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Macleod, Calum (2003) *Novel titanium alkylidenes and their application in the synthesis of indoles and quinolines.* PhD thesis.

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Novel Titanium Alkylidenes and their Application in the Synthesis of Indoles and Quinolines

A Thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

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February 2003

Dedicated to my family

(for everything)

Acknowledgements

Summary

Initially, we attempted to synthesise β-heterosubstituted vinylboronates by employing boronate-containing titanium alkylidene reagents, but our approach was unsuccessful.

We synthesised functionalised titanium alkylidenes from thioacetals **i** and we then employed them to convert resin-bound esters **ii** into immobilised enol ethers **iii**. Cleavage from the resin in mild acid with concomitant cyclisation yielded indoles **iv**. This chameleon catch strategy ensures the high purity of indole products. This is a novel synthesis of indoles, but also represents a traceless solid-phase indole synthesis as no trace of the former site of attachment to the solid-support remains in the indole products.
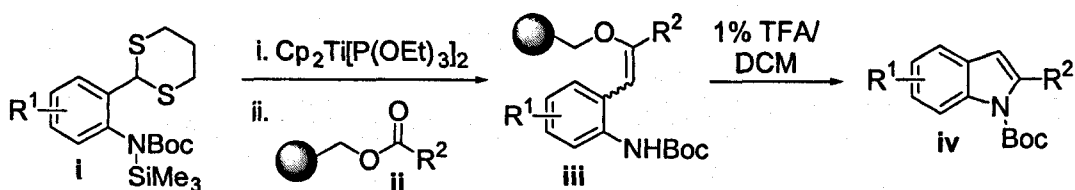
Similarly, we used titanium alkylidenes, prepared from thioacetals **v**, to convert resin-bound esters **ii** into the corresponding enol ethers, which were cleaved from the resin in mild acid to yield ketones **vi**. Boc deprotection and cyclisation to give indoles **vii**, was then achieved in acid.
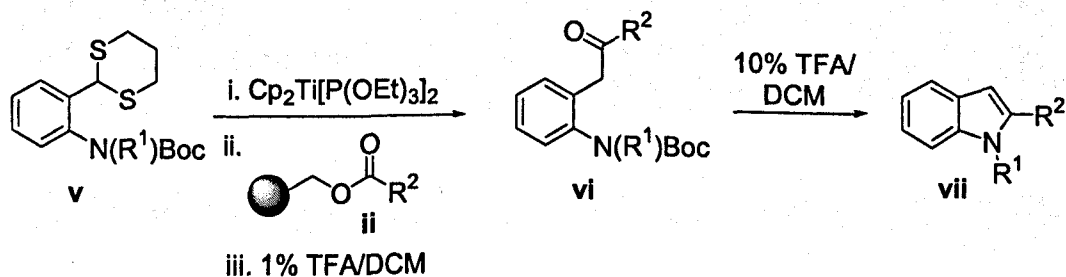
Titanium alkylidenes, prepared from thioacetals **viii**, converted resin-bound esters **ii** into the corresponding enol ethers, which were cleaved from the resin in acid to yield ketones **ix**. Cyclisation and oxidation to yield quinolines **x** was achieved employing manganese dioxide in dichloromethane (DCM).

CONTENTS

Abbreviations

Å	angstrom
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
atm	atmosphere (pressure)
bmim	1-butyl-3-methylimidazolium tetrafluoroborate
Bn	benzyl
Boc	*tert*-butyl carbamate
n-Bu	normal butyl
t-Bu/ *tert*-Bu	tertiary butyl
b.p.	boiling point
bs	broad singlet (NMR spectroscopy)
°C	degrees centigrade
cal	calories
cat.	catalyst
CI	chemical ionisation
cm	centimetre
cod	cis,cis-1,5-cyclooctadiene
conc.	concentrated
Cp	cyclopentadienyl anion
Cp*	pentamethylcyclopentadienyl anion
Cy	cyclohexyl
d	doublet (NMR spectroscopy)
dba	dibenzylideneacetone
DBU	1,8-diazabycyclo[2.2.2]octane
DCC	1,3-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DIC	1,3-diisopropylcarbodiimide
DIPEA	N,N-diisopropylethylenediamine
DMAP	4-N,N-dimethylaminopyridine
DMF	dimethylformamide
DMFDMA	dimethylformamide dimethyl acetal
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,2-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
EI	electron impact
eq.	equivalent(s)
FAB	fast atom bombardment
h	hour(s)
h	Planck constant
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high pressure liquid chromatography
HMP	hydroxymethylphenoxy
Hz	hertz
IDO	indoleamine 2,3-dioxygenase
IR	infrared
J	joules
K_B	Boltzmann constant

k_C	rate of rotation
LDA	lithium diisopropylamide
Ln	ligand
M	molarity
m	multiplet (NMR spectroscopy)
MAS	magic angle spinning
MHz	megahertz
MLT	melatonin
MT	methoxytryptamine
MOM	methoxymethyl
min(s)	minute(s)
m.p.	melting point
MS	molecular sieves
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidone
NSAID	nonsteroidal anti-inflammatory drug
PG	protecting group
Ph	phenyl
PhH	benzene
PhMe	toluene
PPTS	pyridinium *para*-toluene sulphonate
quant.	quantitative
q	quartet (NMR spectroscopy)
qn	quintet (NMR spectroscopy)
R	gas constant
RCM	ring closing metathesis
rt	room temperature
SEM	trimethylsilylethoxymethyl
SM	starting material
SPS	solid-phase synthesis
STABASE	base stable
t	triplet (NMR spectroscopy)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
T_C	temperature of coalescence
TFA	trifluoroacetic acid
TfO	triflate (trifluoromethanesulfonate)
TFP	trifurylphosphine
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	*N, N, N', N'*-tetramethylethylenediamine
TMG	tetramethylguanidine
TMS	trimethylsilyl
Ts	Tosyl (*para*-toluenesulphonyl)

Introduction

Chapter 1 - Background

Initially, we aimed to develop a novel, connective, synthesis of β-hetero-substituted alkenylboronic esters. They are useful intermediates for many transformations, including cross-coupling reactions (section 1.3) and to date can only be made by the hydroboration of 1-ethoxy-1-alkynes. Our strategy, involved generating titanium alkylidenes **1** from thioacetals **2** under Takeda conditions, which could then alkylidenate a range of esters or thioesters **3**, to give β-hetero-substituted alkenylboronates **4** (Scheme 1). Takeda alkylidenation, would allow *tetra*-substituted β-hetero-substituted alkenylboronic esters, with the hetero atom *cis* to the boronic ester, inaccessible by hydroboration/thioboration.
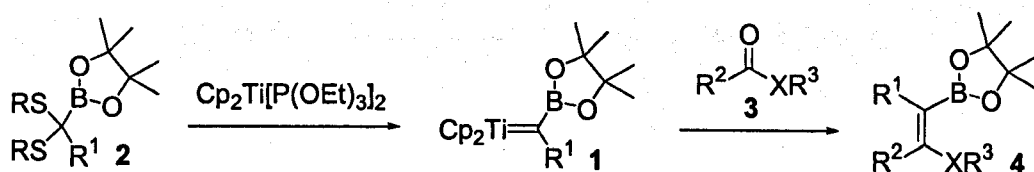
Scheme 1

Recent work within the group has seen the development of a novel synthesis of Benzo[*b*]furans, carried out on solid phase (section 8.1).[1] I aimed to investigate the scope of this methodology, and then extend it to the synthesis of nitrogen containing heterocycles. The proposed synthesis employs titanium benzylidenes **5** containing a suitably protected ortho-aniline, which would convert resin-bound **6** esters into enol ethers **7** (Scheme 2). Concomitant deprotection, cleavage from resin, and cyclisation under mild acid conditions, would then yield indoles **8**. Substrates, should be prepared from readily available precursors, so as to maximise the diversity of the synthesis. The choice of protecting group is critical, as it should be easily formed, stable to the reaction conditions, acid labile, and by-products formed upon its removal should be volatile, thus avoiding contamination of the heterocyclic products.
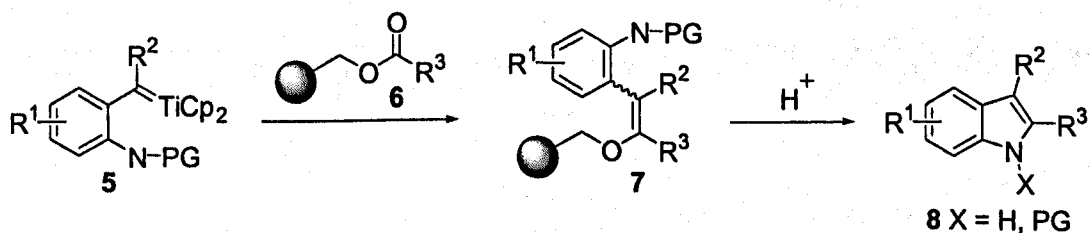
Scheme 2

Chapter 2 - Alkylidenation Reactions

2.1 The Wittig and related reactions

Wittig olefination

The Wittig reaction is one of the most effective and general methods for the conversion of carbonyl compounds into alkenes and it has become the standard by which all subsequent methodology is judged.[2] The reaction involves the addition of an aldehyde or ketone **9** to a phosphonium ylide **10**, producing the corresponding alkene **11** and phosphine oxide **12** as a by-product (Scheme 3).
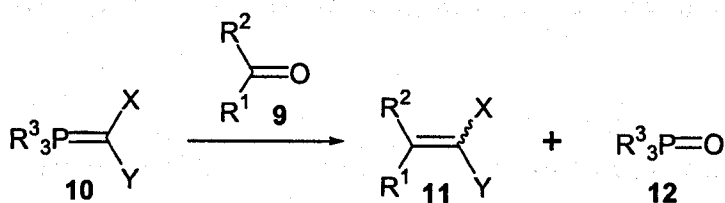
Scheme 3

The Wittig reaction is synthetically useful as it proceeds with defined positional selectivity, often with chemoselectivity, and the stereochemistry of the alkene can be controlled as generally a stabilised ylide will produce an *E* alkene and an unstabilised ylide will produce a *Z* alkene.[3] Mechanistic studies have shown that the reaction of aldehyde **13** with non-stabilised triphenylphophorous ylid **14**, proceeds *via* observable (by NMR) 1,2 oxaphosphetanes **15** and **16**, which then eliminate to give alkene **17**.[4] Two steps of the Wittig reaction are thought to be responsible for the stereochemical outcome.[4] Firstly, the initial formation and therefore, the ratio of the *cis*- and *trans*-oxaphosphetanes **15** and **16** obtained. Secondly, the ability of these intermediates to further equilibrate by reversal to reactants **13** and **14** (Scheme 4). Elimination of phosphine oxide occurs, stereospecifically, in a *syn* manner.[3]
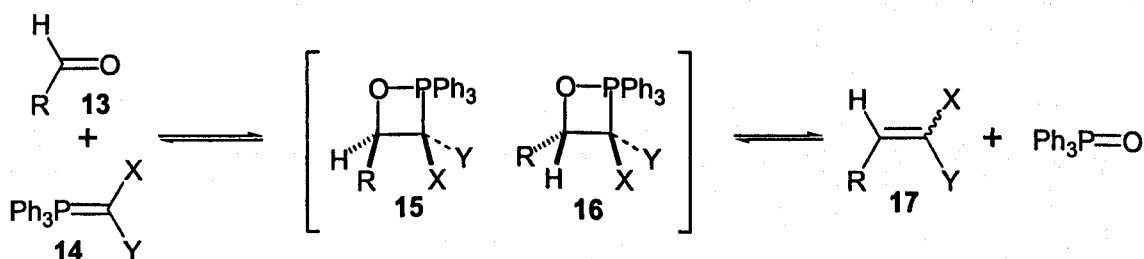
Scheme 4

Maryanoff has reported examples where the initial ratios of oxaphosphetanes **15** and **16** (observed by NMR spectroscopy), do not correspond to the final *E:Z* ratios formed in alkene products.[4] He proposes this is caused by decomposition of oxaphosphetanes to the reactants (*cis* oxaphosphetanes were more likely to fragment), followed by recombination, and has termed this phenomenon "stereochemical drift". Vedejs and coworkers have reported that salt-free (soluble lithium salts are known to enhance equilibration) Wittig reactions of unbranched aliphatic aldehydes, occur with less than 2% equilibration.[5] He suggests that in this case the reaction is under kinetic control, and has proposed a theory, which suggests that non-stabilised ylides add in an early transition state, giving a high ratio of *cis*- to *trans*-oxaphosphetanes. Stabilised ylides, as a result of a later transition state, give more of the *trans* isomer. Both cases being under Kinetic control and equilibration occurring only in special circumstances.[5]

Horner[6, 7] and Wadsworth and Emmons[8, 9] used the anions of phosphine oxide **18** and diethyl phosphonate **19** (Figure 1) respectively, to alkenate carbonyls [the Horner-Wadsworth-Emmons (HWE) reaction]. These reagents are more nucleophilic than the corresponding phosphonium ylides. Therefore, they are more reactive towards carbonyls and the HWE reaction has proven to be effective with hindered ketones that are unreactive in the classical Wittig reaction.[3] Also, the reaction by-products are water soluble, and by altering the bulk on the phosphonate moiety either the *E*- or the *Z*-alkene can be prepared.
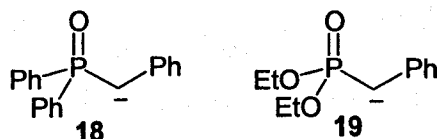
Figure 1

Peterson olefination

Alternatives to the Wittig reaction include the Peterson olefination[10] which utilises an α-silyl-substituted alkyl anion **20**. These reagents convert carbonyl compounds to β-silylcarbinols **21**, which in turn can undergo acid catalysed elimination or can be treated with base, resulting in intramolecular alkoxide attack on silicon and then elimination of the silanolate, to give the alkene **22** (Scheme 5). Peterson alkenation has the advantage that the by-product (hexamethyldisiloxane) is volatile and thus easier to remove than the phosphine oxides produced in the Wittig reaction. The reagent is more basic and less sterically hindered than the phosphorous ylide and so more reactive. However, when alkenation is not simply methylenation, the anion can be more difficult to prepare (limited to alkyllithium addition to vinyl silanes or transmetalation of silanes with α-halogens). Also, selectivity in the stereochemistry of elimination, requires separation of the β-silylcarbinols **21**, to ensure control of alkene geometry.[3]
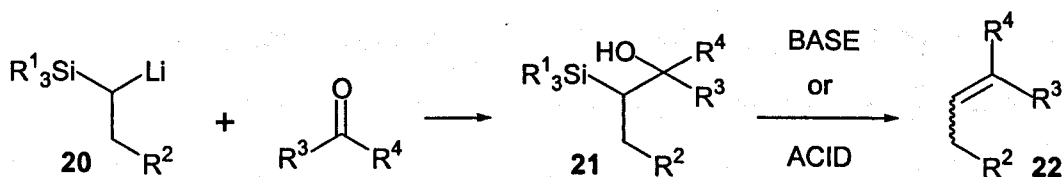
Scheme 5

Julia Olefination

Marc Julia introduced the use of sulfur-stabilised carbanions in alkenations[11, 12] In this reaction a metalated sulfone derivative **23** is added to a carbonyl compound **24**, followed by functionalisation [quench with an electrophile (E)] and reductive elimination (usually with sodium amalgam) to give the alkene **25** (Scheme 6). As well as giving excellent yields of the alkene, the reaction gives high *E*-selectivity for di-substituted alkenes as demonstrated by Kocienski and Lythgoe.[3] It is hypothesised that this aspect of the reaction is due to anion **26** adopting the lower energy *trans* conformation before loss of the leaving group (OR).[3] More recently a one-pot procedure was introduced by Sylvestre Julia.[13]
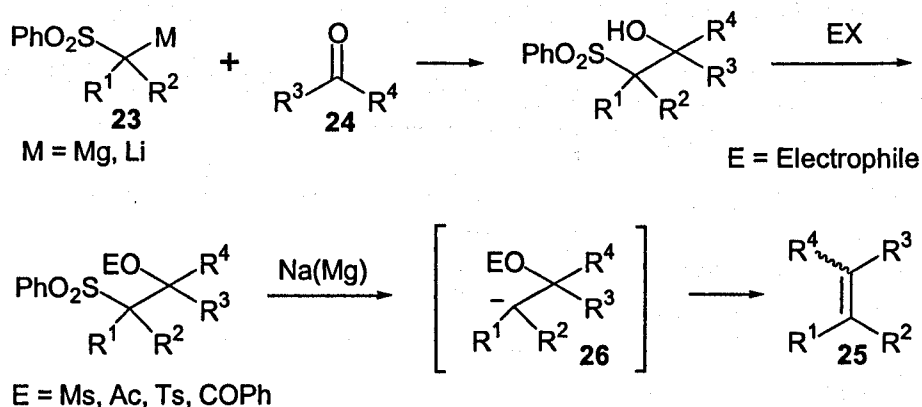
Scheme 6

A disadvantage of the Julia, Wittig and related reactions is that the basic reagents employed can deprotonate alpha to enolisable carbonyl groups, leading to side products.[3] Other problems with the Wittig reaction include the lack of reactivity with respect to sterically hindered carbonyls, and their inability to convert carboxylic acid derivatives into alkenes. These problems have been addressed through the use of transition metal alkylidene chemistry and in particular titanium-based reagents.[14] This area has been recently reviewed.[15]

2.2 Titanium alkylidenes (Schrock carbenes) and 1,1-bimetallics

Tebbe reagent

The Tebbe reagent **27** is commercially available as a 0.50 mol dm^{-3} solution in toluene, and is prepared from titanocene dichloride and 2 eq. of trimethylaluminium in toluene (Scheme 7).[16, 17] When treated with a Lewis base such as pyridine or THF, this titanium-aluminium metallacycle **27** forms a highly reactive titanocene alkylidene **28**. This methylenates a range of carbonyl compounds **29**, including carboxylic and carbonic acid derivatives,[18] to give alkenes **30**. Titanocene methylidene **28** is a typical Schrock carbene being an electron-deficient (16e) complex of an early transition metal in high formal oxidation state [Ti(IV)].[19] Schrock carbenes are nucleophilic at carbon and electrophilic at titanium, with their reactivity, and hence nucleophilicity towards carbonyl groups, being dominated by their high energy HOMOs.[19]
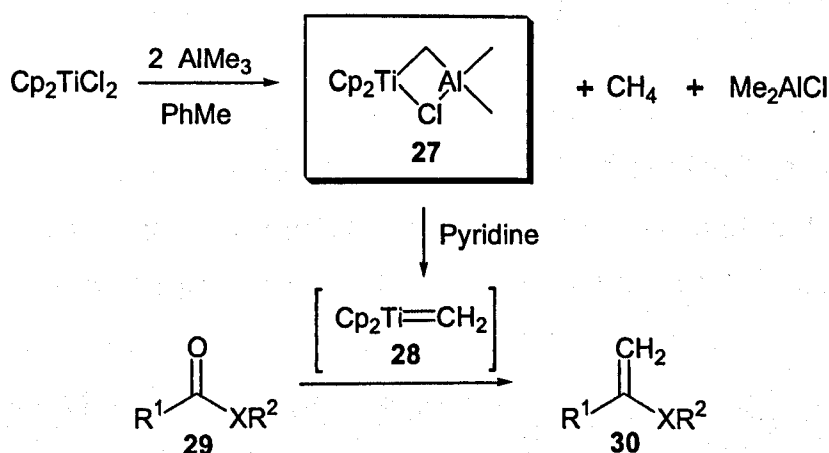
Scheme 7

Tebbe methylenation of aldehydes and ketones in the presence of esters or amides is straightforward and the selective methylenation of aldehyde **31** can be achieved in Lewis basic THF (Scheme 8).[20]

Scheme 8
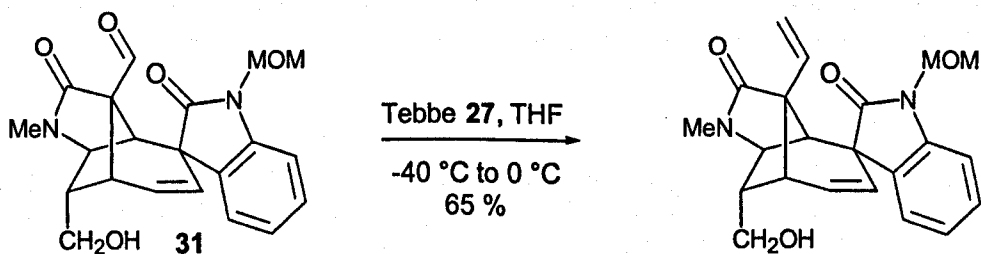
There are many recent examples of the methylenation of esters and lactones, by the Tebbe reagent, to give enol ethers.[15] Regioselective Tebbe methylenation of esters and lactones are possible in the presence of more sterically hindered esters.[21, 22] Methylenation of α,β-unsaturated esters giving higher yields with the Tebbe reagent than with the Petasis reagent (discussed below), have been reported.[23] Methylenation of thioesters to give vinyl sulfides is much rarer,[15] with the only recent example[24] being the conversion of thiolactone **32** into the corresponding alkenyl sulfide **33** in low yield (Scheme 9). Methylenation of tertiary amides[25] and carbonates[26] give enamines and ketene acetals, respectively.
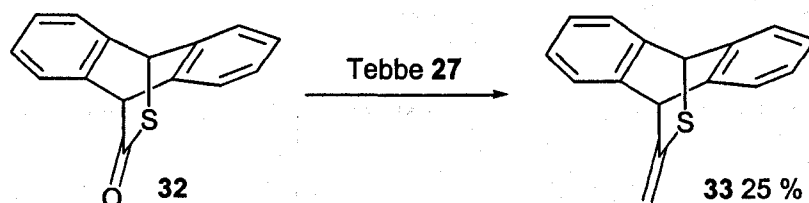
Scheme 9

Carbonyls with good leaving groups undergo reactions other than methylenation when treated with the Tebbe reagent. Titanium enolates **34** [presumably formed *via* oxatitanacyclobutanes **35**] are the products formed in the reaction of acid chlorides with Tebbe reagent **27**, in the presence of a Lewis base (Scheme 10).[27, 28] Anhydrides and imides react in a similar way to acid chlorides, when subjected to the Tebbe reagent.[29] This is in contrast to the Petasis reagent described below.
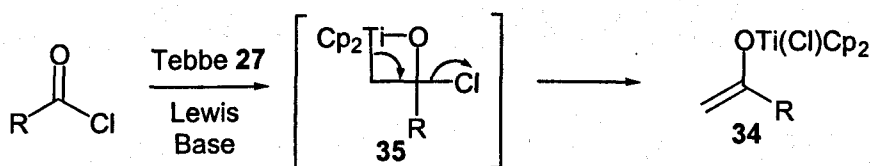
Scheme 10

The Tebbe reagent in Lewis basic solvents also catalyses alkene metathesis,[26] but metathesis is usually slower than methylenation of carbonyl groups. Alkenes including dienes[30] and terminal alkenes react with the Tebbe reagent slower than the Tebbe reagent reacts with carbonyl groups.[31] Therefore, lactone **36** gave enol ether **37** in moderate yield when treated with the Tebbe reagent (Scheme 11).[32] However, lactone **36** is both methylenated and methylated giving enol ether **38** when exposed to a vast excess of Tebbe reagent, presumably *via* titanacyclobutane **39** (Scheme 11).[32]
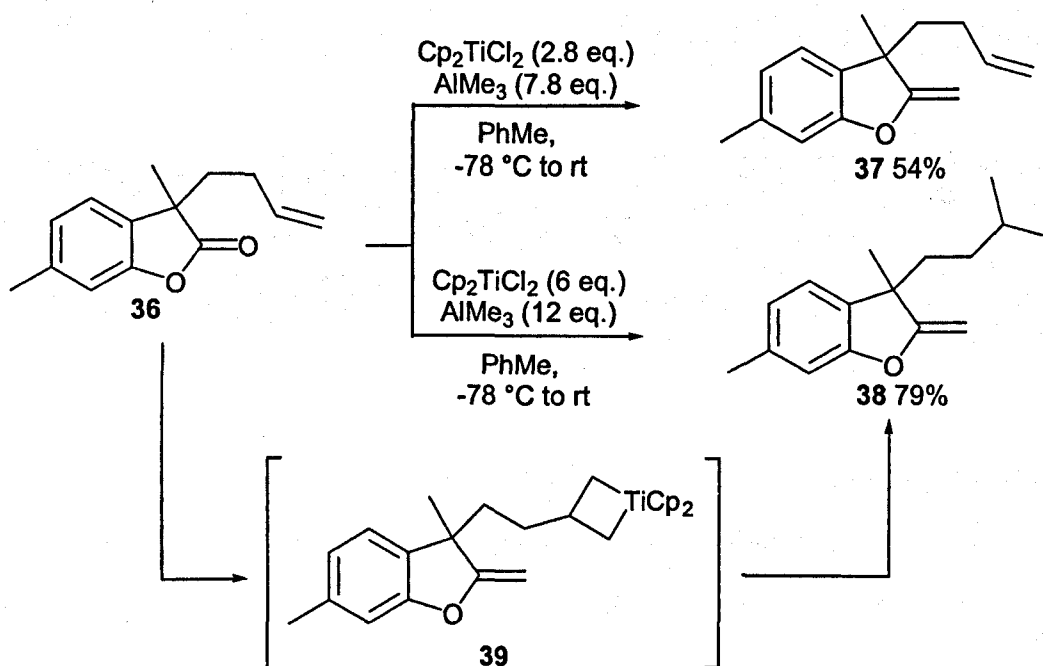
Scheme 11

The Tebbe reagent has also been employed in the methylenation of resin-bound esters to give the corresponding enol ethers (Section 4.2.5).

Tebbe methylenation has been accomplished in the presence of a wide range of functional groups, with alkyl and aryl halides, ethers, silyl ethers, acetals, selenoglycosides and thioglycosides, unprotected indoles, carbamates including NHBoc, and also sulfonamides, reportedly surviving the reaction conditions.[15]

The main advantage of the Tebbe reagent over other titanium reagents used in alkenations is that the reactive titanium methylidene **28**, is generated, and can be reacted, at low temperature. Its disadvantages include its sensitivity to both moisture and air, and its Lewis acidic character. More importantly, it is limited to methylenation and employing triethylaluminium does not give ethylidenation.[33] Pine *et al.* have published the definitive procedure for the preparation of the Tebbe reagent.[34]

Grubbs reagents

Grubbs later reported that Titanacycles **40** and **41** can be prepared by the reaction of the Tebbe reagent **27** with the corresponding terminal alkenes in the presence of a Lewis base.[16, 26] These complexes are more air stable than the Tebbe reagent **27** and when these complexes are heated titanocene methylidene **28** is formed (Scheme 12). Intramolecular versions of this reaction are known.[35, 36]
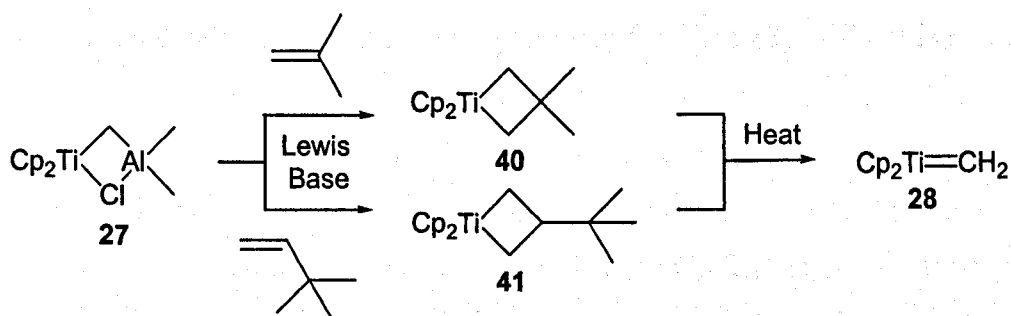
Scheme 12

Dimethyltitanocene **42** is non-pyrophoric, relatively stable to both air and water, and is prepared by adding methyllithium[37] or methylmagnesium chloride[38] to titanocene dichloride. Hughes *et. al.* have published the definitive procedure for the preparation of dimethyltitanocene.[38, 39] Petasis reported that this compound methylenates carbonyl compounds when heated to 60-75 °C in THF or toluene.[37, 40] The reaction is presumed to proceed *via* formation of titanocene methylidene **28**, which is formed by α-elimination, which in turn can then react with the carbonyl moiety (Scheme 13).[41] There is evidence for the proposal[41] that titanocene methylidene **28** is the active species.[15] Reactions are zero order in carbonyl and first order in dimethyltitanocene, with ethyl acetate and methyl benzoate methylidenated at similar rates, which confirms that only dimethyltitanocene is involved in the rate determining step. Also, reactions of $Cp_2Ti(CD_3)_2$ with esters produce substantial kinetic isotope effects of 9-10. Moreover, no scrambling of isotopic labels from ester substrates is observed.[15] Finally, dimethyltitanocene has been shown to catalyse alkene metathesis including the ring-opening metathesis polymerisation of norbornene, in which titanocene methylidene **28** is thought to be the active species.[42]
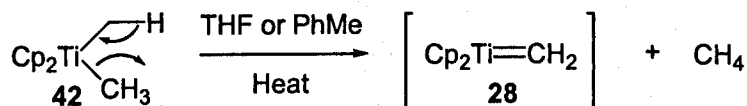
Scheme 13

As with the Tebbe reagent, aldehydes and ketones can be selectively methylenated in the presence of less electrophilic carbonyl groups including esters, amides and carbamates.[43, 44] Dimethyltitanocene will methylenate esters (including silyl esters)[40] and lactones,[40] and by careful choice of conditions, it is possible to methylenate the less sterically hindered of two esters[45, 46] using the Petasis reagent. Petasis methylenation of 2-alkynoate esters and α,β-unsaturated esters are also successful.[40] Highly strained β-lactones **43** undergo Petasis methylenation in 20-86% yield with excellent chemoselectivity (Scheme 14).[47, 48] However, Tebbe methylenation is unsuccessful for the same transformation, probably due to the greater Lewis acidity of the Tebbe reagent.
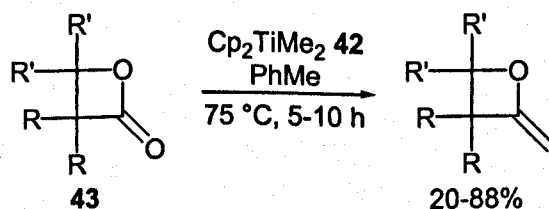
Scheme 14

Thioesters, selenoesters, and acylsilanes are effective substrates for Petasis methylenation, as are carbonates (Scheme 15).[40]
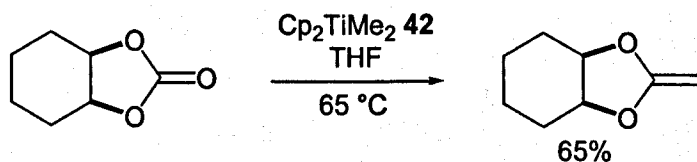
Scheme 15

Titanocene methylidene **28**, generated under Petasis conditions, gives methylenation of amides and lactams (but not carbamates) although more slowly than for the methylenation of other carbonyls.[40] The resulting, highly polar, enamines are often difficult to purify, and are reacted further without prior purification.[40] Herdeis and Heller avoided these problems in their route to pipecolic acid derivatives. Petasis methylenation of *N*-methoxycarbonyl-protected lactam **44** gave carbamate **45** *via* selective methylenation of the amide-like carbonyl group (Scheme 16).[49] The methoxycarbonyl group presumably not only protects but also activates the lactam towards methylenation.[15]
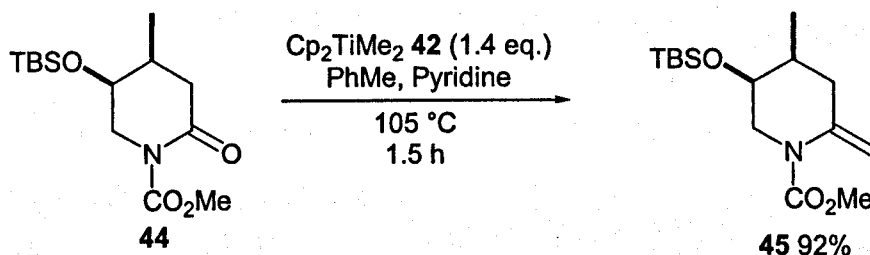
Scheme 16

In a later paper, Tehrani and De Kimpe reported the methylenation of β-lactams and α-lactams but the resulting strained enamines were difficult to purify.[50] However, Martínez and Howell used an excess of dimethyltitanocene to synthesise 2-methyleneacetidines in good isolated yields, and with excellent chemoselectivity, when the reactions were quenched upon consumption of β-lactams.[51] Methylenation of the strained β-lactam **46** gave 2-methyleneacetidine **47** in high yield, without affecting the acetate ester or the Boc group (Scheme 17).

Scheme 17

11
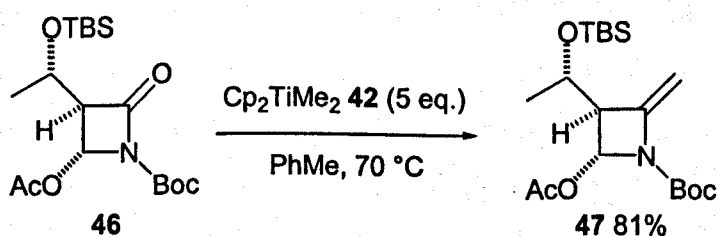
Selective mono- or bismethylenation of acid anhydrides,[40, 52] or cyclic thioanhydrides[52] by the Petasis reagent, is successful. The selective mono- and bis-methylenation[40] of imide **48** is also possible (Scheme 18), in contrast to the Lewis acidic Tebbe reagent above.

Cp₂TiMe₂ **42**

PhMe, 75 °C
75%

48

1.5 eq. of **42**   1 : 0
4.0 eq. of **42**   1 : 20
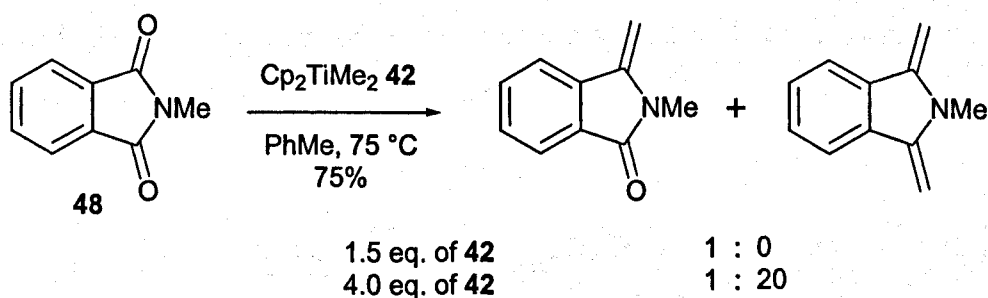
Scheme 18

Petasis' method of generating titanocene methylidene **28**, allows the preparation of a range of dialkyltitanocenes **49** which can alkylidenate carbonyls **50** in the same way to give a mixture of the *cis*- and *trans*- alkenes **51** (Scheme 19). Where R^2 is hydrogen (aldehydes) or R^2 is the smallest substituent (ketones), *trans*-alkenes are normally formed preferentially, albeit with poor selectivity. Any selectivity can be explained by minimisation of steric interactions in the reaction intermediates.[53] Titanium alkylidenes **52**, generated by α-elimination, are thought to be the active alkylidenating species. However, as β-elimination is generally faster than α-elimination, dialkyltitanocenes with hydrogen atoms (β to the titanium atom) will readily undergo β-elimination and are unlikely to form effective alkylidenating agents.[54]

Cp₂Ti

49

THF or PhMe
Heat

Cp₂Ti=

52

50

+

51
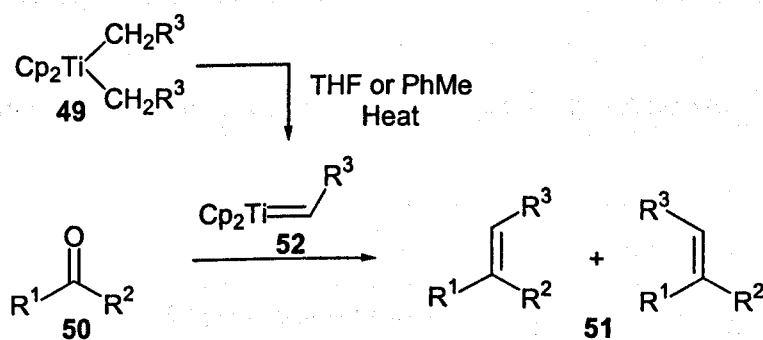
Scheme 19

Dibenzyltitanocene **53** is easily prepared from benzylmagnesium chloride and titanocene dichloride, and when heated with aldehydes and ketones, gives the corresponding di- and tri-substituted alkenes respectively, as mixtures of isomers.[53] Dibenzyltitanocene **53** also converts esters **54**, into *Z* and *E* enol ethers **55** and **56** (Scheme 20).[53] Unless R^1 is small (R^1 = H or Me), the products are formed with good *Z*-selectivity. The *Z*-selectivity is explained by considering the relative steric interactions in formation of

oxatitanacyclobutane intermediates **57** and **58** (Scheme 20).[55] Large R^1 will disfavour formation of intermediate **58**. Although large R^2 will disfavour formation of intermediate **57**, in this model, Z-enol ethers **55** are favoured because the oxygen atom acts as a spacer, favouring the formation intermediate **57**. However, some isomerization can be observed if acid-washed glassware is used, or if reactions are spiked with trace ammounts of acid, (presumably *via* protonation of the enol ether).
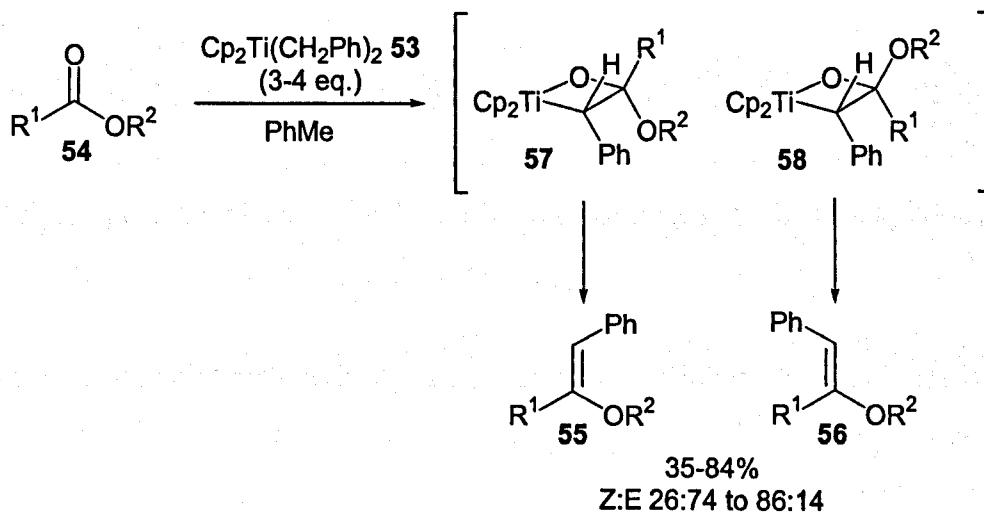
Scheme 20

Reaction with amides gives enamines, in modest yield (45-48%) and good *E*-selectivity (*E:Z* = 71:29 to >99:1) and the stereoselectivity can be explained using a similar argument to that presented for *Z*-selectivity in enol ether formation above.[40]

Bis(3-fluorobenzyl)titanocene and bis(3-chlorobenzyl)titanocene **59** also benzylidenate carbonyl compounds more readily and with greater selectivity than the parent complex **53**. Therefore, lactone **60** is converted into enol ether **61** in quantitative yield with total *Z*-selectivity (Scheme 21).[53]
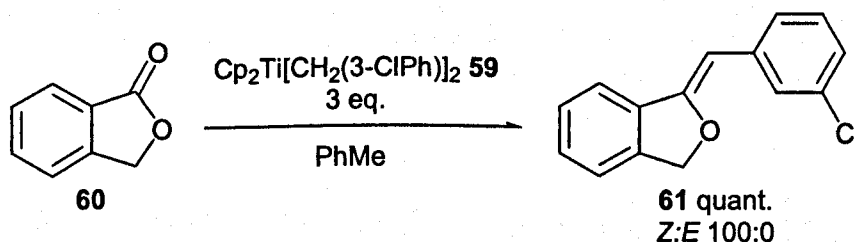
Scheme 21

Bis(trimethylsilylmethyl)titanocene [Cp$_2$Ti(CH$_2$TMS)$_2$] **62** and tris(trimethylsilylmethyl)-titanium complex [CpTi(CH$_2$TMS)$_3$] **63** can be prepared from titanocene dichloride using two or three equivalents of trimethylsilylmethyllithium, respectively.[56] An improved procedure for the synthesis of complex **63** involves consecutive addition of trimethylsilylmethylmagnesium bromide and trimethylsilylmethyllithium.[57] Both will alkylidenate esters, but complex **62** requires a higher temperature (110 °C in ethylene glycol diethyl ether) presumably due to its higher thermal stability, and also gives lower yields.[56] Also, Z-selectivities are slightly lower than observed in the corresponding benzylidenations discussed above. Again, acid chlorides do not give alkylidenation products but give α-trimethylsilylketones when treated with either complex **62** or **63**.[56] Esters, thioesters and amides derived from trifluoroacetate have been alkylidenated with complex **63**, though the thioester gave a very poor yield and no stereoselectivity.[58]

A better trimethylsilylmethylenating agent is titanacyclobutene **64**, formed in near quantitave yield by the thermolysis of complex **62** in the presence of bis(trimethylsilyl)ethyne (Scheme 22).[57] Esters are alkylidenated in high yield using 1.5 eq. of complex **64** at only 25-60 °C. Thioester **65** is converted into vinyl sulfide **66** in excellent yield, though the Z:E stereoselectivity was only 2.2:1.
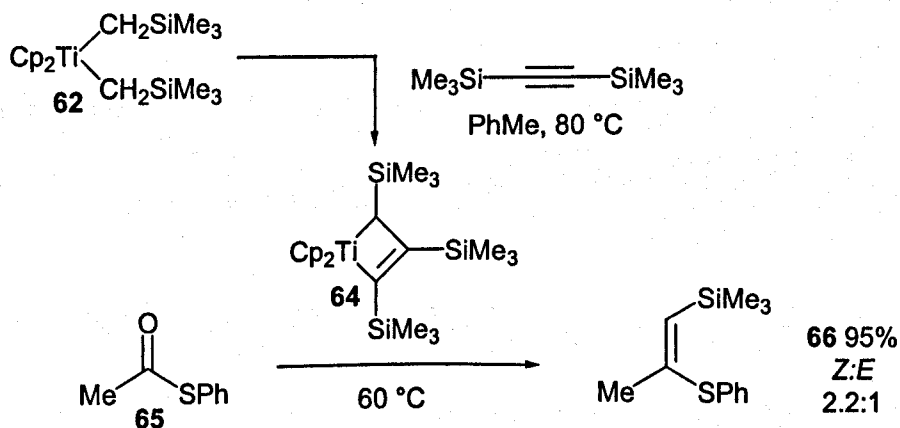
Scheme 22

Bis(cyclopropyl)titanocene **67** is easily prepared from titanocene dichloride and cyclopropyllithium, which is generated from cyclopropyl bromide and lithium metal.[59] Although thermally unstable at room temperature, bis(cyclopropyl)titanocene can be stored at -20 °C for several months. Esters, including formate esters and lactones [lactone **68** gives enol ether **69** in good yield (Scheme 23)], are cyclopropylidenated with 2.5 eq. of complex **67**.[59]
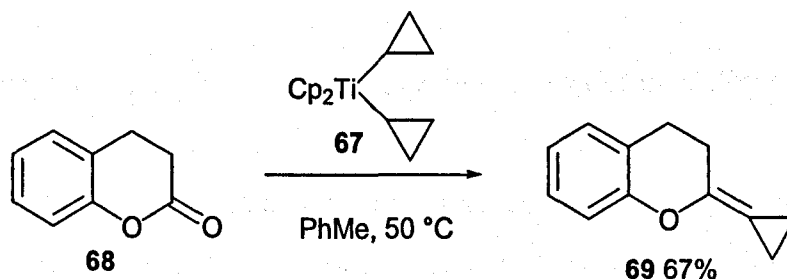
Scheme 23

Bis(alkenyl)titanocenes **70** can be synthesised from titanocene dichloride with two equivalents of an alkenyl magnesium bromide. Bis(vinylic)titanocenes **70** undergo thermal α-elimination to give the corresponding vinylidenes **71**, which react with aldehydes and ketones to form allenes. Bis(vinylic)titanocene **70** (R^1, R^2 = H) converted ketone **72** into allene **73** in good yield, without affecting the ester carbonyl moiety (Scheme 24). However, alkenylidenation was unsuccessful with esters and lactones, presumably due to facile product decomposition.[60]

Scheme 24

15
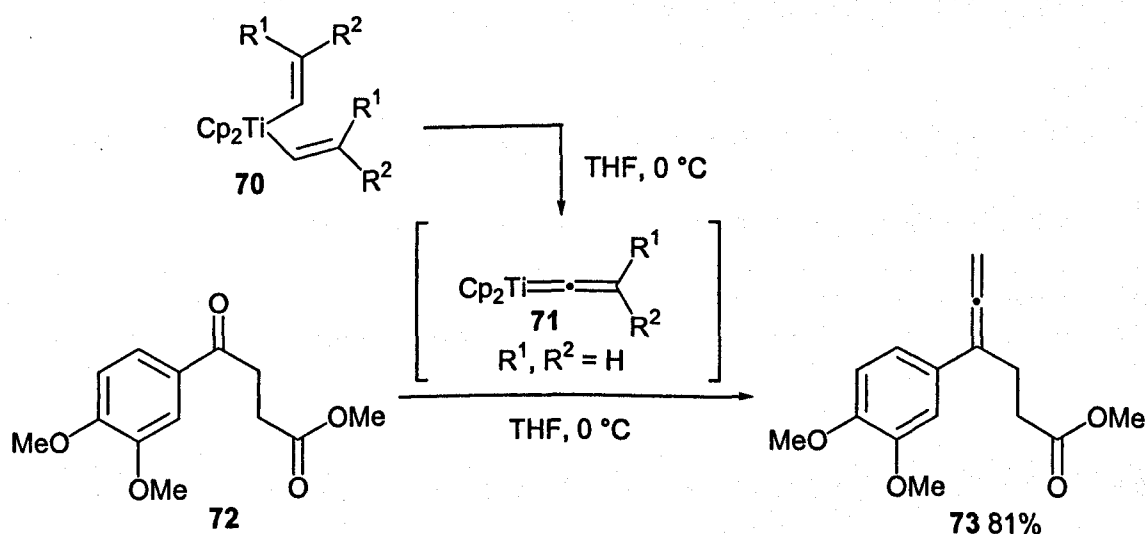
Petasis alkylidenation has been accomplished in the presence of alkenes, alkyl and aryl halides, ethers, silyl ethers, acetals, amines and carbamates. Hydroxyl groups are best protected, but Petasis methylenation has been carried out in the presence of free hydroxyls employing an excess of the reagent.[15]

Advantages of the Petasis alkylidenation, include the stability to both air and moisture of dialkyltitanocenes **42** and **53**, the absence of Lewis acids from the reaction, and the ease of purification following reaction (titanium impurities can often be precipitated from reaction mixtures). A range of dialkyltitanocenes can be prepared but only dimethyltitanocene **42** has proved popular.[15] The disadvantages of Petasis reagents include, the high temperature (65 °C) required for α-elimination, several equivalents of the reagent are often necessary for complete reaction, and reactive organometallics are required for their synthesis. Furthermore, alkylidenations with titanium alkylidenes containing alkyl groups with β-hydrogens (with respect to titanium) are not possible. Petasis has published a full review on his work with these titanocene reagents.[61]

Takeda reagents

Takeda *et al* have demonstrated that thioacetals can be reduced by low valent titanium(II) complex $Cp_2Ti[P(OEt)_3]_2$ **74** to give titanium reagents that will alkylidenate a wide variety of carbonyl derivatives. Takeda has reviewed his work on the desulfurisation of thioacetals and applications including alkylidenation reactions.[62]

Titanium complex **74** is generated by the reduction of titanocene dichloride with magnesium in the presence of 2 eq. of triethylphosphite and 4 Å Molecular sieves, in dry THF (Scheme 25).[63] Thioacetals **75** are added to the low valent titanium reagent **74** presumably generating titanium alkylidenes **76**, perhaps *via* geminal bimetallic species **77**. Both 1,3-dithianes and diphenyldithioacetals may be used,[63] but the latter are more reactive.[62] Alkylidenes **76** alkenate carbonyls **78** to give alkenes **79**. Methylenation is ineffective under Takeda conditions but allylic, benzylic or alkyl thioacetals are suitable substrates for generating alkylidenating reagents.
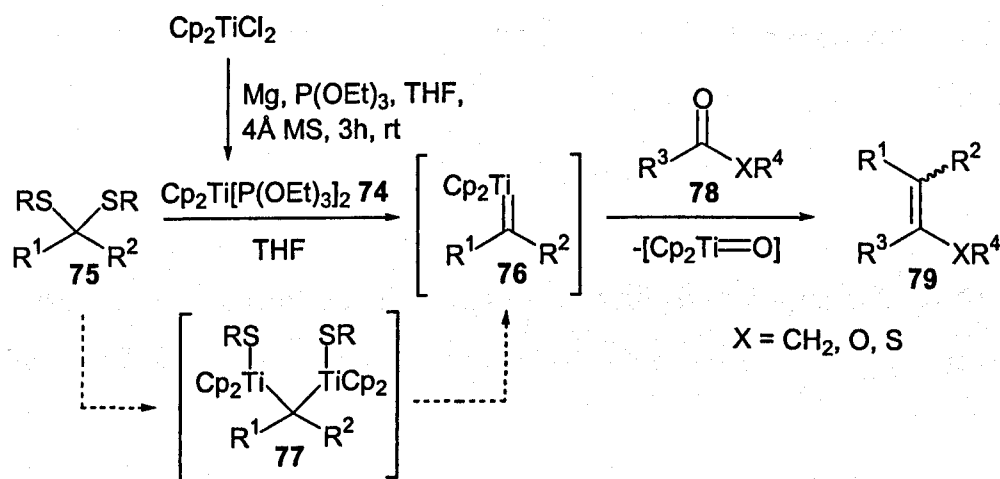
Scheme 25

The reaction proceeds smoothly with aldehydes and ketones, however, the *E*-selectivity obtained in products is poor, e.g. the *E:Z* ratio of alkenes **80** is only 56:44 (Scheme 26).[62]
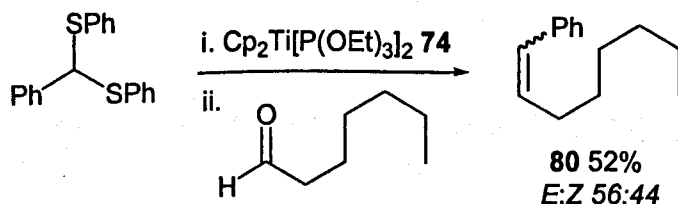
Scheme 26

Esters[63] and thioesters[64] are effectively alkylidenated. In the case of esters, alkylidenation proceeds with high Z-selectivity.[63] The Z-selectivity can be explained using the same arguments as presented for Petasis benzylidenation and indeed the selectivity is slightly higher in Takeda benzylidenations. The titanium alkylidene derived from dithiane **81**, converts methyl benzoate into dienes **82** (Scheme 27).[63] In the case of thioesters, alkylidenation proceeds with substrate-dependant variation in Z-selectivity. When thioacetal **83** is treated with low valent titanium complex **74** and then with thioester **84** in refluxing THF, vinyl sulfides **85** are produced with high Z-selectivity (Scheme 27).[64]
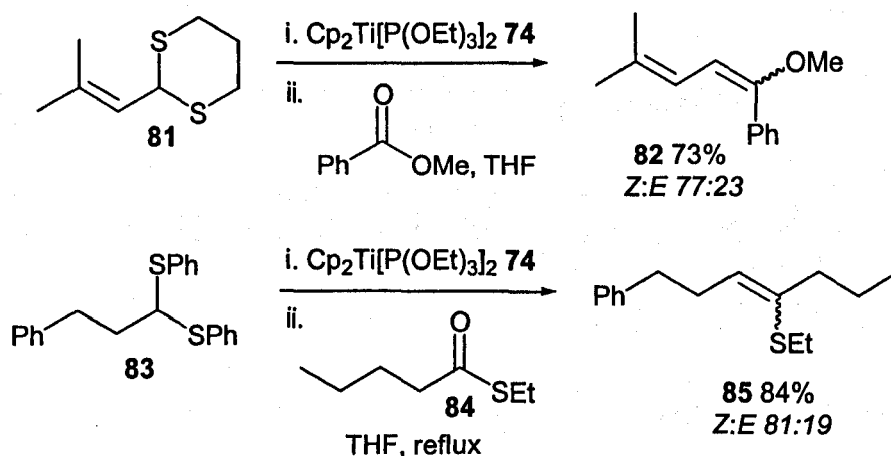
Scheme 27

Titanium cyclobutylidene complex **86**, generated from 1,1-bis(phenylthio)cyclobutane **87**, alkylidenates ketones, esters and thioesters to give alkylidene cyclobutanes **88** in high yields (Scheme 28).[65]
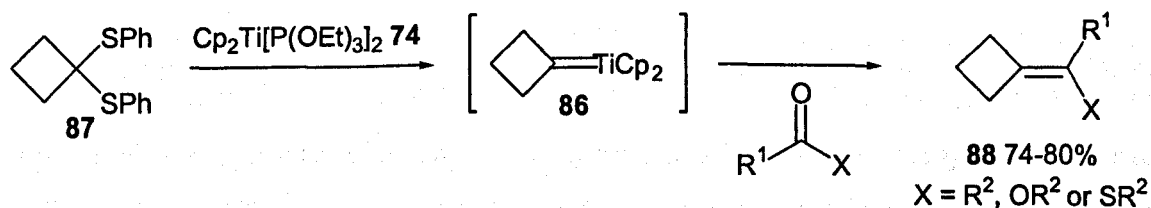
Scheme 28

The titanium alkylidene generated from methoxybis[(phenylthio)methane] **89** converts aldehydes and ketones into enol ethers.[66] Esters and thioesters yield β-(alkoxy)vinyl ethers and β-(alkylthio)vinyl ethers, respectively, and ester **90** gave vinyl ethers **91** in good yield but poor stereoselectivity (Scheme 29).[66] In a similar way, triphenyl trithio-orthoformate **92** converts aldehydes and ketones into vinyl sulphides.[66] Esters and thioesters, similarly yield β-(alkoxy)vinylsulfides and β-(alkylthio)vinyl sulfides, respectively, with modest *E*-selectivity, exemplified by thioester **93** and triphenyl trithio-orthoformate **92** giving β-(propylthio)vinyl sulfide **94** in good yield and moderate *E*-selectivity (Scheme 29).[66]
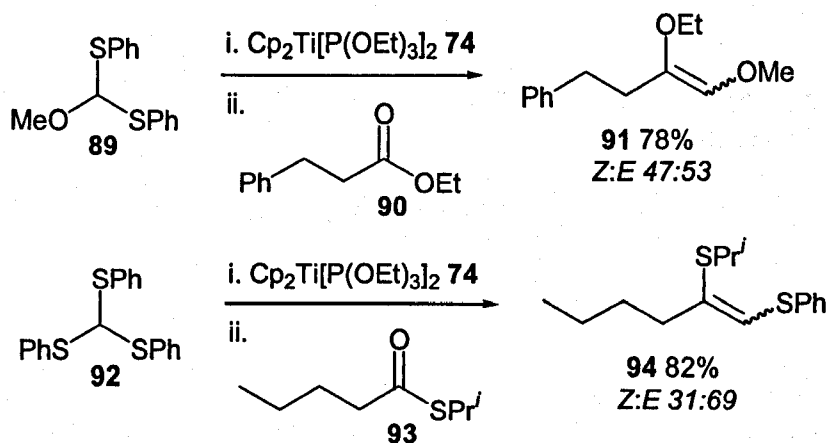
Scheme 29

Allylsilanes can be prepared by Takeda alkylidenation of aldehydes, ketones, esters, lactones, or thioesters using β-trialkylsilylthioacetals as substrates.[67] Allylsilanes are formed from aldehydes and ketones with moderate *E*-selectivity. γ-(Alkylthio)allylsilanes are formed with moderate *Z*-selectivity, seemingly unaffected by the bulk of the *S*-alkyl group in the thioester substrates. γ-(Alkoxy)allylsilanes are formed from ester substrates, with better *Z*-selectivity in most cases, and a branch α to the ester carbonyl group leads to complete stereoselectivity as exemplified by formation of γ-(ethoxy)allylsilane **95** from ester **96** (Scheme 30).[67] The alkene configuration was not determined but it is assumed to be *Z*-selective.[15]
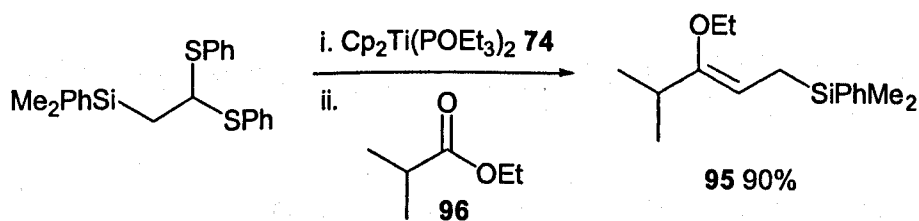
Scheme 30

Intramolecular alkylidenations are also possible. Treatment of *S*-[3,3-bis(phenylthio)propyl]thioalkanoates with 4 eq of low-valent titanium complex **74** in THF produced 5-substituted 2,3-dihydrothiophenes.[68] Improved yields were obtained when there was a branch α to the carbonyl group as in thioester **97** (Scheme 31). Isomerisation to the exocyclic alkenes was initially observed but by carrying out both the reaction and work-up in the dark this was suppressed. Indeed, the product vinyl sulfide **98** isomerises in light to give an equilibrium mixture (80% *exo*) of alkenes.[68]
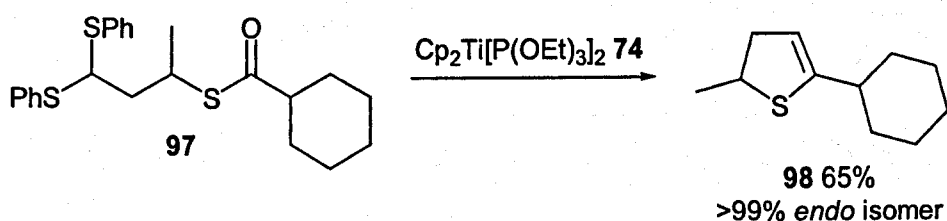
Scheme 31

Titanium alkylidenes generated from ω,ω-bis(phenylthio)alkyl esters (e.g. **99**) undergo oligomerisation as well as cyclisation. The best yield obtained was for cyclic enol ether **100** and this was only 32% (Scheme 32).[69] However, the reaction provides a useful route to ω-hydroxy ketones (e.g. **101**), and by carrying out the alkylidenation reaction under reflux in THF, and then hydrolysing the resulting crude cyclic enol ether (e.g. **100**) *in situ*, yields are improved considerably.
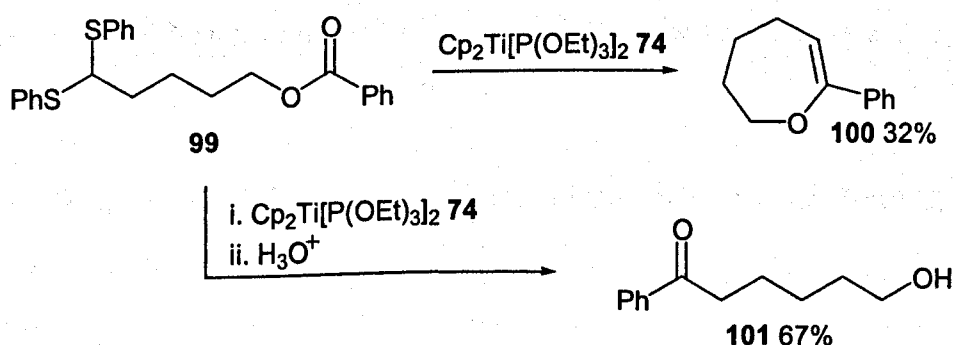
Scheme 32

Intramolecular alkylidenation is more effective when the oxygen atom of the product enol ether is exocyclic and 5-, 6-, 7- and 9-membered rings have been made in this way, with thioacetal **102** giving cyclic *E*-enol ether **103** in 70% yield (Scheme 33).[70] Again, some isomerisation of the alkene products was observed in some cases but was suppressed by carrying out the reactions at lower temperatures. Reactions were carried out under high dilution conditions, on 0.50 mmol scale, and attempts at scale-up resulted in lower yields being obtained.
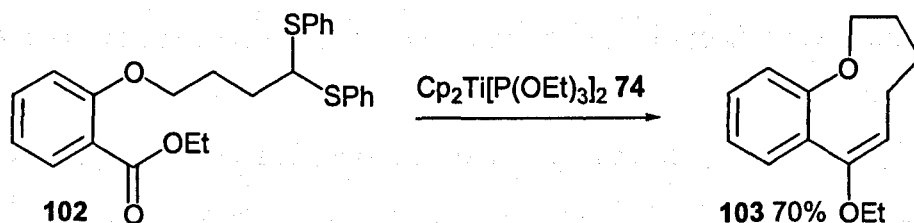
Scheme 33

The generation of titanium alkylidenes from thioketals is generally problematic due to competing formation of vinyl sulfides.[71] However, the use of more easily reduced *gem* dichlorides, allows the conversion of carbonyl compounds into tetra-substituted olefins. Takeda's group have recently reported a convenient synthesis of *gem* dihalides (e.g. **104**), *via* oxidation of hydrazones (e.g. **105**, Scheme 34), produced by treatment of carbonyls with hydrazine hydrate.[72] Aldehydes and ketones are converted into tri- and tetra-substituted alkenes respectively, and esters and lactones into trisubstituted enol ethers (e.g. **106**, Scheme 34).[71] The reaction is effective even if all of the substituents are acyclic. This is the first practical procedure for the preparation of trisubstituted enol ethers and *E:Z* ratios range from 60:40 to 90:10.[71] However, Takeda's procedure is unsuccessful for the formation of benzylic dihalides as vinyl halides are the main products formed, and there remains no reported method for the production of titanium benzylidenes with an alpha substituent.[15]
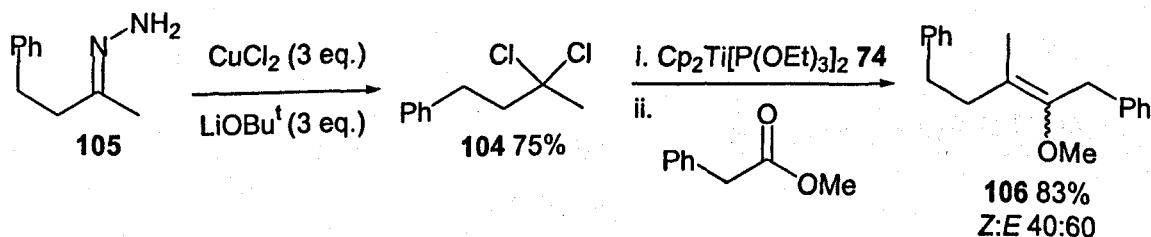
Scheme 34

Under Takeda conditions, titanium alkylidenes are thought to be the active species as they have been shown to catalyse alkene metathesis.[15] The titanocene(II)-promoted formation of titanium alkylidenes from thioacetals, and subsequent metathesis reaction of these alkylidenes with terminal trialkyl(allyl)silanes, stereoselectively forms the corresponding Z-γ-substituted allylsilanes.[73] Ring-closing alkene metathesis of thioacetals containing an alkene moiety proceeds smoothly upon treatment with 3-4 eq. of low-valent titanocene **74** at rt, and then heating under reflux in THF.[74, 75, 76] Loss of the terminal alkene allowed the synthesis of 5-, 6-, and 7-membered cycloalkenes in good yields. Similarly the 7- and 8-membered unsaturated cyclic ethers[75] and cyclic amines[77] were also prepared. Employing 4 eq. of low-valent titanocene complex **74**, initially at rt and then heating under reflux in THF, converted thioacetal **107** into cyclic amine **108** in good yield (Scheme 35). Generally, the titanocene promoted ring-closing metathesis (RCM) reactions are done under high dilution to suppress the intermolecular reactions. More recently (Z)-Alk-2-ene-1,5-diols have been prepared stereoselectively *via* the titanocene promoted RCM of trialkyl silyl ethers containing both a thioacetal and terminal alkene moiety, followed by oxidative cleavage of the resulting cyclic silyl ethers.[76, 78]
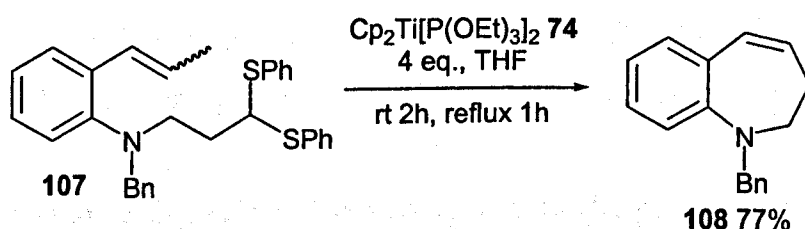
Scheme 35

Titanium alkylidenes, formed under Takeda conditions from thioacetals **109**, add to alkynes to give the corresponding titanacyclobutenes, which then undergo β–hydride elimination and subsequent reductive elimination to give the corresponding dienes **110** in good yields and high stereoselectivity (Scheme 36).[79]
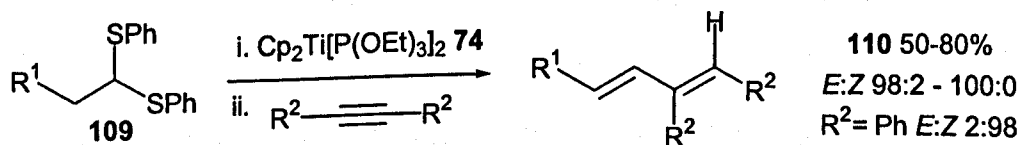
Scheme 36

Titanium alkylidenes, formed under Takeda conditions, add to nitriles and then undergo a β–hydride elimination to give vinylimido complexes **111**. These can then be hydrolysed directly to give ketones **112**, or *in-situ* addition of an alkyl halide followed by hydrolysis gives monoalkylated ketones **113** (Scheme 37).[80]
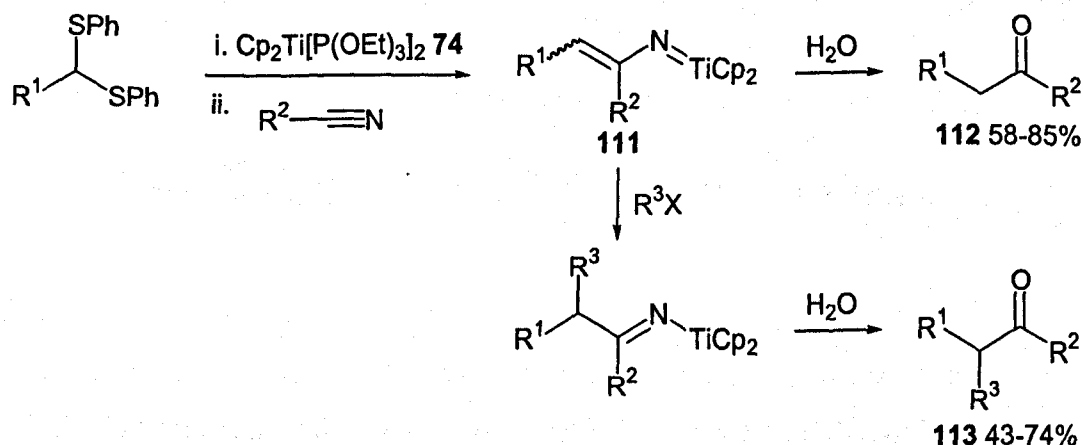
Scheme 37

Titanium allylidenes, formed from β,γ-unsaturated thioacetals **114**, can cyclopropanate alkenes to give the corresponding vinylcyclopropanes **115** (Scheme 38), which probably proceeds *via* the reductive elimination of a titanacyclobutane intermediate.[81] Similarly, γ-cyclopropyl allylsilanes are prepared from 2,4-bis(phenylthio)but-3-enylsilanes, upon treatment with low-valent titanium complex **74** and then a terminal alkene.[82] Titanium allylylidenes can also be alkylated with tertiary alkyl chlorides before quenching.[83]
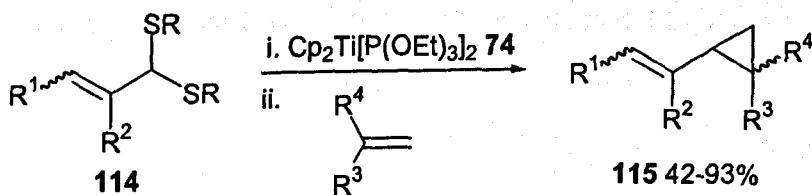
Scheme 38

Titanium propargylidenes, formed from 1,1-bis(phenylthio)-2-alkynes **116**, can also cyclopropanate terminal alkenes to give the corresponding alkynylcyclopropanes **117** (Scheme 39), which presumably proceeds *via* the reductive elimination of the titanacyclobutane intermediate. In order to obtain good yields excess triethyl phosphite is required.[84]
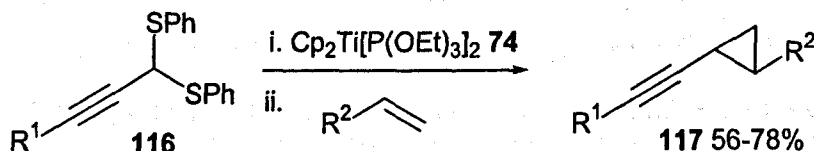
Scheme 39

Previous to our work, functional group tolerance within titanium alkylidenes generated under Takeda conditions and within carboxylic and carbonic acid derivatives treated with such reagents, was not fully explored. A full discussion is given later in the results and discussion section.

The key advantage of Takeda alkylidenation, is the easy access to a range of alkylidenating agents produced from thioacetals that are easily made from carbonyl compounds. The reaction is not limited to methylenation or benzylidenation and the preparation of a wide range of alkylidene reagents is theoretically possible. The mildness of the reaction conditions (with both formation and often reaction of the titanium alkylidene being conducted at rt) and the lack of Lewis acidic conditions, are also attractive. The main disadvantage is the requirement for excess titanocene (at least 3 eq.) and triethylphosphite (at least 6 eq.), which often makes product purification problematic.

Takai reagents

Takai has reported a simple and general method for the alkylidenation of carbonyls **118** to give alkenes **119**, using a reagent prepared in a reaction mixture containing a 1,1-dibromoalkane, zinc, titanium(IV) chloride and *N,N,N',N'*-tetramethylenediamine (TMEDA) in THF (Scheme 40).[85] Takai reagents are prepared by addition of 4 eq. titanium(IV) chloride in dichloromethane to THF, followed by 8 eq. TMEDA, which turns the suspension from yellow to orange/brown. Addition of 9 eq. of zinc then leads to a dark blue/green suspension. Upon addition of 1 eq. of the ester and 2.2 eq. of a dibromoalkane, the reaction mixture turns dark brown or black, and is then quenched with aqueous potassium carbonate giving the alkene **119**. Trace amounts of lead(II) salts are reportedly vital for successful reaction,[86] and so a small quantity of lead(II) chloride is generally added, though lead is often a contaminant of commercial zinc powder. Although, the commercially available DCM solution of titanium(IV) chloride can be used, optimal yields are obtained with freshly prepared solutions from high quality titanium(IV) chloride,[87, 88] and also employing a DCM-THF[89] mixed solvent system. However, reactions in only THF are also successful.[15] The definitive procedure for the preparation of this reagent has been published.[90]

$$X = Cl, Br \quad YR^3 = R^3, OR^3, OSiR_3, SR^3, NR^3_2$$
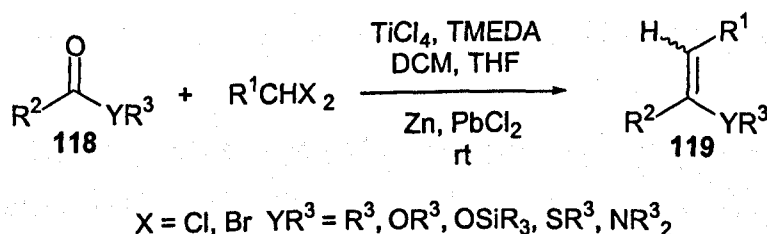
Scheme 40

The reaction mechanism is not yet fully understood. In the absence of lead, zinc is known to rapidly insert into diiodomethane giving carbenoid **120**, but second insertion is slow to give geminal dizinc **121** (Scheme 41).[15] It is known that lead(II) chloride accelerates the conversion of diiodomethane into geminal dizinc **121**,[86] and so would seem to catalyse the conversion of zinc carbenoid **120** into geminal dizinc **121**. Takai proposed that transmetalation from zinc to lead gives rise to lead carbenoid **122**, which is further reduced by zinc to give lead-zinc compound **123**. He suggested that since the Pb-C bond has greater covalent character, lead carbenoid **122** is more easily reduced than the corresponding zinc carbenoid **120**. He proposed that transmetalation from lead to zinc then gives geminal dizinc **121**.[86] However, titanium complexes must be involved in the reduction of the dibromoalkanes used in Takai alkylidenation of esters, as the rate of conversion of

dibromomethane into a geminal dizinc (even with catalytic lead) in the absence of titanium salts is too slow to account for the alkylidenation reaction times.[15]

$$CH_2I_2 \xrightarrow{\text{Zn, THF}} ICH_2ZnI \xrightarrow[\text{Slow}]{\text{Zn}} CH_2(ZnI)_2$$
$$\mathbf{120} \qquad\qquad \mathbf{121}$$

X = Cl, I   *Fast*   PbX$_2$ ... ZnX$_2$ *Fast*

$$ICH_2PbX \xrightarrow[\text{Fast}]{\text{Zn}} IZnCH_2PbX$$
$$\mathbf{122} \qquad\qquad \mathbf{123}$$
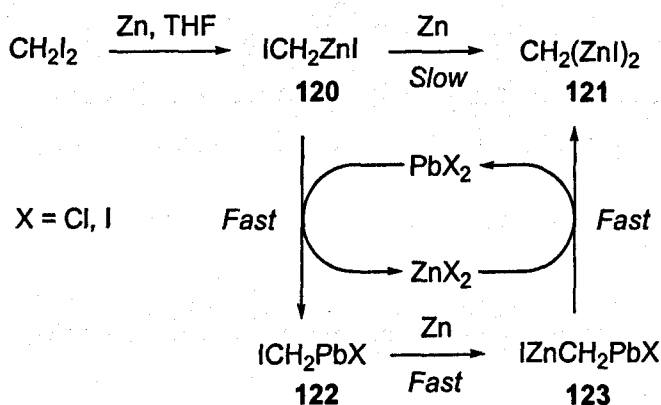
Scheme 41

It is also evident that low valent titanium complexes are generated prior to the addition of dibromoalkanes, but the identity of these low valent titanium complexes has not yet been established. Blue titanium(III) complex **124** can be obtained from titanium(IV) chloride in DCM-THF by treating it with 2 eq. TMEDA, and only 1.1 eq. of zinc (half the stoichiometry used in the generation of the alkylidenating agent) and 6 mol% lead(II) chloride (Scheme 42).[91] Also, when TiCl$_3$(THF)$_3$ is reduced in THF with excess lithium in the presence of 6 eq. TMEDA, violet titanium(II) complex **125** is formed slowly (2 d) *via* the brown mixed valence titanium(II)/titanium(III) species **126** (Scheme 42).[92] Complex **125** dissolves in THF to give a golden yellow solution, but is oxidised easily back to the mixed valence titanium(II)/titanium(III) species **126**. A mixture of titanium species **124**, **125** and **126** would account for the greenish blue colour formed under Takai conditions in THF.

TiCl$_4$ i. DCM-THF   ii. TMEDA (2 eq.)   iii. Zn (1.1 eq.), PbCl$_2$ (6 mol %)   →   **124**

TiCl$_3$(THF)$_3$ i. THF   ii. TMEDA (6 eq.)   iii. Li   →   **126**   →   **125**
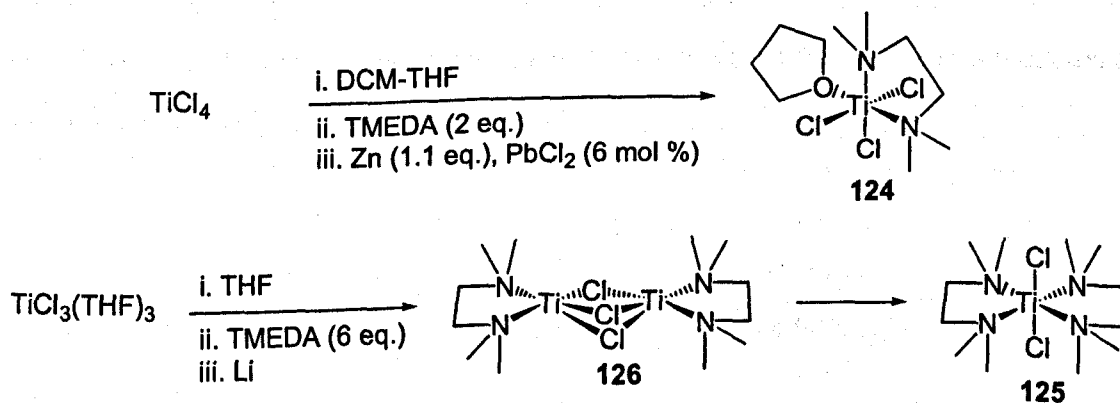
Scheme 42

Takai proposed that in the presence of titanium(IV) salts, geminal dizinc **121** transmetallates to give a titanium-containing geminal dimetallic **127** or a titanium methylidene **128**, one of which is the active species (Scheme 43).[86] We propose that the Takai reaction [and related reactions employing Ti(II) salts], requires oxidative addition to a titanium(II) intermediate, which is involved in the formation of at least one of the carbon-metal bonds to give a titanium(IV)-containing geminal dimetallic **127** [or less likely a titanium(IV) alkylidene **128**], as the active species.

$$CH_2(ZnI)_2 \xrightarrow{\text{TiCl}_4} \left[\begin{array}{c} X_nMCH_2TiX_n \\ \textbf{127} \end{array} \right] \text{ or } \left[\begin{array}{c} H_2C\!=\!\!=\!TiX_n \\ \textbf{128} \end{array} \right]$$

121

M = Ti or Zn
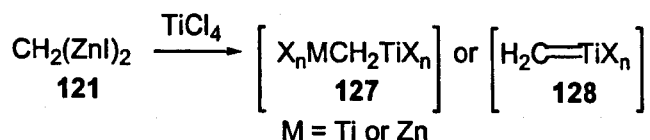
Scheme 43

There are numerous examples of the methylenation of aldehydes and ketones (when Lewis acid mediators are used) employing geminal dizinc and related reagents.[93, 94, 95] Matsubara and co-workers have demonstrated that pre-formed bis(iodozincio)methane **121** methylenates aldehydes effectively. When 2 eq. of **121** is used in conjunction with titanium(IV) chloride, ketones are effectively methylenated, although poor yields are observed with the use of 1 eq. of **121**. This suggests that 1 eq. of **121** reduces titanium(IV) chloride to titanium(II) chloride which mediates the olefination reaction.[96] They later, demonstrated that a reagent derived from pre-formed bis(iodozincio)methane **121**, TMEDA, and titanium(II) chloride in THF, can carry out the methylenation of esters (Scheme 44).[97] The reagent requires 2 eq. of titanium(II) chloride and 4 eq. of TMEDA, with respect to geminal dizinc **121**, for optimal results. They also state that NMR studies on the *CH* coupling constants in the active species formed from titanium(II) chloride suggests that the carbon atom has sp^3 character. A different colour (reddish brown) results from this reagent than that of the Takai reagent (brown or black), and it also methylenates esters more effectively than the Takai reagent.[97]

$$R^2\!\!-\!\!\underset{\displaystyle O}{\overset{\displaystyle \|}{C}}\!\!-\!\!OR^3 \xrightarrow[\substack{\text{TiCl}_2,\ \text{TMEDA}\\ \text{THF}}]{CH_2(Zn\ I)_2\ \textbf{121}} R^2\!\!-\!\!\underset{\displaystyle OR^3}{\overset{\displaystyle CH_2}{C}}$$

46-90%
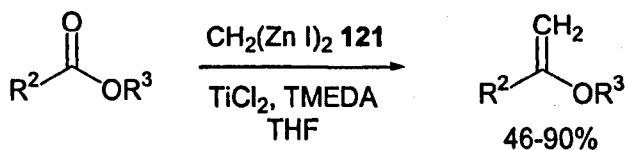
Scheme 44

Takai reports no examples of the alkylidenation of aldehydes and only one example of the reaction of a ketone.[85] In this example, ketone 129 was converted into a mixture of alkenes 130 in good yield (Scheme 45).
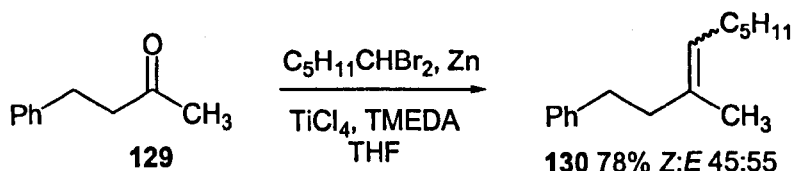
Scheme 45

Takai reagents alkylidenate esters 131 effectively, generally giving enol ethers 132 in yields over 70% (Scheme 46). All reactions are Z-selective and stereoselectivities are generally over 89%. The reaction is not very sensitive to the bulk of R^3 (although bulky R^3 can reduce yields), but bulky R^2 reduces the stereoselectivity and a branch in R^1 α to the carbonyl group ensures total Z-selectivity. The stereoselectivity can be explained using the same arguments as presented for Petasis benzylidenation and Takeda alkylidenation, where stereoselectivity is a result of limiting any steric interactions in the formation of intermediates (possibly oxatitanacyclobutanes). Takai and co-workers reported that methylenation gave poor yields,[85] and in general Takai alkylidenations are more reliable and generally higher yielding than the corresponding methylenation.[15] Takai claims this is due to the increased nucleophilicity provided on account of electron-donation from the alkyl groups in the active species.[85] Silyl esters are also effectively alkylidenated to give the corresponding silyl enol ethers, with Z-selectivities generally similar to those for alkyl esters, but stereoselectivities being reduced when the bulk of substituents on silicon is increased.[98] Lactones produce mixtures of the desired enol ethers and hydroxy ketones, the former presumably being a result of enol ether hydrolysis.[85] Alkylidenation is also successful with diiodoalkanes, but the yields are lower than with the corresponding dibromides.[85]
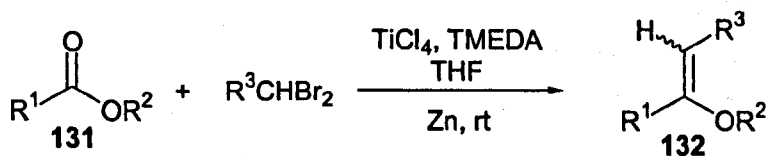
Scheme 46

Takai alkylidenation of thioesters **133** gives *Z*-alkenyl sulfides **134** (Scheme 47).[99] The *Z*-selectivity is lower than for alkylidenation of esters, but total *Z*-selectivity is obtained when both R^1 and R^2 are branched. S-phenyl thioesters gave lower yields and slightly lower *Z*-selectivity. However, α,β-unsaturated thioesters do not give conjugated vinyl sulfides although 1,3-dithian-2-ones are converted into the corresponding ketene dithioacetals in good yield.[99]

$$R^1\text{-C(=O)-SMe} \; (\mathbf{133}) \;+\; R^2CHBr_2 \;\xrightarrow[\text{Zn, rt}]{\text{TiCl}_4,\ \text{TMEDA} \atop \text{THF}}\; \mathbf{134}$$

134 75-97 %
Z:E 73:27 - 100:0
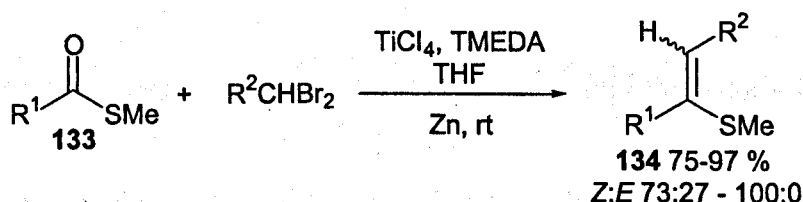
Scheme 47

Tertiary amides **135** give enamines **136** in good yields, and with >96% *E*-selectivity, when R^1 = Ph or primary alkyl (Scheme 48). However, when R^1 = cyclohexyl, stereoselectivity is lost. A mixture of regioisomers is obtained from straight chain amides **135** (R^1 = primary alkyl), presumably due to isomerisation of the initially formed enamine *via* an iminium ion intermediate.[99]

$$\mathbf{135} \;\xrightarrow[\substack{R^2CHBr_2 \\ \text{rt}}]{\text{TiCl}_4,\ \text{TMEDA} \atop \text{Zn, THF}}\; \mathbf{136}$$

136 70-87 %
Z:E 53:47 - >99:1
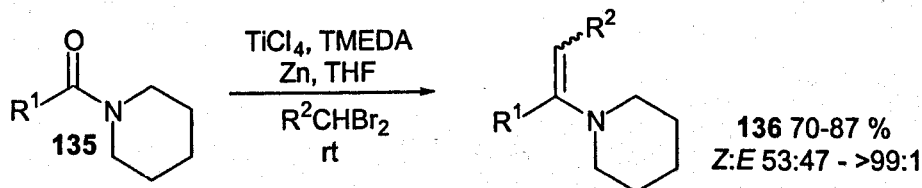
Scheme 48

The synthesis of β-hetero-substituted vinylsilanes *via* Takai trimethylsilylmethylenation of esters has been achieved using (dibromomethyl)trimethylsilane as the 1,1-dibromide.[89] The reactions are slower (3-5 h) than other alkylidenations, and 3.3 eq. rather than 2.2 eq. of dibromide is needed to obtain good yields. Enol ethers are formed with >86% *Z*-stereoselectivity, and a branch α to the carbonyl group again ensures virtually complete *Z*-selectivity. Ester **137** gives essentially only *Z*-enol ether **138** (Scheme 49). Trimethylsilylmethylenation of thioesters is less *Z*-selective, and yields are slightly lower than the corresponding reaction with esters.[89]
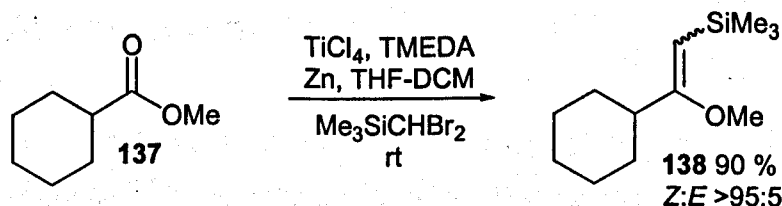
Scheme 49

Aromatic esters can be cyclopropanated with an excess of Takai reagent. Methylenation of methyl azulene carboxylates **139** and **140** proceeds smoothly under standard Takai conditions, but when an excess of the reagent is used, cyclopropyl ethers **141** and **142** are produced in good yield (Scheme 50).[100] Methyl benzoate undergoes the same reaction, albeit in modest yield, but methyl phenylacetate does not. Enol ethers are not cyclopropanated under these conditions. This indicates that a titanium-containing intermediate derived from the ester reacts with excess reagent.[15]
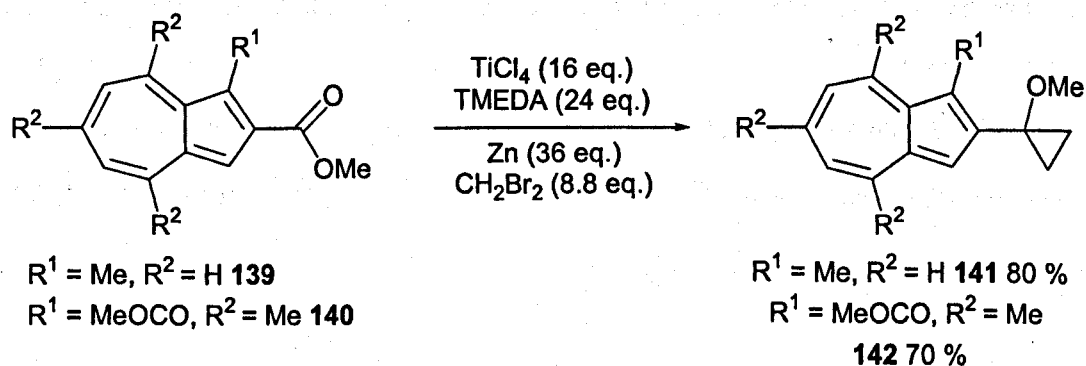
Scheme 50

There have been recent reports of Takai reagents giving the products of alkene metathesis.[101] However, the researchers proposed that a titanium alkylidene is generated from an allylic group (see Grubbs reagents) present in the substrate, which then alkylidenates the carbonyl group intramolecularly.[15]

The advantage of Takai alkylidenation is that it is a mild one-pot procedure that allows the alkylidenation of a range of carboxylic acid and carbonic acid derivatives, often with very high stereoselectivity. Takai alkylidenation tolerates many functional groups, in the ester substrates, including aryl and vinyl halides, alkenes, ethers, silyl ethers and acetals.[15] Its main disadvantage is that it requires a source of 1,1-dihaloalkanes, which can be difficult to prepare.

30

Chapter 3 - Alkenylboronates

Boronic esters are useful synthetic intermediates as they undergo palladium-catalysed cross-coupling reactions.[102] They couple with aryl, alkynyl, and vinyl halides providing a general technique for carbon-carbon bond formation (Scheme 51).[102] The reaction is compatible with a wide range of functional groups due to the mild reaction conditions employed. Many other organometallic reagents are equally successful but organoboronates have advantages in that they are thermally stable, inert to water and oxygen, and the boron-containing side products are non-toxic.[102]

$$R^1-X \quad + \quad R^2-B(OR)_2 \quad \xrightarrow{\text{Pd[O] Cat.}} \quad R^1-R^2$$

Scheme 51

β-(Alkoxy-substituted alkenyl)boronic esters are also useful intermediates but can only be made by the hydroboration of alkynes. β-(Ethoxy)alkenylboronic ester **143**, with the hydrogen atom *cis* to the boron atom, was prepared from 1-ethoxy-1-alkyne **144** and was then used in a subsequent cross coupling reaction (Scheme 52).[103]
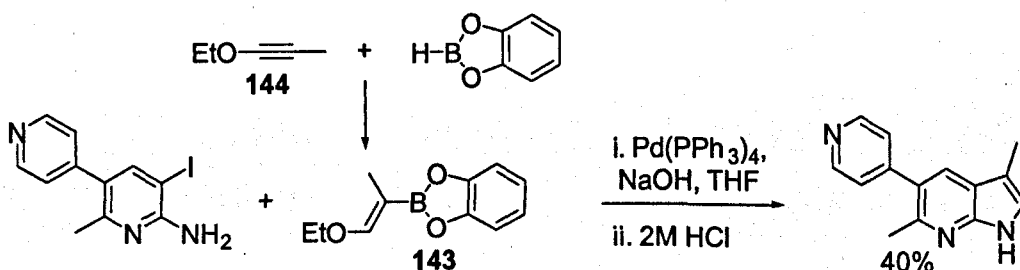
Scheme 52

Similarly, β-(alkylthio)alkenylboronic esters **145** have been synthesised both regioselectively and stereoselectively using palladium- or nickel-catalysed hydroboration (Scheme 53).[104] Thioboration allows the synthesis of related (Z)-vinylboranes but has not yet been applied to the synthesis of boronic esters.[105]

Scheme 53

31
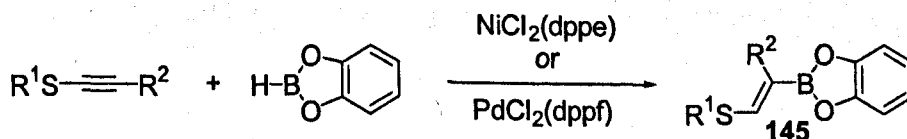
Dienylboronate **146** has also been used in diastereoselective Diels-Alder reactions, quantitatively yielding *endo* functionalised cyclohexane **147**, which could then be further reacted with aldehydes as shown (Scheme 54). The dienylboronates were prepared by the hydroboration of terminal eneynes.[106]
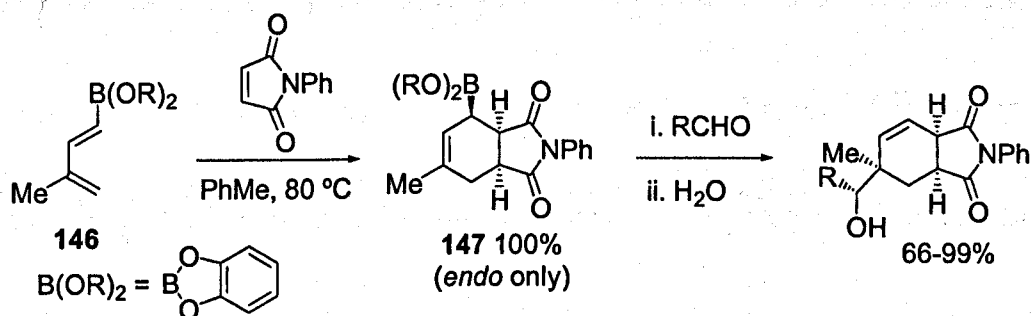
Scheme 54

Alkenylboronic esters are also useful substrates for diastereoselective reduction, allowing the control of stereochemistry at up to three adjacent centres, in both cyclic and acyclic systems. *Z*-Alkenylboronic ester **148** was reduced diastereoselectively, giving alkylboronate **149**, which could then be either oxidised or aminated as shown (Scheme 55).[107]
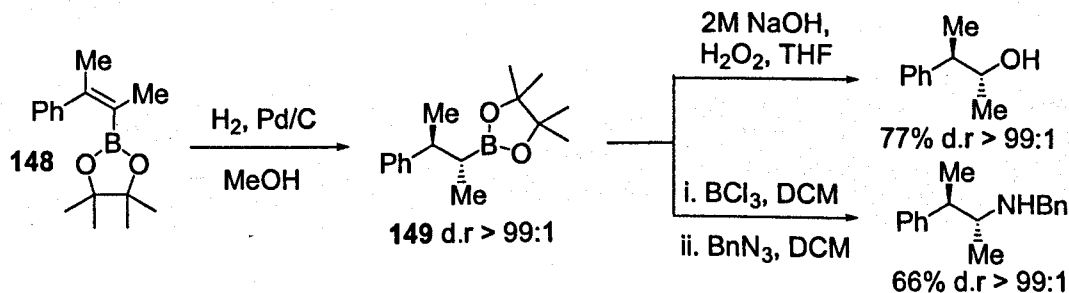
Scheme 55

Chapter 4 - Solid-Phase Chemistry

4.1 Background

The pioneer in the field of solid-phase chemistry was Merrifield, who in 1963 described the use of solid-support in peptide synthesis.[108] Since that time the use of solid phase synthesis (SPS) has grown to encompass the synthesis of small organic molecules and many different organic reactions have been carried out on solid-phase.[109, 110, 111, 112]

One of the main attractions of SPS to the organic chemist is the ease of product isolation. Assuming that complete conversion from resin-bound starting material to product occurs, purification merely requires the washing away of reagents and side products, thus avoiding the need for costly chromatography. Indeed, most SPS reactions can be driven to completion by use of excess reagents, despite reducing the atom-economy of the transformations. However, it must be noted that not all reactions can be moved seamlessly from solution to solid-phase and it often requires time to develop optimal conditions for solid-phase procedures. In addition, the introduction of two extra steps in linking compounds to and cleaving compounds from the resin must be taken into account, and these procedures are often not trivial. In these steps the choice of linker (the moiety which attaches the molecule to the resin) can be of vital importance.[110]

4.2 Linkers

4.2.1 Introduction

The criteria used when assessing which type of linker to employ in a solid-phase reaction should be much the same as when making a choice of protecting group. Indeed a linker could be described as a bifunctional protecting group, in that it is attached to the molecule being synthesised through a bond labile to the cleavage conditions and attached to the resin through a more stable bond (Figure 2).[113]

Protecting Group-/-Functional Group-Molecule

↓ Deprotection

Functional Group-Molecule

Polymer-Spacer-Linker-/-Functional Group-Molecule

↓ Cleavage

Functional Group-Molecule

Figure 2

An ideal linker would be cheap; its attachment to the starting material would be facile and high yielding; it would withstand all the synthetic steps in the synthesis; most importantly it must be possible to cleave the final product from the resin under conditions that do not destroy it. The cleavage step can be problematic, particularly with traditional peptide linkers, which tend to require harsh conditions for cleavage (e.g. HF). Despite this, peptide linkers have found a role in the SPS of small molecules. However, a new generation of traceless linkers, not based on the traditional protecting group strategy, are becoming increasingly common (see section 4.2.3).[110, 113]

I will begin with a discussion of common acid labile linkers, and will then explain what is meant by "traceless", "safety catch" and "chameleon catch" linkers, and finally "cyclative termination". These are the strategies most relevant to my work. However, it should be noted that there are numerous SPS strategies and linker types, and they have been fully reviewed elsewhere.[113] The SPS synthesis of indoles and quinolines will be discussed in detail in chapters 5 and 6, respectively.

4.2.2 Acid-Labile linkers

Merrifield gave his name to the original linker used in peptide synthesis.[108] Merrifield resin **150** comprises cross-linked polystyrene functionalised with a chloromethyl group (Figure 3). Carboxylic acids are attached by reacting the resin with the caesium carboxylates and cleavage of the resin-bound ester occurs when the resin is treated with HF. In 1973 Wang reported a second major class of ester linker **151** (Figure 3).[114] This linker comprises an activated benzyl alcohol design and is also known as HMP (hydroxymethylphenoxy resin). It is more acid labile than the corresponding Merrifield linker, due to the increased stability of the resulting benzylic cation, and so cleavage can occur under milder conditions (50% TFA in DCM).[115] A linker that is even more sensitive to acid was reported by Mergler *et al.* in 1988. The SASRIN (Super Acid Sensitive Resin) resin **152** resembles Wang resin but has an additional methoxy substituent, and successful cleavage can occur with only 0.5-1% TFA in DCM (Figure 3).[116]
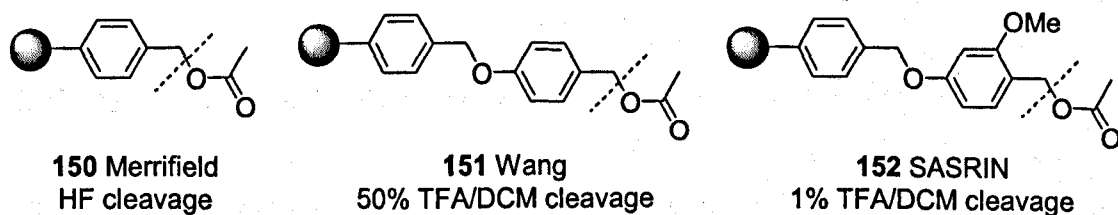

150 Merrifield
HF cleavage

151 Wang
50% TFA/DCM cleavage

152 SASRIN
1% TFA/DCM cleavage

**Figure 3**

4.2.3 Traceless linkers

Cleavage of a product from a conventional linker generally leaves functionality (e.g. a carboxylic acid, amide or alcohol) at the former site of attachment to the solid support. Such extraneous functionality may affect structure-activity relationships in drug-like molecules. Consequently *traceless linkers*, where there is no apparent sign of the original site of attachment, have been developed. Many traceless strategies have been reported and reviewed extensively and only a brief discussion of the more general strategies will be discussed herein.[117, 118, 119] The initial definition of "traceless" referred to the introduction of a hydrogen atom at the former linkage site. However, since reports of syntheses of various functional groups at the former site of attachment have been reported to occur in a "traceless" fashion, the definition was extended to include examples where the former attachment site bears no resemblance to the linkage site before cleavage (such a definition is so broad as to include most cleavage reactions). A more recent definition describes tracelessness as being the result of overall reduction of functionality at the site of attachment upon cleavage from the support.[118] We will use a loose "no apparent sign of the original site of attachment" definition of tracelessness.

Ellman was a pioneer in this field with the development of aryl silicon linkers. The original linker was cleaved under strongly acidic conditions (HF), forming a new carbon-hydrogen bond at the site of attachment.[120] More recently, silicon linkers that are cleaved under milder conditions have been reported, with one example being utilised in the synthesis of tricyclic compounds **153** (Scheme 56).[117]
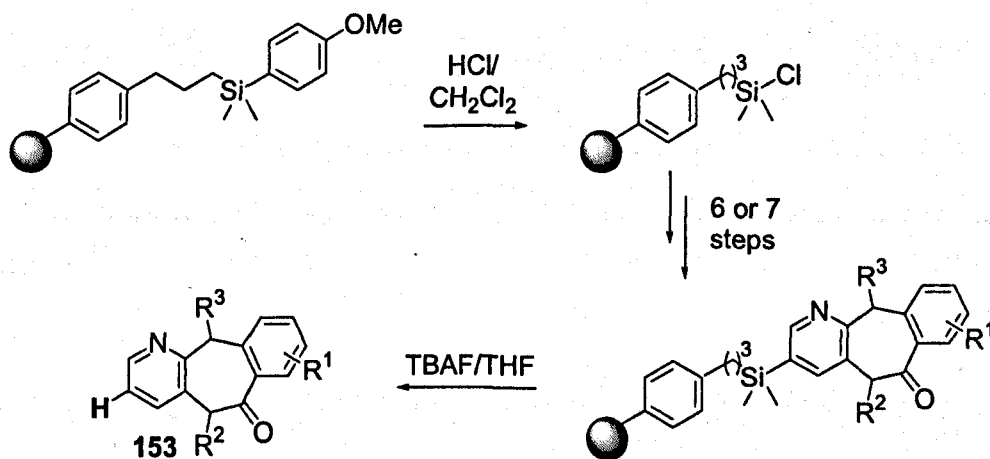
Scheme 56

Selenium has proved a useful element for traceless solid-phase synthesis, due the susceptibility of alkenyl selenides to homolysis.[117] However, seleno-polystyrene resin-bound 154 can undergo oxidative cleavage generating alkene 155, as well as radical cleavage to give alkane 156 (Scheme 57).[121]
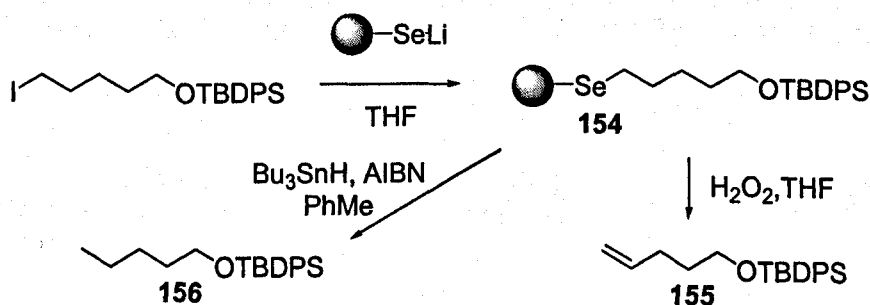
Scheme 57

Numerous examples of traceless cleavage employing nitrogen linkers have been reported where cleavage is facilitated by nitrogen quaternization followed by elimination.[117, 118] Rees and co-workers reported the traceless synthesis of tertiary amines 157, employing the Michael addition of secondary amines 158 onto the regeneratable Michael (REM) linker 159 (Section 11.3), followed by quaternization and Hofmann elimination (Scheme 58).[122]
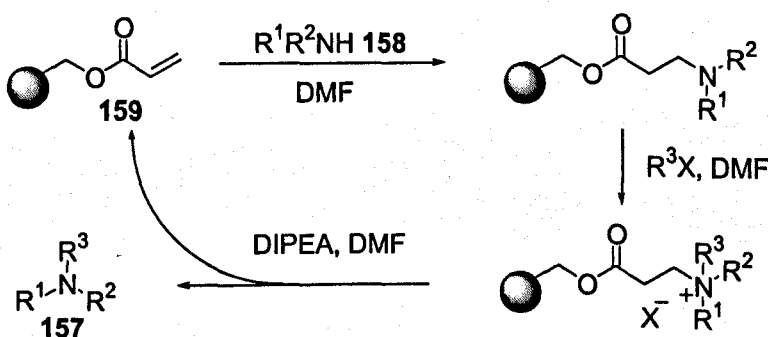
Scheme 58

Many other traceless cleavage strategies rely on release from the resin upon aromatization.[118]

4.2.4 Safety-catch linkers

Safety-catch linkers that rely on a two-step cleavage process are often more general traceless linkers. A stable linker used throughout a synthesis in a relatively stable form is then activated, ensuring that the following cleavage step occurs under mild conditions. Wagner and co-worker's cleavage of benzylsulfonium salts **160**, formed by S-alkylation, under palladium cross-coupling conditions to give biphenylmethyl derivatives **161** (Scheme 59), illustrates this methodology.[123]
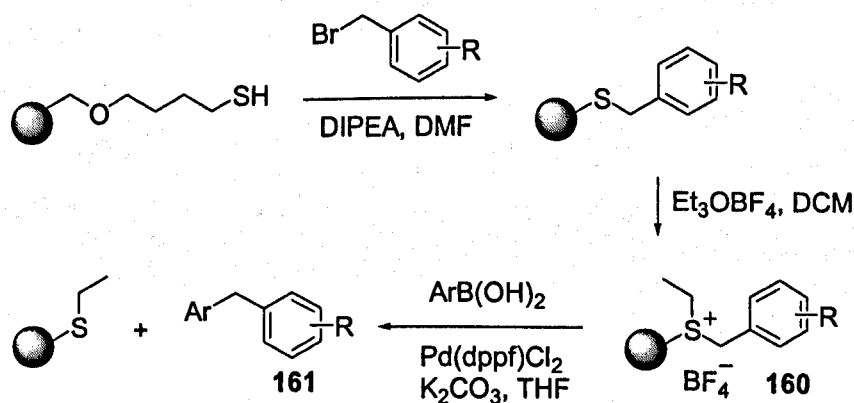
Scheme 59

4.2.5 Chameleon-Catch linkers

Chameleon-catches are linkers which can be switched to another linker type during the synthesis.[124] The original linker can be cleavable but is converted into a more labile linker (often this involves converting an acid cleavable linker into a more acid labile linker). This strategy ensures high purity in products cleaved fom the resin, but can also increases diversity by introducing further functionality during the linker switch. Barrett and co-workers used the Tebbe reagent **27** (Section 2.2) to methylenate resin-bound esters **162** yielding dienes **163**, which underwent Diels-Alder cycloadditions followed by cleavage from resin in mild acid to give the corresponding cyclohexanone derivatives **164** (Scheme 60).[124] Resin-bound enol ethers **165** formed in the same fashion, underwent [3 + 2] cycloadditions with ethyl chlorooximidoacetate **166**, allowing concomitant aromatization/cleavage in mild acid to give isoxazoles **167** (Scheme 60).[125]
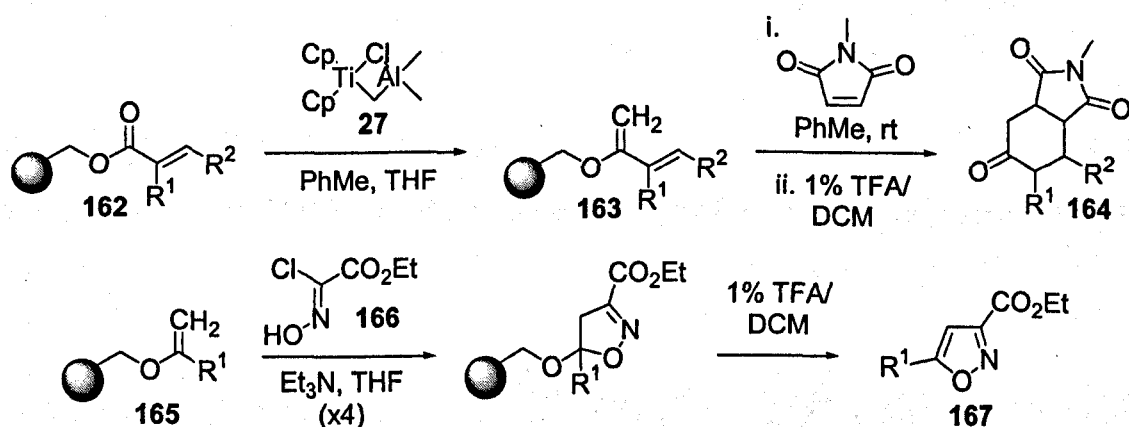
Scheme 60

4.2.6 Cyclative cleavage

Cyclative cleavage is when cyclisation induces cleavage fom the resin. The key advantage of cyclative cleavage is that only cyclised compounds are released from resin, which ensures the high purity of the products. There are numerous examples of cyclative cleavage, including the cyclisation of internal nucleophiles such as alcohols, amines, anilines, ureas, thioureas, and guanidines onto carboxylic acid derivatives that form the link to the resin.[117] A recent example, involves cyclisation of resin-bound guanidine **168** to give quinazoline **169** (Scheme 61).[126]
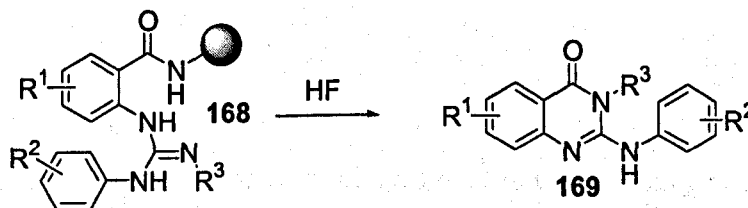
Scheme 61

There are also numerous examples of cyclative cleavage by ruthenium-catalysed ring closing metathesis (RCM).[117] RCM cyclative cleavage of substrates **170** gives lactams **171** (Scheme 62).[127]
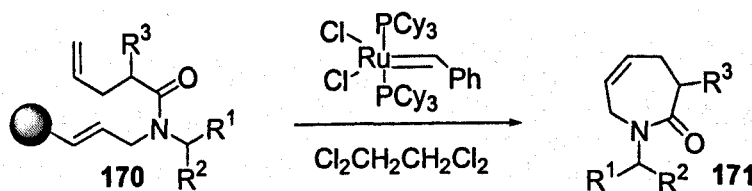
Scheme 62

Other cyclative cleavage strategies include reactions of stabilised phosphorus[128] (Section 5.3) and sulfur[129] ylides, which proceed in a traceless fashion.

4.3 Product characterisation/Automation tools

Infra Red (IR) Spectroscopy

Although not useful for quantitative analysis, IR spectroscopy proves a non-destructive method for the qualitative analysis of certain functional groups on solid phase. Dried polystyrene resin can be used to prepare KBr discs that provide adequate spectra.[110] The more recent Golden Gate IR technology, means that the resin can be analysed with no further manipulation.

Nuclear Magnetic Resonance (NMR) Spectroscopy

Gel phase NMR spectra can be obtained but suffer from significant line broadening due to chemical-shift anisotropy and dipolar coupling. For this reason, only nuclei with a strong chemical shift dispersion such as ^{13}C, ^{15}N, ^{19}F and ^{31}P give useful spectra, while ^1H NMR spectra remain poorly resolved. However the development of magic angle spinning (MAS) NMR has addressed this problem. This technique was developed particularly for resin-bound compounds. Well-resolved spectra including high quality ^1H NMR spectra can be produced.[110]

Use of IRORI 'kans'

IRORI 'kans' are polypropylene reaction vessels, often described as 'plastic tea bags', as the resin remains within the reactor while the reaction mixture can flow in and out through the plastic mesh. A number of sizes of kan exist; the 'macrokan' used by our group is the largest and holds approximately 0.3 mmol of resin-bound material. Advantages of the IRORI technology include the 'split and mix' strategy, where different resin-bound products can be formed in one pot by adding reagents to a flask containing a mixture of kans, each containing different resin-bound substrates. Thus, kans are used in industry in a combinatorial fashion, where a radio-labelled tag is present in each kan, therefore allowing product identification at each stage, and so suitable for automation. Also, kans can be useful in heterogeneous reactions (such as the Takeda reaction, which uses powdered molecular sieves and generates insoluble titanium salts), where by using loose resin, it can be difficult to separate the resin from the heterogeneous reagent.

Chapter 5 - Indoles

5.1 Activity

The indole nucleus is present in numerous natural products, including the indole alkaloids, which have been extensively reviewed.[130, 131] So numerous are biologically active indole containing compounds that only very recent studies, with particular emphasis on 2-substituted indoles, will be discussed herein.

Many inflammatory and neurodegenerative diseases are thought to be caused by the aberrant metabolism of the amino acid L-tryptophan **172** (Figure 4).[132] Indoleamine 2,3-dioxygenase (IDO) is known to be the first enzyme involved in the degradation of tryptophan in certain cells.[133] A recent enantioselective synthesis of L-isotryptophan **173**, and its D-enantiomer have been reported with a view to determining the IDO activity of L-tryptophan analogues.[132] Racemic isotryptophan has also been reported to show some bacteriostatic activity.[134]

172 L-tryptophan   **173** L-isotryptophan

Figure 4

Melatonin (*N*-acetyl-5-methoxytryptamine, MLT, **174**, Figure 5) influences a variety of functions in animals, and although its exact role in humans remains unclear, it is thought possible clinical implications may include the treatment of circadian-rhythm-based sleep disorders, and protection of the cardiovascular system by reducing the risk of atherosclerosis and hypertension.[135, 136] Most functions in humans are associated with the action of MLT on the high-affinity, G-protein, membrane methoxytriptamine receptors MT_1 and MT_2.[136] Derivatives with 2-alkyl amine, 4-methoxy and *N*-aryl substituents, show higher affinity for the MT_1 receptor than MLT **174**, with indole **175** (Figure 5) exhibiting submicromolar activity as a partial agonist for MT_1.[135] Interestingly, a related study found that indole **176** (Figure 5) showed similar affinity as MLT to the MT_1 receptor but much lower affinity for the MT_2 receptor.[136] Therefore 2-substituted analogues of naturally occurring indoles, may exhibit greater selectivity for certain receptors.
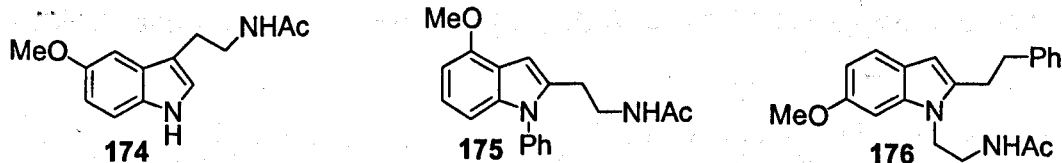
Figure 5

The neurotransmitter serotonin (5-hydroxytryptamine **177**, Figure 6) is a secondary metabolite of tryptophan **172**. A number of different classes of serotonin receptors (5-HT$_1$ - 5-HT$_7$) have been identified. One of the more recently identified populations are the 5-HT$_6$ receptors, which are found primarily in the central nervous system. Although their exact clinical significance is still unknown, a number of antipsychotic agents and antidepressants bind with high affinity at 5-HT$_6$ receptors and 5-HT$_6$ ligands are thought to be involved in various disorders including anxiety, memory deficiency, mood dependant behaviour and motor related function.[137] A recent study identified indole **178** (Figure 6) as the most selective 5-HT$_6$ agonist reported to date with other 2-substituted analogues acting as antagonists.[137] A related study found that indole **179** (Figure 6) also showed high affinity for the same receptor.[138]
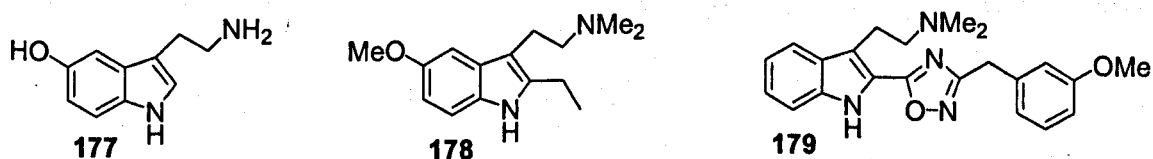
Figure 6

Recent independent studies identified a range of ligands as potent and selective Factor Xa (a pivotal enzyme in blood coagulation) inhibitors. 2-Substituted indole **180** was identified as a subnanomolar inhibitor,[139] whereas indoles **181** and **182** showed nanomolar activity and high selectivity[140] for Factor Xa (Figure 7). Such compounds could potentially lead to the development of safer and more effective antithrombotic agents.
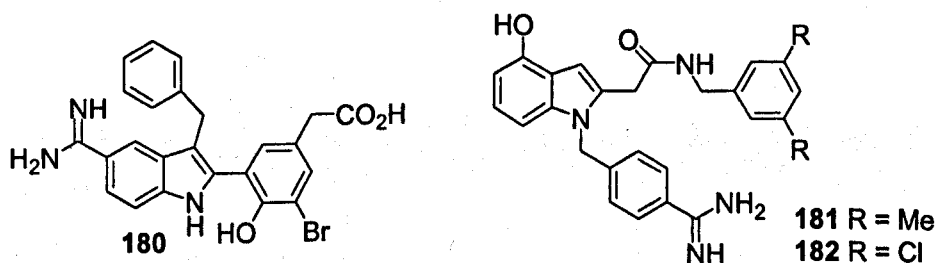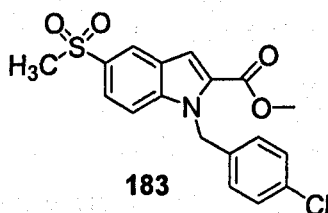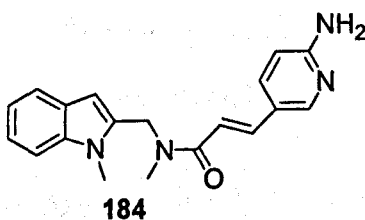

Figure 7

Nonsteroidal anti-inflammatory drugs (NSAIDs) target cyclooxygenases, but show undesirable gastric side effects. Potent selective cyclooxygenase-2 inhibitors have recently been reported, with indole **183** (Figure 8) identified as a lead candidate for a potentially effective NSAID without the usual side effects.[141]

Figure 8

Bacterial enoyl-ACP reductase (FabI) catalyses the final step in each cycle of bacterial fatty acid biosynthesis and so is an attractive target for the development of new antibacterial agents. A recent study identified indole **184** (Figure 9) as a low micromolar inhibitor of FabI. It caused inhibition of fatty acid biosynthesis and so can be considered a valid antibacterial target.[142]

Figure 9

Both natural and synthetic bisindoles have recently been investigated, and members of the indolocarbazole family are known to exhibit nanomolar topoisomerase inhibitory action.[143, 144] Amongst the indolopyrrolocarbazoles currently in clinical trials is NCS 655649 **185** and carbazole **186** was also shown to be strongly cytotoxic towards four tumour cell lines (Figure 10).[144]
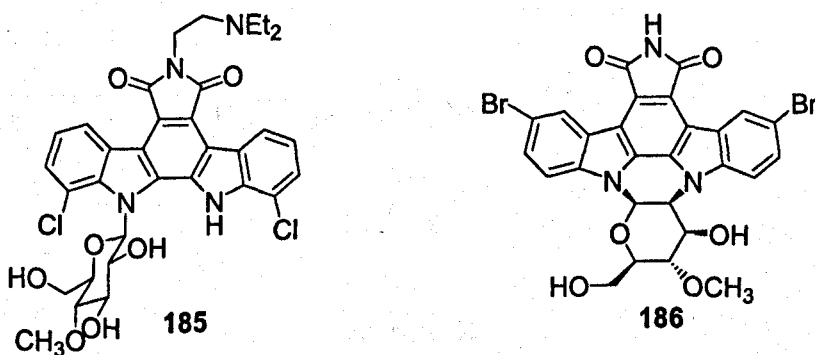
Figure 10

5.2 Indole Synthesis

The synthesis of the indole nucleus has been an object of research for over a century.[145] As a result, numerous strategies for the construction of indole derivatives have been reported and extensively reviewed,[146] and so only those employing classical N-C$_2$ indole ring constructions (formation of the indole nucleus is attained *via* formation of a bond between the indole nitrogen and C$_2$ of the indole ring) and/or very recent examples will be discussed here. However, methodologies for the synthesis of the indole skeleton on solid-phase (Section 5.3) will be covered comprehensively.

The Reissert synthesis of indoles, relies on the acidity of the methyl protons *ortho* to a nitro substituent on an aromatic ring. The resulting anion from 2-nitrotoluidine undergoes condensation with oxalate to give anion **187**, which in turn undergoes a reductive cyclisation/dehydration to yield indole **188** (Scheme 63).[147]
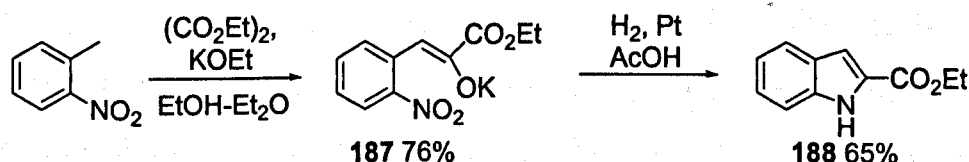
Scheme 63

Similarly, the Leimgruber-Batcho synthesis involves the condensation of 2-nitrotoluidines with dimethylformamide dimethyl acetal (DMFDMA), with reductive cyclisation of the resulting enamine giving an indole.[148] The DMFDMA reagent supposedly generates *in situ* MeOCH=N$^+$Me$_2$, and methoxide ion which deprotonates a toluidide proton, and the resulting anion reacts with the electrophilic MeOCH=N$^+$Me$_2$ component. A useful extension of this methodology involves acylating the intermediate enamine, which ultimately allows substitution at the indole C-2 position. Trisubstituted enamine **189** was prepared and underwent reductive cyclisation to yield indole **190** (Scheme 64).[149]
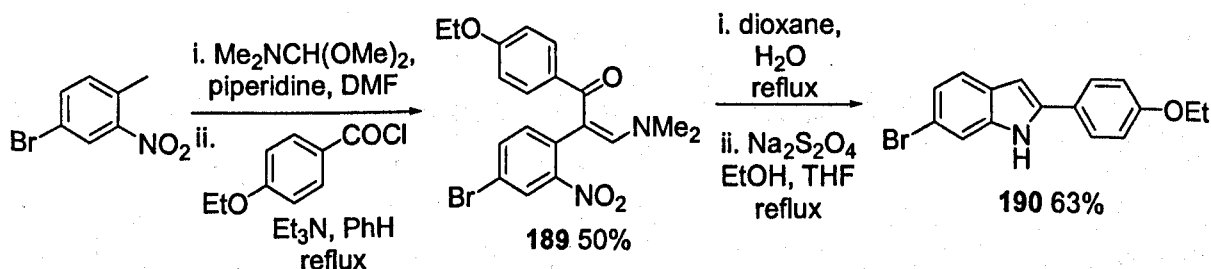
Scheme 64

The Sugasawa indole synthesis utilises the cyclisation of *ortho*-chloroacetyl arylamines (e.g. **191**), which are prepared from unprotected anilines *via* a regioselective Friedel-Crafts acylation (Scheme 65).[150] Cyclisation onto the *ortho*-chloroacetyl moiety, followed by reduction of the ketone to the alcohol, with subsequent dehydration gives the indole nucleus.
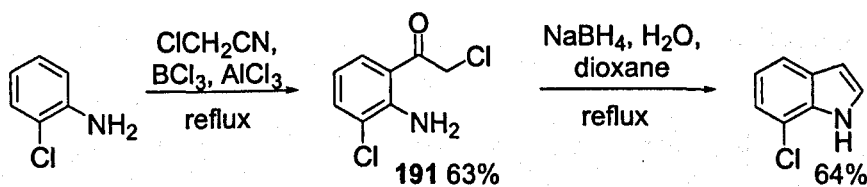
Scheme 65

The cyclisation of nitrenes, generated by the triethyl phosphite deoxygenation of ortho-nitrostyrenes or ortho-nitrostilbenes, is termed the Cadogan-Sundberg synthesis.[146] A further variation of this deoxygenation method employs CO and Se, which the authors propose forms carbonyl selenide (COSe), as the deoxygenating species (Scheme 66).[151] Other variations of this deoxygenation method are possible, including the thermolysis of ortho-azidostyrenes.[146]

R = Me, OMe, CF$_3$
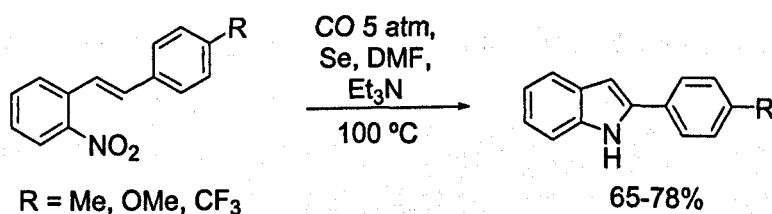
Scheme 66

Heating β,β-difluorostyrenes **192** containing *ortho*-tosylamino groups with sodium hydride in DMF promotes a normally disfavoured 5-*endo-trig* cyclisation, yielding 2-fluoroindoles **193** (Scheme 67).[152]
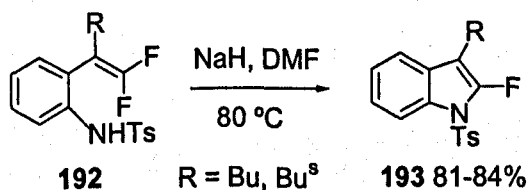
Scheme 67

The Watanabe indole synthesis involves the metal-catalysed oxidative cyclisations of anilines with glycols or ethanolamines.[146] Intramolecular versions of this reaction on *ortho*-aminophenethyl alcohols **194**, are known, with a recent example employing [Cp*IrCl$_2$]$_2$ as catalyst, giving a range of indoles **195** (Scheme 68).[153] Remarkably, the catalyst also worked for *ortho*-nitrophenethyl alcohol when propan-2-ol was used as the solvent giving indole (Scheme 68).[153] Propan-2-ol presumably acts as a hydride source enabling reduction of the nitro group. Both nitro reduction and alcohol oxidation are catalysed in one pot by 5 mol % of [Cp*IrCl$_2$]$_2$.

Scheme 68

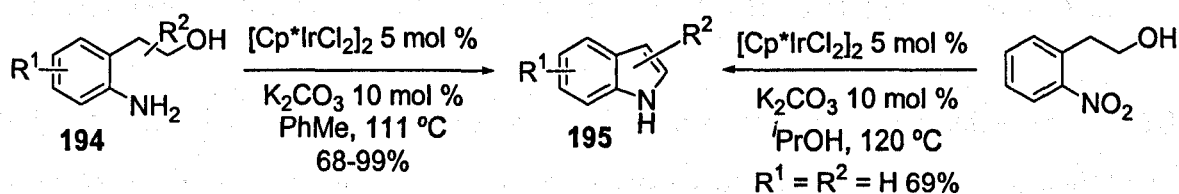Intramolecular Heck reactions have been employed for the cyclisations of *ortho*-allyl substituted anilines yielding indoles, representing an *N*-C$_2$ indole formation as shown (Scheme 69).[146] Heck reactions have also been used for the C$_3$-benzene ring indole (formation of the indole nucleus is attained *via* formation of a bond between the benzene ring and C$_3$ of the indole) forming reaction, which has been demonstrated on solid-phase and is discussed in section 5.3.
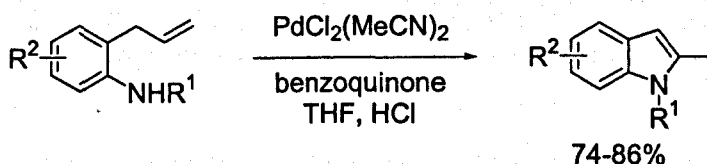
Scheme 69

Perhaps the most common method for indole synthesis involves Pd-catalysed Sonagashira cross-coupling reactions of *ortho*-halo anilines with alkynes. The *ortho*-ethynylanilines can then be cyclised to the indole, using a variety of reagents, including Cu(I) salts, Pd(II) species, NaAuCl$_4$•H$_2$O catalyst, alkoxides, and tetrabutylammonium fluoride.[154] Restrictions include the requirement for *N*-protection and cyclisation onto alkynes with electron-withdrawing groups often fail. A more recent method overcomes these restrictions, employing Cu(II) salts [Cu(OAc)$_2$ or Cu(OTf)$_2$ are optimal]. This has also been applied to tandem cyclisations, *via* the intramolecular displacement of a tosylate group, yielding 2,3-fused indole **196** (Scheme 70).[155]
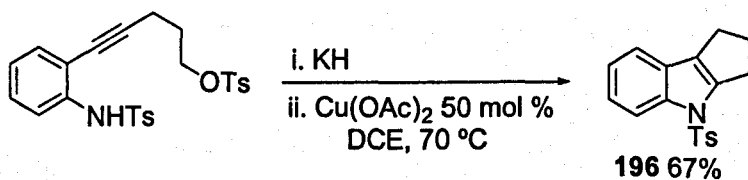
Scheme 70

Recently, the Sonagashira cross-coupling has been applied to indole synthesis employing triflates rather than *ortho*-halo anilines.[156] A range of triflates were synthesised from commercially available 2-aminophenols, allowing increased structural diversity in the cyclisation substrates. Triflates **197** underwent Pd(0)-Cu(I) coupling with terminal alkynes, employing triethylamine as base and *n*-Bu₄NI as a necessary additive (Scheme 71). It was proposed that iodide acts by replacing the triflate anion in the square-planar Pd(II) complex, or by forming a new pentacoordinated anionic palladium species, making the following transmetalation occur easily. Cyclisation to indoles **198** was accomplished with *t*-BuOK in *N*-methyl-2-pyrollidinone (NMP).
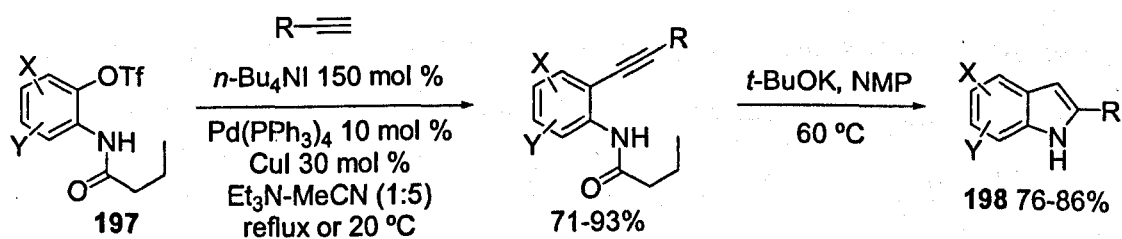
Scheme 71

The intramolecular Pd-coupling of *ortho*-halo anilines with alkynes, with subsequent annulation to the indole in one operation has been termed the Larock indole synthesis.[146] The method is very common and has also been applied to the synthesis of indoles on solid-phase and it is discussed further in section 5.3.

Similarly, vinyl triflates react with *ortho*-aminophenylacetylene in a palladium-catalysed reaction giving a range of 2-substituted indoles.[146] More recently (2-alkynyl)phenylisocyanates **199** have been shown to couple with allyl carbonates **200**, employing a Pd-Cu bimetallic catalyst to afford indoles **201** (Scheme 72).[157] The best copper additive was CuI, which may act as a Lewis acid and coordinate to the alkyne, activating it to promote insertion into a π -allyl palladium intermediate. However an alternative mechanism involving activation of the nitrogen nucleophile by copper, with alkyne activation a result of coordination to the π -allyl palladium species, cannot be ruled out.
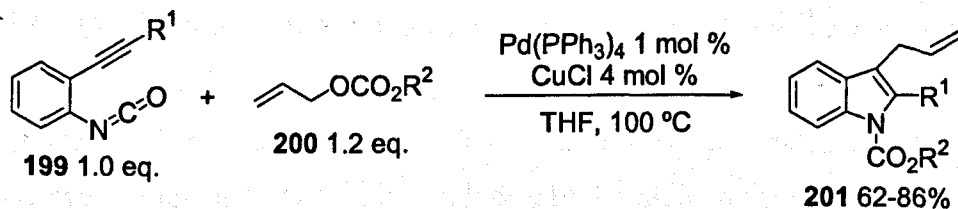
Scheme 72

A very recent, related indole construction, employs a reductive annulation of aromatic nitroso compounds **202** with alkynes (Scheme 73).[158] The unstable, highly polar intermediate, was tentatively assigned as the *N*-hydoxy indole **203**, which was then converted into indole **204** by hydrogenolysis. Complete regioselectivity was observed with terminal alkynes giving substituents at the indole 3-position. Disubstituted alkynes with one conjugating group gave 2,3-substituted indoles with the conjugating group at the indole 3-position. The transformation could also be carried out in one pot in the presence of [Cp*Ru(CO)₂]₂ and carbon monoxide but yields were lower. This transformation has the advantage that no functionality is required ortho to the nitro moiety in substrate **202**.
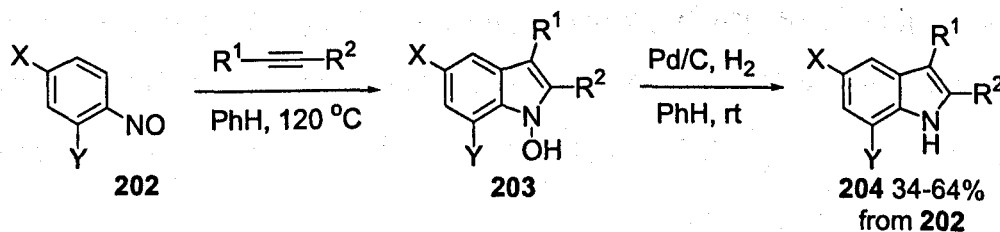
Scheme 73

Intramolecular alkylidenations of amides or imides have also been used to generate indoles. Such alkylidenations include Wittig reactions of benzyltriphenylphosphonium salts,[146] with an example having been carried out on solid-phase (section 5.3). A more recent example involved treating (2-aminobenzyl)triphenylphosphonium bromides **205** with acid anhydrides in the presence of base (Scheme 74).[159] Presumably (2-diacylaminobenzyl)triphenylphosphonium bromides **206** were the active intermediates undergoing cyclisation under basic conditions. Acid chlorides could be used, when 2,6-lutidine was employed as base but the yields were lower.
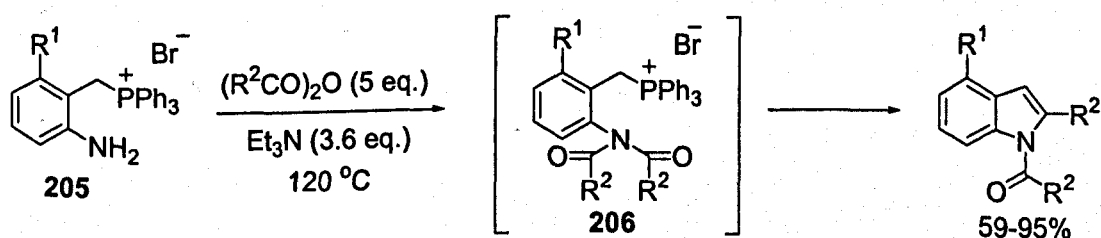
Scheme 74

A related C_1-C_2 (formation of the indole nucleus is attained *via* formation of a bond between C_1 and C_2 of the indole ring) synthetic strategy relied on the synthesis of *N*-H insertion product **207**, from 2-aminobenzophenone **208** and α-diazophosphonates **209**, with subsequent cyclisation in base to give indole **210** in high yield (Scheme 75).[160] This methodology was also employed in the synthesis of benzothiophenes and isocoumarins.

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
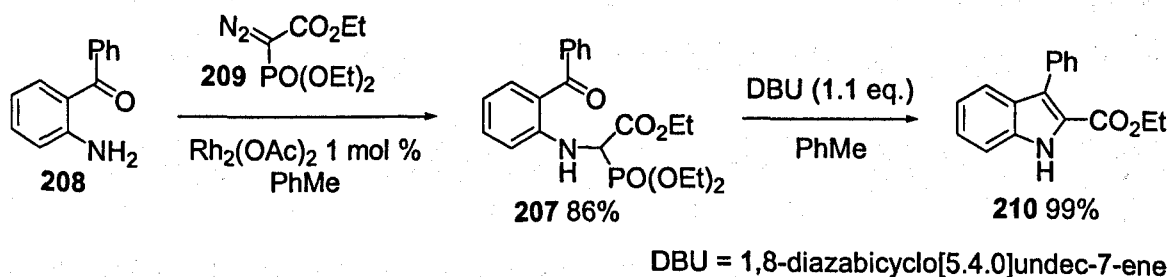
Scheme 75

A recent report described the cyclisation of an amine onto an intramolecular enol ether, under acidic conditions.[161] Treatment of amidine-protected diiodoamidine **211** with *i*-PrMgCl, transmetalation with CuCN·2LiCl, and allylation with 2-methoxyallyl bromide, gave enol ether **212**. Grignard formation with *i*-PrMgCl from aryl iodide **212**, transmetalation to give the corresponding arylcuprate, followed by allylation and then cyclisation in acid, gave indole **213** in high yield (Scheme 76).[161]
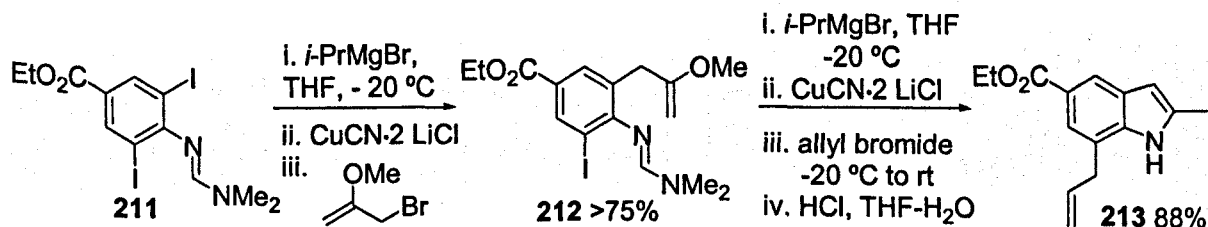
Scheme 76

5.3 Solid-Phase Indole Synthesis

Due to the huge range of biological activity exhibited by compounds containing the indole skeleton, the search for new and/ or improved methodologies for their synthesis continues.[162] In particular, the adaptation of syntheses (both modern and classical) to solid-phase (S-P) is important for drug discovery through automated high speed parallel syntheses. Numerous useful approaches to the construction of the indole core on solid phase have been reported.[163]

The Fischer indole synthesis has been adapted to solid phase.[164] A polystyrene-bound ketone **214** reacted with phenylhydrazine hydrochloride, under Lewis acid conditions to give hydrazone **215** which cyclised *in situ* (Scheme 77). Nucleophilic cleavage from the resin with MeOH in triethylamine gave the 2-phenyl indole **216**. However, the synthesis is not traceless, leaving an ester at the site were the resin was attached, and the yields and purity were variable. Employing different hydrazine hydrochlorides, allows the only point of diversity, although poor results were obtained when electron-deficient hydrazine hydrochlorides were used. Yang used a similar approach for the synthesis of a library of somatostatin agonists.[165]

i. PhNHNH₂, HCl, ZnCl, AcOH, 70 °C
ii. 9:1 MeOH:Et₃N, 50 °C

= Polystyrene
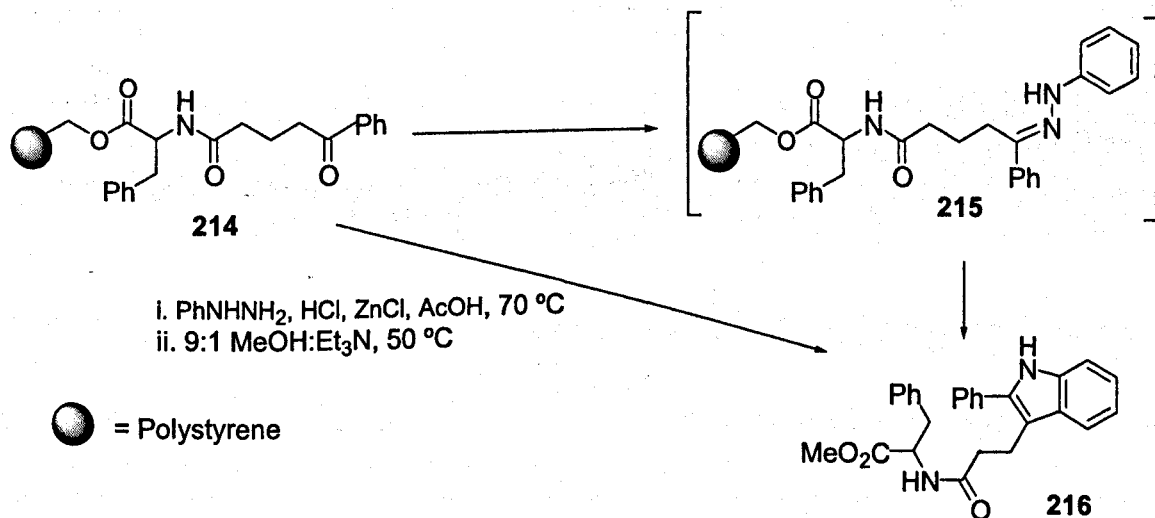
Scheme 77

A recent concise solid-phase synthesise of *N*-hydroxy indoles involving tin chloride reduction of aromatic nitro compounds and subsequent dehydration of ortho-ketones has been reported.[166] A Wang resin-bound ester was employed as the linker, and upon cleavage, an extraneous carboxyl group remained at the indole 6-position.

The Nenitzescu indole synthesis has been applied to solid-phase with the synthesis of 5-hydroxyindole-3-carboxamides **217** (Scheme 78).[167] ArgoPore®-Rink-NH-Fmoc resin **218** was deprotected and then treated with diketene to introduce the dicarbonyl species giving resin-bound acetoacetamide **219**. Treatment with a primary amine, in the presence of trimethylorthoformate as dehydrating agent, gave resin-bound enaminamides **220**. Subsequent treatment with benzoquinones at room temperature for 1-2 days gave the resin-bound indoles **221** which were then cleaved in acid. A wide range of primary amines were employed but many resulted in low yields. Indoles produced in this way have a primary amide at the site where the resin was attached, so the method is not traceless. Complete regioselectivity was observed, with monosubstituted benzoquinones giving substitution at C-6 of the indole and 2,5-disubstituted benzoquinones giving 4,7-disubstituted indoles, although 2,3-disubstituted and 2,6-disubstituted benzoquinones were unsuccessful.
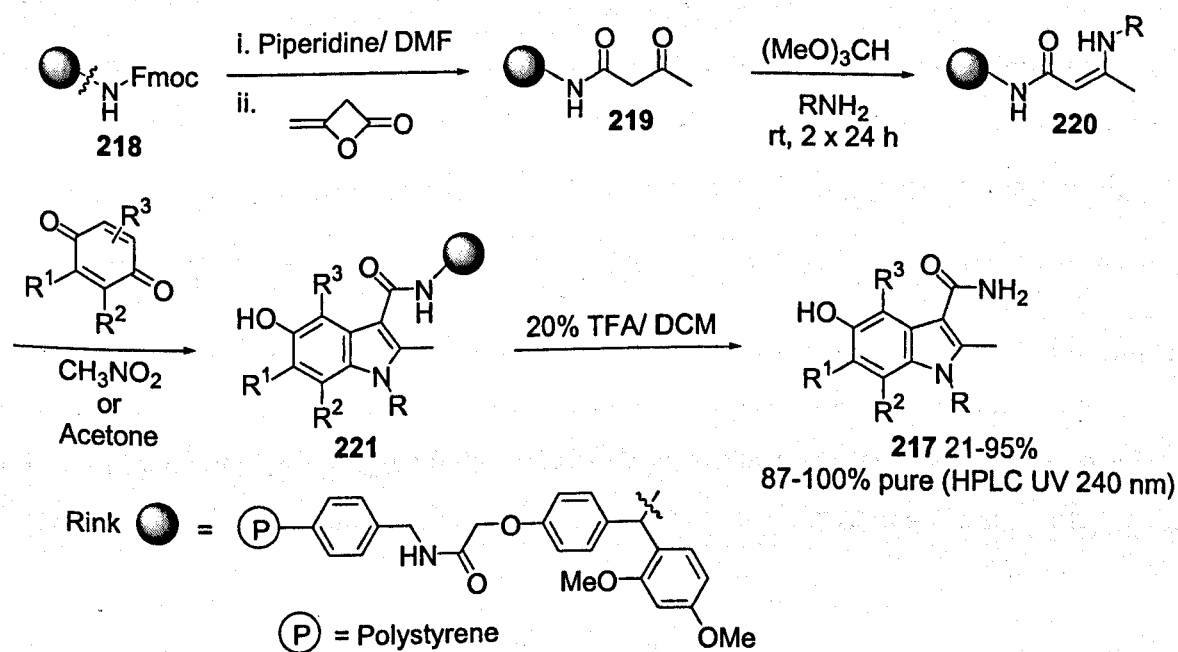
Scheme 78

A recent palladium-catalysed tandem C,N-arylation of resin-bound enamines has been reported.[168] In a one pot procedure, resin-bound N-acetyl dehydroalanine **222** and 1,2-dibromo aniline undergo a Heck coupling followed by an amination reaction to give the corresponding resin-bound indole (Scheme 79). Cleavage from the resin by transesterification, yielded indolecarboxylate **223** in good yield, upon aqueous work-up and column chromatography. The ester moiety marks the site of resin-attachment.
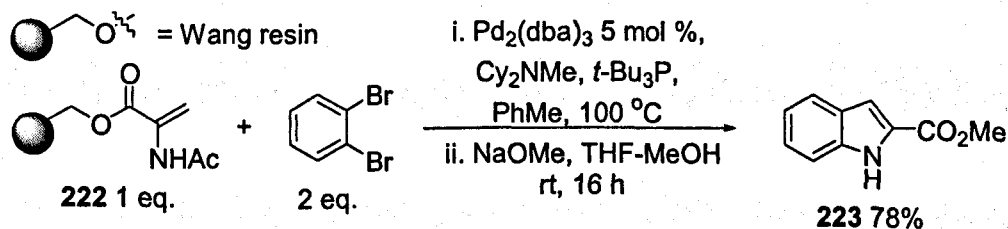
Scheme 79

Palladium-catalysed cyclisation of α-anilino-α,β-unsaturated resin-bound esters containing a halogen *ortho* to the aniline to give polymer-bound 2-indolecarboxylates, has been reported recently.[169] Similarly, Heck-type cyclisations of resin-bound N-allyl-substituted *ortho*-haloanilines for the construction of the indole nucleus have been reported.[170, 171] Zhang *et. al.*[171] utilised Rink amide resin **224**, which was coupled with γ–bromocrotonic acid, aminated with a range of *ortho*-iodoanilines, and then alkylated with benzyl bromides to give resin-bound cyclisation precursors **225** (Scheme 80). A 5-*exo*-trig Heck cyclisation, followed by resin-cleavage gave indoles **226** in high yields and reasonable purity. Again, a 3-methylcarboxamide group is left at the former site of attachment to solid-support.

Scheme 80

53
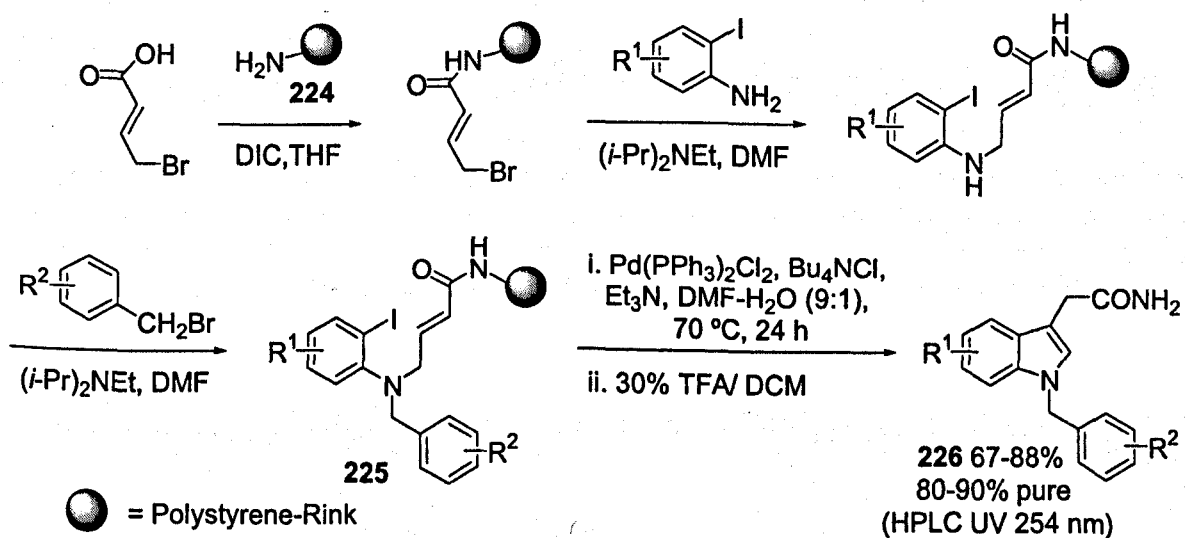
The most common method for the solid-phase synthesis of indoles involves the palladium-catalysed heteroannulation of internal alkynes, which in turn are prepared from *ortho*-haloanilines. A synthesis of 6-indole carboxylic acids utilised TentaGel-S® resin-bound esters containing an *ortho*-iodo *N*-acetoxy-anilines and coupling/cyclisation with a terminal alkyne.[172] Trisubstituted 6-indole carboxylic acids were prepared using a similar approach employing Wang resin-bound esters containing *ortho*-iodoanilines.[173] Zhang reported a similar approach, employing Rink amide AM® resin-bound amides **227** containing *ortho*-iodoanilines to give 5-carboxamide indoles **228** (Scheme 81).[162, 174] 2,3-Disubstituted indoles **228** had the more sterically demanding group at the 2-position, due to insertion of the intermediate arylpalladium species into the less hindered end of the alkyne. Using the same linker but employing an *N*-(butyn-1-yl)acetamide as the alkyne under microwave assistance, allowed the synthesis of 5-carboxamido-*N*-acetyltryptamine.[175]
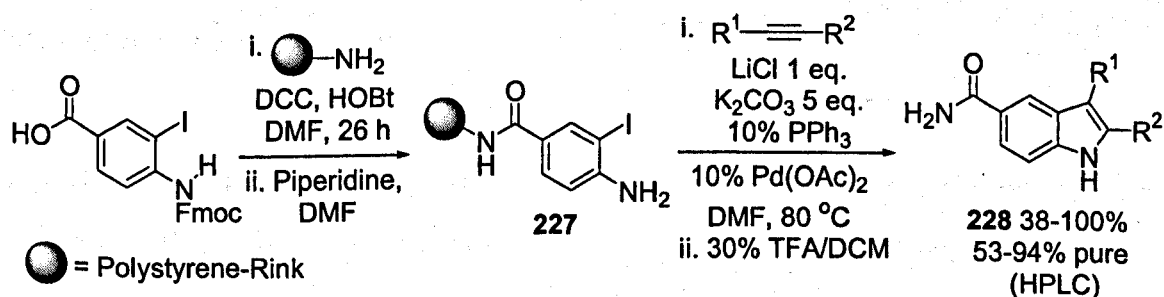
Scheme 81

All the methods discussed above, involve cleavage strategies which leave polar substituents at the site where the resin was attached, and so are of limited use in the synthesis of libraries for drug discovery, as such groups are known to affect structure activity relationships.[176]

Therefore traceless solid-phase methodologies are required for the synthesis of indoles, where the former site of resin-attachment is not apparent in the final cleaved product.[117] A number of such traceless indole syntheses have appeared, employing the heteroannulation of internal alkynes, coupled to *ortho*-haloanilines which are immobilised *via* an *N*-aniline linker. The first approach involved loading 2-iodoaniline onto Ellman's THP resin **229** with pyridinium tosylate (PPTS) to give aminal linked aryl iodide **230** (Scheme 82).[177] Palladium-catalysed cross-coupling/cyclisation with alkynes in the presence of tetramethylguanidine (TMG) base gave resin-bound indoles **231**. Unfortunately, the coupling reaction must be repeated in order to drive it to completion. Coupling is generally regioselective with bulky substituents ending up at the 2-position of the indole. Problems arise when the opposite regiochemistry is required, and yields are reduced when alkynes with sterically demanding substituents are used. Cleavage from the resin gave 2,3-disubstituted indoles **232** or 3-substituted indoles **233** upon protodesilylation, although details of purity were not given.
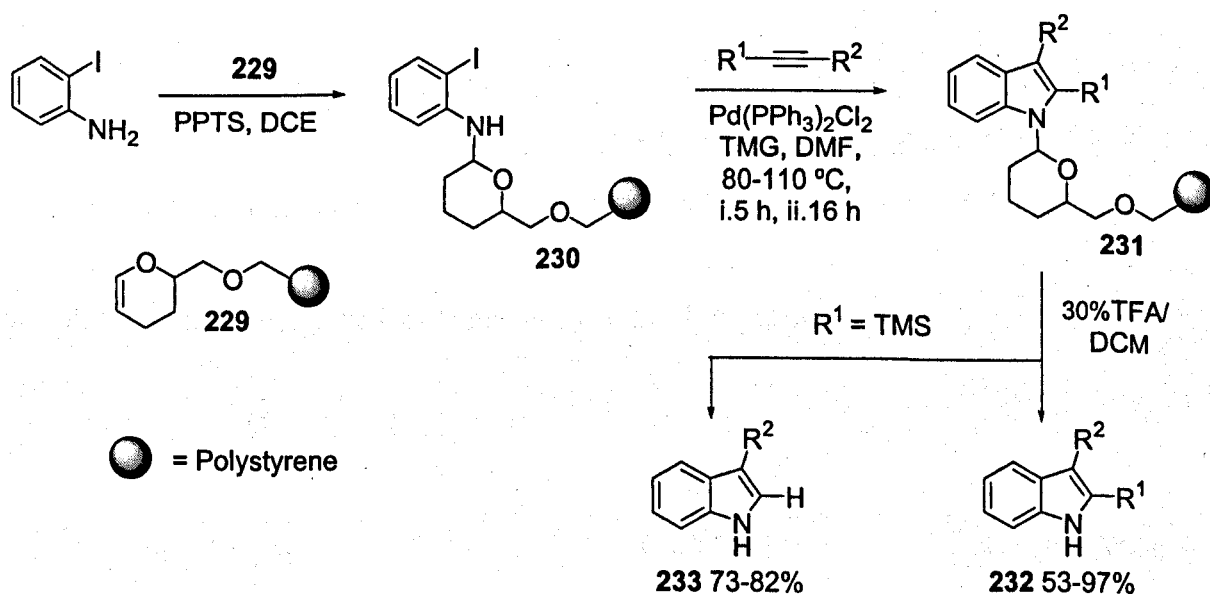
Scheme 82

Gmeiner has reported a similar linkage strategy,[178] which was used to immobilise 5-cyano indoles. Upon further functionalisation by a Mannich reaction on resin, and by resin-cleavage a range of highly selective Dopamine D$_4$ receptor partial agonists were synthesised.[179]

Zhang reported a similar linkage strategy, employing an *N*-sulfonyl linker, which can be cleaved using tetrabutylammonium flouride in a traceless fashion. 2-Substituted indoles[180] and 3-substituted 2-arylindoles[181] were prepared in this way, *via* successive palladium-catalysed reactions. The same linker was employed in a recent synthesis of 2,3,5-trisubstituted indoles.[182] 4-Bromo-2-iodoaniline was loaded onto the commercially available PS-TsCl (polystyrene sulfonyl chloride) resin **234** giving resin-bound aniline **235** (Scheme 83). A selective coupling reaction of a range of terminal alkynes with the 2-iodo moiety of **235** was carried out in the presence of the 4-bromo group, followed by intramolecular cyclisation to give resin-bound indoles **236**. Subsequent acylation at the 3-position employing aluminium trichloride gave 3-acyl indoles **237**. Further functionalisation at the 5-position, *via* either a Sonagashira coupling with terminal alkynes, or a Suzuki coupling with aryl boronic acids were successful. Cleavage from the resin was then achieved with base, and acidification gave the corresponding indoles **238a**. By carrying out the cleavage in the presence of methyl iodide, *N*-methyl indoles **238b** were prepared. Other alkylations were unsuccessful. The methodology is restricted to aryl, acyl and alkynyl substituents at the 2-, 3-, and 5-positions, respectively. Also, it does not allow substitution at either the 4-, 6-, or 7-positions and gives only *N*-methylation. Despite these limitations, it is amongst the most diversity-based, traceless, solid-phase, indole synthesis reported to date, and as it employs IRORI technology it seems ideal for automation. Schultz recently utilised the same linkage strategy for preparing *N*,*N*-dimethyltryptamines on solid-phase, although the indole nucleus was not formed on resin.[183]

Scheme 83

56
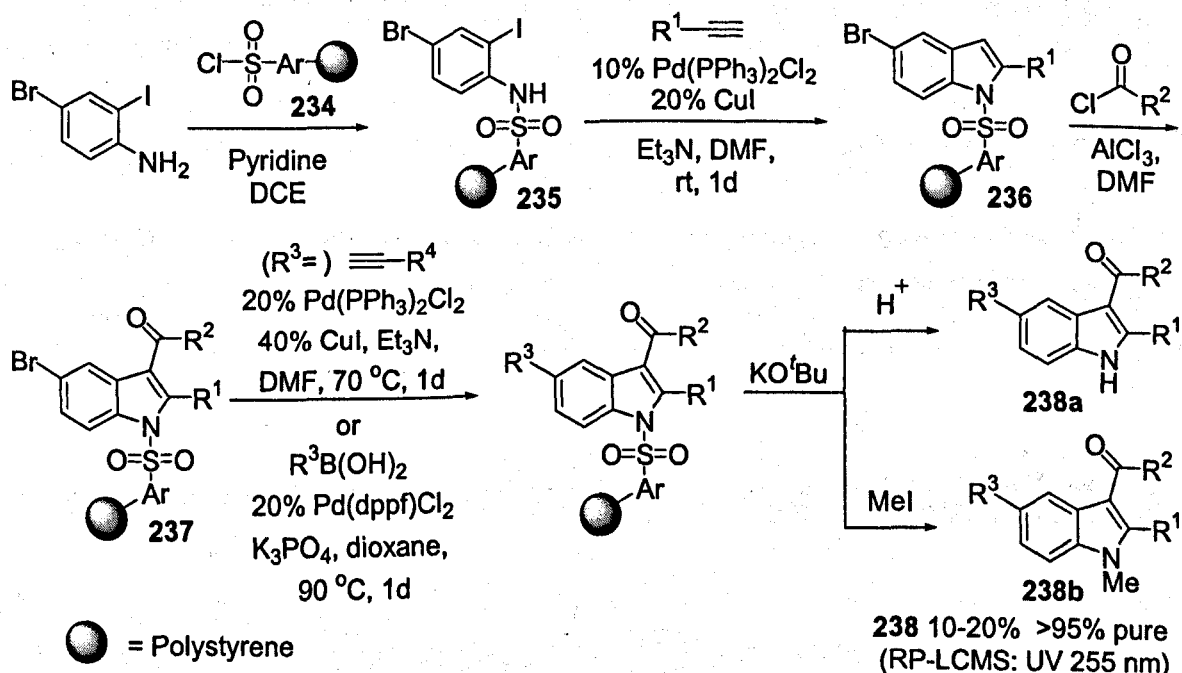
An intramolecular Wittig reaction, of a polymer-bound phosphonium salt, has been applied to traceless solid-phase indole synthesis.[128] Phosphonium salt **239** was easily prepared from resin-bound triphenylphosphine **240** (Scheme 84). Reduction of the nitro group, followed by regeneration of the bromine counter ion, gave polymer-bound aniline **241**. Acylation gave amide **242**, which underwent an intramolecular Wittig reaction, under strictly anhydrous conditions, generating indole **243**. The phosphine oxide by-products stay attached to the resin, so the method is traceless and also ensures high purity in the final products. However, only one indole was made in this way.
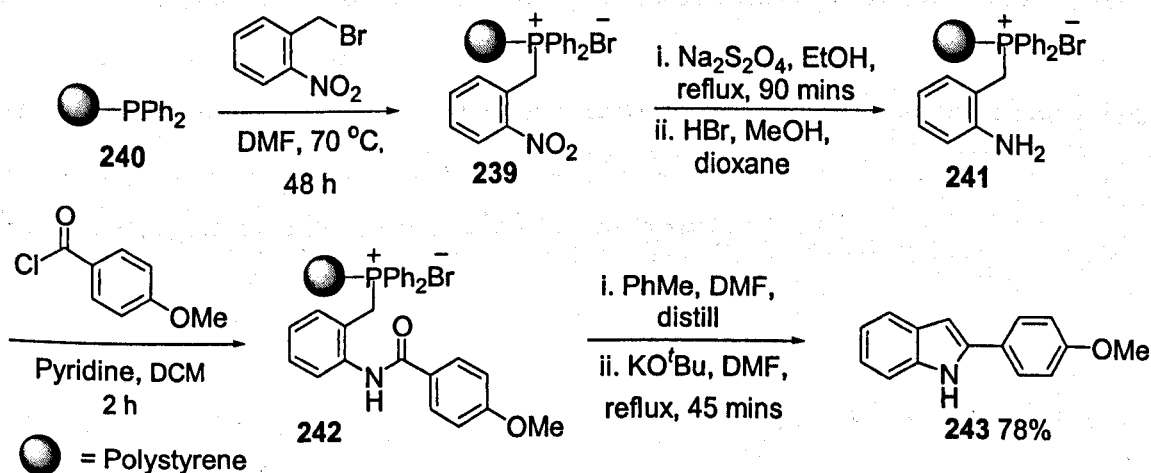
Scheme 84

More recently, a modified Madelung synthesis of indoles has been carried out on solid-phase.[184] Aniline **244** was loaded onto Bal-resin **245**, and the resulting imine was reduced to give secondary amine **246** (Scheme 85). Acylation was followed by an intramolecular cyclisation-dehydration step to give the resin-bound indole **247**, which was cleaved from the resin under strongly acidic conditions to give the 3-cyano indoles **248**.
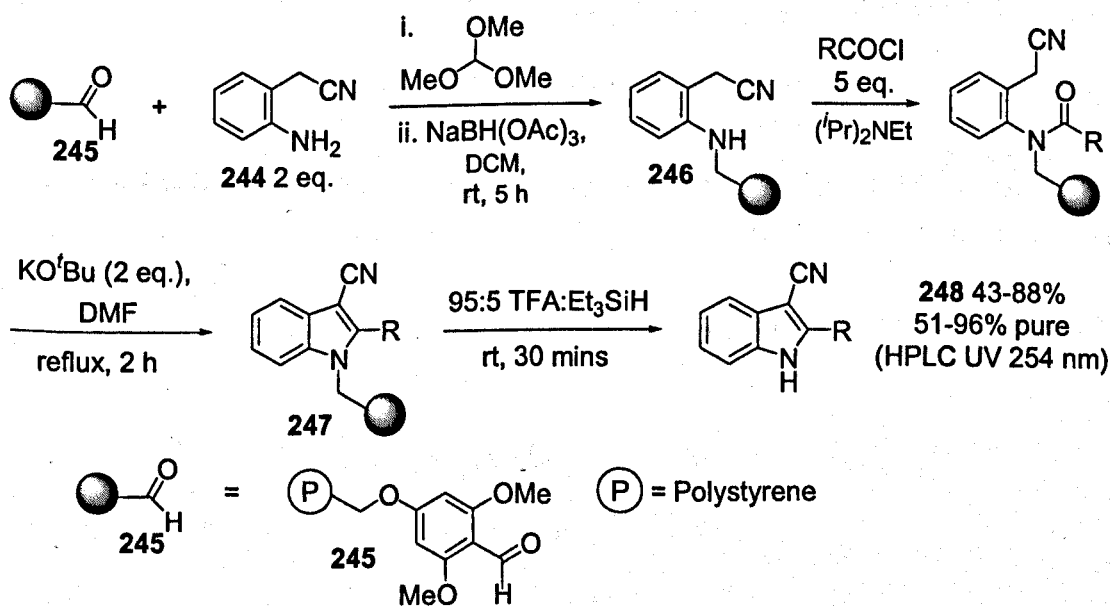
Scheme 85

Chapter 6 - Quinolines

6.1 Activity

The quinoline nucleus plays an important role as an intermediate for the design of many pharmacologically active compounds.[185] An example being chloroquine **249** (Figure 11), which has been by far the most successful antimalarial, being cheap, highly efficacious, and of relatively low toxicity. However, due to the advance of multidrug resistance, chloroquine and other available drugs are becoming less and less effective. Therefore, the search for successful alternatives, including analogues of current drugs, continues. A recent study found that having a moderately lipophilic group at the 7-position, was optimal against a chloroquine resistant strain of *Plasmodium falciparum*.[186] Another study found that some short chain alkyl amine derivatives [e.g. **250** (Figure 11)] were more potent than chloroquine, against the same strain of *Plasmodium falciparum*.[187]

Chloroquine **249**   **250**

Figure 11
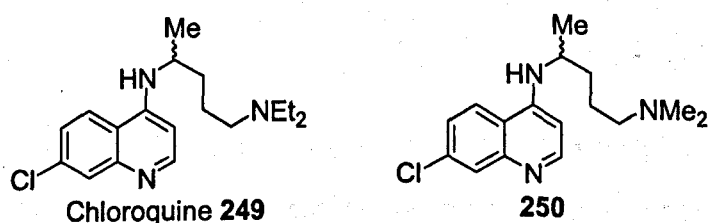
A range of 2-phenyl-4-diaminoquinolines **251** (Figure 12) have shown potent immunostimulant activity in a mouse protection assay.[188]
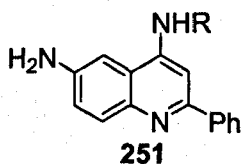

251

Figure 12

Quinoline **252** (Figure 13), one of a range of quinoline alkaloids isolated from the bark of *Galipea officinalis*, showed activity against a range of strains of mycobacterium tuberculosis.[189]
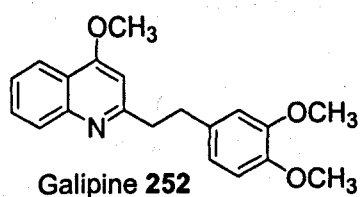

Galipine **252**

Figure 13

6.2 Quinoline Synthesis

There are numerous examples of syntheses of the quinoline nucleus.[185] Indeed so many only the most general of the classical approaches and a variety of very recent methods will be discussed here.

The Combes synthesis involves the condensation of a 1,3-dicarbonyl compound (e.g. **253**) with an arylamine (e.g. **254**) to give the β-amino-enone (e.g. **255**). Cyclisation by electrophilic substitution in acid on β-amino-enone **255**, followed by dehydration affords quinoline **256** (Scheme 86).[190]
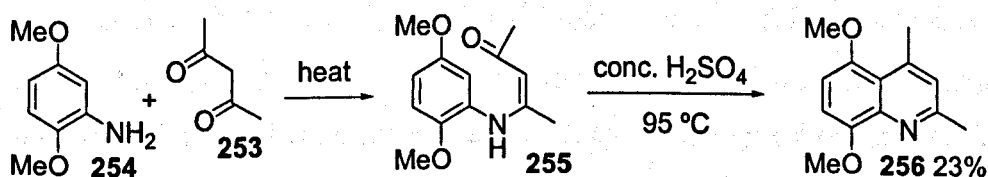
Scheme 86

The Skraup quinoline synthesis utilises an arylamine (e.g. **257**) and an α,β-unsaturated carbonyl compound (e.g. **258**) in the presence of an oxidising agent (Scheme 87).[191] The conjugate addition product (e.g. **259**) cyclises to the dihydroquinoline, which is oxidised *in situ* to give the quinoline (Scheme 87). When using *meta*-substituted aryl amines, electron-donating and halide substituents give mainly 7-substituted quinolines, whereas electron-withdrawing substituents give predominantly the 5-substituted quinolines.
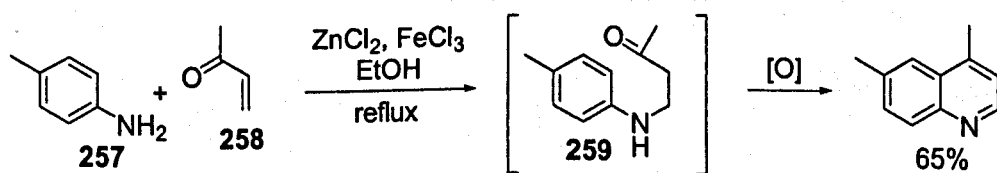
Scheme 87

The analogous Doebner-Miller reaction employs α,β-unsaturated aldehydes although aldehyde polymerisation is commonly a problem. It was recently reported that utilising a bi-phasic system, yields improved considerably and the reaction proceeded smoothly in the absence of oxidants (Scheme 88).[192]
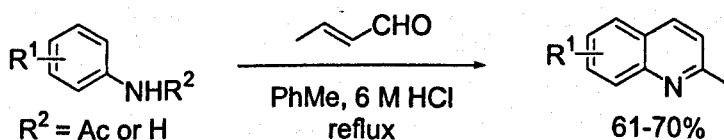
Scheme 88

The Friedländer synthesis involves the condensation of *ortho*-acylarylamines (e.g. **260**) with a ketone (e.g. **261**) or an aldehyde (containing an α–methylene group), to give quinolines (Scheme 89). The condensation can be carried out employing acid or base catalysis and the orientation of the condensation depends on the regioselectivity in formation of the enol or enolate, respectively.[193]

Scheme 89

A recent, ruthenium-catalysed modified Friedländer reaction of 2-aminobenzyl alcohol with ketones **262** has been reported.[194] Methyl ketones with one enolisable substituent gave 2-substituted quinolines **263** (Scheme 90) althou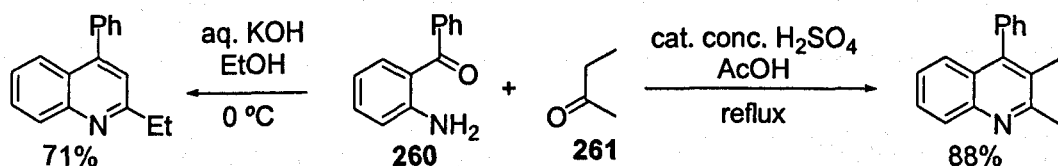gh cyclic ketones were also converted to the corresponding 2,3-fused quinolines. The reaction is thought to proceed *via* oxidation of the alcohol to the aldehyde, followed by cross aldol reaction with the ketone.[194] The resulting α,β-unsaturated ketone is then proposed to be hydrogenated to the product by a dihydroruthenium (RuH_2), generated by the initial oxidation of the starting alcohol. Another recent variation employs the microwave-assisted, one pot reaction of amines and aldehydes forming enamines, which then react with 2-azidobenzophenones affording 2-aminoquinolines.[195]
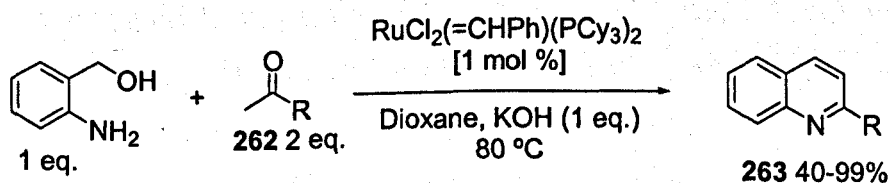
Scheme 90

Recently, cyclisation of Baylis-Hillman adducts (of 2-nitrobenzaldehydes) **264** have been applied to quinoline synthesis (Scheme 91). Formation of 3-acetoxymethyl-2-alkylquinolines **265** occurred under reflux with Fe/AcOH, and could then be converted into the corresponding 3-hydroxymethyl-2-alkylquinolines **266** by hydrolysis.[196]
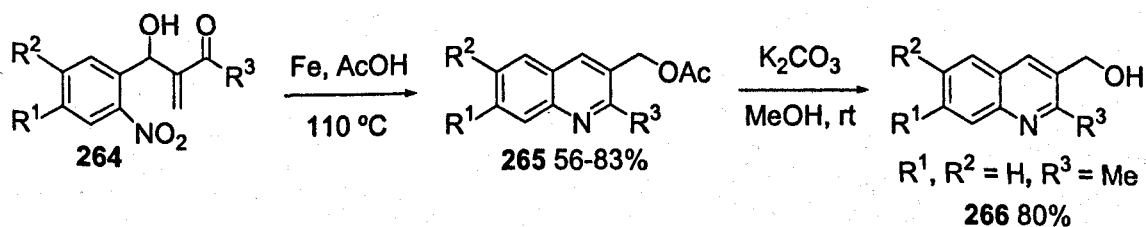
Scheme 91

Baylis-Hillman acetates (from benzaldehydes) **267** have also been employed in quinoline synthesis (Scheme 92). Adducts **267** undergo rearrangement to tosylamide derivatives **268**, and in the presence of iodobenzene diacetate and iodine were converted into a mixture of *N*-tosyl dihydroquinolines **269** and quinolines **270**. The mixture containing dihydroquinolines **269**, could then be quantitatively converted into quinolines **270** *via* the elimination of *p*-toluenesulphinic acid. The cyclisation reaction is thought to proceed *via* an *N*-tosylamidyl radical, which cyclises to give an aryl stabilised C-centred radical, followed by oxidation to the dihydroquinolines **269**.[197]
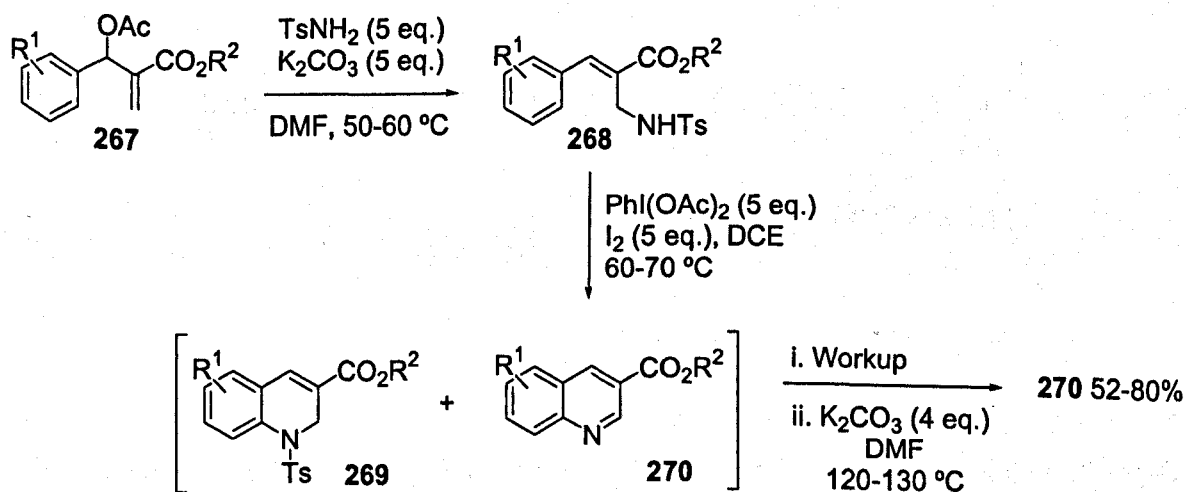
Scheme 92

Reductive cyclisation of nitroarenes with trialkylamines, catalysed by ruthenium complexes, yielding quinolines, has been reported recently.[194] $RuCl_2(PPh_3)_3$ was shown to be the optimal catalyst, for the reduction of nitrobenzene with tributylamine employing $SnCl_2 \cdot 2H_2O$ as reductant, to give 3-ethyl-2-propylquinoline (Scheme 93).[194] Similarly, a range of nitroarenes reacted with other trialkylamines, to give the corresponding quinolines. The mechanism for this remarkable transformation is not yet entirely clear.
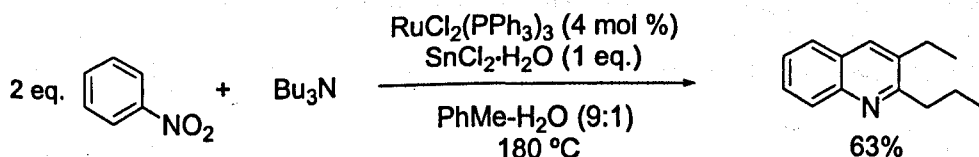
Scheme 93

A recent quinoline synthesis involves the palladium-catalysed hydroarylation of alkynes, with aryl iodides, in the room temperature ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [(bmim)BF4].[198] A range of Pd(0) catalysts were tested but the [(*E*,*E*,*E*,)-1,6,11-tris(*p*-toluenesulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-triene]Pd(0) complex [Pd(0)L] proved to be optimal. A range of aryl iodides, were coupled with 3,3-di-1-phenyl-1-propyne **271** under the conditions shown, to give a range of quinolines as a mixture of isomers **272** and **273** (Scheme 94).[198]
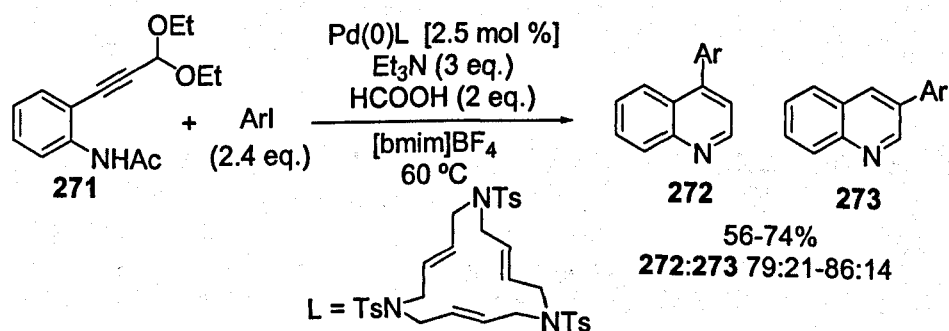
Scheme 94

Rh(I) complexes were recently reported to catalyse the coupling cyclisation of *N*-aryl trifluoroacetimidoyl chlorides **274** with symmetrical alkynes **275** to afford 2-trifluoromethylated quinolines **276** (Scheme 95).[199] A combination of [RhCl(cod)]2 and either of the Ph2P(CH2)2PPh2 (dppe) **277** or P(2-furyl)3 (TFP) **278** phosphine ligands, with triethylamine in toluene under reflux were successful (Scheme 95). Using unsymmetrical alkynes results in quinolines being formed regioselectively, and bulky substituents are placed at the quinoline 4-position but electron-withdrawing groups at the 3-position. Terminal alkynes give 4-substituted quinolines, or 3-substituted quinolines when the substituent is electron-withdrawing.[199]
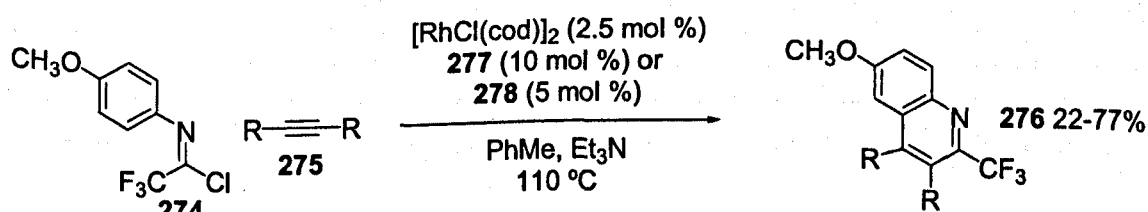
Scheme 95

N-Allyl-*N*-protected-*ortho*-aminostyrenes **279** have recently been shown to undergo ene-ene metathesis to give 1,2-dihydroquinolines **280**, which are then converted into quinoline **281** quantitatively by silica gel chromatography and air oxidation (Scheme 96).[200] Although Grubbs' first generation catalyst was successful with the Boc protecting group (PG), it gave lower yields of metathesis product, and also failed when utilising acetyl as PG. However, Grubbs' second generation catalyst **282**, gave excellent yields.[200]

PG = Boc 97%
PG = Ac 98%
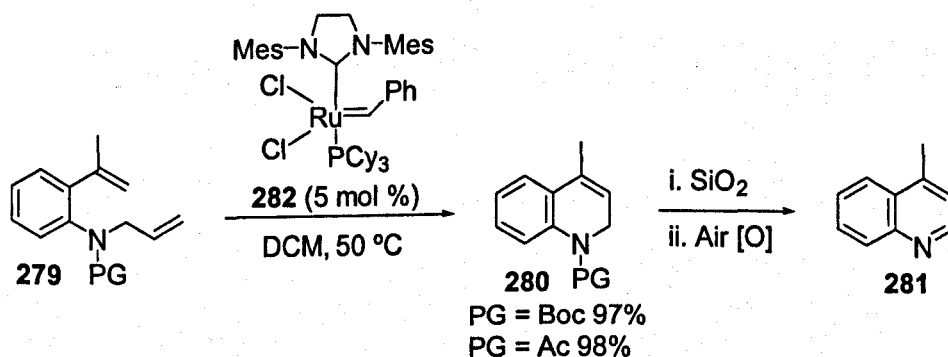
Scheme 96

Symmetrical zirconacyclopentadienes **282** couple with 2-bromo-3-iodopyridine **283** in the presence of CuCl and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), to afford quinolines **284** in moderate to good yields (Scheme 97).[201] Unsymmetrical zirconacyclopentadienes gave mixtures of regioisomers. This methodology was also employed for the synthesis of isoquinolines and anthracenes.[201]
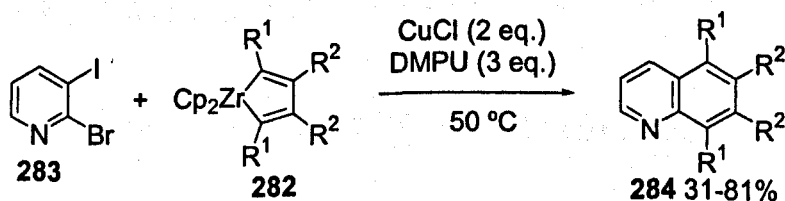
Scheme 97

To our knowledge, there are no reported syntheses of quinolines on solid-phase to date.

Results and Discussion

Chapter 7 - Synthesis of Alkenylboronates

7.1 Synthesis and Takeda reactions of boronic esters

As discussed in section 1.1, we aimed to synthesise thioacetals **2**, which under Takeda conditions would alkylidenate a range of esters or thioesters **3** to give β-hetero-substituted alkenylboronates **4** (Scheme 98).
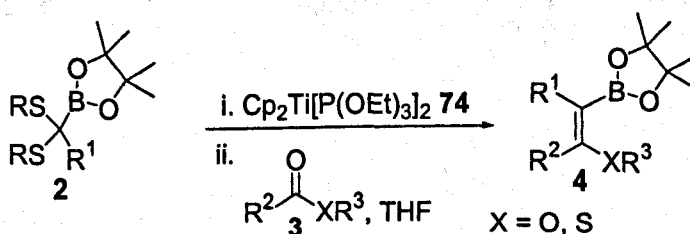
Scheme 98

Before attempting the synthesis/reactions of thioacetals **2**, it was necessary to repeat a standard Takeda alkylidenation in order to establish conditions that would be successful in my hands. Therefore, thioacetal **285** was synthesised by a literature procedure[202] and was used to convert cyclohexanone into alkene **286** in reasonable yield (Scheme 99). Cyclohexanone was chosen initially, as it is more electrophilic than an ester or thioester and gives a more stable product. It is also symmetrical so there is no issue of geometrical isomers. The moderate yield is most likely a result of the difficulty in isolation of, as opposed to the conversion to, alkene **286**.
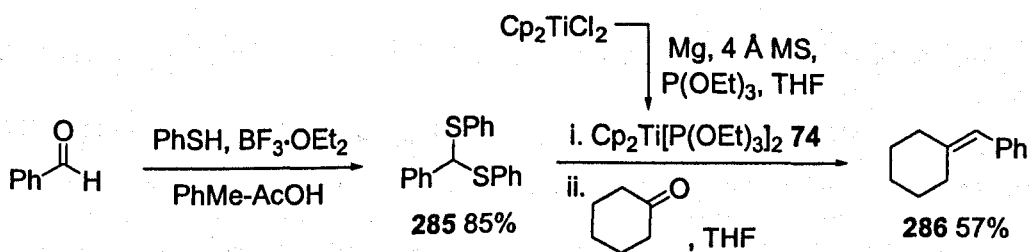
Scheme 99

We then turned our attention to the synthesis of boronates **287** and **288** from bis(phenylthio)methane and 1,3-dithiane, respectively (Scheme 100). A literature procedure was employed,[203] and boronic esters **287**[203] and **288** were obtained in moderate yields and purity upon distillation/low temperature crystallisation. However, thioacetals **287** and **288** failed to yield alkenylboronate **289**, when employed separately under standard Takeda reactions (Scheme 100). The crude ^{1}H NMR spectrum upon work-up, filtration

through celite, and removal of triethyl phosphite by Kugelrohr distillation, showed no evidence of signals corresponding to either an alkene proton or the methyl groups of the pinacol moiety. It should be noted that hydrolysis of the boronic ester during work-up of the Takeda reaction, to generate the corresponding boronic acid cannot be ruled out. However, signifigant amounts of cyclohexanone were observed in the crude ^{1}H NMR spectrum [δ 2.64 (4H, t, J 5.8, CH_2CO)], suggesting that the Takeda reaction was not very successful.
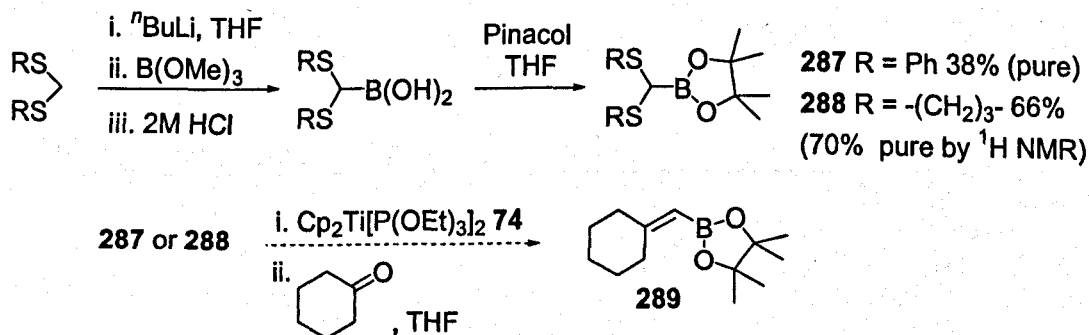
Scheme 100

In order to overcome the problems associated with product isolation, we attempted to alkylidenate Wang resin-bound ester **290** (Section 8.2), with the titanium alkylidene derived from thioacetal **287**. However, a complex mixture was obtained after the Takeda reaction, washing of the resin, and subjecting to standard acid conditions for cleavage from the resin. We concluded that the reaction was not very successful as the ^{1}H NMR spectrum confirmed that this mixture contained mostly dihydrocinnamic acid and triethyl phosphite with some other impurities. The presence of ketone **291**, or the corresponding boronic acid, in this mixture cannot be ruled out, but the mass recovery for the reaction was very low.
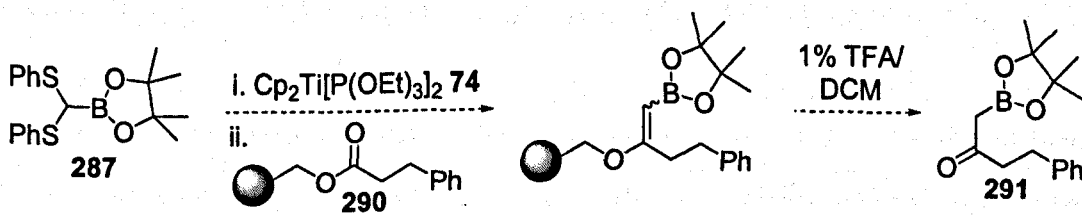
Scheme 101

The failure of thioacetals **287** and **288** in the above Takeda reactions may not be surprising as the Takeda procedure is not particularly useful for methylenation (see section 2.2). Boronates **287** and **288** may suffer similar problems to methylene thioacetals in either the formation or the reactivity of the resulting titanium carbene. Therefore, we attempted to synthesise the corresponding thioacetals with a substituent α to the boron atom.

7.2 Lithiation/Alkylation of thioacetals

7.2.1 Generation and reactivity of bis(phenylthio)phenylmethyllithium

Initially, we attempted to synthesise boronate **292** from thioacetal **285** (Scheme 102), following Mendoza and Mattesson's procedure,[203] as above. We hoped that benzylic thioacetal **292** would be more susceptible to reduction to give a titanium alkylidene, and so would allow the synthesis of α-phenyl-β-hetero-vinylboronates **293** (Scheme 102).
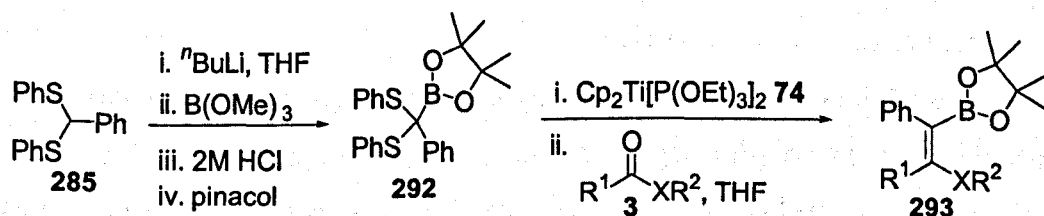
Scheme 102

In order to synthesise boronic ester **292**, we needed to generate bis(phenylthio)phenylmethyllithium, and then react it with a boron electrophile (Scheme 103).
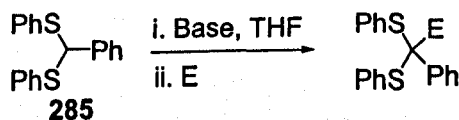
Scheme 103

Following Mendoza and Mattesson's procedure[203] (Method A, Table 1), we found that considerable carbon-sulfur bond cleavage occurred, confirmed by the detection of 1-(phenylthio)phenylmethane[204] and 1-(phenylthio)butane[205] in the crude ^{1}H NMR spectrum (see experimental). Starting material (SM) was always isolated and an almost identical result was obtained with the use of *N, N, N', N'*- tetramethylethylenediamine (TMEDA)-butyllithium complex under similar conditions (Method B).[206] Using the less nucleophilic base, lithium di-isopropylamide [(LDA), Method C], only starting material was recovered. Employing LDA but quenching with D$_2$O gave 40% conversion to the deuterated product (Method D). Slight variations of temperature and reaction times gave similar results. Finally, the generation of the more "naked" potassium ion, by means of the "superbasic Schlosser's base" (Method E) also proved unsuccessful.[207]

Table 1

METHOD	BASE	ELECTROPHILE (E)	RESULTS
A	*n*-BuLi	B(OMe)$_3$	SM + C-S cleavage (38%)
B	*n*-BuLi-TMEDA	B(OMe)$_3$	SM + C-S cleavage (40%)
C	LDA	B(OMe)$_3$	SM
D	LDA	D$_2$O	40% conversion
E	KO^{t}Bu- *n*-BuLi	B(OMe)$_3$	SM

Deprotonation and alkylation of diphenyldithioacetals is difficult. This is particularly the case for bis(phenylthio)phenylmethane **285** due to steric hindrance and the presence of the extra anion stabilising phenyl group.[206, 208] Lithiation generally results in a yellow/orange anion which reacts with benzoyl chloride but not aldehydes and ketones.[206] Attack of butyl anion on a sulfur atom in thioacetal **285** to yield anion **294** could explain the formation of both the observed side products (Scheme 104).
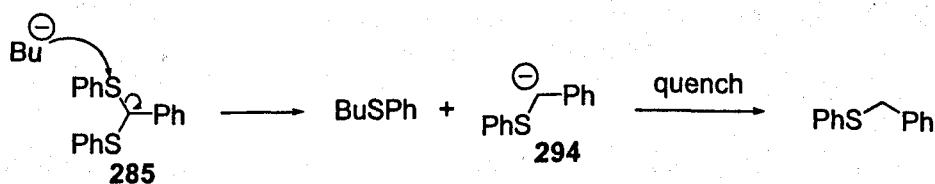
Scheme 104

Interestingly, a recent report by Yu and Jin[209] stated that a 1,1-bis(phenylthio)alkylpotassium undergoes rearrangement when it is treated with alkyl halides, but the anion reacts in high yield with D$_2$O. They propose that elimination of phenylthiolate to form a carbene is accelerated by addition of certain electrophiles.[209] In the case of bis(phenylthio)phenylmethyllithium **295**, elimination of phenylthiolate could form carbene **296**, which could further react and/or be quenched in the work-up (Scheme 105). This suggests that the problems could arise both in the preparation of the carbanion, and in reacting the carbanion with electrophiles (E).
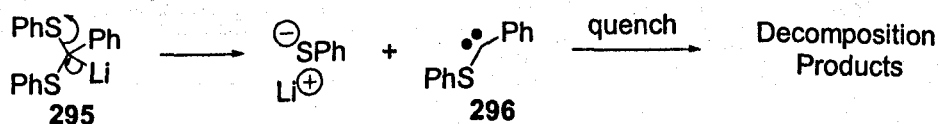
Scheme 105

7.2.2 Generation and reactivity of 2-Lithio-2-phenyl-1,3-dithiane

We reasoned that dithianes would be less susceptible to nucleophilic attack at sulfur. Therefore, 2-phenyl-1,3-dithiane **297** was synthesised from benzaldehyde as before, and then I attempted to generate 2-lithio-2-phenyl-1,3-dithiane and react it, initially with boron electrophiles, and later with a range of other electrophiles to probe the reactivity of the lithium salt (Scheme 106).
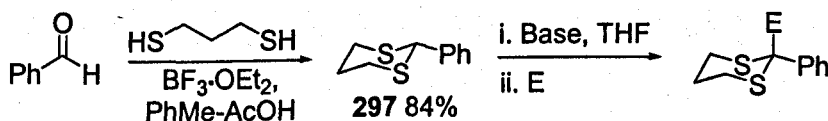
Scheme 106

Lithiation of 2-phenyl-1,3-dithiane **297** by a standard procedure (see experimental),[205] and quenching with trimethylborate (Method A, Table 2) gave considerable amounts of starting material and approximately 40% conversion to an unknown undesired product(s). Quenching with D_2O (Method B, Table 2) gave similar results, but quenching with benzaldehyde (Method C, Table 2) gave complete conversion to benzoin thioacetal **298** [(Figure 14), see experimental]. The use of LDA (Method D, Table 2) and Schlosser's base[207] (Method E, Table 2) were also unsuccessful. Replacing trimethylborate with the more reactive boron trichloride, by adding a solution of the anion in THF *via* cannula to the boron trichloride solution, gave a mixture of starting material and considerably more of the unknown by-product(s) (Method F, Table 2).

Table 2

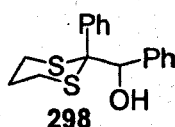| METHOD	BASE	ELECTROPHILE (E)	RESULTS
A	*n*-BuLi	B(OMe)$_3$	SM + side product(s) (40%)
B	*n*-BuLi	D$_2$O	SM + side product(s) (50%)
C	*n*-BuLi	Benzaldehyde	complete conversion
D	LDA	D$_2$O	SM
E	KO^{t}Bu- *n*-BuLi	B(OMe)$_3$	SM
F	*n*-BuLi	BCl$_3$, DCM	SM + side product(s) (75%)

Figure 14

Lithiation and alkylation of dithianes is common, but in the case of 2-phenyl-1,3-dithiane 297, the phenyl group stabilises the anion and so reduces its reactivity.[210] Lithiation and alkylation of dithiane 297 has been reported,[211] and the generation of a carbanion and successful reaction with benzaldehyde is consistent with this. The failure to react with D_2O remains unexplained (quenching with MeOD may have given better results). The formation of undesired by-products in some runs, may occur by attack of a butyl anion at sulfur, and/or by generation and reaction of a carbene (as for thioacetal 285, scheme 105). However, the lack of self-consistency in Table 2 makes any explanation tentative.

7.2.3 Generation and reactivity of 2-Lithio-2-(1-styryl)-1, 3-dithiane

Allylic thioacetals would be expected to be easily reduced by low-valent titanium complex 74 to give titanium allylidenes. Therefore, 2-(1-styryl)-1,3-dithiane[212] 299 was synthesised from cinnamaldehyde according to the literature procedure (Scheme 107). I then attempted to generate of 2-lithio-2-(1-styryl)-1,3-dithiane and react it with a range of electrophiles, including boronates, to probe the reactivity of the lithium salt (Scheme 107).
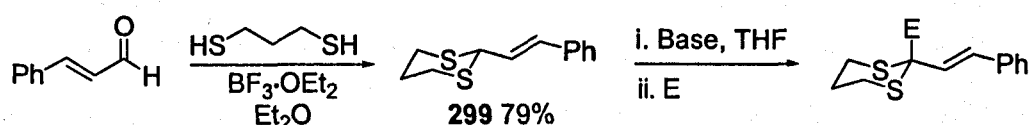
Scheme 107

Although the lithiated adduct of thioacetal 299 can react α or γ to the sulfur atoms, hard electrophiles react at the α-position.[212] Consequently, we expected boron electrophiles to react at the α-position. Lithiation under the standard conditions (see experimental) gave the dark orange anion.[212] Although deuteration (Method A, Table 3) was successful giving a mixture of 2-deuterio-2-(1-styryl)-1,3-dithiane 300 (Figure 15) and SM 299 (80 % conversion by ^{1}H NMR spectroscopy, see experimental), the anion failed to react in the desired way with any boron electrophiles (Methods B, C and D Table 3). Indeed, employing $B(O^iPr)_3$ led to a significant amount of side product(s), but the ^{1}H NMR spectrum was complex and difficult to interpret.

Table 3

METHOD	BASE	ELECTROPHILE (E)	RESULTS
A	n-BuLi	D_2O	80% conversion
B	n-BuLi	$B(O^iPr)_3$	SM + side product(s) (25%)
C	n-BuLi	$B(OMe)_3$	SM
D	KO^tBu- n-BuLi	$B(OMe)_3$	SM
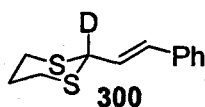
Figure 15

The formation of undesired by-products may be due to the carbene formation as proposed for thioacetals **285** and **297**.

Conclusions

It would appear that thioacetals **287** and **288** are not sufficiently reactive under Takeda reaction conditions. Moreover, 2-lithium salts of thioacetals **285**, **297** and **299** seem difficult to generate, are unreactive with boron electrophiles, and are prone to decomposition. The employment of thioacetals with a simple alkyl group may allow the generation of suitably reactive carbanions, which would then react with boronates. However, due to the difficulties we had in preparing suitable substrates for novel Takeda reactions, we decided that this route to vinylboronates was not general enough to merit more time being invested on it.

Chapter 8 – Synthesis of *N*-Boc Indoles

8.1 Background

As discussed in section 1.1, recent work within the group has seen the development of a novel benzo[*b*]furan synthesis on solid phase.[1] Thioacetals **301**, containing an *ortho*-protected phenol, alkylidenate Wang-resin-bound esters **302** (Scheme 108) under Takeda conditions as discussed in section 2.2. The resulting resin-bound enol ethers **303** can be cleaved from the resin to give ketones **304**. Alternatively, removal of the TBS protecting group followed by cleavage from the resin, allows concomitant cyclisation to give the 2-substituted benzo[*b*]furans **305**. The resin was contained in IRORI macroKans, which can be described as porous polypropylene, tubular, reactor vessels.
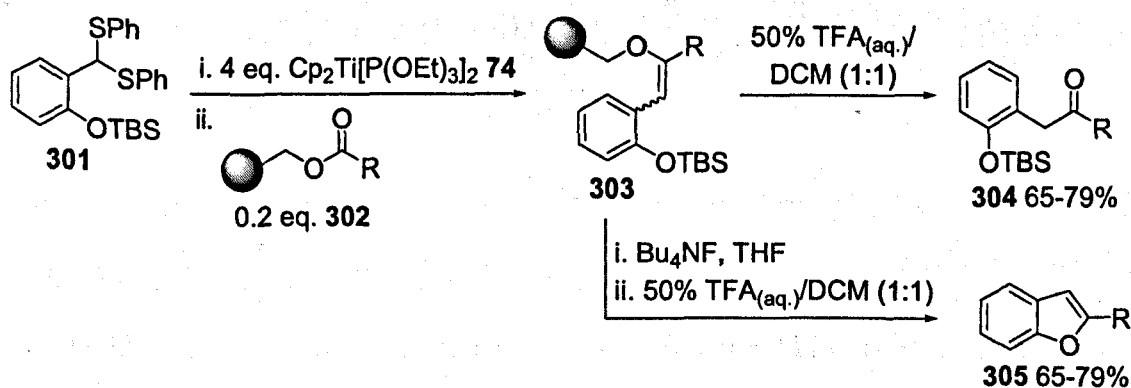
Scheme 108

As discussed in Section 1.1, we aimed to extend this methodology to the synthesis of nitrogen-containing heterocycles, and in particular to indoles[213, 214]. Thioacetals **306**, with a suitably protected *ortho*-aniline moiety should be prepared from readily available precursors. The titanium alkylidenes of thioacetals **306** should akylidenate resin-bound esters **302** yielding enol ethers **307** (Scheme 109). The protecting group should be easily formed, stable to the reaction conditions, preferably acid labile, and by-products formed upon its removal should be volatile. Should these requirements be met, then cleavage from the resin and concomitant cyclisation should allow isolation of the indole in high purity upon solvent removal.
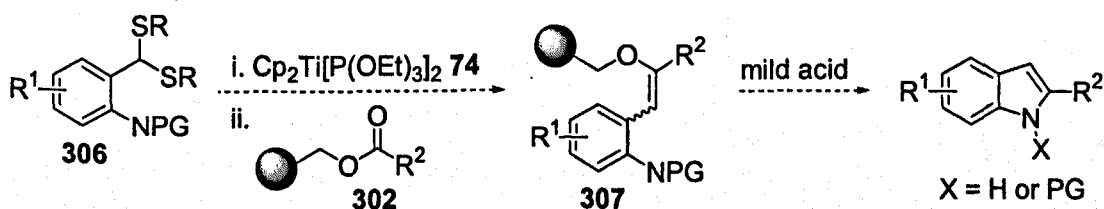
Scheme 109

8.2 Synthesis of resin-bound esters

Esters were formed on Wang and Merrifield resins using standard methods. The difference in reactivity of these two resins under acid conditions has been discussed earlier (see section 4.2.2).

The formation of Wang resin-bound ester **290** was achieved by reacting Wang resin (swollen) in THF with dihydrocinammic acid employing 1,3-diisopropylcarbodiimide (DIC) as coupling agent with a catalytic amount of 4-dimethylaminopyridine (DMAP) (Scheme 110). DIC was employed instead of the more commonly used 1,3-dicyclohexylcarbodiimide (DCC) due to the greater solubility of its by-product in organic solvents.
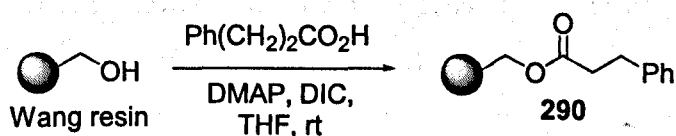
Scheme 110

Treating Merrifield resin (swollen) in DMF with 5 eq. of caesium carboxylates **308** at 60-70 °C yielded Merrifield resin-bound esters **309** (Scheme 111). The caesium salt has a larger cation than the equivalent lithium or sodium salt. This results in a greater dissociation between the ion pair, particularly when using a polar solvent such as DMF. The resulting naked carboxylate anions give a higher rate of ester formation than that achieved with other metal counterions.[215]
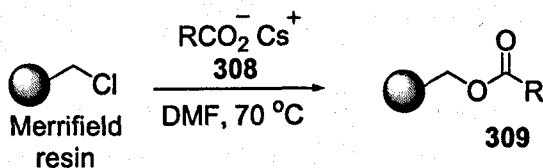
Scheme 111

For both Merrifield and Wang resin-bound esters, IRORI macroKans were employed (see Section 4.3) with 3-12 kans used per reaction.

8.3 Initial Studies

8.3.1 Use of 2-Aminophenones

As 2-aminophenones are readily available, we envisioned that thioacetalization, followed by base stable (STABASE) or silyloxyethoxy methyl (SEM) amine protection, would provide us with suitable substrates for Takeda alkylidenation. Both SEM and STABASE protecting groups can be removed in mild acid conditions, and are standard amine protecting groups.[216]

Initially, we formed thioacetal **310** from 2-aminoacetophenone, but purification by chromatography led to decomposition of the thioacetal to give the 2-aminoacetophenone (the ^{1}H NMR spectrum showed identical signals to that of a spectrum of 2-aminoacetophenone) and 1,3-propanedithiol (Scheme 112). Crystallisation was also unsuccessful. However, thioacetal **311** was synthesised in good yield (Scheme 112). Attempts to protect aniline **311** as the SEM **312** and STABASE **313** analogues were unsuccessful (Scheme 112). In the case of SEM, the use of K_2CO_3 as base, only yielded a complex mixture of compounds that was uninterpretable by ^{1}H NMR spectroscopy although considerable amounts of starting material **311** and SEMCl could be identified. Adaptation of a literature procedure employing NaH as base,[217, 218] gave similar results. The attempted STABASE procedure[219] gave mixtures that contained mostly unreacted starting material (from the ^{1}H NMR spectrum), but TLC analysis confirmed the presence of at least four products.

R = CH$_3$ **310** 32% (95% pure)
R = Ph **311** 82%
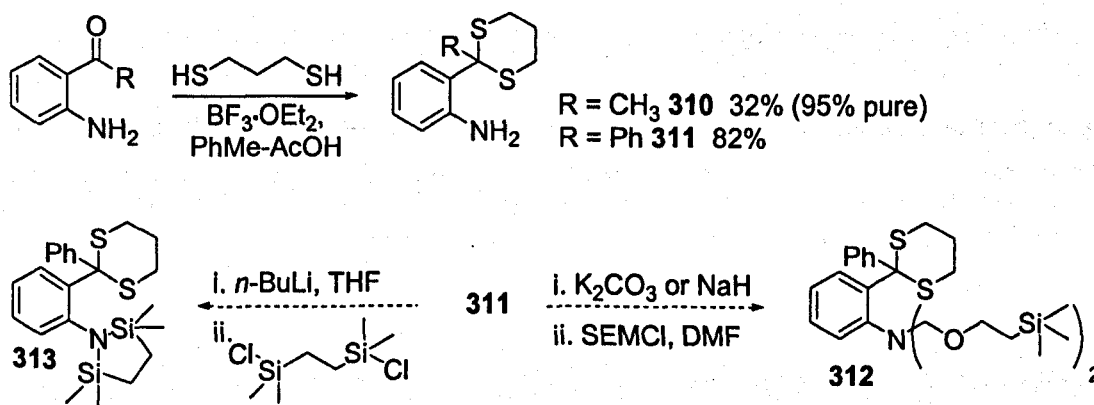
Scheme 112

Although a common protecting group for *N*-heterocycles, SEM is rarely used for anilines. Both the SEM and STABASE protections may well have suffered from severe steric hindrance caused by the bulky substituent *ortho* to the amino group.

As dithianes are easier to prepare from 2-aminobenzophenones than the corresponding, bis(phenylthio) thioketals, we decided to test the reactivity of dithianes **314** and **315** under Takeda conditions (Scheme 113). Employing thioacetal **314** would help establish optimum conditions for desulfurising dithianes, and the use of thioketal **315** would determine if 3-substituted heterocycles could be accessed by this methodology. Thioacetal **314** was prepared by a literature procedure,[220] and thioketal **315** was prepared by adapting Barton's procedure,[202] and then both were protected as *tert*-butyldimethylsilyl ethers (Scheme 113). Thioacetal **316**, under Takeda conditions, converted Wang resin-bound ester **290** into the corresponding enol ether **317**. Cleavage from the resin then generated the ketone **318** in good yield and high purity. Thioacetal **319**, under the same standard conditions, gave only hydrocinammic acid with minute quantities of another compound that may have been the desired ketone **320**, observed by ^{1}H NMR spectroscopy.
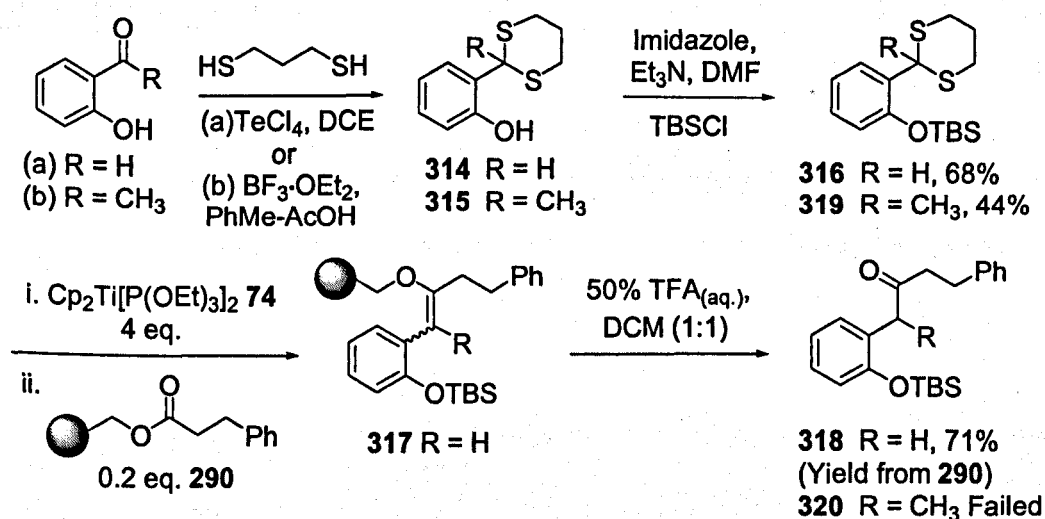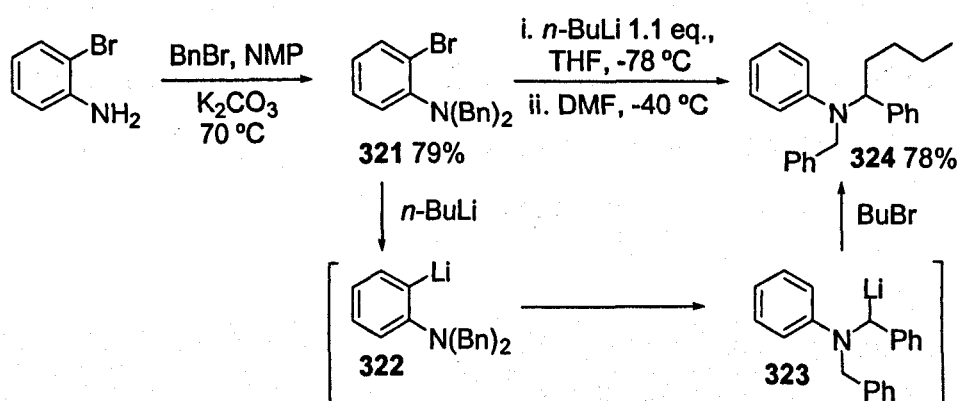

Scheme 113

These results confirmed that dithianes could be employed. However, benzylic thioketals fail to generate effective alkylidenating reagents under Takeda conditions, in agreement with Takeda's reports[71] (see section 2.2).

8.3.2 Introduction of Formyl group *ortho* to a protected aniline

Our next approach was to introduce the *ortho*-aldehyde moiety in the presence of a protected aniline. The aldehyde could then be converted into a thioacetal. It was important to demonstrate that a protected aniline *ortho* to the thioacetal could survive the Takeda reaction conditions, allowing both formation and reaction of the titanium alkylidene.

2-Bromo-*N,N*-dibenzylaniline **321** was prepared (Scheme 114), in the hope of inducing lithium-halogen exchange and quenching the resulting anion with *N,N*-dimethylformamide (DMF). Although anion **322** presumably was formed employing *n*-BuLi, intramolecular deprotonation then occurred, yielding a more stable benzylic anion **323**, which then reacted with butyl bromide to give aniline **324**. Indeed, the reaction would require an extra equivalent of *n*-BuLi to prevent butylation but formylation would presumably still occur at the benzylic position.

Scheme 114

Next we hoped to carry out a Vilsmeier-Haack reaction[221] on *N,N*-dibenzyl-*p*-toluidine **325**, readily prepared from *p*-toluidine (Scheme 115), using the methyl moiety as a blocking group. However, the main products observed in the crude ^{1}H NMR spectrum were 2,4-dimethylaniline [2.21 ppm (3H, s, CH$_3$), 2.23 ppm (3H, s, CH$_3$), 3.47 ppm (2H, s, NH$_2$),] and considerable amounts of benzaldehyde [10.0 ppm (1H, s, CHO)].
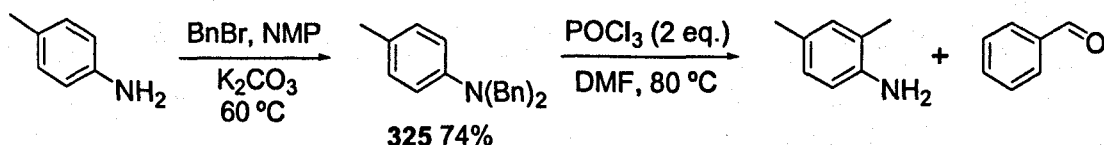
Scheme 115

Finally, we carried out the Vilsmeier-Haack reaction[221] on *N,N*-dimethyl-*p*-toluidine which gave aldehyde **326** in moderate yield after chromatography (Scheme 116). Thioacetal **327** was prepared from aldehyde **326** in moderate yield after chromatography, and then subjected to the standard solid phase Takeda reaction sequence, employing Merrifield resin-bound ester **309a'**. To our satisfaction ketone **328** was obtained in moderate yield and very high purity. Although the *N,N*-dimethyl moiety did not allow deprotection to give the aniline and so consequent cyclisation to the indole, its use confirmed that a protected aniline *ortho* to the thioacetal could survive the Takeda reaction.
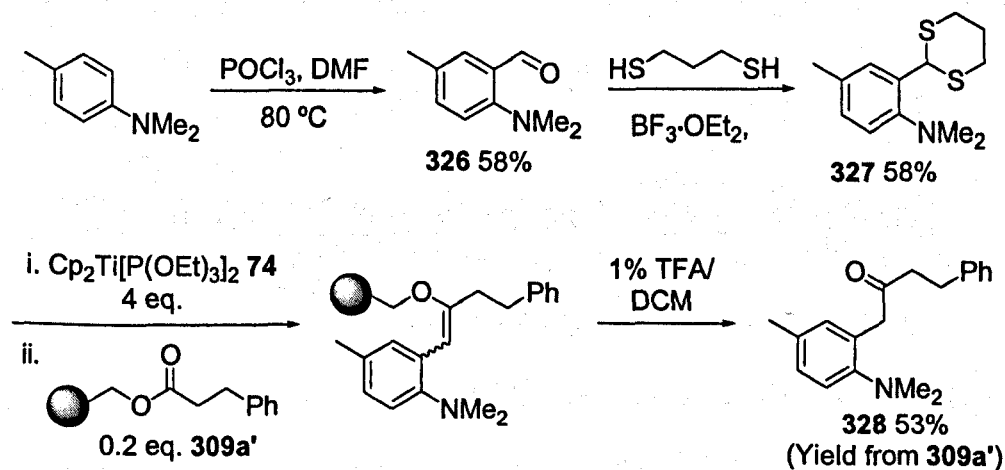
Scheme 116

8.4 Use of 2-Nitrobenzaldehydes

We then planned to investigate routes to suitable thioacetals from 2-nitrobenzaldehydes, as 2-aminobenzaldehydes self-condense. 2-Nitrobenzaldehyde was converted into thioacetals **329** and **330** (Scheme 117). Thioacetal **330** was then reduced with sodium borohydride and Pd/C[222] to give aniline **331**. The reduction of nitro compound **329** was unsuccessful, as elimination of the thioacetal occurred yielding 2-nitrobenzaldehyde (aldehyde singlet at 9.10 ppm observed in the crude ^{1}H NMR spectrum), amongst a complex mixture of other compounds. SEM protection of aniline **331**, employing *n*-butyllithium as base, yielded a complex mixture of compounds with considerable amounts of starting material **331** and SEMCl still present in the ^{1}H NMR spectrum (Scheme 117).
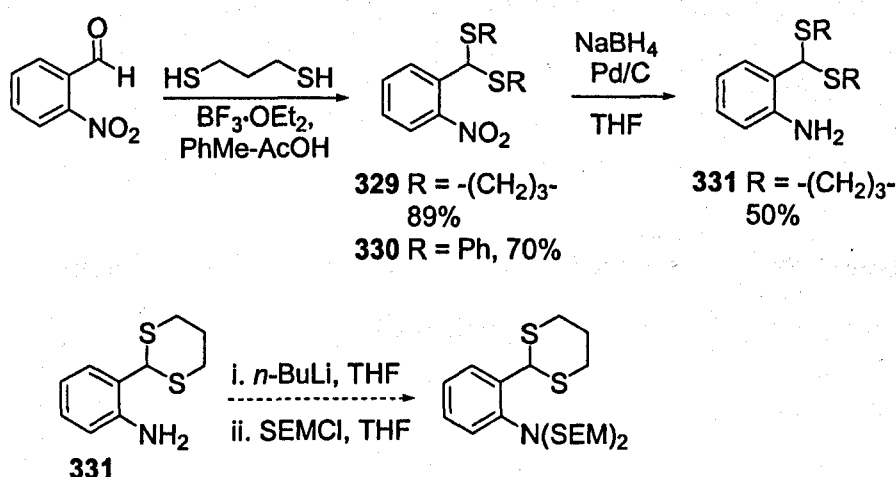
Scheme 117

Thioacetals **330** and **331** were subjected to the standard solid-phase Takeda reaction sequence (Scheme 118). We hoped that the titanium complex **74**, would reduce both the nitro and thioacetal moieties in thioacetal **330**, and allow alkylidenation of Wang resin-bound ester **290**. However, after subjecting the resin to the standard cleavage conditions, only hydrocinnamic acid and cyclopentadienyl titanium by-products (singlets at 6.49 ppm) were observed in the ^{1}H NMR spectrum. Similarly, thioacetal **331** failed to form an effective alkylidenating reagent, as there was no evidence of indole **332** observed in the crude ^{1}H NMR spectrum after reacting with Merrifield resin-bound ester **309a'**.
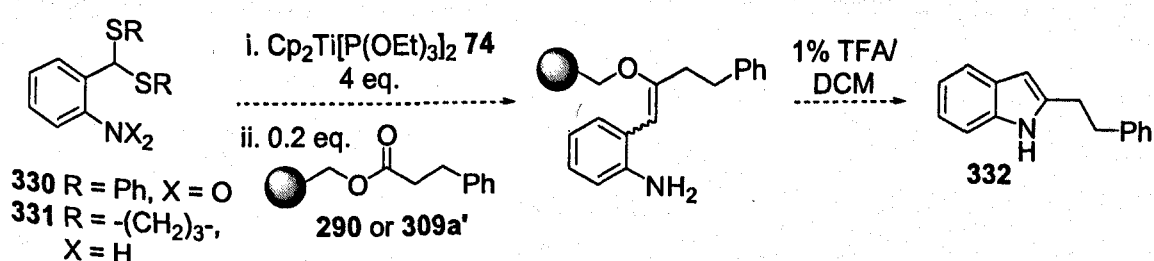
Scheme 118

Due to the difficulties we had in protecting aniline **331** we decided to employ Boc protection. Despite containing a carbonyl moiety we hoped that the electron-rich nature of the carbamate carbonyl, combined with steric hindrance from the *tert*-butyl group, would render the carbonyl group(s) inert to alkylidenation.

Aniline **331** was synthesised as before (Scheme 117) but on scale up, azoxy dimer **333** was also formed, which we isolated by chromatography and recrystallisation (Scheme 119). A crystal structure of dimer **333** was obtained (appendix 2). Diazine-*N*-oxides are common intermediates/by-products in nitro reductions.[223] It should be noted than when dimer **333** was re-exposed to the reduction conditions, aniline **331** was not isolated. Aniline **331** was converted into imide **334** with 2.2 eq. Boc anhydride and sodium hexamethyldisilazide (NaHMDS) as base, and also to carbamate **335a** by heating with 1.1 eq. Boc anhydride in THF (Scheme 119).
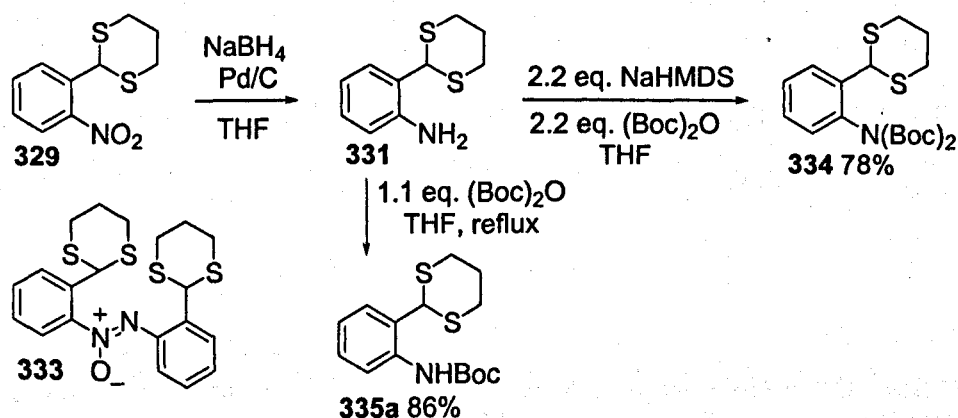
Scheme 119

Thioacetals **334** and **335a** were both, in turn, subjected to the standard solid-phase Takeda reaction sequence employing Merifield resin-bound ester **309a'**. When employing imide **334** there was little evidence of indole **336aa'** (in the ¹H NMR spectrum) upon subjecting the resin to the standard cleavage conditions (Scheme 120). It was concluded that failure was due to intramolecular nucleophilic attack on one of the imide carbonyls.
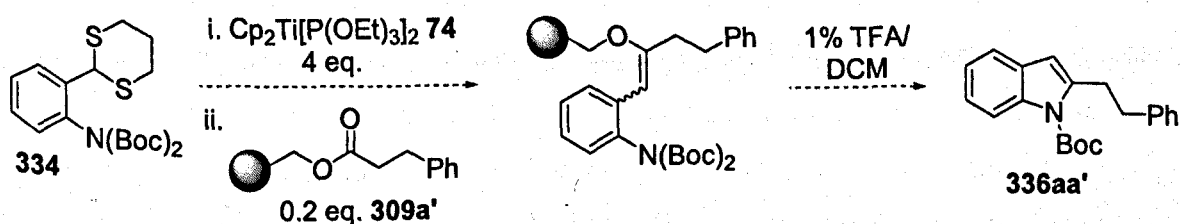
Scheme 120

When employing carbamate **335a**, although the mass recovery of crude material was low (13%), indole **336aa'** was obtained in poor yield after column chromatography (Scheme 121). The low yield is probably the result of intramolecular deprotonation of the carbamate *N*-H by benzylic titanium intermediates.
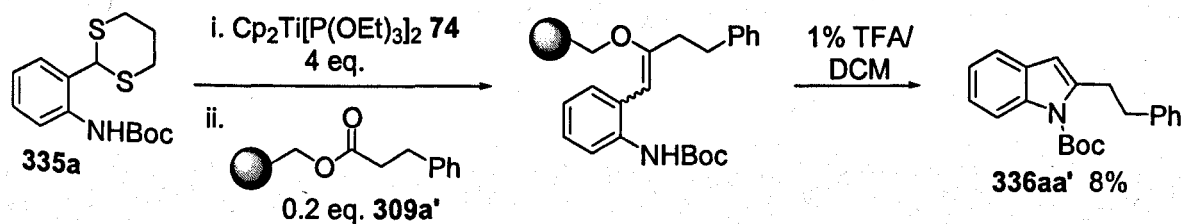
Scheme 121

When imide **334** was treated with 2.7 eq. of low-valent titanium complex **74** and then quenched in 2 mol dm^{-3} HCl, toluidines **337** and **338**[224] were isolated along with thiol **339** (Scheme 122). These were present in a 1: 1: 9 ratio in the ^{1}H NMR spectrum of the crude mixture, but mass recovery was poor. Toluidine **337** was presumably formed by quenching the resultant titanium alkylidene derived from thioacetal **334**. Toluidine **338** could have been formed in the same way with Boc deprotection occurring during the acid quench.

337: 338: 339 (1:1:9)

Scheme 122

Thiol **339** was difficult to isolate and on silica gel, appeared to oxidise to the corresponding disulfide, which was not isolated. The formation of thiol **339**, could be explained by titanium insertion into one C-S bond, followed by acyl migrat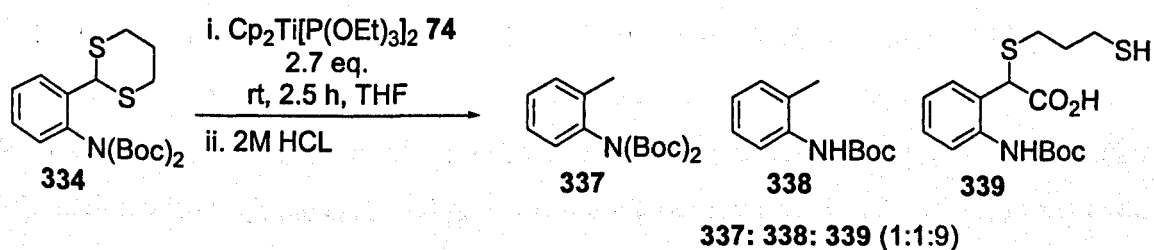ion to the benzylic position, and subsequent quench in acid (Scheme 123). The imide nitrogen lone pair in intermediate **340** is cross-conjugated, making the carbonyls more electrophilic than simple carbamates and hence susceptible to intramolecular nucleophilic attack by the organotitanium moiety in **340**. Furthermore, the crystal structure[214] of imide **334** (Figure 16) suggests that one of the carbonyl moieties in intermediate **340** would be in an ideal orientation to undergo nucleophilic attack. Titanium-mediated intramolecular nucleophilic acyl substitution reactions have been used to synthesise cyclopropanols, lactones and other cyclic compounds.[225] Related zirconium-mediated acyl migrations from carbamate groups have been employed recently in the synthesis of γ-aminobutyric acid derivatives.[226]
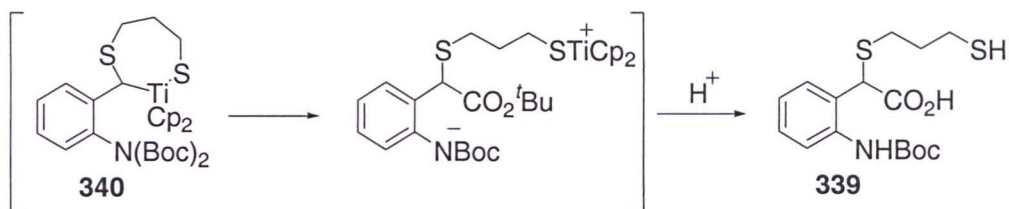
Scheme 123
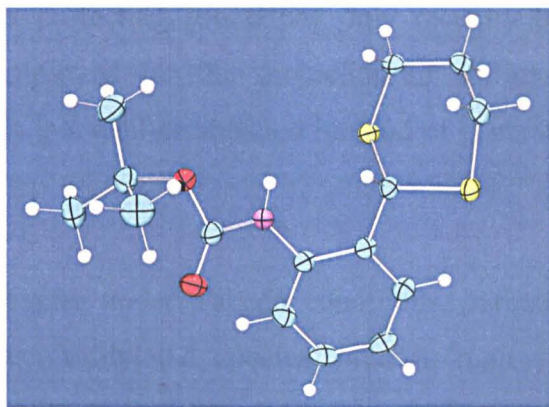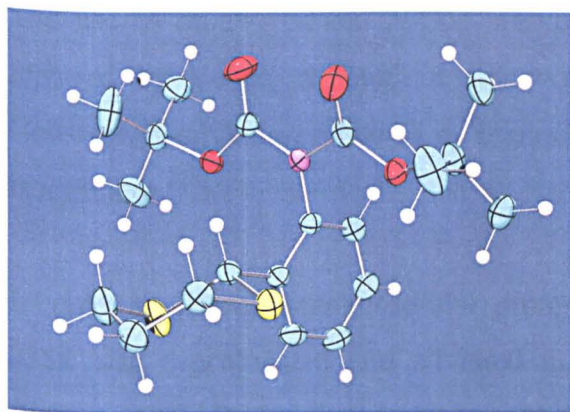
Figure 16 Crystal structure of imide **334**   **Figure 17** Crystal structure of carbamate **335a**

When carbamate **335a** was treated with 2.7 eq. of low-valent titanium complex **74** under similar conditions, toluidine **338**[224] and thiol **341** were formed in the ratio shown (Scheme 124). Insertion of titanium into one C-S bond [as for imide **334** (Scheme 123)], followed by intramolecular deprotonation of the carbamate N-H and subsequent quench in acid, could explain the formation of thiol **341**. The nitrogen anion would be stabilised by conjugation with both the carbonyl group and the aromatic ring. Furthermore, in the crystal structure[214] of carbamate **335a** (Figure 17) the N-H bond is orientated towards the benzylic carbon atom. A conformation with the N-H and N-Boc bonds coplanar with the aromatic ring must be energetically accessible in solution, as C4 and C6 of the dithiane are equivalent in the ^{13}C NMR spectrum.

338: 341 (2:9)
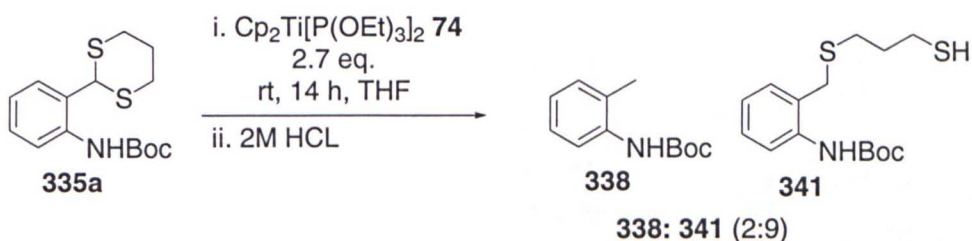
Scheme 124

We hoped that a salt generated by deprotonating carbamate **335a**, would be stable to the formation of the titanium carbene, and would allow complete reaction with the resin-bound ester. However, we encountered severe solubility problems in THF, when trying to form the sodium (NaHMDS) and lithium (LDA) salts of carbamate **335a** (see section 9.1).

8.5 Use of *N*-TMS-*N*-Boc Protection in *N*-Boc indole synthesis

The use of an *N*-silylated *N*-Boc species as protecting group has only recently been reported by Voyer, although it was not employed for the protection of anilines.[227] However, *N*-silylation followed by thermolysis is a well-established method of generating isocyanates.[228]

In order to prevent intramolecular proton-transfer under Takeda conditions, carbamate **335a** was deprotonated and silylated to give *N*-silylated species **342a** in high yield (Scheme 125). Due to the insoluble nature of salts derived from carbamate **335a**, we used an *in situ* quench by adding LDA to a mixture of the carbamate and TMSCl in THF. *N*-silylated carbamate **342a** is unstable, mostly decomposing to carbamate **335a**, when stored under argon overnight. This made full characterisation difficult. However, the ^{13}C NMR spectrum (at 52 C to allow rapid equilibration of the carbamate geometrical isomers) of *N*-silylated carbamate **342a** was obtained. As expected, C4 and C6 of the dithiane ring were found to be non-equivalent showing that rotation about the aryl-nitrogen bond is slow on an NMR timescale. *N*-silylated carbamate **342a** was then subjected to our standard solid-phase reaction sequence employing resin-bound ester **309a'** (Scheme 125). Resin-wash with solvents including methanol, presumably ensures *N*-desilylation to yield enol ether **343**, which when treated with 1% TFA, gave *N*-Boc indole **336aa'** in good yield and high purity after removal of the solvent (see appendix 1 for ^{1}H NMR spectra).
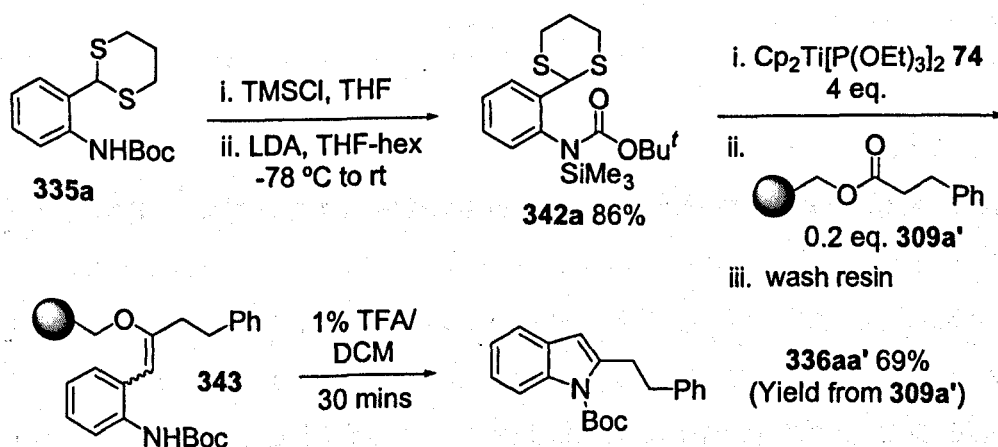
Scheme 125

It should be noted that this is the first reported example of a carbonyl moiety surviving within a titanium alkylidene reagent.[15]

With this result in hand we set about preparing a range of thioacetal substrates to further examine the functional group tolerance of the Takeda alkylidenation. Readily available 2-nitrobenzaldehydes **344** were converted into thioacetals **329a-d** (Scheme 126). An improved procedure for the reduction of nitro groups, employing iron/ammonium chloride[229] as reducing agent, prohibited the formation of diazine-*N*-oxides and yielded anilines **331a-d**. Boc protection as before[230] yielded carbamates **335**, except in the case of the unstable electron-rich aniline **331c**, which always gave a mixture of mono- and di-protected anilines. Consequently, nitro compound **329c** was reduced, converted to the corresponding imide, and mono-deprotected[231] without purifying the intermediates. Phenol **335d** was converted into TMS ether **335e** employing TMSCl in pyridine. *N*-Silylation of carbamates **335a-c** and **335e** as above, gave unstable *N*-silylated carbamates **342a-c** and **342e**.
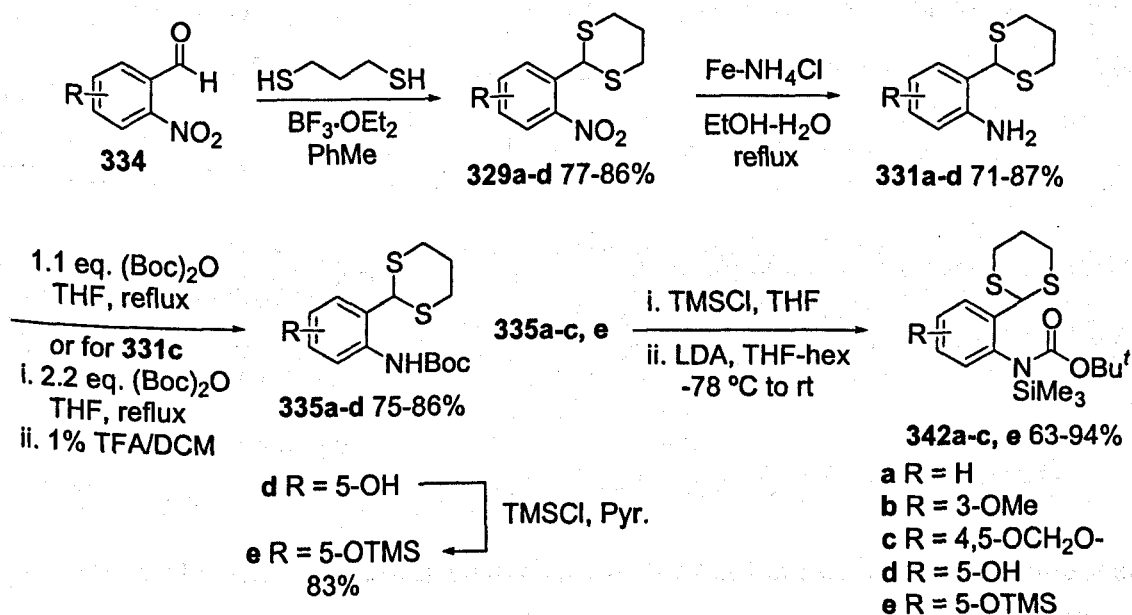
Scheme 126

N-silylated carbamates **342a-c** and **342e** were then subjected to our standard solid-phase reaction sequence employing resin-bound esters **309** (Scheme 127). Upon washing the resin and resin-cleavage, *N*-Boc indoles **336** were obtained in good yield and high purity, with the exception of the *N*-Boc-7-methoxyindoles **336b**. *N*-Boc-7-methoxyindole **336ba'** was contaminated with trace amounts of the deprotected indole, and *N*-Boc-7-methoxyindoles **336bb'** and **336bc'** underwent significant spontaneous Boc deprotection under the resin-cleavage conditions, and so were fully deprotected[232] by treating with 20%

TFA in dichloromethane for 1 h. *N*-H indoles **332ba'** and **332bb'** were isolated in high purity (appendix 1) following solvent removal, but the deprotection conditions led to substantial decomposition in the case of 2-methylindole **332bc'**. It should also be noted that indoles **336d** were fully O-TMS deprotected under the resin-cleavage conditions.
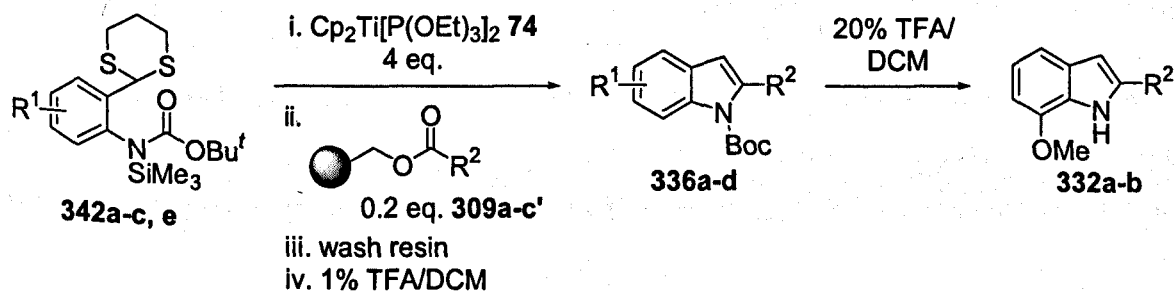
Scheme 127

The yields obtained for *N*-Boc indoles and *N*-H indoles are based on the loading of the Merrifield resin used to prepare Merrifield resin-bound esters **309** (yields, Figure 18).

336aa' R = $(CH_2)_2Ph$ 69%
336ab' R = Ph 59%
336ac' R = CH_3 59%

336ba' R = $(CH_2)_2Ph$ 59%
336bb' R = Ph, not isolated
336ba' R = CH_3, not isolated

332ba' R = $(CH_2)_2Ph$ 59%
332bb' R = Ph 69%
332ba' R = CH_3, decomposed

336ca' R = $(CH_2)_2Ph$ 69%
336cb' R = Ph 70%
336cc' R = CH_3 58%

336da' R = $(CH_2)_2Ph$ 68%
336db' R = Ph 72%
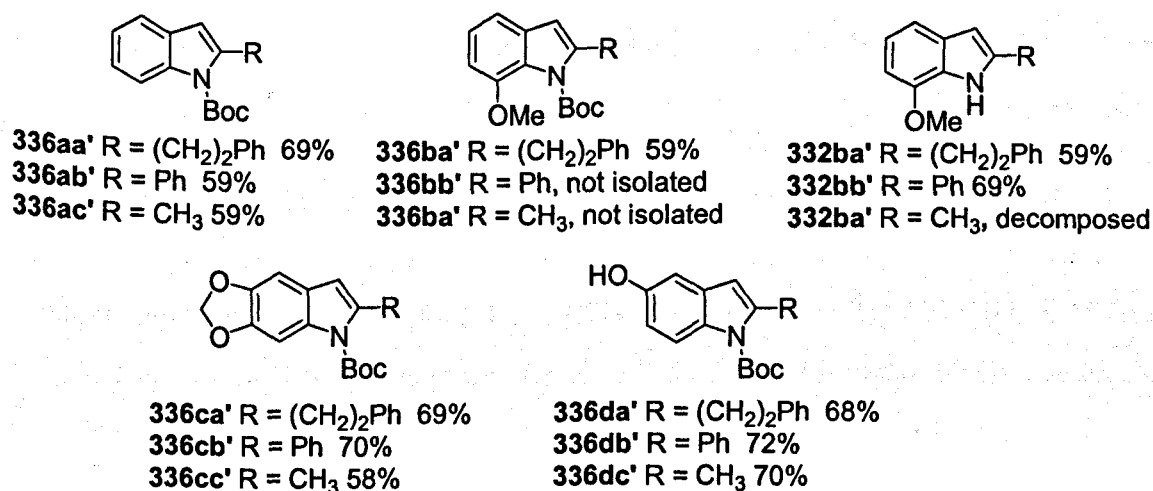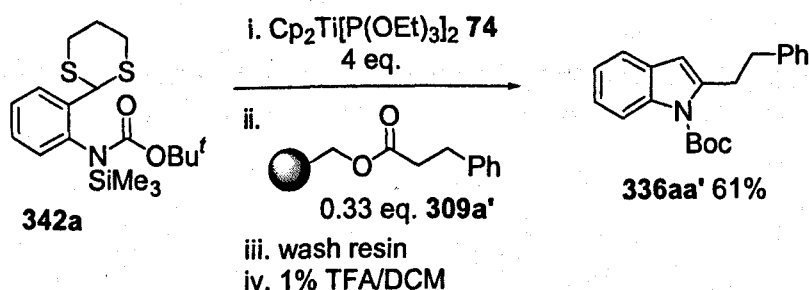**336dc'** R = CH_3 70%

Figure 18

Later, we investigated using fewer equivalents of the titanium carbene, and found that 3 equivalents of thioacetal **342a** converted resin-bound ester **309a'** into indole **336aa'** without significant loss of yield (Scheme 128) under the standard reaction sequence.
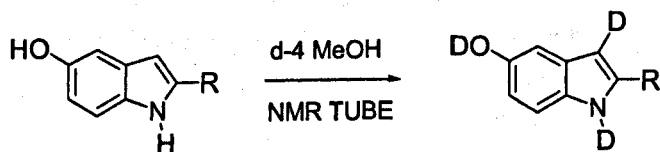

Scheme 128

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8.6 Deprotection of *N*-Boc indoles

Next we attempted the deprotection of *N*-Boc indoles prepared above. Initially, we followed the procedure used for indoles **332b** employing TFA in DCM,[232] and found in some cases significant indole decomposition/oxidation occurred. Indoles **336ab'**, **336ea'** and **336ec'** gave pure products **332ab'**, **332ea'** and **332ec'**, with or without column chromatography (Scheme 129). However, in the deprotection of **336aa'**, **336ac'** and **336eb'** complex mixtures of products were obtained, with the crude ^{1}H NMR spectra being difficult to interpret (Scheme 129). Due to the small scale of these reactions, further purification of such impure indoles was not attempted.
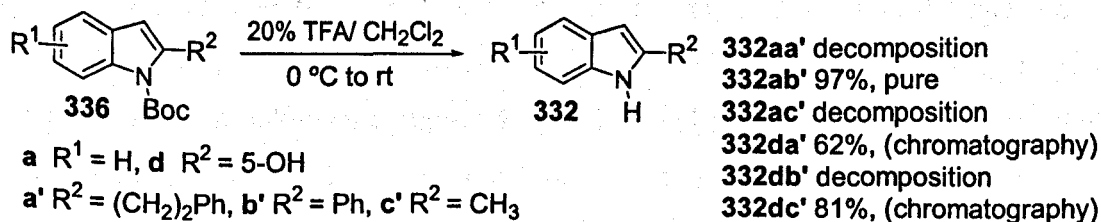
Scheme 129

Indoles **332da'** and **332dc'** were each dissolved in d-4 MeOH in an attempt to obtain their ^{13}C NMR spectra. Indole **332dc'** underwent complete conversion in the NMR tube to indole **345dc'** within 20 mins (Scheme 130). This was confirmed by the disappearance of the relevant proton signals [δ 4.44 (1H, s, OH), 6.10 (1H, s, H-3), 7.72 (1H, s, NH)] of indole **332dc'** in the ^{1}H NMR spectrum. Indole **332da'**, after 2 h in d-4 MeOH, underwent partial deuteration at the 3-position as confirmed by the disappearance of the signal [δ 6.16 (1H, d, *J* 1.4, H-3)] in the ^{1}H NMR spectrum (Scheme 130). However, even, after heating in d-4 MeOH or allowing the sample to stand for two months, complete deuteration at this position was not observed, and so full characterisation of indole **345da'** was not possible.
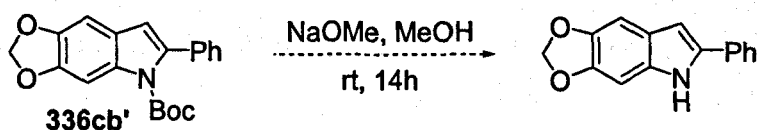

332da' R = (CH$_2$)$_2$Ph, partial deuterium incorporation
332dc' R = CH$_3$, complete deuterium incorporation giving **345dc'**

Scheme 130

Next, we attempted the nucleophilic deprotection of *N*-Boc indole **336cb'**, employing NaOMe in MeOH (Scheme 131). However, after work-up of the reaction, only unreacted starting material was recovered.

Scheme 131

We then attempted a literature procedure for *N*-Boc deprotection,[233] employing TBAF and heating under reflux in THF. *N*-Boc indole **336cb'** was converted into indole **332cb'** (Scheme 132), purified by triteration from chloroform, and a ^{1}H NMR spectrum was obtained. However, in an attempt to acquire a ^{13}C NMR spectrum in CDCl$_3$, significant decomposition to an unknown compound was observed and so full characterisation of the highly electron-rich indole **332cb'** was not possible. These results confirm how reactive 2-substituted indoles are at the 3-position, particularly when they are electron-rich.
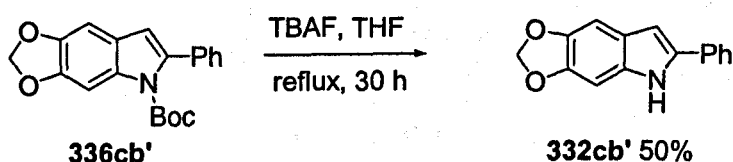
Scheme 132

The authors report two possible mechanisms for the TBAF deprotection.[233] Fluoride could act as a nucleophile, attacking the carbamate carbonyl, eliminating the amine as a leaving group (Mechanism A, Figure 19). Alternatively, E$_2$ elimination could eliminate the amine as shown (Mechanism B, Figure 19). In both cases, CO$_2$ would be produced, and the HF formed would be neutralised by the released amine.

Mechanism A   Mechanism B
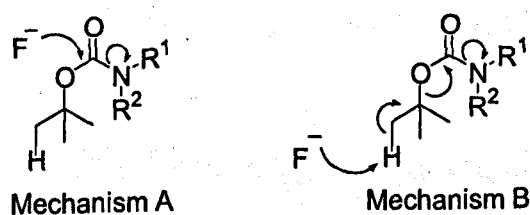
Figure 19

8.7 Use of chloro-substituted thioacetals

We felt it was important to investigate the stability of an aryl halide bond within the titanium alkylidene reagent. 5-Chloro-2-nitrobenzaldehyde **334f** is commercially available but is contaminated with 15% of the 4-chloro isomer. The mixture was converted into the corresponding thioacetals and after recrystallisation gave thioacetal **329f**[234] contaminated with 7% of the 4-chloro isomer (Scheme 133). Nitro reduction as above, yielded pure aniline **331f**[234] after two recrystallisations. Boc protection as before gave carbamate **335f**, and this was followed by N-silylation to yield N-silylated carbamate **342f**.
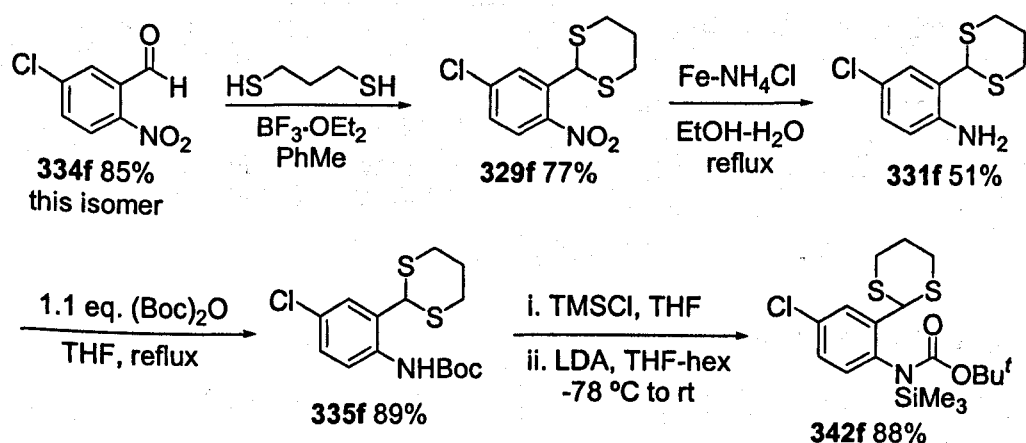
Scheme 133

N-silylated carbamate **342f** was subjected to our standard solid-phase reaction sequence employing resin-bound esters **309a-c'** (Scheme 134). In each case, following cleavage from the resin, a 2:1 mixture of indoles **336a** and **336f** were obtained in poor yield. Presumably this is the result of titanium insertion into the C-Cl bond under the conditions used to generate the titanium alkylidene.

Scheme 134

86
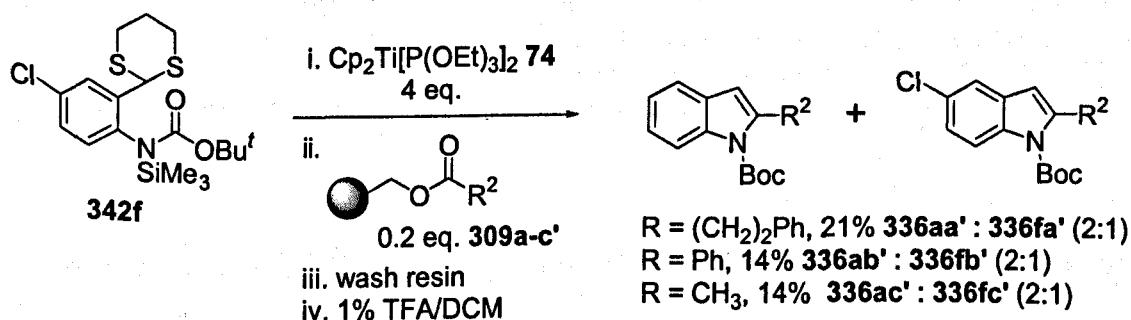
Further attempts to generate an alkylidenating reagent from thioacetal **342f** (Scheme 135), without affecting the aryl chloride moiety by employing fewer equivalents of low-valent titanium complex **74** were relatively unsuccessful (Table 4). The use of 2 equivalents of low-valent titanium complex **74** did prevent C-Cl reduction but gave indole **336fa'** in only 14% yield. Reverse addition (Table 4), i.e. adding a THF solution of low-valent titanium complex **74** to thioacetal **342f** in an attempt to keep the thioacetal in excess, also proved unsuccessful.
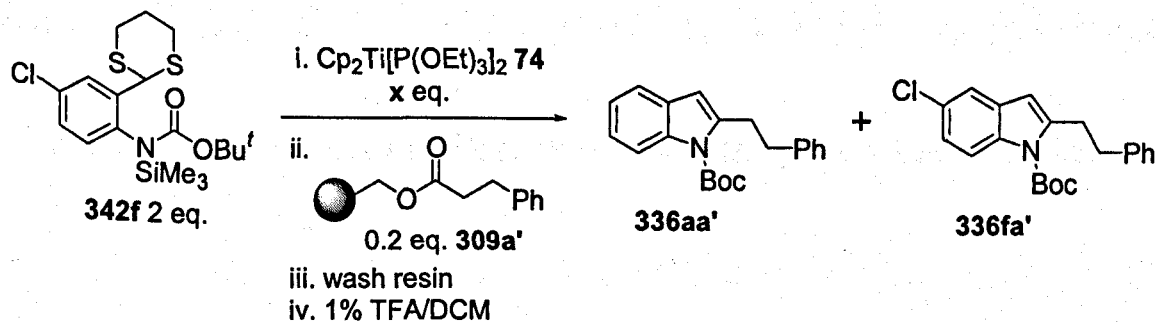
Scheme 135

Table 4

74(A) & 342f(B) order of add.	equivalents of 74 (x)	ratio of a: f obtained	yield of 336aa' & 336fa'
B added to A	4	1: 2	21%
A added to B	4	1: 3	12%
B added to A	3	7: 1	16%
B added to A	2	1: 0	14%

Thus, it can be concluded that there is poor chemoselectivity for the Takeda reduction of a benzylic thioacetal in the presence of an aryl chloride.

Chapter 9 – Synthesis of *N*-Alkyl Indoles

9.1 Use of *N*-alkyl-*N*-Boc carbamates

Next, we aimed to test if the *N*-alkyl-*N*-Boc moiety survived the Takeda reaction conditions, and if so, utilise this amine protection in the synthesis of *N*-alkyl indoles. Carbamate **335a** was deprotonated with LDA in THF, concentrated *in vacuo*, before dissolving in DCM (as the lithium salt was insoluble in THF as described above), and then methylated by adding MeI. *N*-Methyl carbamate **346** was then subjected to our standard solid-phase reaction sequence employing resin-bound ester **309a'** (Scheme 136). Washing of the resin and treatment with 1% TFA gave ketone **347aa'** (see section 9.3) in good yield and high purity (see appendix 1 for ^{1}H NMR spectra). Clearly, the *N*-Boc group is not very susceptible to benzylidenation.
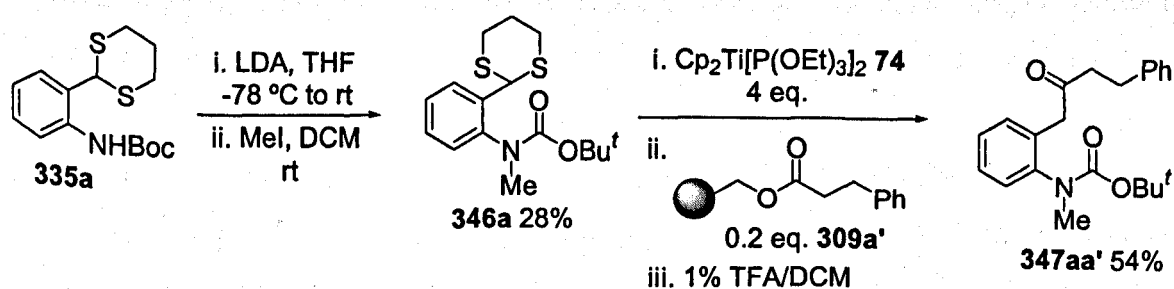
Scheme 136

We required an improved procedure for carbamate alkylation and found that adding NaH to a mixture of carbamate **335** and alkyl halide in DMF resulted in excellent conversion to *N*-alkyl carbamates **346a-d** (Scheme 137). No chromatography was required, and tertiary carbamates **346a-d** were simply purified by recrystallisation. Carbamate **346a** was then subjected to our standard solid-phase reaction sequence employing resin-bound esters **309a-d'**. The resulting ketones were not isolated but instead further treated with TFA (10% in DCM), and upon aqueous work-up yielded indoles **348a** in excellent purity without need for further purification. Similarly, *N*-benzyl carbamate **346b** and *N*-prenyl carbamate **346c** gave indoles **348b** and **348c**, respectively. However, *N*-allyl carbamate **346d** failed to generate an effective alkylidenating reagent, and complex mixtures of products were observed by ^{1}H NMR spectroscopy. The failure of *N*-allyl carbamate **346d** is not surprising as Takeda and co-workers have shown that titanium alkylidenes generated from thioacetals bearing terminal or disubstituted alkenes undergo metathesis reactions (see section 2.2).[74, 75, 77]
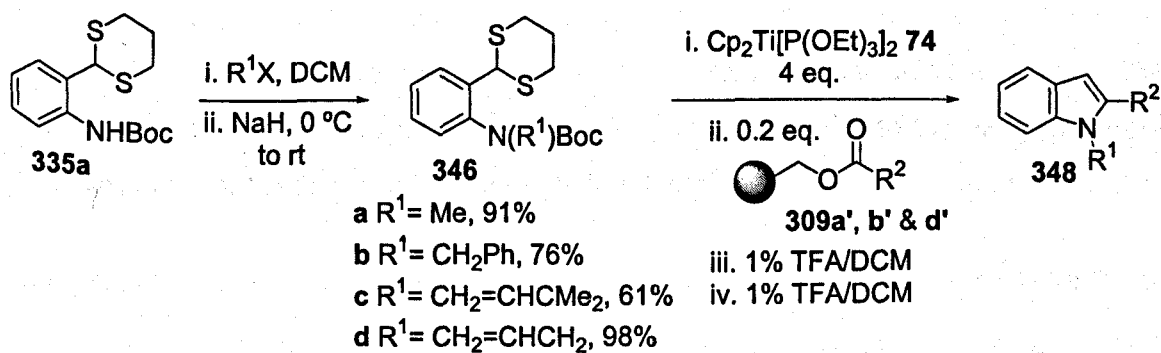
Scheme 137

The N-alkyl indoles **348** that were prepared are shown in Figure 20, and the yields shown are based on the loading of Merrifield resin used to prepare esters **309**. The yields are moderate to good, suggesting that in some instances some intramolecular alkylidenation of the carbamate carbonyl may occur. However, the purity obtained in all cases was excellent.
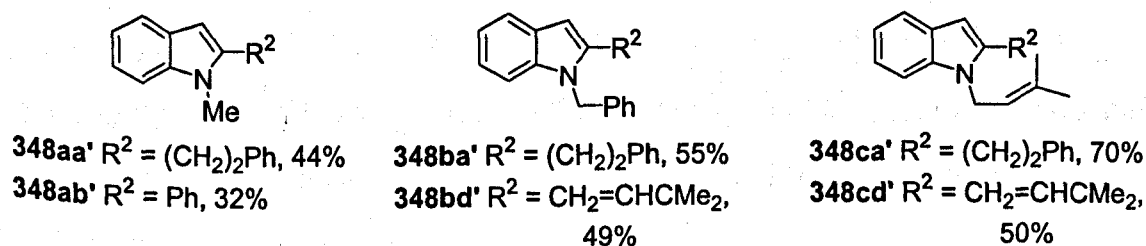

348aa' R^2 = $(CH_2)_2Ph$, 44%
348ab' R^2 = Ph, 32%

348ba' R^2 = $(CH_2)_2Ph$, 55%
348bd' R^2 = $CH_2=CHCMe_2$, 49%

348ca' R^2 = $(CH_2)_2Ph$, 70%
348cd' R^2 = $CH_2=CHCMe_2$, 50%

Figure 20

The success of N-alkyl carbamates under the Takeda reaction conditions may at first seem surprising. However, it is evident from the crystal structures[214] of carbamates **346a** (Figure 21) and **346c** (Figure 22) that the carbonyl group of tertiary carbamates **346a** and **346c** will be less electrophilic than that of secondary carbamate **335a** as the nitrogen lone pair is less conjugated to the aromatic ring. The degree of conjugation is determined by the torsion angle C1'-C2'-N1-C1" (or C3'-C2'-N1-C1"). The C1'-C2'-N1-C1" torsion angles in the crystal structures of tertiary carbamates **346a** and **346c** are 78.71(16)° and 77.30(16)° respectively, as compared to 36.3(3)° for C3'-C2'-N1-C2" in secondary carbamate **335a**. Indeed, in solution there is restricted rotation about the Ar-N bonds of all the tertiary carbamates **342** and **346** making C4 and C6 (CH_2S) of the dithiane moiety non-equivalent in the ^{13}C NMR spectra, with two signals appearing in the chemical shift range of 31-33 ppm. Furthermore, the benzylic hydrogen atoms of carbamate **346b** and the allylic hydrogen atoms of carbamates **346c** and **346d** are inequivalent in the ^1H NMR spectra of these compounds, confirming that they are diastereotopic. Interestingly, each crystal of

dithiane **346a** is homochiral (though of course the material as a whole is racemic), while carbamate **346c** produces racemic crystals. Presumably, the lower electrophilicity of tertiary carbamates **346a-c** compared to both secondary carbamate **335a** and imide **334**, combined with the absence of an acidic proton in close proximity to the benzylic carbon atom, must account for their stability to the Schrock carbene.
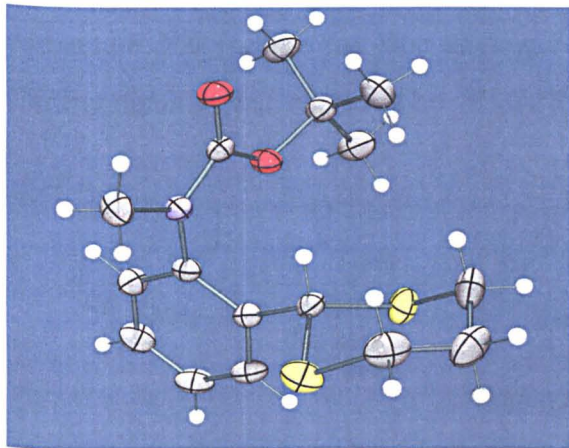
Figure 21 Structure of carbamate **346a**
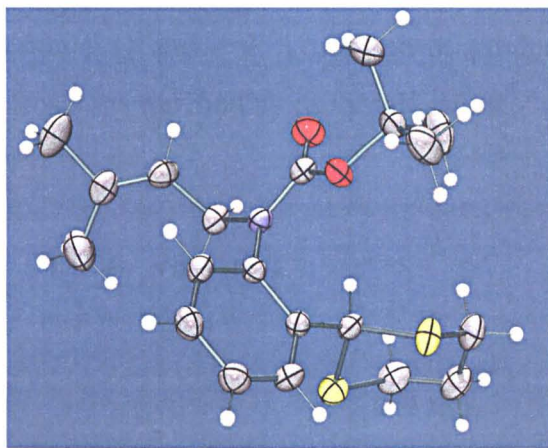
Figure 22 Structure of carbamate **346c**

As in the *N*-Boc indole series, we investigated using fewer equivalents of the titanium carbene, and found that 3 equivalents of thioacetal **346a** converted resin-bound ester **309a'** into indole **348aa'** in almost identical yield (Scheme 138), under the standard reaction sequence (see appendix 1 for ^{1}H NMR spectra of indole **348aa'**).
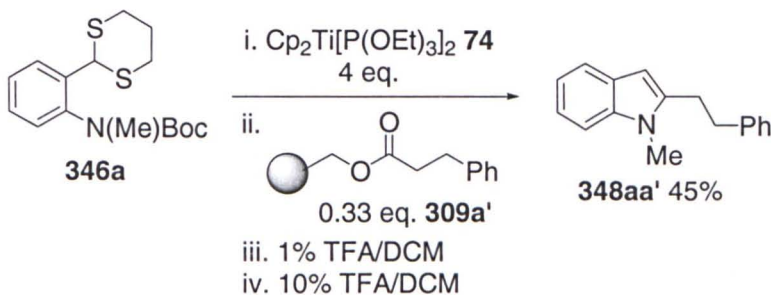
Scheme 138

Although in theory only two equivalents of titanium(II) complex **74** should be needed to generate titanium alkylidenes from thioacetals, we found that using fewer than 4 equivalents of titanocene dichloride with respect to the thioacetals gave very poor yields of indoles. Thus, the optimum ratio of reagents for the benzylidenation reaction appears to be 12 eq. titanocene dichloride: 3 equivalents of thioacetal: 1 equivalent of resin-bound ester.

9.2 Use of *O*-Benzyl and *O*-Methyl carbamates

Next we investigated the stability of carbamates other than the *tert*-butyl carbamate under Takeda conditions. *N*-Methyl carbamate **349** was synthesised from aniline **331** in two steps (Scheme 139). *O*-Methyl carbamate **350** was prepared in high yield employing methyl chloroformate. Deprotonation using LDA and quenching the anion with MeI then gave *N*-methyl carbamate **349**. No solubility problems were encountered with the lithium salt of carbamate **350** (unlike the Boc analogue - section 9.1) and a 9: 1 mixture of product: starting material was observed by ¹H NMR spectroscopy, purified by recrystallisation.
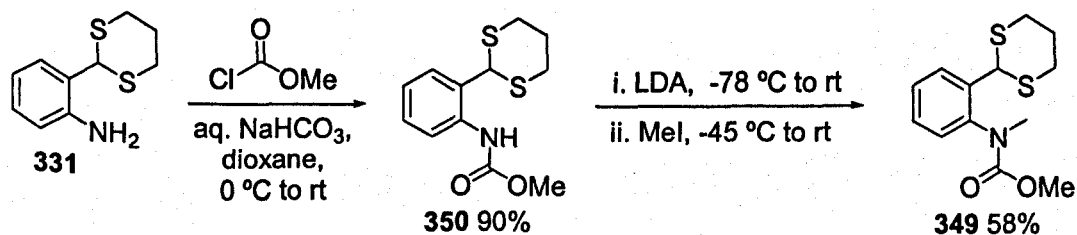
Scheme 139

N-Methyl carbamate **351** was synthesised in a similar fashion. *O*-Benzyl carbamate **352** was synthesised employing benzyl chloroformate,[235] but was not isolated as it decomposed on silica gel during chromatography (Scheme 140). Alkylation by adding NaH to a mixture of carbamate **352** and MeI in DMF yielded *N*-methyl carbamate **351**, purified by chromatography.
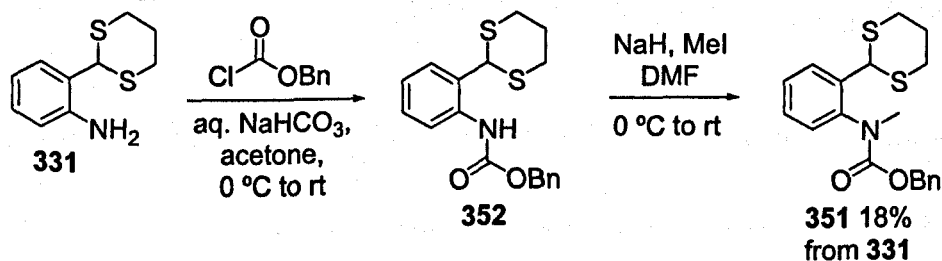
Scheme 140

In solution there is restricted rotation about the Ar-N bonds of tertiary carbamates **349** and **351** making C4 and C6 (CH$_2$S) of the dithiane moiety non-equivalent in the ^{13}C NMR spectra, as with the tertiary *tert*-butyl carbamates. Furthermore, the benzylic hydrogen atoms of carbamate **351** are inequivalent in its ^{1}H NMR spectrum, confirming that they are diastereotopic. Thus, the carbonyl groups of these tertiary carbamates would be electronically less electrophilic than secondary carbamate **335a** and imide **334**. Despite these observations, *O*-methyl carbamate **349** and *O*-benzyl carbamate **351** failed to give the corresponding ketone products when subjected to the standard solid-phase Takeda/cleavage sequence of reactions. Thus, steric hindrance must contribute to the lack of reactivity of the *N*-Boc group towards the Schrock carbene.

The ^{1}H NMR spectrum of ketone **347** is more complicated than would normally be expected and so we took its ^{1}H NMR spectrum over a range of temperatures (Figure 23).

(a) 253 K

At 253 K   2 AB systems

2 *N*Me

2 'Bu

(b) 273 K

At 273 K   1 AB system

1 *N*Me

2 'Bu

(c) 333 K

At 333 K   1 AB system

1 *N*Me

1 'Bu
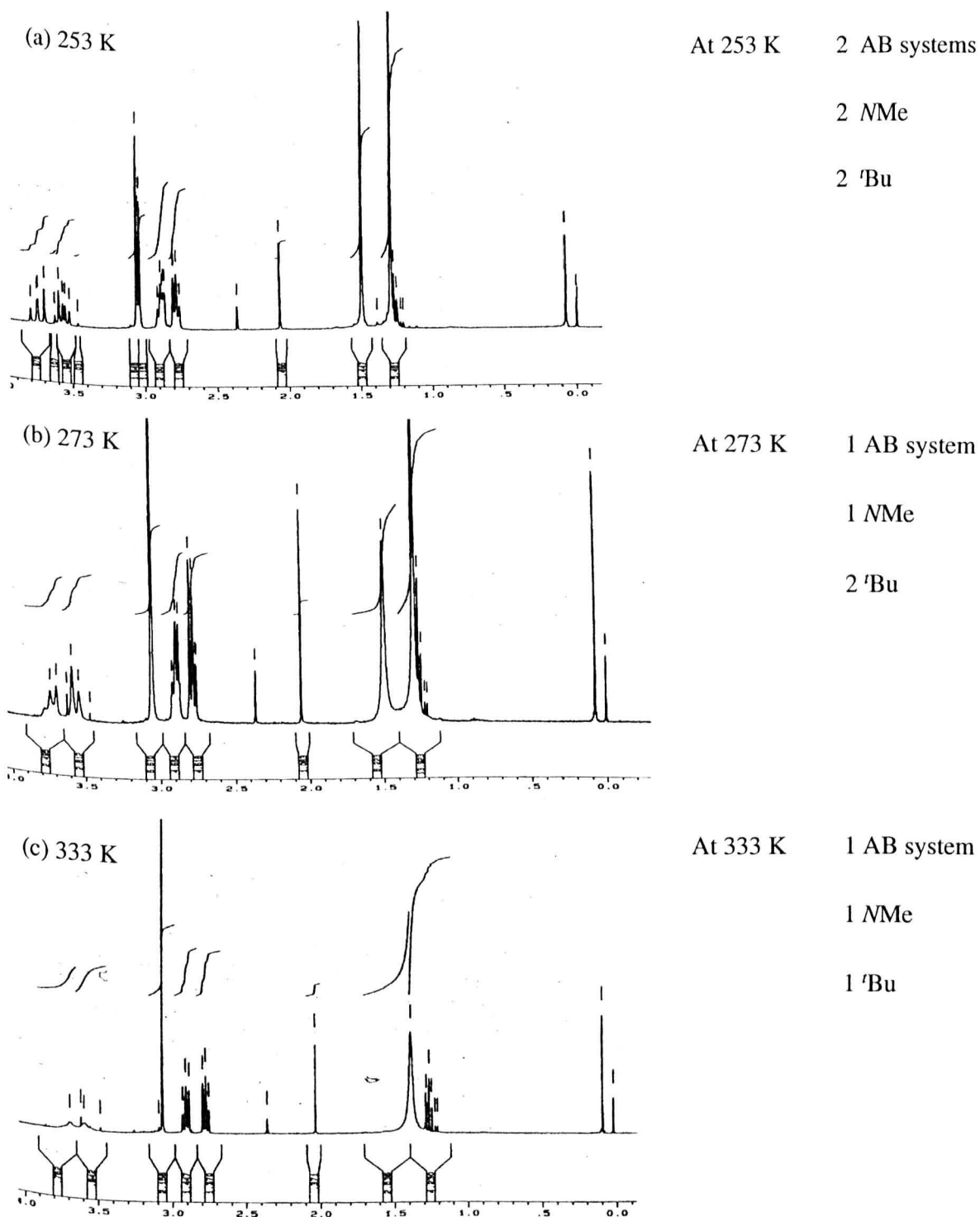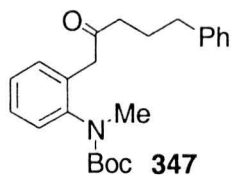
Figure 23

We believe that as the Ar-N(Me)Boc moiety is non-planar (resulting in diastereotopicity), restricted rotation around the C2'-N1, C1-C1' and N1-C1" bonds in ketone **347** (Figure 24) could be responsible for the complexity in the ^{1}H NMR spectrum at certain temperatures.
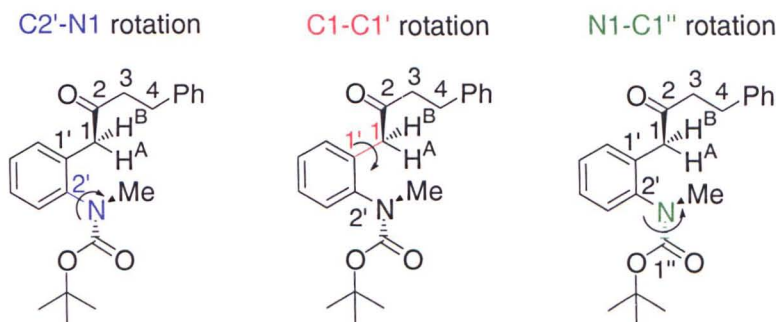
Figure 24

Restricted rotation around the C2'-N1 bond would result in the Ar-N(Me)Boc moiety being non-planar. This would cause H^A and H^B to be diastereotopic and give ketone **347** as a pair of enantiomers (Figure 25).
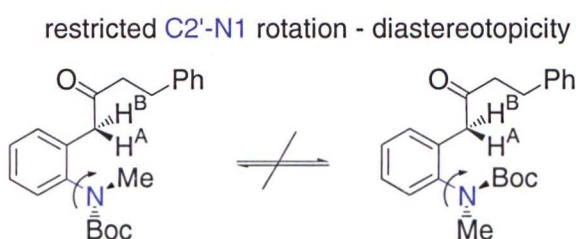
Figure 25

Similarly, restricted rotation around the C1-C1' bond would also cause diastereotopicity and give ketone **347** as a pair of enantiomers (Figure 26).

Figure 26

The combination of restricted rotation around the C2'-N1 and C1-C1' bonds would give rise to diastereomers. Restricted rotation around the C2'-N1 (causing diastereotopicity) and C1-C1' bonds would prevent interconversion (*via* a higher energy intermediate) of the two diastereomers (Figure 27). This phenomenon would result in doubling of signals in the ^{1}H NMR spectrum.

restricted C2'-N1 and C1-C1' rotation
diastereomers do not interconvert rapidly - doubling of signals
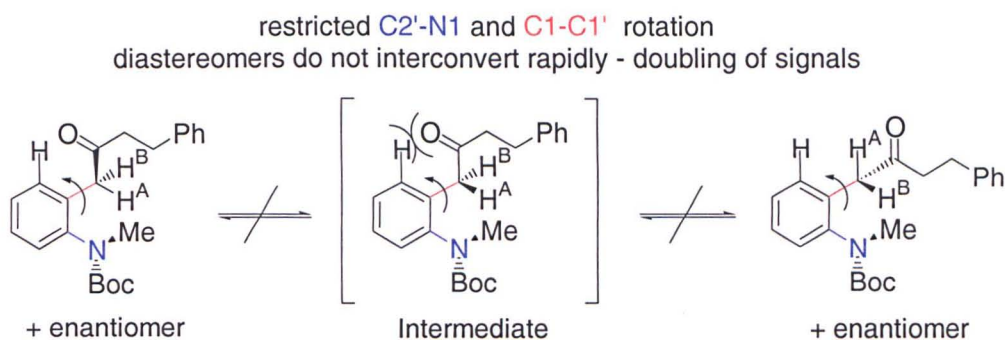
Figure 27

Restricted rotation around the N1-C1" bond (an electronic effect as having nitrogen coplanar with the carbonyl group allows conjugation) would lead to the presence of two geometrical isomers, also causing doubling of signals in the ^{1}H NMR spectrum (Figure 28). However, this interconversion alone cannot lead to diastereotopicity.
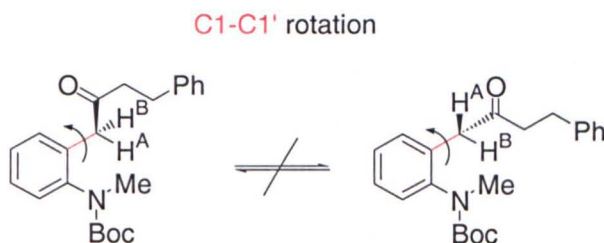
restricted N1-C1" rotation
geometrical isomers do not interconvert - doubling of signals
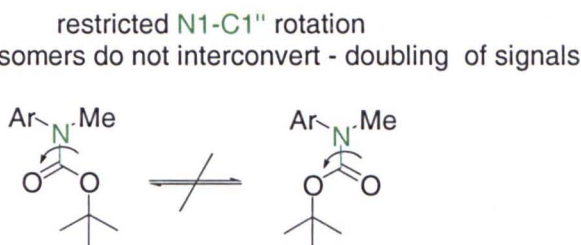
Figure 28

Therefore, if there is restricted rotation around all three C2'-N1, C1-C1' and N1-C1" bonds, ketone **347** will exist as two diastereomers of each geometrical isomer (Figure 29). As a result there will be up to four signals for each inequivalent proton and an AB system will also be observed in the ^{1}H NMR spectrum.

Figure 29

95
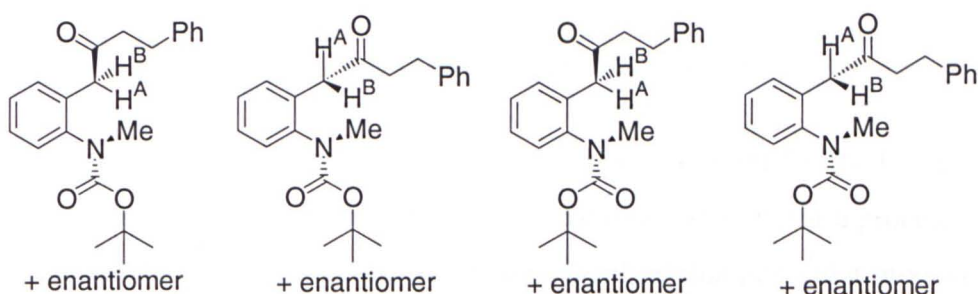
Nuclei involved in a given exchange process, can at higher temperatures, experience an 'average environment' as the process becomes rapid. In NMR spectroscopy, two separate signals (corresponding to nuclei being distinct as a result of this exchange process) move towards the mean as this 'averaging' process increases. Two distinct signals in an NMR spectrum can therefore coalesce to give one signal at the mid-point of the two original signals, upon reaching the coalescence temperature, T_C. Additionally, a given exchange process can cause extra complexity to more than one signal in the NMR spectrum and the order which they begin to coalesce depends on the separation (Hz) of these signals with the closest achieving coalescence first.

Before further considering the phenomenon of coalescence, some relevant rate theory expressions must first be introduced. The Erying equation for simple transformations, including certain bond rotations, can be written:

$$k = KK_B T/ h \exp (-\Delta G^{\neq}/ RT)$$

In this expression, k is the rate constant, K_B is the Boltzmann constant, h is the Planck constant, R is the gas constant, T is the temperature, and $\Delta G^{\neq}$ is the free energy of activation. Moreover, K is also constant, and provided the transition state can easily transfer energy to the surroundings, then K is near unity.

For first order cases of mutual exchange, the Gutowsky equation states that the rate of rotation, k_C, at the temperature of coalescence, T_C, where $\Delta \upsilon$ is the measured difference in frequency (Hz) of the NMR signals which are approaching coalescence, is given by

$$k_C = \pi (\Delta \upsilon)/ \sqrt{2}$$

If k_C is substituted for k in the Erying equation, natural log is converted into $\log_{10}$, and then the values for K_B, h, and R are included, then the equation simplifies to

$$\Delta G^{\neq} (cal) = 4.57 \, T_C (10.32 + \log_{10} T_C - \log_{10} k_C) \text{ or}$$

$$\Delta G^{\neq} (J) = 2.303 \times 8.314 \, T_C (10.32 + \log_{10} T_C - \log_{10} k_C)$$

and despite the difficulty in identifying the exact coalescence point T_C, the Erying equation in these forms can be used to calculate approximate energy barriers for a process. Also, $\Delta \upsilon$ can be used for any coalescing signals, which are a result of that particular process.

At 253 K there may be restricted rotation around the C2'-N1, C1-C1' and N1-C1" bonds in ketone **347** which would result in a mixture of two diastereomers of each geometrical isomer (Figure 29). The ^{1}H NMR spectrum is complex, and although up to four signals for each inequivalent proton and an AB system could be observed, we actually observe two *t*-Bu singlets, two *N*Me singlets and two AB systems (Figure 23a).

At 273 K the ^{1}H NMR spectrum contains two *t*-Bu singlets, one *N*Me singlet, and one AB system (Figure 23b). This may suggest that diastereomers are no longer present because there is rapid rotation on the NMR timescale about the C1-C1' bond at 273 K. The AB system remains as there is still restricted rotation about the C2'-N1 bond. Thus, there remains one compound as a mixture of geometric isomers (Figure 30) due to restricted rotation about the N1-C1" bond. For this situation we would expect to see up to two signals for each inequivalent proton and AB system, but actually we only observe two signals for the Boc group.
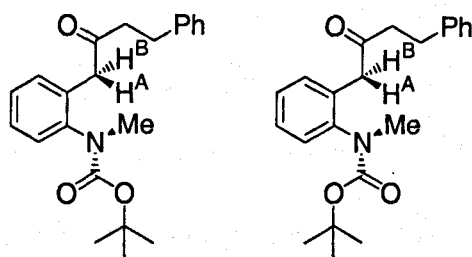
Figure 30

At 333 K the ^{1}H NMR spectrum contains one *t*-Bu group, one *N*Me singlet, and one broadened AB system (Figure 23c). This suggests that there is still restricted rotation about the C2'-N1 bond, but broad singlets are observed as the temperature is close to the coalescence temperature. No geometric isomers remain as there is now free rotation about the N1-C1" bond. Therefore, the ^{1}H NMR spectrum (Figure 23c) contains one signal for each inequivalent proton, but an AB system, as expected.
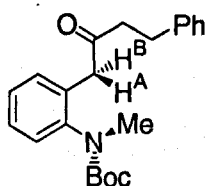
Figure 31

The order in which restriction of rotation around the C2'-N1, N1-C1", and C1-C1' bonds are overcome upon raising the temperature, cannot be definitively stated. Either restriction of rotation around the C1-C1' or C2'-N1 bonds must be overcome last as ketone **347** still contains an AB system at 333 K. However, the ^{1}H NMR spectra of tertiary carbamates **346a** and **346c** prove that H^A and H^B are diastereotopic (Chapter 9.1) as a result of restricted rotation around their analogous C2'-N1 bonds. Also, the crystal structures of carbamates **346a** and **346c** show that the C1'-C2'-N1-C1 torsion angles are 78.71(16)° and 77.30(16)° respectively (Chapter 9.1), suggesting that there is a substantial energy barrier to coplanarity of the Boc and aryl groups in these compounds. Therefore, we propose that there is a similar energy barrier for rotation around the C2'-N1 bond in ketone **347** and so this is the last barrier to be overcome. At 273 K the ^{1}H NMR spectrum contains two *t*-Bu groups, suggesting that the restriction on rotation around the N1-C1" bond is overcome second upon raising the temperature.

If we approximate 273 K as T_C and take $\Delta\upsilon = 10.42$ (obtained from fine doublet splitting of the AB system in the NMR spectrum in Figure 23a) in the simplified Erying equation above, we obtain a value of 59.54 KJMol^{-1} for the free energy barrier to rotation around the C1-C1' bond. This energy barrier seems very high for the rotation depicted in Figure 27, and so we conclude that another explanation cannot be ruled out.

Therefore, if there is only restricted rotation around the C2'-N1 and N1-C1" bonds at low temperature, and not around the C1'-C2 bond, ketone **347** will exist as atropisomers (and so containing diastereotopic protons) and as a pair of geometrical isomers (Figure 32). As a result up to two signals for each inequivalent proton and AB system could be observed in the ^{1}H NMR spectrum.

Figure 32

At 253 K if there is restricted rotation around the C2'-N1 and N1-C1" bonds ketone **347** could contain diastereotopic protons and exist as a pair of geometrical isomers (Figure 32). The ^{1}H NMR spectrum is complex and we observe two *t*-Bu singlets, two *N*Me singlets

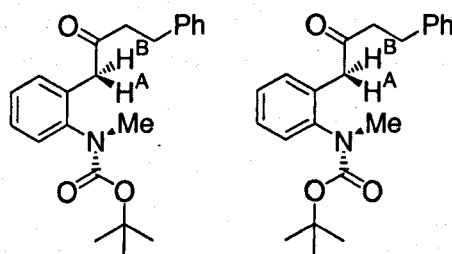and two AB systems (Figure 23a), which is correct for having two signals for each inequivalent proton and AB system.

At 273 K the ^{1}H NMR spectrum contains two broad *t*-Bu singlets, one *N*Me singlet, and one broadened AB system (Figure 23b). We have passed the coalescence temperature for the *N*Me signals and the signals for one of the diastereotopic AB hydrogens have coalesced; the other now being close to its coalescence temperature. At 273 K we are approaching, but have not passed, the coalescence temperature for the Boc groups resulting from restricted rotation about the N1-C1" bond. It should be noted at this temperature that the presence of the AB system and the two Boc groups must be a result of two different processes since the AB system integrates exactly as 1:1 although the two Boc signals quite clearly do not.

At 333 K the ^{1}H NMR spectrum contains one broad *t*-Bu singlet, one *N*Me singlet, and one broadened AB system (Figure 23c). This suggests that there is now rapid rotation on the NMR timescale about the N1-C1" bond. However, the AB system resulting from restricted rotation about the C2'-N1 bond has not yet coalesced, although broad singlets are observed as the temperature is close to the coalescence temperature.
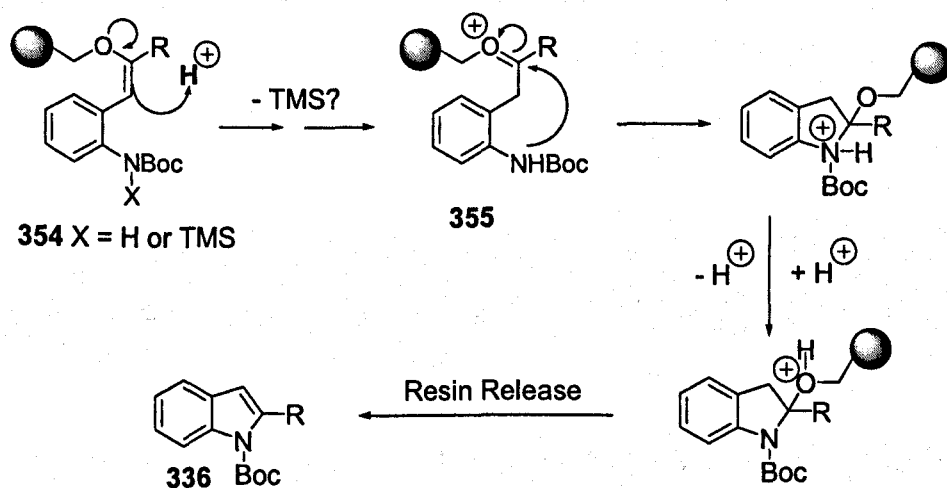
If we approximate 273 K as T_C and take $\Delta\upsilon = 10.42$ (obtained from fine doublet splitting of the AB system in the NMR spectrum in Figure 23a) in the simplified Erying equation above, we obtain a value of 59.54 KJMol^{-1} for the free energy barrier to rotation around the N1-C1" bond. If we approximate 333 K as T_C and take $\Delta\upsilon = 73.77$ (obtained from the difference in frequency of the two Boc singlets in the NMR spectrum in Figure 23a) in the simplified Erying equation above, we obtain a value of 67.67 KJMol^{-1} for the free energy barrier to rotation around the N1-C1" bond. This value is too high as the coalescence temperature for the Boc signals is below 333 K. Therefore, for the rotation around the N1-C1" bond $\Delta G^{\neq} \leq 59.54$ KJMol^{-1}. Similarly, if we approximate 333 K as T_C and take $\Delta\upsilon = 68.39$ (obtained from doublet splitting of the AB system in the NMR spectrum in Figure 23a) in the simplified Erying equation above, we obtain a minimum value of 67.97 KJMol^{-1} for the free energy $\Delta G^{\neq}$ barrier to rotation around the C2'-N1 bond. This value can only be taken as a minimum as the coalescence point has not yet been reached at 333 K. The minimum value is only approximate but seems appropriate as the C-N barrier to rotation in $CH_3CON(CH_3)_2$ is around 80 KJMol^{-1}.

Therefore, we conclude that both explanations are possible and so we cannot definitively state (based on the information we have) which sequence of events is occurring.

Chapter 10 – Mechanisms of Cleavage from Resin

Release of *N*-Boc indoles **336** could either involve cyclative termination (Scheme 141), or postcleavage cyclisation (Scheme 142) of a ketone **353**, that is released by one of the mechanisms below. In the cyclative cleavage pathway (Scheme 141), protonation of enol ethers **354** to give oxonium ions **355** is followed by intramolecular addition. An elimination reaction then gives *N*-Boc indoles **336**. Release of ketones **353** (Scheme 142) from the resin (as in synthesis of *N*-alkyl indoles) must involve protonation as above to give enol ether **356**, followed by nucleophilic attack by an external nucleophile (TFA anion or water). This nucleophilic attack could either proceed *via* acetal hydrolysis (arrows a), or S_N1 substitution (arrow b) or S_N2 substitution (arrows b and c) to yield ketone **353**. In the case of *N*-Boc indoles, any ketones **353** formed by this mechanism, would most probably undergo *N*-desilylation before release from the resin, given that *N*-Si cleavage is facile (as discussed earlier).

Cyclative termination Pathway

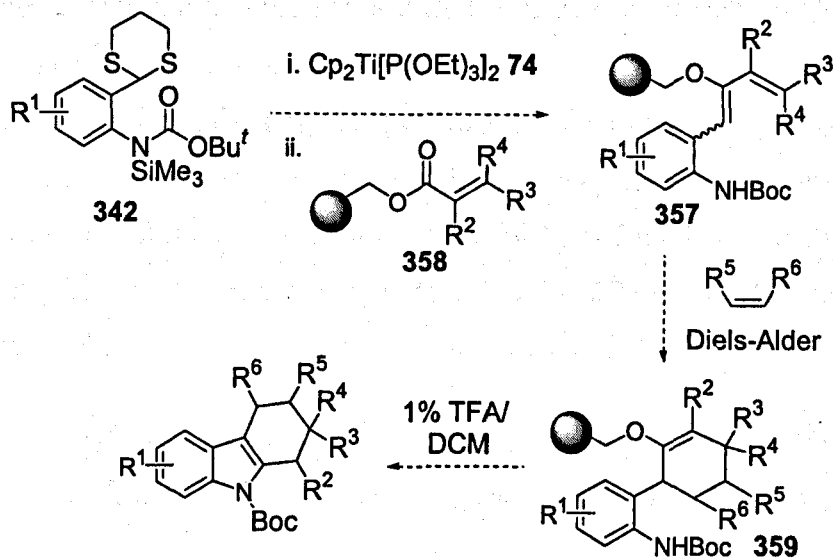**Scheme 141**
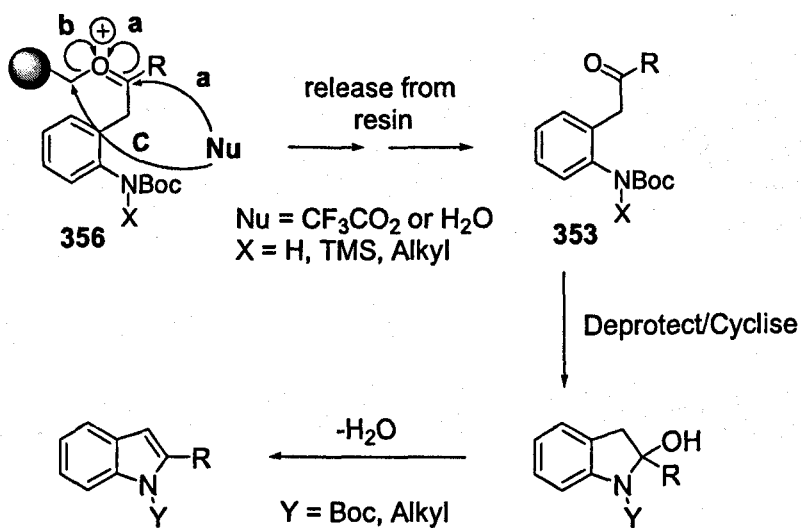
Scheme 142

The solid-phase synthesis of ketones **353** shows that cyclative termination is not necessary for release. However, introducing a spacer group between the benzylic polystyrene moiety and the ester/enol ether oxygen moiety may ensure cyclative termination by preventing S_N1 and S_N2 cleavage (although if pathway a is responsible for cleavage, it cannot be avoided).

# Chapter 11 – Extension of the Indole Synthesis Methodology

11.1 Towards 2,3-fused

We then investigated carrying out Diels-Alder reactions on dienol ethers **357**, attainable by carrying out Takeda reactions on resin-bound acrylic acid derivatives **358** (Scheme 143). The resulting enol ether **359** would allow cleavage and cyclisation to yield the corresponding 2,3-fused indoles.

Scheme 143

Treating *N*-silyl carbamate **342a** with low-valent titanium complex **74** and then ester **309d'** gave the corresponding enol ether **360**. We cleaved dienol ether **360** under the usual resin-cleavage conditions and obtained the corresponding *N*-Boc indole **336ad'** in high yield (Scheme 144). Dienol ether **360** was treated with *N*-methylmaleimide under literature solid-phase Diels-Alder[124] conditions, and then the standard resin-cleavage conditions (Scheme 144); this yielded only pure indole **336ad'** (60-65% yield) with no sign of the 2,3-fused indole **361** by ¹H NMR spectroscopy.
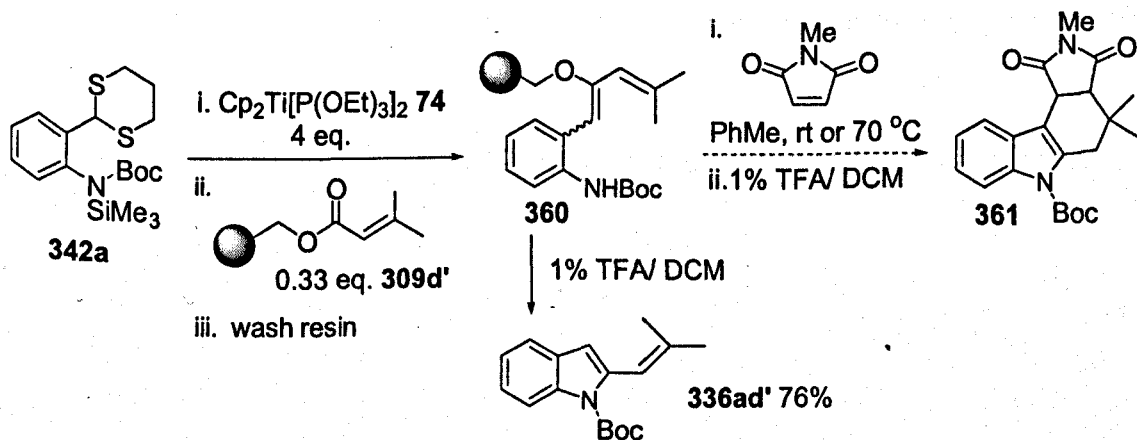
Scheme 144

Presumably, the steric hindrance due to the geminal dimethyl moiety at the dieneol ether terminus in **360** renders such substrates unsuitable for Diels-Alder cycloadditions.

It was decided to employ a simpler system to attempt solid-phase Diels-Alder reactions. We tried, in turn, to alkylidenate commercially available Merrifield REM resin **361** and the resin-bound ester **362** (derived from *trans*-methyl acrylic acid) with the titanium carbene derived from thioacetal **285**. It was hoped that the reduction in steric hindrance at the dienol ether terminus would allow successful cycloaddition to occur. However, after standard resin-cleavage conditions, ketones **363** and **364** were generated in low purity (Scheme 145). The ^{1}H NMR spectra in each case, showed complex mixtures of products were obtained, but significantly, large singlets (δ 6.59, 6.61 and 6.65 ppm) corresponding to cyclopentadienyl (Cp) ligands were observed. This suggests that side reactions, such as 1,4-additions of nucleophilic titanium alkylidenes (and/or of intermediates formed in their preparation) or alkene metathesis reactions (see section 2.2) on acrylate derivatives **361** and **362**, contributed to the low purity of ketones **363** and **364**.
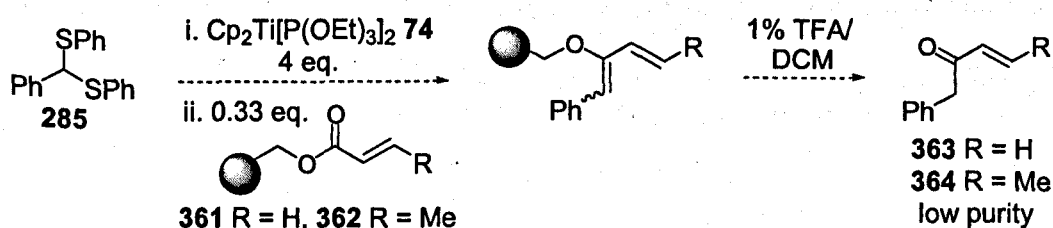
Scheme 145

11.2 Towards Bis-indoles

We then envisaged carrying out two alkylidenations on resin-bound oxalate esters **365** to generate resin-bound bis-enol ethers **366**, which could then undergo cleavage from resin and cyclisation to yield symmetrical bis-indoles **367** (Scheme 146).
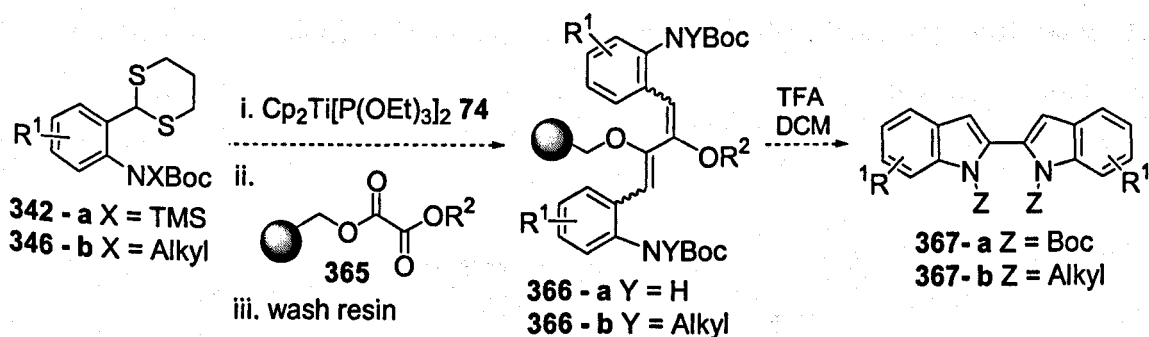
Scheme 146

Resin bound oxalate **368** was synthesised by adding methyl oxalyl chloride to Wang resin. Resin-bound oxalate **369** was synthesised, by adding oxalyl chloride to Wang resin and quenching the intermediate with ethanol. In both cases, two ester stretches were observed in the Infrared (Golden Gate) spectrum (Scheme 147), confirming product formation.
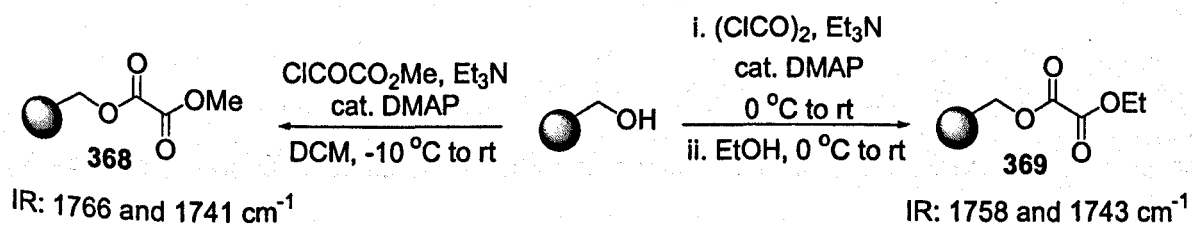
Scheme 147

Standard alkylidenation reactions were carried out in turn, on resin bound oxalates **368** and **369**, employing 6 equivalents of thioacetal and 24 equivalents of low-valent titanium complex **74**, which corresponds to our proposed optimal number of equivalents for both ester groups (Scheme 148). Both resins were subjected to cleavage conditions, employing 5% TFA in DCM, and the solvent was then removed. In each case we found that the ^{1}H NMR spectrum (obtained in d-6 acetone as the mixture was insoluble in CDCl$_3$) confirmed that there was little evidence of aromatic signals corresponding to the desired product **370**, with large singlets (δ 6.30-6.70 ppm) corresponding to cyclopentadienyl (Cp) ligands observed.
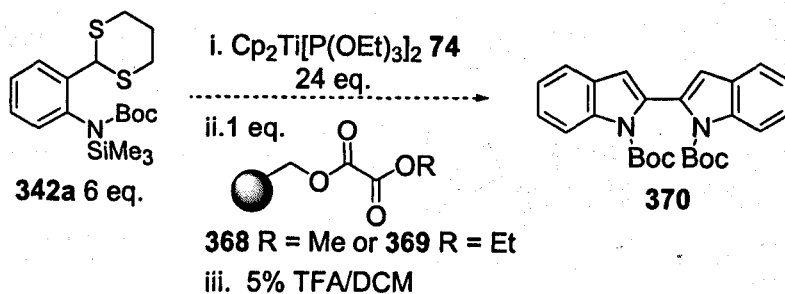
Scheme 148

As little or no aromatic containing product was cleaved from the resin, it suggests that formation of the enol ether from the resin's benzylic ester does not occur. A number of explanations for such a failure are possible. We tentatively propose that co-ordination of a titanium intermediate to either a resin-bound oxalate (such as intermediate **371**, Figure 32) or to a resin-bound enol ether (such as intermediate **372**, Figure 32), could promote premature cleavage from the resin. Also, steric hindrance introduced after alkylidenation at the terminal ester could prevent the second alkylidenation and encourage Michael addition to an intermediate such as **373** (Figure 33). Finally, reduction of the 1,2-dicarbonyl moiety in esters **368** or **369** by the low-valent titanium complex **74** cannot be ruled out.
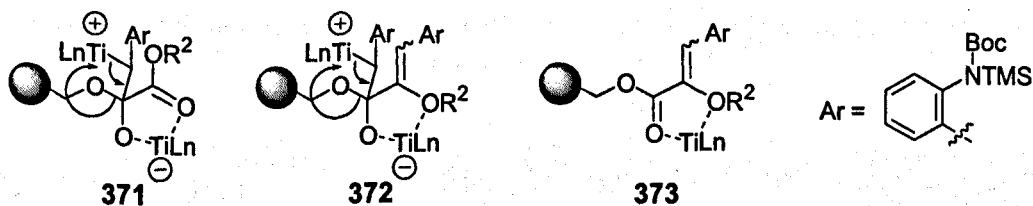

Figure 33

11.3 Towards *iso*-Serotonin Derivatives

We hoped to develop a convenient route to *iso*-serotonin derivatives employing REM[122] resin. Treating REM resin with a range of dialkylamines would generate resin-bound β–amino esters 374,[122] which we hoped to alkylidenate using benzylidene reagents 375, and then transform the corresponding enol ethers into indoles 376 (Scheme 149) by the same methods as used for the conventional indoles (Chapters 8 and 9). Although natural indoles are almost always 3-substituted, 2-substituted indoles are currently of interest (section 5.1). A large range of amines could in theory be tolerated, as well as a wide degree of functionality around the indole ring, allowing an attractive, diversity-based synthesis of serotonin analogues.
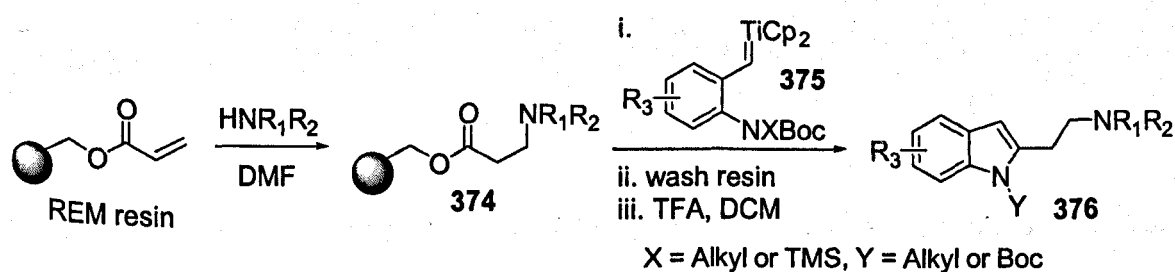
Scheme 149

Initial studies were carried out using GSK "in-house" REM resin 377, which had not been fully characterised. The exact method of preparation of resin 377 is unknown, but it was thought to have been derived from Merrifield resin (1.70 mmol g^{-1} loading) which would result in a loading of 1.64 mmol g^{-1} for resin 377. Resin 377 was treated with morpholine in DMF to yield resin-bound β–amino ester 378, which in turn was used in a range of Takeda reactions employing the titanium alkylidene derived from thioacetal 285 (Scheme 150).
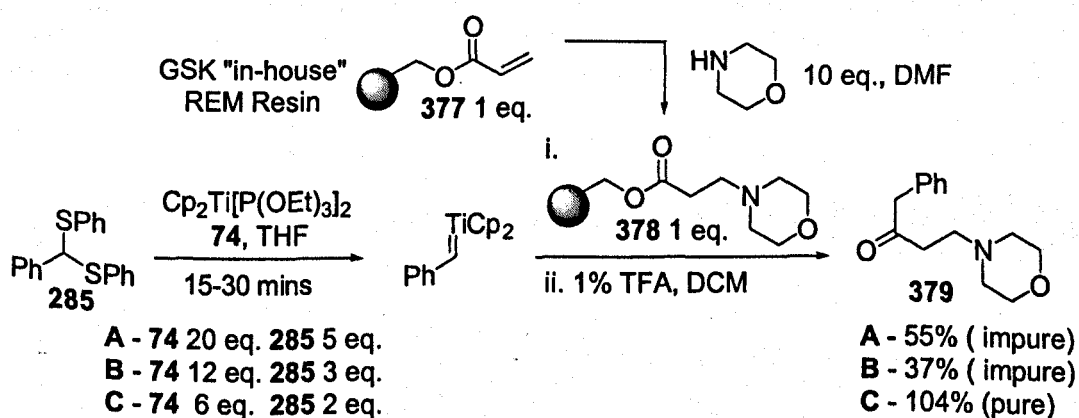
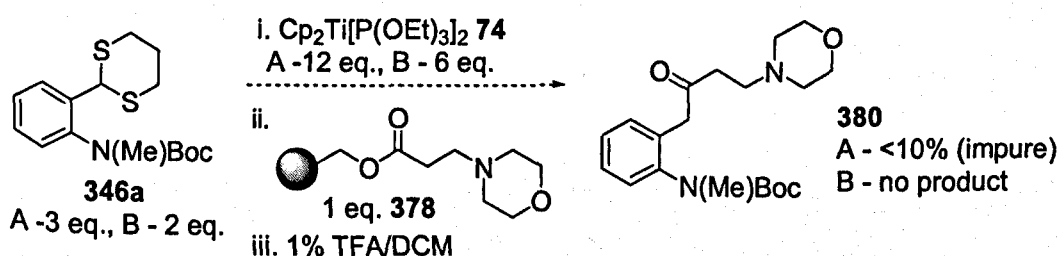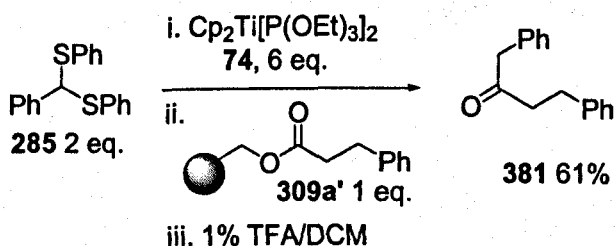**Scheme 150**

The 12-20 eq. of titanocene **74** (assuming complete conversion of Cp_2TiCl_2 to complex **74**) and 3-5 eq. of thioacetal **285** used in our standard Takeda reactions (methods A and B) failed to generate ketone **379** in good purity from ester **378**, upon cleavage from the resin (Scheme 150). The yields obtained were low to moderate and ketone **379** was contaminated with CpTi containing impurities in both cases. We decided to further reduce the excess of reagents used in the Takeda reaction. Employing 6 eq. low-valent titanium complex **74** and 2 eq. of thioacetal **285** (method C), with resin-bound ester **378** yielded ketone **379** in high purity but in greater than 100% yield, confirming that REM resin **377** was not prepared from 1.70 mmol g^{-1} Merrifield resin (Scheme 150). However, this demonstrated that thioacetal **285** could be effectively reduced using just 3 eq. of low-valent titanium complex **74** to form the titanium carbene. It also suggests that alkylidenation of β–amino ester **378** gives cleaner products if less low-valent titanium complex **74** is employed.

Employing thioacetal **346a** and resin-bound ester **378**, our standard conditions (A, scheme 151) yielded ketone **380** in poor yield and very low purity. We then investigated reducing thioacetal **346a** with 3 eq. of low-valent titanium complex **74** (B, scheme 151) but after resin-cleavage ketone **380** was not observed by ^{1}H NMR.

Scheme 151

Employing 6 eq. of low-valent titanium complex **74** and 2 eq. of thioacetal **285**, the standard Merrifield resin-bound ester **309a'**, upon cleavage from the resin, yielded ketone **381** in high yield and excellent purity (Scheme 152). This confirms that 1 eq. of thioacetal **285** requires only 3 eq. of low-valent titanium complex **74** for effective reduction. The lower yield obtained than with ester **378** may simply be explained by poorer loading of ester **309a'** compared to ester **378**.

Scheme 152

Due to the uncertainty in the nature of resin **377**, and therefore β–amino ester **378**, we decided to use commercially available Merrifield-REM resin **382**. Resin **382** was treated with morpholine to give β–amino ester **383**, which was subjected to a range of alkylidenation reactions. Our standard reaction conditions (A, Scheme 153) yielded ketone **379** in poor yield and low purity (CpTi impurities). Employing 10% TFA in DCM as the cleavage conditions improved yields but products were still contaminated with CpTi impurities. Employing 6 eq. of low-valent titanium complex **74** and 2 eq. of thioacetal **285** (B, Scheme 153), gave very low yields (<10%) and CpTi impurities were also observed. We also washed the resin with TMEDA, after subjectiing it to Takeda conditions (B, Scheme 153), in the hope that the co-ordinating solvent could remove Ti containing impurities. However, we were unsuccessful with the same by-products being obtained.
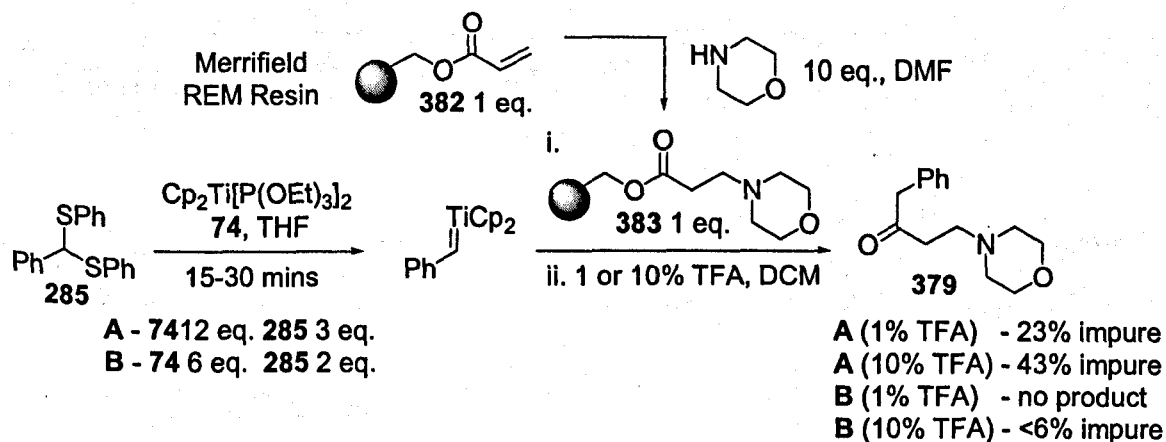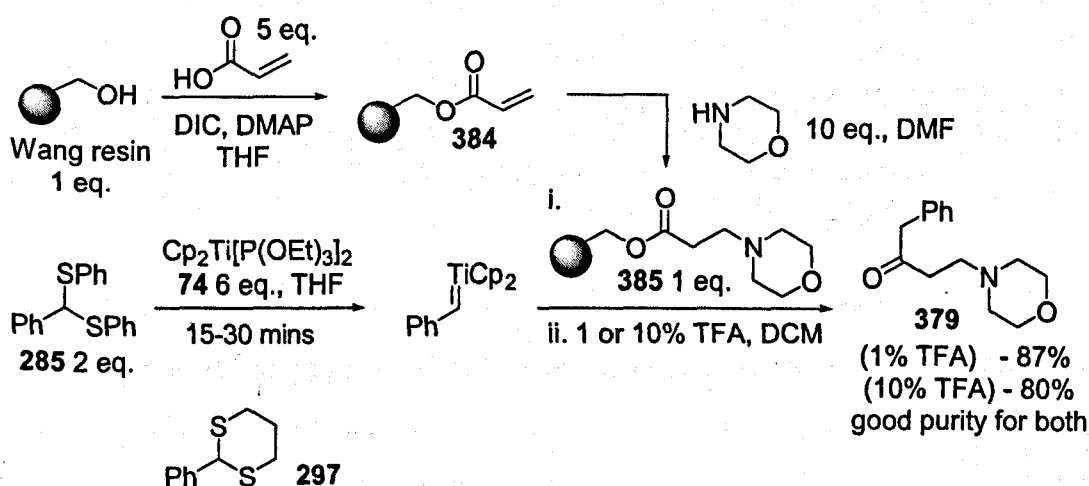

Scheme 153

Employing thioacetal **346a** and resin-bound ester **383**, our standard conditions (Scheme 154) yielded ketone **380** in poor yield and very low purity, even when employing 10 % TFA in DCM as the cleavage conditions.
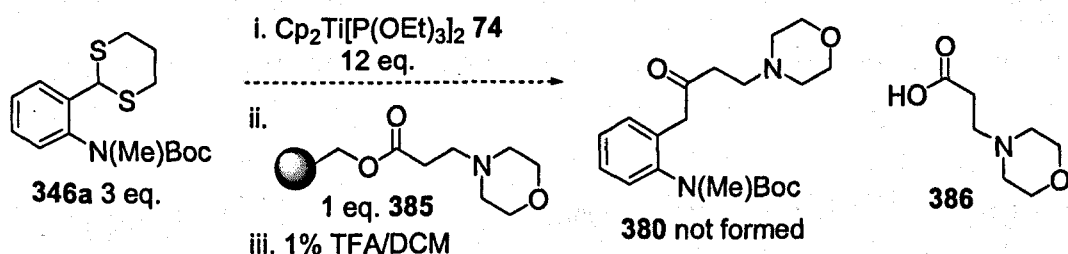

Scheme 154

108
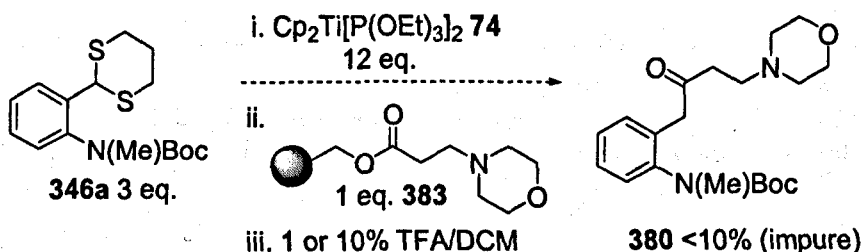
Next we prepared Wang REM resin **384** by coupling acrylic acid to Wang resin (using the standard coupling procedure used for ester **290**, see section 8.2), which was then treated with morpholine to yield β–amino ester **385** (Scheme 155). 2 eq. of thioacetal **285** was reduced employing 6 eq. of low-valent titanium complex **74**, and the resulting Ti carbene solution was added to ester **385** (Scheme 155). Upon resin-wash and cleavage from the resin (both methods), ketone **379** was obtained in high yields and good purity with tiny amounts of CpTi impurities being observed by ^{1}H NMR. Employing ester **385**, 2 eq. of thioacetal **297** failed to be effectively reduced by 6 eq. low-valent titanium complex **74**, as ketone **379** was not cleaved from the resin with aromatic signals not observed in the ^{1}H NMR spectrum.

Scheme 155

Employing thioacetal **346a** and resin-bound ester **385**, our standard conditions (scheme 156) failed to yield ketone **380** upon resin-cleavage. Only the corresponding carboxylic acid **386** was observed in the ^{1}H NMR spectrum of the crude material following cleavage from resin (this is a result of unreacted ester **385** being cleaved from the resin by the TFA solution).
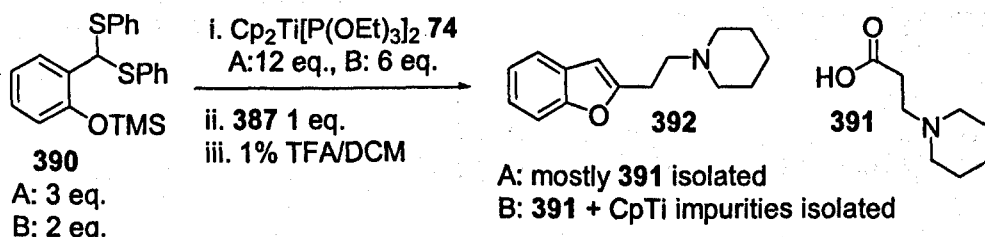

Scheme 156

It was important to establish if the problems experienced were not simply due to the oxygen atom in the morpholine moiety (perhaps providing an extra co-ordination point for titanium intermediates). Thus piperidene was added to Wang REM resin 384 to yield resin-bound β–amino ester 387. Thioacetal 342a was reduced using the standard conditions, and the mixture was added to ester 387, which upon resin-cleavage yielded a crude mixture of products containing mostly indole 389, but it also contained impurities including CpTi containing compounds and at least one other aromatic compound (Scheme 157).
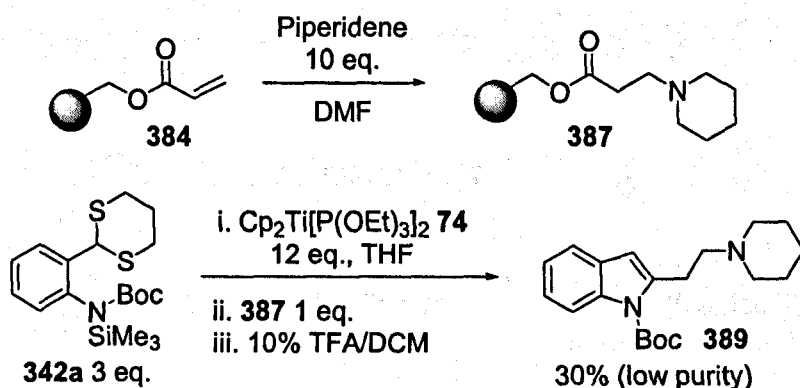
Scheme 157

Next we investigated using thioacetal 390[214] (obtained from another member of the group). Co-ordination of the *ortho* protected nitrogen moiety to a titanium intermediate could not be ruled out, and so the protected oxygen moiety could behave differently. We checked if the bis(thiophenyl) thioacetal moiety could be reduced with 3 eq. of low-valent titanium 74 (A, Scheme 158). After subjecting ester 387 to the low-valent titanium carbene mixture, and then washing the resin and cleaving from the resin, only carboxylic acid 391 was isolated with no sign of the desired benzofuran 392 observed by ^{1}H NMR. Using our standard, optimal set of conditions (B, Scheme 158), similar results were obtained along with large amounts of CpTi containing impurities. If, indeed co-ordination of the *ortho*-nitrogen atom is the problem, then the same could be occurring in the oxygen series.

Scheme 158

Next we prepared Merrifield REM resin **393** by reacting acrylic acid with Merrifield resin by a standard procedure.[122] This was treated with morpholine to yield β–amino ester **394** (Scheme 159). Employing thioacetal **346a** and resin-bound ester **394**, our standard conditions (A, Scheme 159) failed to yield ketone **380** upon cleavage from the resin. Lowering the number of equivalents (B, Scheme 159) was also unsuccessful. In both cases mostly CpTi signals were observed in the crude ^{1}H NMR spectrum.
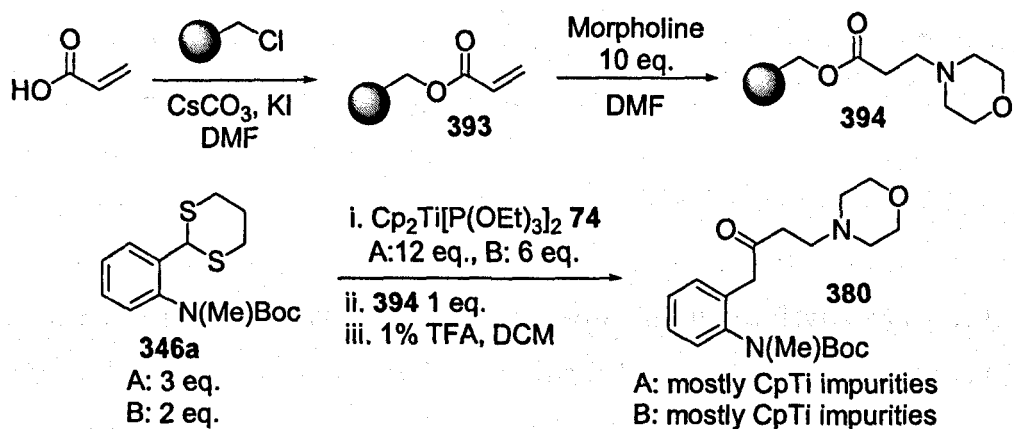
Scheme 159

Finally we employed thioacetal **346b** and resin-bound ester **394**, under standard conditions (scheme 160). Upon cleavage from the resin, ketone **395** was the main product, but signals in the ^{1}H NMR spectrum were broad and difficult to interpret. The crude material was subjected to the standard deprotection cyclisation conditions, and yielded a mixture of compounds. This mixture contained mostly the desired indole **396** and was purified by chromatography and a ^{1}H NMR spectrum was obtained. Purification was difficult due to the small amounts of material obtained, and indole **396** was not obtained completely pure, and so was not fully characterised.
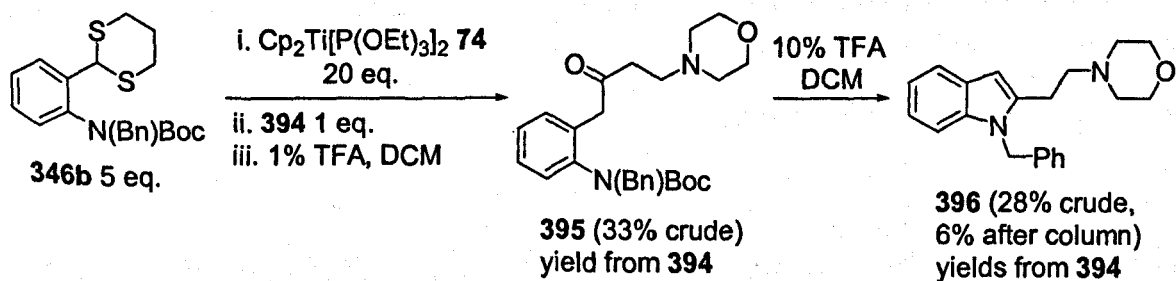
Scheme 160

The failure to effectively alkylidenate resin-bound β–amino esters with titanium benzylidenes containing a heteroatom in *ortho* position remains unexplained. However, thioacetal **285**, which is more easily reduced (with 3 eq. of low-valent titanium complex **74**), cleanly reacted with β–amino esters under Takeda conditions. PhS thioacetals are known to be more easily reduced than 1,3-dithianes but the failure to effectively reduce thioacetal **390** (with 3 eq. of low-valent titanium complex **74**) suggests that the *ortho* heteroatom is significant. This could be explained, by its presence slowing down titanium alkylidene formation at the more electron-rich benzylic position, hence resulting in a larger excess of low-valent titanium **74** being required for successful reduction. Excess titanium intermediates present could then interact with any unreacted β–amino ester.

However, the two most successful attempts [formation of indoles **389** (Scheme 157) and **396** (Scheme 160)] utilised titanium alkylidenes with the largest degree of steric hindrance around the *ortho* nitrogen heteroatom. If the nitrogen lone pair is out of the plane (therefore not in conjugation with the aromatic ring), the less electron-rich benzylic thioacetals may be more easily reduced with low-valent titanium complex **74**. However, to achieve clean reaction with β–amino esters, PhS thioacetals may be required.

It should also be noted that the nature of resin **377** still remains unclear.

Chapter- 12 Synthesis of Quinolines

12.1 Strategy

We envisaged using thioacetals **397** to generate titanium alkylidenes that would allow the synthesis of quinolines using our methodology. Merrifield resin-bound esters **309** would be converted into the corresponding enol ethers, which after cleavage from resin would yield ketones **398** (Scheme 161). A Boc-deprotection/cyclisation/oxidation series of reactions (preferably in one pot) would then yield quinolines **399**.
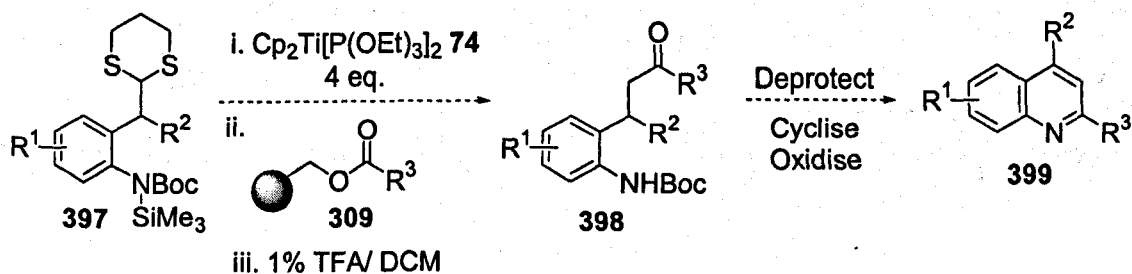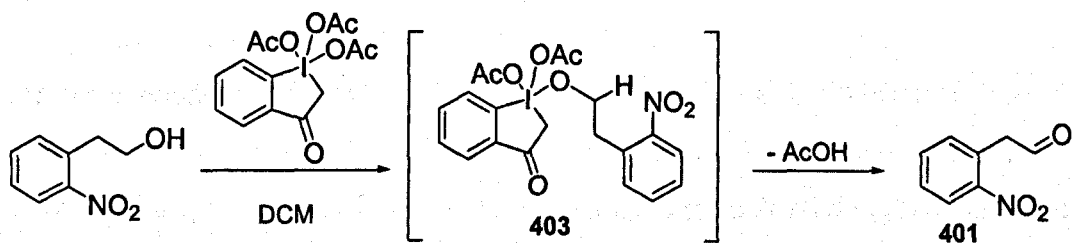

Scheme 161

12.2 Synthesis of Thioacetal Substrates

Our first strategy for the synthesis of thioacetals **397** involved oxidation of commercially available 2-nitro-phenethyl alcohol **400** to yield aldehyde **401**, which could then be converted into the corresponding thioacetal **401** (Scheme 162). Work in this area was carried out by an undergraduate project student, who found that this strategy although successful, gave poor results on reaction scale-up. Both the Parikh-Doering modified Swern[237] (activation by pyridine-sulfur trioxide complex) and pyridinium chlorochromate[238] (PCC) oxidations, were attempted. Improved results were obtained when the aldehyde was converted into the thioacetal without isolation (Scheme 162). Presumably, the *ortho*-nitro moiety causes problems with the standard oxidation methods, and 14% was the best yield obtained for the two step process. Employing PCC oxidation, I encountered similar problems, with by-products being formed during oxidation even when carefully monitoring the reaction progress by TLC.
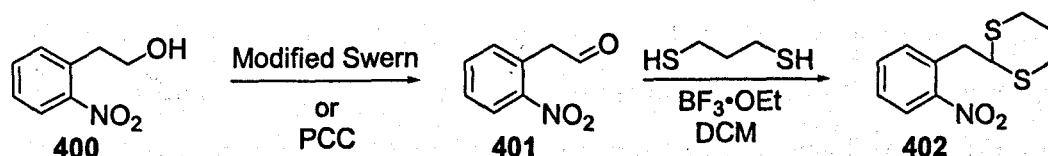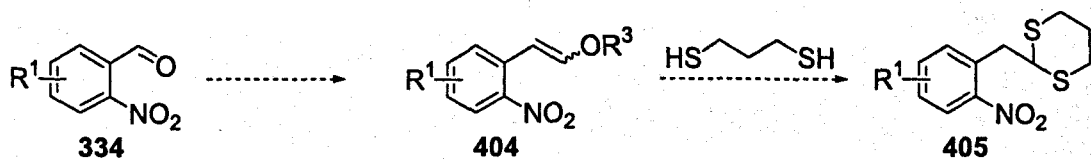

Scheme 162

The use of the commercially available Dess-Martin periodinane[239] allowed the oxidation of 2-nitro-phenethyl alcohol to aldehyde **401** with >90% conversion determined from the ^{1}H NMR spectrum of the crude mixture (Scheme 163). Although the exact mechanism of the reaction is unknown it is believed to proceed *via* an intermediate such as **403** which, could collapse to yield the aldehyde **401** with elimination of acetic acid. Aldehyde **401** was not isolated as we abandoned this route because no other 2-nitro-phenethyl alcohols are commercially available, and as a result a more general synthesis of thioacetal substrates was developed.

Scheme 163

We envisaged an improved strategy would involve Wittig alkenation of 2-nitrobenzaldehydes **334** (a range of which are available) to form the corresponding enol ethers **404** which could then be converted into thioacetals **405** (Scheme 164).
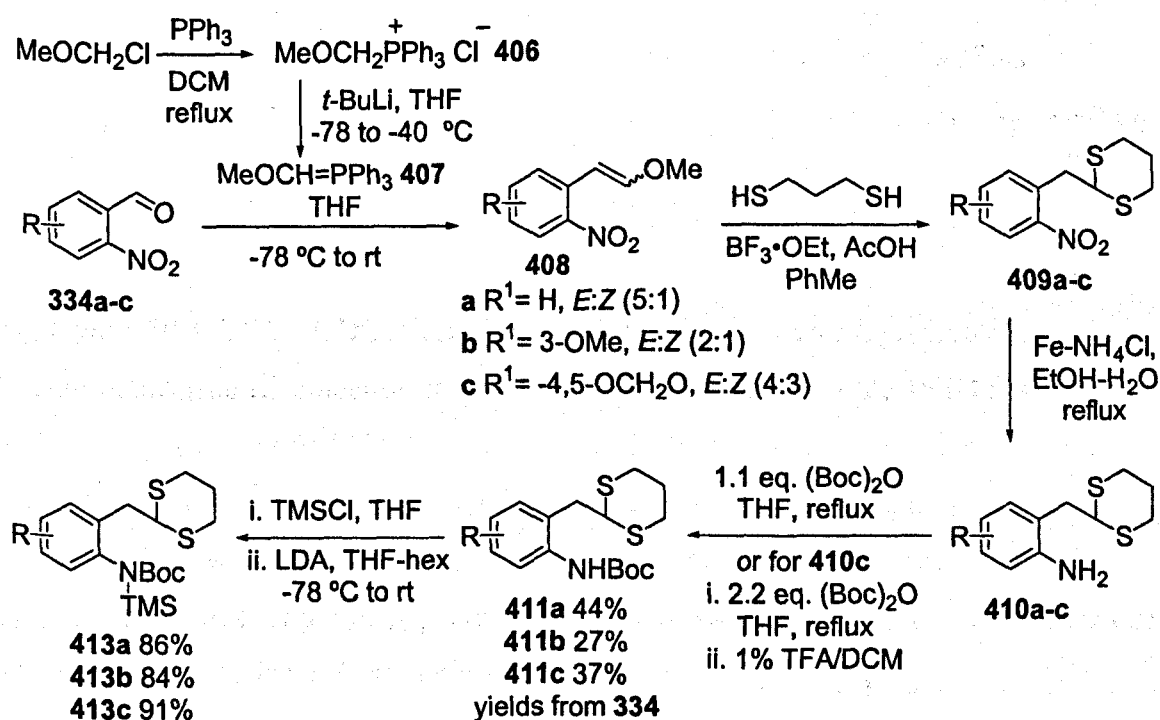

Scheme 164

The phosphonium salt **406** of methoxymethyl chloride (MOMCl) was prepared by a litterature procedure,[240] heating a slight excess of MOMCl with triphenylphosphine under reflux in DCM (Scheme 165). This was then converted into phosphonium ylid **407** employing *tert*-butyllithium in THF. The Wittig reaction then proceeded upon addition of the 2-nitrobenzaldehydes **334a-c** to the phosphonium ylid **407** in THF at low temperature, followed by warming to room temperature to yield enol ethers **408a-c**. Thus, 2-nitrobenzaldehyde **334a** was converted into enol ethers **408a**, isolated as a mixture of geometrical isomers (predominantly the *E* isomer). Enol ethers **408a** were not purified but were converted into thioacetal **409a** directly, following work-up of the Wittig reaction. During thioacetal formation, a white precipitate formed, which was filtered off once TLC confirmed complete consumption of starting material. ^{1}H NMR spectroscopy confirmed that this solid consisted of triphenylphosphine containing products. Presumably the boron

trifluoride complexes of triphenyl phosphine and triphenyl phosphine oxide are insoluble in toluene. Thus, after work-up thioacetal **409a** was isolated in good purity. In a similar fashion, 2-nitrobenzaldehydes (R = -3-OMe **334b**, R = -4,5-OCH$_2$O **334c**) yielded the respective enol ethers **408b** and **408c**, as mixtures of isomers. These were then directly converted into thioacetals **409b** and **409c**, respectively, with removal of most of the triphenyl phosphine and triphenyl phosphine oxide impurities, as above. Only small portions of thioacetals **409a-c** were purified by recrystallisation for characterisation. The bulk of the nitro compounds **409a-c** were reduced to give anilines **410a-c** (Scheme 165). Anilines **410a** and **410b** were not isolated, but were converted into carbamates **411a** and **411b**, respectively, by heating with di-*tert*-butyl-dicarbonate. Aniline **410c** was converted into the corresponding imide **412** before mono-deprotecting using TFA in DCM to yield carbamate **411c**. Purification by recrystallisation gave pure carbamates **411a-c** in good yields over 4-5 steps. *N*-Silylation as before, then gave pure *N*-silyl carbamates **413a-c** in good yields, which were again of low stability making full characterisation difficult.
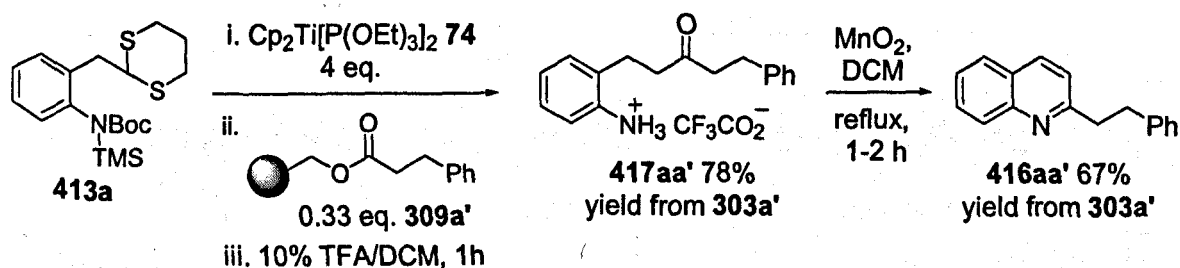

Scheme 165

12.3 Synthesis of Quinolines

N-Silyl carbamate **413a** was subjected to our standard solid phase reaction sequence, using resin-bound ester **309a'** and we obtained ketone **414**, presumably *via* resin-bound enol ether **415** (Scheme 166). A range of Boc deprotection/cyclisation strategies were tested, including treating the ketone with stronger TFA under an oxygen atmosphere and use of acidic oxidant nitric acid. Both gave dissapointing results, yielding complex mixtures of compounds by ^{1}H NMR spectroscopy, which did contain quinoline **416aa'**, but some uncyclised compounds were also present.
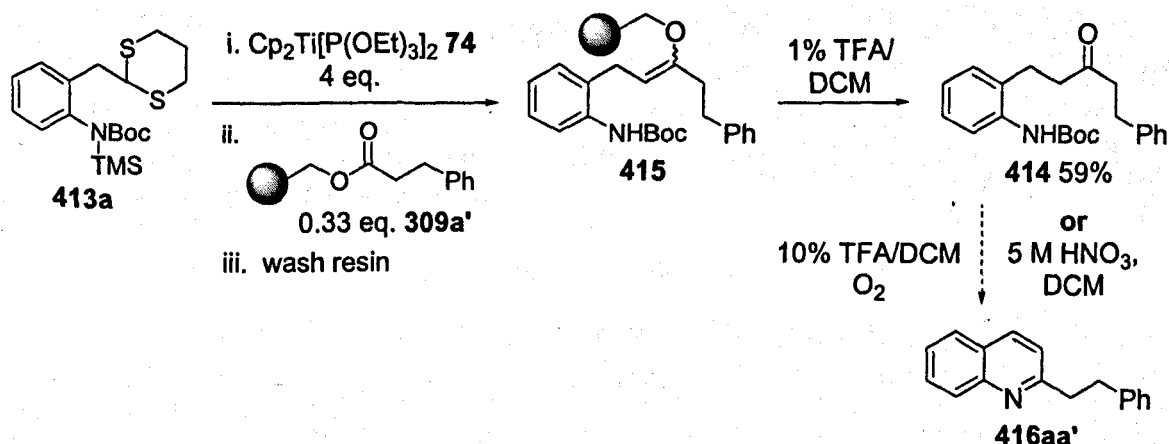
Scheme 166

Employing 10% TFA in DCM and leaving for 1 h, gave cleavage from the resin and concommitant Boc deprotection to yield the aniline trifluoroacetate salt **417aa'** (Scheme 167). Simply heating salt **417aa'** in DCM gave the desired quinoline **416aa'** in good purity (see appendix 1 for ^{1}H NMR spectra of trifluoroacetate salt **417aa'** and quinoline **416aa'**). However, this was not completely reproducable, and we found that adding 5 eq. of manganese dioxide and heating under reflux, in DCM for 1-2 h lead to excellent conversion to quinoline **416aa'** in high purity (Scheme 167).

Scheme 167

Using the standard Takeda conditions, the new procedure for cleavage from the resin, and the oxidative cyclisation strategy, a range of quinolines were synthesised in moderate to good yields and high purity. The intermediate TFA salts **417** were not always pure, and in some cases significant amounts of quinoline products along with other intermediate compounds were present, after the cleavage from the resin. Therefore salts **417a-c** were not isolated but simply converted into quinolines **416a-c** (Scheme 168). The impurities in the triflouroacetate salts **417** must be converted into the quinoline products, as these are isolated in high purity.
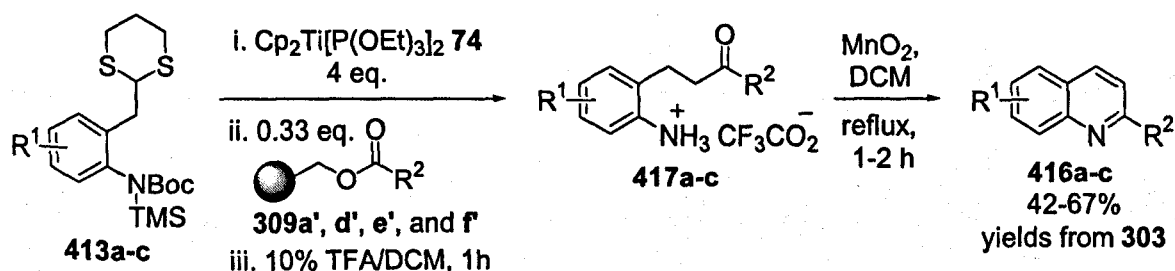
Scheme 168

A couple of more interesting esters were employed, including the successful use of fluorine and a heterocycle in the resin-bound ester (Figure 34). Only one example failed to yield the quinoline in good purity; namely quinoline **416cd'** which failed to cyclise cleanly. The other examples were formed in excellent purity, although it was difficult to obtain ^{1}H NMR spectra without the presence of water, and these quinolines are thought to be hygroscopic.
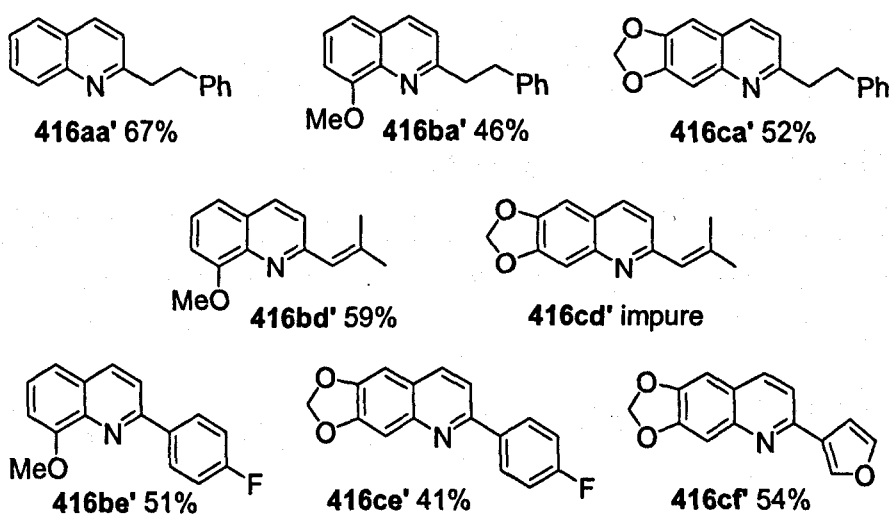
Figure 34

12.4 Future Work

The extension of this methodology to synthesise 2,4-disubstituted quinolines **399**, employing titanium alkylidenes derived from thioacetals **397** (which could be prepared as above from readily available 2-nitrophenones **418**), is on going within our group (Scheme 169).
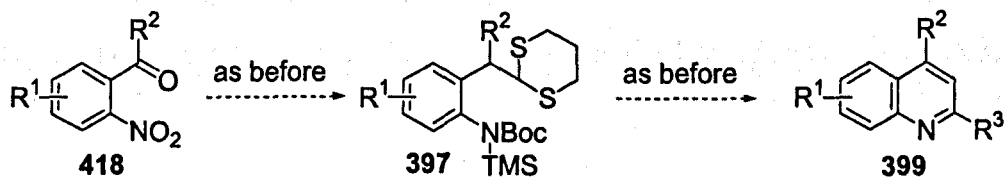
Scheme 169

It may also be possible to extend our methodology to the synthesis of N-, 2-, 4-trisubstituted tetrahydroquinolines **419** (Scheme 170), employing a reductive cyclisation of ketones **420** (utilising titanium alkylidenes derived from N-alkyl-N-Boc thioacetals **421**).
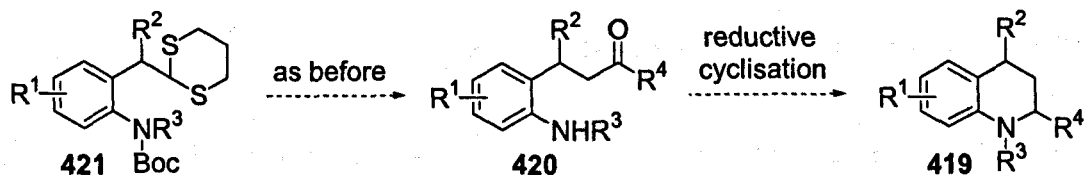
Scheme 170

Chapter 13 - Unsuccessful Resin-bound Esters

It is important to discuss the functional group tolerance within the Merrifield resin-bound esters (Section 3.2). The esters used in the attempted synthesis of 2,3-fused indoles, bis-indoles, and iso-serotonin derivatives are discussed elsewhere (Chapter 11). Also, all successful esters have already been discussed earlier.
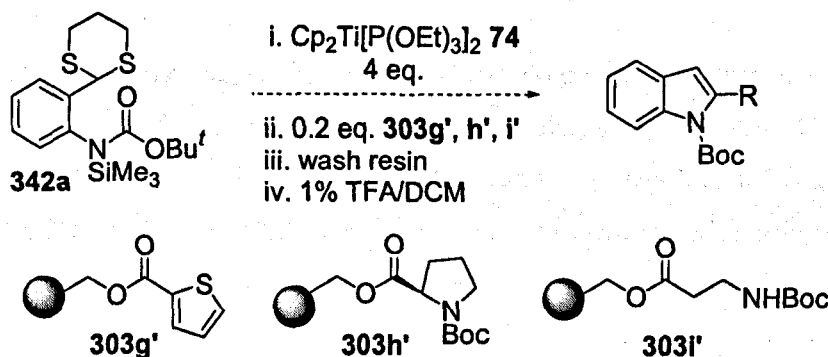
Esters **303g'**, **303h'** and **303i'** were however, unsuccessful when treated with the titanium alkylidene derived from thioacetal **342a** under our standard conditions (Scheme 421).


Scheme 421

Heteroaromatic substituents are tolerated as with the successful use of furanyl ester **303f'**. However, the 2'-thiophenyl substituent in ester **303g'** does not give clean products and the ^{1}H NMR spectra contained large CpTiLn singlets, presumably due to the thienyl moiety acting as a ligand towards titanium. Although the 2'-position of the heteroatom could account for extra co-ordination to titanium intermediates, previous work within the group showed that the 3'-thiophenyl substituent gave a similar result in the benzofuran series. Ester **303h'** resulted in poor mass recovery and CpTiLn contaminated mixtures of products. This failure could be due to a variety of reasons including the low reactivity of the sterically hindered ester carbonyl, competing alkylidenation with the Boc carbonyl, and co-ordination of titanium intermediates between the ester and Boc carbonyls. The failure of ester **303i'** is not surprising as we have already shown that acidic protons tend to quench the titanium carbenes (see section 8.4).

Chapter 14 Experimental

General Experimental details

All reactions were carried out under an inert atmosphere unless otherwise stated, using oven-dried or flame-dried glassware. Solutions were added *via* syringe unless otherwise stated. THF, was freshly distilled from sodium–benzophenone; dichloromethane, toluene, triethylphosphite and pyridine were distilled from CaH_2 prior to use. Petroleum ether refers to the fraction boiling at 40–60 °C. Reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Purification by column chromatography was carried out using Fisher Matrex TM silica gel (mesh size 35–70 μm) or neutral alumina (mesh size 35–70 μm) as the stationary phase. Melting points are uncorrected. IR spectra were recorded using a Nicolet Impact 410 FTIR or JASCO FT/IR 410 spectrometer. NMR spectra were recorded using a Bruker DPX-400, DPX-360 or DPX-250 spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane using residual $CHCl_3$ as an internal standard (7.26 ppm). Chemical shifts in ^{13}C NMR spectra are given in ppm relative to $CDCl_3$ as internal standard (77.00 ppm). All NMR *J* values are given in Hz. Mass spectra were recorded on a JEOL JMS700 spectrometer. Combustion analysis was carried out using a Carlo-Erba 1106 or Exeter Analytical inc. CE 440 elemental analyser. For X-ray crystallography, single crystals of suitable size were attached to a glass fibre using acrylic resin, and mounted on a goniometer head in a general position. Data were collected on an Enraf-Nonius KappaCCD diffractometer, running under Nonius Collect software, and using graphite monochromated X-radiation (λ=0.71073 Å). Precise unit cell dimensions were determined by post-refinement of a significant percentage of the data sets. The frame images were integrated using Denzo(SMN) and the resultant raw intensity files processed using a locally modified version of DENZOX. Data were then sorted and merged using SORTAV and an empirical absorption correction applied at this stage. All non-H atoms were allowed anisotropic thermal motion. Aliphatic and aromatic C-H hydrogen atoms were included at calculated positions, with C-H = 0.96 Å, and were refined with a riding model. Refinement with SHELXL97-2 used full-matrix least-squares on F^2 and all the unique data were included in the refinements. The absolute configuration of compound **346c** was confirmed by the refinement of the Flack absolute structure parameter, which refined to zero within error. Calculations using PLATON indicated that there were no voids in the lattices capable of containing any further solvent molecules. Thermal ellipsoid plots were obtained using the program ORTEP-3 for Windows. All calculations were carried out using the WinGX package of crystallographic programs.

General Experimental Procedures

Merrifield resin-bound esters 303 - Method A

303
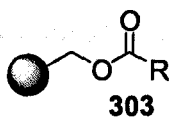
Six Kans with chloromethyl polystyrene resin (each containing 150 mg of resin, 0.28 mmol/kan, 1.68 mmol) in DMF (150 cm^3) were stirred with the corresponding caesium carboxylate [prepared by adding CsOH (50% H$_2$O) drop-wise to an ethanol solution of the carboxylic acid (1.50 mmol) until pH 7 was achieved] at 50-60 °C for 15 h. The Kans were then washed with DMF (x 2), water (x 2) and then alternately with MeOH and DCM (x 5), before finally washing with MeOH and diethyl ether and dried under vacuum.

Merrifield resin-bound esters 303a'-c', g' and h' - Method B

303
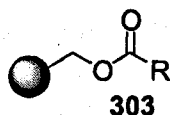
Chloromethyl polystyrene resin (3.00 g, 6.00 mmol) and the caesium caboxylate [prepared as for method A, (30 mmol)] in DMF (25 cm^3), were agitated on a Quest Controller apparatus, at 50 °C for 20 h. The resin was then washed with DMF (x 5), alternately with MeOH/DCM (x 5), before finally washing with MeOH and EtOAc to give the desired resin bound esters **303a-c** which were dried under vacuum. Magic angle spinning (MAS) proton NMR confirmed greater than 90% loading was achieved for esters **303a'-c', g'** and **h'**.

Solid-phase Takeda reaction – general method A

Titanocene dichloride (1.51 g, 6.00 mmol, 20.0 eq.), magnesium turnings (0.20 g, 8.23 mmol) and 4Å molecular sieves (0.60 g) were heated briefly under vacuum. After allowing to cool, the reaction flask was purged with argon, and THF (6.0 cm^3) and triethylphosphite (2.1 cm^3, 12.2 mmol) were added and the reaction mixture was stirred, cooling using an ice bath for 30 mins. After stirring for a further 2-2.5 h, a THF (6.0 cm^3) solution of the thioacetal (1.50 mmol, 5.0 eq.) was added, and the solution stirred for 15 mins. The reaction mixture was added *via* syringe into a flask containing 1 Kan of resin bound ester (0.28-0.31 mmol, 1 eq.), pre-swollen in THF (3 cm^3). The mixture was stirred under argon for 15-18 h. After this time, the Kan was removed and then washed with THF (x 5), alternately with MeOH and DCM (x 5), then MeOH and finally with diethyl ether. The resin was then dried under vacuum.

Solid-phase Takeda reaction – general method B

Titanocene dichloride (0.90 g, 3.60 mmol, 12.0 eq.), magnesium turnings (0.10 g, 3.96 mmol) and 4Å molecular sieves (0.20 g) were heated briefly under vacuum. After allowing to cool, the reaction flask was purged with argon, and THF (5.0 cm^3) and triethylphosphite (1.2 cm^3, 7.2 mmol) were added and the reaction mixture was stirred, cooling using an ice bath for 30 mins. After stirring for a further 2-2.5 h, a THF (4.0 cm^3) solution of the thioacetal (0.90 mmol, 3.0 eq.) was added, and the solution stirred for 15 mins. The reaction mixture was added *via* syringe into a flask containing 1 Kan of resin bound ester (0.28-0.31 mmol, 1 eq.), pre-swollen in THF (3 cm^3). The mixture was stirred under argon for 15-18 h. The kan was then washed and dried as for solid-phase Takeda reaction Method A.

Solid-phase Takeda reaction – general method C

Titanocene dichloride (0.45 g, 1.80 mmol, 6.0 eq.), magnesium turnings (0.05 g, 2.00 mmol) and 4Å molecular sieves (0.10 g) were heated briefly under vacuum. After allowing to cool, the reaction flask was purged with argon, and THF (4.0 cm^3) and triethylphosphite (0.6 cm^3, 2.0 mmol) were added and the reaction mixture was stirred for 30 mins. After stirring for a further 2-2.5 h, a THF (4.0 cm^3) solution of the thioacetal (0.60 mmol, 2.0 eq.) was added, and the solution stirred for 20-30 mins. The reaction mixture was added *via* syringe into a flask containing 1 Kan of resin bound ester (0.28-0.31 mmol, 1 eq.), pre-swollen in THF (3 cm^3). The mixture was stirred under argon for 15-18 h. The kan was then washed and dried as for solid-phase Takeda reaction Method A.

Solid-phase Takeda reaction – general method D

Titanocene dichloride (3.60 g, 14.4 mmol, 12.0 eq.), magnesium (0.38 g, 15.8 mmol) and 4Å molecular sieves (1.20 g) were heated briefly *in vacuo* and then allowed to cool. The reaction flask was purged with argon before adding THF (24 cm^3) and triethylphosphite (4.80 cm^3, 28.8 mmol). The reaction mixture was cooled using an ice bath and stirred for 30 mins. After stirring for a further 2.5 h at rt, a THF (16 cm^3) solution of the thioacetal (3.60 mmol, 3.0 eq.) was added, and the mixture was stirred for 15 mins. After this time the reaction mixture was added in four equal portions *via* syringe, into four flasks each containing 1 Kan of resin-bound ester (0.30 mmol, 1.0 eq.), each pre-swollen in THF (6 cm^3). The kan was then washed and dried as for solid-phase Takeda reaction Method A.

General solution-Phase Takeda reaction

Titanocene dichloride (2.04 g, 8.18 mmol), magnesium turnings (0.23 g, 9.82 mmol) and 4Å molecular sieves (0.81 g) were heated briefly under vacuum, allowed to cool, and the reaction flask was purged with argon. THF (20 cm^3) and triethylphosphite (2.8 cm^3, 16.6 mmol) were then added, and the reaction mixture was allowed to stir for 3 h under argon. After this time, a THF (3.0 cm^3) solution of the thioacetal (3.00 mmol) was added, and the reaction mixture was stirred for 2 h at rt. The reaction was quenched by adding aqueous HCl (20 cm^3, 2 mol dm^{-3}) and the residue was then filtered through wet celite washing with DCM (2 x 40 cm^3). The combined organic phases were then washed with water (2 x 40 cm^3), dried over sodium sulfate, and concentrated *in vacuo*.

Cleavage from Merrifield resin - general procedure A

Following the Takeda reaction, the resin bound product (1 Kan) was treated with 1% TFA in DCM (5 cm^3, 0.65 mmol) and placed on a shaker for 30 min. The Kan was washed with DCM (3 x 5 cm^3) and the organic washings were combined and then concentrated.

Cleavage from Merrifield resin - general procedure B

Following the Takeda reaction, the resin bound product (1 Kan) was treated with 10% TFA in DCM (5 cm^3, 6.50 mmol) and placed on a shaker for 1 h. The Kan was washed with DCM (3 x 5 cm^3) and the organic washings were combined and then concentrated.

General Indole-Boc deprotection method[232]

Following a literature procedure,[232] trifluoroacetic acid (0.5 cm^3, 6.50 mmol) was added to a solution of the Boc-protected indole in DCM (2.0 cm^3), at 0 °C under argon, and the reaction mixture was allowed to warm to rt and stirred for 1 h. After this time, the reaction mixture was concentrated *in vacuo* to yield the desired indole.

General procedure for carbamate alkylation

Sodium hydride [60% in mineral oil, (0.66 g, 16.5 mmol)], was added portion-wise to a solution of carbamate **335a** (4.04 g, 13.0 mmol) and alkyl halide (16.5 mmol), in DMF at 0 °C under argon. The reaction mixture was then allowed to warm to rt and stirred for 2-3 h. After this time the reaction mixture was carefully poured into iced water and extracted into ethyl acetate (2 x 50 cm^3). The combined organic phases were then washed with water (3 x 150 cm^3), dried with magnesium sulphate, and concentrated to yield the desired amine.

## General procedure for ketone cyclisation

TFA (0.5 cm³, 6.50 mmol) was added dropwise to a solution of the crude ketone in DCM (5 cm³), at 0 °C under argon, allowed to warm to rt and was then stirred for 1-3 h. After this time, the reaction mixture was poured into saturated sodium bicarbonate and extracted into DCM (2 x 10 cm³). The combined organic phases were then washed with saturated sodium bicarbonate (20 cm³), water (20 cm³), dried over sodium sulphate, and concentrated to yield the resulting *N*-alkyl indole.

## Cyclisation/Oxidation - general method for forming quinolines

Manganese dioxide (0.09 g, 1.00 mmol) was added to a solution of the crude amine salt in DCM (10 cm³) and the reaction mixture was heated under reflux for 1-2 h. After this time, the reaction mixture was filtered through a celite plug, washing with DCM (10 cm³). The combined organic phases were washed with saturated sodium bicarbonate (20 cm³), dried over sodium sulfate, and concentrated to yield the desired quinoline.

[Manganese dioxide was synthesised by adding potassium permanganate (10 g, 63.3 mmol) in water (500 cm³) to manganese sulfate tetrahydrate (16.9 g, 75.8 mmol) in water (500 cm³) at 0 °C. The reaction mixture was stirred for 5 mins and then filtered. The resulting black solid was then washed with water (500 cm³) and dried in an oven at 120 °C.]

Bis(phenylthio)phenylmethane[241] 285
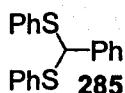
Thiophenol (7.70 cm³, 75.1 mmol) was added to a solution of benzaldehyde (3.19 g, 30.1 mmol), acetic acid (20 cm³) and boron trifluoride diethyletherate (3.2 cm³, 27.0 mmol) in toluene (30 cm³), under nitrogen, and stirred for 68 h at rt. After this time, the reaction mixture was quenched by adding water (40 cm³) and extracted with diethyl ether (3 x 40 cm³). The combined organic phases were washed with saturated sodium bicarbonate solution until the acid was neutralised, dried over magnesium sulfate, and concentrated to yield a yellow oil. Crystallisation from Pet. ether gave bis(phenylthio)phenylmethane[240] 285 as needles (7.87 g, 25.6 mmol, 85%); Mpt: 47-49 °C (Lit.[241] Mpt: 52-53 °C); δ_H (400 MHz, CDCl₃): 5.42 [1H, s, C*H*(SPh)₂], 7.20 (15H, m, Ar-H); δ_C (100 MHz, CDCl₃): 60.4 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 128.8 (CH), 132.5 (CH), 134.5 (C) 139.5(C); m/z, EI+ (%): 308 (M⁺˙, 2), 199 (M⁺˙-C₆H₅S, 100).

Phenylmethylidenecyclohexane[242] 286
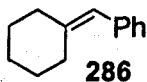
Finely powdered molecular sieves 4Å (0.30 g), magnesium turnings (0.66 g, 2.70 mmol), and titanocene dichloride (0.56 g, 2.25 mmol), were heated briefly under vacuum and then allowed to cool to rt. The flask was then purged with argon, before adding THF (4 cm^3) and triethylphosphite (0.77 cm^3, 4.50 mmol). The reaction mixture was then allowed to stir at rt, for 3 h under argon. Thioacetal 285 (0.17 g, 0.55 mmol) in THF (1 cm^3) was added to the reaction mixture, and was then further stirred for 10 mins, before cyclohexanone (0.05 g, 0.50 mmol) in THF (1.5 cm^3), was added drop-wise over 15 mins and then allowed to stir at rt for 15 h. The reaction mixture was quenched by the addition of hexane (15 cm^3), the resulting insoluble materials were removed by filtration through celite, and the solution was then concentrated to yield a red oil. Kugelrohr distillation of the residue (80-90 °C / 1mm Hg) removed some triethylphosphite and triethylphosphate to leave the crude desired product, which was purified by flash column chromatography (SiO$_2$, Pet. ether: ethyl acetate 19: 1) to yield phenylmethylidenecyclohexane[242] 286 (0.05 g, 0.29 mmol, 57%) as a yellow oil; R$_f$ (Pet. ether: ethyl acetate 19: 1): 0.45; δ_H (400 MHz, CDCl$_3$): 0.85-0.90 (2H, m, CH$_2$), 1.52-1.67 (4H, m, CH$_2$), 2.26 (2H, t, J 5.5, CH$_2$), 2.36 (2H, t, J 5.5, CH$_2$), 6.22 (1H, s, CH=C), 7.15-7.35 (5H, m, Ar-H).

2-[Bis(phenylthio)methyl]–4,4,5,5-tetramethyl-1,3,2-dioxoborolane[203] 287
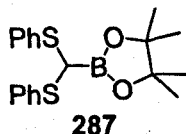
Following the procedure of Mendoza and Matteson,[203] n-butyllithium (17.1 cm^3, 42.6 mmol, 2.5 mol dm^{-3} in hexane) was added to a solution of bis(phenylthio)methane (10.00 g, 42.6 mmol) in THF (50 cm^3), at 0 °C under nitrogen, and stirred for 30 mins. After this time, the reaction mixture was cooled to -78 °C and trimethylborate (4.9 cm^3, 42.6 mmol) was added. The reaction mixture was then warmed to rt and stirred for 2 h, before cooling to –60 °C and quenching with aqueous HCl (90 cm^3, 2 mol dm^{-3}). The resulting mixture was diluted with water (100 cm^3) and extracted with diethyl ether (2 x 50 cm^3). Precipitation of the ether soluble material was achieved by adding hexane (100 cm^3) to give a 7: 4 ratio of 2-[bis(phenylthio)methyl]boronic acid [203] A: bis(phenylthio)methane B as a white solid (10.35 g, 88%); δ_H (400 MHz, CDCl$_3$): 4.16 (1H^A, s, CHB), 4.35 (2H^B, s, CH$_2$), 5.10 (2H^A, s, OH), 7.25-7.51 (10H^{A+B}, m, Ar-H). Pinacol (5.28 g, 44.8 mmol) was

added to a solution of the crude 2-[bis(phenylthio)methyl]boronic acid (10.00 g, 42.6 mmol) in THF (50 cm³), under nitrogen at rt, and stirred for 18 h. After this time, the reaction mixture was concentrated to leave a colourless oil. Purification by Kugelrohr distillation (70-80 °C, 1mm Hg), removed pinacol and bis(phenylthio)methane. Further Kugelrohr distillation (200-220 °C, 1mm Hg), gave the impure product as an oil (8.33 g) which upon low temperature crystallisation (freezer) from Pet. ether, yielded 2-[bis(phenylthio)methyl]–4,4,5,5-tetramethyl-1,3,2-dioxoborolane[203] **287** as plates (5.37 g, 15 mmol, 2 steps 33%); Mpt: 34-37 °C, (Lit.[203]: oil); v_{max} (KBr)/cm^{-1} 3059 (CH), 2680 (CH), 1583 (C=C), 1391 (B-O), 847 (B-C), 747 (CH), 689 (CH); δ_H (400 MHz, CDCl₃): 1.13 (12H, s, CH₃), 4.20 (1H, s, C*H*B), 7.17-7.30 (6H, m, Ar-H), 7.48-7.50 (4H, m, Ar-H); δ_C (100 MHz, CDCl₃): 24.9 (CH₃), 85.1 (C), 127.6 (CH), 129.1 (CH), 131.8 (CH), 135.7 (C), 138.5 (C); m/z, EI+ (%): 358 (M$^{+\bullet}$, 100), 249 (M$^{+\bullet}$–SC₆H₅, 100), 149 (95); Accurate mass: C₁₉H₂₃^{10}BO₂S₂: requires 357.1269, found 357.1264, C₁₉H₂₃^{11}BO₂S₂: requires 358.1233, found 358.1230; Microanalysis Found: C 63.64%, H 6.41%; Theoretical: C 63.72%, H 6.47%.

1,3-Dithian-2-yl-1,3,2-dioxoborolane 288

288
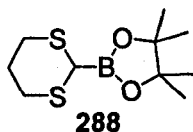
n-Butyllithium (7.5 cm³, 18.8 mmol, 2.5 mol dm^{-3} in hexane) was added to a solution of 1,3-dithiane (2.25 g, 18.8 mmol) in THF (20 cm³), under nitrogen at 0 °C, and stirred for 30 mins. After this time, the reaction mixture was cooled to -78 °C, and trimethylborate (2.2 cm³, 18.8 mmol) was added. The reaction mixture was then warmed to 25 °C and stirred for 2 h, before cooling to –60 °C and quenched with aqueous HCl (2 mol dm^{-3}, 40 cm³). The resulting mixture was then diluted with water (50 cm³) and extracted with diethyl ether (2 x 50 cm³). Precipitation of the ether-soluble material by adding hexane (100 cm³) proved unsuccessful and so the solution was concentrated under vacuum to leave a yellow oil, which solidified on standing to yield a yellow solid (2.99 g). Pinacol (4.43 g, 18.8 mmol) was added to a solution of this crude material (2.99 g, 18.4 mmol, 97%, assuming pure boronic acid) in THF (10 cm³), under nitrogen at rt and stirred for 16 h. After this time, the reaction mixture was concentrated to leave a colourless oil. Purification by Kugelrohr distillation (80-100 °C, 1.1 mm Hg), removed pinacol and 1,3-dithiane. Further Kugelrohr distillation (100-160 °C, 1.1 mm Hg), yielded 1,3-dithian-2-yl-1,3,2-dioxoborolane **288** (A) as a colourless oil [70% pure, contaminated with pinacol and an unknown impurity (B)] that crystallised on standing in the freezer (3.05 g, 12.4 mmol, 2

steps 66%); bp 100-160 °C (1.1 mm Hg); v_{max} (KBr)/cm^{-1} 2980 (CH), 2926 (CH$_2$), 2845 (CH$_2$), 1458 (CH$_2$), 1382 (B-O), 847 (B-C); δ_H (400 MHz, CDCl$_3$): 1.24 (12H^B, s) 1.27 (12H^A, s, CCH$_3$), 2.02-2.04 (2H^A + 2H^B, m, CH$_2$), 2.77-2.93 (4H^A + 4H^B, m, SCH$_2$), 3.72 (1H^A, bs, CHB), 3.78 (1H^B, m); δ_C (100 MHz, CDCl$_3$): 24.6 (CH$_3$), 24.7 (CH$_3$), 24.9 (CH$_2$), 26.1 (CH$_2$), 29.7 (CH$_2$), 84.6 (C) 138.1 (C); m/z, EI+ (%): 246 (M$^{+•}$, 8), 120 (M$^{+•}$-C$_6$H$_{12}$^{10}BO$_2$, 53), 59 (100); Accurate mass: C$_{10}$H$_{19}$^{10}BO$_2$S$_2$ requires 245.0956, found 245.0955, C$_{10}$H$_{19}$^{11}BO$_2$S$_2$ requires 246.0920, found 246.0922.

Attempted formation of Alkenyl boronate 289 - using thioacetals 287 or 288
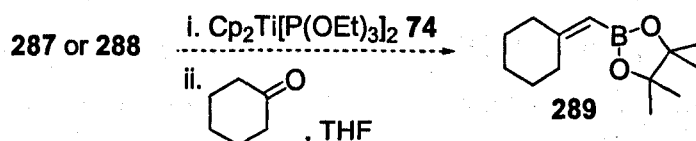
Cp$_2$Ti[P(OEt)$_3$]$_2$ **74** was prepared on the same scale and by the same method as in the procedure for alkene **286**. After allowing the low-valent titanium **74** mixture to stir for 3 h, thioacetal **287** (195 mg, 0.55 mmol) or thioacetal **288** (135 mg, 0.55 mmol) in THF (1 cm^3) was added, and the reaction mixture was then allowed to stir for 10 mins. Cyclohexanone (0.05 g, 0.50 mmol) in THF (2 cm^3), was then added drop-wise over 10 mins, the reaction mixture was stirred for 18 h, and then quenched by the addition of hexane (20 cm^3). The resulting insoluble materials were removed by filtering through celite and the solution was then concentrated to yield a red oil. Distillation of the residue (100 °C / 1mm Hg) removed triethylphosphite and the ^{1}H NMR spectrum of the resulting residue confirmed there was no sign of the desired product **289**, in both cases.
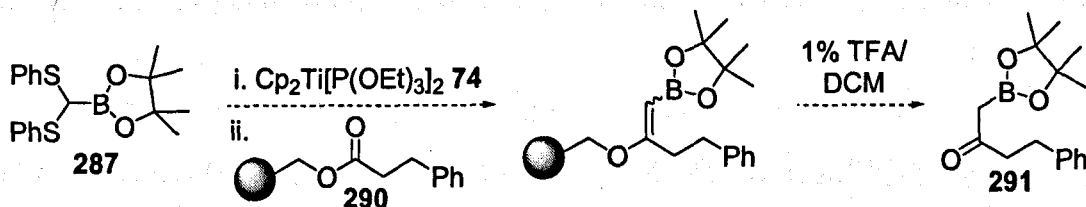
Wang resin-bound ester 290
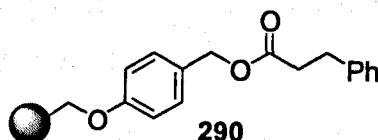
Six Kans of Wang resin (each containing 168 mg resin, 0.29 mmol/kan, 1.74 mmol) were stirred in THF (100 cm^3) at rt with hydrocinnamic acid (1.28 g, 8.53 mmol, 4.9 eq.) and DMAP (0.20 g, 1.64 mmol, 0.94 eq.). 1,3-Diisopropylcarbodiimide DIC (1.3 cm^3, 8.5 mmol) was added drop-wise and the reaction mixture was stirred for a further 24 h. The THF solution was removed and the Kans were then washed with THF, MeOH/DCM alternate (x 4), MeOH and finally with diethyl ether. The resin was then dried under vacuum overnight and re-treated as above. Washing and drying of the resin as before yielded the desired resin-bound ester **290**: δ_C (90 MHz, Gel-Phase, CDCl$_3$): 30.8 (CH$_2$),

35.8 (CH_2), 40.2 (Wang CH_2), 66.0 (Wang CH_2), 126.2 (Wang C), 127.9 (Wang CH), 128.2 (CH), 128.4 (CH), 128.7 (Wang CH), 129.1 (C), 130.0 (C), 132.1 (Wang C), 172.5 (C).

Attempted formation of boronate 291

Following the general solid-phase Takeda reaction (method A), employing thioacetal **287** (0.52 g, 1.45 mmol) and Wang resin-bound ester **290** (0.29 mmol), and then subjecting the resin to the standard Merrifield resin cleavage conditions - A, a brown solid was obtained (0.016 g). ^{1}H NMR spectroscopy confirmed that this was mostly dihydrocinamic acid and triethylphosphite with some other unknown impurities.

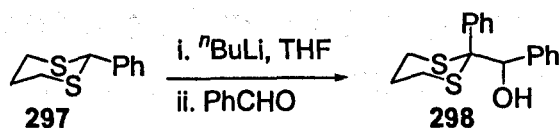## General procedure for lithiation of bis(phenylthio)phenylmethane 285 and quenching with trimethylborate
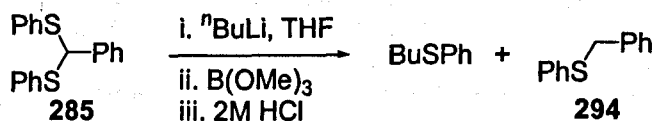
n-Butyllithium (2.6 cm^3, 6.50 mmol, 2.5 mol dm^{-3} in hexane) was added to a solution of bis(phenylthio)phenylmethane **285** (2.00 g, 6.50 mmol) in THF (10 cm^3), under nitrogen at 0 °C and stirred for 30 min. After this time, the dark orange mixture was cooled to -78 °C, and trimethylborate (0.8 cm^3, 6.50 mmol) was added. The reaction mixture was then warmed to 25 °C and stirred for 2 h, before cooling to –60 °C and then quenched with aqueous HCl (2 mol dm^{-3}, 10 cm^3). The resulting mixture was then diluted with water (20 cm^3) and extracted with diethyl ether (2 x 25 cm^3). The combined organic phases were then dried over sodium sulphate, and concentrated under vacuum to leave a yellow oil. ^{1}H NMR spectroscopy confirmed that a 8: 5: 5 mixture of bis(phenylthio)phenylmethane **285** (A): 1-(phenylthio)butane[205] (B): (phenylthio)phenylmethane[204] **294** (C) remained; δ_H (400 MHz, CDCl$_3$): 0.87 (3H^B, t, *J* 7.6, C*H$_3$*-CH$_2$), 1.40-1.54 (2H^B, m, CH$_2$), 1.60-1.67 (2H^B, m, CH$_2$), 2.90 (2H^B, t, *J* 7.4, C*H$_2$*-S), 4.11 (2H^C, s, CH$_2$), 5.42 (1H^A, s, CH), 7.15-7.37 (15H^A + 5H^C + 10H^C, m, Ar-H).

2-Phenyl-1,3-dithiane[243] 297

$$\text{S}\diagup\text{S}\diagdown\text{Ph}$$

297
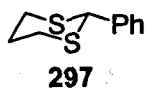
As above, 1,3-propanedithiol (6.0 cm^3, 60.0 mmol), benzaldehyde (3.10 cm^3, 30.0 mmol), acetic acid (20 cm^3) and boron trifluoride diethyletherate (3.2 cm^3, 27.0 mmol) in toluene (30 cm^3), followed by the same work-up as for thioacetal **285**, yielded the desired thioacetal **297** as a white solid. Recrystallisation from Pet. ether gave 2-phenyl-1,3-dithiane [243] **297** as needles (4.92 g, 25.0 mmol, 84%); Mpt: 67-69 °C, (Lit.[243] Mpt: 69-70 °C); δ_H (400 MHz, CDCl$_3$): 1.89-1.97 (1H, m, CH$_{ax}$), 2.14-2.21 (1H, m, CH$_{eq}$), 2.89-2.94 (2H, m, CH$_2$-S), 3.03-3.11 (2H, m, CH$_2$-S), 5.30 (1H, s, PhCH), 7.26-7.48 (5H, m, Ar-H); δ_C (100 MHz, CDCl$_3$): 25.1 (CH$_2$), 32.1 (CH$_2$), 51.5 (CH), 127.8 (CH), 128.4 (CH), 128.7 (CH), 139.1 (C); m/z, EI+ (%): 196 (M$^{+\cdot}$, 100), 122 (M$^{+\cdot}$-C$_3$H$_6$S, 60), 121 (M$^{+\cdot}$-C$_3$H$_7$S, 61).

General procedure for lithiation of 2-phenyl-1,3-dithiane 297 and formation of benzoin propylenethioacetal[244] 298

$$\text{S}\diagup\text{S}\diagdown\text{Ph} \quad \xrightarrow[\text{ii. PhCHO}]{\text{i. }^n\text{BuLi, THF}} \quad \text{S}\diagup\text{S}\diagup\text{C(Ph)-CH(Ph)OH}$$
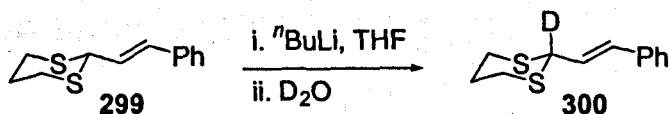
297   **298**

n-Butyllithium (0.6 cm^3, 1.30 mmol, 2.5 mol dm^{-3} in hexane) was added to a solution of 2-phenyl-1,3-dithiane **297** (0.25 g, 1.27 mmol) in THF (5 cm^3), under nitrogen at -30 °C, and stirred for 1 h. After this time, the dark green reaction mixture was cooled to -78 °C, and benzaldehyde (0.15 cm^3, 1.50 mmol) was added. The resulting yellow solution was then warmed to 25 °C and stirred for 18 h. After this time, the reaction mixture was poured into saturated ammonium chloride solution (10 cm^3) and extracted with chloroform (2 x 10 cm^3). The combined organic phases were then washed with water (20 cm^3) and brine (20 cm^3), dried over sodium sulphate and concentrated *in vacuo* to leave a yellow oil. ^{1}H NMR spectroscopy confirmed that this was a mixture of the desired product **298** (A)[244]: thioacetal **297** starting material (B): benzaldehyde (C), 5: 1: 1; δ_H (400 MHz, CDCl$_3$): 1.75-1.95 (2H^A, m, CH$_2$), 1.89-1.97 (1H^B, m, CH$_{ax}$), 2.14-2.21 (1H^B, m, CH$_{eq}$), 2.55-2.70 (4H^A, m, CH$_2$-S), 2.89-3.11 (1H^A + 4H^B, m, CH^AOH + CH_2^B-S), 4.98 (1H^A, s, OH), 5.30 (1H^B, S, PhCH), 6.84-6.86 (2H^A, m, Ar-H), 7.08-7.12 (2H^A, m, Ar-H), 7.16-7.20(1H^A, m, Ar-H), 7.24-7.48 (4H^A + 5H^B, m, Ar-H), 7.50-7.52 (1H^A, m, Ar-H), 7.66-7.69 (3H^C, m, Ar-H), 7.85-7.87 (2H^C, m, Ar-H), 9.95 (1H^C, s, CHO).

2-(1-Styryl)-1,3-dithiane[212] 299
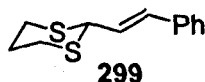
Boron trifluoride diethyletherate (1.0 cm^3, 8.00 mmol) was added drop-wise to a solution of cinnamaldehyde (2.64 g, 20.0 mmol) and propane-1,3-dithiol (2.2 cm^3, 20.0 mmol) in dry diethyl ether (40 cm^3) at 0 °C under nitrogen. The ice bath was then removed and the reaction mixture was stirred for 3 h at rt, and then quenched by pouring into aqueous sodium hydroxide (10%, 50 cm^3). The resulting mixture was then extracted with chloroform (3 x 40 cm^3) and the combined chloroform extracts were then washed with water (50 cm^3) and brine (50 cm^3), dried over sodium sulfate, and concentrated under vacuum to yield a yellow oil which crystallised on standing (4.40 g). Recrystallisation from hexane, gave 2-(1-styryl)-1,3-dithiane [212] 299, as a yellow solid (3.51 g, 15.8 mmol, 79%); Mpt: 57-59 °C, (Lit.[212] Mpt: 57-58 °C); δ_H (400 MHz, CDCl$_3$): 1.85-1.95 (1H, m, CH$_{ax}$), 2.10-2.17 (1H, m, CH$_{eq}$), 2.86-3.10 (4H, m, CH$_2$-S), 4.80 (1H, d, J 7.7, S$_2$CH), 6.23 (1H, dd, J 7.7 and 16.0, CH=CHPh), 6.74 (1H, d, J 16.0, CH=CHPh), 7.23-7.39 (5H, m, Ar-H); δ_C (100 MHz, CDCl3): 25.2 (CH$_2$), 30.2 (CH$_2$), 47.7 (CH), 126.0 (CH), 126.7 (CH), 128.1 (CH), 128.6 (CH), 133.4 (CH), 136.1(C).

General procedure for lithiation of 2-(1-styryl)-1,3-dithiane 299 in the formation of thioacetal 300

n-Butyllithium (0.40 cm^3, 1.00 mmol, 2.5 mol dm^{-3} in hexane) was added to a solution of 2-(1-styryl)-1,3-dithiane 299 (0.20 g, 0.90 mmol) in THF (5 cm^3), under nitrogen at -40 °C, warmed to -20 °C and stirred for 1 h. After this time, the dark orange reaction mixture was cooled to -40 °C, and D$_2$O (0.20 cm^3, 10.0 mmol) was added. The yellow solution was then warmed to 25 °C and stirred for 45 mins. The reaction mixture was poured into saturated brine (10 cm^3) and extracted with chloroform (2 x 10 cm^3). The combined organic phases were then washed with water (30 cm^3) and brine (30 cm^3), dried over sodium sulphate and concentrated under vacuum to leave a yellow oil. ^{1}H NMR spectroscopy confirmed this contained a mixture of 2-deuterio-2-(1-styryl)-1,3-dithiane 300 A: 2-(1-styryl)-1,3-dithiane 299 B (4: 1); δ_H (400 MHz, CDCl$_3$): 1.85-1.95 (1H^{A+B}, m, CH$_{ax}$), 2.10-2.17 (1H^{A+B}, m, CH$_{eq}$), 2.86-3.10 (4H^{A+B}, m, CH$_2$-S), 4.80 [1H^B, d, J 7.7, S$_2$CH], 6.23 (1H^A, d, J 16.0, CH=CHPh), 6.24 (1H^B, dd, J 7.7 and 16.0, CH=CHPh), 6.74 (1H^{A+B}, d, J 16.0, CH=CHPh), 7.19-7.39 (5H^{A+B}, m, Ar-H).
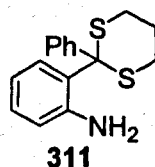
2-(2'-Aminophenyl)-2-methyl-1,3-dithiane 310

310

Boron trifluoride diethyletherate (2.0 cm³, 16.0 mmol) was added dropwise to a solution of 2-aminoacetophenone (1.35 g, 10 mmol) and propanedithiol (2.2 cm³, 20.0 mmol) in diethyl ether (10 cm³), and the reaction mixture was heated under reflux for 60 h. After this time the reaction mixture was washed with sodium hydroxide (1 mol dm⁻³, 3 x 10 cm³) and water (30 cm³), dried over sodium sulfate, and concentrated to leave a yellow oil. The crude ¹H NMR spectrum confirmed 87% conversion to the desired product. Purification by column chromatography (SiO₂, DCM), resulted in elimination of the thioacetal moiety explaining the poor yield obtained as the majority of the product was contaminated with 2-aminoacetophenone. Some of the desired product **310** was obtained in moderate purity as a yellow oil (0.72 g, 3.20 mmol, 32%, 95% pure); R_f (SiO₂, DCM): 0.15, δ_H (400 MHz, CDCl₃): 1.97-1.99 (5H, m, CH₂ and CH₃), 2.83-2.86 (4H, m, CH₂-S), 4.88 (2H, s, NH₂), 6.65 (1H, dd, J 1.2 and 7.9, H-3'), 6.77 (1H, dt, J 1.3 and 8.2, H-5'), 7.10 (1H, dt, J 1.5 and 7.9, H-4'), 7.78 (1H, dd, J 1.4 and 8.0, H-6'); δ_C (100 MHz, CDCl₃): 24.6 (CH₂), 27.5 (CH₃), 28.2 (CH₂), 53.0 (C), 118.1 (CH), 118.6 (CH), 124.6 (C), 128.9 (CH), 130.5 (CH), 145.9 (C).

2-(2'-Aminophenyl)-2-phenyl-1,3-dithiane 311

311

Boron trifluoride diethyletherate (7.8 cm³, 60.8 mmol) was added drop-wise to a solution of 2-aminobenzophenone (6.0 g, 30.4 mmol) in 1,3-propanedithiol (6.6 cm³, 60.8 mmol), and the reaction mixture was stirred for 20 h at rt. After this time DCM (30 cm³) was added and the residue was washed with sodium hydroxide (1 mol dm⁻³, 3 x 30 cm³) and water (30 cm³), dried over sodium sulfate, and concentrated to leave a yellow solid (8.44 g, 29.4 mmol, 97%). Recrystallisation from ethyl acetate gave 2-(2'-aminophenyl)-2-phenyl-1,3-dithiane **311** as needles (7.19 g, 24.9 mmol, 82%); R_f (SiO₂, DCM): 0.30; Mpt: 113-116 °C; ν_{max} (KBr)/cm⁻¹ 3433 (NH₂), 3330 (NH₂), 1443 (CH), 1484 (CH); δ_H (400 MHz, CDCl₃): 1.95-2.03 (2H, m, CH₂), 2.71-2.96 (4H, m, CH₂-S), 4.50 (2H, s, NH₂), 6.64 (1H, dd, J 1.1 and 7.9, H-3') 6.71 (1H, m, H-5'), 7.11 (1H, m, H-4'), 6.97 (1H, d, J 8.0, H-6'),

7.28-7.36 (2H, m, Ar-H), 7.50 (1H, d, *J* 7.8, Ar-H), 7.65 (2H, d, *J* 7.7, Ar-H); δ_C (100 MHz, CDCl$_3$): 24.4 (CH$_2$), 29.5 (CH$_2$), 61.4 (C), 117.5 (CH), 118.4 (CH), 124.1 (C), 127.9 (CH), 128.6 (CH) 128.8 (CH), 129.1 (CH), 132.2 (CH), 141.2 (C), 145.7 (C); m/z, EI+ (%): 287 (M$^{+\bullet}$, 25), 213 (M$^{+\bullet}$-C$_3$H$_6$S, 30), 212 (M$^{+\bullet}$-C$_3$H$_7$S, 32), 180 (100); Accurate mass: C$_{16}$H$_{16}$NS$_2$: requires 287.4497, found 287.4477; Microanalysis Found: C 66.79%, H 5.82%, N 4.73%; Theoretical C$_{16}$H$_{16}$OS$_2$: C 66.89%, H 5.92%, N 4.88%.

## 2-(2'-Hydroxyphenyl)-1,3-dithiane[245] 314

314
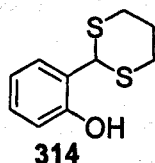
Following a known procedure for thioacetallisation,[220] tellerium tetrachloride (0.27 g, 1.00 mmol) was added to a solution of salicaldehyde (2.44 g, 20.0 mmol) and 1,3-propanedithiol (2.0 cm^3, 20.0 mmol) in dichloroethane (30 cm^3), and was stirred at rt for 3 h. After this time 0.60 g of sodium bicarbonate was added and the residue were filtered off. The organic phases were then dried over sodium sulfate and concentrated to leave a pale yellow solid (4.23 g, 19.9 mmol, 99.5%). Washing the resultant solid with cold Pet. ether and drying under vacuum gave 2-(2'-hydroxyphenyl)-1,3-dithiane **314** as a white solid (4.03 g, 19.0 mmol, 95%): Mpt: 125-127 °C (Lit.[245] Mpt: not quoted); ν_{max} (KBr)/cm^{-1} 3319 (OH), 2980 (CH), 1591 (CH), 1498 (CH$_2$), 1498 (CH$_2$), 1248 (OH), 758 (CH); δ_H (400 MHz, CDCl$_3$): 1.89-2.00 (1H, m, CH$_{ax}$), 2.16-2.22 (1H, m, CH$_{eq}$), 2.91-2.95 (2H, m, CH$_2$), 3.04-3.11 (2H, m, CH$_2$), 5.41 (1H, s, CH), 6.33 (1H, s, OH), 6.86-6.90 (2H, m, H-3'and H-6'), 7.19 (1H, dt, *J* 1.6 and 7.7, H-5'), 7.82 (1H, dt, *J* 1.7 and 8.0, H-4'); δ_C (100 MHz, CDCl$_3$): 24.9 (CH$_2$), 31.6 (CH$_2$), 47.5 (CH), 117.4 (CH), 120.8 (CH), 123.5 (C), 129.1 (CH), 130.1 (CH), 154.5 (C); m/z, EI+ (%): 212 (M$^{+\bullet}$, 100), 138 (96), 137 (80); Accurate mass: C$_{10}$H$_{12}$OS$_2$: requires 212.0330, found 212.0328; Microanalysis Found: C 56.64%, H 5.34%; Theoretical C$_{10}$H$_{12}$OS$_2$: C 56.87%, H 5.21%.

2-(2'-*tert*-Butyldimethylsilyloxyphenyl)-1,3-dithiane 316


316
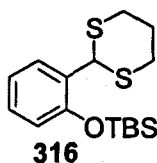
Triethylamine (2.3 cm^3, 16.5 mmol), was added to a solution of 2-(2′-hydroxyphenyl)-1,3-dithiane **314** (3.18 g, 15.0 mmol), *tert*-butyldimethylchlorosilane (2.49 g, 16.5 mmol), imidazole (1.12 g, 16.5 mmol), in DMF (15 cm^3) and was allowed to stir for 16 h. The reaction mixture was poured into sat. sodium bicarbonate solution (30 cm^3) and extracted into diethyl ether (3 x 30 cm^3). The combined organic phases were washed with water (5 x 100 cm^3), dried over sodium sulfate and concentrated to yield a pale yellow solid (4.88 g, 16.5 mmol, 100%). Recrystallisation from Pet. ether gave 2-(2′-*tert*-butyldimethylsilyloxyphenyl)-1,3-dithiane **316** as needles (3.66 g, 11.2 mmol, 75%); Mpt: 77-80 °C; ν_{max} (KBr)/cm^{-1} 2952 (CH), 2856 (CH), 1286 (SiMe$_2$), 1089 (O-Si), 909 (O-Si), 831 (SiMe$_2$); δ_H (400 MHz, CDCl$_3$): 0.26 (6H, s, SiMe$_2$), 1.06 (9H, s, CMe$_3$), 1.91-1.98 (1H, m, CH$_{ax}$), 2.13-2.19 (1H, m, CH$_{eq}$), 2.87-2.93 (2H, m, CH$_2$-S), 3.00-3.07 (2H, m, CH$_2$-S), 5.60 (1H, s, CH), 6.78 (1H, dd, J 1.1 and 8.1, H-3′), 6.93 (1H, dt, J 1.1 and 7.5, H-5′), 7.12 (1H, dt, J 1.8 and 7.5, H-4′), 7.52 (1H, dd, J 1.7 and 7.7, H-6′); δ_C (100 MHz, CDCl$_3$): -4.4 (CH$_3$), 18.3 (C), 25.3 (CH$_2$), 25.8 (CH$_3$), 32.5 (CH$_2$), 44.8 (CH), 118.8 (CH), 121.7 (CH), 129.0 (CH), 129.2 (CH), 129.8 (C), 138.1 (C); m/z, EI+ (%): 326 (M$^{+\bullet}$, 20), 269 (100), 223 (16), 195 (87), 161 (34), 135 (20), 82.9 (16), 73 (86); Accurate mass: C$_{16}$H$_{16}$OS$_2$Si: requires 326.5973 found 326.5976; Microanalysis Found: C 58.83%, H 7.80%; Theoretical C$_{16}$H$_{16}$OS$_2$Si: C 58.89%, H 7.97%.

1-(2'-*tert*-Butyldimethylsilyloxyphenyl)-4-phenylbutan-2-one[214] 318
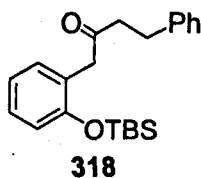

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Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing thioacetal **316** (0.48 g, 1.45 mmol) and Wang resin-bound ester **290** (0.29 mmol), yielded 1-(2′-*tert*-butyldimethylsilyloxyphenyl)-4-phenylbutan-2-one[214] **318** as an oil (0.070 g, 0.210 mmol, 71%): δ_H (400 MHz, CDCl$_3$): 0.20 (6H, s, Me$_2$Si), 0.97 (9H, s, *t*-BuSi), 2.69 (2H, t, J 8.0, CH$_2$), 2.83 (2H, t, J 7.9, CH$_2$), 3.64 (2H, s, CH$_2$), 6.81 (1H, d, J 8.1, H-3′), 6.87 (1H, dt, J 7.4 and 1.0, H-5′), 7.06-7.12 (5H, m, Ar-H), 7.22- 7.25 (2H, m, Ar-H).

2-(2'-*tert*-Butyldimethylsilyloxyphenyl)-2-methyl-1,3-dithiane 319

319
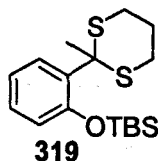
1,3-Propanedithiol (13.4 cm^3, 124 mmol) was added to a solution of 2-hydroxyacetophenone (10.0 g, 73.5 mmol), and boron trifluoride diethyletherate (15 cm^3, 118 mmol) in THF (40 cm^3), under nitrogen, and stirred for 15 h at rt. After this time, the reaction mixture was quenched by adding water (80 cm^3) and extracted with diethyl ether (3 x 60 cm^3). The combined organic phases were then washed with saturated sodium bicarbonate solution until the acid was neutralised, dried over sodium sulfate, and concentrated *in vacuo* to yield a colourless oil [(16.81 g, 74.3 mmol, 101%), [due to poor separation between R$_f$ of product and starting material in all solvents tried, the crude product (approx 86% conversion) was protected without purification]. Triethylamine (14 cm^3, 100 mmol) was added to a crude mixture of thioacetal **315** [(assume 73.5 mmol), 86:14 mole ratio thioacetal **315**: 2-hydroxyacetophenone by ^{1}H NMR with some 1,3-propanedithiol], imidazole (6.81 g, 100 mmol), and *tert*-butyldimethylchlorosilane (15.07 g, 100 mmol) in DMF (50 cm^3) under nitrogen, and stirred for 16 h. The reaction mixture was quenched into sodium bicarbonate solution (30 cm^3) and extracted into diethyl ether (2 x 40 cm^3). The combined organic phases were then washed with water (3 x 100 cm^3), dried over sodium sulphate and concentrated to leave a yellow oil (27.1 g). Column chromatography of a 3.00 g portion [SiO$_2$, DCM: Pet. ether 1: 1], gave the desired product **319** (2.14 g, 6.28 mmol). Recrystallisation of the white solid from Pet. ether gave the desired product as plates (1.73 g, 5.08 mmol). The remainder was then purified by crystallisation from Pet. ether, induced by seeding, to yield 2-(2'-*tert*-butyldimethylsilyloxyphenyl)-2-methyl-1,3-dithiane **319** as plates (12.24 g, 35.9 mmol, 44% for 2 steps); R$_f$ (DCM: Pet ether 1: 1): 0.40; Mpt: 56-59 °C; ν_{max} (KBr)/cm^{-1} 2960 (CH), 2856 (CH), 1251 (SiMe$_2$), 1058 (O-Si), 911 (O-Si), 825 (SiMe$_2$); δ_H (400 MHz, CDCl$_3$): 0.32 (6H, s, SiMe$_2$), 1.04 (9H, s, CMe$_3$), 1.89-1.97 (2H, m, CH$_2$), 2.00 (3H, s, CH$_3$), 2.75-2.82 (4H, m, CH$_2$-S), 6.85 (1H, dd, J 1.0 and 8.0, H-3'), 6.90 (1H, dt, J 1.1 and 7.8, H-5'), 7.13 (1H, dt, J 1.7 and 7.8, H-4'), 7.92 (1H, dd, J 1.7 and 7.9, H-6'); δ_C (100 MHz, CDCl$_3$): -3.3 (CH$_3$), 19.1 (C), 24.8 (CH$_2$), 26.5 (CH$_3$), 28.4 (CH$_2$), 28.7 (CH$_3$), 118.4 (C), 119.7 (CH), 119.9 (CH), 128.4 (CH), 131.1 (CH), 132.3 (C), 134.1 (C); m/z, EI+ (%): 340 (M$^{+\cdot}$, 16), 283 (16), 209 (100); Accurate mass: C$_{17}$H$_{28}$OS$_2$Si$_2$: requires 340.6262, found 340.6245; Microanalysis Found: C 59.60%, H 8.21%; Theoretical C$_{16}$H$_{16}$OS$_2$: C 60.00%, H 8.23%.

N,N-Dibenzyl-2-bromoaniline 321

321
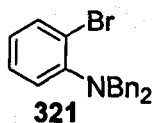
Benzyl bromide (11.6 cm^3, 93.0 mmol), was added to a solution of 2-bromoaniline (4.0 g, 23.3 mmol) and potassium carbonate (12.9 g, 93.0 mmol) in NMP (25 cm^3) under nitrogen, and the reaction mixture was heated at 60-70 °C for 16 h. After allowing to cool, water (50 cm^3) was added and stirred for 10 min. The mixture was extracted with diethyl ether (3 x 30 cm^3), and the combined organic phases were washed with water (10 x 80 cm^3) and dried over sodium sulfate, before concentrating *in vacuo* to yield a yellow oil. Column chromatography (SiO$_2$, eluting with Pet. ether and then DCM) yielded N,N-dibenzyl-2-bromoaniline **321** as a colourless oil (6.44 g, 18.3 mmol, 79%): R$_f$ (SiO$_2$, Pet. ether): 0.10; ν_{max} (Thin Film)/cm^{-1} 3061 (CH), 3026 (CH), 783 (CH), 753 (CH); δ_H (400 MHz, CDCl$_3$): 4.17 (4H, s, NCH$_2$), 6.83 (1H, dt, *J* 1.6 and 7.5, H-4), 6.89 (1H, dd, *J* 1.5 and 8.0, H-6), 7.07 (1H, dt, *J* 1.5 and 8.1, H-5) 7.17-7.35 (10H, m, Ar-H), 7.56 (1H, dd, *J* 1.5 and 7.9, H-3); δ_C (100 MHz, CDCl$_3$): 56.4 (CH$_2$), 121.4 (C), 124.5 (CH), 124.7 (CH), 127.0 (CH), 127.6 (CH), 128.2 (CH), 128.6 (CH), 133.8 (CH), 138.0 (C), 148.8 (C); m/z, EI+ (%): 351 (M$^{+\bullet}$, 22), 260 (M$^{+\bullet}$-CH$_2$Ph, 19), 180 (20), 91 (100); Accurate mass: C$_{20}$H$_{18}$N^{79}Br: requires 351.0623, found 351.0625, C$_{20}$H$_{18}$N^{81}Br: requires 353.0604, found 353.0601; Microanalysis: Found C 68.13%, H 5.10%, N 3.98%, Br 22.80%; Theoretical C$_{20}$H$_{18}$NBr: C 68.18%, H 5.11%, N 3.98%, Br 22.73%.

N-Benzyl-N-phenyl-N-(1'-phenylpent-1'-yl) 324

324
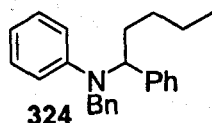
n-Butyllithium (1.80 cm^3, 4.40 mmol, 2.5 mol dm^{-3} in hexane) was added to a solution of N,N-dibenzyl-2-bromoaniline **321** (1.30g, 3.69 mmol) in THF (12 cm^3), under nitrogen at -78 °C, and slowly allowed to warm to -40 °C over 30 mins. After this time, DMF (0.80 cm^3, 10.4 mmol) was added and the reaction mixture was then slowly warmed to 25 °C and stirred for 1 h. The reaction mixture was then poured into water (30 cm^3) and extracted with diethyl ether (2 x 30 cm^3). The combined organic phases were then washed with water (2 x 30 cm^3) and brine (30 cm^3), dried over sodium sulfate and concentrated to give a yellow solid (1.20 g). Recrystallisation from propan-2-ol gave N-benzyl-N-phenyl-N-(1'-phenylpent-1'-yl) **324** as golden yellow needles (0.90 g, 2.90 mmol, 78%); Mpt: 98-101 °C; ν_{max} (KBr)/cm^{-1} 2945 (CH), 2926 (NCH$_2$), 2840 (NCH$_2$), 753 (CH), 726 (CH), 700 (CH);

135

δ_H (400 MHz, CDCl$_3$): 0.84 (3H, t, J 7.2, CH$_3$), 1.27-1.51 (4H, m, CH_2CH_2CH$_3$), 1.96 (2H, m, NCH-CH_2), 4.25 (1H, d, J 17.0, NCH^AH^{B}Ph), 4.41 (1H, d, J 17.0, NCH^{A}CH^BPh), 5.02 (3H, t, J 7.2, NCHPh), 6.68 (1H, t, J 7.2, H-4), 6.80 (2H, d, J 8.1, H-2 and H-6), 7.11-7.31 (12H, m, Ar-H); δ_C (100 MHz, CDCl$_3$): 14.0 (CH$_3$), 22.8 (CH$_2$), 29.5 (CH$_2$), 31.7 (CH$_2$), 49.9 (CH$_2$), 62.9 (CH), 115.0 (CH), 117.3 (CH), 126.3 (CH), 126.7 (CH), 127.0 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 128.9 (CH), 139.8 (C), 141.4 (C), 149.5 (C); m/z, EI+ (%): 329 (M$^{+\bullet}$,12), 272 (M$^{+\bullet}$-C$_4$H$_9$, 100); Accurate mass: C$_{24}$H$_{27}$N: requires 329.2143, found 329.2145; Microanalysis: Found C 87.54%, H 8.21%, N 4.25%; Theoretical C$_{24}$H$_{27}$N: C 87.32%, H 8.21%, N 4.12%.

N,N-Dibenzyl-4-methylaniline[246] 325

325
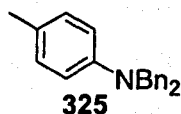
Benzyl bromide (14.0 cm^3, 112 mmol) was added to a solution of *p*-toluidine (3.00 g, 28.0 mmol) and potassium carbonate (15.5 g, 112 mmol) in NMP (30 cm^3) under nitrogen, and the reaction mixture was heated at 60-70 °C for 60 h. After cooling, water (100 cm^3) was added and stirred for 10 mins before extracting with diethylether (3 x 30 cm^3). The combined organic phases were washed with water (4 x 60 cm^3), dried over sodium sulfate and concentrated *in vacuo*, to give an orange oil (8.91 g). Column chromatography of a 1.00 g portion (SiO$_2$, DCM), gave the desired amine **325** as a white solid (0.37 g). Recrystallisation from DCM/ propan-2-ol gave the desired product **325**, as needles (0.27 g). The remainder of the reaction mixture was purified by crystallisation, induced by seeding, to give *N,N*-dibenzyl-4-methylaniline **325** as needles (5.94 g, 20.7 mmol, 74%); Mpt: 53-56 °C, (Lit.[246], Oil); δ_H (400 MHz, CDCl$_3$): 2.22 (3H, s, CH_3), 4.62 (4H, s, NCH_2), 6.64 (2H, d, J 8.4, H-2 and H-6), 6.97 (2H, d, J 8.3, H-3 and H-5), 7.22-7.33 (10H, m, Ar-H); δ_C (100 MHz, CDCl$_3$): 20.2 (CH$_3$), 54.4 (CH$_2$), 112.6 (CH), 126.7 (CH), 126.8 (CH), 128.6 (CH), 129.7 (CH), 138.1 (C), 138.8 (C), 196.1 (C); m/z, EI+ (%): 287 (M$^{+\bullet}$, 100), 210 (M$^{+\bullet}$-C$_6$H$_5$, 27), 180 (M$^{+\bullet}$-C$_7$H$_7$, 27), 91 (100); Microanalysis: Found C 87.85%, H 7.45%, N 4.85%; Theoretical C$_{21}$H$_{21}$N: C 87.81%, H 7.32%, N 4.88%.

2-*N*,*N*-Dimethylamino-5-methyl benzaldehyde 326

326
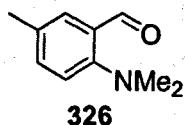
Phosphorous oxychloride (5.70 cm^3, 60.0 mmol) was added to DMF (14 cm^3) at 0 °C, and was allowed to stir for 15 min. After this time *N*,*N*-dimethyl-*p*-toluidine (2.20 cm^3, 20 mmol) was added and the reaction was allowed to warm to 60 °C stirred for 16 h. After this time the reaction was then poured into sodium hydroxide (2 mol dm^{-3}, 40 cm^3) and extracted into diethyl ether (3 x 30 cm^3). The combined organic phases were then washed with water (6 x 100 cm^3), dried over sodium sulfate and concentrated to yield a yellow oil (2.76 g, 16.9 mmol). Column chromatography (SiO$_2$, hexane: diethyl ether 9: 1) gave the desired product 2-*N*,*N*-dimethylamino-5-methyl benzaldehyde **326** as a yellow oil (1.99 g, 12.2 mmol, 61%): R$_f$ (SiO$_2$, hexane: diethyl ether 9: 1): 0.10; v_{max} (KBr)/cm^{-1} 2945 (NMe$_2$), 2837 (NMe$_2$), 2792 (NMe$_2$), 1686 (C=C); δ_H (400 MHz, CDCl$_3$): 2.31 (3H, s, Ar-CH$_3$), 2.87 (6H, s, NMe$_2$), 6.97 (1H, d, *J* 8.3, H-3), 7.27 (1H, dd, *J* 2.2 and 8.3, H-4), 6.97 (1H, d, *J* 1.8, H-6); δ_C (100 MHz, CDCl$_3$): 20.3 (CH$_3$), 45.8 (CH$_3$), 118.0 (CH), 127.3 (C), 130.4 (CH), 130.6 (C), 135.4 (CH), 154.1 (C), 191.6 (CH); m/z, EI+ (%): 163 (M$^{+•}$, 100), 134 (M$^{+•}$-CHO, 45), 120 (M$^{+•}$-C$_2$H$_3$O, 64); Accurate mass: C$_{10}$H$_{13}$NO: requires 163.2193, found 163.2201; Microanalysis Found: C 73.42%, H 7.97%, N 8.57%; Theoretical: C$_{10}$H$_{13}$NO: C 73.61%, H 7.98%, N 8.59%.
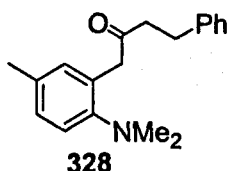
2-[2'-(*N*,*N*-Dimethylamino)-5-methylphenyl]-1,3-dithiane 327

327
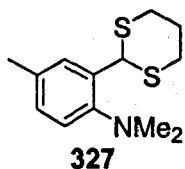
Boron trifluoride diethyletherate (2.6 cm^3, 20.0 mmol) was added to a mixture of 2-(*N*,*N*-dimethylamino)-5-methylbenzaldehyde **326** (1.60 g, 9.80 mmol) and 1,3-propanedithiol (2.0 cm^3, 20.0 mmol), was heated at 70 °C for 15 h. The reaction mixture was worked up as for thioacetal **319** to yield a yellow oil (2.09 g, 84%). Column chromatography (SiO$_2$, DCM) gave the desired product as a colourless oil (1.36 g, 5.68 mmol, 58%). Recrystallisation from DCM/ Pet. ether gave 2-[2'-(*N*,*N*-dimethylamino)-5-methylphenyl]-1,3-dithiane **327** as needles (0.99 g, 3.92 mmol, 40%): R$_f$ (SiO$_2$, DCM): 0.45; Mpt: 54-57 °C; δ_H (400 MHz, CDCl$_3$): 1.90-2.00 (1H, m, CH$_{ax}$), 2.15-2.20 (1H, m, CH$_{eq}$), 2.29 (3H, s, CH$_3$), 2.72 (6H, s, NMe$_2$), 2.86-2.91 (2H, m, CH$_2$-S), 3.07-3.15 (2H, m, CH$_2$-S), 5.75 (1H, s, S$_2$CH), 6.99-7.05 (2H, m, H-3' and H-6'), 7.41 (1H, s, H-4'); δ_C (100 MHz, CDCl$_3$): 20.7

(CH$_3$), 25.4 (CH$_2$), 32.6 (CH$_2$), 45.7 (CH), 45.8 (CH$_3$), 119.5 (CH), 129.7 (CH), 130.0 (CH), 130.1 (C), 133.5 (C); m/z, EI+ (%): 253 (M$^{+\bullet}$, 77), 238 (M$^{+\bullet}$-CH$_3$, 16), 220 (17), 146 (100); Accurate mass: C$_{13}$H$_{19}$NS$_2$: requires 253.4326, found 253.4305; Microanalysis Found: C 61.27%, H 7.60%, N 5.24%; Theoretical C$_{16}$H$_{16}$OS$_2$: C 61.66%, H 7.51%, N 5.53.

1-(2'-*N,N*-Dimethylamino-5'-methylphenyl)-4-phenylbutan-2-one 328

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Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing 2-(2'-*N,N*-dimethylamino-5'-methylphenyl)-1,3-dithiane **327** (0.37 g, 1.45 mmol), and resin-bound ester **309a** (0.30 mmol, Method A), yielded 1-(2'-*N,N*-Dimethylamino-5'-methylphenyl)-4-phenylbutan-2-one **328** as a yellow oil (0.044 g, 0.16 mmol, 53%); ν_{max} (Solt^n, CDCl$_3$)/cm^{-1}: 2940 (CH), 2900 (CH), 2825 (NMe$_2$); δ_H (400 MHz, CDCl$_3$): 2.34 (3H, s, CH$_3$), 2.91-2.98 (4H, m, C*H$_2$*C*H$_2$*Ph), 3.21 (6H, s, NMe$_2$), 4.15 (2H, s, CH$_2$CO), 6.85 (1H, s, H-6'), 7.19-7.31 (7H, m, Ar-H); δ_C (100 MHz, CDCl$_3$): 20.8 (CH$_3$), 29.7 (CH$_2$), 43.9 (CH$_2$), 46.1 (CH$_2$), 47.6 (CH$_3$), 119.7 (CH), 126.0 (CH), 127.5 (C), 128.4 (CH), 128.5 (CH), 130.0 (CH), 133.7 (CH), 140.1 (C), 140.7 (C), 140.9 (C), 206.4 (C); m/z, EI+ (%): 281.1 (M$^{+\bullet}$, 54), 162.1 (25), 148.1 (100); Accurate mass: C$_{19}$H$_{21}$NO: requires 281.3997, found 281.3992.

## 2'-Nitro-(bisthiophenyl)benzaldehyde thioacetal[247] 330

330
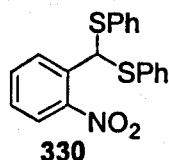
Thiophenol (7.70 cm^3, 75.0 mmol) was added to a solution of 2-nitrobenzaldehyde (4.53 g, 30.0 mmol), acetic acid (20 cm^3) and boron trifluoride diethyletherate (3.9 cm^3, 30.0 mmol) in toluene (25 cm^3), under nitrogen, and stirred for 30 h at rt. Work up as for thioacetal **315** gave 2'-nitro-(bisthiophenyl)benzaldehyde thioacetal **330** as a yellow solid, which was analytically pure (8.82 g, 21.0 mmol, 70%). Recrystallisation of a 0.50 g portion from diethyl ether gave the desired 2'-nitro-(bisthiophenyl)benzaldehyde thioacetal **330** as yellow needles (0.35 g, 1.00 mmol, 58%): Mpt: 98-101 °C, (Lit.[247] Mpt: 101 °C); ν_{max} (KBr)/cm^{-1} 1526 (NO$_2$), 1361 (NO$_2$); δ_H (400 MHz, CDCl$_3$): 6.43 (1H, s, CH-S$_2$), 7.22-7.26 (6H, m, SPh), 7.34-7.36 (5H, m, SPh + H-5'), 7.52 (1H, dt, *J* 1.2 and 7.7, H-4'),

7.79 (1H, dd, J 1.2 and 8.1, H-3'), 7.91 (1H, dd, J 1.3 and 8.0, H-6'); δ_C (100 MHz, CDCl$_3$): 54.5 (CH), 124.4 (CH), 128.3 (CH), 128.6 (CH), 129.0 (CH), 130.7 (CH), 132.8 (CH), 133.1 (CH), 133.3 (C), 134.5 (C), 147.7 (C); m/z, EI+ (%): 244 (M$^{+\bullet}$,100), 109 (43); Accurate mass: C$_{19}$H$_{15}$NO$_2$S$_2$: requires 353.0544, found 353.0546; Microanalysis Found: C 64.63%, H 4.31%, N 3.92%; Theoretical C$_{19}$H$_{15}$NO$_2$S$_2$: C 64.59%, H 4.25%, N 3.96%.

2-(2'-Nitrophenyl)-1,3-dithiane 329a

329a
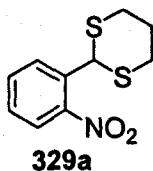
1,3-Propanedithiol (12.0 cm^3, 120 mmol) was added to a solution of 2-nitrobenzaldehyde (15.0 g, 99.0 mmol) and boron trifluoride diethyletherate (13.5 cm^3, 120 mmol) in toluene (50 cm^3), under nitrogen and stirred for 16 h at rt. After this time, the reaction was quenched by adding water (50 cm^3) and then extracted into DCM (2 x 50 cm^3). The combined organic phases were washed with sodium hydroxide (1 mol dm^{-3}, 2 x 50 cm^3), water (2 x 100 cm^3), dried over sodium sulfate and concentrated under vacuum to give a yellow solid. Recrystallisation from propan-2-ol gave 2-(2'-nitrophenyl)-1,3-dithiane **329a** as yellow needles (20.72 g, 86.0 mmol, 87%): R$_f$ (SiO$_2$, DCM): 0.48; Mpt: 114-116 °C; ν_{max} (KBr)/cm^{-1}: 2954 (CH), 2832 (CH), 1524 (NO$_2$), 1351 (NO$_2$); δ_H (400 MHz, CDCl$_3$): 1.89-2.01 (1H, m, CH$_{ax}$), 2.17-2.24 (1H, m, CH$_{eq}$), 2.90-2.96 (2H, m, CH$_2$-S), 3.09-3.16 (2H, m, CH$_2$-S), 5.89 (1H, s, CH-S$_2$), 7.42 (1H, dt, J 1.3 and 8.2, H-4'), 7.60 (1H, dt, J 1.2 and 7.6, H-5'), 7.87-7.90 (2H, m, H-3' and H-6'); δ_C (100 MHz, CDCl$_3$): 25.4 (CH$_2$), 32.7 (CH$_2$), 46.4 (CH), 125.1 (CH), 126.2 (C), 129.5 (CH), 131.1 (CH), 133.9 (CH), 138.5 (C); m/z, EI+ (%): 241 (M$^{+\bullet}$-OH, 17), 224 (M$^{+\bullet}$-O$_2$H, 6), 166 (49), 147 (24), 135 (32), 106 (100); Accurate mass: C$_{10}$H$_{11}$NO$_2$S$_2$: requires 241.0231, found 241.0233; Microanalysis Found: C 49.80%, H 4.49% N 5.81%; Theoretical C$_{10}$H$_{11}$NO$_2$S$_2$: C 49.79%, H 4.56% N 5.81%
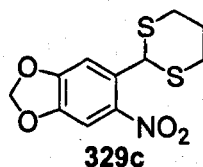
2-(3'-Methoxy-2'-nitrophenyl)-1,3-dithiane 329b

329b
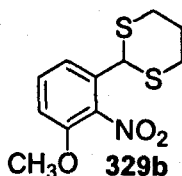
As above, using 1,3-propanedithiol (3.30 cm^3, 33.0 mmol), 3-methoxy-2-nitrobenzaldehyde (5.00 g, 27.6 mmol) and boron trifluoride diethyletherate (3.70 cm^3, 33.0 mmol) in toluene (40 cm^3), gave pure desired product (6.64 g, 23.5 mmol, 85%).

Recrystallisation of a 1.00 g portion from propan-2-ol, gave 2-(3'-methoxy-2'-nitrophenyl)-1,3-dithiane **329b** as yellow needles (0.90 g, 3.30 mmol, 77%): R_f (DCM, SiO$_2$): 0.60; Mpt: 188-191 °C; ν_{max} (KBr)/cm^{-1} 2843 (COMe), 1607 (C=C), 1534 (NO$_2$), 1369 (NO$_2$), 1283 (OMe); δ_H (400 MHz, CDCl$_3$): 1.86-1.97 (1H, m, CH$_{ax}$), 2.13-2.20 (1H, m, CH$_{eq}$), 2.86-2.92 (2H, m, CH$_2$-S), 3.01 (2H, td, J 14.7 and 2.3, CH$_2$-S), 3.88 (1H, s, OCH$_3$), 5.14 (1H, s, CH-S$_2$), 6.98 (1H, dd, J 0.9 and 8.3, H-4'), 7.34 (1H, dd, J 1.1 and 7.9, H-6'), 7.41 (1H, t, J 8.1 H-5'); δ_C (100 MHz, CDCl$_3$): 24.8 (CH$_2$), 32.1 (CH$_2$), 45.5 (CH), 56.5 (CH$_3$), 112.6 (CH), 120.9 (CH), 131.5 (CH), 132.0 (C), 150.5 (C); m/z, EI+ (%): 271 (M$^{+\bullet}$, 7), 254 (M$^{+\bullet}$-OH, 10), 119 (44), 106 (100); Accurate mass: C$_{11}$H$_{13}$NO$_3$S$_2$: requires 271.0337, found 271.0339; Microanalysis Found: C 48.76%, H 4.87% N 5.14%; Theoretical C$_{11}$H$_{13}$NO$_3$S$_2$: C 48.69%, H 4.83%, N 5.13%.

## 2-(4',5'-Methylenedioxy-2'-nitrophenyl)-1,3-dithiane 329c

329c

As above, using 1,3-propanedithiol (3.10 cm^3, 30.1 mmol), 2-nitropiperonal (4.90 g, 25.1 mmol) and boron trifluoride diethyletherate (3.40 cm^3, 30.1 mmol) in toluene (70 cm^3), gave thioacetal **329c** (6.99 g, 24.5 mmol, 98%). Recrystallisation of a 0.40 g portion from propan-2-ol, yielded 2-(4',5'-methylenedioxy-2'-nitrophenyl)-1,3-dithiane **329c** as yellow needles (0.35 g, 1.23 mmol, 86%): R_f (SiO$_2$, DCM): 0.60; Mpt: 156-158 °C; ν_{max} (KBr)/cm^{-1} 2913 (OCH$_2$O), 1521 (NO$_2$), 1377 (NO$_2$); δ_H (250 MHz, CDCl$_3$): 1.84-2.00 (1H, m, CH$_{ax}$), 2.14-2.17 (1H, m, CH$_{eq}$), 2.87-2.96 (2H, m, CH$_2$-S), 3.06-3.18 (2H, m, CH$_2$-S), 5.99 (1H, s, CH-S$_2$), 6.12 (2H, s, OCH$_2$O), 7.32 (1H, s, H-6'), 7.41 (1H, s, H-3'); δ_C (63 MHz, CDCl$_3$): 25.0 (CH$_2$), 32.3 (CH$_2$), 46.4 (CH), 103.2 (CH$_2$), 105.6 (CH), 109.6 (CH), 130.2 (C), 141.8 (C), 147.7 (C), 152.0 (C); m/z, EI+ (%): 285 (M$^{+\bullet}$, 10), 268 [(M$^{+\bullet}$-OH), 24], 179 (42), 106 (80), 83 (100); Accurate mass: C$_{11}$H$_{11}$NO$_4$S$_2$: requires 285.0130, found 285.0133; Microanalysis Found: C 46.46%, H 3.97%, N 4.81%; Theoretical C$_{11}$H$_{11}$NO$_4$S$_2$: C 46.31%, H 3.86%, N 4.91%.

2-(5'-Hydroxy-2'-nitrophenyl)-1,3-dithiane 329d

329d
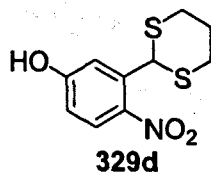
The reaction was carried out as above, employing 1,3-propanedithiol (4.20 cm^3, 40.7 mmol), 5-hydroxy-2-nitrobenzaldehyde (5.67 g, 33.9 mmol) and boron trifluoride diethyletherate (4.60 cm^3, 40.7 mmol) in DCM (80 cm^3). The reaction mixture was quenched into saturated sodium bicarbonate (80 cm^3). The organic phases were separated and then washed with water (2 x 100 cm^3), dried over sodium sulfate, and concentrated under vacuum to yield a yellow solid (8.88 g, 102%). Recrystallisation from toluene, gave 2-(5'-hydroxy-2'-nitrophenyl)-1,3-dithiane **329d** as yellow needles (6.70 g, 26.1 mmol, 77%): R_f (SiO$_2$, DCM): 0.46; Mpt: 156-159 °C; v_{max} (KBr)/cm^{-1} 3441 (NH$_2$), 1583 (C=C), 1520 (NO$_2$), 1333 (NO$_2$), 1304 (OH); δ_H (400 MHz, CDCl$_3$): 1.88-2.00 (1H, m, CH$_{ax}$), 2.17-2.24 (1H, m, CH$_{eq}$), 2.91-2.95 (2H, m, CH$_2$-S), 3.10-3.18 (2H, m, CH$_2$-S), 5.82 (1H, bs, OH), 6.07 (1H, s, CH-S$_2$), 6.83 (1H, dd, J 9.0 and 2.3, H-4'), 7.30 (1H, d, J 2.8, H-6'), 7.95 (1H, d, J 9.0 H-3'); δ_C (100 MHz, CDCl$_3$): 25.1 (CH$_2$), 32.3 (CH$_2$), 46.2 (CH), 115.7 (CH), 117.2 (CH), 128.1 (CH), 136.8 (C), 160.1 (C); m/z, EI+ (%): 257 (M$^{+\bullet}$, 7), 240 (M$^{+\bullet}$-OH, 27), 160.0 (100); Accurate mass C$_{10}$H$_{11}$NO$_3$S$_2$: requires 257.0180, found 257.0178; Microanalysis Found: C 46.76%, H 4.33%, N 5.54%; Theoretical C$_{10}$H$_{11}$NO$_3$S$_2$: C 46.67%, H 4.31%, N 5.44%.

2-(5'-Chloro-2'-nitrophenyl)-1,3-dithiane[234] 329f

329f
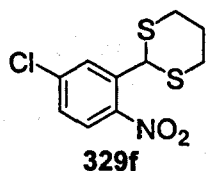
As above, using 1,3-propanedithiol (8.20 cm^3, 81.7 mmol), 5-chloro-2-nitrobenzaldehyde [15% 4-chloro-2-nitrobenzaldehyde (12.63 g, 68.1 mmol)] and boron trifluoride diethyletherate (9.20 cm^3, 81.7 mmol) in toluene (100 cm^3), gave a yellow solid (19.86 g). Two recrystallisations from propan-2-ol yielded a 12: 1 mixture of thioacetal **329f**[234] (A): 2-(4'-chloro-2'-nitrophenyl)-1,3-dithiane (B), as yellow needles (14.50 g, 52.6 mmol, 77%): R_f (DCM, SiO$_2$): 0.67; δ_H (400 MHz, CDCl$_3$): 1.94-1.98 (1H^{A+B}, m, CH$_{ax}$), 2.17-2.22 (1H^{A+B}, m, CH$_{eq}$), 2.91-2.97 (2H^{A+B}, m, CH$_2$-S), 3.08-3.15 (2H^{A+B}, m, CH$_2$-S), 5.11

(1H[B], s, CH-S$_2$), 5.90 (1H[A], s, CH-S$_2$), 7.39 (1H[A], dd, J 14.0 and 3.7, H-4'), 7.44-7.46 (2H[B], m, Ar-H), 7.73-7.74 (1H[B], m, Ar-H), 7.85-7.88 (2H[A], m, H-3' and H-6').

2-(2'-Aminophenyl)-1,3-dithiane[234] 331a

331a

THF (150 cm^3) was added to a 3-necked flask charged with argon, containing 2-(2'-nitrophenyl)-1,3-dithiane **329a** (20.7 g, 86.0 mmol) and the reaction mixture was cooled using an ice bath. Palladium on charcoal (5% loading/ 50% water, 13.8 g) was added, followed by sodium borohydride (11.13 g, 294 mmol) in three equal portions over 10 min, and the reaction mixture was allowed to stir at rt for 18 h. After this time, the mixture was acidified to pH 6 with hydrochloric acid (2 mol dm^{-3}). Chloroform (150 cm^3) was added and the mixture stirred for 10 mins. The solution was then filtered and the organic layer was washed with water (2 x 200 cm^3), dried over sodium sulfate and concentrated to leave a yellow solid. Recrystallisation from propan-2-ol gave 2-(2'-aminophenyl)-1,3-dithiane[234] **331a** as needles (15.42 g, 73.0 mmol, 85%), R$_f$ (SiO$_2$, DCM): 0.14; Mpt: 112-115 °C (Lit.[234] 114-115 °C); ν_{max} (KBr)/cm^{-1}: 3434 (NH$_2$), 3340 (NH$_2$), 1623 (NH$_2$); δ_H (400 MHz, CDCl$_3$): 1.88-1.99 (1H, m, CH$_{ax}$), 2.15-2.22 (1H, m, CH$_{eq}$), 2.90-2.95 (2H, m, CH$_2$-S), 3.06-3.13 (2H, m, CH$_2$-S), 4.15 (2H, bs, NH$_2$), 5.30 (1H, s, S$_2$CH), 6.68 (1H, dd, J 1.0 and 7.9, H-3'), 6.75 (1H, dt, J 1.1 and 7.5, H-5'), 7.09 (1H, dt, J 1.5 and 7.5, H-4'), 7.30 (1H, dd, J 1.4 and 7.7, H-6'); δ_C (100 MHz, CDCl$_3$): 25.3 (CH$_2$), 32.0 (CH$_2$), 48.7 (CH), 117.0 (CH), 119.1 (CH), 123.1 (C), 128.5 (CH), 129.3 (CH), 144.4 (C); m/z, EI+ (%): 211 (M$^{+\cdot}$, 70), 178 (M$^{+\cdot}$-SH, 17), 136 (100); Accurate mass: C$_{10}$H$_{13}$NS$_2$: requires 211.0489, found 211.0490; Microanalysis Found: C 66.79%, H 5.82%, N 4.73%; Theoretical C$_{10}$H$_{13}$NS$_2$: C 66.89%, H 5.92%, N 4.88%.

Diazine-n-oxide 333
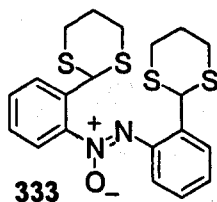
333

THF (150 cm^3) was added to a 3-necked flask, charged with argon, containing 2-(2'-nitrophenyl)-1,3-dithiane **329a** (14.15 g, 58.6 mmol) and the reaction was cooled using an ice bath. Palladium on charcoal (5% loading/ 50% water, 4.38 g) followed by sodium borohydride (5.54 g, 147 mmol) in three equal portions over 15 mins were added, and the

reaction was stirred at rt for 18 h. After this time the reaction was worked up exactly as for 2-(2′-aminophenyl)-1,3-dithiane **331a** above to leave an orange oil (13.52 g). ^{1}H NMR spectroscopy confirmed that an 18: 8: 2 mixture of aniline **331a**: dimer **333**: starting material **329a** was obtained. Column chromatography (SiO$_2$, CHCl$_3$) gave pure starting material **329a** (0.50 g, 2.07 mmol), aniline **331a** (5.21 g, 24.7 mmol) and dimer **333** (1.93 g, 4.43 mmol) which was recrystallised from ethyl acetate to give the pure diazine-*N*-oxide **333** as orange/yellow needles (1.59 g, 3.65 mmol); R$_f$ (SiO$_2$, CHCl$_3$): 0.25; Mpt: 202-204 °C; ν_{max} (KBr)/cm^{-1}: 1630 (CH), 1460 (N=NO), 1390 (N=NO), 765 (CH), δ_H (400 MHz, CDCl$_3$): 1.86-1.97 (2H, m, CH$_{ax}$), 2.09-2.15 (2H, m, CH$_{eq}$), 2.81-2.85 (4H, m, CH$_2$-S), 3.04-3.12 (4H, m, CH$_2$-S), 5.75 (1H, s, S$_2$CH), 6.00 (1H, s, S$_2$CH), 7.41-7.47 (3H, m, Ar-H), 7.53-7.54 (1H, m, Ar-H), 7.71 (1H, dd, *J* 1.2 and 7.9, Ar-H), 7.81-7.83 (1H, m, Ar-H), 7.89 (1H, dd, *J* 1.3 and 7.8, Ar-H), 8.55-8.57 (1H, m, Ar-H); δ_C (100 MHz, CDCl$_3$): 25.0 (CH$_2$), 25.1 (CH$_2$), 32.0 (CH$_2$), 32.1 (CH$_2$), 45.6 (CH), 122.0 (CH), 124.1 (CH), 128.4 (CH), 129.0 (CH), 129.1 (CH), 130.0 (CH), 130.1 (CH), 130.7 (CH), 132.1 (C), 136.5 (C), 140.2 (C), 147.8 (C); m/z, CI+ (%): 435 [(M+H)$^+$, 15], 417 [(M+H)$^+$-H$_2$O, 23], 311 (45), 237 (42), 221 (100); Accurate mass: C$_{20}$H$_{22}$N$_2$OS$_4$: requires 435.0693, found 435.0693; Microanalysis: Found C 55.21%, H 5.05%, N 6.43%; Theoretical C$_{20}$H$_{22}$N$_2$OS$_4$: C 55.14%, H 5.09%, N 6.43%.

2-(2'-Amino-3'-methoxyphenyl)-1,3-dithiane 331b
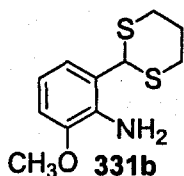
Following the above procedure, 2-(3'-methoxy-2'-nitrophenyl)-1,3-dithiane **329b** (6.24 g, 23.0 mmol), palladium on charcoal (5% loading/ 50% water, 3.69 g) and sodium borohydride (2.61 g, 69.0 mmol) in THF (50 cm^3), gave the pure desired aniline **331b** as a white crystalline solid (4.64 g, 19.2 mmol, 83%). Recrystallisation of a 0.50 g portion from propan-2-ol, gave 2-(2'-amino-3'-methoxyphenyl)-1,3-dithiane **331b** as tiny needles (0.43 g, 1.87 mmol, 71%): R$_f$ (SiO$_2$, DCM): 0.17; Mpt: 121-124 °C; ν_{max} (KBr)/cm^{-1}: 3421 (NH$_2$), 3333 (NH$_2$), 1617 (NH$_2$), 1480 (OCH$_3$); δ_H (400 MHz, CDCl$_3$): 1.88-2.00 (1H, m, CH$_{ax}$), 2.15-2.19 (1H, m, CH$_{eq}$), 2.89 (2H, dt, *J* 3.3 and 14.3, CH$_2$-S), 3.06-3.13 (2H, m, CH$_2$-S), 3.83 (3H, s, OCH$_3$), 4.16 (2H, bs, NH$_2$), 5.33 (1H, s, S$_2$CH), 6.71-6.76 (2H, m, H-4' and H-5'), 6.96 (1H, dd, *J* 2.2 and 6.8, H-6'), δ_C (100 MHz, CDCl$_3$): 25.3 (CH$_2$), 31.8 (CH$_2$), 48.4 (CH), 55.7 (CH$_3$), 110.0 (CH), 118.2 (CH), 120.3 (CH), 123.2 (C), 134.2 (C), 147.7 (C); m/z, EI+ (%): 241 (M$^{+\bullet}$, 100), 224 (5), 208 [(M$^{+\bullet}$-CH$_5$O), 17], 116 (C$_{10}$H$_{14}$S, 75), 152 (27); Accurate mass: C$_{11}$H$_{15}$NOS$_2$: requires 241.0595, found 241.0597;

Microanalysis Found: C 54.72%, H 6.15%, N 5.78%; Theoretical $C_{11}H_{15}NOS_2$: C 54.74%, H 6.26%, N 5.80%.

2-(2'-Amino-4',5'-methylenedioxyphenyl)-1,3-dithiane 331c

331c
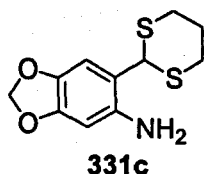
Following a literature procedure,[229] a mixture of iron powder (4.70 g, 28.0 mmol), 2-(4',5'-methylenedioxy-2'-nitrophenyl)-1,3-dithiane **329c** (8.00 g, 50.0 mmol) and ammonium chloride (7.49 g, 140 mmol), in ethanol (125 cm^3) and water (75 cm^3), was heated under reflux for 1 h. After allowing to cool, the reaction mixture was filtered through celite, washing with ethanol. The dark green solution was then concentrated *in vacuo*. The resulting slurry was partitioned between ethyl acetate (150 cm^3) and brine (200 cm^3). The organic phases were then separated and washed with water (2 x 100 cm^3), dried over magnesium sulfate, and concentrated *in vacuo* to yield 2-(2'-amino-4',5'-methylenedioxyphenyl)-1,3-dithiane **331c** (which was one product by both ^{1}H NMR spectroscopy and TLC analysis and was not further purified due to it's instability in previous purification attempts), as a yellow solid (7.69 g, 108%): R$_f$ (SiO$_2$, DCM): 0.42; δ_H (400 MHz, CDCl$_3$): 1.85-1.97 (1H, m, CH$_{ax}$), 2.13-2.20 (1H, m, CH$_{eq}$), 2.88 (2H, dt, *J* 3.2 and 14.5, CH$_2$-S), 3.05 (2H, td, *J* 14.5 and 2.5, CH$_2$-S), 5.25 (1H, s, CH-S$_2$), 5.86 (2H, s, OCH$_2$O), 6.31 (1H, s, H-3'), 6.87 (1H, s, H-6'); m/z, EI+ (%): 255 (M$^{+\bullet}$, 78), 180 (100); Accurate mass: $C_{11}H_{13}NO_2S_2$: requires 255.0388, found 255.0385.
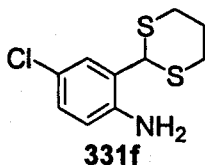
2-(2'-Amino-5'-hydroxyphenyl)-1,3-dithiane 331d

331d
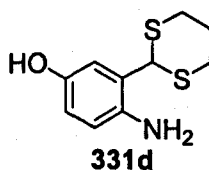
Following the above procedure, iron powder (7.54 g, 135 mmol) was added to a solution of 2-(5'-hydroxy-2'-nitrophenyl)-1,3-dithiane **329d** (12.87 g, 50.0 mmol) and ammonium chloride (12.04 g, 225 mmol), in ethanol (200 cm^3) and water (200 cm^3) and heated under reflux for 2 h. Work up as above yielded pure aniline **331d** as a yellow solid (9.87 g, 43.4 mmol, 87%). Recrystallisation of a 0.30 g portion from propan-2-ol, gave 2-(2'-amino-5'-hydroxyphenyl)-1,3-dithiane **331d** as needles (0.24 g, 70%); R$_f$ (SiO$_2$, EtOAc): 0.46; Mpt: 156-159 °C; ν_{max} (KBr)/cm^{-1} 3441 (NH$_2$), 1583 (C=C), 1520 (NO$_2$), 1333 (NO$_2$), 1304 (OH); δ_H (250 MHz, C$_2$D$_6$SO): 1.61-1.77 (1H, m, CH$_{ax}$), 2.08-2.15 (1H, m, CH$_{eq}$), 2.80-

144

2.88 (2H, m, CH$_2$-S), 3.04-3.16 (2H, m, CH$_2$-S), 4.57 (2H, bs, NH$_2$), 5.39 (1H, s, CH-S$_2$), 6.43-6.49 (2H, m, H-4' and H-6'), 6.69 (1H, d, J 2.5, H-3'), 8.51 (1H, s, OH); δ$_C$ (63 MHz, C$_2$D$_6$SO): 25.5 (CH$_2$), 31.6 (CH$_2$), 46.0 (CH), 114.8 (CH), 116.3 (CH), 117.3 (CH), 123.6 (C), 137.5 (C), 148.9 (C); m/z, EI+ (%): 257 (M$^{+\bullet}$, 7), 240 [(M$^{+\bullet}$-OH), 27], 160 (100); Accurate mass: C$_{10}$H$_{13}$NOS$_2$: requires 257.0180, found 257.0178; Microanalysis Found: C 52.86%, H 5.76%, N 6.13%; Theoretical C$_{10}$H$_{13}$NOS$_2$: C 52.86%, H 5.73%, N 6.17%.

2-(2'-Amino-5'-chlorophenyl)-1,3-dithiane[248] 331f

331f

Following the above procedure, iron powder (8.81 g, 158 mmol) was added to a solution of a 12: 1 mixture of 2-(5'-chloro-2'-nitrophenyl)-1,3-dithiane **329f** and 2-(4'-chloro-2'-nitrophenyl)-1,3-dithiane (14.50 g, 52.6 mmol), ammonium chloride (14.07 g, 263 mmol), in ethanol (200 cm^3) and water (100 cm^3), and heated under reflux for 2 h. Following work up as above, yielded aniline **331f** as a yellow solid (9.64 g, 39.2 mmol). Two recrystallisations from propan-2-ol, gave 2-(2'-amino-5'-chlorophenyl)-1,3-dithiane[248] **331f** as yellow needles (6.55 g, 51%); R$_f$ (SiO$_2$, DCM): 0.45; Mpt: 99-101 °C (Lit.[248] oil); δ$_H$ (250 MHz, CDCl$_3$): 1.84-2.00 (1H, m, CH$_{ax}$), 2.14-2.18 (1H, m, CH$_{eq}$), 2.88-2.97 (2H, m, CH$_2$-S), 3.02-3.14 (2H, m, CH$_2$-S), 4.15 (2H, bs, NH$_2$), 5.22 (1H, s, CH-S$_2$), 6.60 (1H, d, J 8.5, H-3'), 7.04 (1H, dd, J 8.5 and 2.4, H-4'), 7.29 (1H, d, J 2.4, H-6').

2-[2'-(*N,N*-Di-*tert*-butyloxycarboxyamino)phenyl]-1,3-dithiane 334

334
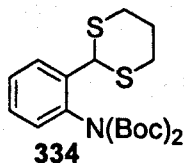
Sodium hexamethyldisilazane (22.0 cm^3, 22.0 mmol, 1 mol dm^{-3} in THF) was added to a solution of 2-(2'-aminophenyl)-1,3-dithiane **331a** (2.11 g, 10.0 mmol) and di-*tert*-butyl-dicarbonate (5.46 g, 25.0 mmol) in THF (50 cm^3) at 0 °C under nitrogen. The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was then quenched by pouring into water (50 cm^3), extracted into DCM (2 x 30 cm^3). The combined organic phases were then washed with water (2 x 50 cm^3), dried over sodium sulfate and concentrated to yield a yellow solid (3.53 g). Recrystallisation from Pet. ether gave 2-[2'-(*N,N*-di-*tert*-butyloxycarboxyamino)phenyl]-1,3-dithiane **334** as needles (3.21 g, 7.80 mmol, 78%); R$_f$ (SiO$_2$, Hexane: DCM 1: 9): 0.10; Mpt: 106-109 °C; ν$_{max}$ (KBr)/cm^{-1} 2983

(CH), 2890 (CH), 1789 s (CO), 780 (CH); δ_H (400 MHz: CDCl$_3$): 1.36 [18H, s, C(CH$_3$)$_3$], 1.91-1.95 (1H, m, CH$_{ax}$), 2.13-2.17 (1H, m, CH$_{eq}$), 2.84-2.89 (2H, m, CH$_2$-S), 2.98-3.05 (2H, m, CH$_2$-S), 5.22 (1H, s, NH), 5.30 (1H, s, S$_2$CH), 7.06 (1H, dd, J 1.2 and 7.8, H-6'), 7.27 (1H, dt, J 1.6 and 7.5, H-5'), 7.31 (1H, dt, J 1.2 and 7.5, H-4'), 7.67 (1H, dd, J 1.5 and 7.7, H-3'); δ_C (100 MHz: CDCl$_3$): 25.1 (CH$_2$), 27.6 (CH$_3$), 32.0 (CH$_2$), 45.8 (CH), 82.8 (C), 128.4 (CH), 128.5 (CH), 129.0 (CH), 136.2 (C), 136.5 (C), 150.9 (C); m/z, CI+ (%): 412.1 [(M+H)$^+$, 18], 312.1 [(M+H)$^+$-C$_5$H$_8$O$_2$, 20], 278.1 (100); Microanalysis: Found C 58.37%, H 6.97%, N 3.29%; Theoretical C$_{20}$H$_{29}$NO$_4$S$_2$: C 58.36%, H 7.10%, N 3.40%.

2-[2'-(*N-tert*-Butyloxycarboxyamino)phenyl]-1,3-dithiane 335a

335a
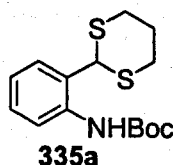
Following a known procedure,[230] a solution of 2-(2'-aminophenyl)-1,3-dithiane **331a** (3.18 g, 15.0 mmol) and di-*tert*-butyl-dicarbonate (3.60 g, 16.5 mmol) in THF (25 cm^3) was heated under reflux, under nitrogen for 5 h. After this time the reaction mixture was poured into water (50 cm^3) and extracted into DCM (2 x 30 cm^3). The combined organic phases were washed with water (2 x 50 cm^3), dried over sodium sulfate and concentrated to yield a yellow solid (4.34 g). Recrystallisation from propan-2-ol gave 2-[2'-(*N-tert*-butyloxycarboxyamino)phenyl]-1,3-dithiane **335a** as golden plates (4.00 g, 12.8 mmol, 86%), R$_f$ (SiO$_2$, DCM): 0.32; Mpt: 142-144 °C; ν_{max} (KBr)/cm^{-1}: 3400 (NH), 2980 (CH), 2965 (CH), 1737 s (CO); δ_H (400 MHz, CDCl$_3$): 1.54 [9H, s, (CH$_3$)$_3$], 1.88-1.99 (1H, m, CH$_{ax}$), 2.17-2.23 (1H, m, CH$_{eq}$), 2.91-2.95 (2H, m, CH$_2$-S), 3.07-3.14 (2H, m, CH$_2$-S), 4.75 (1H, s, NH), 5.30 (1H, s, S$_2$CH), 7.05 (1H, dt, J 1.0 and 7.6, H-5'), 7.27 (1H, dt, J 1.5 and 8.6, H-4'), 7.40 (1H, dd, J 1.2 and 7.7, H-6'), 7.30 (1H, bd, J 7.1, H-3'); δ_C (100 MHz, CDCl$_3$): 25.1 (CH$_2$), 28.4 (CH$_3$), 31.9 (CH$_2$), 48.3 (CH), 80.5 (C), 122.9 (CH), 124.1 (CH), 128.3 (CH), 129.1 (CH), 136.1 (C), 138.1 (C), 153.2 (C); m/z, EI+ (%): 311 (M$^{+\bullet}$, 10), 255 (M$^{+\bullet}$-C$_4$H$_{10}$, 100), 254 (70); Accurate mass: C$_{15}$H$_{21}$NO$_2$S$_2$: requires 311.1014, found 311.1014; Microanalysis Found: C 57.95%, H 6.80%, N 4.40%; Theoretical C$_{15}$H$_{21}$NO$_2$S$_2$: C 57.84%, H 6.80%, N 4.50%.

# Use of 2-[2'-(*N,N*-Di-*tert*-butyloxycarboxyamino)phenyl]-1,3-dithiane 334 under solution-phase Takeda conditions
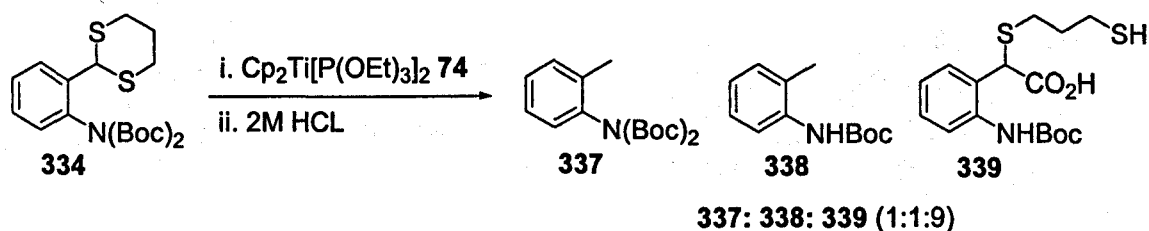
337: 338: 339 (1:1:9)

Employing thioacetal **334** (1.23 g, 3.00 mmol), under the conditions described above, yielded an orange oil (0.95 g). ^{1}H NMR analysis confirmed that a mixture of products (**337**: **338**: **339**/ 1: 1: 9) was obtained with considerable amounts of triethylphosphite and other impurities present. Column chromatography (SiO$_2$, EtOAc: Pet. ether 1:1) of a 0.50 g portion gave *N,N*-di-*tert*-butyloxycarboxyamino-2-toluidine **337** as a white solid (0.26 g): R$_f$ (SiO$_2$, EtOAc: Pet. ether 1:1): 0.11; δ$_H$ (400 MHz, CDCl$_3$): 1.66 [18H, s, C(CH$_3$)$_3$], 3.65 (3H, s, CH$_3$), 7.11 (1H, t, *J* 7.6, H-4'), 7.23 (1H, d, *J* 7.3, H-6'), 7.28 (1H, t, *J* 7.8, H-5'), 7.77 (1H, d, *J* 8.3, H-3'); *N*-*tert*-butyloxycarboxyamino-2-toluidine **338**[224] as a white solid (0.24 g): R$_f$ (SiO$_2$, EtOAc: Pet. ether 1:1): 0.40; Mpt: 79-81 °C (Lit. Mpt: 82-83 °C)[224]; δ$_H$ (400 MHz, CDCl$_3$): 1.52 [9H, s, C(CH$_3$)$_3$], 2.25 (3H, s, CH$_3$), 6.25 (1H, s, NH), 6.97 (1H, dt, *J* 0.9 and 7.5, H-4'), 7.13 (1H, d, *J* 7.4, H-6'), 7.17 (1H, t, *J* 7.4, H-5'), 7.78 (1H, d, *J* 8.3, H-3'); and the corresponding thiol **339** (most of this compound appeared to be converted to the corresponding disulfide on silica) was obtained as a colourless oil (0.07 g); R$_f$ (SiO$_2$, EtOAc: Pet. ether 1:1): 0.35, ν$_{max}$ (Thin film)/cm^{-1}: 3443 (NH), 3158 (NH), 3054 (SH), 2973 (OH), 2936 (OH), 2895 (OH), 1787 (CO), 1719 (CO), 1447 (NH), 1380 (OH), 1167 (COC); δ$_H$ (400 MHz, CDCl$_3$): 1.33 (1H, t, *J* 8.1, SH), 1.64 [9H, s, C(CH$_3$)$_3$], 1.87-1.93 (2H, m, CH$_2$C*H$_2$*CH$_2$), 2.60 (2H, q, *J* 7.3, C*H$_2$*-SH), 2.71 (1H, td, *J* 7.4 and 12.8, C*H^A*H^{B}CH$_2$CH$_2$SH), 2.92 (1H, td, *J* 6.8 and 12.8, CH^A*H^B*CH$_2$CH$_2$SH), 4.37 (1H, s, SCH), 7.17 (1H, t, *J* 7.6, H-5), 7.32 (1H, t, *J* 7.8, H-4), 7.38 (1H, d, *J* 7.4, H-6), 7.80 (1H, d, *J* 8.4, H-6); δ$_C$ (100 MHz, CDCl$_3$): 23.7 (CH$_2$), 28.5 (CH$_3$), 29.0 (CH$_2$), 33.3 (CH$_2$), 45.4 (CH), 85.0 (C), 115.5 (CH), 124.8 (C), 125.1 (CH), 125.4 (CH), 129.8 (CH), 140.4 (C), 149.5 (C), 173.8 (C).

Use of 2-[2'-(N-*tert*-Butyloxycarboxyamino)phenyl]-1,3-dithiane 335a under solution-phase Takeda conditions

i. Cp$_2$Ti[P(OEt)$_3$]$_2$ **74**

ii. 2M HCL

335a   →   **338**   **341**
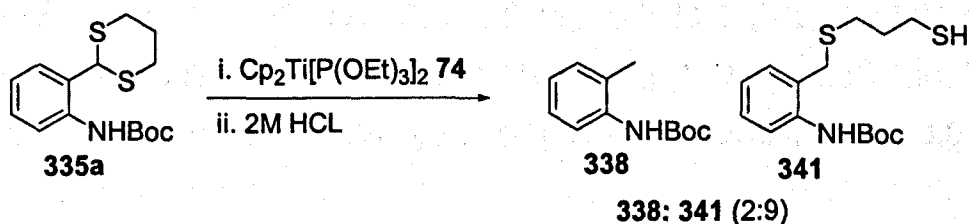
338: 341 (2:9)

Employing thioacetal **335a** (1.23 g, 3.00 mmol) under the conditions described above, yielded a red oil (1.93 g). ^{1}H NMR analysis confirmed that a mixture of products (**338**: **341** 2: 9) was obtained with considerable amounts of triethylphosphite and impurities with signals corresponding to cyclopentadienyl ligands. Column chromatography (Al$_2$O$_3$, Et$_2$O: Pet. ether 1: 1) of a 0.50 g portion of the crude material gave *N-tert*-butyloxycarboxyamino-2-toluidine **338**[224] as a white solid (0.09 g): R$_f$ (Al$_2$O$_3$, Et$_2$O: Pet. ether 1: 1): 0.30, ^{1}H NMR as before; and ring opened thiol **341** (most of this compound appeared to be converted to the corresponding disulfide on Al$_2$O$_3$ gel) was obtained as a colourless oil (0.20 g): R$_f$ (Al$_2$O$_3$, Et$_2$O: Pet. ether 1: 1): 0.20; ν$_{max}$ (Thin film)/cm^{-1}: 3675 (NH), 3036 (NH), 3054 (SH), 1702 (CO), 1553 (C=C), 1472 (NH), 1169 (COC); δ$_H$ (400 MHz, CDCl$_3$): 1.28 (1H, t, J 8.1, SH), 1.53 [9H, s, C(CH$_3$)$_3$], 1.80 (2H, qn, J 7.0 CH$_2$CH_2CH$_2$), 2.49 (2H, t, J 7.1, CH$_2$-S-CH_2), 2.55 (2H, td, 7.0 and 7.9, CH_2SH), 3.72 (2H, s, ArCH_2-S-), 6.98 (1H, dt, J 1.2 and 7.5, H-5), 7.11 (1H, dd, J 1.5 and 7.6, H-3), 7.26 (1H, dt, J 1.6 and 7.6, H-4), 7.82 (1H, d, J 8.0, H-6); δ$_C$ (100 MHz, CDCl$_3$): 23.3 (CH$_2$), 28.4 (CH$_3$), 29.7 (CH$_2$), 32.9 (CH$_2$), 33.5 (CH$_2$), 80.5 (C), 122.6 (CH), 123.4 (CH), 126.5 (C), 128.5 (CH), 130.4 (CH), 137.0 (C), 153.2 (C); m/z, EI+ (%): 313 (M$^{+\bullet}$, 4), 257 (7), 151 (41), 106 (50), 57 (100); Accurate mass: C$_{15}$H$_{23}$NO$_2$S$_2$: requires 313.1168, found 313.1170.
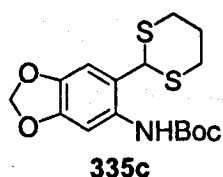
2-[2'-(*N-tert*-Butyloxycarboxyamino)-3'-methoxyphenyl]-1,3-dithiane 335b

CH$_3$O   **335b**
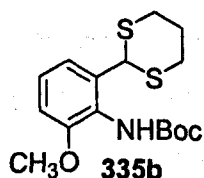
Following the procedure for carbamate **335a**, a solution of 2-(2'-amino-3'-methoxyphenyl)-1,3-dithiane **331b** (4.10 g, 17.0 mmol) and di-*tert*-butyl-dicarbonate (4.08 g, 18.7 mmol) in THF (30 cm^3), was heated under reflux for 40 h. After this time the reaction mixture was poured into water (50 cm^3) and extracted into diethylether (2 x 60 cm^3). The combined organic phases were washed with water (2 x 100 cm^3), dried over sodium sulfate and

concentrated to yield a white solid (4.76 g). Recrystallisation, from propan-2-ol, yielded 2-[2'-(*N-tert*-butyloxycarboxyamino)-3'-methoxyphenyl]-1,3-dithiane **335b** as needles (4.34 g, 12.7 mmol, 75%), Mpt: 174-177 °C; ν_{max} (KBr)/cm^{-1}: 3317 (NH), 2359 (NCO), 1714 (CO), 1496 (C=C), 1473 (COMe); δ_H (400 MHz, CDCl$_3$): 1.49 [9H, s, (CH$_3$)$_3$], 1.87-1.98 (1H, m, CH$_{ax}$), 2.13-2.20 (1H, m, CH$_{eq}$), 2.87 (2H, dt, *J* 14.4 and 4.0, CH$_2$-S), 3.03 (2H, td, *J* 2.4 and 14.6, CH$_2$-S), 3.83 (3H, s, OMe), 5.40 (1H, s, CH), 6.03 (1H, bs, NH), 6.83-6.87 (1H, m, H-5'), 7.20-7.24 (2H, m, H-4' and H-6'); δ_C (100 MHz, CDCl$_3$): 25.3 (CH$_2$), 28.2 (CH$_3$), 32.3 (CH$_2$), 47.3 (CH$_3$), 55.8 (CH), 80.2 (C), 111.1 (CH), 120.3 (CH), 123.6 (C), 127.8 (CH), 136.9 (C), 154.7 (C); m/z, EI+ (%): 341 (M$^{+\bullet}$, 12), 285 (M$^{+\bullet}$-C$_4$H$_8$, 63), 284 (40), 240 (M$^{+\bullet}$-C$_5$H$_9$O, 63), 178 (100); Accurate mass: C$_{16}$H$_{23}$NO$_3$S$_2$: requires 341.1119, found 341.1112; Microanalysis Found: C 56.40%, H 6.83%, N 4.17%; Theoretical C$_{16}$H$_{23}$NO$_3$S$_2$: C 56.27%, H 6.79%, N 4.10%.
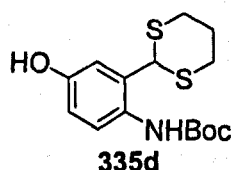
2-[2'-(*N-tert*-Butyloxycarboxyamino)-4',5'-methylenedioxyphenyl]-1,3-dithiane 335c

335c

Following the procedure for carbamate **335a**, a solution of 2-(2'-amino-4',5'-methylenedioxyphenyl)-1,3-dithiane **331c** (5.61 g, 22.0 mmol) and di-*tert*-butyl-dicarbonate (11.52 g, 52.8 mmol) in THF (75 cm^3), was heated under reflux for 15 h. After this time the reaction mixture was poured into water (100 cm^3) and extracted into ethyl acetate (2 x 60 cm^3). The combined organic phases were washed with brine (100 cm^3) and water (100 cm^3), dried over sodium sulfate, and concentrated to yield 2-[2'-(*N*-Di-*tert*-butyloxycarboxyamino)-4',5'-methylenedioxyphenyl]-1,3-dithiane   with   was contaminated with some di-*tert*-butyl-dicarbonate as a brown/green solid (15.04 g, 120%); R$_f$ (SiO$_2$, DCM): 0.52, δ_H (400 MHz, CDCl$_3$): 1.55 [18H, s, (CH$_3$)$_3$], 1.87-1.98 (1H, m, CH$_{ax}$), 2.13-2.22 (1H, m, CH$_{eq}$), 2.91-2.95 (2H, m, CH$_2$-S), 3.07-3.14 (2H, m, CH$_2$-S), 5.24 (1H, s, CH-S$_2$), 5.96 (2H, s, OCH$_2$O), 6.96 (1H, s, H-3'), 6.28 (1H, s, H-6'). Triflouroacetic acid (2.6 cm^3, 33.0 mmol) was added drop-wise to the crude 2-[2'-(*N*-di-*tert*-butyloxycarboxyamino)-4',5'-methylenedioxyphenyl]-1,3-dithiane (15.04 g, assumed 22.0 mmol) in DCM (250 cm^3) and the reaction mixture was stirred for 15 h. After this time the reaction mixture was washed with sodium bicarbonate (2 x 100 cm^3) and water (100 cm^3), dried over sodium sulfate and concentrated to yield a yellow solid (6.89 g). Recrystallisation from propan-2-ol gave 2-[2'-(*N-tert*-Butyloxycarboxyamino)-4',5'-

methylenedioxyphenyl]-1,3-dithiane **335c** as yellow needles (6.53 g, 18.4 mmol, 83% from **329c**), R_f (SiO$_2$, DCM): 0.15; Mpt: 156-158 °C; v_{max} (KBr)/cm^{-1}: 3404 (NH), 2975 (OCH$_2$O), 1727 (CO), 1508 C=C), 1154 (COC); δ_H (400 MHz, CDCl$_3$): 1.53 [9H, s, (CH$_3$)$_3$], 1.85-1.95 (1H, m, CH$_{ax}$), 2.15-2.21 (1H, m, CH$_{eq}$), 2.88 (2H, dt, J 14.4 and 3.3, CH$_2$-S), 3.05-3.12 (2H, m, CH$_2$-S), 5.22 (1H, s, CH-S$_2$), 5.93 (2H, s, OCH$_2$O), 6.94 (1H, s, H-3′), 6.24 (1H, s, H-6′); δ_C (90 MHz, CDCl$_3$): 25.1 (CH$_2$), 28.4 (CH$_3$), 32.0 (CH$_2$), 47.7 (CH), 80.5 (C), 101.5 (CH$_2$), 105.6 (C), 107.7 (CH), 130.1 (C), 144.6 (C), 147.9 (C), 153.5 (C); m/z, EI+ (%): 355 (M$^{+\bullet}$, 50), 298 (M$^{+\bullet}$-C$_4$H$_8$, 55), 282 (M$^{+\bullet}$-C$_4$H$_9$O, 29), 225 (M$^{+\bullet}$-C$_6$H$_{10}$O$_3$, 58), 192 (M$^{+\bullet}$-C$_6$H$_{12}$NO$_4$, 100); Accurate mass: C$_{16}$H$_{21}$NO$_4$S$_2$: requires 355.0912, found 355.0914; Microanalysis Found: C 54.23%, H 6.05%, N 3.86%; Theoretical C$_{16}$H$_{21}$NO$_4$S$_2$: C 54.08%, H 5.91%, N 3.94%.

2-[2′-(*N-tert*-Butyloxycarboxyamino)-5′-hydroxyphenyl]-1,3-dithiane 335d


335d

Following the procedure for carbamate **335a**, a solution 2-(2′-amino-5′-hydroxyphenyl)-1,3-dithiane **331d** (9.09 g, 40.0 mmol) and di-*tert*-butyl-dicarbonate (10.48 g, 48.0 mmol) in THF (100 cm^3), was heated under reflux for 64 h. After this time the reaction mixture was poured into water (50 cm^3), extracted into ethyl acetate (2 x 60 cm^3). The combined organic phases were washed with brine (100 cm^3) and water (100 cm^3), dried over sodium sulfate and concentrated to yield a yellow solid (15.8 g, 114%). Recrystallisation, from ethanol/ water and subsequent drying in a vacuum oven yielded 2-[2′-(*N-tert*-butyloxycarboxyamino)-5′-hydroxyphenyl]-1,3-dithiane **335d** as needles (10.0 g, 30.6 mmol, 76%); Mpt: 155-157 °C; v_{max} (KBr)/cm^{-1}: 3426 (OH), 3310 (NH), 1685 (CO), 1584 (C=C), 1504 (OH), 1157 (COC); δ_H (250 MHz, CDCl$_3$): 1.53 [9H, s, (CH$_3$)$_3$], 1.88-1.94 (1H, m, CH$_{ax}$), 2.15-2.21 (1H, m, CH$_{eq}$), 2.87 (2H, dt, J 14.3 and 4.0, CH$_2$-S), 3.03 (2H, td, J 2.5 and 14.6, CH$_2$-S), 5.23 (1H, s, S$_2$CH), 5.57 (1H, s, OH), 6.03 (1H, bs, NH), 6.65 (1H, dd, J 8.7 and 2.9, H-4′), 6.92 (1H, d, J 2.9, H-6′), 7.37 (1H, bd, J 8.4, H-3′); δ_C (63 MHz, CDCl$_3$): 25.2 (CH$_2$), 28.4 (CH$_3$), 31.9 (CH$_2$), 47.6 (CH), 80.6 (C), 115.1 (CH), 116.1 (CH), 128.0 (C), 153.3 (C), 154.3 (C); m/z, EI+ (%): 327 (M$^{+\bullet}$, 28), 271 (M$^{+\bullet}$-C$_4$H$_8$, 100), 270 (50), 253 (M$^{+\bullet}$-C$_4$H$_9$O, 29), 152 (98); Accurate mass: C$_{15}$H$_{21}$NO$_3$S$_2$: requires 327.0963, found 327.0959; Microanalysis Found: C 55.01%, H 6.65%, N 4.09%; Theoretical C$_{15}$H$_{21}$NO$_3$S$_2$: C 55.09%, H 6.47%, N 4.28%.

2-[2'-(*N-tert*-Butyloxycarboxyamino)-5'-trimethylsilyloxyphenyl]-1,3-dithiane 335e

335e
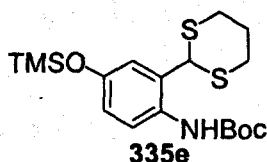
Trimethylsilyl chloride (3.1 cm^3, 24.0 mmol) was added dropwise to a solution of 2-[2'-(*N-tert*-butyloxycarboxyamino)-5'-hydroxyphenyl]-1,3-dithiane **335d** (6.54 g, 20.0 mmol) in dry pyridine (40 cm^3) and the reaction mixture was stirred under argon for 15 h. After this time the solvent was removed *in vacuo* and diethyl ether (50 cm^3) was added. The resulting precipitate was filtered off and the ethereal solution was concentrated to leave a white solid. Recrystallisation, from propan-2-ol, gave 2-[2'-(*N-tert*-butyloxycarboxyamino)-5'-trimethylsilyloxyphenyl]-1,3-dithiane **335e** as a white powder (6.63 g, 16.6 mmol, 83%); Mpt: 116-119 °C; ν_{max} (KBr)/cm^{-1}: 3433 (NH), 1716 (CO), 1509 (C=C), 1253 (SiMe$_3$), 1158 (COC); δ_H (400 MHz, CDCl$_3$): 0.25 [9H, s, Si(CH$_3$)$_3$], 1.53 [9H, s, (CH$_3$)$_3$], 1.91-1.98 (1H, m, CH$_{ax}$), 2.16-2.22 (1H, m, CH$_{eq}$), 2.89 (2H, dt, J 14.4 and 3.9, CH$_2$-S), 3.06-3.13 (2H, m, CH$_2$-S), 5.22 (1H, s, S$_2$CH), 6.75 (1H, dd, J 8.8 and 2.8, H-4'), 6.96 (1H, d, J 2.7, H-6'), 7.52 (1H, bs, H-3'); δ_C (90 MHz, CDCl$_3$): 0.2 (CH$_3$), 25.2 (CH$_2$), 28.4 (CH$_3$), 32.0 (CH$_2$), 47.6 (CH), 80.4 (C), 114.8 (C), 115.9 (C), 119.6 (CH), 120.4 (CH), 125.4 (C), 129.2 (C), 153 8 (C); m/z, EI+ (%): 399 (M$^{+\bullet}$, 31), 343 (M$^{+\bullet}$-C$_4$H$_8$, 65), 236 (100); Accurate mass: C$_{18}$H$_{29}$NO$_3$S$_2$Si: requires 399.1358, found 399.1358.

2-[2'-(*N-tert*-Butyloxycarboxyamino)-5'-chlorophenyl]-1,3-dithiane 335f

335f
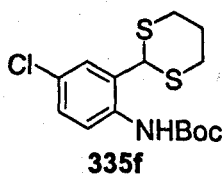
A solution of 2-(2'-amino-5'-chlorophenyl)-1,3-dithiane **331f** (6.14 g, 25.0 mmol) and di-*tert*-butyl-dicarbonate (6.55 g, 30.0 mmol) in THF (75 cm^3) was heated under reflux for 64 h. After this time the reaction mixture was poured into water (100 cm^3), extracted into diethylether (2 x 75 cm^3). The combined organic phases were washed with water (2 x 150 cm^3), dried over sodium sulfate and concentrated to yield a yellow solid (9.40 g). Recrystallisation, from propan-2-ol gave 2-[2'-(*N-tert*-butyloxycarboxyamino)-5'-chlorophenyl]-1,3-dithiane **335f** as yellow needles (7.65 g, 22.1 mmol, 89%); Mpt: 125-127 °C; ν_{max} (KBr)/cm^{-1}: 3398 (NH), 1734 (CO), 1496 (C=C), 1150 (COC); δ_H (250 MHz, CDCl$_3$): 1.54 [9H, s, (CH$_3$)$_3$], 1.90-1.96 (1H, m, CH$_{ax}$), 2.18-2.19 (1H, m, CH$_{eq}$), 2.89 (2H,

dt, J 14.4 and 4.0, CH$_2$-S), 3.04 (2H, td, J 4.0 and 12.3, CH$_2$-S), 5.23 (1H, s, S$_2$CH), 7.22 (1H, dd, J 9.2 and 2.4, H-4'), 7.39 (1H, d, J 2.5, H-6'), 7.77 (1H, bd, J 8.8, H-3'); δ_C (63 MHz, CDCl$_3$): 25.0 (CH$_2$), 28.3 (CH$_3$), 31.8 (CH$_2$), 47.7 (CH), 80.8 (C), 124.1 (CH), 128.3 (CH), 129.0 (CH), 129.6 (C), 134.8 (C), 152.9 (C); m/z, EI+ (%): 345 (M$^{+\bullet}$, 12), 288 (M$^{+\bullet}$-C$_4$H$_8$, 78), 287 (M$^{+\bullet}$-C$_4$H$_9$, 53), 183 (91), 57 (100); Accurate mass: C$_{15}$H$_{20}$^{35}ClNO$_2$S$_2$: requires 345.0624, found 345.0625, C$_{15}$H$_{20}$^{37}ClNO$_2$S$_2$: requires 347.0596, found 347.0596.

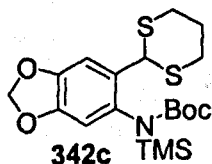### 2-[2'-(*N*-tert-Butyloxycarboxy-*N*-trimethylsilylamino)phenyl]-1,3-dithiane 342a
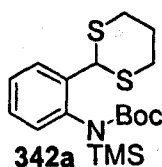
A solution of lithium di-isopropylamine (7.2 cm^3, 14.4 mmol, 2.0 mol dm^{-3} in THF, ethyl benzene and heptanes) in THF (22.8 cm^3) was added dropwise to a solution of carbamate **335a** (3.74 g, 12.0 mmol) and chlorotrimethylsilane (2.0 cm^3, 14.4 mmol) in THF (70 cm^3), at -78 °C under argon. The reaction mixture was allowed to warm to rt over 45 mins and was allowed to stir for a further 1 h at this temperature. After this time, the solvent was removed in vacuo and ether (100 cm^3) was added. The resulting precipitate was filtered off and the ethereal solution was concentrated to yield 2-[2'-(*N*-tert-butyloxycarboxy-*N*-trimethylsilylamino)phenyl]-1,3-dithiane **342a** (^{1}H and ^{13}C NMR were carried out at 52 °C to allow rapid rotation around the C2'-N1 bond on the NMR timescale) as a white solid (3.95 g, 10.3 mmol, 86%); Mpt: 100-103 °C; ν_{max} (KBr)/cm^{-1}: 1680 (CO), 1250 (SiMe$_3$), 1162 (Si-N), 850 (SiMe$_3$); δ_H (400 MHz, 52 °C, CDCl$_3$): 0.23 [9H, s, Si(CH$_3$)$_3$], 1.43 [9H, s, C(CH$_3$)$_3$], 1.90-1.99 (1H, m, CH$_{ax}$), 2.11-2.16 (1H, m, CH$_{eq}$), 2.85-3.02 (4H, m, CH$_2$-S), 5.22 (1H, s, S$_2$CH), 6.93 (1H, dd, J 1.1 and 7.0, H-6'), 7.18-7.25 (2H, m, H-4' and 5'), 7.62 (1H, dd, J 1.9 and 7.4, H-3'); δ_C (100 MHz, 52 °C, CDCl$_3$): 0.0 (CH$_3$), 25.3 (CH$_2$), 28.1 (CH$_3$), 32.7 (CH$_2$), 32.8 (CH$_2$), 46.9 (CH), 80.4 (C), 127.4 (CH), 128.5 (CH), 129.0 (CH), 129.3 (CH), 137.2 (C), 138.7 (C), 156.7 (C); m/z, EI+ (%): 383 (M$^{+\bullet}$, 7), 327 (M$^{+\bullet}$-C$_4$H$_9$, 73), 282 (M$^{+\bullet}$-C$_7$H$_{18}$, 100); Accurate mass: C$_{18}$H$_{29}$NO$_2$S$_2$Si: requires 383.1409, found 383.1413; Microanalysis Found: C 56.26%, H 7.66%, N 3.44%; Theoretical C$_{18}$H$_{29}$NO$_2$S$_2$Si: C 56.35%, H 7.62%, N 3.65%.

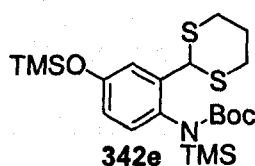## 2-[2'-(*N-tert*-Butyloxycarboxy-*N*-trimethylsilylamino)-3'-methoxyphenyl]-1,3-dithiane 342b
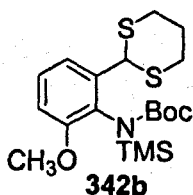
Exactly as for thioacetal **342a**, employing carbamate **335b** (4.10 g, 12.0 mmol) gave 2-[2'-(*N-tert*-butyloxycarboxy-*N*-trimethylsilylamino)-3'-methoxyphenyl]-1,3-dithiane **342b** (a 50:50 mixture of the two geometrical isomers a:b) as a yellow solid (4.52 g, 10.9 mmol, 91%); ν_{max} (G Gate)/cm^{-1}: 2837 (OCH$_3$), 1684 (CO), 1253 (SiMe$_3$), 1157 (Si-N), 840 (SiMe$_3$); δ_H (400 MHz, CDCl$_3$): 0.23 [9H, s, Si(CH$_3$)$_3$], 1.35 [9H^a, s, C(CH$_3$)$_3$], 1.58 [9H^b, s, C(CH$_3$)$_3$], 1.94-2.02 (1H^{a+b}, m, CH$_{ax}$), 2.16-2.20 (1H^{a+b}, m, CH$_{eq}$), 2.89-3.02 (4H^{a+b}, m, CH$_2$-S), 5.26 (1H^{a+b}, s, S$_2$CH), 6.82 (1H^{a+b}, bd, *J* 7.4, H-6'), 7.19-7.34 (2H^{a+b}, m, H-4' and H-5'); m/z, EI+ (%): 413 (M$^{+\bullet}$, 20), 356 (M$^{+\bullet}$-C$_4$H$_9$, 70), 312 (M$^{+\bullet}$-C$_5$H$_9$O$_2$, 77), 250 (79), 73 (100); Accurate mass: C$_{19}$H$_{31}$NO$_3$S$_2$Si: requires 413.1515, found 413.1513.

2-[2'-(*N-tert*-Butyloxycarboxy-*N*-trimethylsilylamino)-4',5'-methylenedioxy]-1,3-dithiane 342c
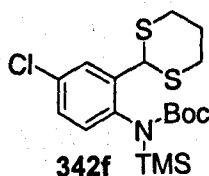

Exactly as for thioacetal **342a**, employing carbamate **335c** (3.55 g, 10.0 mmol), yielded 2-[2'-(*N-tert*-butyloxycarboxy-*N*-trimethylsilylamino)-4',5'-methylenedioxy]-1,3-dithiane **342c** as yellow needles; (4.01 g, 9.39 mmol, 94%); ν_{max} (G Gate)/cm^{-1}: 2765 (OCH$_2$O), 1677 (CO), 1246 (SiMe$_3$), 1157 (Si-N), 845 (SiMe$_3$); δ_H (250 MHz, CDCl$_3$): 0.10 [9H, s, Si(CH$_3$)$_3$], 1.30 [9H, s, C(CH$_3$)$_3$], 1.69-1.79 (1H, m, CH$_{ax}$), 1.94-1.99 (1H, m, CH$_{eq}$), 2.71-2.86 (4H, m, CH$_2$-S), 5.02 (1H, s, S$_2$CH), 5.77-5.79 (2H, m, OCH$_2$O), 6.28 (1H, s, H-3'), 6.97 (1H, s, H-6'); m/z, EI+ (%): 427 (M$^{+\bullet}$, 23), 371 (M$^{+\bullet}$-C$_4$H$_8$, 70), 326 (M$^{+\bullet}$-C$_5$H$_9$O$_2$, 48), 265 (61), 73 (100); Accurate mass: C$_{19}$H$_{29}$NO$_4$S$_2$Si: requires 427.1307, found 427.1308.

2-[2'-(N-tert-Butyloxycarboxy-N-trimethylsilylamino)-5'-trimethylsilyloxyphenyl]-1,3-dithiane 342e

342e

Exactly as for thioacetal **342a**, employing carbamate **335e** (4.80 g, 12.0 mmol) gave 2-[2'-(N-tert-butyloxycarboxy-N-trimethylsilylamino)-5'-trimethylsilyloxyphenyl]-1,3-dithiane **342e** as a yellow oil; (3.57 g, 7.56 mmol, 63%); ν_{max} (Thin Film)/cm^{-1}: 1683 (CO), 1292 (SiMe$_3$), 1248 (SiMe$_3$), 1159 (Si-O), 842 (SiMe$_3$); δ_H (250 MHz, CDCl$_3$): 0.07 [9H, s, Si(CH$_3$)$_3$], 0.11 [9H, s, Si(CH$_3$)$_3$], 1.28 [9H, s, C(CH$_3$)$_3$], 1.82-1.90 (1H, m, CH$_{ax}$), 2.10-2.16 (1H, m, CH$_{eq}$), 2.89-3.00 (4H, m, CH$_2$-S), 4.98 (1H, s, S$_2$CH), 6.49 (1H, dd, J 8.5 and 2.8, H-4'), 6.61 (1H, d, J 8.5, H-3'), 6.97 (1H, d, J 2.7, H-6'); m/z, EI+ (%): 471 (M$^{+\bullet}$, 10), 415 (M$^{+\bullet}$-C$_4$H$_8$, 48), 370 (M$^{+\bullet}$-C$_5$H$_9$O$_2$, 30), 309 (70), 73 (100); Accurate mass: C$_{21}$H$_{37}$NO$_3$S$_2$Si$_2$: requires 471.1753, found 471.1755.
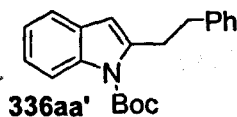
2-[2'-(N-tert-Butyloxycarboxy-N-trimethylsilylamino)-5'-chlorophenyl]-1,3-dithiane 342f

342f

Exactly as for thioacetal **342a**, employing carbamate **335f** (4.15 g, 12.0 mmol) gave 2-[2'-(N-tert-butyloxycarboxy-N-trimethylsilylamino)-5'-chlorophenyl]-1,3-dithiane **342f** as yellow needles (4.43 g, 10.6 mmol, 88%); ν_{max} (G Gate)/cm^{-1}: 1677 (CO), 1246 (SiMe$_3$), 1155 (Si-N), 843 (SiMe$_3$); δ_H (400 MHz, CDCl$_3$): 0.23 [9H, s, Si(CH$_3$)$_3$], 1.44 [9H, s, C(CH$_3$)$_3$], 1.92-1.95 (1H, m, CH$_{ax}$), 2.14-2.18 (1H, m, CH$_{eq}$), 2.87-3.01 (4H, m, CH$_2$-S), 5.13 (1H, s, S$_2$CH), 6.88 (1H, d, J 8.3, H-6'), 7.18 (1H, dd, J 8.3 and 2.5, H-4'), 7.63 (1H, d, J 2.5, H-3'); m/z, EI+ (%): 417 (M$^{+\bullet}$, 3), 361 (M$^{+\bullet}$-C$_4$H$_8$, 70), 316 (M$^{+\bullet}$-C$_5$H$_9$O$_2$, 49), 73 (91), 57 (100); Accurate mass: C$_{18}$H$_{28}$^{35}ClNO$_2$S$_2$Si: requires 417.1019, found 417.1016; C$_{18}$H$_{28}$^{37}ClNO$_2$S$_2$Si: requires 419.0994, found 419.0992.

N-*tert*-Butyloxycarboxy-2-phenethyl indole 336aa'

336aa' Boc

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342a** (0.58 g, 1.50 mmol) and resin-bound ester **309a'** (Method B, 0.28 mmol), yielded N-*tert*-butyloxycarboxy-2-phenethyl indole **336aa'** in excellent purity as a grey oil (0.062 g, 0.195 mmol, 69%); ν_{max} (Solt^n, CDCl$_3$)/cm^{-1}: 3065 (C=C), 1749 (CO), 1454 (CH); δ_H (400 MHz, CDCl$_3$): 1.68 [9H, s, (CH$_3$)$_3$], 3.00 (2H, t, J 8.4, CH$_2$), 3.32 (2H, t, J 8.4, CH$_2$), 6.34 (1H, d, J 0.6, H-3), 7.16-7.30 (7H, m, Ar-H), 7.42 (1H, dd, J 1.0 and 7.7, H-4), 8.07 (1H, d, J 8.3, H-7); δ_C (100 MHz, CDCl$_3$): 28.3 (CH$_3$), 31.8 (CH$_2$), 35.2 (CH$_2$), 83.8 (C), 107.4 (CH), 115.6 (CH), 119.8 (CH), 122.6 (CH), 123.3 (CH), 126.0 (CH), 128.4 (CH), 129.3 (C), 136.5 (C), 141.5 (C), 141.6 (C), 150.6 (C); m/z, EI+ (%): 321 (M$^{+\cdot}$, 21), 265 (M$^{+\cdot}$-C$_4$H$_8$, 58), 220 (M$^{+\cdot}$-C$_5$H$_9$O$_2$, 10), 174 (80), 130 (100); Accurate mass: C$_{21}$H$_{23}$NO$_2$: requires 321.1729, found 321.1726.
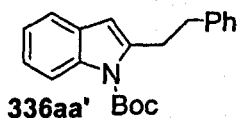
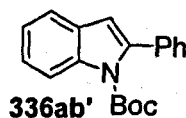## N-*tert*-Butyloxycarboxy-2-phenethyl indole 336aa'

336aa' Boc

Following the solid-phase Takeda Method B and resin-cleavage procedure A, employing silylated carbamate **342a** (0.35 g, 0.90 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), yielded indole **336aa'** in excellent purity as a grey oil (0.059 g, 0.180 mmol, 61%); δ_H (400 MHz, CDCl$_3$): as above.

N-*tert*-Butyloxycarboxy-2-phenyl indole[249] 336ab'

336ab' Boc

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342a** (0.58 g, 1.50 mmol) and resin-bound ester **309b'** (Method B, 0.28 mmol), yielded N-*tert*-butyloxycarboxy-2-phenyl indole[249] **336ab'** in excellent purity as a white solid (0.048 g, 0.165 mmol, 59%); Mpt: 75-78 °C; ν_{max} (KBr)/cm^{-1}: 2980 (C=C), 1728 (CO), 1454 (CH); δ_H (400 MHz, CDCl$_3$): 1.30 [9H, s, (CH$_3$)$_3$], 6.55 (1H, s, H-3), 7.23-7.43 (7H, m, Ar-H), 7.54 (1H, d, J 7.6, H-4), 8.07 (1H, d, J 8.3, H-7); δ_C (100 MHz, CDCl$_3$): 27.5 (CH$_3$), 83.3 (C), 109.9 (CH), 115.2 (CH), 120.4 (CH), 122.9 (CH), 124.3

(CH), 127.5 (CH), 127.8 (CH), 128.7 (CH), 129.2 (C), 135.0 (C), 137.3 (C), 140.5 (C), 150.2 (C); m/z, EI+ (%): 293 (M$^{+\bullet}$, 8), 237 (M$^{+\bullet}$-C$_4$H$_8$, 23), 193 (M$^{+\bullet}$-C$_5$H$_8$O$_2$, 50), 85 (63), 83 (100); Accurate mass: C$_{19}$H$_{19}$NO$_2$: requires 293.1416, found 293.1418.

N-tert-Butyloxycarboxy-2-methyl indole[249] 336ac'

336ac' Boc

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342a** (0.58 g, 1.50 mmol) and resin-bound ester **309c'** (Method B, 0.28 mmol), yielded *N-tert*-butyloxycarboxy-2-methyl indole[249] **336ac'** in excellent purity as a off white solid (0.038 g, 0.165 mmol, 59%); Mpt: 49-52 °C; ν_{max} (KBr)/cm^{-1}: 2950 (C=C), 1724 (CO), 1338 (CH); δ_H (400 MHz, CDCl$_3$): 1.68 [9H, s, (CH$_3$)$_3$], 2.59 (3H, s, CH$_3$), 6.31 (1H, s, H-3), 7.15-7.25 (2H, m, H-5 and H-6), 7.41-7.43 (1H, m, H-4), 8.09 (1H, d, *J* 8.2, H-7); δ_C (100 MHz, CDCl$_3$): 17.1 (CH$_3$), 28.3 (CH$_3$), 83.6 (C), 107.9 (CH), 115.4 (CH), 119.4 (CH), 122.5 (CH), 123.0 (CH), 129.3 (C), 136.5 (C), 137.8 (C), 150.7 (C); m/z, EI+ (%): 231 (M$^{+\bullet}$, 4), 175 (M$^{+\bullet}$-C$_4$H$_8$, 10), 131 (M$^{+\bullet}$-C$_5$H$_8$O$_2$, 12), 83 (100); Accurate mass: C$_{14}$H$_{17}$NO$_2$: requires 231.1256, found 231.1259.

N-tert-Butyloxycarboxy-2-(2'-methyl-propenyl) indole 336ad'
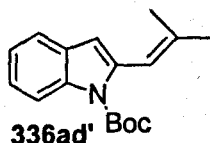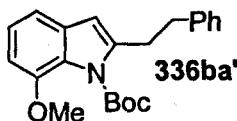

336ad' Boc

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342a** (0.58 g, 1.50 mmol) and resin-bound ester **309d'** (Method B, 0.311 mmol), yielded *N-tert*-butyloxycarboxy-2-(2'-methyl-propenyl) indole **336ad'** in excellent purity as a yellow oil (0.064 g, 0.236 mmol, 76%); ν_{max} (Thin film)/cm^{-1}: 3052 (NH), 2977 (CH), 1731 (CO), 1454 (CH), 802 (CH=CMe$_2$); δ_H (400 MHz, CDCl$_3$): 1.68 [9H, s, (CH$_3$)$_3$], 1.94 (3H, s, CH$_3$=C), 1.97 (3H, s, CH$_3$=C), 6.42 (1H, s, C=CH), 6.51 (1H, s, H-3), 7.21 (1H, dt, *J* 1.2 and 7.3, H-6), 7.26 (1H, dt, *J* 1.4 and 7.5, H-5), 7.50 (1H, d, *J* 7.3, H-4) 8.13 (1H, d, *J* 8.2, H-7); δ_C (100 MHz, CDCl$_3$): 19.9 (CH$_3$), 26.5 (CH$_3$), 28.2 (CH$_3$), 83.5 (C), 109.3 (CH), 115.5 (CH), 118.0 (CH), 122.6 (CH), 123.6 (CH), 129.5 (C), 135.9 (C), 136.3 (C), 137.7 (C), 150.6 (C); m/z, EI+ (%): 271 (M$^{+\bullet}$, 17), 215 (M$^{+\bullet}$-C$_4$H$_8$, 100), 171 (M$^{+\bullet}$-C$_6$H$_{12}$O$_2$, 42), 130 (M$^{+\bullet}$-C$_7$H$_{15}$O$_2$, 39); Accurate mass: C$_{17}$H$_{21}$NO$_2$: requires 271.1572, found 271.1570.

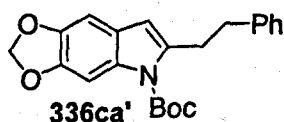## N- *tert*-Butyloxycarboxy-7-methoxy-2-phenethyl indole 336ba'

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342b** (0.62 g, 1.50 mmol) and resin-bound ester **309a'** (Method B, 0.28 mmol), yielded *N*-tert-butyloxycarboxy-7-methoxy-2-phenethyl indole **336ba'** was obtained in excellent purity as a grey oil (0.058 g, 0.162 mmol, 59%); ν_{max} (Solt^n, CDCl$_3$)/cm^{-1}: 2957 (C=C), 2832 (COCH$_3$), 1445 (CH); δ_H (400 MHz, CDCl$_3$): 1.53 [9H, s, (CH$_3$)$_3$], 2.91 (2H, t, J 8.6, CH$_2$), 3.05-3.09 (2H, m, CH$_2$), 3.83 (3H, s OCH$_3$), 6.17 (1H, s, H-3), 6.61 (1H, dd, J 7.8 and 1.8, H-6), 6.98-7.04 (2H, m, H-4 and H-5), 7.09-7.23 (5H, m, Ar-H); δ_C (100 MHz, CDCl$_3$): 27.7 (CH$_3$), 30.1 (CH$_2$), 35.4 (CH$_2$), 55.1 (CH$_3$), 83.4 (C), 104.6 (CH), 112.7 (CH), 122.7 (CH), 125.5 (CH), 126.0 (CH), 128.4 (CH), 128.5 (CH), 131.2 (C), 141.1 (C), 141.4 (C), 147.4 (C), 151.0 (C); m/z, EI+ (%): 351 (M$^{+\bullet}$, 15), 251 (M$^{+\bullet}$-C$_5$H$_8$O$_2$, 25), 160 (M$^{+\bullet}$-C$_{12}$H$_{15}$O$_2$, 100); Accurate mass: C$_{22}$H$_{25}$NO$_2$: requires 351.1834, found 351.1837.

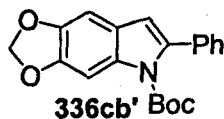## *N-tert*-Butyloxycarboxy-5,6-methylenedioxy-2-phenethyl indole 336ca'

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342c** (0.64 g, 1.50 mmol) and resin-bound ester **309a'** (Method B, 0.28 mmol), yielded *N*-tert-butyloxycarboxy-5,6-methylenedioxy-2-phenethyl indole **336ca'** in excellent purity as a white/brown solid (0.071 g, 0.195 mmol, 69%); Mpt: 102-105 °C; ν_{max} (KBr)/cm^{-1}: 2974 (C=C), 2930 (OCH$_2$O), 1465 (CH); δ_H (400 MHz, CDCl$_3$): 1.66 [9H, s, (CH$_3$)$_3$], 2.98 (2H, t, J 8.4, CH$_2$), 3.25-3.29 (2H, m, CH$_2$), 5.93 (1H, s, OCH$_2$O), 6.21 (1H, s, H-3), 6.82 (1H, s, H-4), 7.17-7.30 (5H, m, Ar-H), 7.65 (1H, s H-7); δ_C (100 MHz, CDCl$_3$): 28.2 (CH$_3$), 31.8 (CH$_2$), 35.3 (CH$_2$), 83.8 (C), 97.6 (CH), 98.8 (CH), 100.8 (CH$_2$), 107.4 (CH), 123.2 (C), 125.9 (CH), 128.3 (CH), 128.4 (CH), 131.1 (C), 140.2 (C), 141.5 (C), 144.0 (C), 145.2 (C), 150.4 (C); m/z, EI+ (%): 365 (M$^{+\bullet}$, 10), 309 (M$^{+\bullet}$-C$_4$H$_8$, 17), 218 (M$^{+\bullet}$-C$_{11}$H$_{15}$, 59), 174 (M$^{+\bullet}$-C$_{12}$H$_{15}$O$_4$, 48), 83 (100); Accurate mass: C$_{22}$H$_{23}$NO$_4$: requires 365.1627, found 365.1629.

N-*tert*-Butyloxycarboxy-5,6-methylenedioxy-2-phenyl indole 336cb'

336cb' Boc

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342c** (0.64 g, 1.50 mmol) and resin-bound ester **309b'** (Method B, 0.28 mmol), yielded N-*tert*-butyloxycarboxy-5,6-methylenedioxy-2-phenyl indole **336cb'** in excellent purity as a brown oil (0.066 g, 0.20 mmol, 70%); ν_{max} (Solt^n, CDCl$_3$)/cm^{-1}: 3149 (C=C), 2980 (OCH$_2$O), 1730 (CO), 1464 (CH); δ_H (400 MHz, CDCl$_3$): 1.28 [9H, s, (CH$_3$)$_3$], 5.97 (1H, s, OCH$_2$O), 6.41 (1H, s, H-3), 6.92 (1H, s, H-4), 7.31-7.38 (5H, m, Ar-H), 7.76 (1H, s, H-7); δ_C (100 MHz, CDCl$_3$): 27.5 (CH$_3$), 83.4 (C), 97.0 (CH), 99.0 (CH), 101.0 (CH$_2$), 109.9 (CH), 123.1 (C), 127.3 (CH), 127.7 (CH), 128.6 (CH), 132.4 (C), 135.1 (C), 139.2 (C), 144.4 (C), 146.0 (C), 150.2 (C); m/z, EI+ (%): 337 (M$^{+\bullet}$, 18), 281 (M$^{+\bullet}$-C$_4$H$_8$, 58), 237 (M$^{+\bullet}$-C$_5$H$_8$O$_2$, 100); Accurate mass: C$_{20}$H$_{19}$NO$_4$: requires 337.1682, found 337.1678.

N-*tert*-Butyloxycarboxy-2-methyl-5,6-methylenedioxy indole 336cc'
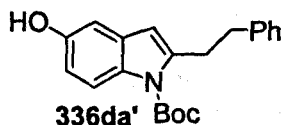

336cc' Boc

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342c** (0.64 g, 1.50 mmol) and resin-bound ester **309c'** (Method B, 0.28 mmol), yielded N-*tert*-butyloxycarboxy-2-methyl-5,6-methylenedioxy indole **336cc'** in excellent purity as a white/brown solid (0.044 g, 0.160 mmol, 58%); Mpt: 95-98 °C; ν_{max} (KBr)/cm^{-1}: 2982 (C=C), 2927 (OCH$_2$O), 1726 (CO); δ_H (400 MHz, CDCl$_3$): 1.66 [9H, s, (CH$_3$)$_3$], 2.52 (3H, s, CH$_3$), 5.93 (1H, s, OCH$_2$O), 6.17 (1H, s, H-3), 6.81 (1H, s, H-4), 7.66 (1H, s, H-7); δ_C (100 MHz, CDCl$_3$): 17.2 (CH$_3$), 28.2 (CH$_3$), 83.7 (C), 96.7 (CH), 98.5 (CH), 100.8 (CH$_2$), 108.0 (CH), 123.3 (C), 131.0 (C), 136.3 (C), 144.0 (C), 145.0 (C), 150.6 (C); m/z, EI+ (%): 275 (M$^{+\bullet}$, 14), 219 [(M$^{+\bullet}$-C$_4$H$_8$), 44], 175 [(M$^{+\bullet}$-C$_5$H$_8$O$_2$), 45], 83 (100); Accurate mass: C$_{15}$H$_{17}$NO$_4$: requires 275.1161, found 275.1158.

N-*tert*-Butyloxycarboxy-5-hydroxy-2-phenethyl indole 336da'
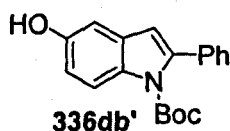

336da' Boc

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342e** (0.71 g, 1.50 mmol) and resin-bound ester **309a'** (Method B, 0.28 mmol), yielded N-*tert*-butyloxycarboxy-5-hydroxy-2-phenethyl indole **336da'** in excellent purity as a yellow oil (0.064 g, 0.190 mmol, 68%); v_{max} (KBr)/cm^{-1}: 3432 (OH), 2925 (C=C), 1731 (CO), 1455 (CH), 1382 (OH); δ_H (400 MHz, CDCl$_3$): 1.66 [9H, s, (CH$_3$)$_3$], 2.98 (2H, t, J 8.4, CH$_2$), 3.29 (2H, t, J 7.4, CH$_2$), 4.97 (1H, s, OH), 6.24 (1H, s, H-3), 6.74 (1H, dd, J 8.9 and 2.5, H-6), 6.86 (1H, d, J 2.4, H-4), 7.17-7.30 (5H, m, Ar-H), 7.92 (1H, d, J 8.9, H-7); δ_C (100 MHz, CDCl$_3$): 28.2 (CH$_3$), 32.7 (CH$_2$), 35.1 (CH$_2$), 83.7 (C), 105.1 (CH), 107.1 (CH), 111.9 (CH), 116.4 (CH), 126.0 (CH), 128.4 (CH), 130.3 (C), 131.4 (C), 141.4 (C), 142.7 (C), 150.5 (C); m/z, EI+ (%): 337 (M$^{+\bullet}$, 12), 281 (M$^{+\bullet}$-C$_4$H$_8$, 26), 237 (M$^{+\bullet}$-C$_5$H$_8$O$_2$, 20), 190 (51), 146 (100); Accurate mass: C$_{21}$H$_{23}$NO$_3$: requires 337.1682, found 337.1678.

N-*tert*-Butyloxycarboxy-5-hydroxy-2-phenyl indole 336db'

336db' Boc

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342e** (0.71 g, 1.50 mmol) and resin-bound ester **309b'** (Method B, 0.28 mmol), yielded N-*tert*-butyloxycarboxy-5-hydroxy-2-phenyl indole **336db'** in excellent purity as a yellow oil (0.062 g, 0.201 mmol, 72%); v_{max} (Solt^n, CDCl$_3$)/cm^{-1}: 3696 (OH), 3600 (OH), 3152 (HC=C), 1476 (CH), 1384 (OH); δ_H (400 MHz, CDCl$_3$): 1.29 [9H, s, (CH$_3$)$_3$], 6.34 (1H, s, OH), 6.44 (1H, s, H-3), 6.84 (1H, dd, J 8.9 and 2.6, H-6), 6.97 (1H, d, J 2.4, H-4) 7.33-7.41 (5H, m, Ar-H), 8.05 (1H, d, J 8.9, H-7); δ_C (100 MHz, CDCl$_3$): 27.5 (CH$_3$), 83.5 (C), 105.7 (CH), 109.7 (CH), 113.1 (CH), 116.0 (CH), 127.6 (CH), 127.8 (CH), 128.7 (CH), 130.2 (C), 132.3 (C), 134.8 (C), 138.1 (C), 141.4 (C), 150.3 (C); m/z, EI+ (%): 309 (M$^{+\bullet}$, 15), 253 (M$^{+\bullet}$-C$_4$H$_8$, 32), 209 (M$^{+\bullet}$-C$_5$H$_8$O$_2$, 100); Accurate mass: C$_{19}$H$_{19}$NO$_3$: requires 309.1364, found 309.1364.

## N-*tert*-Butyloxycarboxy-5-hydroxy-2-methyl indole 336dc'

HO⟍⟍⟍
336dc' Boc

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate **342e** (0.71 g, 1.50 mmol) and resin-bound ester **309c'** (Method B, 0.28 mmol), yielded N-*tert*-butyloxycarboxy-5-hydroxy-2-methyl indole **336dc'** in excellent purity as a pink oil (0.048 g, 0.196 mmol, 70%); v_{max} (Solt^n, CDCl$_3$)/cm^{-1}: 3691 (OH), 3601 (OH), 3154 (C=C), 1474 (CH), 1379 (OH); δ_H (400 MHz, CDCl$_3$): 1.67 [9H, s, (CH$_3$)$_3$], 2.56 (3H, s, CH$_3$), 5.94 (1H, s, OH), 6.73 (1H, s, H-3), 6.73 (1H, dd, J 8.9 and 2.5, H-4), 6.86 (1H, d, J 2.5, H-4), 7.93 (1H, d, J 8.9, H-7); δ_C (100 MHz, CDCl$_3$): 17.0 (CH$_3$), 28.3 (CH$_3$), 83.7 (C), 105.0 (CH), 107.7 (CH), 111.7 (CH), 116.2 (CH), 120.4 (C), 130.4 (C), 131.4 (C), 138.9 (C), 150.7 (C); m/z, EI+ (%): 247 (M$^{+\bullet}$, 12), 191 (M$^{+\bullet}$-C$_4$H$_8$, 28), 147 (M$^{+\bullet}$-C$_5$H$_8$O$_2$, 40), 83 (100); Accurate mass: C$_{14}$H$_{17}$NO$_3$: requires 247.1208, found 247.1212.

N-*tert*-Butyloxycarboxy-5-chloro-2-phenethyl indole 336fa'

Cl⟍⟍⟍—Ph
336fa' Boc
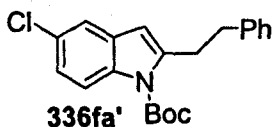
Titanocene dichloride (2.26 g, 9.00 mmol), magnesium turnings (0.30 g, 12.6 mmol) and 4Å molecular sieves (0.90 g) were heated briefly *in vacuo*, allowed to cool and then the reaction flask was purged with argon. THF (9.0 cm^3) and triethylphosphite (3.2 cm^3, 18.6 mmol) were then added and the reaction mixture stirred, cooling using an ice bath for 30 mins. After stirring for a further 2 h at rt, a THF (18.0 cm^3) solution of the thioacetal **342f** (1.56 g, 4.50 mmol) was added, and the solution stirred for 15 mins. The reaction mixture was then added *via* syringe, in three equal portions, into three separate flasks each containing 1 Kan of resin bound ester **309a'** (Method B, 3 x 0.28 mmol), pre-swollen in THF (3 x 3 cm^3). The mixture was stirred under argon for 15h. The Kans were then washed as in the standard Takeda procedures, and one Kan when treated under the standard resin-cleavage conditions A, yielded N-*tert*-butyloxycarboxy-5-chloro-2-phenethyl indole **336fa'** as a yellow oil (0.015 g, 0.04 mmol, 14%); δ_H (400 MHz, CDCl$_3$): 1.68 [9H, s, (CH$_3$)$_3$], 3.01 (2H, t, J 8.3, CH$_2$), 3.33 (2H, t, J 8.3, CH$_2$), 6.28 (1H, s, H-3), 7.16-7.21 (6H, m, Ar-H), 7.39 (1H, d, J 2.0, H-4), 7.99 (1H, d, J 8.8, H-7).

2-Phenyl-1H-indole[250] 332ab'
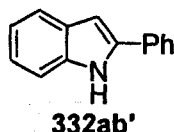
332ab'

Following the general Boc deprotection procedure, using *N*-Boc indole **336ab'** (0.048 g, 0.164 mmol), yielded 2-phenyl-1H-indole[249] **332ab'** as a grey solid (0.031 g, 0.16 mmol, 97%); Mpt: 178-181 °C (Lit.[249] Mpt: 189-200 °C); ν_{max} (Solt^n, CDCl$_3$)/cm^{-1}: 3441 (NH), 2925 (CH), 1635 (HC=C); δ_H (400 MHz, CDCl$_3$): 6.82 (1H, s, H-3), 7.12 (1H, t, *J* 7.8, H-6), 7.19 (1H, td, *J* 7.6 and 1.0, H-5), 7.32 (1H, t, *J* 7.4, Ar-H), 7.35-7.45 (3H, m, Ar-H), 7.64-7.66 (3H, m, Ar-H), 8.31 (1H, bs, NH); δ_C (100 MHz, CDCl$_3$): 99.8 (CH), 110.7 (CH), 120.1 (CH), 120.5 (CH), 122.2 (CH), 125.0 (CH), 127.5 (CH), 128.8 (C), 132.2 (C), 136.4 (C), 137.5 (C); m/z, EI+ (%): 193 (M$^{+\bullet}$, 100), 165 (15), 84 (28); Accurate mass: C$_{14}$H$_{11}$N: requires 193.0891, found 193.0894.

7-Methoxy-2-phenethyl-1H-indole 332ba'
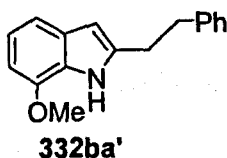
332ba'

Following the general Boc deprotection procedure, using *N*-Boc indole **336ba'** (0.033 g, 0.09 mmol), yielded 7-methoxy-2-phenethyl-1H-indole **332ba'** as a purple solid (0.024 g, 0.09 mmol, 100%); Mpt: 85-88 °C; ν_{max} (Solt^n, CDCl$_3$)/cm^{-1}: 3151 (NH), 3095 (HC=C), 2932 (COCH$_3$), 1791 (HC=C); δ_H (400 MHz, CDCl$_3$): 2.96-3.09 (4H, m, C*H*$_2$C*H*$_2$Ph), 3.93 (3H, s OCH$_3$), 6.24 (1H, d, *J* 2.2, H-3), 6.56 (1H, dd, *J* 2.3 and 7.6, H-6), 6.96 (1H, dt, *J* 7.8 and 3.1, H-4), 7.13 (1H, d, *J* 7.9, H-5), 7.13-7.25 (3H, m, Ar-H), 7.28-7.31 (2H, m, Ar-H), 8.04 (1H, bs, NH); δ_C (100 MHz, CDCl$_3$): 30.2 (CH$_2$), 35.6 (CH$_2$), 55.3 (CH$_3$), 100.1 (CH), 101.3 (CH), 112.8 (CH), 119.9 (CH), 126.1 (CH), 128.4 (CH), 128.5 (CH), 129.0 (C), 130.0 (C), 138.5 (C), 141.2 (C), 145.6 (C); m/z, EI+ (%): 251 (M$^{+\bullet}$, 42), 160 (M$^{+\bullet}$-C$_7$H$_8$, 100), Accurate mass: C$_{17}$H$_{17}$NO: requires 251.1310, found 251.1308.

7-Methoxy-2-phenyl-1H-indole 332bb'

332bb'
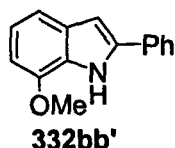
Following the solid-phase Takeda Method A, resin-cleavage procedure A and general Boc deprotection procedure, employing silylated carbamate **342b** (0.62 g, 1.50 mmol) and resin-bound ester **309b'** (Method B, 0.28 mmol), yielded 7-methoxy-2-phenyl-1H indole **332bb'** as a pale green solid (0.043 g, 0.19 mmol, 69% from **309b'**); Mpt: 82-85 °C; ν_{max} (KBr)/cm^{-1}: 3440 (NH), 2925 (COCH$_3$), 1681 (HC=C); δ_H (400 MHz, CDCl$_3$): 3.97 (3H, s OCH$_3$), 6.63 (1H, d, J 7.7, H-6), 6.79 (1H, d, J 1.9, H-3), 7.01-7.05 (1H, m, Ar-H), 7.22-7.33 (2H, m, Ar-H), 7.39-7.44 (2H, m, Ar-H), 7.64-7.56 (2H, m, Ar-H), 8.57 (1H, bs, NH); δ_C (100 MHz, CDCl$_3$): 55.3 (CH$_3$), 100.2 (CH), 102.2 (CH), 113.3 (CH), 120.5 (CH), 125.1 (CH), 127.2 (C), 127.5 (CH), 128.9 (CH), 130.4 (C), 132.3 (C), 137.5 (C), 145.9 (C); m/z, EI+ (%): 223 (M$^{+\bullet}$, 77), 180 (42), 83 (100); Accurate mass: C$_{15}$H$_{13}$NO: requires 223.0997, found 223.0998.

5,6-Methylenedioxy-2-phenyl-1H-indole 332cb'

332cb'
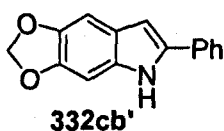
Tetrabutylammonium fluoride [(TBAF), 1 mol dm^{-3} in THF, 0.7 cm^3, 70 mmol] was added drop-wise, to a solution of *N*-Boc indole **336cb'** (0.033 g, 0.10 mmol), in THF (2 cm^3) under argon in THF. The reaction mixture was then heated under reflux for 30 h. After this time the reaction mixture was poured into water (10 cm^3) and extracted into ethyl acetate (2 x 5 cm^3). The combined organic phases were then washed with water (2 x 10 cm^3), dried over sodium sulphate, and concentrated to yield a 10: 1 mixture of indole **332cb'**: indole **336cb'** (starting material) and some tetrabutylammonium salts (0.020 g). Tritteration of the mixture from chloroform, yielded 5,6-methylenedioxy-2-phenyl-1H-indole **332cb'** as a white solid (0.011 g, 0.050 mmol, 50%); δ_H (400 MHz, CDCl$_3$): 5.95 (2H, s, OCH$_2$O), 6.70 (1H, s, H-3), 6.87 (1H, s, H-4), 7.00 (1H, s, H-7), 7.29 (1H, d, J 7.4, H-4'), 7.42 (2H, t, J 7.5, H-3' and H-5'), 7.59 (2H, d, J 7.3, H-2' and H-6'), 8.21 (1H, s, NH); m/z, EI+ (%): 237 (M$^{+\bullet}$, 100). However in an attempt to obtain a ^{13}C NMR spectrum, substantial decomposition occurred, and so no further characterisation of indole **332cb'** was possible.

5-Hydroxy-2-phenethyl-1H-indole[251] 332da'
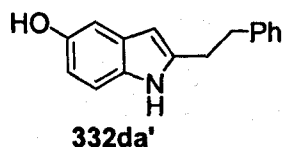
332da'

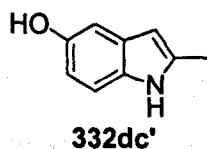Following the general Boc deprotection procedure, using *N*-Boc indole **336da'** (0.048 g, 0.142 mmol), followed by column chromatography (SiO$_2$, DCM: MeOH, 19: 1), yielded the desired 5-hydroxy-2-phenethyl-1H-indole[251] **332da'** as a grey solid (0.021 g, 0.09 mmol, 62%); R$_f$ (SiO$_2$, DCM: MeOH, 19: 1): 0.31; δ_H (400 MHz, CDCl$_3$): 3.00-3.08 (4H, m, C*H$_2$*C*H$_2$*Ph), 4.42 (1H, s, OH), 6.16 (1H, d, *J* 1.4, H-3), 6.67 (1H, dd, *J* 2.4 and 8.6, H-6), 6.94 (1H, d, *J* 2.4, H-4), 7.10 (1H, d, *J* 8.6, H-7), 7.20-7.32 (5H, m, Ar-H), 7.64 (1H, s, NH); m/z, EI+ (%): 237 (M$^{+\bullet}$, 38), 146 (M$^{+\bullet}$-C$_7$H$_7$, 100); Accurate mass: C$_{16}$H$_{15}$NO: requires 237.1154, found 237.1157.

2-Methyl-5-hydroxy-1H-indole 332dc'

332dc'

Following the general Boc deprotection procedure, but leaving for 64 h, using *N*-Boc indole **336dc'** (0.036 g, 0.145 mmol), followed by column chromatography (SiO$_2$, DCM), yielded 2-methyl-5-hydroxy-1H-indole **332dc'** as a grey solid (0.017 g, 0.12 mmol, 81%); R$_f$ (SiO$_2$, DCM): 0.10; δ_H (400 MHz, CDCl$_3$): 2.41 (3H, s, CH$_3$), 4.44 (1H, s, OH), 6.10 (1H, s, H-3), 6.67 (1H, dd, *J* 2.4 and 8.6, H-6), 6.92 (1H, d, *J* 2.4, H-4), 7.12 (1H, d, *J* 8.6, H-7), 7.72 (1H, s, NH); m/z, EI+ (%): 147 (M$^{+\bullet}$, 88), 146 (M$^{+\bullet}$-H, 92), 84 (100); Accurate mass: C$_9$H$_9$NO: requires 147.0684, found 147.0682.

N-Deutero-3-deutero-5-deuteroxy-2-methyl indole 345dc'
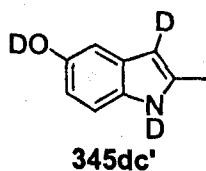
345dc'

Dissolving indole **332dc'** in d-4 MeOH in an NMR tube, gave *N*-deutero-3-deutero-5-deuteroxy-2-methyl indole **345dc'**; Mpt: 120-123 °C; δ_H (400 MHz, d-4 MeOH): 2.25 (3H, s, CH$_3$), 6.45 (1H, dd, *J* 2.4 and 8.6, H-6), 6.69 (1H, d, *J* 2.2, H-4), 6.95 (1H, d, *J* 8.6, H-7); δ_C (100 MHz, d-4 MeOH): 13.9 (CH$_3$), 105.0 (CH), 111.1 (CH), 111.9 (CH), 131.6 (C), 133.3 (C), 137.7 (C), 151.5 (C).

## 2-[2'-(N-tert-Butyloxycarboxy-N-methylamino)phenyl]-1,3-dithiane 346a - A

346a Boc

Lithium di-isopropylamine [generated by adding *n*-butyl lithium (2.70 cm^3, 6.60 mmol, 2.5 mol dm^{-3} in hexanes), to a solution of di-isopropylamine (1.20 cm^3, 7.20 mmol) in THF (8.0 cm^3) at -78 °C and stirring at this temperature for 1 h], was added drop-wise to a solution of carbamate **335a** (1.86 g, 6.00 mmol) and the reaction was allowed to warm to rt over 1 h. After this time, a white precipitate resulted from which the solvent was removed in *vacuo*, and DCM (30 cm^3) was added. The reaction mixture was allowed to stir for a further 1 h before methyl iodide (1.80 cm^3, 30.0 mmol) was added and stirred for 22 h at rt. The reaction mixture was worked up by pouring into water and extracting with DCM (20 cm^3). The DCM extracts were then dried over sodium sulfate and concentrated to yield a yellow oil (1.26 g, 65%). ^{1}H NMR analysis confirmed that a 12: 5 mixture of starting material **335a**: product **346a** remained. Column chromatography (SiO$_2$, DCM) gave pure starting material **335a** (0.58 g, 1.87 mmol, 31%) and 2-[2'-(N-tert-butyloxycarboxy-N-methylamino)phenyl]-1,3-dithiane **346a** (0.54 g, 1.66 mmol, 28%); R$_f$ (SiO$_2$, DCM): 0.13; Mpt: 103-105 °C; ν_{max} (KBr)/cm^{-1}: 2822 (NMe), 1688 (CO), 1363 (NCO); δ_H (400 MHz, CDCl$_3$): 1.35 [9H, s, (CH$_3$)$_3$], 1.88-1.99 (1H, m, CH$_{ax}$), 2.13-2.20 (1H, m, CH$_{eq}$), 2.85-3.11 (4H, m, CH$_2$-S), 3.22 (3H, s, NCH$_3$), 5.24 (1H, s, CH), 7.10 (1H, d, *J* 6.4, H-3'), 7.26-7.32 (2H, m, H-4' and H-6') 7.67 (1H, dt, *J* 6.6 and 1.9, H-5'); δ_C (100 MHz, CDCl$_3$): 25.1 (CH$_2$), 28.0 (CH$_3$), 32.1 (CH$_2$), 32.5 (CH$_2$), 37.5 (CH$_3$), 45.9 (CH), 80.2 (C), 127.7 (CH), 128.0 (CH), 129.0 (CH), 129.2 (CH), 136.6 (C), 140.8 (C), 155.1 (C); m/z, EI+ (%): 325 (M$^{+\bullet}$, 9), 269 (M$^{+\bullet}$-C$_4$H$_8$, 64), 224 (M$^{+\bullet}$-C$_5$H$_{11}$O$_2$, 62), 162 (100); Accurate mass: C$_{16}$H$_{23}$NO$_2$S$_2$: requires 325.1170, found 325.1172; Microanalysis Found: C 59.05%, H 7.12%, N 4.35%; Theoretical C$_{16}$H$_{23}$NO$_2$S$_2$: C 59.04%, H 7.12%, N 4.30%.

2-[2'-(N-tert-Butyloxycarboxy-N-methylamino)phenyl]-1,3-dithiane 346a – B

346a Boc

Following the general procedure for carbamate alkylation, using methyl iodide (1.10 cm^3, 16.5 mmol) in DMF (60 cm^3), and allowing to stir for 2 h, gave pure amine **346a** as a pale yellow solid (3.85 g, 11.8 mmol, 91%); δ_H (400 MHz, CDCl$_3$): as above.

2-[2'-(*N*-Benyl-*N*-*tert*-butyloxycarboxyamino)phenyl]-1,3-dithiane 346b

346b Boc
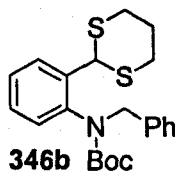
Following the general procedure for carbamate alkylation, using benzyl bromide (2.50 cm³, 16.5 mmol) in DMF (60 cm³), and allowing to stir for 2 h, gave a yellow solid (6.09 g). Recrystallisation, from propan-2-ol, yielded 2-[2'-(*N*-benyl-*N*-*tert*-butyloxycarboxyamino)phenyl]-1,3-dithiane **346b** as white needles (3.82 g, 9.51 mmol, 76%); R_f (SiO₂, DCM): 0.35; Mpt: 128-130 °C; ν_{max} (KBr)/cm⁻¹: 2931 (NCH₂), 1691 (CO), 1388 (NCO); δ_H (400 MHz, CDCl₃): 1.37 [9H, s, (CH₃)₃], 1.86-1.98 (1H, m, CH$_{ax}$), 2.12-2.18 (1H, m, CH$_{eq}$), 2.82-3.03 (4H, m, CH₂-S), 4.33 (1H, d, *J* 18.5, NCH$_A$H$_B$), 5.20-5.24 (2H, m, NCH$_A$H$_B$ and S₂CH), 6.68 (1H, s, H-3'), 7.09 (1H, t *J* 7.4, Ar-H), 7.22-7.28 (6H, m, Ar-H), 7.64 (1H, dd, *J* 7.8 and 1.2, H-6'); δ_C (100 MHz, CDCl₃): 25.2 (CH₂), 28.1 (CH₃), 32.2 (CH₂), 32.5 (CH₂), 46.3 (CH), 53.5 (CH₂), 80.5 (C), 127.3 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.9 (CH), 129.3 (CH), 129.4 (CH), 136.7 (C), 138.2 (C), 139.2 (C), 155.3 (C); m/z, EI+ (%): 401 (M⁺˙, 4), 345 (M⁺˙-C₄H₈, 37), 300 (M⁺˙-C₅H₉O₂, 58), 254 (100); Accurate mass: C₂₂H₂₇NO₂S₂: requires 401.1483, found 401.1486; Microanalysis: Found: C 65.51%, H 6.84%, N 3.54%; Theoretical C₂₂H₂₇NO₂S₂: C 65.87%, H 6.78%, N 3.49%.

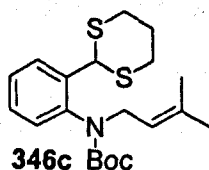## 2-[2'-(*N*-*tert*-Butyloxycarboxy-*N*-prenylamino)phenyl]-1,3-dithiane 346c

346c Boc

Following the general procedure for carbamate alkylation, using prenyl bromide (1.90 cm³, 16.5 mmol) in DMF (60 cm³), and allowing to stir for 2.5 h, the pure desired product **346c** was obtained as a yellow solid (5.23 g). Recrystallisation from hexane, yielded 2-[2'-(*N*-*tert*-butyloxycarboxy-*N*-prenylamino)phenyl]-1,3-dithiane **346c** as plates (3.03 g, 8.00 mmol, 61%); Mpt: 96.5-98.5 °C; ν_{max} (KBr)/cm⁻¹: 2929 (NCH₂), 1687 (CO), 1391 (NCO), 870 (CH); δ_H (400 MHz, CDCl₃): 1.35 [9H, s, (CH₃)₃], 1.42 (3H, s, CCH₃), 1.67 (3H, s, CCH₃), 1.88-1.99 (1H, m, CH$_{ax}$), 2.14-2.18 (1H, m, CH$_{eq}$), 2.85-2.91 (2H, m, CH₂-S), 2.95-3.08 (2H, m, CH₂-S), 4.03 (1H, dd, *J* 14.8 and 7.8, NCH$_A$H$_B$), 4.46 (1H, dd, *J* 14.5 and 5.9, NCH$_A$H$_B$), 5.25 (1H, s, S₂CH), 5.34 (1H, t, *J* 7.5, NCH₂C*H*), 7.03 (1H, d *J* 6.9, H-3'), 7.21-7.30 (1H, m, Ar-H), 7.65 (1H, dd, *J* 7.6 and 1.2, H-6'); δ_C (100 MHz, CDCl₃):

17.7 (CH$_2$), 25.2 (CH$_3$), 25.7 (CH$_2$), 28.1 (CH$_2$), 32.2 (CH$_3$), 32.5 (CH$_3$), 46.4 (CH$_2$), 47.5 (CH), 80.1 (C), 119.9 (CH), 127.9 (CH), 128.5 (CH), 129.1 (CH), 136.0 (C), 137.0 (C), 139.4 (C), 154.9 (C); m/z, EI+ (%): 379 (M$^{+\bullet}$, 10), 323 (M$^{+\bullet}$-C$_4$H$_8$, 31), 278 (M$^{+\bullet}$-C$_5$H$_9$O$_2$, 50), 254 (100); Accurate mass: C$_{23}$H$_{25}$NO$_2$S$_2$: requires 379.1640, found 379.1638; Microanalysis: Found: C 63.25%, H 3.59%, N 7.61%, S 16.86; Theoretical C$_{23}$H$_{25}$NO$_2$S$_2$: C 63.28%, H 3.69%, N 7.65%, S 16.90.
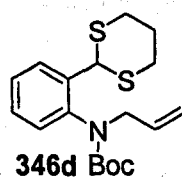
2-[2'-(N-Allyl-N-tert-butyloxycarboxyamino)phenyl]-1,3-dithiane 346d
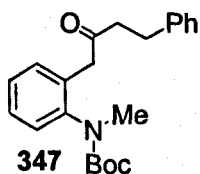

346d Boc

Following the general procedure for carbamate alkylation, using allyl bromide (1.40 cm^3, 16.5 mmol) in DMF (60 cm^3), and allowing to stir for 2.5 h, gave the pure desired amine **346d** was obtained as a yellow solid (4.50 g, 12.8 mmol, 98%). Recrystallisation of a 0.50 g portion, from propan-2-ol, gave 2-[2'-(N-allyl-N-tert-butyloxycarboxyamino)phenyl]-1,3-dithiane **346d** as white prisms (0.32 g, 0.91 mmol, 63%); R$_f$ (SiO$_2$, DCM): 0.35; Mpt: 87-90 °C; ν$_{max}$ (KBr)/cm^{-1}: 2929 (NCH$_2$), 1697 (CO), 1385 (NCO); δ$_H$ (400 MHz, CDCl$_3$): 1.36 [9H, s, (CH$_3$)$_3$], 1.88-1.99 (1H, m, CH$_{ax}$), 2.13-2.20 (1H, m, CH$_{eq}$), 2.85-2.93 (2H, m, CH$_2$-S), 2.97-3.08 (2H, m, CH$_2$-S), 3.91 (1H, dd, J 15.0 and 7.2, NCH$_A$H$_B$), 4.46 (1H, d, J 11.0, NCH$_A$H$_B$), 5.10-5.15 (2H, m, CH=CH$_2$), 5.22 (1H, s, S$_2$CH), 5.92-6.02 (1H, m, CH=CH$_2$), 7.06 (1H, d J 6.8, H-3'), 7.25 (1H, dt, J 1.5 and 7.4, Ar-H), 7.30 (1H, dt, J 1.3 and 7.4, Ar-H), 7.68 (1H, dd, J 7.6 and 1.6, H-6'); δ$_C$ (100 MHz, CDCl$_3$): 25.2 (CH$_2$), 28.1 (CH$_3$), 32.2 (CH$_2$), 32.4 (CH$_2$), 46.2 (CH), 52.8 (CH$_2$), 80.4 (C), 117.9 (CH$_2$), 128.1 (CH), 128.6 (CH), 129.0 (CH), 129.3 (CH), 133.7 (CH), 136.8 (C), 139.4 (C), 154.8 (C); m/z, EI+ (%): 351 (M$^{+\bullet}$, 10), 295 (M$^{+\bullet}$-C$_4$H$_8$, 64), 250 (M$^{+\bullet}$-C$_5$H$_9$O$_2$, 50), 188 (100); Accurate mass: C$_{18}$H$_{25}$NO$_2$S$_2$: requires 351.1327, found 351.1328; Microanalysis: Found: C 61.40%, H 7.12%, N 3.95%; Theoretical C$_{18}$H$_{25}$NO$_2$S$_2$: C 61.50%, H 7.17%, N 3.98%.

1-(2'-N-tert-Butyloxycarboxy-N-methylamino-5-phenyl)-4-phenylbutan-2-one 347

347

The general solid-phase Takeda Method A using amine **346a** (0.47 g, 1.45 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), followed by the general resin-cleavage procedure A, yielded 1-(2'-N-tert-butyloxycarboxy-N-methylamino-5-phenyl)-4-phenylbutan-2-one **347** as a black oil [a mixture of diasteriomers of geometrical isomers, see chapter 9.3, (0.055 g, 0.16 mmol, 54%); v_{max} (Solt^n, CDCl$_3$)/cm^{-1}: 2980 (NMe), 1792 (CO), 1690 (NCO$_2$); δ_H (360 MHz, 253 K, CDCl$_3$): 1.29 and 1.50 [9H, s, 2 x C(CH$_3$)$_3$], 2.79 (2H, t, J 7.1, CH$_2$), 2.87-2.92 (2H, m, CH$_2$), 3.04 and 3.06 (3H, 2 x s, NCH$_3$), 3.54-3.78 (2H, complex AB system, C$H^A H^B$CO), 7.11-7.33 (9H, m, Ar-H); δ_H (360 MHz, 273 K, CDCl$_3$): 1.30 and 1.50 [9H, s, 2 x C(CH$_3$)$_3$], 3.06 (3H, s, NCH$_3$), 3.57-3.72 (2H, AB system, C$H^A H^B$CO), 7.12-7.28 (9H, m, Ar-H); δ_H (360 MHz, 333 K, CDCl$_3$): 1.37 [9H, s, C(CH$_3$)$_3$], 2.73-2.77 (2H, m, CH$_2$), 2.89 (2H, t, J 7.2, CH$_2$), 3.09 (3H, s, NCH$_3$), 3.61 (1H, s, CH^AH^B), 3.60 (1H, s, CH$^A H^B$CO), 7.10-7.27 (9H, m, Ar-H); m/z, EI+ (%): 353 (M$^{+\bullet}$, 3), 297 (M$^{+\bullet}$-C$_4$H$_8$, 18), 253 (M$^{+\bullet}$-C$_5$H$_8$NO$_2$, 50), 120.1 (100); Accurate mass: C$_{22}$H$_{27}$NO$_3$: requires 353.1991, found 353.1987.

N-Methyl-2-phenethyl indole 348aa'
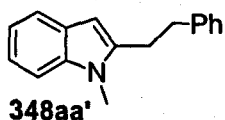
348aa'

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine **346a** (0.42 g, 1.50 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), yielded N-methyl-2-phenethyl indole **348aa'** in excellent purity as a yellow oil (0.028 g, 0.126 mmol, 44% from ester **309a'**); R$_f$ (SiO$_2$, DCM): 0.64; v_{max} (Solt^n, CDCl$_3$)/cm^{-1}: 3055 (HC=C), 3025 (CH), 2925 (NCH$_3$), 1468 (CH), 1454 (CH); δ_H (400 MHz, CDCl$_3$): 3.05 (4H, s, CH_2 CH_2Ph), 3.61 (3H, s, NCH$_3$), 6.31 (1H, s, H-3), 7.05-7.09 (1H, m, Ar-H), 7.16 (1H, dt, J 1.1 and 7.1, Ar-H), 7.21-7.32 (6H, m, Ar-H), 7.53 (1H, d, J 7.8, H-7); δ_C (100 MHz, CDCl$_3$): 28.9 (CH$_2$), 29.3 (CH$_3$), 35.1 (CH$_2$), 98.8 (CH), 108.7 (CH), 119.3 (CH), 119.7 (CH), 120.7 (CH), 126.2 (CH), 128.4 (CH), 128.5 (CH), 137.4 (C), 138.1 (C), 140.5 (C), 141.3 (C); m/z, EI+ (%):

235 (M$^{+\bullet}$, 30), 144 [(M$^{+\bullet}$-C$_7$H$_7$), 100]; Accurate mass: C$_{17}$H$_{17}$N: requires 235.1361, found 235.1359.

N-Methyl-2-phenethyl indole 348aa'

348aa'

Following the general solid-phase Takeda Method B, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine **346a** (0.29 g, 0.90 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), yielded *N*-methyl-2-phenethyl indole **348aa'** (0.314 g, 0.133 mmol, 45% from ester **309a'**); δ_H (400 MHz, CDCl$_3$): as above.

N-Methyl-2-phenyl indole[252] 348aa'
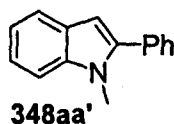
348aa'

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine **346a** (0.42 g, 1.50 mmol) and resin-bound ester **309b'** (Method A, 0.30 mmol), yielded *N*-methyl-2-phenyl indole[252] **348aa'** as a white solid (0.012 g, 0.057 mmol, 32% from ester **309b'**); Mpt: 98-101 °C; (Lit.[252] Mpt 99-101 °C); δ_H (400 MHz, CDCl$_3$): 3.75 (3H, s, NCH$_3$), 6.56 (1H, s, H-3), 7.14-7.16 (1H, m, Ar-H), 7.24-7.27 (1H, m, Ar-H), 7.35-7.53 (6H, m, Ar-H), 7.63 (1H, dd, *J* 7.8 and 0.8, H-7).

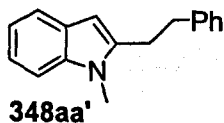### *N*-Benzyl-2-phenethyl indole 348ba'

348ba'

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine **346b** (0.60 g, 1.50 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), yielded *N*-benzyl-2-phenethyl indole **348ba'** in excellent purity as a grey solid (0.051 g, 0.165 mmol, 55% from ester **309a'**); R$_f$ (SiO$_2$, DCM): 0.58; Mpt: 66-69 °C; ν_{max} (KBr)/cm^{-1}: 3027 (HC=C), 2925 (NCH$_2$), 1463 (CH), 1452 (CH); δ_H (400 MHz, CDCl$_3$): 2.93-3.02 (4H, m, CH$_2$CH$_2$Ph], 5.25 (2H, s, NCH$_2$Ph), 6.40 (1H, s, H-3), 6.88-6.93 (2H, m, Ar-H), 6.98-7.38 (11H, m, Ar-H), 7.56-7.60 (1H, m, Ar-H); δ_C (100 MHz, CDCl$_3$): 28.6 (CH$_2$), 35.1 (CH$_2$), 46.3 (CH$_2$), 99.7

(CH), 109.3 (CH), 119.6 (CH), 119.9 (CH), 121.0 (CH), 125.9 (CH), 126.1 (CH), 127.2 (CH), 128.1 (C), 128.3 (CH), 128.4 (CH), 128.7 (CH), 137.1 (C), 137.8 (C), 140.5 (C), 141.2 (C); m/z, EI+ (%): 311 (M$^{+\bullet}$, 40), 220 (M$^{+\bullet}$-C$_7$H$_7$, 100); Accurate mass: C$_{23}$H$_{21}$N: requires 311.1674, found 311.1675.

N-Benzyl-2-(2 -methyl-propenyl) indole 348bd'

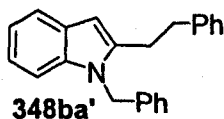

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine **346b** (0.60 g, 1.50 mmol) and resin-bound ester **309d'** (Method A, 0.30 mmol), yielded *N*-benzyl-2-(2 -methyl-propenyl) indole **348bd'** in excellent purity as a light brown solid (0.038 g, 0.147 mmol, 49% from ester **309d'**); Mpt: 80-83 °C; ν_{max} (KBr)/cm^{-1}: 3043 (HC=C), 2966 (NCH$_2$), 2929 (CH$_2$), 1450 (CH$_3$), 842 (CH), 792 (CH); δ_H (400 MHz, CDCl$_3$): 1.89 (3H, s, CH$_3$), 1.99 (3H, s, CH$_3$), 5.28 (2H, s, NC*H*$_2$Ph), 6.04 [1H, s, C*H*C(CH$_3$)$_2$], 6.40 (1H, s, H-3), 6.92 (2H, d, *J* 7.1, Ar-H), 6.98-7.20 (6H, m, Ar-H), 7.52-7.54 (1H, m, H-7); δ_C (100 MHz, CDCl$_3$): 17.3 (CH$_3$), 23.9 (CH$_3$), 43.6 (CH$_2$), 98.8 (CH), 106.8 (CH), 111.3 (CH), 116.6 (CH), 117.1 (CH), 118.3 (CH), 123.0 (CH), 124.1 (CH), 125.2 (C), 125.6 (CH), 133.5 (C), 134.5 (C), 135.1 (C), 137.2 (C); m/z, EI+ (%): 261 (M$^{+\bullet}$, 100), 246 (M$^{+\bullet}$-CH$_3$, 66), 170 (37); Accurate mass: C$_{19}$H$_{19}$N: requires 261.1517, found 261.1517.

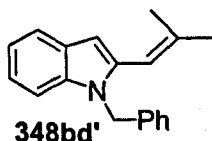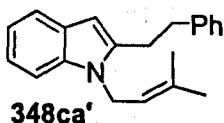## 2-Phenethyl-*N*-prenyl indole 348ca'

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine **346c** (0.57 g, 1.50 mmol) and resin-bound **309a'** (Method A, 0.30 mmol), yielded 2-phenethyl-*N*-prenyl indole **348ca'** in excellent purity as a yellow/brown oil (0.060 g, 0.210 mmol, 70% from ester **309a'**); Mpt: 64-67 °C; ν_{max} (KBr)/cm^{-1}: 3054 (HC=C), 3023 (HC=C), 2927 (NCH$_2$), 1461 (CH$_3$), 781 (C=CH), 744 (C=CH); δ_H (400 MHz, CDCl$_3$): 1.68 (3H, d, *J* 1.0, CH$_3$), 1.80 (3H, s, CH$_3$), 2.99-3.08 (4H, m, C*H*$_2$C*H*$_2$Ph), 4.63-4.69 (2H, m, C*H*$_2$CH), 5.11-5.15 (1H, m, NCH$_2$C*H*), 6.31 (1H, s, H-3), 7.06 (1H, dt, *J* 1.0 and 7.3, H-5), 7.13 (1H, dt, *J* 1.1 and 7.0, H-6), 7.17-7.32 (6H, m, Ar-H), 7.49 (1H, d, *J* 7.6, H-7); δ_C (100 MHz, CDCl$_3$): 18.1 (CH$_3$), 25.5

(CH$_3$), 28.8 (CH$_2$), 35.1 (CH$_2$), 41.3 (CH$_2$), 99.0 (CH), 119.2 (CH), 119.9 (CH), 120.6 (CH), 120.9 (CH), 126.1 (CH), 128.0 (C), 128.3 (CH), 128.5 (CH), 134.1 (C), 136.5 (C), 140.1 (C), 141.4 (C); m/z, EI+ (%): 289 (M$^{+•}$, 56), 198 (M$^{+•}$-C$_7$H$_7$, 100); Accurate mass: C$_{21}$H$_{23}$N: requires 289.1830, found 289.1831.
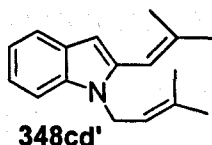
2-(2 -Methyl-propenyl)-*N*-prenyl-indole 348cd'

348cd'

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine **346c** (0.57 g, 1.50 mmol) and resin-bound ester **309d'** (Method A, 0.30 mmol), yielded 2-(2 -methyl-propenyl)-*N*-prenyl-indole **348cd'** in excellent purity as a yellow/brown oil (0.036 g, 0.150 mmol, 50% from ester **309d'**); ν_{max} (KBr)/cm^{-1}: 3053 (HC=C), 3029 (HC=C), 2925 (NCH$_2$), 1460 (CH$_3$), 777 (CH=C), 792 (CH=C); δ_H (400 MHz, CDCl$_3$): 1.69 (3H, d, *J* 0.8, CH$_3$), 1.81 (3H, s, CH$_3$), 1.95 (3H, d, *J* 0.5, CH$_3$), 1.97 (3H, s, CH$_3$), 4.67 (2H, d, *J* 6.4, NC*H*$_2$CH), 5.16-5.20 (1H, m, NCH$_2$C*H*), 6.18 (1H, d, *J* 0.7, C*H*=CMe$_2$), 6.38 (1H, s, H-3), 7.06 (1H, dt, *J* 0.9 and 7.8, H-5), 7.14 (1H, dt, *J* 1.0 and 7.1, H-6), 7.27 (1H, m, H-4), 7.56 (1H, d, *J* 7.7, H-7); δ_C (100 MHz, CDCl$_3$): 18.0 (CH$_3$), 20.2 (CH$_3$), 25.5 (CH$_3$), 26.9 (CH$_3$), 41.5 (CH$_2$), 101.3 (CH), 109.2 (CH), 114.7 (CH), 119.3 (CH), 120.9 (CH), 128.2 (C), 134.0 (C), 136.0 (C), 137.1 (C), 139.5 (C); m/z, EI+ (%): 239 (M$^{+•}$, 100), 171 (M$^{+•}$-C$_5$H$_8$, 80); Accurate mass: C$_{17}$H$_{21}$N: requires 239.1674, found 239.1676.

2-[2'-(*N*-Methyloxycarboxyamino)phenyl]-1,3-dithiane 350

350
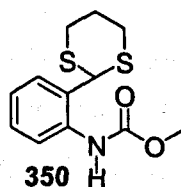
Methylchloroformate (0.80 cm^3, 12.0 mmol) was added dropwise to a solution of amine **331** (2.11 g, 10.0 mmol), saturated sodium bicarbonate (0.80 cm^3), in dioxane (60 cm^3) and the reaction mixture was allowed to stir for 16 h. After this time, the reaction mixture was poured into water (60 cm^3) and extracted into diethyl ether (2 x 60 cm^3). The combined organic phases were then washed with water (2 x 60 cm^3), brine (60 cm^3), dried over magnesium sulphate, and concentrated to yield a white solid (2.41 g, 90%, 8.96 mmol). Recrystallisation of a 0.50 g portion, from propan-2-ol, yielded 2-[2'-(*N*-

methyloxycarboxyamino)phenyl]-1,3-dithiane **350** as white needles (0.36 g, 72%); R_f (SiO$_2$, DCM): 0.30; Mpt: 95-97 °C; ν_{max} (KBr)/cm^{-1}: 3295 (NH), 2851 (OCH$_3$), 1731 (CO); δ_H (400 MHz, CDCl$_3$): 1.89-1.99 (1H, m, CH$_{ax}$), 2.17-2.22 (1H, m, CH$_{eq}$), 2.91-2.94 (2H, m, CH$_2$-S), 3.05-3.12 (2H, m, CH$_2$-S), 3.81 (3H, s, OCH$_3$), 5.31 (1H, s, S$_2$CH), 7.06 (1H, t, J 7.4, H-5'), 7.30 (1H, t, J 7.6, H-4'), 7.39 (1H, d, J 7.6, H-6'), 7.62 (1H, s, H-3'), 7.89 (1H, s, NH); δ_C (100 MHz, CDCl$_3$): 25.0 (CH$_2$), 31.9 (CH$_2$), 48.8 (CH), 52.5 (CH$_3$), 122.6 (C), 124.6 (CH), 128.6 (CH), 129.3 (CH), 136.0 (C), 154.3 (C); m/z, EI+ (%): 269 (M$^{+\bullet}$, 80), 163 (C$_{10}$H$_{11}$S, 30), 136 (100); Accurate mass: C$_{12}$H$_{15}$NO$_2$S$_2$: requires 269.0544, found 269.0544; Microanalysis Found: C 53.43%, H 5.60%, N 5.28%; Theoretical C$_{12}$H$_{15}$NO$_2$S$_2$: C 53.57%, H 5.62%, N 5.21%.

2-[2'-(*N*-Methyl-*N*-methyloxycarboxyamino)phenyl]-1,3-dithiane 349

349
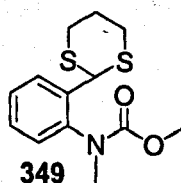
Lithium di-isopropylamine (3.75 cm^3, 7.50 mmol, 2.0 mol dm^{-3} in THF, ethyl benzene and heptanes), in THF (4.0 cm^3) was added drop-wise to a solution of carbamate **350** (1.88 g, 7.00 mmol) in THF (20 cm^3), under argon at -78 °C, and the reaction mixture was allowed to warm to rt and then stirred for 1 h. The reaction mixture was then cooled to -40 °C before methyl iodide (1.80 cm^3, 30.0 mmol) was added and the reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was then poured into water and extracted with ethyl acetate (2 x 30 cm^3). The combined organic phases were then washed with water (3 x 100 cm^3), dried over sodium sulfate and concentrated to yield a yellow solid (1.79 g) containing mostly the desired product **349** and a small amount of starting material **350**. Recrystallisation from propan-2-ol, yielded 2-[2'-(*N*-methyl-*N*-methyloxycarboxyamino)phenyl]-1,3-dithiane **349** as a white solid (1.15 g, 4.06 mmol, 58%); Mpt: 105-107 °C; ν_{max} (KBr)/cm^{-1}: 2925 (NCH$_3$), 1700 (CO); δ_H (400 MHz, CDCl$_3$): 1.87-1.98 (1H, m, CH$_{ax}$), 2.14-2.21 (1H, m, CH$_{eq}$), 2.85-2.92 (2H, m, CH$_2$-S), 3.02-3.10 (2H, m, CH$_2$-S), 3.28 (3H, s, NCH$_3$), 3.64 (3H, s, OCH$_3$), 5.24 (1H, s, S$_2$CH), 7.14 (1H, d, J 7.1, H-3'), 7.29-7.36 (2H, m, H-4' and H-5'), 7.71 (1H, dd, J 7.2 and 1.8, H-6'); δ_C (100 MHz, CDCl$_3$): 25.2 (CH$_2$), 32.1 (CH$_2$), 32.4 (CH$_2$), 38.4 (CH$_3$), 45.7 (CH), 53.1 (CH$_3$), 127.9 (CH), 128.5 (CH), 129.3 (CH), 129.7 (CH), 136.6 (C), 140.1 (C), 156.6 (C); m/z, EI+ (%): 283 (M$^{+\bullet}$, 37), 208 (20), 177 (100); Accurate mass: C$_{13}$H$_{17}$NO$_2$S$_2$: requires 283.0701, found 283.0703; Microanalysis Found: C 55.13%, H 5.98%, N 4.83, S 22.72%; Theoretical C$_{13}$H$_{17}$NO$_2$S$_2$: C 55.09%, H 6.05%, N 4.94, S 22.63%.

2-[2'-(N-Benzyloxycarboxy-N-methylamino)phenyl]-1,3-dithiane 351
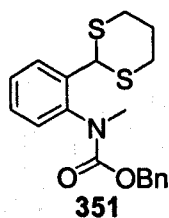

351

Following a known procedure,[235] benzylchloroformate (2.20 cm^3, 15.0 mmol) was added dropwise to a solution of amine **331** (3.17 g, 15.0 mmol) and sodium bicarbonate (2.52 g, 30.0 mmol), in acetone: water (4: 1, 125 cm^3) at 0 °C. The reaction mixture was allowed to warm to rt and then further stirred for 2 h. After this time the reaction mixture was concentrated *in vacuo*, water (100 cm^3) was added, and the mixture was extracted with ethyl acetate (2 x 50 cm^3). The combined organic phases were then washed with water (2 x 100 cm^3), dried over magnesium sulphate, and concentrated to yield crude carbamate **351** as a yellow oil (5.28 g). DMF (90 cm^3) and methyl iodide (1.90 cm^3, 30 mmol) were added and the mixture was cooled to 0 °C, under argon. Sodium hydride [60% in mineral oil, (0.75 g, 18.8 mmol)], was then added portion-wise over 10 mins and the reaction mixture was allowed to warm to rt and stirred for 3 h. After this time the reaction mixture was carefully poured into iced water and extracted into ethyl acetate (2 x 80 cm^3). The combined organic phases were then washed with water (2 x 200 cm^3), dried over sodium sulphate, and concentrated to yield a yellow/orange oil (1.15 g, 4.06 mmol, 58%). Column chromatography (SiO$_2$, DCM) yielded 2-[2'-(N-benzyloxycarboxy-N-methylamino)phenyl]-1,3-dithiane **351** as a yellow oil (0.98 g, 2.73 mmol, 18%); R$_f$ (SiO$_2$, DCM): 0.25; ν_{max} (KBr)/cm^{-1}: 2908 (NMe), 1699 (CO), 781 (CH); δ_H (400 MHz, CDCl$_3$): 1.82-1.94 (1H, m, CH$_{ax}$), 2.05-2.13 (1H, m, CH$_{eq}$), 2.79-3.02 (4H, m, CH$_2$-S), 3.28 (3H, s, NCH$_3$), 5.05 (1H, d, *J* 12.7, NCH$_A$CH$_B$), 5.10 (1H, d, *J* 12.6, NCH$_A$CH$_B$), 5.23 (1H, s, S$_2$CH), 7.11 (1H, d, *J* 7.2, H-3'), 7.23-7.34 (7H, m, Ar-H) 7.71 (1H, dd, *J* 7.6 and 1.7, H-6'); δ_C (100 MHz, CDCl$_3$): 24.9 (CH$_2$), 31.9 (CH$_2$), 32.2 (CH$_2$), 38.3 (CH$_3$), 45.7 (CH), 67.0 (CH$_2$), 127.4 (CH), 127.5 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 129.2 (CH), 129.4 (CH), 136.5 (C), 136.6 (C), 139.9 (C), 155.7 (C); m/z, EI+ (%): 359 (M$^{+\bullet}$, 18), 268 [(M$^{+\bullet}$-C$_7$H$_7$), 64], 91 (100); Accurate mass: C$_{19}$H$_{21}$NO$_2$S$_2$: requires 359.1014, found 359.1012; Microanalysis Found: C 63.46%, H 5.83%, N 4.02%, S 18.05%; Theoretical C$_{19}$H$_{21}$NO$_2$S$_2$: C 63.48%, H 5.84%, N 3.90%, S 17.84%.

Attempted solid-phase Diels-Alder reaction
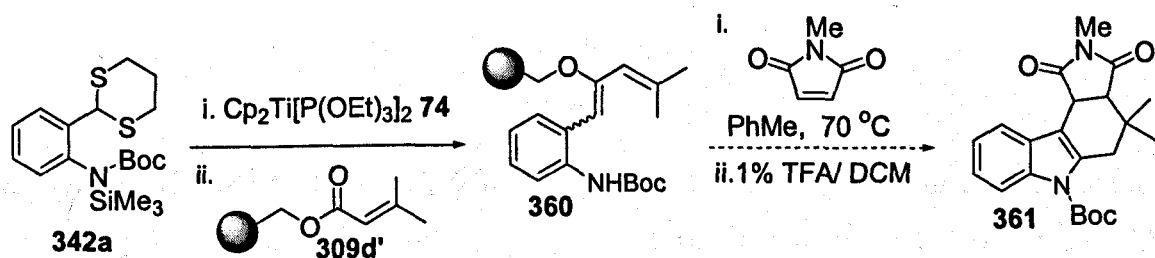
Following the general Takeda procedure B, using *N*-silyl carbamate **342a** (0.58 g, 1.50 mmol) and resin-bound ester **309d'** (0.311 mmol), the corresponding enol ether **360** was obtained as a bright red coloured resin. Following a literature procedure,[124] *N*-methylmaleimide (0.33 g, 3.00 mmol) was added to a flask containing enol ether **360** (1 Kan, 0.311 mmol) and toluene (40 cm^3), and the reaction mixture was allowed to stir at 70 °C for 40 h. After this time, the Kan was washed with toluene (x 5), alternatively with MeOH/ DCM, MeOH and finally with diethyl ether to leave an orange coloured resin. Subsequent subjection to the above standard resin cleavage conditions A, yielded *N*-Boc indole **336ad'** (^{1}H NMR as before) in very high purity and good yield (60%), with no sign of any other compound present the ^{1}H NMR spectrum.

Attempted formation of Ketone 363
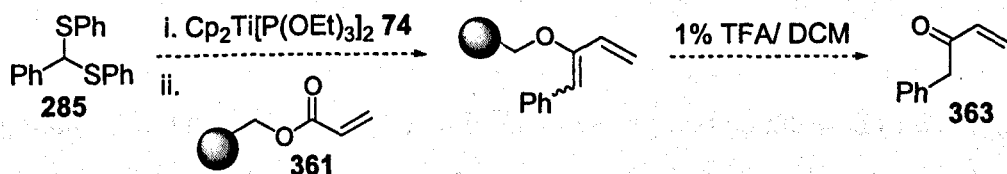
Following the general Takeda procedure B using thioacetal **285** (0.46 g, 1.50 mmol) and REM resin (0.300 mmol, 1.43 mmol g^{-1}), followed by the standard resin-cleavage procedure method A generated an orange solid (0.016 g). ^{1}H NMR spectroscopy confirmed a mixture of products was obtained, including what may have been the desired ketone **363**. Large singlets (corresponding to cyclopentadienyl ligands) were also observed, suggesting that titanium residues remained also.

Resin-bound ester 368

368
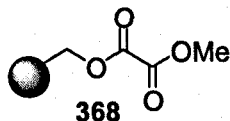
Methyl oxalyl chloride (0.6 cm³, 6.00 mmol) was added drop-wise to a reaction flask, containing 3 Kans of hydroxymethyl polystyrene (each containing 230 mg resin, 0.87 mmol g⁻¹, 0.20 mmol/kan, 0.6 mmol), triethylamine (0.85 cm³, 6.00 mmol) and dimethylamino pyridine (0.07 g, 0.60 mmol) in DCM (50 cm³), at -10 °C under argon, and allowed to stir at this temperature for 30 mins. The reaction mixture was then allowed to warm to rt and stirred for 15 h. The Kans were washed with DCM (x 2), and then alternately with MeOH and DCM (x 4), before finally washing with MeOH and dried under vacuum to yield resin-bound ester **368**; v_{max} (G Gate)/cm⁻¹: 1766 (CO), 1741 (CO).

Resin-bound ester 369
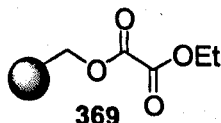
369

Oxalyl chloride (0.6 cm³, 6.00 mmol) was added drop-wise to a reaction flask, containing 3 Kans of hydroxymethyl polystyrene (each containing 230 mg resin, 0.87 mmol g⁻¹, 0.20 mmol/kan, 0.6 mmol), triethylamine (0.85 cm³, 6.00 mmol) and dimethylamino pyridine (0.07 g, 0.60 mmol) in DCM (50 cm³), at 0 °C under argon, and allowed to warm to rt and stirred for 2 h. The reaction mixture was then cooled to 0 °C, dry ethanol was added drop-wise, and the reaction mixture was allowed to warm to rt and stirred for 15 h. The Kans were then washed with DCM (x 2), and then alternately with MeOH and DCM (x 5), before finally washing with MeOH and dried under vacuum to yield resin-bound ester **369**; v_{max} (G Gate)/cm⁻¹: 1758 (CO), 1743 (CO).

Attempted formation of bis-indole 370

342a 6 eq.

i. $Cp_2Ti[P(OEt)_3]_2$ **74**
24 eq.
-----------→
ii. 1 eq.

368 R = Me or **369** R = Et

iii. 5% TFA/DCM

370
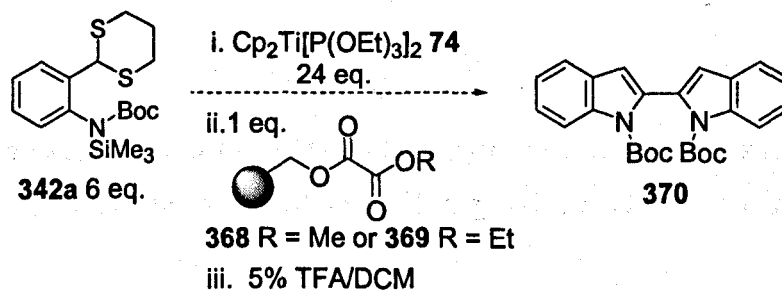
Titanocene dichloride (1.20 g, 4.80 mmol, 24.0 eq.), magnesium turnings (0.13 g, 5.30 mmol) and 4Å molecular sieves (0.30 g) were heated briefly *in vacuo* and then allowed to cool. The reaction flask was purged with argon before adding THF (10 cm³) and triethylphosphite (1.60 cm³, 9.60 mmol). The reaction mixture was cooled using an ice bath and stirred for 30 mins. After stirring for a further 3 h at rt, a THF (8 cm³) solution of thioacetal **342a** (0.46 g, 1.20 mmol, 6.0 eq.) was added, and the mixture was stirred for 15 mins. After this time the reaction mixture was added *via* syringe, into a flask containing 1 Kan of resin-bound ester **368** or **369** (0.20 mmol, 1.0 eq.), pre-swollen in THF (8 cm³). The mixture was stirred under argon for 15-18 h, before washing the Kan with THF (x 5), alternately with MeOH and DCM (x 5), then MeOH and dried under vacuum. The Kan was then treated with 5% TFA in DCM (5 cm³, 3.25 mmol) and placed on a shaker for 30 mins. The Kan was washed with DCM (3 x 5 cm³) and the organic washings were combined and then concentrated to yield a red oil (<10 mg). ¹H NMR spectroscopy confirmed that only titanium residues (large singlets corresponding to cyclopentadienyl ligands were observed), triethylphosphite and THF remained.

General method for the synthesis of resin-bound β–amino esters

The dialkyl amine (18 mmol, 10 eq), was added to a flask containing six Kans of REM resin (each containing approximately, 0.30 mmol/kan, 1.80 mmol) in DMF (100 cm³) at rt and stirred for 15 h. The Kans were then washed with DMF (x 2), and then alternately with MeOH and DCM (x 4), before finally washing with MeOH and diethyl ether to give the desired resin-bound β-amino esters.

Resin-bound β–amino ester 378

378
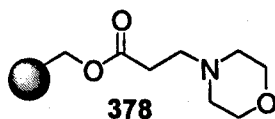
Following the general method for β-amino ester synthesis, employing six Kans with GSK in-house REM resin **377** (each containing 176 mg resin, 1.64 mmol g^{-1}, 0.29 mmol/kan, 1.74 mmol) and morpholine (1.60 cm^3, 18 mmol, 10 eq) yielded β-amino ester **378**; v_{max} (G Gate)/cm^{-1}: 1735 s (CO).

4-Morpholin-4-yl-1-phenyl-butan-2-one[253] 379

379

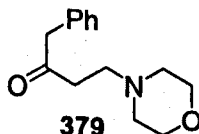The general solid-phase Takeda procedure C and general resin-cleavage conditions-A, employing thioacetal **285** (0.19 g, 0.60 mmol) and resin-bound ester **378** (0.30 mmol), yielded 4-morpholin-4-yl-1-phenyl-butan-2-one[253] **379** as a yellow oil (0.070 g, 0.30 mmol, 104%); v_{max} (Thin film)/cm^{-1}: 1720 (CO); δ_H (400 MHz: CDCl$_3$): 2.83 (2H, t, J 9.7, NCH_ACH$_B$), 3.05 (2H, t, J 6.3, COCH_ACH_B), 3.28 (2H, t, J 6.3, COCH_ACH$_B$), 3.39 (2H, d, J 11.7, NCH$_A$CH_B), 3.74 (2H, s, PhCH_2CO), 3.80-3.94 (4H, m, NCH$_2$CH_2O), 7.17 (2H, d, J 6.7, H-1′ and H-6′), 7.26-7.38 (3H, m, Ar-H); δ_C (100 MHz: CDCl$_3$): 35.5 (CH$_2$), 49.7 (CH$_2$), 51.8 (CH$_2$), 52.4 (CH$_2$), 63.7 (CH$_2$), 127.5 (CH), 128.9 (CH), 129.4 (CH), 132.9 (C), 204.3 (C); m/z, EI+ mode (%): 233 (M$^{+\cdot}$, 40), 114 (C$_6$H$_{12}$NO, 16), 100 (C$_5$H$_{10}$NO, 100); Accurate mass: C$_{14}$H$_{19}$NO$_2$: requires 233.1416, found 233.1415.

1,4-Diphenyl-butan-2-one[254] 381

381

The general solid-phase Takeda method C and general resin-cleavage procedure A employing thioacetal **285** (0.19 g, 0.60 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), yielded 1,4-diphenyl-butan-2-one[254] **381** (0.041 g, 0.184 mmol, 61%); δ_H (400 MHz, CDCl$_3$): 2.68-2.81 (4H, m, CH_2CH_2Ph), 3.59 (2H, s, COCH_2Ph), 7.21-7.32 (10H, m, Ar-H).
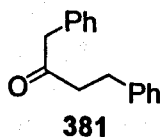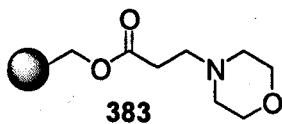
Merrifield resin-bound β–amino ester 383

383

Following the general method for β-amino ester synthesis, employing six Kans of Polymerlabs REM resin **382** (each containing 188 mg resin, 1.60 mmol g^{-1}, 0.30 mmol/kan, 1.80 mmol) and morpholine (1.60 cm^3, 18.0 mmol, 10 eq) yielded β-amino ester **383**; v_{max} (G Gate)/cm^{-1}: 1732 (CO).

Wang resin-bound β–amino ester 385

385
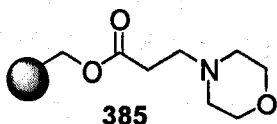
Six Kans of Wang resin (each containing 176 mg resin, 1.70 mmol g^{-1}, 0.30 mmol/kan, 1.80 mmol) were stirred in THF (100 cm^3) at rt with acrylic acid (0.60 cm^3, 9.00 mmol) and DMAP (0.22 g, 1.80 mmol). 1,3-Diisopropylcarbodiimide DIC (1.4 cm^3, 9.00 mmol) was added drop-wise and the reaction mixture was stirred for 24 h at rt. The THF solution was removed and the Kans were then washed with THF, MeOH/DCM alternate (x 4), MeOH and finally with diethyl ether. The resin was then dried under vacuum overnight and re-treated as above to yield Wang REM resin **384**. Following the general method for β-amino ester synthesis, employing six Kans of Wang REM resin **384** (1.80 mmol) and morpholine (1.60 cm^3, 18.0 mmol, 10 eq) yielded β-amino ester **385**.

Wang resin-bound β–amino ester 387

387
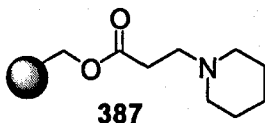
Wang REM resin **384** was synthesised as for ester **385**. Following the general method for β-amino ester synthesis, employing two Kans of Wang REM resin **384** (0.60 mmol) and piperidine (0.30 cm^3, 3.00 mmol, 5 eq) yielded β-amino ester **387**.

Formation of crude indole 389

Boc **389**
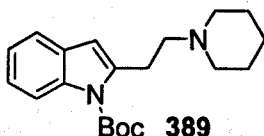
Following the general solid-phase Takeda method B and general resin-cleavage procedures but using 10% TFA in DCM, employing thioacetal **342a** (0.35 g, 0.90 mmol) and resin-bound ester **387** (0.30 mmol), yielded crude indole **396** as an impure mixture (0.032 g, 30%). The crude ^{1}H spectrum contained signals corresponding to the indole **396** [δ_H (400 MHz, CDCl$_3$): 1.41-1.46 (6H, m, NCH$_2$CH$_2$CH$_2$), 1.70 [9H, s, C(CH$_3$)$_3$], 2.45-2.76 (4H, m, NCH$_2$CH$_2$), 2.93-3.00 (2H, m, ArCH$_2$CH$_2$N), 3.33-3.36 (2H, m, ArCH$_2$CH$_2$N), 6.44 (1H, s, H-3), 7.14-7.19 (2H, m, Ar-H), 7.20-7.30 (4H, m, Ar-H), 7.45 (1H, d, J 7.3, Ar-H), 7.45 (1H, d, J 8.0, Ar-H)] with some other signals which could not be interpreted.

Resin-bound β–amino ester 394

394
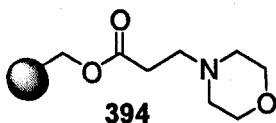
Following a literature procedure,[122] 4 Kans containing Merrifield resin (each containing 164 mg resin, 1.83 mmol g^{-1}, 0.30 mmol/kan, 1.20 mmol) were stirred with acrylic acid (0.40 cm^3, 6 mmol, 5 eq), cesium carbonate (1.96 g, 6.00 mmol, 5 eq) and potassium iodide (0.12 g, 6.00 mmol, 5 eq) in DMF (60 cm^3), at 70 °C for 18 h. The Kans were then washed with DMF (x 2), water (x 2), and then alternately with MeOH and DCM (x 5), before finally washing with MeOH and diethyl ether, and drying under vacuum to leave REM resin **393**. Following the general method for β-amino ester synthesis, employing two Kans of REM resin **393** (0.60 mmol) and morpholine (0.60 cm^3, 6.00 mmol, 10 eq), yielded β-amino ester **394**.

2-Ethylmorpholin-4-yl-*N*-benzyl-indole 396

396   └─Ph
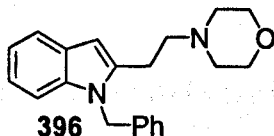
The general solid-phase Takeda method A, general resin-cleavage procedure A, and ketone cyclisation conditions employing thioacetal **346b** (0.60 g, 1.50 mmol) and resin-bound ester **394** (0.30 mmol), yielded crude indole **396** as an impure mixture (0.017 g, 0.08 mmol, 28%). Purification by column chromatography (SiO$_2$, ethyl acetate), yielded 2-

ethylmorpholin-4-yl-*N*-benzyl-indole **396** as a yellow solid (0.04 g, 0.02 mmol, 6%); R_f (SiO$_2$, ethyl acetate) 0.13; δ_H (400 MHz, CDCl$_3$): 2.45-3.50 (4H, m, NCH_2CH$_2$O), 2.67 (2H, t, *J* 7.2, CH_2CH$_2$N), 2.88 (2H, t, *J* 7.4, CH$_2$CH_2N), 3.68-3.71 (4H, m, NCH$_2$CH_2O), 5.35 (2H, s, NCH_2Ph), 6.37 (1H, s, H-3), 6.95 (2H, dd, *J* 8.2 and 1.6, Ar-H), 7.06-7.13 (2H, m, Ar-H), 7.20-7.30 (4H, m, Ar-H), 7.57 (1H, dd, *J* 6.6 and 1.8, Ar-H).

2-(2'-Nitrophenyl)acetaldehyde 401

401
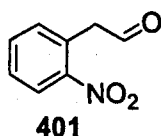
2'-Nitrophenethyl alcohol (0.15 cm^3, 1.00 mmol) in DCM (2 cm^3), was added dropwise to a solution of the Dees-Martin periodinane reagent (0.51 g, 1.20 mmol) in DCM (3 cm^3), at rt under argon, for 30 mins. After this time, the reaction mixture was quenched by pouring into sodium hydroxide (1.0 mol dm^{-3}, 40 cm^3) and diethyl ether (30 cm^3) was added. The resulting white precipitate was filtered. The organic layer was separated, washed with water (2 x 50 cm^3), dried over magnesium sulfate and concentrated to yield a yellow oil (0.11 g, 67%). The crude ^{1}H spectrum confirmed that greater than 95% conversion to aldehyde **401** was achieved [δ_H (400 MHz, CDCl$_3$): 4.03 (2H, s, CH_2CHO), 7.24 (1H, dd, *J* 7.6 and 0.8, H-6'), 7.42 (1H, t, *J* 7.6, H-5'), 7.42 (1H, t, *J* 7.6, H-4'), 7.80 (1H, dd, *J* 7.6 and 1.1, H-3'), 9.24 (1H, s, CHO)] along with some other signals which could not be interpreted.

Methoxymethyl triphenylphosphonium chloride[239] 406

406
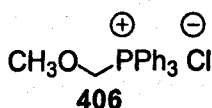
Methoxymethyl chloride (10.0 cm^3, 110 mmol) was added slowly to a solution of triphenylphosphine (26.2 g, 100 mmol) in DCM (150 cm^3) and the reaction mixture was heated under reflux for 15 h. Toluene (150 cm^3) was added and the solution was evaporated to dryness and then repeated to yield methoxymethyl triphenylphosphonium chloride **406** as a white crystalline solid (34.0 g, 99.0 mmol, 99%): δ_H (400 MHz, CDCl$_3$): 3.74 (1H, s, OCH$_3$), 6.00 (2H, d, *J* 3.9, CH_2PPh$_3$), 7.67-7.71 (6H, m, Ar-H), 7.79-7.86 (9H, m, Ar-H).

2-(2'-Nitrobenzyl)-1,3-dithiane 409a

409a
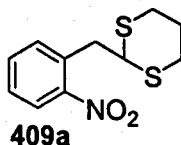
tert-Butyllithium (1.50 mol dm^{-3} in hexane, 53.3 cm^3, 80 mmol) was added dropwise to a solution of methoxymethyltriphenylphosphonium chloride **406** (15.0 g, 99.0 mmol) in THF (180 cm^3), at -78 °C under argon. The reaction mixture was stirred at -78 °C for 15 mins, and then warmed to -40 °C over 15 mins, and stirred at this temperature for 30 mins. The reaction mixture was then cooled to -78 °C and a solution of 2-nitrobenzaldehyde **334a** (9.06 g, 60.0 mmol) in THF (120 cm^3) was added *via* canula, stirred at this temperature for 15 mins before allowing to warm to rt and allowed to stir for 18h. After this time, the reaction mixture was quenched by pouring into water (200 cm^3) and extracted into DCM (2 x 100 cm^3). The combined organic phases were then washed with water (2 x 150 cm^3), brine (200 cm^3), dried over sodium sulfate, and concentrated to yield a brown solid (29.83 g). Signals in the ^{1}H NMR (400 MHz, CDCl$_3$) spectrum confirmed that this was the desired enol ether **408a** as a 5: 1 mixture of *trans* **A**: *cis* **B** isomers [δ 3.75 (3H^A, s, OCH$_3$), 3.80 (3H^B, s, OCH$_3$), 5.70 (1H^B, d, *J* 7.2, C*H*=CHOCH$_3$), 6.31 (1H^B, d, *J* 7.2, CH=C*H*OCH$_3$), 6.39 (1H^A, d, *J* 12.8, C*H*=CHOCH$_3$), 7.05 (1H^A, d, *J* 12.8, CH=C*H*OCH$_3$)] with significant amounts of triphenylphosphine-containing side-products remaining but no evidence of any aldehyde starting material. 1,3-Propanedithiol (6.6 cm^3, 66 mmol) was added to a solution of crude enol ether **408a** (assume 60.0 mmol), acetic acid (60 cm^3) and boron trifluoride diethyletherate (23.0 cm^3, 180 mmol) in toluene (100 cm^3), under nitrogen, and stirred for 20 h at rt. After this time, the resulting white solid was filtered off and the filtrate was poured into water (200 cm^3) and extracted into ethyl acetate (2 x 50 cm^3). The combined organic phases were washed with water (100 cm^3), sodium hydroxide (2 mol dm^{-3}, 2 x 100 cm^3), water (200 cm^3), brine (200 cm^3), dried over sodium sulfate, and concentrated to yield a brown solid (16.99 g). ^{1}H NMR analysis confirmed that this was the desired thioacetal **409a** with significant amounts of triphenylphosphine-containing impurities remaining. Recrystallisation of a 0.50 g portion from propan-2-ol, yielded 2-(2'-nitrobenzyl)-1,3-dithiane **409a** as orange/yellow needles (0.32 g, 1.25 mmol): R$_f$ (SiO$_2$, DCM): 0.48; ν$_{max}$ (GGate)/cm^{-1}: 2925 (CH$_2$), 2896 (CH), 1512 (NO$_2$), 1495 (NO$_2$); δ$_H$ (400 MHz, CDCl$_3$): 1.83-1.93 (1H, m, CH$_{ax}$), 2.08-2.17 (1H, m, CH$_{eq}$), 2.79-2.91 (4H, m, CH$_2$-S), 3.39 (2H, d, *J* 7.4, C*H$_2$*CHS), 4.36 (1H, t, *J* 7.5, CH$_2$C*H*S), 7.42-7.45 (2H, m, H-4' and H-6'), 7.56 (1H, dt, *J* 1.2 and 7.0, H-5'), 8.01 (1H, dd, *J* 1.2 and 7.1, H-3'); δ$_C$ (100 MHz, CDCl$_3$): 25.6 (CH$_2$), 30.1 (CH$_2$), 38.9 (CH$_2$), 46.6 (CH), 125.1 (CH),

128.3 (CH), 132.4 (C), 132.8 (CH), 133.5 (CH), 149.1 (C); m/z, EI+ (%): 255 (M$^{+\bullet}$, 8), 119 (100); Accurate mass: $C_{11}H_{13}NO_2S_2$: requires 255.0387, found 255.0388.

2-(3'-Methoxy-2'-nitrobenzyl)-1,3-dithiane 409b
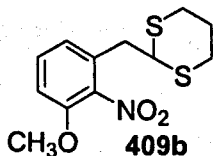
As for thioacetal **409a**, *tert*-Butyllithium (1.50 mol dm^{-3} in hexane, 37.0 cm^3, 55 mmol) was added dropwise to a solution of methoxymethyltriphenylphosphonium chloride **406** (20.6 g, 60.0 mmol) in THF (120 cm^3), at -78 °C under argon. The reaction mixture was stirred at -78 °C for 15 mins, and then warmed to -40 °C over 30 mins and stirred at this temperature for 30 mins. The reaction mixture was then cooled to -78 °C and a solution of 3-methoxy-2-nitrobenzaldehyde **334b** (7.25 g, 40.0 mmol) in THF (40 cm^3) at rt was added *via* syringe, stirred at -78 °C for 15 mins before allowing to warm to rt over 1 h and allowing to further stir for 18 h. After this time, the reaction was quenched by pouring into water (400 cm^3) and extracted into DCM (2 x 200 cm^3). The combined organic phases were then washed with water (3 x 300 cm^3), brine (300 cm^3), dried over sodium sulfate, and concentrated to yield a brown solid (20.14 g). Signals in the ^{1}H NMR spectrum (400 MHz, CDCl$_3$), confirmed that this was the desired enol ether **408b** as a 2: 1 mixture of *trans* **A**: *cis* **B** isomers [δ 5.03 (1H^B, d, *J* 7.2, C*H*CHOCH$_3$), 5.62 (1H^A, d, *J* 12.8, C*H*CHOCH$_3$), 6.26 (1H^B, d, *J* 7.1, CHC*H*OCH$_3$), 7.07 (1H^A, d, *J* 12.8, CHC*H*OCH$_3$)] with significant amounts of triphenylphosphine-containing by-products remaining, but no evidence of any aldehyde starting material. Following the procedure for the formation of thioacetal **409a**, employing crude enol ether **409b** (20.14 g, assumed 40.0 mmol), 1,3-propanedithiol (4.40 cm^3, 44.0 mmol), acetic acid (40 cm^3), and boron trifluoride diethyletherate (19.0 cm^3, 150 mmol) in toluene (100 cm^3), and following the same work-up procedure, yielded a brown solid (12.03 g). ^{1}H NMR analysis confirmed that this was the desired thioacetal **409b**; δ$_H$ (400 MHz, CDCl$_3$): 1.81-1.92 (1H, m, CH$_{ax}$), 2.04-2.13 (1H, m, CH$_{eq}$), 2.80-2.87 (4H, m, CH$_2$-S), 3.03 (2H, d, *J* 7.7, C*H$_2$*CHS), 3.88 (3H, s, OCH$_3$), 4.23 (1H, t, *J* 7.7, CH$_2$C*H*S), 6.95 (1H, d, *J* 7.8, H-4'), 7.16-7.18 (1H, m, H-6'), 7.36 (1H, t, *J* 8.1, H-5'); R$_f$ (SiO$_2$, DCM): 0.42; with no sign of the enol ether remaining although significant amounts of triphenylphosphine-containing impurities did remain and attempts to recrystallise a 0.40 g portion of this mixture were unsuccessful. This crude mixture was simply used to form the aniline and then Boc protected.

2-(4',5'-Methylenedioxy-2'-nitrobenzyl)-1,3-dithiane 409c

409c
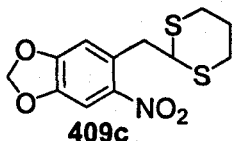
As for thioacetal **409a**, using *tert*-Butylithium (1.50 mol dm^{-3} in hexane, 37 cm^3, 55.0 mmol) was added drop-wise to a solution of methoxymethyltriphenylphosphonium chloride **406** (20.6 g, 60.0 mmol) in THF (120 cm^3), at -78 °C under argon. The reaction mixture was stirred at -78 °C for 15 mins, and then warmed to -40 °C over 30 mins and stirred at this temperature for 30 mins. The reaction mixture was then cooled to -78 °C and a solution of 2-nitropiperanal **334c** [(7.80 g, 40.0 mmol) in THF (60 cm^3) at rt] was added *via* syringe, stirred at -78 °C for 15 mins before allowing to warm to rt over 1 h and then allowed to stir for 18 h. After this time, the reaction mixture was quenched by pouring into water (400 cm^3) and extracted with DCM (2 x 200 cm^3). The combined organic phases were then washed with water (3 x 300 cm^3), brine (300 cm^3), dried over sodium sulfate, and concentrated to yield a brown solid (20.96 g). Signals in the ^{1}H NMR (400 MHz, CDCl$_3$) spectrum confirmed that this was the desired enol ether **408c** as a 4: 3 mixture of *trans* **A** *cis* **B** isomers [δ 5.52 (1H^A, d, *J* 12.8, C*H*CHOCH$_3$), 5.83 (1H^B, d, *J* 7.3, C*H*CHOCH$_3$), 6.24 (1H^B, d, *J* 7.3, CHC*H*OCH$_3$), 6.95 (1H^A, d, *J* 12.8, CHC*H*OCH$_3$)] with significant amounts of triphenylphosphine-containing side-products remaining. Following the procedure for the formation of thioacetal **409a**, employing crude enol ether **408c** (20.96 g, assume 40.0 mmol), yielded a brown solid (12.85 g). ^{1}H NMR analysis confirmed that this was thioacetal **409c** with significant amounts of triphenylphosphine-containing impurities but no evidence of any aldehyde starting material remained. Recrystallisation of a 0.40 g portion from propan-2-ol, gave 2-(4',5'-methylenedioxy-2'-nitrobenzyl)-1,3-dithiane **409c** as yellow needles (0.28 g, 0.94 mmol): R$_f$ (SiO$_2$, DCM): 0.42; Mpt: 136-138 °C; ν$_{max}$ (GGate)/cm^{-1}: 2962 (CH$_2$), 2900 (CH), 1496 (NO$_2$), 1477 (NO$_2$); δ$_H$ (400 MHz, CDCl$_3$): 1.83-1.94 (1H, m, CH$_{ax}$), 2.08-2.15 (1H, m, CH$_{eq}$), 2.81-2.89 (4H, m, CH$_2$-S), 3.33 (2H, d, *J* 7.4, C*H$_2$*CHS), 4.37 (1H, t, *J* 7.5, CH$_2$C*H*S), 6.11 (2H, s, OC*H$_2$*O), 6.80 (1H, s, H-6'), 7.56 (1H, s, H-3'); δ$_C$ (100 MHz, CDCl$_3$): 25.7 (CH$_2$), 30.2 (CH$_2$), 39.6 (CH$_2$), 46.8 (CH), 103.0 (CH$_2$), 106.0 (CH), 112.0 (CH), 129.6 (C), 129.7 (C), 147.3 (C), 151.4 (C); m/z, EI+ (%): 299 (M$^{+\bullet}$, 5), 282 (M$^{+\bullet}$-OH, 8), 193 (18), 119.0 (100); Accurate mass: C$_{12}$H$_{13}$NO$_4$S$_2$: requires 299.0286, found 299.0286; Microanalysis Found: C 48.15%, H 4.27%, N 4.53%, S 21.38%; Theoretical C$_{12}$H$_{13}$NO$_4$S$_2$: C 48.14%, H 4.38%, N 4.68%, S 21.42%.

2-[2'-(*N-tert*-Butyloxycarboxyamino)benzyl]-1,3-dithiane 411a

411a
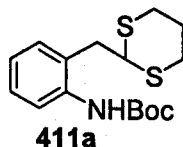
Iron powder (10.05 g, 180 mmol) was added to the crude thioacetal **409a** (assuming 60 mmol) and ammonium chloride (16.05 g, 300 mmol), in an ethanol (200 cm^3) and water (100 cm^3) solution, and the reaction mixture was heated under reflux for 4 h. After cooling, the reaction mixture was filtered through celite, washing with ethyl acetate (100 cm^3) and then concentrated *in vacuo*. The resulting slurry was partitioned between ethyl acetate (100 cm^3) and water (150 cm^3) and the organic phases were then washed with water (2 x 150 cm^3), brine (150 cm^3), dried over magnesium sulfate, and concentrated under vacuum to give a brown oil; (14.16 g). ^{1}H NMR analysis confirmed that this was the desired amine **410a** [R$_f$ (SiO$_2$, DCM): 0.12] with significant amounts of triphenylphosphine-containing by-products remaining. Di-*tert*-butyl-dicarbonate (13.10 g, 60.0 mmol), was added to a solution of the crude amine **410a** in THF (120 cm^3) and was heated under reflux, under nitrogen, for 20 h. After this time, the reaction mixture was poured into water (200 cm^3) and extracted into diethyl ether (2 x 100 cm^3). The combined organic phases were washed with water (2 x 200 cm^3), brine (2 x 200 cm^3), dried over sodium sulfate and concentrated to yield a white/brown solid (18.16g). Recrystallisation from cyclohaxane: propan-2-ol (4: 1) yielded 2-[2'-(*N-tert*-butyloxycarboxyamino)benzyl]-1,3-dithiane **411a** as a pale yellow solid (8.61 g, 26.5 mmol, 44% from **334a**), R$_f$ (SiO$_2$, DCM): 0.17; Mpt: 130-133 °C; ν_{max} (GGate)/cm^{-1}: 3300 (NH), 2976 (CH$_2$), 2927 (CH), 2898 (CH), 1685 (CO); δ_H (400 MHz, CDCl$_3$): 1.52 [9H, s, (CH$_3$)$_3$], 1.85-1.92 (1H, m, CH$_{ax}$), 2.09-2.14 (1H, m, CH$_{eq}$), 2.84-2.86 (4H, m, CH$_2$-S), 3.03 (2H, d, *J* 7.1, C*H$_2$*CHS), 4.21 (1H, t, *J* 7.5, CH$_2$C*H*S), 6.51 (1H, s, NH), 7.10 (1H, dt, *J* 1.1 and 8.0, H-5'), 7.22-7.28 (2H, m, H-4' and H-6'), 7.65 (1H, bd, *J* 7.8, H-3'); δ_C (100 MHz, CDCl$_3$): 25.2 (CH$_2$), 28.3 (CH$_3$), 30.4 (CH$_2$), 37.4 (CH$_2$), 47.8 (CH), 80.5 (C), 124.0 (CH), 124.6 (CH), 127.9 (CH), 129.3 (C), 130.6 (CH), 136.1 (C), 153.5 (C); m/z, EI+ (%): 325 (M$^{+\bullet}$, 42), 268 (M$^{+\bullet}$-C$_4$H$_9$, 64), 119 (100); Accurate mass: C$_{16}$H$_{23}$NO$_2$S$_2$: requires 325.1170, found 325.1173; Microanalysis Found: C 59.16%, H 7.12%, N 4.30%, S 19.70%; Theoretical C$_{16}$H$_{23}$NO$_2$S$_2$: C 59.04%, H 7.16%, N 4.33%, S 19.71%.

2-[2'-(*N-tert*-Butyloxycarboxyamino)-3'-methoxybenzyl]-1,3-dithiane 411b
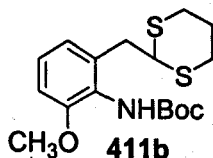
Iron powder (6.70 g, 120 mmol), was added to a solution of crude thioacetal **409b** (12.03 g, assumed 40.0 mmol) and ammonium chloride (10.70 g, 200 mmol), in ethanol (120 cm^3) and water (40 cm^3) and heated under reflux for 2 h. After allowing to cool, the reaction mixture was filtered through celite, washing with ethyl acetate (200 cm^3). The dark green solution was then concentrated in *vacuo*. The resulting brown solid was partitioned between ethyl acetate (250 cm^3) and water (400 cm^3). The organic phases were separated and washed with water (400 cm^3), brine (200 cm^3), dried over magnesium sulfate and concentrated under vacuum to yield a brown oil (9.73 g). ^{1}H NMR confirmed that this was mostly the desired aniline **410b** [R_f (SiO$_2$, DCM): 0.48] in good purity although contaminated with small amounts of starting material and triphenylphosphine-containing by-products. Di-*tert*-butyl-dicarbonate (8.73 g, 40.0 mmol) was added to this crude material in THF (150 cm^3), and the mixture was heated under reflux for 42 h. After this time, the reaction mixture was poured into water (150 cm^3) and extracted into diethyl ether (2 x 80 cm^3). The combined organic phases were then washed with water (2 x 150 cm^3), brine (150 cm^3), dried over sodium sulfate and concentrated to yield a brown oil (8.13 g). Crystallisation, from propan-2-ol/cyclohexane, yielded 2-[2'-(*N-tert*-butyloxycarboxyamino)-3'-methoxybenzyl]-1,3-dithiane **411b** as needles (3.82 g, 10.7 mmol, 27% from **334b**): R_f (SiO$_2$, DCM): 0.17; Mpt: 125-126 °C; ν_{max} (GGate)/cm^{-1}: 3300 (NH), 2978 (CH$_2$), 2908 (CH), 1685 (CO); δ_H (400 MHz, CDCl$_3$): 1.50 [9H, s, (CH$_3$)$_3$], 1.81-1.92 (1H, m, CH$_{ax}$), 2.05-2.13 (1H, m, CH$_{eq}$), 2.78-2.87 (4H, m, CH$_2$-S), 3.13 (2H, d, *J* 7.4, C*H$_2$*CHS$_2$), 3.82 (3H, s, OCH$_3$), 4.21 (1H, t, *J* 7.5, CH$_2$C*H*S$_2$), 5.99 (1H, s, NH), 6.81 (1H, d, *J* 8.2, H-4'), 6.90 (1H, d, *J* 7.5, H-6'), 7.17 (1H, t, *J* 8.0, H-5'); δ_C (100 MHz, CDCl$_3$): 25.8 (CH$_2$), 28.3 (CH$_3$), 30.3 (CH$_2$), 37.8 (CH$_2$), 47.6 (CH), 55.7 (CH$_3$), 80.1 (C), 109.8 (CH), 122.5 (CH), 124.9 (C), 127.1 (CH), 136.4 (C), 154.8 (C), 154.8 (C); m/z, EI+ (%): 355 (M$^{+\cdot}$, 10), 299 (M$^{+\cdot}$-C$_4$H$_8$, 12) 148 (30), 199 (100); Accurate mass: C$_{17}$H$_{25}$NO$_3$S$_2$: requires 355.1276, found 355.1278; Microanalysis Found: C 57.29%, H 7.12%, N 3.86%; Theoretical C$_{17}$H$_{25}$NO$_3$S$_2$: C 57.43%, H 7.09%, N 3.94%.

2-[2'-(*N-tert*-Butyloxycarboxyamino)-4',5'-methylenedioxybenzyl]-1,3-dithiane 411c
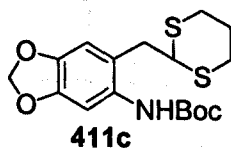
Using both exactly the same reagent quantities and procedure as for the reduction of thioacetal **409b**, employing crude thioacetal **409c** (12.03 g, assumed 40.0 mmol), yielded amine **410c** as a brown oil (9.89 g). ^{1}H NMR confirmed that this was mostly the desired aniline **410c** [R$_f$ (SiO$_2$, DCM): 0.41] although contaminated with significant amounts of triphenylphosphine-containing by-products. Di-*tert*-butyl-dicarbonate (17.5 g, 80.0 mmol) was added to this crude material in THF (150 cm^3), and the mixture was heated under reflux for 42 h. After this time the reaction mixture was poured into water (200 cm^3) and extracted into ethyl acetate (2 x 100 cm^3). The combined organic phases were washed with water (3 x 100 cm^3), brine (200 cm^3), dried over sodium sulfate, and concentrated to yield the corresponding imide **412** [R$_f$ (SiO$_2$, DCM): 0.54] which was contaminated with some di-*tert*-butyl-dicarbonate and triphenylphosphine-containing by-products, as a brown solid (13.35 g). Triflouroacetic acid (3.1 cm^3, 40.0 mmol) was added drop-wise to the crude imide (13.35 g, assumed 44.0 mmol) in DCM (400 cm^3) and the mixture was stirred for 18 h. After this time the reaction mixture was washed with sodium bicarbonate (2 x 100 cm^3) and then water (3 x 100 cm^3), dried over sodium sulfate, and concentrated to yield carbamate **411c** as a brown solid (11.82 g). Recrystallisation from propan-2-ol, yielded 2-[2'-(*N-tert*-butyloxycarboxyamino)-4',5'-methylenedioxybenzyl]-1,3-dithiane **411c** as tiny needles (5.50 g, 14.9 mmol, 37% from **334c**), R$_f$ (SiO$_2$, DCM): 0.19; Mpt: 163-165 °C; ν_{max} (KBr)/cm^{-1}: 3246 (NH), 2900 (CH$_2$), 1672 (CO), 1157 (COC); δ_H (400 MHz, CDCl$_3$): 1.50 [9H, s, (CH$_3$)$_3$], 1.84-1.93 (1H, m, CH$_{ax}$), 2.09-2.14 (1H, m, CH$_{eq}$), 2.81-2.86 (4H, m, CH$_2$-S), 2.94 (2H, d, *J* 7.1, C*H$_2$*CHS$_2$), 4.16 (1H, t, *J* 7.1, CH$_2$C*H*S$_2$), 5.93 (2H, s, OCH$_2$O), 6.32 (1H, s, NH), 6.70 (1H, s, H-6'), 7.04 (1H, s, H-3'); δ_C (100 MHz, CDCl$_3$): 25.6 (CH$_2$), 28.5 (CH$_3$), 30.4 (CH$_2$), 37.3 (CH$_2$), 48.3 (CH), 80.4 (C), 101.4 (CH$_2$), 106.7 (CH), 109.5 (CH), 124.4 (C), 145.2 (C), 146.9 (C), 154.0 (C); m/z, EI+ (%): 369 (M$^{+\bullet}$, 22), 313 (M$^{+\bullet}$-C$_4$H$_8$, 8), 150 (27), 119 (100); Accurate mass: C$_{17}$H$_{23}$NO$_4$S$_2$: requires 369.1069, found 369.1069; Microanalysis Found: C 55.36%, H 6.17%, N 3.65%, S 17.29%; Theoretical C$_{17}$H$_{23}$NO$_4$S$_2$: C 55.26%, H 6.27%, N 3.79%, S 17.36%.

2-[2'-(*N*-tert-Butyloxycarboxy-*N*-trimethylsilylamino)benzyl]-1,3-dithiane 413a

413a
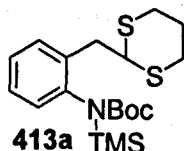
Lithium di-isopropylamine (1.2 cm^3, 2.40 mmol, 2.0 mol dm^{-3} in THF, ethyl benzene and heptanes) was added drop-wise to a solution of carbamate **411a** (0.65 g, 2.00 mmol) and chlorotrimethylsilane (0.45 cm^3, 3.50 mmol) in THF (15 cm^3), at -78 °C under argon. The reaction mixture was allowed to warm to rt over 30 mins and was then allowed to stir for a further 30 mins at this temperature. After this time the solvent was removed *in vacuo* and diethyl ether (15 cm^3) was added. The resulting precipitate was filtered off and the ethereal solution was concentrated to yield 2-[2'-(*N*-tert-butyloxycarboxy-*N*-trimethylsilyl-amino)benzyl]-1,3-dithiane **413a** as a pale yellow solid (0.69 g, 1.72 mmol, 86%); δ_H (400 MHz, CDCl$_3$): 0.21 [9H, s, Si(CH$_3$)$_3$], 1.51 [9H, s, C(CH$_3$)$_3$], 1.80-1.91 (1H, m, CH$_{ax}$), 2.06-2.11 (1H, m, CH$_{eq}$), 2.78-2.88 (5H, m, CH$_2$-S and C*H*$_A$H$_B$CHS$_2$), 3.02 (1H, dd, *J* 14.3 and 5.6, CH$_A$*H*$_B$CHS$_2$), 4.29 (1H, dd, *J* 8.8 and 5.6, CH$_A$H$_B$C*H*S$_2$), 6.96 (1H, d, *J* 7.1, H-3'), 7.16-7.52 (3H, m, H-4', H-5' and H-6'); m/z, EI+ (%): 397 (M$^{+\bullet}$, 18), 341 (M$^{+\bullet}$-C$_4$H$_8$, 33), 119 (100); Accurate mass: C$_{19}$H$_{31}$NO$_2$S$_2$Si: requires 397.1566, found 397.1564.

2-[2'-(*N*-tert-Butyloxycarboxy-*N*-trimethylsilylamino)-3'-methoxybenzyl]-1,3-dithiane 413b

413b
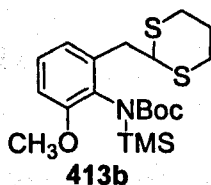
Exactly as for carbamate **413a**, employing lithium di-isopropylamine (2.75 cm^3, 5.50 mmol, 2.0 mol dm^{-3} in THF, ethyl benzene and heptanes), carbamate **411b** (1.78 g, 5.00 mmol) and chlorotrimethylsilane (1.00 cm^3, 8.25 mmol) in THF (40 cm^3), gave 2-[2'-(*N*-tert-butyloxycarboxy-*N*-trimethylsilylamino)-3'-methoxybenzyl]-1,3-dithiane **413b** as a yellow oil (1.80 g, 4.20 mmol, 84%); δ_H (400 MHz, CDCl$_3$): 0.19 [9H, s, Si(CH$_3$)$_3$], 1.59 [9H, s, C(CH$_3$)$_3$], 1.81-1.90 (1H, m, CH$_{ax}$), 2.07-2.11 (1H, m, CH$_{eq}$), 2.77-2.90 (5H, m, C*H*$_2$CH$_2$C*H*$_2$-S and C*H*$_A$H$_B$CHS$_2$), 2.98 (1H, dd, *J* 14.1 and 5.8, CH$_A$*H*$_B$CHS$_2$), 3.77 (3H, s, OCH$_3$), 4.29 (1H, dd, *J* 8.6 and 5.8, CH$_A$H$_B$C*H*S$_2$), 6.79 (1H, bd, *J* 8.2, Ar-H), 6.90 (1H, bd, *J* 7.6, Ar-H), 7.13 (1H, t, *J* 7.9, H-5').

2-[2'-(*N*-*tert*-Butyloxycarboxy-*N*-trimethylsilylamino)-4',5'-methylenedioxy]-1,3-dithiane 413c

413c
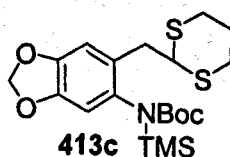
Exactly as for carbamate **413a**, employing lithium di-isopropylamine (3.00 cm^3, 6.00 mmol, 2.0 mol dm^{-3} in THF, ethyl benzene and heptanes), carbamate **411c** (2.00 g, 5.40 mmol) and chlorotrimethylsilane (1.00 cm^3, 8.25 mmol) in THF (40 cm^3), yielded 2-[2'-(*N*-*tert*-butyloxycarboxy-*N*-trimethylsilylamino)-4',5'-methylenedioxy]-1,3-dithiane **413c** as a yellow oil which solidified on standing (2.18 g, 4.90 mmol, 91%); δ_H (400 MHz, CDCl$_3$): 0.22 [9H, s, Si(CH$_3$)$_3$], 1.50 [9H, s, C(CH$_3$)$_3$], 1.79-1.90 (1H, m, CH$_{ax}$), 2.05-2.12 (1H, m, CH$_{eq}$), 2.63-2.85 (5H, m, C*H$_2$*CH$_2$C*H$_2$*-S and C*H$_A$*H$_B$CHS$_2$), 2.93 (1H, dd, *J* 14.2 and 5.6, CH$_A$*H$_B$*CHS$_2$), 4.21 (1H, dd, *J* 9.1 and 5.3, CH$_A$H$_B$C*H*S$_2$), 5.91-5.96 (2H, m, OCH$_2$O), 6.47 (1H, s, H-3'), 6.97 (1H, s, H-6').

1-(2'-*N*-tert-Butyloxycarboxyamino-5'-phenyl)-4-phenylpentan-2-one 414
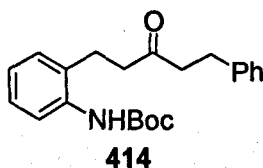
414

Following the general solid-phase Takeda Method D and resin-cleavage procedure A, employing silylated carbamate **413a** (1.43 g, 3.60 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), yielded 1-(2'-*N*-tert-butyloxycarboxyamino-5'-phenyl)-4-phenylpentan-2-one **414** in good purity as a yellow oil (0.063 g, 0.178 mmol, 59%); δ_H (400 MHz, CDCl$_3$): 1.47 [9H, s, C(CH$_3$)$_3$], 2.61 (2H, t, *J* 7.8, C*H$_2$*CH$_2$), 2.68-2.76 (4H, m, C*H$_2$CH$_2$*), 2.79 (2H, t, *J* 7.8, CH$_2$C*H$_2$*), 6.92-7.19 (8H, m, Ar-H), 7.34 (1H, s, NH), 7.62 (1H, d, *J* 7.9, H-6').

1-(2'-Amoniumtrifluoroacetate-5'-phenyl)-4-phenylpentan-2-one 417aa'

417aa'
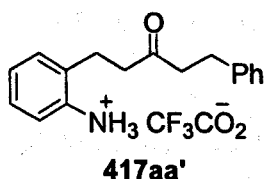
Following the general solid-phase Takeda method D and resin-cleavage procedure B, employing silylated carbamate **413a** (1.43 g, 3.60 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), yielded 1-(2'-amoniumtrifluoroacetate-5'-phenyl)-4-phenylpentan-2-one **417aa'** in good purity as a yellow oil (0.086 g, 0.234 mmol, 78%); δ_H (400 MHz, CDCl$_3$): 2.79 (4H, s, CH_2CH_2), 3.04 (2H, t, J 7.3, CH$_2$CH_2), 3.07 (2H, t, J 7.3, CH_2CH$_2$), 6.04-7.36 (9H, m, Ar-H), 11.13 (3H, s, NH$_3$); δ_C (100 MHz, CDCl$_3$): 20.9 (CH$_2$), 29.0 (CH$_2$), 32.9 (CH$_2$), 39.7 (CH$_2$), 121.7 (CH), 126.4 (C), 127.9 (CH), 128.5 (C), 129.1 (CH), 129.3 (CH), 129.6 (CH), 131.9 (CH), 132.4 (C), 137.7 (C), 187.9 (C).

All the quinolines below were synthesised following the general solid-phase Takeda method D and resin-cleavage procedure B, and then subjecting the crude material to the cyclisation/oxidation conditions (see general procedures).

2-Phenethyl-quinoline[255] 416aa'
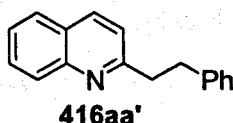
416aa'

Following the above procedures, employing silylated carbamate **413a** (1.43 g, 3.60 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), yielded 2-phenethyl-quinoline[255] **416aa'** as a yellow oil (0.049 g, 0.202 mmol, 67%); ν_{max} (Thin Film)/cm^{-1}: 3032 (CH), 2952 (CH), 2912 (CH), 1618 (C=C), 1589 (C=C), 1512 (C=C), 1495 (C=C), 729 (CH), 696 (CH); δ_H (400 MHz, CDCl$_3$): 3.15-3.19 (2H, m, CH$_2$), 3.29-3.33 (2H, m, CH$_2$), 7.19-7.31 (6H, m, Ar-H), 7.50 (1H, dt, J 1.0 and 7.5, H-6), 7.68-7.73 (1H, m, H-7), 7.79 (1H, d, J 8.1, H-5), 8.06 (1H, d, J 8.6, H-4), 8.08 (1H, d, J 8.8, H-8); δ_C (100 MHz, CDCl$_3$): 35.9 (CH$_2$), 40.8 (CH$_2$), 121.5 (CH), 125.9 (CH), 126.8 (C), 127.5 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.5 (CH), 136.4 (CH), 141.5 (C), 161.8 (C); m/z, EI+ (%): 234 (M$^{+\bullet}$, 20), 233 (M$^{+\bullet}$-H, 100), 233 (M$^{+\bullet}$-H$_2$, 92); Accurate mass: C$_{17}$H$_{16}$N: requires 234.1283, found 234.1280.

8-Methoxy-2-phenethyl-quinoline 416ba'
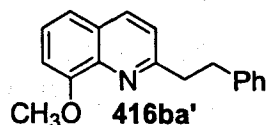
Following the above procedures, employing silylated carbamate **413b** (1.54 g, 3.60 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), yielded 8-methoxy-2-phenethyl-quinoline **416ba'** as a yellow oil (0.037 g, 0.139 mmol, 46%); ν_{max} (Thin Film)/cm^{-1}: 3060 (CH$_2$), 3026 (CH$_2$), 2954 (CH), 2930 (CH), 2852 (OCH$_3$), 1602 (C=C), 1564 (C=C), 1503 (C=C), 751 (CH), 700 (CH); δ_H (400 MHz, CDCl$_3$): 3.14-3.18 (2H, m, CH$_2$), 3.35-3.39 (2H, m, CH$_2$), 4.10 (3H, s, OCH$_3$), 7.05 (1H, d, J 7.5, H-3), 7.09-7.31 (6H, m, Ar-H + H-5), 7.35-7.44 (2H, m, H-6 and H-7), 8.02 (1H, d, J 8.4, H-4); δ_C (100 MHz, CDCl$_3$): 36.1 (CH$_2$), 50.0 (CH$_2$), 56.2 (CH$_3$), 107.8 (CH), 119.5 (CH), 122.0 (CH), 125.9 (CH), 126.0 (CH), 128.0 (C), 128.4 (CH), 128.5 (CH), 136.2 (CH), 139.8 (C), 141.6 (C), 155.0 (C), 161.0 (C); m/z, EI+ (%): 263 (M$^{+\bullet}$, 100), 262 (M$^{+\bullet}$-H, 54); Accurate mass: C$_{18}$H$_{17}$NO: requires 263.1310, found 263.1308.

8-Methoxy-2-(2'-methyl-propenyl)-quinoline 416bd'

Following the above procedures, employing silylated carbamate **413b** (1.54 g, 3.60 mmol) and resin-bound ester **309d'** (Method A, 0.30 mmol), yielded 8-methoxy-2-(2'-methyl-propenyl)-quinoline **416bd'** as a yellow oil (0.038 g, 0.176 mmol, 59%); ν_{max} (Thin Film)/cm^{-1}: 3047 (CH$_2$), 2966 (CH), 2929 (CH), 2835 (OCH$_3$), 1649 (C=C), 1600 (C=C), 1556 (C=C), 1498 (C=C); δ_H (400 MHz, CDCl$_3$): 2.00 (3H, d, J 1.2, CH$_3$), 2.14 (3H, d, J 1.2, CH$_3$), 4.07 (3H, s, OCH$_3$), 6.62 [1H, t, J 1.2, CHC(CH$_3$)$_2$], 7.02 (1H, dd, J 7.5 and 1.2, H-3), 7.33-7.44 (3H, m, H-5, H-6 and H-7), 8.05 (1H, d, J 8.5, H-4); δ_C (100 MHz, CDCl$_3$): 19.9 (CH$_3$), 27.3 (CH$_3$), 55.9 (CH$_3$), 107.6 (CH), 119.2 (CH), 122.7 (CH), 125.8 (CH), 126.2 (CH), 127.3 (C), 135.5 (CH), 139.8 (C), 141.4 (C), 155.2 (C), 156.6 (C); m/z, EI+ (%): 213 (M$^{+\bullet}$, 7), 212 (M$^{+\bullet}$-H, 10), 82 (100); Accurate mass: C$_{14}$H$_{15}$NO: requires 213.1154, found 213.1153.

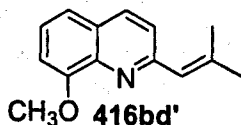## 2-(4'-Fluoro-phenyl)-8-methoxy-quinoline 416be'

Following the above procedures, employing silylated carbamate **413b** (1.54 g, 3.60 mmol) and resin-bound ester **309e'** (Method A, 0.30 mmol), yielded 2-(4'-fluoro-phenyl)-8-methoxy-quinoline **416be'** as a yellow oil (0.039 g, 0.154 mmol, 51%); ν_{max} (Thin Film)/cm^{-1}: 3002 (CH), 2960 (CH), 2937 (CH), 2836 (OCH$_3$), 1615 (C=C), 1601 (C=C), 1559 (C=C), 1497 (C=C), 1330 (CF), 753 (CF); δ_H (400 MHz, CDCl$_3$): 4.10 (3H, s, OCH$_3$), 7.07 (1H, d, J 7.4, H-5), 7.15-7.21 (2H, m, H-3' and H-5'), 7.39-7.47 (2H, m, H-6 and H-7), 8.02 (1H, d, J 8.6, H-3), 8.08-8.13 (3H, m, H-4, H-2' and H-6'); δ_C (100 MHz, CDCl$_3$): 56.1 (CH$_3$), 107.2 (CH), 115.7 (d, J 21.4, CH), 119.1 (CH), 119.3 (CH), 126.6 (CH), 128.2 (C), 129.5 (d, J 8.2, CH), 135.9 (C), 136.9 (CH), 140.1 (C), 155.2 (C), 155.5 (C), 163.3 (d, J 249, CF); m/z, EI+ (%): 253 (M$^{+\bullet}$, 95), 252 (M$^{+\bullet}$-H, 100), 224 (M$^{+\bullet}$-CHO, 57), 223 (M$^{+\bullet}$-CH$_2$O, 51); Accurate mass: C$_{16}$H$_{12}$FNO: requires 253.0903, found 253.0904.

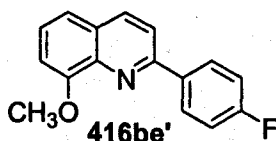## 6,7-Methylenedioxy-2-phenethyl-quinoline 416ca'

416ca'

Following the above procedures, employing silylated carbamate **413c** (1.59 g, 3.60 mmol) and resin-bound ester **309a'** (Method A, 0.30 mmol), yielded 6,7-methylenedioxy-2-phenethyl-quinoline **416ca'** as a yellow oil (0.046 g, 0.202 mmol, 52%); ν_{max} (Thin Film)/cm^{-1}: 3032 (CH$_2$), 2952 (CH$_2$), 2912 (CH), 2856 (CH), 1618 (C=C), 1589 (C=C), 1512 (C=C), 1495 (C=C), 729 (CH), 696 (CH); δ_H (400 MHz, CDCl$_3$): 3.10-3.15 (2H, m, CH$_2$), 3.19-3.24 (2H, m, CH$_2$), 6.09 (2H, s, OCH$_2$O), 7.02 (1H, s, H-5), 7.03 (1H, d, J 8.3, H-3), 7.17-7.30 (5H, m, Ar-H), 7.38 (1H, s, H-8), 7.85 (1H, d, J 8.3, H-4); δ_C (100 MHz, CDCl$_3$): 36.1 (CH$_2$), 40.6 (CH$_2$), 101.6 (CH$_2$), 102.6 (CH), 105.5 (CH), 119.7 (CH), 123.5 (C), 125.9 (CH), 128.3 (CH), 128.5 (CH), 135.1 (CH), 141.6 (C), 146.1 (C), 147.2 (C), 155.6 (C), 159.5 (C); m/z, EI+ (%): 277 (M$^{+\bullet}$, 100), 200 (M$^{+\bullet}$-C$_6$H$_5$, 50); Accurate mass: C$_{18}$H$_{15}$NO$_2$: requires 277.1103, found 277.1102.

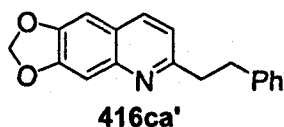## 2-(4'-Fluorophenyl)-6,7-methylenedioxy-quinoline 416ce'

416ce'

Following the above procedures, employing silylated carbamate **413c** (1.59 g, 3.60 mmol) and resin-bound ester **309e'** (Method A, 0.30 mmol), yielded 2-(4'-fluorophenyl)-6,7-methylenedioxy-quinoline **416ce'** as a yellow solid (0.033 g, 0.124 mmol, 41%); Mpt: 139-142 °C; v_{max} (GGate)/cm^{-1}: 2962 (CH), 2915 (CH), 2848 (CH), 2784 (CH$_2$), 1617 (C=C), 1600 (C=C), 1498 (C=C), 1330 (CF), 757 (CF); δ_H (400 MHz, CDCl$_3$): 6.11 (2H, s, OCH$_2$O), 6.77 (1H, s, H-5), 7.17-7.20 (2H, m, H-3' and H-5'), 7.43 (1H, s, H-8), 7.66 (1H, d, J 8.5, H-3), 8.01 (1H, d, J 8.5, H-4), 8.09-8.11 (2H, m, H-2' and H-6'); δ_C (100 MHz, CDCl$_3$): 101.7 (CH$_2$), 102.5 (CH), 106.0 (CH), 115.7 (d, J 21.4, CH), 116.9 (CH), 124.0 (C), 126.6 (CH), 128.4 (C), 129.0 (d, J 8.6, CH), 135.6 (CH), 146.4 (C), 147.8 (C), 151.0 (C), 154.2 (C), 163.7 (d, J 249, CF); m/z, EI+ (%): 267 (M$^{+\bullet}$, 100), 208 (43); Accurate mass: C$_{16}$H$_{10}$FNO$_2$: requires 267.0696, found 267.0695.

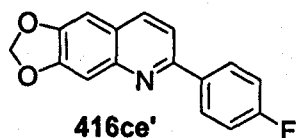## 2-(3'-Furyl)-6,7-methylenedioxy-quinoline 416cf'
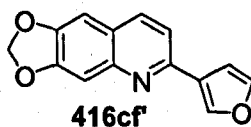
416cf'

Following the above procedures, employing silylated carbamate **413c** (1.59 g, 3.60 mmol) and resin-bound ester **309f'** (Method A, 0.30 mmol), yielded 2-(3'-furyl)-6,7-methylenedioxy-quinoline **416cf'** as a yellow solid (0.039 g, 0.162 mmol, 54%); Mpt: 124-127 °C; v_{max} (GGate)/cm^{-1}: 2914 (CH), 2848 (CH), 1618 (C=C), 1577 (C=C), 1513 (C=C), 1494 (C=C); δ_H (400 MHz, CDCl$_3$): 6.09 (2H, s, OCH$_2$O), 7.02 (1H, s, H-5), 7.04 (1H, d, J 1.6, H-5'), 7.37 (1H, s, H-8), 7.44 (1H, d, J 8.4, H-3), 7.52 (1H, d, J 1.6, H-4'), 7.93 (1H, d, J 8.4, H-4), 8.08 (1H, s, H-2'); δ_C (100 MHz, CDCl$_3$): 101.8 (CH$_2$), 102.7 (CH), 105.8 (CH), 109.0 (CH), 117.1 (CH), 123.9 (C), 127.5 (C), 135.3 (CH), 141.4 (CH), 143.8 (CH), 146.5 (C), 147.5 (C), 149.6 (C), 150.8 (C); m/z, EI+ (%): 239 (M$^{+\bullet}$, 100), 211 (M$^{+\bullet}$-CHO, 18), 153 (12); Accurate mass: C$_{14}$H$_9$NO$_3$: requires 239.0582, found 239.0581.

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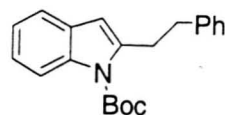# APPENDIX - 1

Representative NMR spectra of selected products

ppm 14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5

Integral
3.794   31.418   4.018   8.012   8.844   39.336   1.205   3.373

ppm   8.5   8.0   7.5   7.0   6.5   6.0   5.5   5.0   4.5   4.0   3.5   3.0   2.5   2.0   1.5   1.0   0.5   0.0

Current Data Parameters
NAME   010618-CMD-B3
EXPNO   10
PROCNO   1

F2 - Acquisition Parameters
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Time   13.31
INSTRUM   dpx400
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PULPROG   zg30
TD   32768
SOLVENT   CDCl3
NS   16
DS   2
SWH   8223.685 Hz
FIDRES   0.250967 Hz
AQ   1.9923444 sec
RG   181
DW   60.800 usec
DE   6.00 usec
TE   298.0 K
D1   0.01000000 sec

========== CHANNEL f1 ==========
NUC1   1H
P1   9.20 usec
PL1   -3.00 dB
SFO1   400.1324689 MHz

F2 - Processing parameters
SI   32768
SF   400.1300262 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   4.00

1D NMR plot parameters
CX   39.01 cm
F1P   9.250 ppm
F1   3701.20 Hz
F2P   -0.500 ppm
F2   -200.06 Hz
PPMCM   0.24992 ppm/cm
HZCM   99.99999 Hz/cm

Integral: 70.079   24.604   0.937   3.436   0.944

ppm   8.5   8.0   7.5   7.0   6.5   6.0   5.5   5.0   4.5   4.0   3.5   3.0   2.5   2.0   1.5   1.0   0.5   0.0
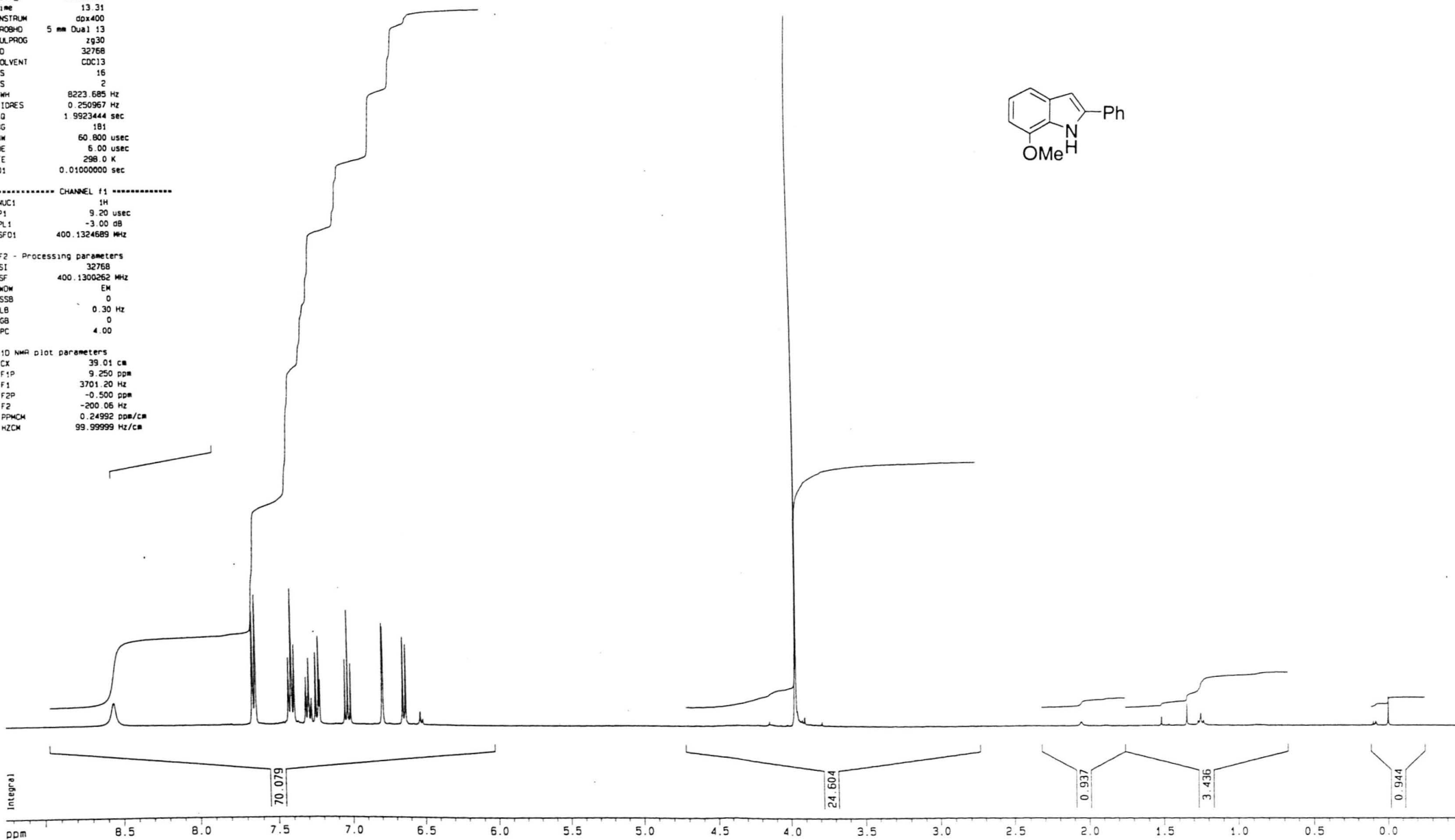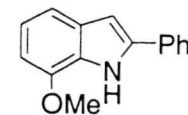
298K

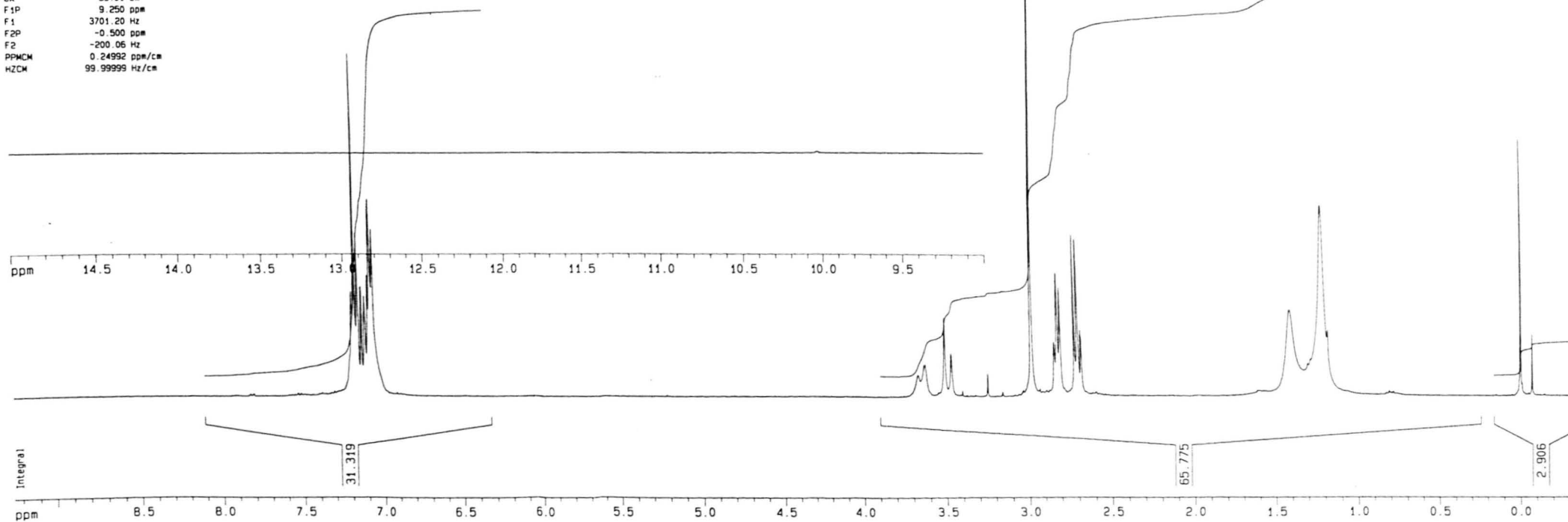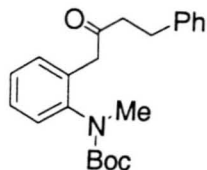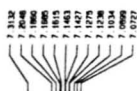Current Data Parameters
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PROCNO   1

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PULPROG   zg30
TD   32768
SOLVENT   CDCl3
NS   16
DS   2
SWH   8223.685 Hz
FIDRES   0.250967 Hz
AQ   1.9923444 sec
RG   181
DW   60.800 usec
DE   6.00 usec
TE   298.0 K
D1   0.01000000 sec

============ CHANNEL f1 ============
NUC1   1H
P1   9.20 usec
PL1   -3.00 dB
SFO1   400.1324689 MHz

F2 - Processing parameters
SI   32768
SF   400.1300388 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   4.00

1D NMR plot parameters
CX   39.01 cm
F1P   9.250 ppm
F1   3701.20 Hz
F2P   -0.500 ppm
F2   -200.06 Hz
PPMCM   0.24992 ppm/cm
HZCM   99.99999 Hz/cm

CMC 47 AT 353K.

BRUKER

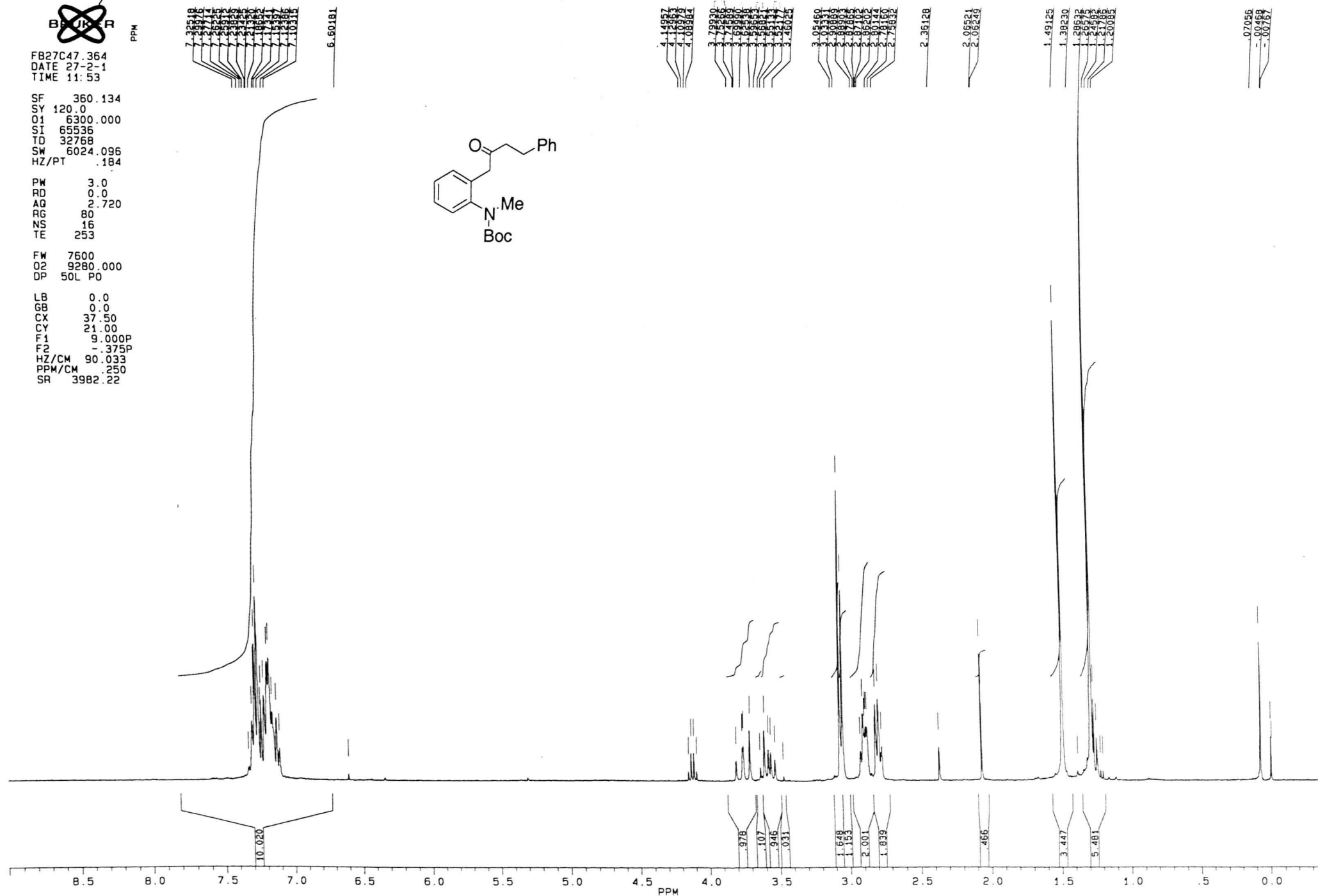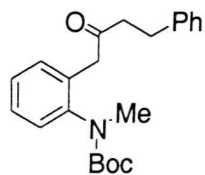PPM

FB27C47.364
DATE 27-2-1
TIME 11:53

SF   360.134
SY   120.0
O1   6300.000
SI   65536
TD   32768
SW   6024.096
HZ/PT   .184

PW   3.0
RD   0.0
AQ   2.720
RG   80
NS   16
TE   253

FW   7600
O2   9280.000
DP   50L PO

LB   0.0
GB   0.0
CX   37.50
CY   21.00
F1   9.000P
F2   -.375P
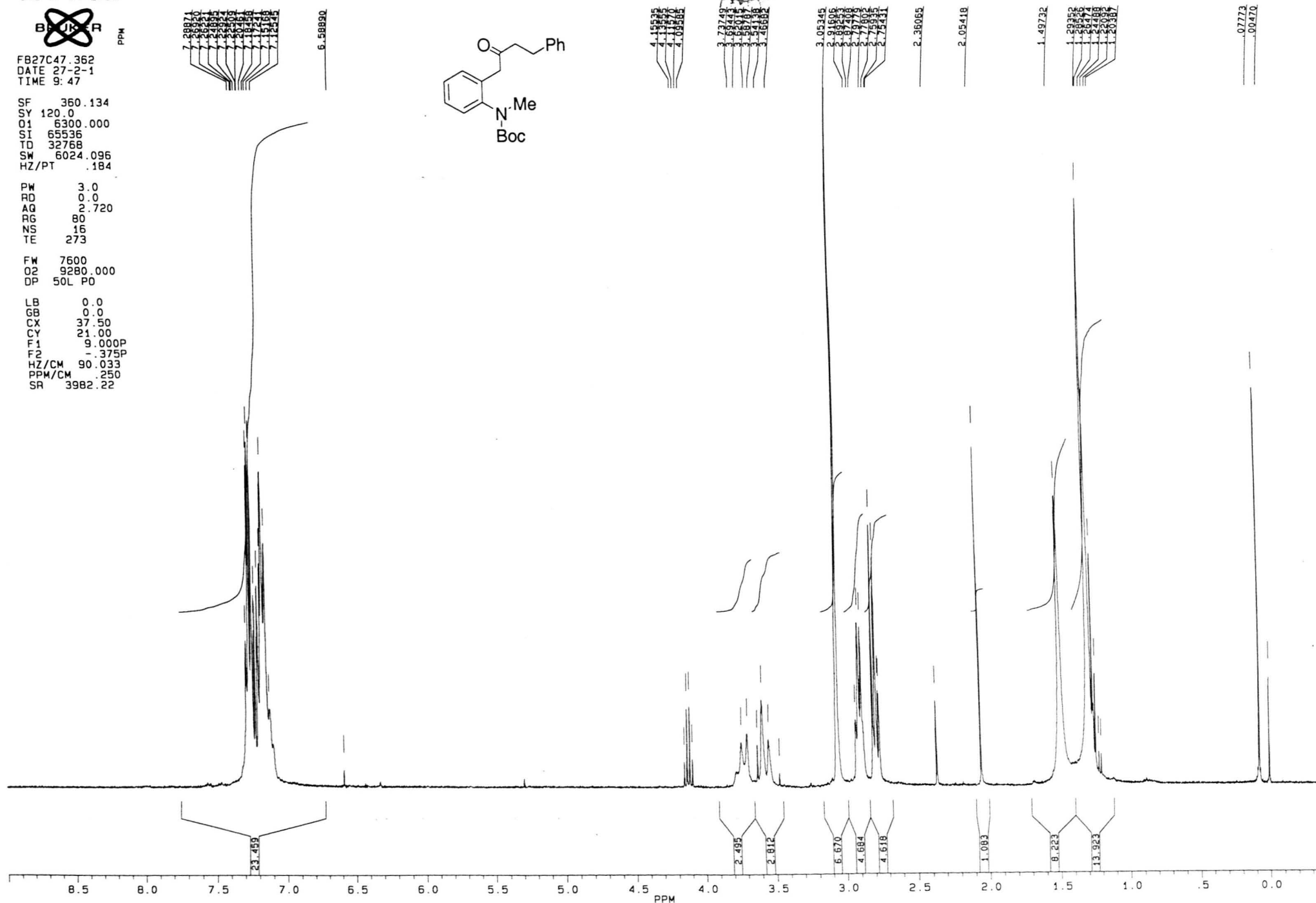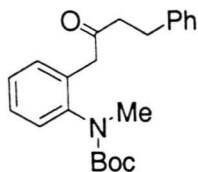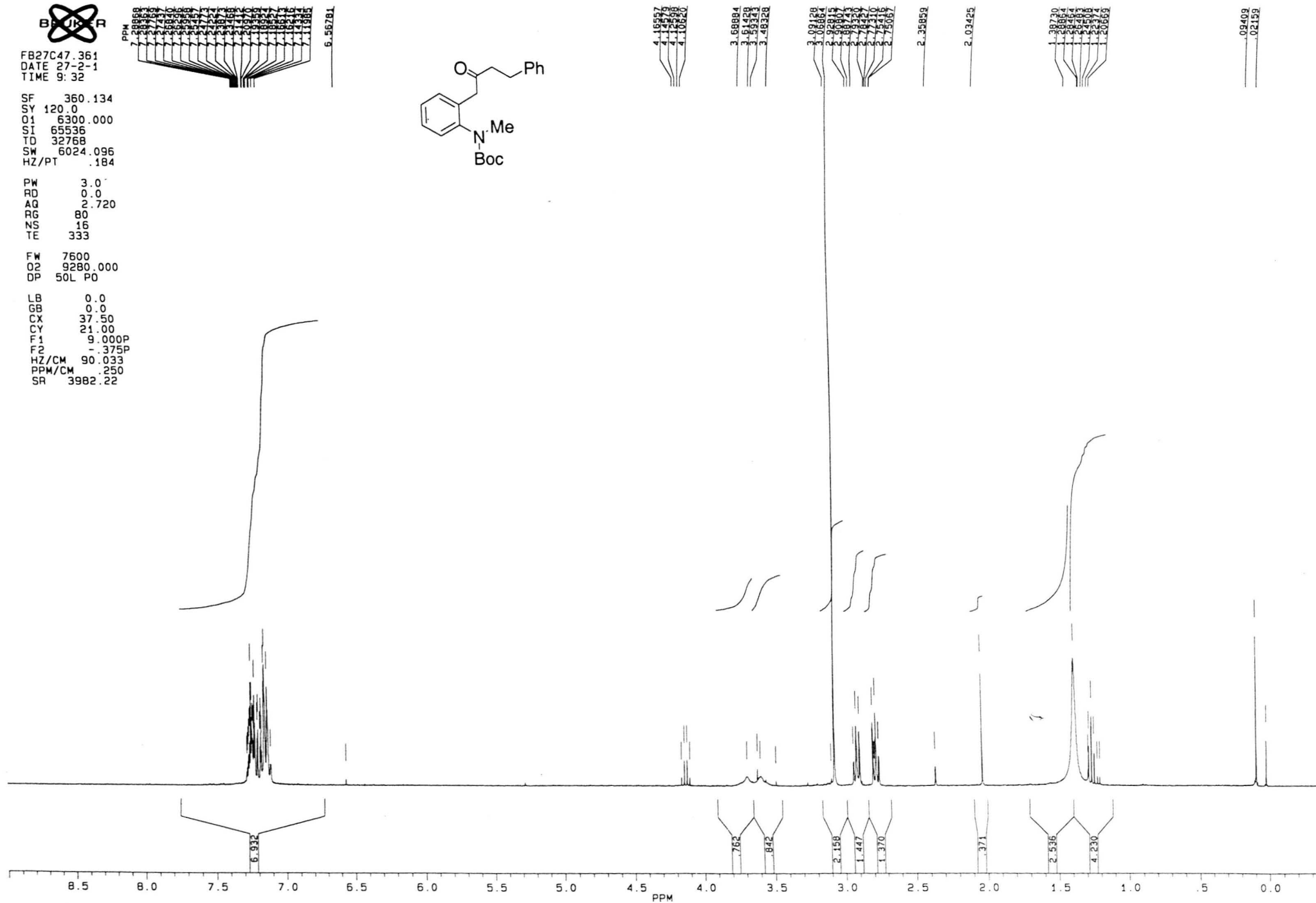HZ/CM   90.033
PPM/CM   .250
SR   3982.22

23.455

2.495 2.812   6.670 4.684 4.618   1.083   8.223   13.923

8.5   8.0   7.5   7.0   6.5   6.0   5.5   5.0   4.5   4.0   3.5   3.0   2.5   2.0   1.5   1.0   .5   0.0
PPM

CMC 47 AT 333K.

BRUKER

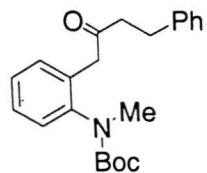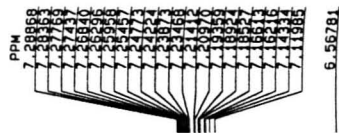FB27C47.361
DATE 27-2-1
TIME 9:32

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SY   120.0
O1   6300.000
SI   65536
TD   32768
SW   6024.096
HZ/PT   .184

PW   3.0
RD   0.0
AQ   2.720
RG   80
NS   16
TE   333

FW   7600
O2   9280.000
DP   50L PO

LB   0.0
GB   0.0
CX   37.50
CY   21.00
F1   9.000P
F2   -.375P
HZ/CM   90.033
PPM/CM .250
SR   3982.22

PPM

6.932   762   842   2.158   1.447   1.370   371   2.536   4.230

8.5   8.0   7.5   7.0   6.5   6.0   5.5   5.0   4.5   4.0   3.5   3.0   2.5   2.0   1.5   1.0   .5   0.0
PPM

Current Data Parameters
NAME   010911-CME37
EXPNO   10
PROCNO   1

F2 - Acquisition Parameters
Date_   20010911
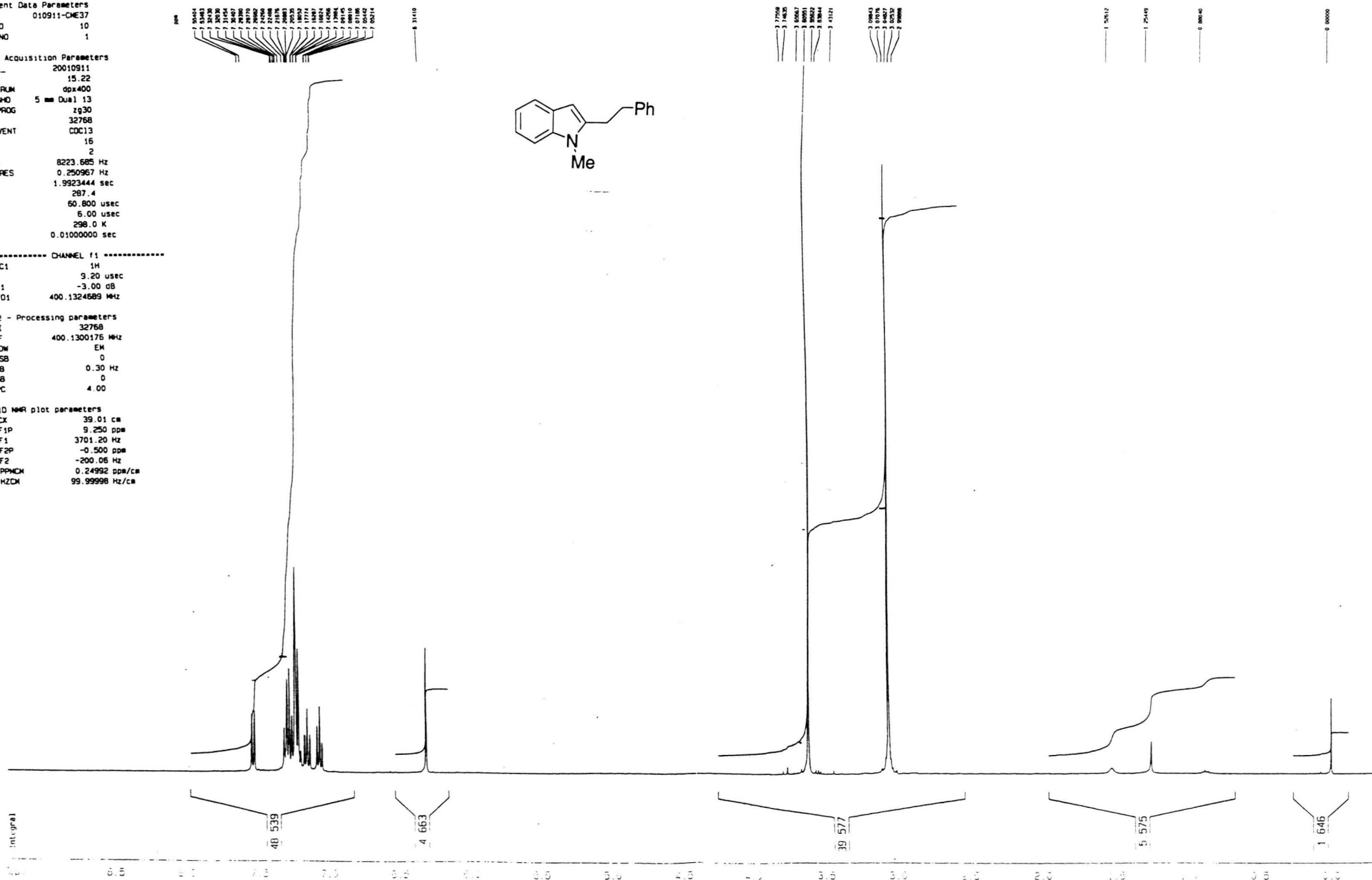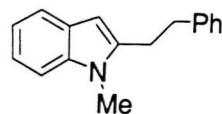Time   15.22
INSTRUM   dpx400
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PULPROG   zg30
TD   32768
SOLVENT   CDCl3
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DS   2
SWH   8223.685 Hz
FIDRES   0.250967 Hz
AQ   1.9923444 sec
RG   287.4
DW   60.800 usec
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TE   298.0 K
D1   0.01000000 sec

============ CHANNEL f1 ============
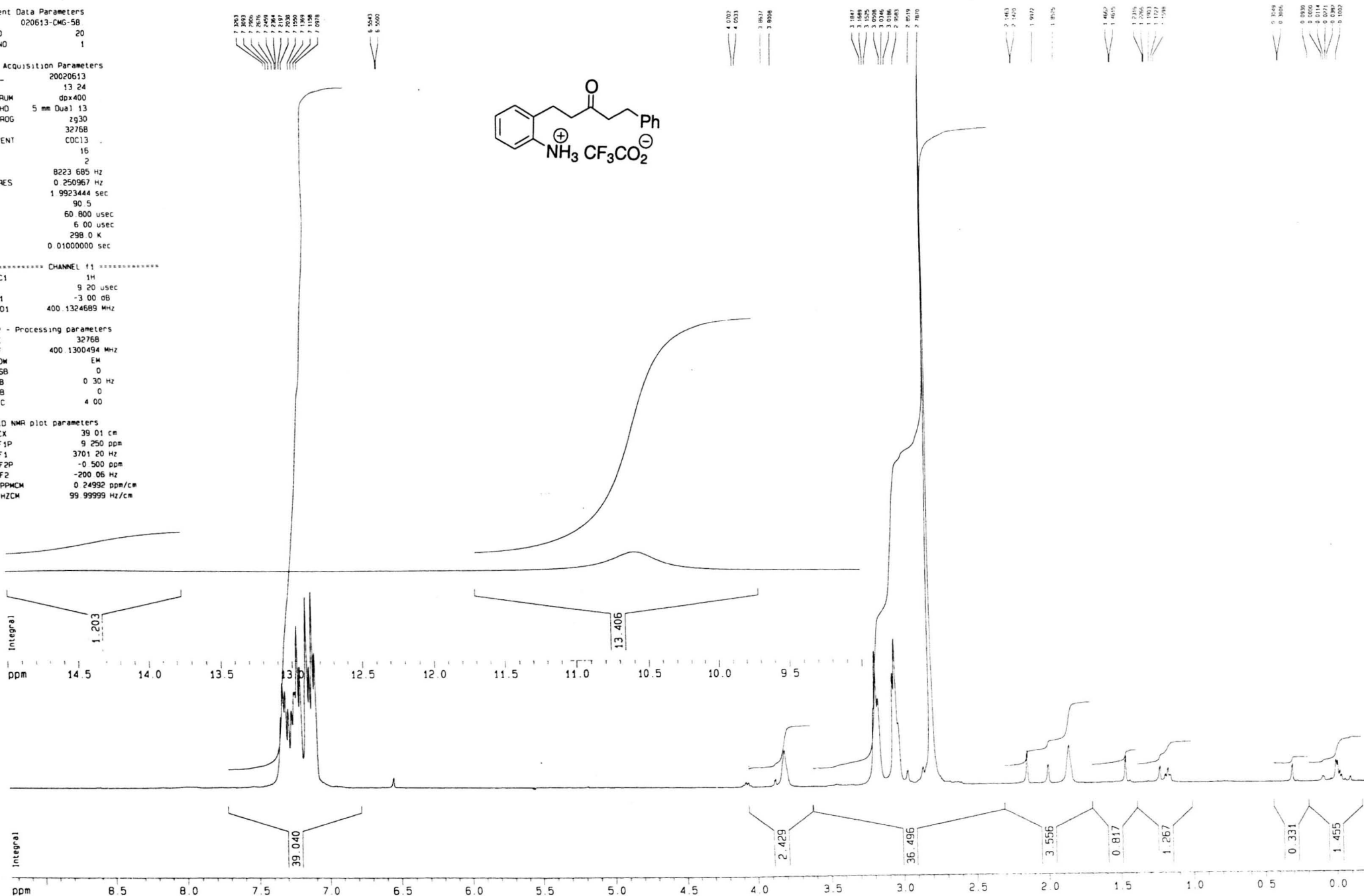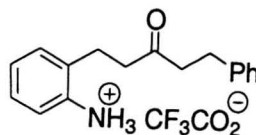NUC1   1H
P1   9.20 usec
PL1   -3.00 dB
SFO1   400.1324589 MHz

F2 - Processing parameters
SI   32768
SF   400.1300176 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   4.00

1D NMR plot parameters
CX   39.01 cm
F1P   9.250 ppm
F1   3701.20 Hz
F2P   -0.500 ppm
F2   -200.06 Hz
PPMCM   0.24992 ppm/cm
HZCM   99.99998 Hz/cm

Integral values: 48.539   4.663   39.577   5.575   1.646

Current Data Parameters
NAME   020930-CMH-65.
EXPNO   10
PROCNO   1

F2 - Acquisition Parameters
Date_   20020930
Time   18.17
INSTRUM   dpx400
PROBHD   5 mm Dual 13
PULPROG   zg30
TD   32768
SOLVENT   CDCl3
NS   16
DS   2
SWH   8223.685 Hz
FIDRES   0.250967 Hz
AQ   1.9923444 sec
RG   574.7
DW   60.800 usec
DE   6.00 usec
TE   298.0 K
D1   0.01000000 sec

========= CHANNEL f1 =========
NUC1   1H
P1   9.20 usec
PL1   -3.00 dB
SFO1   400.1324689 MHz

F2 - Processing parameters
SI   32768
SF   400.1300379 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   4.00

1D NMR plot parameters
CX   39.01 cm
F1P   9.250 ppm
F1   3701.20 Hz
F2P   -0.500 ppm
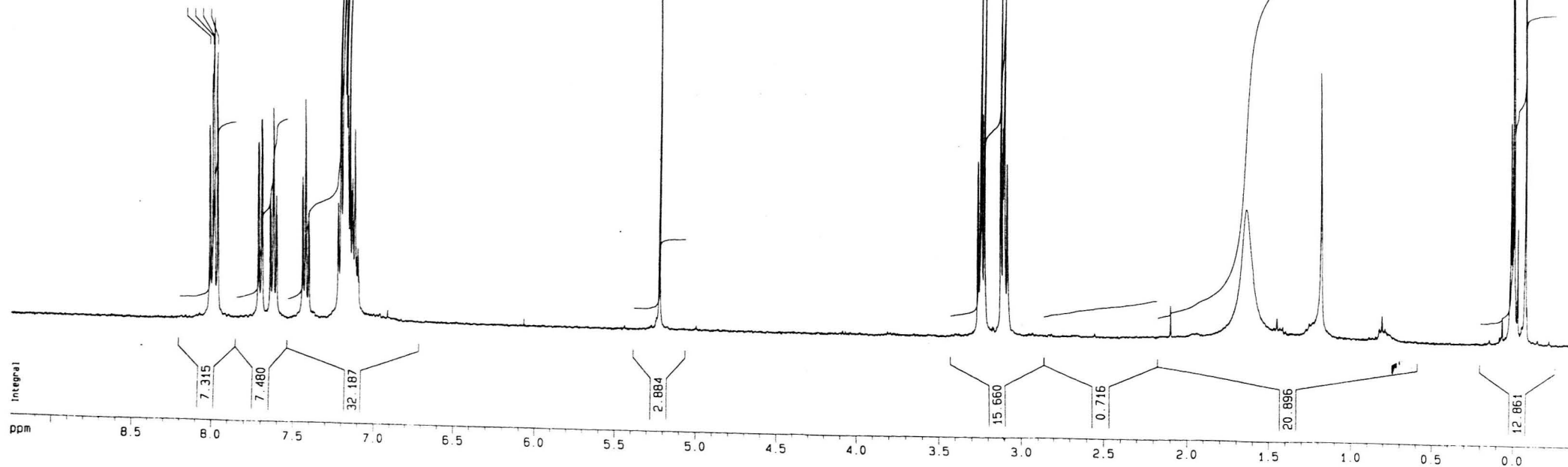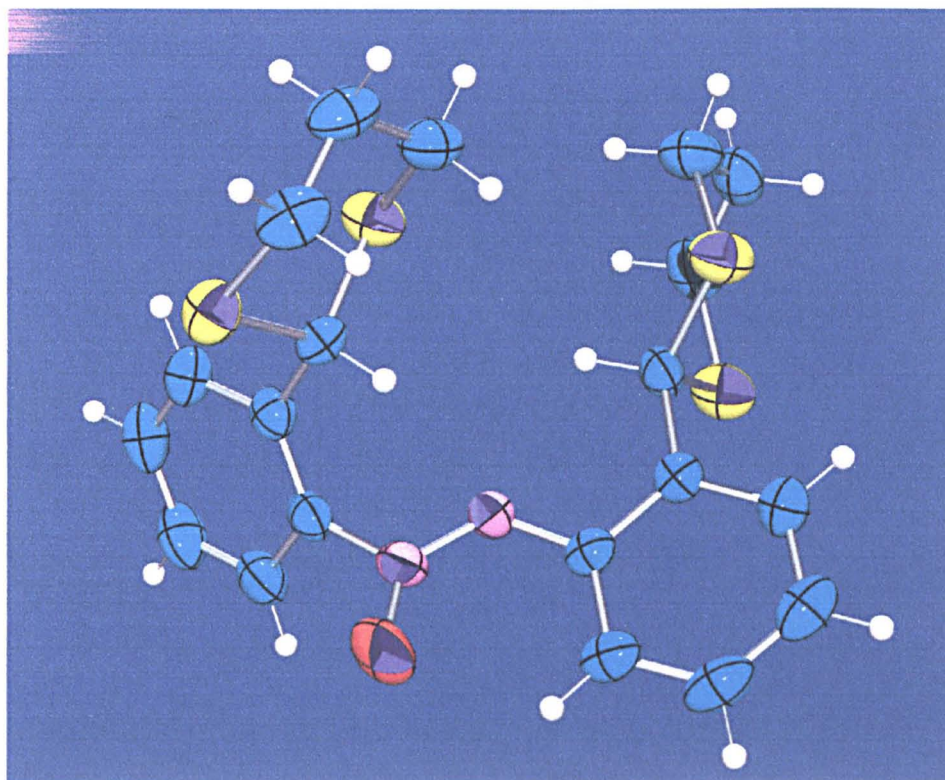F2   -200.06 Hz
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HZCM   99.99999 Hz/cm

Integral: 7.315 7.480 32.187 2.884 15.660 0.716 20.896 12.861

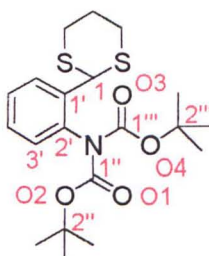# APPENDIX –2

Selective Crystallographic Information

Crystal Structure of Diazine-*N*-oxide 333

# Selected Molecular Geometrical Measurements of N(Boc)₂ Imide

334

Bond Lengths (Å)	Bond Angles (deg)	Torsion Angles (deg)
C2'-N - 1.4508(14)	C2'-N-C1" - 119.59(9)	C1'-C2'-N-C1" - 98.59(13)
N-C1" - 1.4131(14)	C2'-N-C1''' - 120.47(9)	C3'-C2'-N-C1" - [-79.05(14)]
C1"-O1 - 1.1947(15)	C1'''-N-C1" - 119.92(9)	C2'-N-C1"-O1 - [-168.70(13)]
C1"-O2 - 1.3288(14)	N-C1"-O1 - 124.59(11)	C2'-N-C1"-O2 - 11.25(15)
N-C1''' - 1.4058(14)	N-C1"-O2 - 108.42(10)	
C1'''-O3 - 1.1951(15)	O1-C1"-O2 - 126.99(11)	
C1'''-O4 - 1.3309(14)	N-C1'''-O3 - 124.46(11)	
	N-C1'''-O4 - 108.66(9)	
	O3-C1'''-O4 - 126.87(11)	

Selected Molecular Geometrical Measurements of NHBoc Carbamate

335a
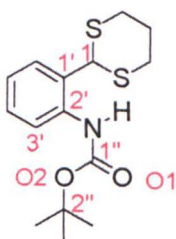
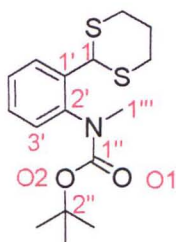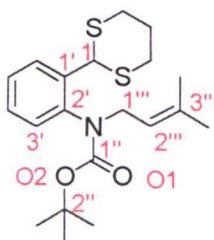| Bond Lengths (Å)	Bond Angles (deg)	Torsion Angles (deg)
C2'-N - 1.419(3)	C2'-N-C1" - 124.96(19)	C1'-C2'-N-C1" - [-143.6(2)]
N-C1" - 1.366(3)	N-C1"-O1 - 125.1(2)	C3'-C2'-N-C1" - 36.3(3)
C1"-O1 - 1.208(3)	N-C1"-O2 - 108.21(18)	C2'-N-C1"-O1 - [-3.6(3)]
C1"-O2 - 1.347(3)	O1-C1"-O2 - 126.7(2)	C2'-N-C1"-O2 – 176.08(17)
	C1'-C2'-C3' - 120.17(19)	
	C1'-C2'-N - 120.65(19)	
	C3'-C2'-N - 119.18(18)	

Selected Molecular Geometrical Measurements of N(Me)Boc Carbamate 346a

Bond Lengths (Å)	Bond Angles (deg)	Torsion Angles (deg)
C2'-N - 1.4407(16)	C1'-C2'-N - 120.78(11)	C1'-C2'-N-C1" - 78.71(16)
N-C1''' - 1.4612(17)	C3'-C2'-N - 118.38(11)	C3'-C2'-N-C1" - [-104.12(15)]
N-C1" - 1.3616(17)	C2'-N-C1" - 122.35(11)	C3'-C2'-N-C1''' - 72.40(16)
C1"-O1 - 1.2222(15)	C2'-N-C1''' - 117.70(11)	C2'-N-C1"-O1 - 179.41(11)
C1"-O2 - 1.3410(16)	C1'''-N-C1" - 119.86(11)	C2'-N-C1"-O2 - [-0.88(17)]
	N-C1"-O1 - 123.62(13)	C1'''-N-C1"-O1 - 3.00(2)
	N-C1"-O2 - 110.41(10)	C1'''-N-C1"-O2 - [-177.33(11)]
	O1-C1"-O2 - 125.97(12)	
	C1"-O2-C2" - 120.92(10)	

Selected Molecular Geometrical Measurements of N(Prenyl)Boc Carbamate 346c

Bond Lengths (Å)	Bond Angles (deg)	Torsion Angles (deg)
C2'-N - 1.4349(16)	C2'-N-C1" - 123.71(11)	C1'-C2'-N-C1" - 77.30(16)
N-C1" - 1.3607(17)	C2'-N-C1''' - 118.23(11)	C3'-C2'-N-C1" - [-106.32(14)]
C1"-O1 - 1.2204(16)	C1"-N-C1''' - 120.62(11)	C2'-N-C1"-O1 - [-178.12(12)]
C1"-O2 - 1.3421(15)	N-C1"-O1 - 123.67(12)	C2'-N-C1"-O2 - 1.92(16)
N-C1''' - 1.4760(16)	N-C1"-O2 - 110.65(11)	C1'''-N-C1"-O1 - 7.81(19)
C1'''-C2''' - 1.4986(19)	C1"-O2-C2" - 120.62(10)	C1'''-N-C1"-O2 - [-172.15(10)]
C2'''-C3''' - 1.328(2)	O1-C1"-O2 - 125.68(12)	C1'-N-C1'''-C2''' - 80.73(14)
	N-C1'''-C2''' - 112.01(10)	