 1H, $H8_{eq}$), 2.2-1.1 (m, 7H, remaining ring protons), 2.05 (s, 3H, $C(O)CH_3$).

^{13}C nmr δ 173.6, 171.9, 170.3, 152.0 (NC(O)O), 147.6 (C8a), 135.1 (4° ar), 128.6, 128.4, 128.4 (3° ar), 112.2 (C9), 68.5 (bn), 61.4 (C10), 57.2 (C1), 51.9 (OCH_3), 41.3 (C4), 41.2 (C3a), 38.8 (C4a), 37.4 (C8), 34.3 (C9a), 31.4 (C5), 29.4 (C6), 27.2 (C7), 20.8 ($C(O)\mathbf{C}H_3$).

Ir (nujol mull) υ_{max} 1760, 1740, 1275, 1255, 1215, 760 cm^{-1}.

Uv (ethanol) λ_{max} 257 nm (ε = 212).

Ms (fab) *m/z* 456 (MH^+).

Or ($CDCl_3$, c = 1.37) $[\alpha]_D$ 120°.

Data for isoindolone **117**

^{1}H nmr δ 7.38-7.30 (m, 5H, ar), 5.29 (ABq, 2H, bn), 5.19 (bs, 1H, CH9a), 4.39 (dd, 1H, H10), 4.21 (dd, 1H, H10), 4.11 (m, 1H, H1), 3.77 (s, 3H, OCH_3), 3.69 (dd, 1H, H3a), 2.89 (dd, 1H, H4,), 2.88 (m, 1H, H9a), 2.44 (m, 1H, H4a), 2.3 (bt, 2H, $H8_{eq}$ and $H5_{eq}$), 2.05 (s, 3H, $C(O)CH_3$), 2.0 (m, 1H, $H8_{ax}$), 1.8 (m, 1H, $H7_{eq}$), 1.8 (m, 1H, $H6_{eq}$), 1.4 (bm, 1H, $H7_{ax}$), 1.0 (bm, 1H, $H5_{ax}$), 1.2 (bm, 1H, $H6_{ax}$).

^{13}C nmr δ 173.1, 171.7, 170.4, 151.5 (NC(O)O), 146.4 (4° olefinic), 135.2 (4° ar), 128.8, 128.5, 127.9 (3° ar), 116.5 (C9), 68.2 (bn), 63.8 (C10), 60.8 (C1), 51.7 (OCH_3), 42.1 (C4), 40.2 (C3a), 38.4 (C4a), 36.7 (C8), 36.0 (C9a), 31.5 (C5), 29.3 (C6), 27.1 (C7), 20.7 ($C(O)\mathbf{C}H_3$).

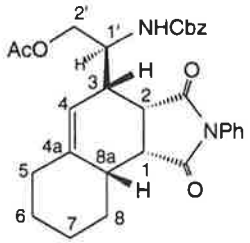
Ir (neat) υ_{max} 1795,1745, 1730, 1700, 1390, 1305, 1230, 1050 cm^{-1}.

Uv (ethanol) λ_{max} 258 nm ($\varepsilon = 213$)

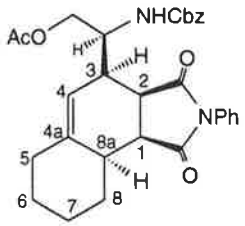
Ms (fab) *m/z* 456 (MH^+).

Or (CH_2Cl_2, c = 1.63) $[\alpha]_D$ -45.2°.

(1*S*, 2*R*, 3*R*, 8a*S*)-3-[(1'*S*)-2'-Acetoxy-1'-*N*'-(benzoxycarbonyl) aminoethyl]-(1,2,3,5,6,7,8,8a) octahydronaphthalene-1,2-dicarboxylic *N*-phenyl imide (126)
and **(1*R*, 2*S*, 3*S*, 8a*R*)-3-[(1'*S*)-2'-acetoxy-1'-*N*'-(benzoxycarbonyl) aminoethyl]-(1,2,3,5,6,7,8,8a) octahydronaphthalene-1,2-dicarboxylic *N*-phenyl imide (127)**



126



127

A solution of diene **41** (302 mg, 0.879 mmol) and *N*-phenylmaleimide **98** (243 mg, 1.403 mmol) in $CDCl_3$ (1.1 ml) was stirred at ambient temperature in a sealed vessel. After 12 h the reaction mixture was analysed by ^1H and ^{13}C nmr spectroscopy. Starting diene **41** was not detected and two sets of resonances due to **126** and **127** predominated each spectrum. The ratio of the resonances at $\delta = 5.50$ ppm (**126**) and at $\delta = 5.62$ ppm (**127**) was 4.4:1.0. An aliquot of the reaction solution was analysed by hplc (35:65 water/methanol). Two peaks were observed at $t_R = 29.2$ min (**127**, 22 %) and $t_R = 30.7$ min (**126**, 100 %). The solvent was evaporated from the reaction mixture and the residue chromatographed (4:6 ethyl acetate/hexane) to yield a mixture of adducts **126** and **127** (241 mg, 53 %). Anal. Calcd. for $C_{30}H_{33}N_2O_6$: C, 69.75; H, 6.24; N, 5.42 %. Found: C, 69.53; H, 6.03; N, 5.10 %. 38 mg of this mixture was separated by hplc (2:8 water/methanol) to afford **126** (17 mg, 24 %) and **127** (7 mg, 11 %) both as a colourless oil.

Data for **126**

^{1}H nmr δ 7.47-7.16 (m, 10H, ar), 6.15 (bd, 1H, NH), 5.50 (bs, 1H, H4), 5.12 (ABq, 2H, bn), 4.39 (bs, 3H, H1' and H2'), 3.36-3.30 (m, 2H, H1 and H2), 2.84 (bs, 1H, H3), 2.45 (bm, 1H, H8a), 2.30-1.25 (m, 8H, H5-8), 2.05 (s, 3H, CH_3).

^{13}C nmr δ 177.9, 176.4, 170.8, 156.4, 142.6, 136.6, 131.5, 129.1, 128.7, 128.4, 128.1, 128.0, 126.4, 119.7, 66.6, 64.1, 51.2, 44.2, 41.7, 37.0, 36.1, 30.7, 25.9, 23.1, 23.0, 20.9.

Ir (neat) υ_{max} 3400 (NH), 1780, 1750, 1720, 1700, 1600, 1410, 1400, 1310, 1230, 1050 cm^{-1}.

Uv (ethanol) λ_{max} 255 nm (ε = 295).

Ms (fab) *m/z* 517 (MH^+).

Or ($CDCl_3$, c = 0.5) $[\alpha]_D$ -54.3°.

Data for **127**

^{1}H nmr δ 7.46-7.16 (m, 10H, ar), 5.62 (bs, 1H, H4), 5.13 (s, 2H, bn), 5.01 (d, 1H, NH), 4.75-4.32 (m, 3H, H1' and H2'), 3.37-3.25 (m, 2H, H1 and H2), 2.48 (bm, 1H, H3), 2.37 (bm, 1H, H8a), 2.28-1.81 (m, 5H, H5-8), 2.06 (s, 3H, CH_3), 1.66-1.26 (m, 3H, H5-8).

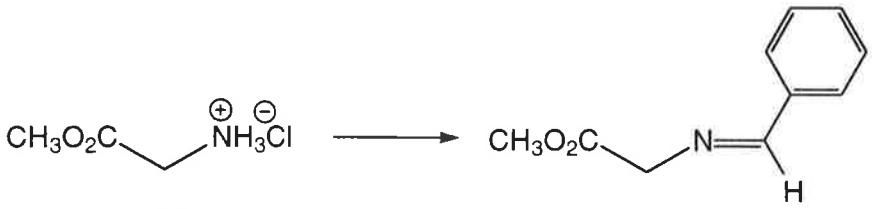
^{13}C nmr δ (incomplete) 155.9, 143.3, 129.1, 128.5, 128.2, 126.5, 120.3, 67.0, 64.8, 50.5, 44.5, 41.8, 37.9, 37.2, 29.1, 24.2, 22.2, 21.7, 20.9.

Ir (neat) υ_{max} 3400 (NH), 1750, 1740, 1715, 1695 cm^{-1}.

Ms (fab) *m/z* 517 (MH^+).

Or ($CDCl_3$, c=0.05) $[\alpha]_D$ +22.0°.

Methyl 2-(*N*-phenylmethylidene)amino acetate (169)[111]



166 **169**

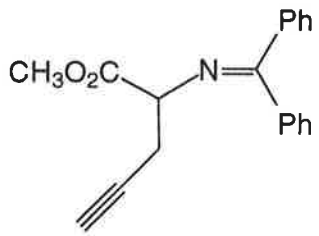
A mixture of magnesium sulfate (5.99 g, 48.9 mmol, dried to constant weight at 160 °C at 0.1 Torr), finely ground methyl ester hydrochloride **166** (3.122 g, 24.9 mmol), triethylamine (2.77 g, 27.4 mmol) and benzaldehyde (2.64 g, 24.9 mmol, distilled under an atmosphere of nitrogen immediately prior to use) in dry dichloromethane (30 ml) was stirred for 1 d. Hexane (40 ml) was added, the resulting mixture filtered through a 1 cm deep pad of kenite and the solvent evaporated. The remaining light yellow oil was magnetically stirred at a reduced pressure of 0.03 Torr for 2 h to afford **169** (4.37 g, 99 %) as a light yellow viscous oil. This material was pure by ^{1}H and ^{13}C nmr spectroscopic analysis.

^{1}H nmr δ 8.26 (bs, 1H, HC=N), 7.79-7.39 (m, 5H, ar), 4.40 (bs, 2H, CH_2N), 3.75 (s, 3H, CH_3).

^{13}C nmr δ 170.3, 165.3, 135.5, 131.1, 128.5, 128.4, 61.7, 51.9.

Ir (neat) υ_{max} 1740, 1625, 1450, 1290, 1200, 1180, 705 cm^{-1}.

Methyl (*R,S*)-2-(*N*-phenylmethylidene)amino pent-4-ynoate (170)



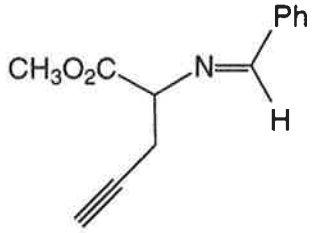
A stirred solution of di*iso*-propylamine (5.109 g, 51.00 mmol) in THF (80 ml) was cooled to -80 °C under an atmosphere of nitrogen. Consecutively the following solutions and pure liquids were added using a syringe:

A freshly prepared 2.3M solution of *n*-butyl lithium in hexanes (the optimum amount was determined by performing trial reactions on a small scale)
A solution of the glycine ester **169** (8.81 g, 50.00 mmol) in THF (20 ml)
1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (10 ml, 82.70 mmol)
freshly distilled propargyl bromide (8.92 g, 75.00 mmol)

Each addition durated 2 min and was followed by a waiting period of 10 min. After the completed addition the mixture was stirred for 1 h and quenched by the addition of sat. NH_4Cl (10 ml) at -80 °C. The flask was removed from the cooling bath and stirring was continued for 10 min. Its contents were poured onto sat. NH_4Cl (100ml) and the aqueous phase was extracted with a 1:1 mixture of hexane/ether (3×50 ml). The combined organic phase was washed with water (2×50 ml), dried ($MgSO_4$) and the solvent evaporated to yield an oily residue which was stirred at 50 °C under reduced pressure (0.5 Torr). The title compound **170** was obtained was obtained (10.44 g, 97 % yield and essentially pure when analysed by ^1H and ^{13}C nmr spectroscopy.

^1H nmr δ 8.29 (bs, 1H, N=CH), 7.77-7.31 (m, 5H, ar), 4.09 (dd, 1H, H2), 3.63 (s, 3H, CH_3), 2.95-2.68 (m, 2H, H3), 2.14 (t, 1H, H5).
^{13}C nmr δ 169.9, 163.9, 134.7, 130.6, 127.9, 127.8, 79.6, 70.8, 70.7, 51.4, 22.4.
Ir (neat) υ_{max} 3300, 1740, 1620, 1450, 1290, 1210, 1180, 705 cm^{-1}.
Ms (ei) *m/z* 215 (M^+).

Methyl (*R,S*)-2-(*N*-diphenylmethylidene)amino pent-4-ynoate (171)



Method 1: Glycine derivative **168** (8.43 g, 33.3 mmol) was treated as described for

the synthesis of **170**. Propargylglycine derivative **171** (9.31 g, 96 %) was obtained as a light yellow oil. ^{1}H and ^{13}C nmr spectroscopic analysis of this material showed less than 4 % of starting **168** as the only dectable impurity. Further purification by chromatography (1:19 ethyl acetate/hexane) afforded **171** in a yield of 91 % as a colourless oil that solidified on standing, m.p. 45-46 °C. Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81 %. Found: C, 78.61; H, 5.88; N, 4.37 %.

Method 2: Sodium hydride as a 80 % dispersion in mineral oil (660 mg) were washed twice with hexane on a sintered glass funnel under an atmoshere of nitrogen. The resulting powder was transferred to the reaction flask that contained DMF (60 ml). The suspension was stirred at 0 °C (ice-bath) under an atmosphere of nitrogen for 15 min before a solution of **168** (4.26 g, 16.8 mmol) in DMF (20 ml) was added from a syringe over a period of 2 min at ambient temperature. A yellow solution resulted that was stirred for 15 min. Propargyl bromide bromide (2.99 g, 25.1 mmol) was quickly added from a syringe. After 30 min the ice-bath was removed and the reaction mixture was poured onto sat. NH_4Cl (100ml). The reaction was worked-up as described for **170** to yield the title compound **171** (4.55 g, 93 %) as a light yellow oil which was pure by ^{1}H and ^{13}C nmr spectroscopic analysis.

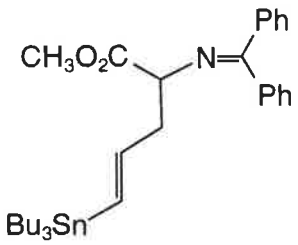
^{1}H nmr δ 7.67-7.24 (m, 10H, ar), 4.32 (dd, 1H, H2), 3.72 (s, 3H, CH_3), 2.91-2.65 (m, 2H, H3), 1.95 (t, 1H, H5).

^{13}C nmr δ 172.0, 171.0, 139.2, 135.8, 130.4, 128.9, 128.7, 128.4, 128.1, 127.9, 80.6, 70.3, 63.9, 52.3, 23.3.

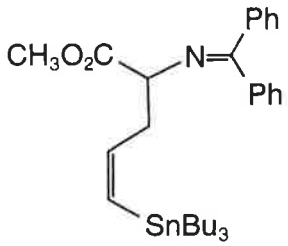
Ms (ei) *m/z* 291 (M^+).

Ir (neat) υ_{max} 3300, 1740, 1620, 1450, 1280, 1220, 1180, 700 cm^{-1}.

Methyl (2*RS*, 4*E*)-2-[*N*-(diphenylmethylidene)amino]-5-(tributylstannyl)but-4-enoate (172) and **methyl (2*RS*, 4*Z*)-2-[*N*-(diphenylmethylidene)amino]-5-(tributylstannyl)but-4-enoate (173)**



172



173

A degassed solution of propargylglycine derivative **171** (60 mg, 0.206 mmol), tributyltin hydride (30 mg, 0.103 mmol) and a small crystal of 2,2'-azobisisobutyronitrile in 1,2-dichlorobenzene (1.0 ml) was heated by inserting the flask into an oil-bath that was preheated to 165 °C. Further tributyltin hydride (70 mg, 0.241 mmol) was added dropwise from a syringe over a period of 15 min. After stirring for 20 min the solution was cooled to ambient temperature and the solvent distilled (0.3 Torr). The ^{1}H nmr spectrum of the crude product displayed resonances at δ = 6.36 ppm (**173**), δ = 5.98 ppm (**172**) and δ = 1.95 ppm (**171**) in a ratio of 2.5:1.0 to 11.0. Chromatograpy of the crude product on basic alumina (1:9 ethyl acetate/hexane) afforded a mixture of vinylstannanes **172** and **173** (40 mg, 33 %) and unchanged **171** (38 mg, 64 %). The mixture of **172** and **173** was separated by mplc (1:4 ethyl acetate/hexane) to afford **172** (13 mg, 11 %) and **173** (23 mg, 19 %) as isomerically, but not chemically pure compounds by ^{1}H nmr spectroscopic analysis. Anal. Calcd for $C_{31}H_{45}NO_2Sn$ (**172**): C, 63.93; H, 7.79; N, 2.41 %. Found: C, 65.18; H, 7.37; N, 3.15 %. Anal. Calcd for $C_{31}H_{45}NO_2Sn$ (**173**): C, 63.93; H, 7.79; N 2.41 %. Found: C, 64.08; H, 7.48; N 2.80 %.

Data for vinylstannane **172**

^{1}H nmr δ 7.62-7.13 (m, 10H, ar), 5.98 (d and tin satellites, J_{SnH} = 74 Hz, 1H, H5), 5.76 (dt, 1H, H4), 4.19 (dd, 1H, H2), 3.71 (s, 3H, CH_3), 2.82-2.70 (m, 2H, H3), 1.48-0.78 (m, 27H, Bu).

^{13}C nmr δ 172.5, 170.8, 144.3, 139.6, 136.4, 131.7, 130.3, 128.8, 128.6, 128.4, 128.0, 65.4, 52.0, 42.2, 29.0, 27.2, 13.6, 9.3 (tin satellites, J_{SnH} = 272 Hz, $SnCH_2$).

Ir (neat) υ_{max} 2953, 1738, 1635, 1460, 1198, 1185, 700 cm^{-1}.

Ms (ei) *m/z* 582 (M^+ for ^{119}Sn).

Data for vinylstannane **173**

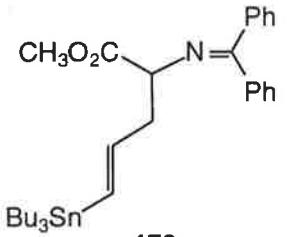
^{1}H nmr δ 7.65-7.13 (m, 10H, ar), 6.36 (dt, J = 13 Hz, 1H, H4), 5.89 (d and tin satellites, J = 13 Hz, J_{SnH} = 68 Hz, 1H, H5), 4.16 (dd, 1H, H2), 3.72 (s, 3H, CH_3), 2.76-2.58 (m, 2H, H3), 1.48-0.78 (m, 27H, Bu).

^{13}C nmr δ 172.3, 170.5, 144.3, 139.6, 136.3, 131.4, 130.3, 128.9, 128.6, 128.4, 128.0, 65.5, 52.1, 40.4, 29.1, 27.3, 13.7, 10.1.

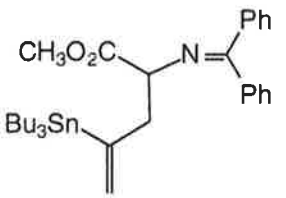
Ir (neat) υ_{max} 2951, 1739, 1635, 1456, 1203, 1185, 700 cm^{-1}.

Ms (ei) *m/z* 582 (M^+ for ^{119}Sn).

Methyl (2*RS*, 4*E*)-2-[*N*-(diphenylmethylidene)amino]-5-(tributylstannyl)but-4-enoate (172) and **methyl (*R*,*S*)-2-[*N*-(diphenylmethylidene)-amino]-4-(tributylstannyl)but-4-enoate (176)**



172



176

To a degassed solution of propargylglycine derivative **171** (867 mg, 2.976 mmol) in benzene (50 ml) was added tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol). When the solution became homogenous tributyltin hydride (1.039 g, 3.571 mmol) was added dropwise from a syringe over a period of 20 min at ambient temperature. After 10 min of stirring the solvent was evaporated and the residue analysed by ^{1}H nmr spectroscopy. Resonances at δ = 5.98 ppm (**172**) and δ = 5.16 ppm (**176**) were detected in a ratio of 1.0:1.3. The crude product was purified by mplc (1:4 ethyl acetate/hexane) to afford **172** (555 mg, 32 %) and **176** (641 mg, 37 %) as isomerically pure compounds by ^{1}H nmr spectroscopic analysis. Anal. Calcd for $C_{31}H_{45}NO_2Sn$ (**176**): C, 63.93; H, 7.79; N, 2.41 %. Found: C, 64.03; H, 6.99; N, 3.37 %.

Data for vinylstannane **176**

^{1}H nmr δ 7.65-7.15 (m, 10H, ar), 5.67 (d and tin satellites, J = 3 Hz, 1H, J_{SnH} = 136 Hz, H5$_{pro\text{-}E}$), 5.16 (d and tin satellites, J = 3 Hz, J_{SnH} = 62 Hz, 1H, H5$_{pro\text{-}Z}$), 4.20 (dd, J = 6 Hz, J = 7 Hz, 1H, H2), 3.69 (s, 3H, CH_3), 2.96 (dd, J = 13 Hz, J = 6 Hz, 1H, H3), 2.65 (dd, J = 13 Hz, J = 7 Hz, 1H, H3), 1.48-0.78 (m, 27H, Bu).

^{13}C nmr δ 172.0, 171.0, 150.1, 140.0, 136.5, 130.3, 128.9, 128.7, 128.6, 128.5, 128.1, 128.0, 65.7, 51.9, 44.8, 29.0, 27.3, 13.7, 9.3.

Ir (neat) υ_{max} 2948, 1740, 1632, 1452, 1203, 1185, 700 cm^{-1}.

Ms (ei) *m/z* 582 (M^+ for ^{119}Sn).

Screening of transition metal complexes as catalysts for the hydrostannation of propargylglycine **171**:

To a degassed solution of propargylglycine derivative **171** (98 mg, 0.336 mmol) in THF (5 ml) was added one of the transition metal complexes (0.017 mmol) that are listed in Table 3 (page 85). Tributyltin hydride (196 mg, 0.672 mmol) was added dropwise from a syringe over a period of 2 h at ambient temperature using a syringe pump. After 10 min of stirring the solvent was evaporated and the residue and a known quantity of benzaldehyde (typically 30 mg, internal standard) were dissolved in $CDCl_3$ (≈ 1 ml). A portion of this sample (≈ 20 %) was analysed by ^{1}H nmr spectroscopy. The intensities of the resonances at δ = 10.2 ppm (benzaldehyde), δ = 5.98 ppm (**172**), δ = 5.16 ppm (**176**), δ = 1.95 ppm (**171**), δ = 4.35 ppm (**171**), and at δ = 5.10-5.00 ppm (**177**) were measured and the amount of compounds **171**, **172**, **176** and **177** present in solution calculated. The results are listed in Table 4 (page 87). In some cases the crude product was purified by mplc (1:4 hexane/ethyl acetate) to afford vinylstannanes **172** and **176**.

According to this general procedure we used the following transition metal complexes: $PdCl_2(PPh_3)_2$, $PdCl_2[P(o\text{-tolyl})_3]_2$, $PdCl_2(PMe_3)_2$, $PdCl_2(PBu_3)_2$, $Pd(OAc)_2$, $PdCl_2$dppe, $PdCl_2(AsPh_3)_2$, Pd on polyimine, Pd on polymer-supported PPh_3, $PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$, amorphous Pd-metal, $RhCl(PPh_3)_3$,

$NiBr_2(PPh_3)_2$, $PtCl_2(PPh_3)_2$, an aged sample of $Pd(PPh_3)_4$ and PPh_3 (control reaction).

"$Pd(AsPh_3)_4$" as a catalyst in the hydrostannation of **171**

A yellow mixture was prepared by stirring tris(dibenzylideneacetonedipalladium(0) (Pd_2dba_3, 7 mg, 7.6 μmol) and triphenylarsine (37 mg, 0.122 mmol) in THF (5 ml) at ambient temperature. Propargylglycine **171** (89 mg, 0.306 mmol) was added followed by tributyltin hydride (178 mg, 0.612 mmol), which was introduced dropwise with a syringe over a period of 20 min. After stirring for 10 min the solvent was evaporated and the residue analysed in the presence of benzaldehyde by ^1H nmr spectroscopy. The resonances were consistent with starting **171** and a trace amount of **177**.

Cp_2ZrHCl as a catalyst in the hydrostannation of **171**

To a stirred solution of propargylglycine **171** (103 mg, 0.354 mmol) in dry dichloromethane (2 ml) at ambient temperature was added Cp_2ZrHCl (5 mg, 18 μmol) under an atmosphere of nitrogen. Tributyltin hydride (206 mg, 0.708 mmol) was added over a period of 10 min. The mixture was stirred for 20 min and the solvent was evaporated. The ^1H nmr spectrum (with benzaldehyde as an internal standard) was consistent with the presence of unchanged starting **171** and allylglycine **177**. A ratio of 11:1 was measured for the signals at $\delta = 4.35$ ppm (**171**) and at $\delta = 5.10$-5.00 ppm (**177**), respectively.

"Ligand-free Ni^0" as a catalyst in the hydrostannation of **171**

To a stirred suspension of anhydrous orange $NiCl_2$ (4 mg, 12 μmol) in dry THF (3 ml) was added at ambient temperature lithium aluminium hydride (4 mg, 0.105 mmol). The mixture darkened and a solution of propargylglycine**171** (72 mg, 0.364 mmol) in THF (2 ml) was quickly added followed by tributyltin hydride (212 mg, 0.728 mmol), which was introduced dropwise with a syringe over a period of 5 min. The solvent was evaporated and the residue was analysed by ^1H nmr spectroscopy in the presence of benzaldehyde. The ratio of the resonances at $\delta = 5.98$ ppm

(**172**), δ = 5.16 ppm (**176**), δ = 4.35 ppm (**171**), and δ = 5.10-5.00 ppm (**177**) was 5:19:27:3, respectively. The crude product was purified by mplc to afford **172** (15 mg, 7 %), **176** (59 mg, 28 %) and **171** (29 mg, 40 %).

Palladium on carbon as a catalyst in the hydrostannation of **171**

Method 1 (THF, piperidine): A solution of propargylglycine derivative **171** (68 mg, 0.233 mmol) in a 1:1 mixture of piperidine and THF (4 ml) was treated as described for the synthesis of **177**. The crude reaction product was purified by mplc to afford compounds **171** (29 mg, 43 %), **172** (44 mg, 33 % yield), **176** (7 mg, 5 % yield) and **177** (8 mg, 11 % yield).

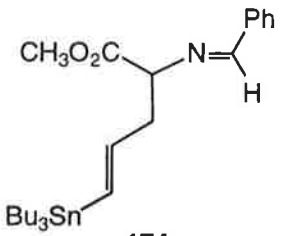
Method 2 (in THF): See Method 1 for the synthesis of **177**.

Aged $Pd(PPh_3)_4$ as a catalyst in the hydrostannation of **171**

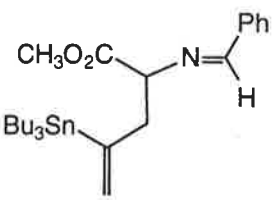
Method 1 (THF, piperidine): A solution of propargylglycine derivative **171** (81 mg, 0.278 mmol) in a 1:1 mixture of piperidine and THF (5 ml) was treated as described for the synthesis of **177**. The crude reaction product was purified by mplc to afford compounds **171** (19 mg, 24 %), **172** (50 mg, 31 % yield), **176** (29 mg, 18 % yield).

Method 2 (in THF): See Method 2 for the synthesis of **177**.

Methyl (2*RS*, 4*E*)-2-[*N*-(benzylidene)amino]-5-(tributylstannyl)but-4-enoate (174) and **methyl (*R*,*S*)-2-[*N*-(benzylidene)amino]-4-(tributylstannyl)but-4-enoate (175)**



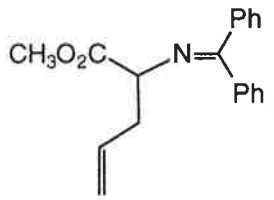
174



175

Propargylglycine **170** (155 mg, 0.720 mmol) was treated with tributyltin hydride as described under the synthesis of **172** and **176**. The ^{1}H nmr spectrum of the crude reaction product showed resonances in the olefinic region (**174** and **175**). Starting propargylglycine derivative **170** and benzaldehyde were not detected. The crude product was then quantitatively analysed in the presence of benzaldehyde (41 mg) as described previously. Resonances were observed at $\delta = 5.91$ ppm (d and tin satellites, $J_{SnH} = 72$ Hz, H5 of **172**) and at $\delta = 5.16$ ppm (d and tin satellites, $J = 3$ Hz, $J_{SnH} = 63$ Hz, 1H, $H5_{pro\text{-}Z}$ of **176**). A yield of 29 % for **174** and of 43 % for **175** was calculated on the basis of the internal standard. No attempt was undertaken to purify the crude reaction product.

Methyl (*R,S*)-2-[*N*-(diphenylmethylidene)amino] but-4-enoate (177)



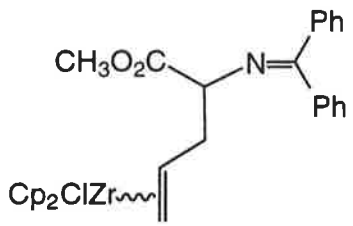
Method 1: To a stirred suspension of propargylglycine **171** (56 mg, 0.192 mmol) and 5% palladium on carbon (77 mg) in THF (5 ml) was added tributyltin hydride (447 mg, 1.536 mmol) from a syringe at 50 °C over a period of 3 h using a syringe pump. The mixture was filtered through kenite and the solvent evaporated. The residue was purified by mplc to afford pure **177** (30 mg, 54 %). The ^{1}H nmr spectral data of **177** were in agreement with the reported values.[156] Other fractions contained **171** (15 mg, 28 %) and **172** (8 mg, 7 %).

Method 2 (in THF): To a solution of propargylglycine derivative **171** (56 mg, 0.192 mmol) and aged (tetrakistriphenylphosphine)palladium (11 mg, 9.5 μmol) in THF (4 ml) was added tributyltin hydride (279 mg, 0.96 mmol) from a syringe at ambient temperature over a period of 3 h using a syringe pump. The solvent was evaporated and the crude product purified by mplc to yield compounds **172** (31 mg, 28 %), **176** (16 mg, 14 %) and **177** (23 mg, 41 %).

Method 3 (Pd on C as a catalyst for the destannylation of **172** and **176**): A 1 to 1 pure mixture of vinylstannanes **172** and **176** (51 mg, 0.175 mmol) was treated with tributyltin hydride (407 mg, 1.400 mmol) and 5% palladium on carbon (37 mg) in THF (5 ml) as described under the synthesis of **177** (Method 1). Signals at δ = 5.10-5.00 ppm due to allylglycine **177** were prominent in the ^{1}H nmr spectrum of the crude reaction product. The crude product was not purified.

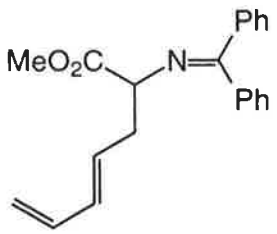
^{1}H nmr δ 7.65-7.15 (m, 10H, ar), 5.74-5.60 (m, 1H, H4), 5.10-5.00 (three bs, 2H, H5), 4.16 (dd, 1H, H2), 3.72 (s, 3H, CH_3), 2.75-2.57 (m, 2H, H3).
^{13}C nmr δ 172.4, 171.0, 139.8, 136.3, 134.2, 130.4, 128.9, 128.7, 128.5, 128.0, 127.9, 117.7, 65.3, 52.1, 38.2.

Methyl (2*RS*, 4*E*)-2-[*N*-(diphenylmethylidene)amino]-5-(dicyclopentadienylchlorozirconyl)but-4-enoate (178) and **methyl (*R*,*S*)-2-[*N*-(diphenylmethylidene) amino]-4-(dicyclopentadienylchlorozirconyl)but-4-enoate (178)**



To a stirred solution of propargylglycine**171** (106 mg, 0.249 mmol) in dry dichloromethane (2 ml) at ambient temperature was added dicyclopentadienylchlorozirconium hydride (98 mg, 0.382 mmol). Following 10 min the mixture became lucid and the solvent was evaporated. The residue was analysed by ^{1}H nmr spectroscopy. The spectrum was consistent with the presence of starting **171** and a significant amount of decomposition product. No purification was persued.

Methyl (2*RS*, 4*E*)-2-[*N*-(diphenylmethylidene)amino]-hepta-4,6-dienoate (197)



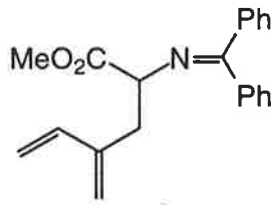
To a degassed solution of vinylstannane **172** (75 mg, 0.129 mmol) in DMF (5 ml) at 0 °C an excess of vinyl bromide (469 mg, 4.386 mmol) was added by conducting a stream of gaseous vinyl bromide through the solution and monitoring the weight of the reaction vessel. Bis(acetonitrile)palladium(II) dichloride (1.7 mg, 6.5 μmol) was added and the mixture stirred in the sealed reaction vessel at ambient temperature for 24 h. The solvent was evaporated and the residue chromatographed (1:12 ethyl acetate/hexane) to afford **197** (28 mg, 69 %) as a colourless clear oil. Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39 %. Found: C, 78.72; H, 6.83; N, 4.11 %.

^{1}H nmr δ 7.69-7.22 (m, 10H, ar), 6.39-6.01 (m, 2H, H5 and H6), 5.56 (m, 1H, H4), 5.09 (dd, J = 17 Hz, J = 2 Hz, 1H, $H7_{pro\text{-}Z}$), 4.98 (dd, J = 10 Hz, J = 2 Hz, 1H, $H7_{pro\text{-}E}$), 4.17 (dd, 1H, H2), 3.75 (s, 3H, CH_3), 2.70 (m, 2H, H3).

Ir (neat) υ_{max} 1740, 1634, 1448, 1280, 1217, 1180, 700 cm^{-1}.

Ms (ei) *m/z* 319 (M^+).

Methyl (*R,S*)-2-[*N*-(diphenylmethylidene)amino]-4-methylene-hexa-6-enoate (198)



Method 1: Vinylstannane **176** (98 mg, 0.168 mmol) was treated with vinyl bromide as described for the synthesis of **197**. The solvent was evaporated and the residue

chromatographed (1:12 ethyl acetate/hexane) to afford **198** (47 mg, 88 %) as a colourless clear oil. Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39 %. Found: C, 78.92; H, 6.71; N, 4.21 %.

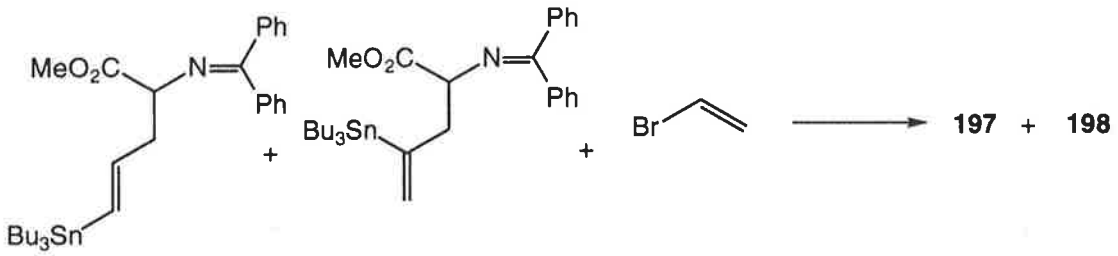
Method 2: Vinylstannane **176** (77 mg, 0.132 mmol) was treated as described under Method 1 except that a reaction temperature of 0 °C was maintained. After 40 min none of the starting stannane **176** was detected by tlc analysis of the reaction mixture (1:5 ethyl acetate/hexane, iodine staining). The crude product was chromatographed to afford diene **198** (38 mg, 91 %).

^{1}H nmr δ 7.71-7.19 (m, 10H, ar), 6.17 (dd, J = 18 Hz, J = 11 Hz, 1H, H5), 5.02 (s, 2H, H1'), 4.94 (d, J = 18 Hz, 1H, $H6_{pro\text{-}Z}$), 4.83 (d, J = 11 Hz, 1H, $H6_{pro\text{-}E}$), 4.29 (dd, J = 6 Hz, J = 7 Hz, 1H, H2), 3.73 (s, 3H, CH_3), 2.99 (dd, J = 13 Hz, J = 6 Hz, 1H, H3), 2.72 (dd, J = 13 Hz, J = 7 Hz, 1H, H3).

Ir (neat) υ_{max} 1738, 1627, 1450, 1280, 1206, 1190, 695 cm^{-1}.

Ms (ei) *m/z* 319 (M^+).

Competition Experiments with Vinylstannanes **172** and **176**

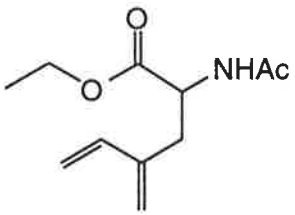


172 **176**

Method 1 (Scheme 66): A 1:1 mixture of vinylstannanes **172** and **176** (148 mg, 0.254 mmol) was treated as described under the synthesis of **198** (Method 2). The ^{1}H nmr spectrum of the crude product displayed resonances at δ = 5.98 ppm (**172**), δ = 5.09 ppm (**197**) and δ = 5.02 ppm (**198**) in a ratio of 7.6:1.0:9.0. The crude product was purified by mplc (1:4 ethyl acetate/hexane) to afford vinylstannane **172** (44 mg, 30 %) and a mixture of dienes **197** and **198** (41 mg, 51 %).

Method 2 (Scheme 68): A yellow mixture was prepared at ambient temperature by stirring tris(dibenzylideneacetone)dipalladium(0) (11 mg, 12 μmol) and triphenylarsine (59 mg, 0.192 mmol) in THF (8 ml) at ambient temperature. A pure 1:1 mixture of vinylstannanes **172** and **176** (280 mg, 0.481 mmol) in THF (13 ml) was added from a syringe. An excess of vinyl bromide (783 mg, 7.320 mmol) was added by conducting a stream of gaseous vinyl bromide through the solution and monitoring the weight of the reaction vessel. The mixture was stirred in the sealed reaction vessel at ambient temperature for 48 h before the solvent was evaporated. The ^{1}H nmr spectrum of the crude product displayed resonances at $\delta = 5.16$ ppm (**176**), $\delta = 5.09$ ppm (**197**) and $\delta = 5.02$ ppm (**198**) in a ratio of 3.9:5.7:1.0. The crude product was purified by mplc (1:4 ethyl acetate/hexane) to afford vinylstannane **176** (87 mg, 31 %) and a mixture of dienes **197** and **198** (81 mg, 53 %).

Ethyl (*R,S*)-2-[*N*-(acetyl)amino]-4-methylene-hexa-6-enoate (199)

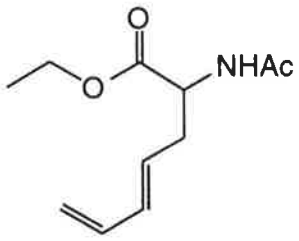


Vinylstannane **164** (78 mg, 0.170 mmol) was treated as described for the synthesis of **197**. After 12 h stannane **164** was still detected by tlc (1:5 ethyl acetate/hexane, iodine staining) and stirring was continued for another 36 h. The solvent was evaporated and the residue chromatographed (1:4 ethyl acetate/hexane) to afford **199** (20 mg, 57 %) as a colourless clear oil. Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63 %. Found: C, 62.16; H, 7.97; N, 6.31 %.

^{1}H nmr δ 6.25 (dd, $J = 17$ Hz, $J = 11$ Hz, 1H, H5), 5.52 (bd, 1H, NH), 5.06 (s, 2H, H1'), 5.01 (d, $J = 17$ Hz, 1H, $H6_{pro\text{-}Z}$), 4.83 (d, $J = 11$ Hz, 1H, $H6_{pro\text{-}E}$), 4.77 (m, 1H, H2), 4.19 (m, 2H, OCH_2), 2.75 (m, 2H, H3), 1.99 (s, 3H, $C(O)CH_3$), 1.28 (t, $J = 7$ Hz, 3H, OCH_2CH_3).

Ms (ei) *m/z* 211 (M^+).

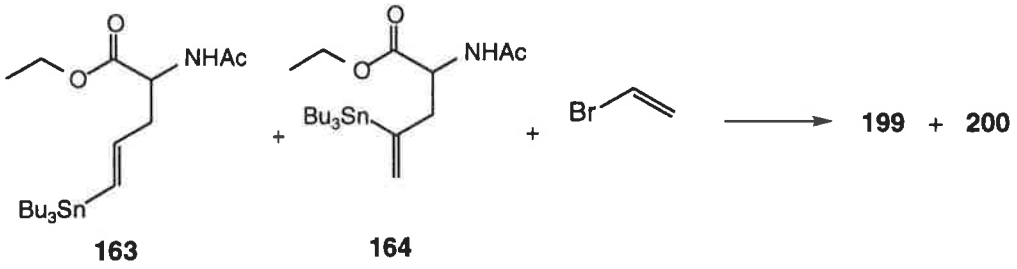
Ethyl (2*RS*,4*E*)-2-[*N*-(acetyl)amino]-hepta-4,6-dienoate (200)



Vinylstannane **163** (52 mg, 0.113 mmol) was treated as described fot the synthesis of **197**. After 48 h the solvent was evaporated and the residue chromatographed (1:4 ethyl acetate/hexane) to afford **200** as a colourless clear oil (9 mg, 38 %). Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63 %. Found: C, 62.58; H, 8.37; N, 6.35 %.

^{1}H nmr δ 6.35-6.05 (m, 2H, CH_2=C**H**-C**H**=C), 5.52 (m, 1H, CH=C**H**CH_2), 5.31 (bd, 1H, NH), 5.15 (dd, J = 17 Hz, J = 2 Hz, 1H, $CH_{trans}\mathbf{H}_{cis}$=CH), 5.02 (dd, J = 10 Hz, J = 2 Hz, 1H, $\mathbf{CH}_{trans}H_{cis}$=CH), 4.72 (dd, 1H, CHN), 4.20 (m, 2H, OCH_2), 2.69 (m, 1H, $\mathbf{CH}_2$CHN), 2.01 (s, 3H, $COCH_3$), 1.27 (t, J = 7 Hz, 3H, OCH_2CH_3).
Ms (ei) *m/z* 211 (M^+).

Competition Experiments with Vinylstannanes **163** and **164** (Scheme 67)



163 **164**

A 1:1 mixture of vinylstannanes **163** and **164** (172 mg, 0.375 mmol) was treated as described for the synthesis of **198** (Method 2). The crude product was purified by mplc (2:3 ethyl acetate/hexane) to afford vinylstannane **164** (34 mg, 20 %) and a mixture of dienes **199** and **200** (28 mg, 36 %). A 1.7:1.0 ratio was determined for the resonances at δ = 5.15 ppm (**200**) and δ = 5.06 ppm (**199**) by ^{1}H nmr spectroscopic analysis of this mixture.

The Syntheses of various Transition Metal Complexes

"Aged" tetrakis(triphenylphosphine)palladium(0)

Tetrakis(triphenylphosphine)palladium(0) that had been stored in a sample vial for several month in a fridge which was occasionally opened exposing the contents to the atmosphere. The sample had a red to brown colour.

Polymer supported palladium(0)[122]

Polystyrene supported triphenylphosphine (1.00 g, contains approximately 3 mmol of P per 1.00 g of resin) and tetrakis(triphenylphosphine)palladium(0) (921 mg, 0.797 mmol) were refluxed in dry benzene (6 ml) for 3 d. The crude product was washed in a Soxhlet extractor with benzene for 24 h and dried for 2 h at a reduced pressure of 0.03 Torr. A brown solid was isolated that weighed 1.142 g. The amount of adsorbed palladium was not determined.

Bis(tri-*o*-tolylphosphino)palladium(II) chloride ($PdCl_2[P(o\text{-tolyl})_3]_2$)[120]

To a degassed mixture of palladium(II) chloride (572 mg, 3.223 mmol), lithium chloride (273 mg, 6.446 mmol) in methanol (5 ml) was added tri-*o*-tolylphosphine (2.057 g, 6.758 mmol). The mixture was refluxed for 2 h under an atmosphere of nitrogen, cooled to 0 °C, filtered and washed with cold methanol (2×1 ml) to give the title compound (2.25 g, 89 %) as a light orange coloured solid. An analytically pure sample was obtained by recrystallisation from $CHCl_3$, m.p. 255-260 °C (decomposition). Anal. Calcd. for $C_{42}H_{42}P_2PdCl_2$: C, 64.18; H, 5.53 %. Found: C, 63.38; H, 5.44 %.

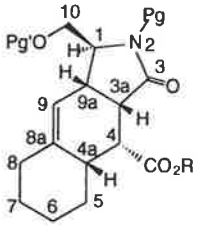
Bis(triphenylarsino)palladium(II) chloride ($PdCl_2(AsPh_3)_2$)

Palladium(II) chloride (119 mg, 0.671 mmol) was treated with triphenylarsine (431 mg, 1.407 mmol) *in lieu of* tri-*o*-tolylphosphine as described for the synthesis of $PdCl_2[P(o\text{-tolyl})_3]_2$. The title compound (445 mg, 84 %) was isolated as a yellow solid, m.p. >260 °C. The crude product had the following analytical data: Anal.

Calcd. for $C_{36}H_{30}As_2PdCl_2$: C, 54.75; H, 3.83; Cl, 8.98 %. Found: C, 54.09; H, 3.67, Cl, 9.95 %.

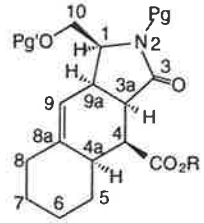
The following complexes were synthesised according to this method: $PdCl_2(PBu_3)_2$, $PdCl_2$dppe and $PdCl_2(PPh_3)_2$. The latter three complexes are also commercially available.

Selected ^{1}H NMR Spectrum of Isoindolones 112, 113c, e, f, 116 and 117.



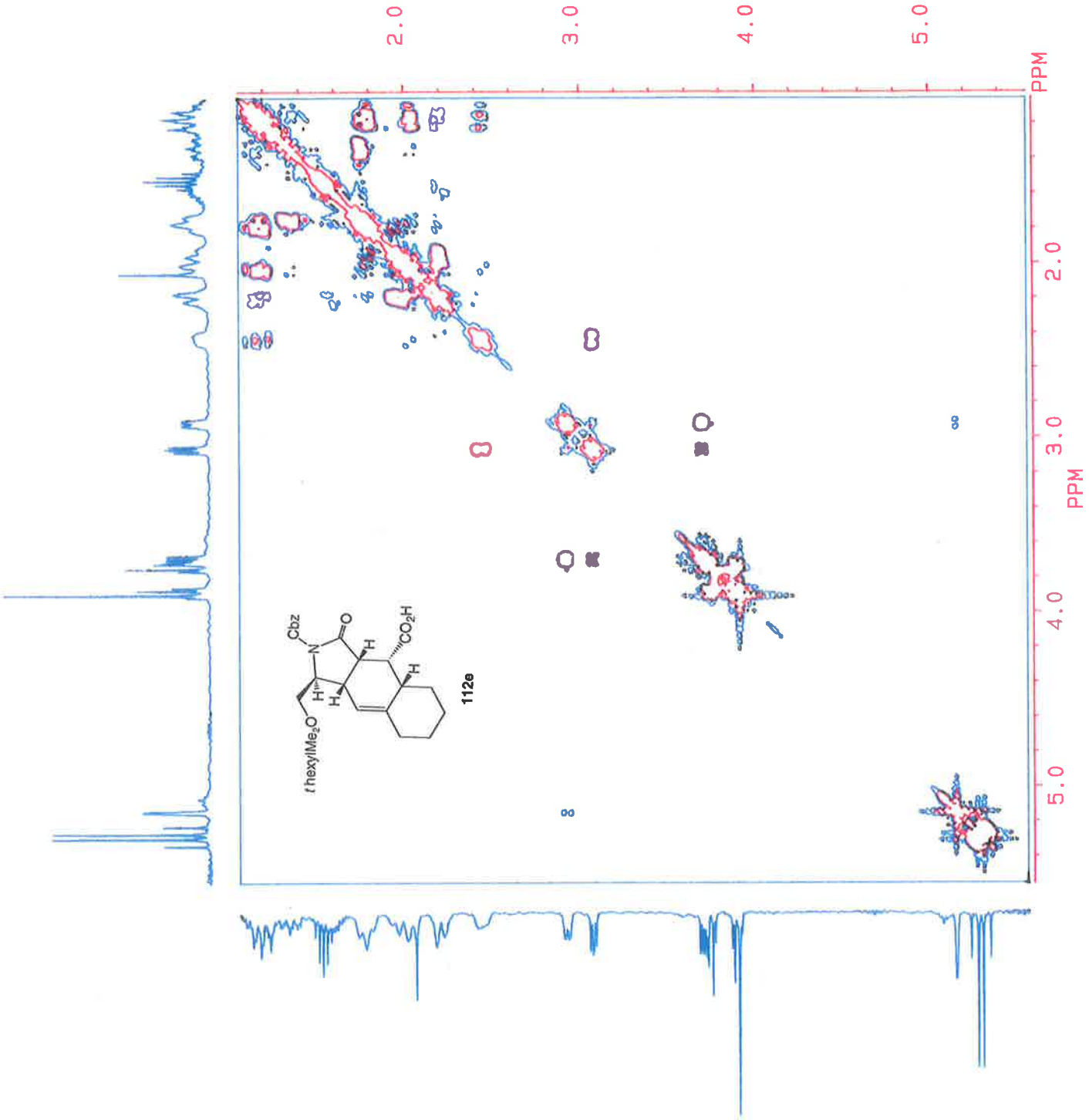
	112a	112b	112c	112d	112e	112f	112g	117	113c	113e	113f	116
Pg'	Ac	H	$C(O)CMe_3$	$C(O)CF_3$	$SiMe_2$*t*hexyl	$SiMe_2$*t*Bu	Ac	Ac	$C(O)CMe_3$	$SiMe_2$*t*hexyl	$SiMe_2$*t*Bu	Ac
Pg	Cbz	Cbz	Cbz	Cbz	Cbz	Cbz	Boc	Cbz	Cbz	Cbz	Cbz	Cbz
R	H	H	H	H	H	H	H	CH_3	H	H	H	CH_3
Position												
H9	5.19 bs	5.18 bs	5.19 bs	5.21 bs	5.19 bs	5.19 bs	5.21 bs	5.19 bs	5.12 bs	5.46 bs	5.51 bs	5.21 bs
H10	4.43 dd	4.04-	4.46 dd	4.47 dd	3.89 m		4.46 dd	4.39 dd	4.76 dd	4.29 dd	4.45 dd	4.86 dd
	4.21 dd	3.68	4.20 dd	4.52 dd			4.23 dd	4.21 dd	4.30 m	3.64 t	3.72 t	4.19 dd
H1	4.13 m	3.8 bm	4.16 m	4.26 t	3.73 dd		4.08 m	4.11 m	4.35 m	4.08 ddd	4.11 m	4.30 ddd
H3a	3.65 dd	3.8	3.60 dd	3.65 dd	3.67 dd	3.79 dd	3.53 dd	3.69 dd	3.30 dd	3.25 dd		3.46 dd
H4	3.01 dd	3.10 dd	3.12 dd	3.03 dd	3.10 dd	3.02 dd	3.15 dd	2.89 m	3.19 dd	3.14 dd		2.92 dd
H9a	2.91 m	2.98 m	2.90 m	2.99 m	2.96 m	2.97 m	2.89 m	2.88 m	3.08 bs	3.05		3.12 dd
H4a	2.44 m	2.46 m	2.49 m	2.45 m	2.46 m	2.45 m	2.50 m	2.44 m	2.53 m	2.47 m	2.52 m	2.46 m
$H8_{eq}$	2.23 bd	2.22 bd	2.23 bd	2.25 bd	2.20 bd	2.21 bd	2.27 bd	2.3	2.24 bd	2.19 bd	2.15 bd	2.23 bd
$H5_{eq}$	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.2				
$H8_{ax}$	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0				
$H5_{ax}$	1.3	1.2	1.2	1.2	1.2	1.2	1.3	1.0				
$J_{H1,H9a}$	0 Hz	0 Hz	0 Hz	0 Hz	0 Hz	0 Hz	0 Hz	0 Hz		6 Hz		7 Hz

Selected ^{13}C NMR Chemical Shift Data for Isoindolones.

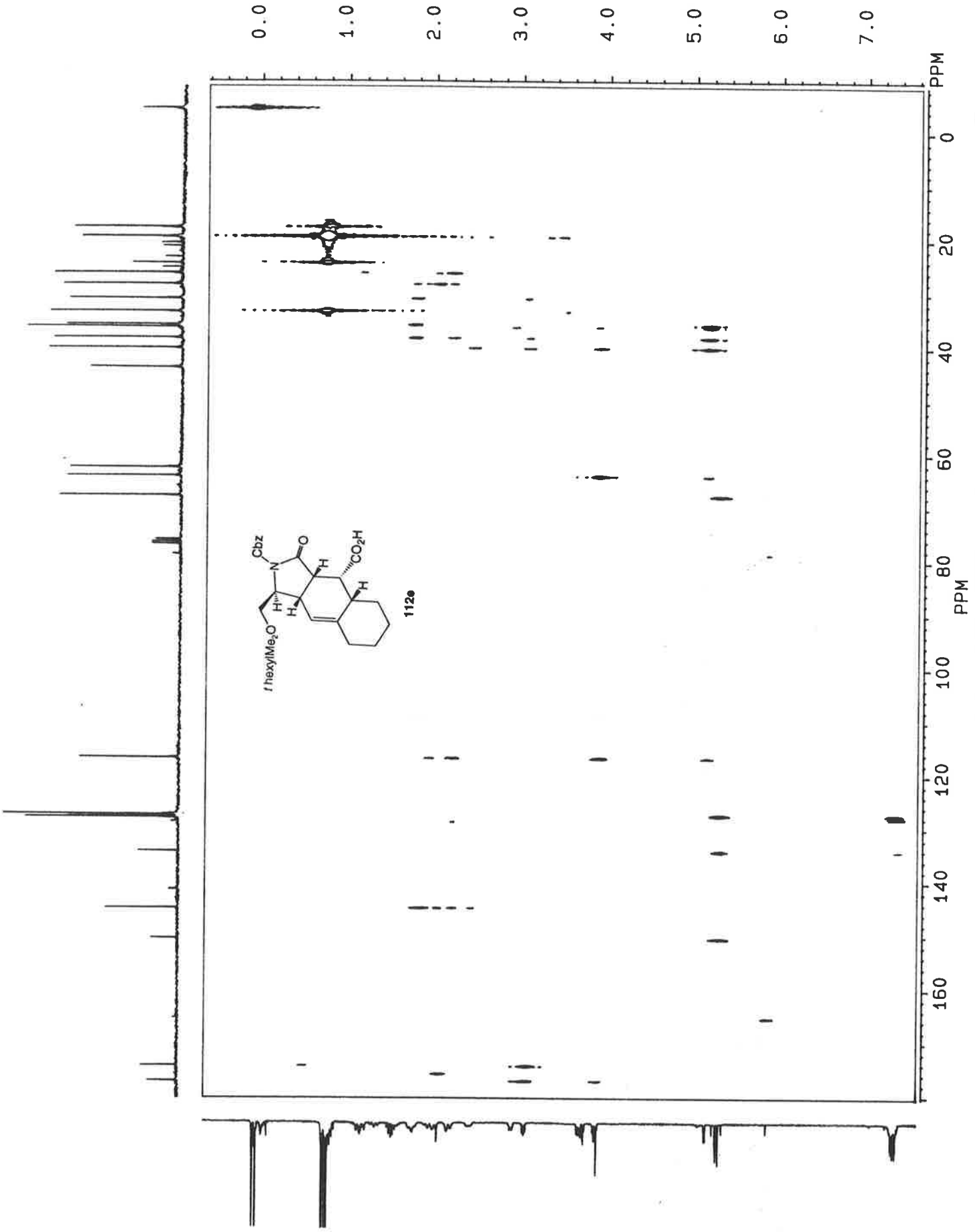


	112a	112b	112c	112d	112e	112f	112g	117	113c	113e	113f	116
Pg'	Ac	H	$C(O)CMe_3$	$C(O)CF_3$	$SiMe_2$*t*hexyl	$SiMe_2$*t*Bu	Ac	Ac	$C(O)CMe_3$	$SiMe_2$*t*hexyl	$SiMe_2$*t*Bu	Ac
Pg	Cbz	Cbz	Cbz	Cbz	Cbz	Cbz	Boc	Cbz	Cbz	Cbz	Cbz	Cbz
R	H	H	H	H	H	H	H	CH_3	H	H	H	CH_3
Position												
C8a	146.2	145.9	146.3	146.8	145.5	145.6	146.0	146.4	147.4	146.3	146.7	147.6
C9	116.6	117.4	116.5	116.0	117.4	117.2	116.7	116.5	111.8	113.0	112.7	112.2
C10	63.9	64.7	63.7	67.0	64.9	64.9	63.8	63.8	60.8	60.5	60.4	61.4
C1	61.6	62.8	61.2	60.8	63.2	64.0	62.1	60.8	57.8	59.5	60.7	57.2
C4	43.2	43.2	44.7	43.5	45.1	45.5	45.2	41.2	43.3	44.4	45.0	41.3
C3a	40.4	40.6	40.6	40.6	40.9	41.0	40.6	40.2	41.4	41.5	41.6	41.2
C4a	38.6	38.5	39.0	38.9	39.1	39.1	39.0	38.4	38.9	39.1	39.2	38.8
C8	36.6	36.4	36.8	36.5	37.0	36.9	36.5	36.7	37.2	37.1	37.0	37.4
C9a	36.4	36.2	36.5	35.9	36.5	36.4	36.3	36.0	35.0	34.6	34.7	34.3
C5	31.6	31.5	31.6	31.3	31.6	31.6	31.6	31.5	31.4	31.5	31.6	31.4
C6	29.0	28.9	28.9	29.0	28.8	28.8	28.9	29.3	28.9	29.0	28.8	29.4
C7	26.9	26.8	26.8	27.0	26.8	26.7	26.7	27.1	27.1	27.0	26.9	27.2

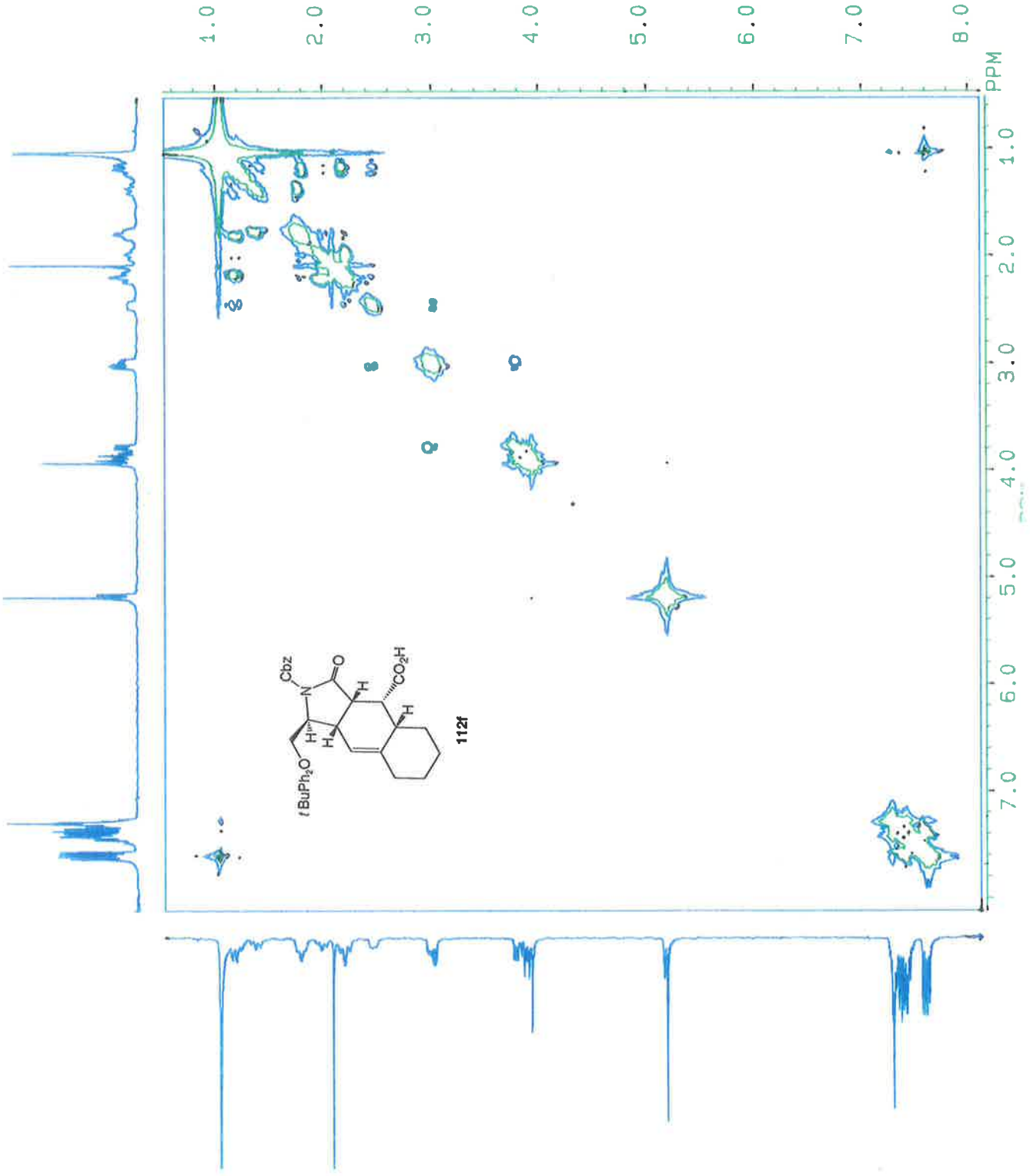
H,H COSY Spectrum of Isoindolone 112e.



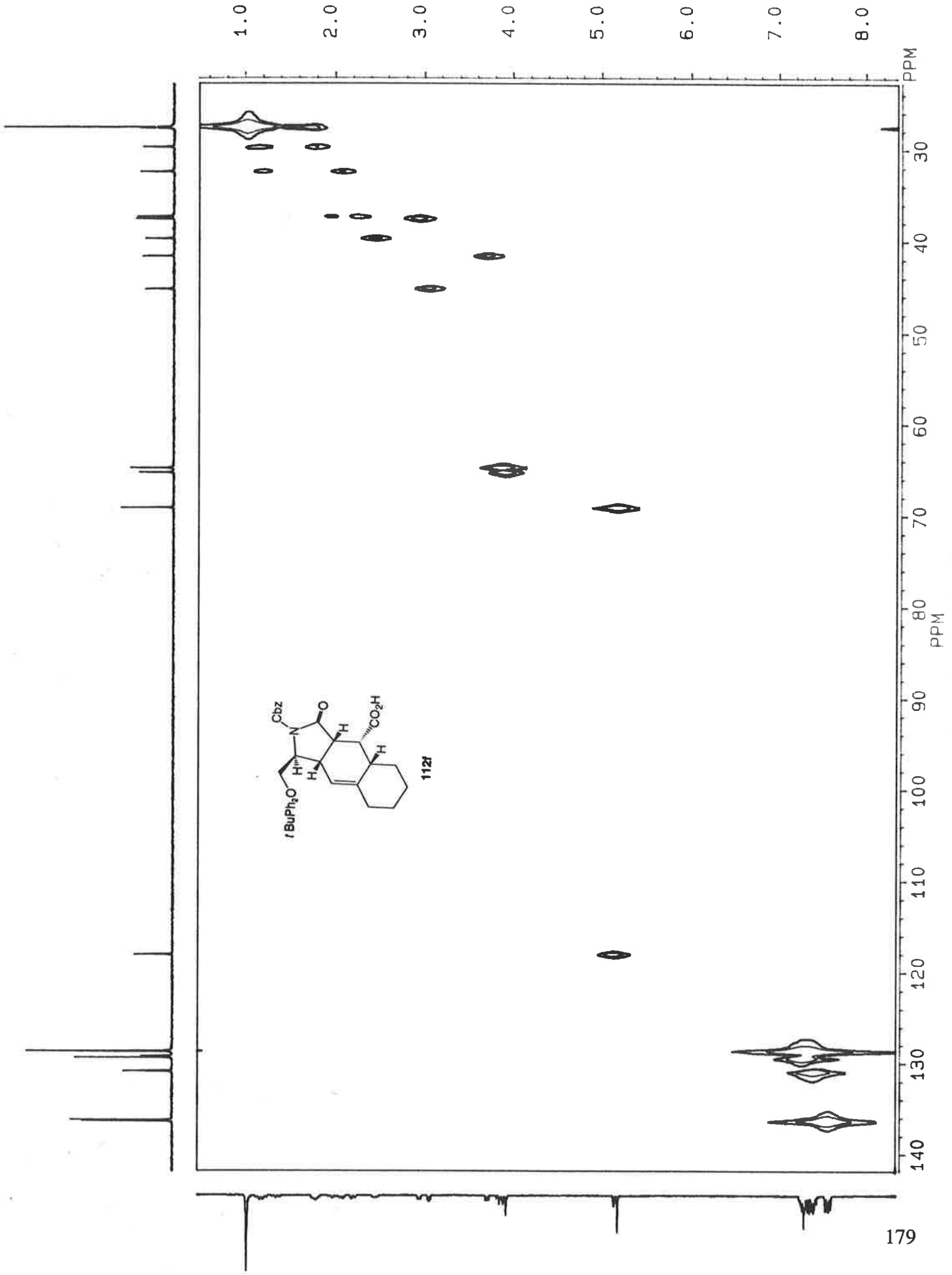
COLOC Spectrum of Isoindolone 112e.



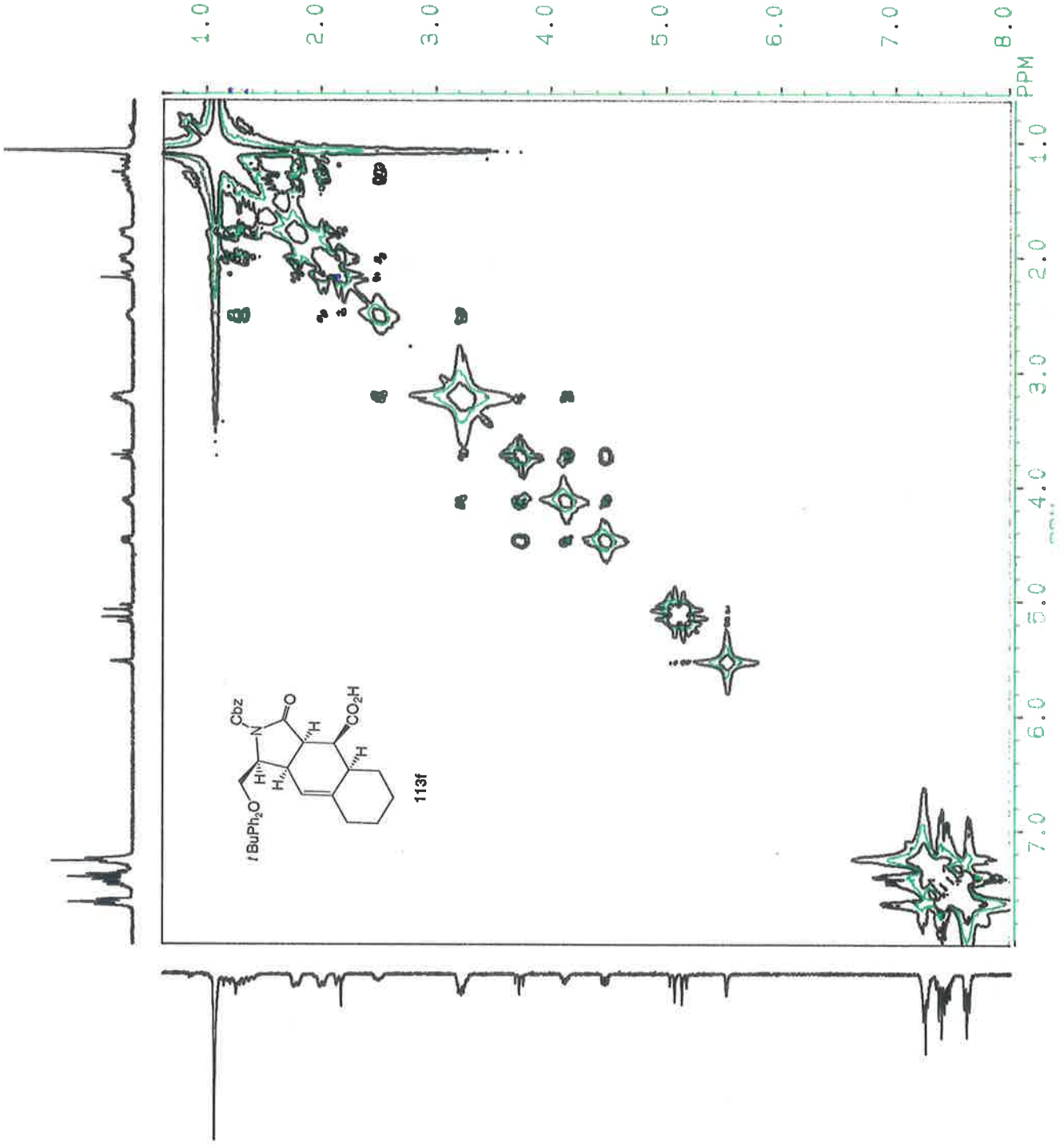
H,H COSY Spectrum of Isoindolone 112f.



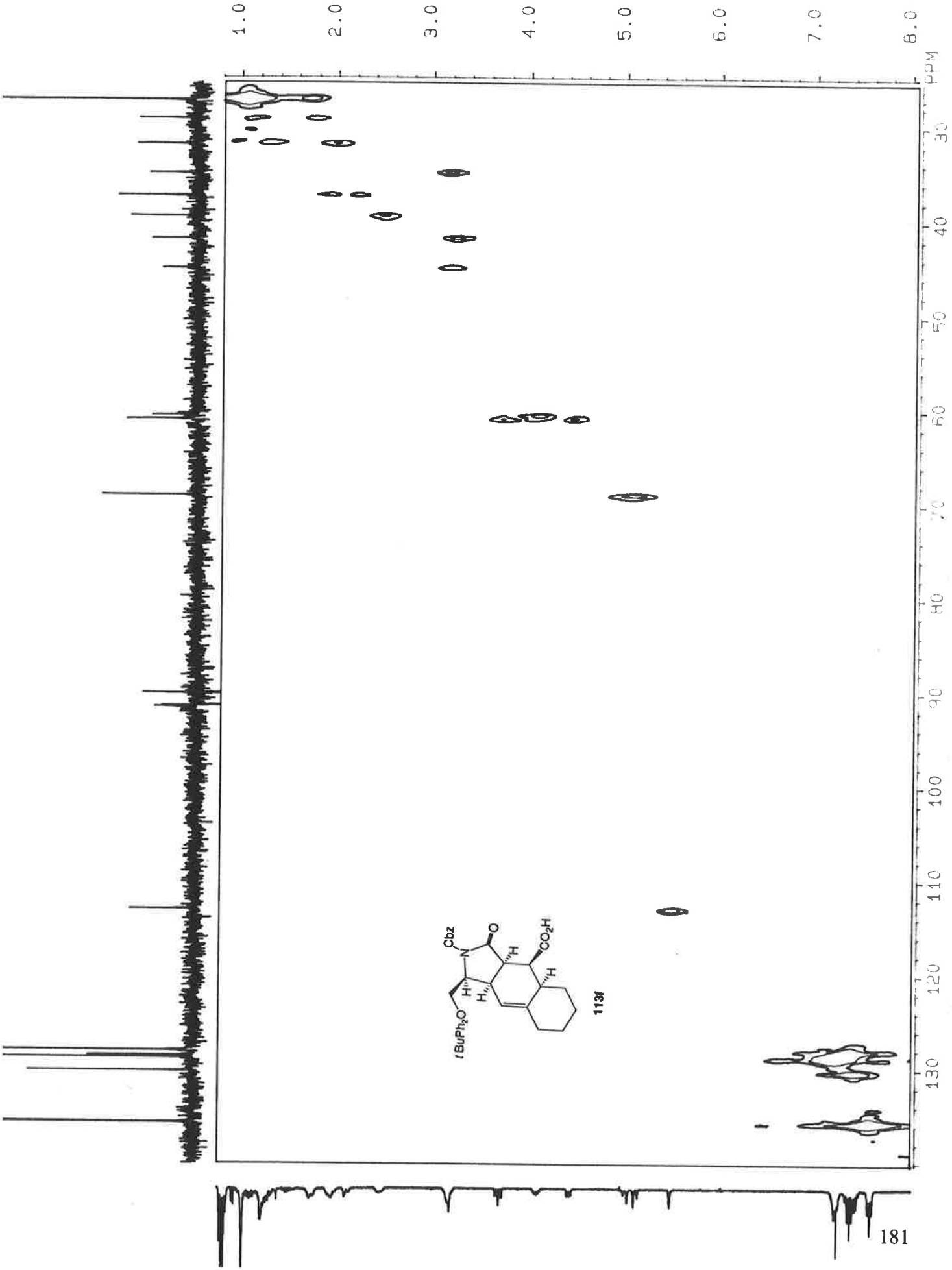
H,C COSY Spectrum of Isoindolone 112f.



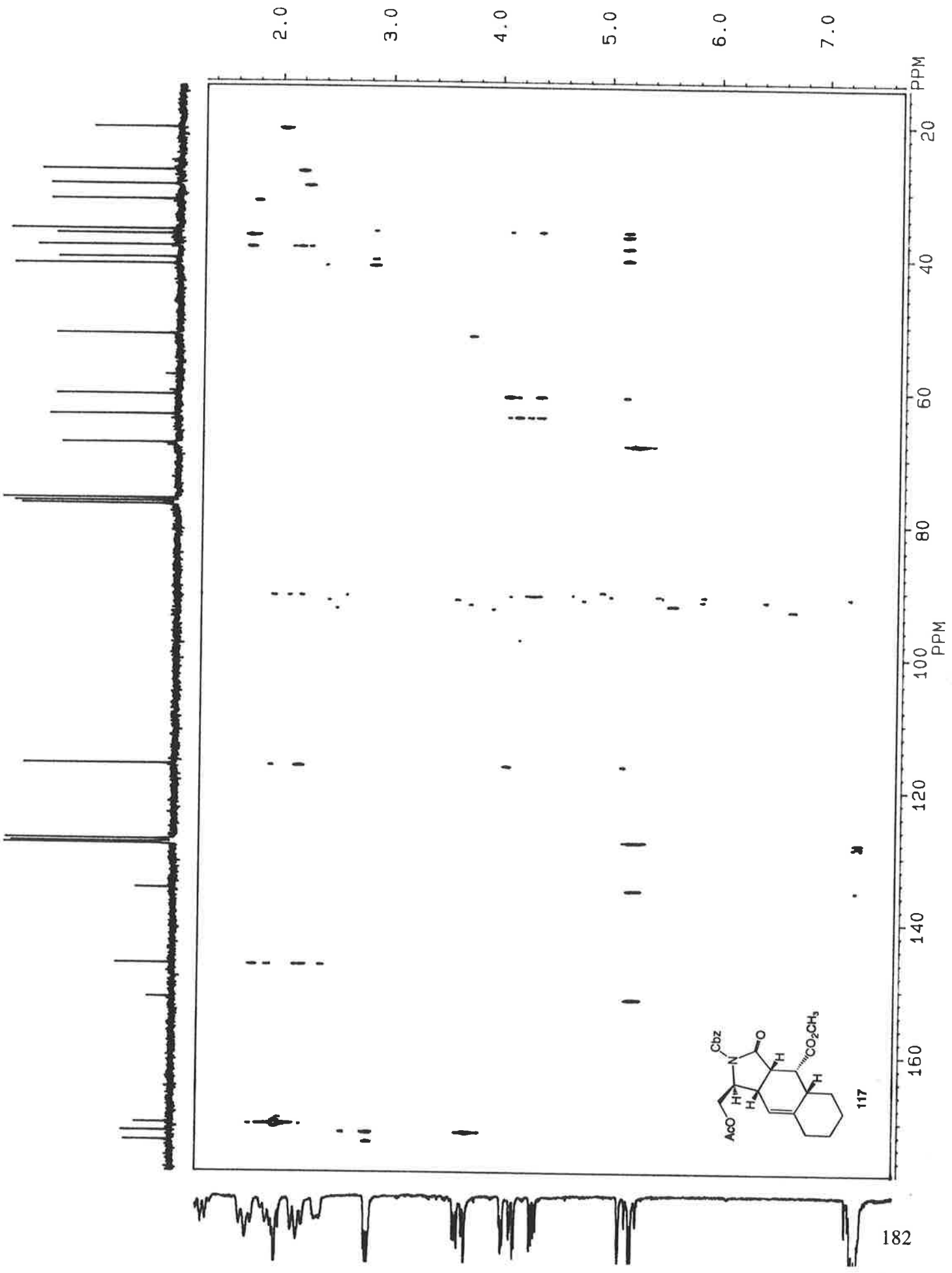
H,H COSY Spectrum of Isoindolone 113f.



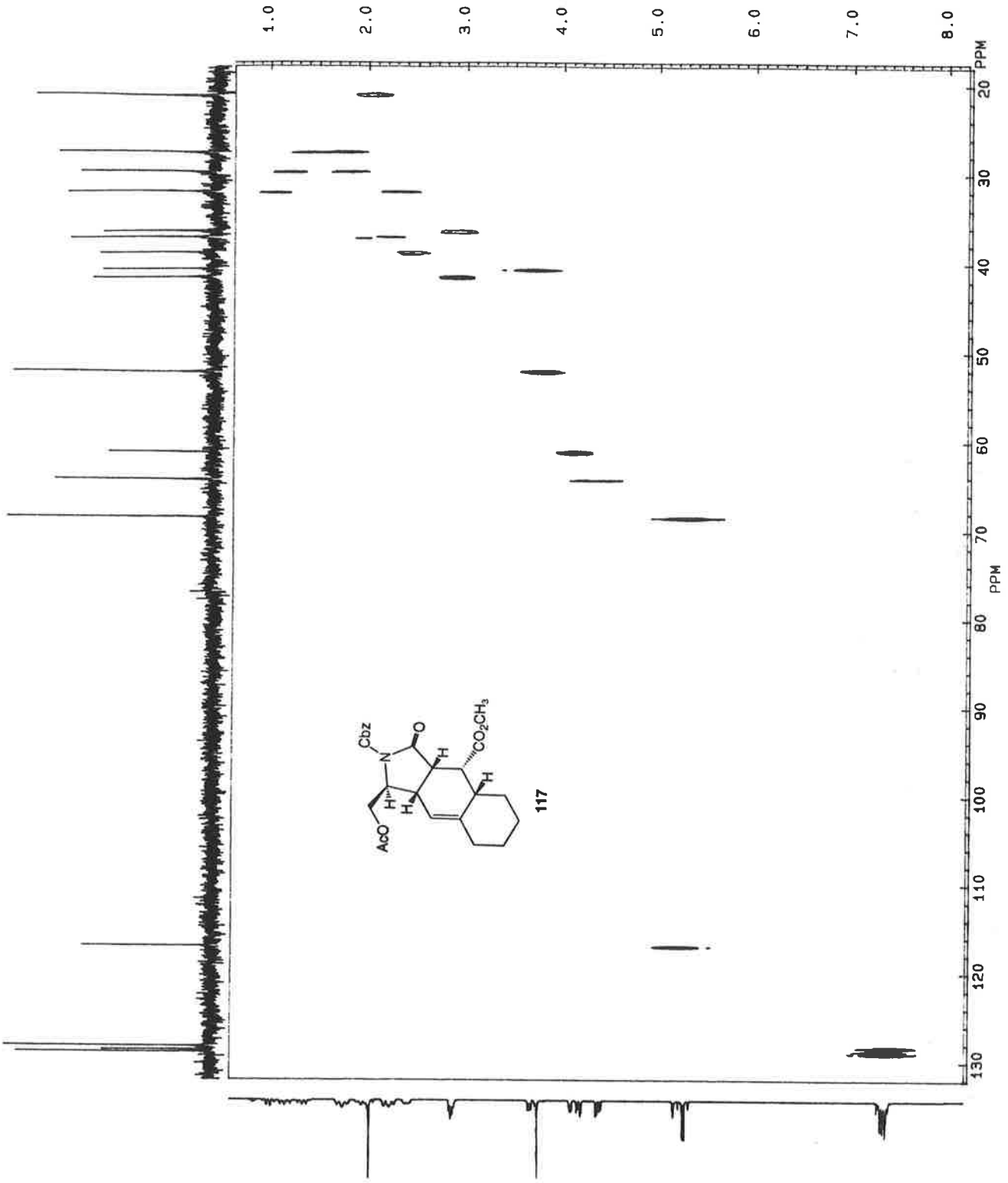
H,C COSY Spectrum of Isoindolone 113f.



COLOC Spectrum of Isoindolone 117.



H,C COSY Spectrum of Isoindolone 117.



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